

UPDATES AND ADDITIONS
for
Herbal Contraindications & Drug Interactions
plus Herbal Adjuncts with Medicines

FOURTH EDITION

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NEW FEATURE: An index for the Updates and Additions is now included at the end.

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NOTICE

Information provided in the book or these updates and additions is not intended as recommendations for self treatment or to substitute or replace instructions provided by one's own doctor or health care provider. Combining herbal use with medications should only be done after consultation with a knowledgeable physician. Preliminary research data on potentially beneficial combinations of herbs and drugs is provided to educate pharmacists and physicians and encourage further clinical research.

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Where the bracketed phrase [Note CORRECTION:] appears before numbers or information in ALL CAPS in these Updates and Additions, it denotes an error found in early printings of the book (those prior to 2013). The corrections were made in ongoing printings and the Kindle version (2013) of the book. It is recommended that if the noted corrections have not been made in the book in your possession, that you make the appropriate changes directly in your hard copy and/or insert a copy of the compilation of all CORRECTIONS that is given before the Index at the end of these Updates after the References.

KEYS TO INTERPRETING THE CONTENT IN THE BOOK AND AT THIS SITE

The following terms are used to describe the different means of determining botanical effects.

[At www.electicherb.com/emp/herb-contraindications-drug-interactions/ a free, printable, tri-fold bookmark with the following designations is available in pdf format.]

Where contradicting data exists for a particular item in any category, this is noted by an indentation, and the sentence will begin with the capitalized word, 'HOWEVER'.

Herbs that have a potential for adverse side effects when taken in excessive doses are marked with an asterisk (*).

Contraindications

- I. **clinical** – (empirical observations, human research, or case reports)
- II. **pre-clinical** – (indirect *in vitro* or *in vivo* laboratory studies (speculative outcomes for humans))

Drug Interactions

- Ia. **human studies** – published research done on healthy individuals
human clinical studies – published research from therapeutic trials on patients being treated for a condition
- Ib. **empirical** – traditional knowledge or consensus based on experience from extensive use
human case reports – published individual responses to using herbal products
human case series – published responses from several patients using a preparation of the same herb
- II. **in animals** (types listed) – laboratory tests using live animals (*in vivo*) and various modes of administering the herb or herbal component(s)
- III. **ex vivo** – laboratory interaction finding on cells, tissue, or organs from animals or humans who were administered the herbal agent (as contrasted to *in vivo* when studies are done on the living organisms themselves)
in vitro – laboratory interaction finding with cell or tissue samples from animals or humans
speculative – using pharmacological evidence from *in vitro* research, animal studies, or human studies to infer probable or potential interactions or effects in humans
- IV. [**dubious interactions**], as shown in brackets with the drugs underlined rather than in bold type, are based on preliminary findings, speculation, inaccurate information, and/or false assumptions that have been contradicted by established evidence.

Complementary Adjuncts

Conditions, symptoms, or markers impacted or the drug adverse effects reduced are designated by bold underline.

- Ia. human clinical trials
- Ib. case reports, empirical observations
- IIa. *in vivo* animal studies
- IIIb. *in vitro* laboratory research

Abbreviations for the various modes of administration are used as follows:

- IM (intramuscular)** – injected into a large skeletal muscle
- IP (intraperitoneal)** – injected into the peritoneal cavity
- IV (intravenous)** – injected into a vein
- PO (*per os*)** – by mouth; orally or through a feeding tube; b.i.d. = 2x/day, t.i.d. = 3x/day
- SC (subcutaneous)** – injected under the skin
- SL (sublingual)** – under the tongue
- TP (topical)** – applied to the surface of the skin or on the mucosa of a body cavity

* An asterisk in front of an herb's scientific name denotes toxic effects from over-consumption of that herb or a major active component.

ADDITIONAL INFORMATION IS AVAILABLE IN THESE UPDATES AND ADDITIONS FOR THE FOLLOWING LISTED HERBS AND APPENDICES, AS DESIGNATED:

+ denotes new contraindication(s), interaction(s), and/or complementary adjuncts not previously listed in the book for the herb

^ denotes new herb with contraindication(s), interaction(s) and/or complementary adjuncts in body of text or an entirely new appendix section

If none of the above are present in the list below, further elaborations have been made to information already included in the book.

HERBAL AGENTS

The following list are those herbs that are new (^), or have new categories added (+), or have information updated.

Aloe +
American ginseng +
Amla ^
Anise +
Arjuna +
Arnica +
Ashwagandha +
Asian ginseng +
Astragalus +
Barberry +
Bayberry +
Bilberry +
Bitter melon
Bitter orange
Black cohosh
[Black cumin +] now: Nigella
Black pepper +
Black raspberry ^
Boldo +
Boneset +
Borage +
Burdock +
Calamus +
Cannabis +
Cassia +
Cat's claw +
Cayenne +
Celandine
Chaga ^
Chamomile
Chili ^
Chinese hibiscus [formerly Hibiscus]
Chinese rhubarb +
Chinese skullcap +
Chokeberry +
Cinchona
Cinnamon +
Clove +
Cocoa +
Cola +
Coptis +
Corn silk ^
Cranberry

Crucifers +
Dan shen +
Devil's claw +
Dog rose +
Dong Quai +
Echinacea angustifolia
Echinacea pallida +
Echinacea purpurea +
Eleuthero +
English plantain +
Eucalyptus +
European pennyroyal +
Evening primrose +
Fenugreek +
Fo-ti
[Frankincense +] now: Indian frankincense
French maritime pine +
Garlic +
Gentian +
Ginger +
Ginkgo
Goldenseal +
Gotu kola +
Grapefruit +
Guarana +
Guggul +
Hawthorn +
[Hibiscus ^] now: Chinese hibiscus
Hops +
Horse chestnut +
Horsetail +
Indian frankincense + [formerly Frankincense]
Jujube +
Kava
Kudzu +
Kutaki +
Larch ^
Licorice +
Long pepper +
Lycium +
Maca
Maitake +
Mango ^
Milk thistle +
Myrrh +
Nigella + [formeraly Black cumin]
Noni +
Oat
Olive +
Oregon grape +
Passion flower

Pau d'Arco +
 Pelargonium ^
 Peppermint +
 Pomegranate +
 Prickly pear
 Psyllium
 Quassia (Surinam) +
 Raspberry +
 Rhodiola +
 Roman chamomile
 Root of Gold ^
 Saffron +
 Sage +
 Sanch ginseng ^
 Saw palmetto +
 Schisandra +
 Sea buckthorn +
 Sheppherd's purse +
 Shiitake ^
 Silk tree +
 Southern schizandra ^
 Soy +
 St. John's wort
 Stinging nettle
 Sweet annie +
 Sweet cherry ^
 Tart cherry ^
 Tea +
 Tea tree +
 Thunder duke [god] vine +
 Tibetan rhodiola ^
 Tulsi ^
 Turmeric +
 Valerian +
 Wild yam +
 Yohimbe

APPENDICES

The following are entirely new sections and subsections.

A.8 Bioactivations of Phytochemical Procarcinogens and Potential Toxins ^

A.8.1 Bioactivations by Cytochrome P450 Isozymes (CYPs) and Sulfotransferases (STs) ^

B.4.3 Botanicals Impacting Metabolism of Oral Hypoglycemic Drugs in Humans

B.7.1.d Influence on Constitutive Androstane Receptor (CAR)

B.7.3.f Influence on Activity of Estrogen Sulfotransferases (SULT1E1)

B.7.4.i 11beta-Hydroxysteroid Dehydrogenase type 1 Conversion of Cortisone to Cortisol ^

B.7.4.j Sterol 27-Hydroxylase (CYP27A1) Conversion of Cholesterol to Bile Acids
and Bioactivation of Vitamin D₃

^

E.5.9 Potential Herbal Prevention of Dermal Photocarcinogenesis

^

- E.5.10 Herbal Prevention of Acute UV-induced Erythema ^
- E.5.11 Herbal Protection Against Radioiodine Therapy Adverse Effects ^
- E.6.11 Botanicals reducing adverse effects caused by antimicrobial agents ^

The following are those sections and subsections for which new information has been added.

A.2 Due to Potential Photosensitizing Effect

A.2.2 Rutacea – Rue Family

A.7 Due to Potential Adverse Effects

A.7.1 Herbals With Toxic Potention

B.1 Modifying Intestinal Absorption of Medicines and Phase III Metabolism

B.1.1 Slowed and/or Reduced Absorption by Herbal Components

B.1.2 Enhancement of Absorption

B.4 Modifying Blood Sugar In Diabetics

B.4.1 Hypoglycemic and/or Antihyperglycemic Herbals

B.4.2 Antihyperglycemic Botanicals Enhancing Oral Hypoglycemic Drugs in Humans

B.5 Modifying the Effects of Anticoagulants

B.5.1 Increasing Potential for Hemorrhage

B.5.2 Increasing Potential for Coagulation

B.7 Modifying Enzyme Activities in Metabolic Conversions

B.7.1 Unspecified Influences of Herbal Agents on Substrate Pharmacokinetics

B.7.2 Influences of Herbal Agents in Phase I on Specific Cytochrome P450 Isozymes

B.7.3 Specific Enzyme Influences of Herbal Agents on Phase II Conjugation

B.7.4 Specific Enzyme Influences of Herbal Agents on Steroid Metabolism

C.1 During Pregnancy

C.1.1 Herbals That May Impact the Uterus or Fetal Development

E.1 Potentially Beneficial Combinations of Herbals with Drugs

E.1.1 Herbs and Those Drugs Which May Potentially Be Complemented

E.2 Herbal Aids for Modifying Substance Abuse

E.2.1 Botanical Adjuncts for Reducing Recreational Drug Use and/or Damage

E.3 Complementing Treatment of Inflammations

E.3.2 Enhancing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

E.3.3 Enhancing Outcomes When Using Analgesics

E.3.4 Protecting Against NSAID-induced Ulcers

E.3.5 Protecting Against Acetaminophen-induced Liver Toxicity

E.4 Enhancing Chemotherapy and Chemoprevention or Reducing the Adverse Effects

E.4.1 Enhancing therapeutic effects of chemotherapy

E.4.2 Reducing adverse effects of chemotherapy

E.4.4 Promoting and/or Enhancing Chemoprevention of Selective Cancers

E.4.5. Reducing Transforming Growth Factor- β 1 Before, During, &/or After Chemotherapy

E.5 Herbals for Preventing and Healing Radiation Adverse Effects and/or Enhancing Radiotherapy or Photodynamic Therapy

E.5.4. Protection from Adverse Effects by Cobalt 60 or Cesium 137 Gamma Radiation

E.5.5 Enhancing Antineoplastic Effects of Radiation

E.5.7. Reducing Transforming Growth Factor- β 1 Before, During, &/or After Radiotherapy

E.6 Herbals and Anti-infection Agents

E.6.1 Botanicals active against antibiotic-resistant strains of bacteria

- E.6.2 Botanicals improving antimicrobial efficacy against resistant strains
- E.6.3 Botanicals enhancing the ordinary efficacy of antibiotics & antiseptics
- E.6.6 Botanicals inhibiting efflux of antimicrobial agents by bacteria
- E.6.7 Botanicals enhancing [or reducing] the efficacy of antifungal agents [^]
- E.6.9 Botanicals enhancing the efficacy of immunizations against infections

REFERENCES

New references citations from 2709 to 3718 can be found at the end of these Updates and Additions. Reference citations prior to # 2709 are available free on this website in pdf file format for downloading or printing for personal use.

NOTE

Only herbs whose preparations are administered to humans orally, externally, or by inhalation are considered in this text. Injectable herbal items lie outside the scope of this text and American practice, though sometimes supportive evidence may involve use of injectables, especially in animal studies. However, it is important to remember that the bioavailability of phytochemicals is much greater with injections, especially of those components that typically undergo metabolism but intestinal flora, and the rate and percentage of absorption of different phytochemicals in a complex preparation will be variable. Therefore, the effects of injections are not likely to be completely representative of oral use. Injections of isolated compounds known to be absorbed intact are more likely to mimic oral use, though effects will differ between the two routes when using the same dose.

Contraindications, Drug Interactions and/or Complementary Adjuncts

ALOE

p. 34

Aloe vera = *Aloe barbadensis* fresh leaf gel (not the dried sap)

Drug Interactions

- Ia. 1) Increased the hypoglycemic effect of **glyburide [glibenclamide]** when given twice daily for 42 days (PO in human clinical study).¹²²

In a randomized, placebo-controlled, double-blind study with 60 hyperlipidemic type 2 diabetic patients of ages 40-60 years being ineffectively treated with glyburide and **metformin**, 600 mg of freeze-dried aloe gel in capsules was given daily for 2 months in addition to the oral hypoglycemic drugs (PO in human clinical study). Compared to placebo, the aloe gel significantly reduced fasting blood glucose, glycosylated hemoglobin, total cholesterol, and LDL-cholesterol levels. No adverse effects or liver and kidney problems were detected.³⁶⁰⁹ A freeze-dried high molecular weight fraction of aloe gel was added at 300 mg daily for 12 weeks to the oral hypoglycemic medications of 15 type 2 diabetic patients who were resistant to their glyburide and metformin (PO in human clinical study). Their fasting blood glucose level was reduced significantly and sustained after 6 weeks and glycosylated hemoglobin was significantly lowered by 20%, compared to baseline. Triglyceride levels decreased significantly after 4 weeks and continued to lower thereafter by 35%.³⁶¹⁰ A meta-analysis of 9 studies with 283 subjects showed a significant reduction in fasting blood glucose, and 5 of these studies with 89 subjects also documented a significant reduction in glycosylated hemoglobin (PO in human clinical studies).³⁶¹¹

Significant hypoglycemic (decreased fasting and postprandial blood glucose levels) and hypolipidemic (decreased total cholesterol, LDL- and VLDL- cholesterol, and triglycerides, plus increased HDL-cholesterol) effects were shown without concurrent medication use with 100 mg or 200 mg of dried gel powder for 3 months in non-insulin dependent diabetics, when compared to control subjects in groups of 30 each (PO in human clinical study).³⁶⁰⁸ The juice processed with catalase and removal of anthroquinones and monosaccharides reduced blood glucose levels to normal in type 2 diabetes with diet-induced obesity apparently by decreasing insulin resistance (PO in mice). Plasma insulin was lowered, as were plasma and liver triglycerides.²⁷⁴¹

Complementary Adjuncts

- Ia. + 2) In a randomized, controlled trial using an aloe mouthwash solution, given to half of 64 patients with lymphoma and leukemia undergoing **chemotherapy** to use for 2 minutes 3 times daily for 14 days, those using the aloe in addition to the routine treatments had significantly less **stomatitis** from the drugs on days 3-7 than those using the ordinary mouthwashes with saline, chlorhexidine, and/or nystatin (TP in human clinical study). In addition, the pain was significantly less in the aloe group from days 3-14. These effects allow better nutritional intake and patient satisfaction.³⁵⁸⁴

AMERICAN GINSENG

p. 37

Panax quinquefolius root

Contraindications

- II. 1) Estrogen-independent proliferation of human breast cancer cell with the alcoholic extract (*in vitro*)¹⁶⁶⁴ suggests avoiding regular consumption with a history of **breast cancer** (speculative).

HOWEVER, a standardized proprietary extract with no effect on the cell cycle significantly inhibited estrogen-receptor positive breast cancer cell proliferation at concentrations of 500 mcg/ml and higher (*in vitro*),⁹⁸¹ as did a water-extract on the same cells (*in vitro*).³⁰⁶³ A freeze-dried water extract of the root significantly reduced proliferation of these estrogen-sensitive human breast cancer cells, as well as antiproliferation and resistance to stimulated COX-2 expression in estrogen-receptor negative breast cancer cells (*in vitro*).³⁰⁶² Though a fresh-root

extract had no effect, a 70% ethanol steam-processed root extract with increased ginsenoside Rg3, as well as isolated Rb3, significantly decreased proliferative activity of estrogen-receptor positive and negative human breast cancer cells by arresting the cell cycle in G1-phase (*in vitro*).³⁰⁶¹ In conjunction with the synergistic effect with chemotherapeutic agents against breast cancer cells [See Complementary Adjuncts IIb. 1.], the weight of *in-vitro* evidence now seems to suggest a potential benefit in breast cancer (speculative).

Drug Interactions

Ia. 1) 3 grams root or more reduced blood sugar in type 2 diabetics treated with **sulfonylureas** or a combination with **metformin** (PO in human study).¹¹¹⁴

In a randomized, placebo-controlled, double-blind, crossover trial with 24 diabetes type 2 patients using conventional treatments of diet or metformin and/or sulfonylurea, a 70% ethanolic extract of the dried root, with 9.67% total ginsenosides and a protopanaxodial-to-protopanaxotril ratio of 3.03, was given at 1 gram 3 times daily with meals for 8 weeks (PO in human clinical study). Compared to placebo, the extract led to significant decreases in HbA1c and fasting blood glucose.³⁷⁰⁴

HOWEVER, in a randomized, placebo-controlled, double-blind, safety study of patients with 74 well-controlled type 2 diabetes mellitus using diet and/or antihyperglycemic medications, 3 g/day of American ginseng ethanolic extract with 10% ginsenosides was used at mealtime as an adjunct for 12 weeks (orally in human clinical study). Of the 65 on medications, 26 used 1 hypoglycemic drug and 39 used ≥ 2 ; of these, 49 used metformin, 43 took sulfonylureas, 11 used **dipeptidyl peptidase-4 inhibitors**, and 4 others took **acarbose**. No changes in kidney, liver or hemostatic functions were detected, and the severity and number of adverse events did not differ between the extract and placebo groups.³⁴¹²

Either 1, 2, 3, 6, or 9 grams of the ground root improved glucose tolerance when given 40 minutes prior to a 25-gram glucose challenge in 10 nondiabetics (PO in human studies).^{1685,2917}

2) After 3 days of **warfarin**, 2 grams root daily for 3 weeks reduced blood levels and anticoagulant effect of warfarin (PO in human study).¹⁶⁰⁰

HOWEVER, based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²

III. 1) The saponin fraction enhanced **phenylephrine** vasoconstrictor effect (*in vitro*).¹⁵⁵⁰

HOWEVER, when 16 hypertensive patients were randomly given 3 grams of root from 6 different farms in Ontario, Canada, for 1 day each, none produced an overall mean change in blood pressure compared to baseline over a period of 160 minutes (PO in human study). Thirteen were taking 1 or more antihypertensive drugs, including 6 on diuretics, 6 on ACE inhibitors, 3 on calcium channel blockers, 2 on beta blockers, and 2 on angiotensin receptor blockers. After monitoring every 10 minutes, increases in mean systolic blood pressure after 140 minutes and diastolic blood pressure after 160 minutes were countered by a lowered mean diastolic pressure at 100 minutes, compared to mean pressures from 2 days on placebo.²⁹¹⁵

2) Using 3 **digoxin** immunoassays, a American ginseng extract increased the digoxin measurement results for the fluorescence polarization immunoassay (*in vitro*).¹⁹⁹⁵

A new analyzer technology from Abbott Laboratories led to development of 2 analyzers, iDig and cDig, using specific monoclonal antibody against digoxin for which American ginseng does not interfere with detection of digoxin (*in vitro*).³⁴³⁵

Complementary Adjuncts

Ia. + 1) In a randomized blinded study with 175 **cancer-related fatigue** patients of whom 57% were still receiving **chemotherapy** and 18% radiation [previously, 65% received chemo and 38% radiation], trends toward improvement in fatigue and vitality were seen in the 94 taking 1000 or 2000 mg of root compared to baseline, whereas 81 patients on 750 mg root or placebo showed no improvements (PO in human clinical study). A total of 40% of patients receiving 1 or 2 gm ginseng compared to 17% on placebo observed a benefit and were satisfied with the treatment. No significant differences in toxicities occurred between any of the groups.²⁹¹⁶ A follow-up

randomized, double-blind study with 2 gm root with 3% ginsenosides showed a significant improvement in 138 cancer-related fatigue after 8 weeks with ginseng, compared to 133 on placebo (PO in human clinical study). The reduction in fatigue was significant after 4 weeks of the root for only those currently undergoing chemotherapy, compared to placebo in those receiving treatment.³²⁹³

+ 2) A 200 mg daily dose of a proprietary extract, CVT-E002 that consists of 80% polysaccharides and oligosaccharides and 10% protein, given in separate studies after **influenza vaccine** in 90% for 2 or 3 months to 97 elderly subjects in institutions or for 1 month before the vaccination and 3 months afterwards to all 22 elderly adults dwelling in the community, led to a significant reduction in the incidence of **influenza** in the institutional groups receiving the extract and significantly reduced duration of acute **respiratory symptoms** in the community group, compared to the 101 and 21 subjects receiving placebo, respectively (PO in human clinical study).^{2918,2919}

3) In a randomized, placebo-controlled, double-blind 12-week trial with 64 **hypertensive diabetic** patients using medications, American ginseng ethanolic extract with 10% total ginsenosides was taken by 30 patients as an adjunct in dose of 1 gram 3 times daily prior to meals (PO in human clinical study). In addition to standard diabetic medications, the antihypertensive drug taken included **ACE inhibitors** by 15, **beta-blockers** by 8, **calcium channel blockers** by 7, and various fixed combinations by 16, plus several other used by 1 or 2 patients. The addition of the extract to the medications led to significant decreases in radial arterial stiffness and systolic blood pressure.³⁴²⁰

In a randomized, placebo-controlled, double-blind, crossover trial with 24 diabetes type 2 patients taking conventional diabetic treatments, as well as use of ACE inhibitors by 10, calcium channel blockers by 5, beta-blockers by 2, **angiotensin receptor blockers** by 2, and combined treatment by 5, the root extract was given at 1 gram 3 times daily with meals for 8 weeks (PO in human clinical study). In addition, 9 were using lipid lowering treatment. Systolic blood pressure was significantly reduced by the extract compared to placebo by 5.6 mmHg, while significant decreases were also seen in LDL-cholesterol by 12.3%, total cholesterol by 9.0%, and LDL/HDL by 13.9%.³⁷⁰⁴

Ila. + 1) Pre-treatment or co-treatment for 3 or 7 days with 50 or 100 mg/kg of the root and **mitomycin C** significantly reduced frequency of mitomycin C-induced **genotoxicity** in bone marrow and peripheral blood (PO in mice).²⁹²²

+ 2) Ginsenoside Rg3, the main ginsenoside in steamed American ginseng roots,²⁹²³ when given with **cyclophosphamide** for 10 days to animals with transplanted SKOV-3 **ovarian cancer cells**, enhanced the quality and duration of life, reduced average tumor weight and significantly reduced angiogenesis more than cyclophosphamide used alone (IP in mice).²⁹²⁴ In other studies, the **DNA damage** to bone marrow cells and peripheral lymphocytes caused by cyclophosphamide was significantly reduced when 20 mg/kg of ginsenoside Rg3 from heat-processed root was given once daily for 2 days prior (PO in mice)²⁹²⁵ and when exposed to the major fresh root ginsenoside Rb1 (*in vitro*).³⁰⁶⁴ Also, cyclophosphamide-induced bone marrow apoptosis, reduction of superoxide dismutase and glutathione peroxidase, and increased production of the lipid peroxidation marker malondialdehyde were all significantly antagonized by Rg3 (PO in mice)²⁹²⁵ and Rb1 (*in vitro*).³⁰⁶⁴ In addition, ginsenoside Rh2 from heat-processed root at 10 and 20 mg/kg significantly enhanced the antitumor effect of cyclophosphamide against B16 **melanoma cells** and Lewis **lung carcinoma cells**, while also significantly reducing cyclophosphamide-induced genotoxicity and DNA damage to bone marrow red blood cells and peripheral white blood cells, respectively (PO in mice).²⁹²⁶

+ 3) Pretreatment with 100 and 200 mg/kg of ginsenosides Rb₁ or Rg₁ caused significant inhibition of **hyperactivity** induced by **methamphetamine** or **cocaine** (IP in mice). Also, methamphetamine- or cocaine-induced conditioned place preference was significantly inhibited

in those pretreated with 100 mg/kg of ginsenosides Rb₁ or Rg₁, along with inhibition of the accompanying dopamine supersensitivity.^{2929,2931}

- Iib. 1) A standardized extract (CNT2000) increased the suppression of growth of estrogen-dependent MCF-7 **breast cancer cells** synergistically when combined with **tamoxifen, cytoxan, doxorubicin, paclitaxel** (Taxol®) and **methotrexate** (*in vitro*).⁹⁸¹

HOWEVER, a methanolic extract was shown to bind to alpha- and beta-estrogen receptors and increase expression of an estrogen-responsive gene, while the water extract was without effect (*in vitro*). A methanolic extract of the roots increased MCF-7 proliferation at 5-100 mcg/ml under low estrogen conditions after 6 days, but a water extract had no effect (*in vitro*). At higher concentrations, both extracts inhibited MCF-7 proliferation (*in vitro*).³²⁹⁴

- + 2) A 70% ethanolic extract of 4-hour steamed roots, with greatly altered ginsenoside content including 78 mg/g Rg3, 25 mg/g 20R-Rg2, 23 mg/g Rg2, 16 mg/g Rb1, and 12 mg/g Rh2, increased apoptosis of HCT116 and SW480 **colorectal cancer cells** maximally when combined antioxidants **N-acetyl cysteine** or **vitamin C** that lowered the reactive oxygen species generated and increased apoptosis (*in vitro*).²⁹²³
- + 3) In a randomized, placebo-controlled, double-blind 12-week trial with 64 **hypertensive diabetic** patients using medications, American ginseng ethanolic extract with 10% total ginsenosides was taken by 30 patients as an adjunct in dose of 1 gram 3 times daily prior to meals (PO in human clinical study). In addition to standard diabetic medications, the antihypertensive drug taken included **ACE inhibitors** by 15, **beta-blockers** by 8, **calcium channel blockers** by 7, and various fixed combinations by 16, plus several other used by 1 or 2 patients. The addition of the extract to the medications led to significant decreases in radial arterial stiffness and systolic blood pressure.³⁴²⁰

AMERICAN GINSENG

^ berry

Complementary Adjuncts

- Iib. 1) A berry extract with 24.5% ginsenoside Rb3 [just over half of total ginsenosides] at 1.0 mg/ml synergistically reduced proliferation of SW-480, HCT-116, and HT-29 human **colorectal cancer cells** by G2/M phase arrest, when combined with **5-fluorouracil** that arrested cells at the cell cycle S phase (*in vitro*).²⁹²⁷

AMLA

NEW

Emblica officinalis = *Phyllanthus emblica* fruit

^ (Indian gooseberry; It. & Port.: Mirabolano emblico; Beng.: amlaki; Punj.: olay; Arab.: haliilaj; Ch.: an mole; Mal.: nellikka; Nep.: amba; Lao & Thai: ma kham pom)

Complementary Adjuncts

- Iia. 1) At 250 and 500 mg/kg, the aqueous extract given for 7 days before a single 40 mg/kg dose of **cyclophosphamide** was shown to inhibit the bone marrow chromosomal **mutations** induced by the anticancer drug (PO in mice).²⁸⁵³ At 100 mg/kg the aqueous extract taken for 10 days reduced **immunosuppression** of humoral immunity by cyclophosphamide (PO in mice).²⁸⁵⁵ This may be due to the reduction of CYP450 levels in the liver, since cyclophosphamide is bioactivated by CYP450, or it may be due to the increased liver and kidney levels of glutathione, glutathione-S-transferase, or other detoxification and antioxidant enzymes as shown in animals with both the aqueous and ethanolic extracts (PO in mice).^{2853,2854,2855}
- 2) When a 50% ethanolic extract was given at 75 mg/kg 4 hours before exposure to 5 g/kg **alcohol (ethanol)** was given to induce **hepatotoxicity**, it significantly reduced serum transaminases ALT and AST and interleukin(IL)-1beta similar to 5 mg/kg silymarin, as compared to controls (PO in rats). Similarly, when 75 mg/kg of the amla extract was given daily for 7 days after 21 days of 4 g/kg/day of ethanol, ALT and IL-1beta were reduced greater than no treatment and slightly better than 5 mg/kg silymarin.²⁸⁵⁶ Amla aqueous extract at 250 mg/kg/day following chronic alcohol liver damage lowered lipid peroxidation and elevated liver antioxidant enzymes

(PO in rats).³¹⁵² In rat liver cells exposed to alcohol, the ALT was also shown to be significantly reduced by the extract at 0.5 mg/ml (*in vitro*).²⁸⁵⁶

The component ellagic acid at 60 mg/kg has been shown to reduce effects of hepatotoxicity induced by 7.9 g/kg ethanol daily for 45 days (PO in rats).³¹⁵³⁻³¹⁵⁵ This includes a reduction of the liver fibrotic markers,³¹⁵³ improved body weight and circulatory antioxidant status,³¹⁵⁴ decreased lipid levels,^{3154,3155} and reduced plasma AST, ALT, and peroxidative markers.³¹⁵⁵

3) A 4:1 strength dry aqueous extract of the dried fruit given at 300 mg/kg for 90 days with the antituberculosis treatment with **isoniazid**, **rifampicin**, and **pyrazinamide** significantly prevented necrotic changes to the liver due to the drugs' **hepatotoxicity** (PO in rats). The effect was enhanced when 100 mg/kg of the aqueous extract of the stem of gulancha (*Tinospora cordifolia*) was added, and even at half this dose was comparable to silymarin at 50 mg/kg in reducing liver damage, though gulancha extract was not effective on its own.²⁸⁵⁷ A 50% hydroalcoholic extract of amla fresh fruit was shown to significantly reduce the increases in transaminases ALT and AST, alkaline phosphatase, and bilirubin induced by the combination of isoniazid, rifampicin, an pyrazinamide, similar to N-acetyl cysteine, while reducing lipid peroxidation and increased glutathione content in liver cells (PO in rats).²⁸⁵⁸

- IIb. 1) Ethanolic extract of the fruit was shown to protect against **cardiotoxicity** of **doxorubicin** by increasing the IC₅₀ 12-fold without impacting its antitumor activity on HeLa cells (*in vitro*).²⁸⁵⁹ The aqueous extracts of the dried fruit increased the cytotoxicity of both doxorubicin and **cisplatin** against human **liver cancer cells** and **lung cancer cells** (*in vitro*).²⁸⁶⁰

ANISE

Pimpinella anisum seed/fruit

Drug Interactions

- IIa. 1) Anise essential oil containing 88.5% anethole was given at the human equivalent dose of 0.3 mg/kg for 5 days prior to a single dose of drugs that are either **sedatives** or **antidepressants** (PO in mice). Combined with **codeine**, the anise oil significantly increased the analgesic activity. The combination with **midazolam** led to greater motor impairment, while the oil also increased the effect of **diazepam** by further decreasing motor activity. So, the sedative effects of these 3 drugs were all enhanced, though anise oil alone was not sedative. On the other hand, anise oil significantly reduced the sleeping time induce by **pentobarbital**. The antidepressant effect of **fluoxetine** and **imipramine** were also diminished by anise oil pretreatment. The potential interactions of anise essential oil with drugs impacting the central nervous system suggests that these combinations in humans should be avoided (speculative).³⁵³⁵

ARJUNA

Terminalia arjuna bark

Complementary Adjuncts

- Ia. 1) An extract made by combining a 90% ethanolic extraction followed by a water extraction and given at 500 mg 3 times/day for 2 weeks improved symptoms of Class IV refractory chronic congestive **heart failure** compared to placebo, when given in a crossover design to 12 patients taking **digoxin**, along with the **diuretic** drugs **furosemide** and **spironolactone** (PO in human clinical study). All were also administered potassium supplements. In addition, **vasodilator** use included 8 on **enalapril**, 3 on **captopril**, 1 on **nifedipine**, and 3 on **isosorbide dinitrate**. In a continuation of the trial signs and symptoms continued improving for 2-3 months and were maintained, while diuretic dosages were reduced.²⁶⁶¹
- 2) When 58 patients with chronic **stable angina** functional NYHA class II or III were given 500 mg of the ethanolic/aqueous combined extract 3 times daily for 1 week in a randomized, double-blind, crossover trial, the incidence of angina and use of the anti-angina drug **isosorbide dinitrate** was significantly less than when taking placebo for 1 week (PO in human clinical study). Patients had stopped their regular use of isosorbide mononitrate and beta-blockers during the study.³²⁸⁶

ARNICA

p. 41

**Arnica montana* flowers

Complementary Adjuncts

- Ia. + 1) A preparation made with 50 g fresh herbal 1:20 tincture in 100 g of gel was compared to a 5% ibuprofen gel for 21 days on hand **osteoarthritis** in 204 randomized subjects for whom 500 mg **acetaminophen (paracetamol)** was allowed not more than once daily for the first 20 days as an "escape treatment" (TP in human clinical study). Gels were applied locally 3 times daily and left on for an hour; this was well tolerated, though skin symptoms resulted for 6 in each group. The gels were equivalent in improving pain and hand function, as well as in reducing joint stiffness and its duration; the arnica and ibuprofen groups' average use of a acetaminophen was 11.2 and 11.3 tablets, respectively, over 3 weeks. Efficacy was assessed as good/very good by physicians and patients in 57% and 59% of cases, respectively, for ibuprofen versus in 64% of cases by both physicians and patients for arnica.²⁸⁰⁵
- 2) A combination spray of arnica tincture with **hydroxyethyl salicylate** for 228 patients with acute unilateral **ankle sprain** produced significantly improved pain on motion after 3-4 days, compared to 228 patients who used a spray with only hydroxyethyl salicylate, 57 patients who only used arnica tincture spray, or 57 patients who used a placebo spray (TP in human clinical study). A dose of 0.5 ml was applied locally 4-5 times daily for 10 days, and the combination also showed better pain relief after 10 days. There were no significant differences in tolerability between the groups. All 4 sprays had a 78% ethanol content along with camphor and essential oils to provide a uniform fragrance.³⁰⁹⁰

ASHWAGANDHA

p. 42

Withania somnifera root

Drug Interactions

- IIa. 2) [Clarification] Using 3 **digoxin** immunoassays for serum, 3 liquid hydroalcoholic extracts were fed to animals, and 2 extracts produced significant false positive apparent digoxin concentrations using fluorescence polarization immunoassay [FPIA], though the Beckman and microparticle enzyme immunoassay [MEIA] were negative (PO in mice).²⁶⁶⁵
- Similar results were found by adding the extracts to serum, except at a concentration representing overdosage when all assays were positive for apparent digitalis (*in vitro*). When digitalis was added with the extracts to the serum pool, the FPIA showed significantly greater digitalis levels, MEIA showed significantly lower digitalis levels, and Beckman assay was unaffected.²⁶⁶⁵ These outcomes were confirmed in a study with a 60-65% ethanolic ashwagandha extract that increased the digoxin measurement results for the FPIA, whereas in the MEIA this extract significantly lowered the serum digoxin measurement (*in vitro*).¹⁹⁹⁵
- HOWEVER, no effect was found on the digitalis measurement done by Tina-quant (*in vitro*).¹⁹⁹⁵ Results with fluorescence polarization immunoassay were negative for carbamazepine, phenytoin, phenobarbital, valproic acid, procainamide, N-acetyl procainamide, theophylline, gentamicin, tobramycin, acetaminophen, or salicylate (*in vitro*).²⁶⁶⁵

Complementary Adjuncts

- Ia. + 1) In new patients with pulmonary **tuberculosis** receiving standard drug treatment with the combination of **rifampicin, pyrazinamide, isoniazid, and ethambutol**, those 17 randomized to also receive 1 gm twice daily of ashwagandha had no evidence of acid-fast bacteria in the sputum after 28 days, whereas 6 of the 17 on drugs alone had positive sputum tests for the TB bacteria (PO in human clinical study). In a further study of 40 other new pulmonary TB patients, the 20 receiving the drugs with ashwagandha had a greater and more rapid lowering of symptom scores on days 15 and 29, along with higher total white blood cell counts, hemoglobin, body weight, and IgM antibodies and lower erythrocyte sedimentation rate. The ashwagandha group had a zero bacterial load count by day 26, while the drugs alone regimen group was still positive after 29

days. The blood levels of pyrazinamide and isoniazid were also higher in the ashwagandha group after dosing on day 29 than in the drugs alone group, while liver function tests significantly improved for those using ashwagandha but the drug group the opposite trend.³²³³

- + 2) The 44 patients with **breast cancer** who received 6 grams daily of an ashwagandha root extract, 50% of whom received a **taxotere, adriamycin, cyclophosphamide** combination plus 48% receiving **cyclophosphamide, epirubicin, and 5-fluorouracil**, had significantly less treatment-related fatigue and significantly improved quality of life in 7 of 18 symptoms, compared to the 41 control patients who received only the chemotherapy treatments, 30% with cyclophosphamide, epirubicin, and 5-fluorouracil and 70% with the taxotere, adriamycin, cyclophosphamide combination (PO in human clinical trial).³²⁵²
- + 3) In a randomized, placebo-controlled, double-blind trial with 30 patients diagnosed with **obsessive-compulsive disorder [OCD]** and being treated with Selective Serotonin Re-uptake Inhibitors [SSRI's], half were given 120 mg daily of an ashwagandha extract for 6 weeks (PO in human clinical trial). In changes to the baseline values for the Yale-Brown Obsessive-Compulsive Scale [Y-BOCS], the ashwagandha group had a significantly greater reduction of -8 for the Y-BOCS score, compared to -2 for the placebo group. No adverse events were reported during the trial, so the extracts appears to be both effective and safe as an SSRI adjunct in treating OCD.³⁵⁴⁸
- IIa. 7) After using root extract, tolerance to **morphine** analgesia was inhibited, and **morphine dependence** was blocked (PO in mice study).¹²⁷⁷

In addition, with 14-day treatment during concurrent morphine use 100 mg/kg of a standardized ashwagandha extract significantly reduced spontaneous morphine **withdrawal** syndrome symptom severity after 1 and 3 days and the spine density in the nucleus accumbens shell, but not when given only during the first 3 days of withdrawal (IP in rats).³⁴⁶⁶
- + 8) The **kidney toxicity** induced by the antibiotic **gentamicin** was significantly reversed by 500 mg/kg ashwagandha root extract given for 14 days before and concurrently for 8 days with gentamicin (PO in rats). The kidney tubular necrosis and toxicity symptoms were reduced including increased kidney weight, urea, creatinine, urinary protein and glucose, and significant reductions in body weight and potassium.³²⁵³

ASIAN GINSENG

p. 44

Panax ginseng root

Contraindications

- II. 2) Do not use with type 1 **diabetes** (speculative)⁸⁹³ because of ginseng extract's anti-hyperglycemic effect (PO in human clinical study).¹⁰⁹

In a randomized, placebo-controlled, double-blind trial, 12 undiagnosed patients with moderately elevated fasting glucose given 960 mg per day of a hydrolyzed ginseng extract for 8 weeks, the fasting and postprandial glucose levels were significantly decreased, compared to 11 in the placebo group (PO in human clinical study).³⁴⁵²

Drug Interactions

- Ia. 2) Uncharacterized "ginseng" with CYP 3A4 substrate **nifedipine** increased the drug peak plasma concentration 29% (PO in human study).¹⁷²⁸

HOWEVER, a 500 mg dose of a standardized extract given twice daily for 28 days to 12 subjects resulted in significant decreases in AUC, half-life and maximum concentration of the CYP 3A4 substrate **midazolam**, indicative of induction (PO in human study). There was no effect on the Pgp substrate fexofenadine.²⁹⁶⁵
- 3) A randomized trial using red ginseng doses of 2 grams 3 times daily for 12 weeks in 19 patients with diabetes type 2, in combination with diet alone in 5 or diet plus **hypoglycemic drugs** alone and/or in combinations of **metformin, sulfonylurea, rosiglitazone, and acarbose** in 14 resulted in significant reductions in oral glucose tolerance test [GGT] indices by 8-11%,

fasting and GGT plasma insulin by 33-38%, and fasting and GGT insulin resistance by 33% (PO in human clinical study).²⁰⁴²

The ginsenoside metabolite compound K at 10 mg/kg and metformin at 150 mg/kg were given alone and combined to diabetic subjects (in mice). The compound K increased insulin secretion and reduced GGT glucose levels at 12.5 mg/kg alone. Combined with metformin, plasma glucose and insulin resistance were reduced more than for each one separately.³⁶⁷¹

In a randomized double-blind crossover study with 20 type 2 diabetics using diet and/or oral hypoglycemic agents to treat their diabetes, 740 mg of ginseng t.i.d. for 4 weeks led to significantly lower fasting plasma glucose and assessed insulin resistance compared to placebo (PO in human clinical study). Oral glucose tolerance tests were unaffected, though both the insulin response and fasting insulin tended to be reduced by ginseng.²⁷⁸⁸

- Ib. + 5) A man taking the known liver toxin **imatinib** for 7 years without incident developed acute lobular hepatitis 3 months after he began daily consuming an energy drink containing ginseng extract (PO in human case report). When the imatinib and energy drink were stopped and prednisone given for 19 days, the liver enzyme levels were normalized for 4 weeks. [According to the drink label, the product also contained taurine, caffeine, guarana extract, carnitine fumarate, vitamins B3, B6, and B12.] When the CYP 3A4 substrate imatinib was reintroduced for 3 months, no liver enzyme elevations occurred.²⁷⁶⁴ Asian ginseng root has been shown to inhibit CYP 3A4 and thereby increase the level of the drug substrate (PO in human study).¹⁷²⁸
- II. 4) While feeding with fructose-rich chow, treatment with 125 mg/kg ginseng root 3 times daily after 5-15 days reduced the delay in the glucose-lowering response to 10 mg/kg IP **tolbutamide** (PO in rats). This is explained by tolbutamide increasing endogenous insulin secretion in response to developing insulin resistance, and ginseng acting to increase insulin sensitivity. Ginseng given alone for 3 days with fructose-rich chow did not result in elevated plasma glucose, whereas it did in controls.³⁵²⁰
- III. 3) Using 5 **digoxin** immunoassays on 2 liquid Asian ginseng extracts and 1 capsule, only one of the liquid extracts increased the digoxin measurement results only for the fluorescence polarization immunoassay (*in vitro*, *ex vivo* with rats).^{1352,1995}
- A new analyzer technology from Abbott Laboratories led to development of 2 analyzers, iDig and cDig, using specific monoclonal antibody against digoxin for which Asian ginseng does not interfere with detection of digoxin (*in vitro*).³⁴³⁵

Complementary Adjuncts

- Ia. 2) Red ginseng taken daily with **zidovudine** by **HIV-1** patients for 4-6 years maintained CD4+ T cell counts and delayed resistance mutations to zidovudine (PO in human clinical study).¹³³⁵
- In an analysis of 252 HIV-1 patients prior to antiretroviral therapy, the 162 who were treated with Korean red ginseng for an average of 86 months showed a significant slowing in CD4+ T-cell decrease and a significant increase in survival duration in correlation with the total amount of ginseng consumed (PO in human clinical study).³⁶⁸⁵
- 3) Following surgery for stage III **gastric cancer**, red ginseng powder doubled survival rates in patients given **5-fluorouracil** and **cisplatin** (PO in human clinical study).¹³⁸²
- The aqueous extract of the steamed Korean red ginseng root at a concentration of 2.5 mcg/ml containing ginsenosides Rb₁ and Rg₁ significantly attenuated **auditory hair cell damage** caused by cisplatin (*in vitro*). This prevention of ototoxicity was due to inhibition of the free radical generation and apoptosis by cisplatin (*in vitro*).²⁷²⁵
- + 5) Just under half of the 61 patients between the ages of 50-80 years with **Alzheimer's disease** who were being treated with **donepezil**, **galantamine**, **memantine**, or **rivastigmine** were also given 4.5 g/day or 9.0 g/day of Korean red ginseng root powder for 12 weeks and monitored by cognitive tests (PO in human clinical trial). At the open-label study's end, those receiving the higher ginseng dose had significantly lower scores on the Alzheimer's Disease Assessment Scale [ADAS] and its cognitive component and the Clinical Dementia Rating scale.³⁰⁵⁹ In a similar 12-week study by the same researchers with Alzheimer's patients ages 47-83 years, 39 active

treatment controls and 49 additionally receiving 4.5 g/day Korean white ginseng root powder and 9 given 9 g/day ginseng, significant improvements were shown on the ADAS cognitive subscale and the mini-mental state examination for the ginseng groups (PO in human clinical study). There were no significant differences in scores between the 2 ginseng doses. When the ginseng use was stopped, the improved scores decreased over 12 weeks to control levels.³⁰⁶⁰

- + 6) In a randomized, controlled, single-blinded study of 38 patients with **chronic hepatitis B** treated with antiviral agents **adefovirdipivoxil**, **entecavir**, **lamivudine**, or **tenofovir**, half were also given 3 grams daily of red ginseng powder in capsules in 3 divided doses (PO in human clinical study). The ginseng group had further reductions in the non-invasive fibrosis serologic markers hyaluronic acid and transforming growth factor- β , significantly decreased from the levels in the groups using antiviral agents only.³⁶⁶¹
- + 7) In a randomized, placebo-controlled, double-blind trial of 30 patients with **epithelial ovarian cancer** who completed 6 cycles of taxane-based [**paclitaxel** or **docetaxel**] and platinum-based [**carboplatin** or **cisplatin**] **chemotherapy**, 3000 mg of red ginseng daily was given to 15 subjects for 3 months (PO in human clinical study). A significant reduction in micronuclei yield was noted, when compared to the placebo group. Significant improvements in health-related quality of life were shown with emotional functioning. In addition, there were reduced symptoms of **nausea and vomiting**, **fatigue**, anxiety, dyspnea, and pain interfering with enjoyment of life, while daytime somnolence improved. There was no significant impact on prognosis of the ovarian cancer.³⁷²⁵
- IIa. + 3) Pretreatment with 100 and 200 mg/kg of ginsenosides Rb₁ or Rg₁ caused significant inhibition of **hyperactivity** induced by **methamphetamine** or **cocaine** (IP in mice). Also, methamphetamine- or cocaine-induced conditioned place preference was significantly inhibited in those pretreated with 100 mg/kg of ginsenosides Rb₁ or Rg₁, along with inhibition of the accompanying dopamine supersensitivity.^{2929,2931} The inhibition of methamphetamine-induced hyperlocomotion and conditioned place preference by 50 and 150 mg/kg of unspecified ginsenosides was associated with stimulation of adenosine A_{2A} receptors (IP in mice).²⁹³⁰
- + 4) After 4 weeks of **cyclosporine** use, blood glucose increased and insulin decreased due to oxidative **pancreatic injury** to beta cells, but 0.4 g/kg daily of red ginseng extract given concurrently ameliorated the high blood glucose and glucose intolerance (PO in mice). The ginseng extract also reduced pro-inflammatory molecules and apoptotic cell death.³⁵²²

ASTRAGALUS

p. 51

Astragalus membranaceus, *Astragalus mongholicus* root

Complementary Adjuncts

- IIa. + 3) Equal quantities of astragalus root and dong quai (*Angelica sinensis*) root were extracted with ethanol and water, the extracts combined, and 2.1 grams daily given with or without the ACE inhibitor **enalapril** to monitor **kidney fibrosis** and compared to enalapril alone (PO in rats). The tubulointerstitial fibrosis was reduced by the herbal extract and enalapril separately along with transforming growth factor- β 1 [TGF- β 1], but the herbal-drug combination had the greatest effect by significantly reducing TNF- α , collagen accumulation, fibroblast activation, tubular cell apoptosis more than enalapril alone.²⁷²⁸ A decoction of equal parts of the 2 roots given at the same dose was previously shown a decrease in TGF- β 1 puromycin-induced nephrosis similar to enalapril (PO in rats),²⁷²⁹ while 3.6 g/kg daily dose of a 5:1 mixture of astragalus and dong quai roots, respectively, as a decocted extract also modestly decreased kidney TGF- β 1 mRNA expression following streptozotocin-induced damage, similar to the ACE inhibitor benazepril (PO in rats).²⁷³⁰

BARBERRY

p. 53

**Berberis vulgaris* root bark

Contraindications

- II. 1) Do not use in **jaundice** in **newborns**, from **hemolytic anemia**, or unconjugated hyperbilirubinemia as **Gilbert's syndrome** and **Crigler-Najjar syndrome** (speculative).^{777,1890}
HOWEVER, when berberine-containing herbs were given in herbal concoctions according to traditional dosage and indication to 20 patients with chronic cytopenic hematological conditions, though 3 patients with thalassemia intermedia had transient elevation of serum bilirubin, there was no associated aggravation of anemia or liver dysfunction (PO in human clinical study).³¹⁰⁸

Drug Interactions

- Ia. 1) [The book entry for berbamine and **chemotherapy** has now appropriately been moved to Complementary Adjuncts #Ia. 3).]
- + 1) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the bioavailability of CYP 3A4 substrate **midazolam** by 40% and its maximum plasma concentration by 38%, and significantly decreased its oral clearance by 27% (PO in human study).³²³⁸
- 3) The combination of 1500 mg berberine daily for 3 months in 43 type 2 diabetes patients with one or more **oral hypoglycemic** medications including **sulfonylureas**, **metformin acarbose**, and/or **insulin** resulted in lower blood sugar through week 12 (PO in human clinical study).²³¹⁵
In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered fasting and postload plasma glucose and HbA1c compared to 52 diabetics on placebo, along with significantly reducing the triglycerides, total cholesterol, and LDL-cholesterol, body weight, and systolic blood pressure (PO in human clinical study).²⁹⁰⁷ In 50 type 2 diabetic patients randomly selected to use 1 gm berberine daily, the 26% and 18% significant reductions in fasting blood glucose and HbA1c were equivalent to those of the 26 and 21 diabetic patients who used metformin or rosiglitazone, respectively (PO in human clinical trial). Only the berberine group had a significant reduction of triglycerides. Also, in another group of 18 hepatitis C and 17 chronic hepatitis B patients with type 2 diabetes or impaired fasting glucose, 1 gm/day berberine significantly reduced fasting blood glucose, triglycerides, and the transaminases ALT and AST (PO in human clinical trial).²⁹⁰⁸
- + 4) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the 8-hour urinary ratio of the CYP 2D6 substrate **dextromethorphan** to its metabolite dextrorphan by 9-fold (PO in human study).³²³⁸
- + 5) Berberine at 900 mg daily in 17 healthy males for 14 days doubled significantly the 8-hour urinary ratio of the CYP 2C9 substrate **losartan** to its metabolite E-3174 (PO in human study).³²³⁸
- II. + 2) In doses of 30 mg/kg berberine for 2 weeks, the Pgp substrates **digoxin** and **cyclosporine** had significantly increased maximum serum concentration and bioavailability compared to controls, indicating berberine inhibition of Pgp drug efflux (PO in rats).³¹⁰⁵ Likewise, the oral bioavailability of **ketoconazole** was significantly increased by berberine given at 60 mg/kg (PO in rats). Since ketoconazole is both a substrate and an inhibitor of Pgp and berberine is a Pgp substrate, the pharmacokinetic effect of each on the other may lead to pharmacodynamic synergism against fungal infections (speculative).³¹⁰⁴
- III. 3) [See Complementary Adjuncts Ia. 4) below.]

Complementary Adjuncts

- Ia. 3) [Moved from Drug Interactions Ia. 1).] The alkaloid berbamine given at 150 mg daily for 1-4 weeks helped reverse **leukopenia** induced by cancer **chemotherapy** or radiotherapy, especially when the white blood cell count was not less than 1000/mm³ from anticancer drugs (PO in human clinical study).³⁹⁸
- + 4) When 500 mg berberine hydrochloride was given twice daily with **simvastatin** 20 mg once daily for 2 months to 23 patients in a randomized trial for **high cholesterol**, the 31.8% reduction in LDL cholesterol was significantly better than the 23.8% with berberine in 24 patients or the 14.3% with simvastatin in 16 patients used alone (PO in human clinical study). For triglycerides, the combinations reduced these by 38.9%, significantly better than 22.1% for berberine or 11.4%

for simvastatin alone. Similar results were obtained for total cholesterol. No adverse effects were observed in any group. These results reflected those obtained in animals given 90 mg/kg/day berberine and/or 6 mg/kg/day simvastatin (PO in rats).²⁹⁰⁵ In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered triglycerides, total cholesterol, and LDL-cholesterol compared to 52 diabetics on placebo, along with significantly reducing the fasting and postload plasma glucose, HbA1c, body weight and systolic blood pressure (PO in human clinical study).²⁹⁰⁷

In human liver-derived cells, berberine was found to have an additive effect with lovastatin (*in vitro*). Since lovastatin did not reduce the effect of berberine, this indicated a different mechanism of action for the two (*in vitro*).¹⁶⁵⁶

- Ila. + 4) Berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive **locomotor activity** induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that berberine may help reduce the chronic cocaine psychological dependence (speculative).²⁷⁵³
- + 5) When taken with a **high cholesterol** and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).²⁹³² When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.²⁹³³ The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);²⁹³² berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).²⁹³³
- + 6) The combination of 1 mg/kg berberine with 0.5 mg/kg **amphotericin B** increased the survival for disseminated **candidiasis** to 36 days from 12 days for controls and 17 days and 14 days, respectively, when these 2 antifungal agents were used separately (IP in mice).³¹⁰⁷
- + 7) Compared to those injected with 2.5 mg/kg **doxorubicin** alone every other day for 14 days, those injected with 60 mg/kg berberine an hour prior to the drug had less **cardiotoxicity** as shown by significantly smaller increases in mortality, LDH activity, myocardial injury, and QRS duration (IP in mice). This indicates a potential protective role of berberine against heart damage by doxorubicin.³¹⁴⁸
- + 8) After treatment of **Clostridium difficile infection** with 50 mg/kg **vancomycin** daily for 5 days, the use of berberine at 100 mg/kg for the next 5 days prevented weight loss and improved the disease activity index score and the histopathology score, while decreasing the mortality rate, compared to vancomycin alone (PO in mice). Berberine prevented relapse of *C. difficile* infection and significantly improved survival, while counteracting vancomycin side effects. Berberine appears to be effective by restoring intestinal microbiota and inhibiting expansion of *Enterobacteriaceae* family members.³⁶¹⁹

BAYBERRY

Myrica cerifera bark

p. 57

Complementary Adjuncts

- Ila. 1) The **cardiotoxicity** of 1 dose of **doxorubicin** at 3 mg/kg IP was significantly reduced in a dose-dependent fashion after 28 days, when the component myricitrin from the bark of bayberry [and another member of its genus] was given daily for 7 days prior at doses of 2.5 or 5.0 mg/kg (IP in rats). This was shown by decreases in pathological changes, the cardiac index, and serum

cardiac enzyme levels. The compound reduced cellular oxidative stress and increased antioxidant enzymes significantly *in vitro*, as well.³⁷²⁴

BILBERRY

p. 58

Vaccinium myrtillus fruit

Complementary Adjuncts

- Ia. + 1) When 80 mg bilberry (*Vaccinium myrtillus*) extract with 36% anthocyanins and 40 mg Pycnogenol with 70% procyanidins as a standardized combination was given once daily in the morning to 79 **ocular hypertension** patients either alone or together with **latanoprost** eye drops and compared to latanoprost alone, the extract combination with the drug was best for lowering intraocular pressure and enhancing retinal blood flow (PO in human clinical study). The extract alone eventually was similarly effective as the drug for lowering intraocular pressure, but it took 24 weeks for the extract compared to only 4 weeks with latanoprost. The only adverse effects were those related to latanoprost.²⁹⁶⁶
- IIa. + 2) Supplementing the diet with 1% bilberry extract led to significantly reduced **myocardial damage**, cardiac glutathione depletion, and serum lipid peroxidation following a 15 mg/kg dose of **IP doxorubicin** (PO in rats).³⁵¹⁴ While being given 100 mg/kg of a bilberry methanolic extract for 10 days, 15 mg/kg doxorubicin was administered IP on day 7 (PO in rats). In comparison to controls, after day 10 this extract had likewise reduced cardiac glutathione depletion and malondialdehyde formation. The reduction of cardiac antioxidant enzyme activities for catalase, superoxide dismutase, and glutathione peroxidase was significantly ameliorated by the extract. It also decreased serum levels of troponin I and activities of lactate dehydrogenase, creatine phosphokinase, creatine kinase-MB. Finally, the ECG and pathological changes found in controls were alleviated by the extract.³⁵¹⁵

When 500 mg/kg of bilberry extract was given daily for 10 days in rats treated with 10 mg/kg doxorubicin, it partially prevented the **hematopoietic damage** resulting in reductions in red blood cell count, bone marrow cell counts, and hemoglobin level (PO in rats).³⁵¹⁴

BITTER MELON

p. 59

Momordica charantia fruit / juice and seeds

Contraindications

- I. 1) Avoid in **pregnancy** due to the emmenagogue and abortifacient effects (empirical).⁷⁴ The glycoproteins, a- and b-momorcharin in the seeds have shown abortifacient activity in early pregnancy (IP in mice)³⁰⁵⁶ by inhibiting the differentiating endometrium (*in vitro*, IP in mice),³⁰⁵⁷ and also teratogenic changes during organogenesis due to effects on the visceral yolk sac (*in vitro*).³⁰⁵⁸
- II. 1) It should not be employed for insulin-dependent (**type 1 diabetes** (speculative),⁸⁹³ due to potentially disruptive hypoglycemic effects, as shown in type 2 diabetic humans using the freeze-dried juice (PO in human study).³⁴⁷⁶

Drug Interactions

- I.a. 3) The use of 400 mg of a chloroform/benzene extract of bitter melon in diabetes type 2 patients taking 50% of the therapeutic dose of **metformin** or **glibenclamide** produced a hypoglycemic effect greater than the full dose of these oral hypoglycemic drugs alone, indicative of an additive effect (PO in human clinical study). Combining the extract or juice of the fruit with metformin had a greater hypoglycemic effect than either the drug or fruit preparation alone in animal diabetic models (PO in rats).³⁶⁷⁰

BITTER ORANGE

p. 60

Citrus aurantium fruit, juice, or peel

Drug Interactions

- I.a. 1) The juice consumed by 9 subjects at a dose of 200 ml significantly increased **dextromethorphan** bioavailability during first-pass metabolism both by inhibiting intestinal CYP 3A metabolism and affecting an intestinal transport protein, rather than by inhibition of CYP 2D6 (PO in human study).²⁶⁶⁶

HOWEVER, a product standardized to 4% synephrine and given to 12 subjects at a dose of 700 mg daily did not affect metabolism of midazolam or debrisoquin by CYPs 2D6 or 3A4, respectively, but it was devoid of the CYP3A4 inhibitor 6',7'-dihydroxybergamottin (PO in human study).¹⁵⁸⁹

- 2) Bitter orange juice in a single 240 ml dose also increased **felodipine** bioavailability (PO in human study), due to 6',7'-dihydroxybergamottin, bergamottin, and begapten inhibiting intestinal CYP3A4.¹⁷²⁹ In addition, the juice reduced enterocyte CYP3A4 concentrations (PO in humans).¹⁰³¹

HOWEVER, the bioavailability of indinavir was not impacted by consumption with 240 ml of bitter orange juice in 13 healthy subjects, though there was a delay in indinavir absorption (PO in human study).²⁵⁸⁸ Also, one dose of 240 ml of the juice did not influence cyclosporine metabolism in 7 healthy subjects (PO in humans), probably because of a lack of effect on Pgp by 6',7'-dihydroxybergamottin (*in vitro*).¹⁰³¹

- III. 2) Use of the juice with **substrates of CYP3A4** may increase the absorption (speculative), due a 40% reduction of this isozyme (PO in humans).¹⁰³¹

The decoction of the fruit and unripe fruit were slightly inhibitory of **testosterone** metabolism by CYP3A4 (*in vitro*).¹⁶³³

BLACK COHOSH

p. 61

**Actaea racemosa* = *Cimicifuga racemosa* roots/rhizome

Contraindications

- I. 3) Signs or symptoms of **liver dysfunction** suggest discontinuation due to its association with hepatotoxicity in cases in Europe (empirical).¹⁹⁰¹

HOWEVER, when 87 healthy postmenopausal women with no evidence of liver disease received a daily dose for 12 months of 40 mg dry extract from black cohosh made with 58% ethanol, they were assessed for hepatic function. No significant changes were found in total hepatic blood flow or any liver function tests (PO in human clinical study).²⁹⁹⁴

Complementary Adjuncts

- Ia. 2) Solid black cohosh extract was given randomly for 1 year with **tamoxifen** to 90 premenopausal **breast cancer survivors** and compared to 46 using tamoxifen alone (PO in human clinical study). About 74% of those on only tamoxifen had severe hot flashes, significantly more than the 24% who combined it with extract.¹⁶⁵⁵

Using a 40% isopropanolic extract tablet derived from 20 mg of root following primary cancer treatment, 47 breast cancer patients on tamoxifen with menopausal symptoms that were severe on average used 2 tablets daily for 4 weeks, then 24 adjusted the daily black cohosh tablet dose to 4 [n=15], 3 [n=3], or 1 [n=2] or changed to a product combining the extract with St. John's wort (*Hypericum perforatum*) extract [n=4] (PO in human clinical study). Significant improvements in total symptoms scores and subscores for vegetative symptoms and psychic symptoms occurred at 1, 3, and 6 months, with no adverse effects attributed to the extract. The most severe symptoms of hot flashes, sweating, and sleep problems improved the most. Of the 35 who completed the 6-month, open, uncontrolled trial, 30 wanted to continue its use.²⁸¹⁴

[BLACK CUMIN – now see: NIGELLA]

BLACK PEPPER

p. 67

Piper nigrum fruit

Drug Interactions

- Ia. + 4) A single dose of the potent non-nucleoside inhibitor of HIV-1 reverse transcriptase, **nevirapine** [a CYP 3A substrate] had 120% greater maximum concentration and 170% increased bioavailability in 8 healthy subjects when taken after 6 days of piperine compared to placebo in a crossover trial (PO in human study).³¹³² Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low for use of black pepper as a condiment for flavoring food but high for Pgp and CYP3A4 substrates with piperine in doses in excess of 10 mg (speculative).³²²²

Complementary Adjuncts

- Ia. 1) Piperine increased serum concentrations of **curcumin** and increased curcumin **bioavailability** by 2000% (PO in human study).¹⁵³³
The significant improvements by 200 mg/kg oral curcumin of chronic stress impaired memory performance and serum cortisone, along with oxidative stress parameters including elevated malondialdehyde and decreases in reduced glutathione, superoxide dismutase and catalase, were significantly enhanced with the addition of 20 mg/kg piperine (PO in rats).³³⁹⁶
- Iia. + 1) Piperine at 70 µmol/kg increased plasma **bioavailability** of the chemopreventive agent epigallocatechin gallate [**EGCG**] in green tea by 1.3-fold when given concurrently compared to EGCG given alone (PO in mice). Piperine also increased the maximum plasma concentration of EGCG by inhibiting glucuronidation in mice intestines by 40%. Likewise, the glucuronidation of EGCG was inhibited in human HT-29 colon adenocarcinoma cells (*in vitro*). Piperine also increased EGCG transit time in the intestines (PO in mice).²⁹³⁵
- + 2) Black pepper as 0.5%, or piperine as 0.02%, of the diet for 8 weeks prevented mucosal **stomach damage** by **ethanol (alcohol)** by significantly increasing activity of the endogenous antioxidant enzymes superoxide dismutase, glutathione reductase, and glutathion-S-transferase in the stomach and intestinal mucosa and increasing mucin content in stomach mucosa, compared to having no exposure to the spice (PO in rats).³³⁴⁷
- + 3) Increased **bioavailability** and maximum concentration of a single dose of the chemopreventive compound **emodin** was found when 20 mg/kg was combine with 20 mg/kg of piperine (PO in rats). Emodin glucuronidation in the intestines and liver that normally reduces emodin bioavailability was greatly inhibited.³⁴⁵⁹
- + 4) The **mineral absorption** of **calcium, iron, and zinc** were all significantly improved with the addition of 0.02g% of piperine to the diet, compared to the same diet without piperine (PO in rats). Calcium absorption was improved the most. Piperine increased the uptake of calcium better than either capsaicin or ginger.³⁴⁷¹

BLACK RASPBERRY

NEW

^ *Rubus occidentalis* fruit and seeds

Complementary Adjuncts

- Iia. 1) The component ellagic acid at 60 mg/kg has been shown to reduce effects of **alcohol hepatotoxicity** induced by 7.9 g/kg **ethanol** daily for 45 days (PO in rats).³¹⁵³⁻³¹⁵⁵ This includes a reduction of the liver fibrotic markers,³¹⁵³ improved body weight and circulatory antioxidant status,³¹⁵⁴ decreased lipid levels,^{3154,3155} and reduced plasma AST, ALT, and peroxidative markers.³¹⁵⁵

BOLDO

p. 73

Peumus boldus leaves

Drug Interactions

- Ib. + 2) A 78-year-old man with diabetes, hypertension, and a renal transplant 5 years earlier was taking 2 mg **tacrolimus** twice daily consistently, but suddenly tested for having a significantly low level of <3 ng/ml after taking 600 mg of boldo leaf extract daily (PO in human case report). He reported no complaints, and physical exam was normal. On stopping the boldo, within a week

the tacrolimus level rose to 6.1 ng/ml using the same dose. The prior subtherapeutic dose may have been due to an interaction with boldo (speculative).³⁵²⁷

BONESET

**Eupatorium perfoliatum* herb

p. 74

Contraindications

- I. 2) Do not use during **pregnancy**, due to abortifacient effect (PO in cattle).⁶
Also, potential exists for toxicity from pyrrolizidine alkaloid components or adulteration with species containing pyrrolizidine compounds.^{150,3722}
- II. + 1) Concern exists that long-term use even of low levels of pyrrolizidine alkaloids in contributing to potential **chronic liver disease** such as hepatic veno-occlusive disease (speculative), and analysis of 49 samples of boneset using aqueous ethanol, methanol, or hot water extracts revealed a range of pyrrolizidine alkaloid content of 0.0002% to 0.07% of these compounds (*in vitro*). Both alcoholic and water extracts contained these alkaloids, the majority of which were intermedine and lycopsamine and their N-oxides and acetylated derivatives, considered to be of relatively low toxicity. The presence of some heliotridine- and retronecine-based alkaloids suggested some hybridization, contamination, or different chemotypes. A 3 ml dose of a boneset tincture was estimated to provide about 13 mcg dehydropyrrolizidine alkaloids/kg body weight for a 70 kg human. Recommendation for daily consumption limits range from 0.007 mg/kg to avoid cancer development and 0.1 mcg/kg to avoid non-cancer effects, or 1 mcg/kg daily to avoid hepatic veno-occlusive disease (speculative).³⁷²²
- HOWEVER, given that half drop daily doses of mother tincture given in dilute form 5 times per day for 10 days was shown to be as effective as 500 mg aspirin 3 times daily for treating the common cold (PO in human clinical study), such a low dose for an acute use limited to 10 days or less and applied infrequently may therefore be both safe and effective (speculative).³⁷²³

BORAGE

**Borago officinalis*

SEED OIL

p. 75

Complementary Adjuncts

- IIa. + 1) In conjunction with a high-fat diet, when borage oil was given at 150 mg/kg daily for 30 days along with 4 g/kg **ethanol** and compared to the effects of inducing **steatohepatitis** with the **alcohol** alone in other subjects, antioxidant protection was observed from the oil (PO in rats). The addition of the borage oil decreased lipid accumulation in the liver and significantly reduced serum ALT and GGT activity and total liver CYP450, triglycerides, and peroxidation products that had all been significantly elevated by the ethanol. The oil, which contained 19.5% gamma-linolenic acid (GLA) and 4.3% dihomo-GLA, also significantly increased the reduced glutathione in the liver that had significantly decreased from alcohol alone.³²³⁴

BURDOCK

Arctium lappa root

p. 79

Complementary Adjuncts

- Ia. + 1) A randomized, placebo-controlled, double-blind study of 36 patients with knee **osteoarthritis** used 3 cups [2 g/150 water each] daily of burdock root tea for half, while the control half used 3 cups of boiled water (PO in human clinical study). Both **glucosamine** daily and **acetaminophen** twice daily were considered for each patient. After 42 days, the burdock tea group had significantly lower levels of the lipid peroxidation marker malondialdehyde, as well as inflammatory markers interleukin-6 and high sensitivity C-reactive protein.³⁵³⁹
- IIa. 1) Freeze-dried root extract decreased SGOT, SGPT, and malondialdehyde [MDA] levels caused by **hepatotoxicity** from **acetaminophen** (PO in mice). The decrease in glutathione and cytochrome P450 in the liver caused by acetaminophen was reduced by burdock extract.¹⁴⁰⁴

Either 300 mg/kg burdock root water extract or saline were given, or toxic injections of 800 mg/kg acetaminophen with or without the burdock extract were administered (PO in rats). The acetaminophen-only group had significantly increased plasma transaminases and alkaline phosphatase, along with liver DNA fragmentation, compared to controls and the acetaminophen with burdock extract group. Addition of the burdock extract significantly reduced the elevated liver MDA content caused by acetaminophen, as well as decreasing histopathologic evidence of acetaminophen liver toxicity.³⁵⁴⁰

- + 2) The freeze-dried 4:1 water extract of the roots given at 900 mg/day after 3 weeks of 4 g **ethanol** daily and continued for another 7 days with the **alcohol** led to significant improvement in the **hepatotoxicity** after 1 day and 7 days as expressed by reduced levels of SGOT and SGPT, triglycerides, and malondialdehyde when compared to alcohol alone (PO in rats) Pathological changes in liver cell structure also improved when the extract was combined with the ethanol.³¹⁵⁸
- + 3) The prior oral use of a chloroform extract of burdock roots at doses of 10, 30 or 100 mg/kg significantly reduced **stomach ulcers** induced by **ethanol** by 61%, 70%, and 76%, respectively (PO in rats). The extract given for 7 days at 100 mg/kg decreased stomach ulcers induced by chronic **acetic acid** by 52%. Stomach acid secretion was reduced dose-dependently by the extract when given intraduodenally. Gastric motility was unaffected. The extract demonstrated free radical-scavenging ability *in vitro*.³⁵⁴¹

CALAMUS

p. 81

**Acorus calamus* roots/rhizome

Complementary Adjuncts

- Ia. + 1) When **vincristine** was given IP for 10 consecutive days to induce **neuropathic pain**, a 50% ethanolic extract of the dried rhizome was given in doses of 100 and 200 mg/kg 1 hour before the vincristine and for an additional 4 days, and compared with saline and vincristine, vincristine-only, and calamus-only controls in attenuating thermal and mechanical pain responses (PO in rats). Vincristine-induced pain was accompanied with rises in tissue myeloperoxidase, superoxide anion, total calcium, and histological changes, but the extract attenuated the pain and these changes in a dose-dependent manner. The prevention of pain was thereby associated with anti-inflammatory, antioxidative, neuroprotective and calcium inhibitory effects.³³⁷⁵

CANNABIS

p. 83

**Cannabis sativa* or *Cannabis indica* leaves and tops

Contraindications

- I. + 1) Avoid in **pregnancy**, due to reductions in fetal growth (IH in human studies)^{2,627,629}
A systematic review and meta-analysis of 24 studies compared cannabis use during pregnancy with no use, including 10 from USA, 5 Canadian, 3 Australian, 2 from the Netherlands, and 1 each from Brazil, Iran, Jamaica, and Spain (IH in human studies). A fixed-effects model of 9 studies examining maternal anemia indicated significantly higher odds of anemia when pregnant women smoked cannabis. In 10 studies assessing birth weight and 7 reporting low birth weight, random-effects models showed a significant decrease of birth weight and higher odds of low birth weight in infants exposed to cannabis in utero, compared to no cannabis exposure. In 4 studies on cannabis exposure in utero and placement in neonatal or standard intensive care units [NICU/ICU], 3 showed a positive association of exposure with need for NICU/ICU, and a random-effects model showed higher odds of NICU/ICU with in utero exposure to cannabis versus nonexposure.³⁵⁷⁴
HOWEVER, many cannabis users also use tobacco and/or alcohol, so determining a cannabis-only effect based on the reviewed studies is not possible, since most did not exclude polysubstance use (IH in human studies). Variable amounts and frequencies of cannabis use, and reliance on self-reporting of use, undermines accurate assessments. Therefore, the authors conclude that cannabis effects on fetal and maternal outcomes remain generally unknown.³⁵⁷⁴

2) Do not use in personal or family history of **schizophrenia** (empirical).^{2,627,629}

Cannabis use increases the risk of incidence of psychotic symptoms in the young with stronger effects in those predisposed to psychosis,^{3275,3545,3726} increases the risk of developing schizophrenia and psychotic outcomes,^{3272-3274,3726} and contributes to a poor prognosis for those with established psychotic disorder (IH in human studies).^{3272,3545} The risks increase dose-dependently^{3273,3274} and with frequency of use (human studies).^{3273,3726}

3) Avoid **prolonged use** of smoking cannabis, since this contributes to respiratory tract inflammatory conditions (IH human studies)^{2,627,628,629,3275} and cardiovascular disease, possibly precipitating acute coronary syndrome (IH human studies).^{3275,3277} Prolonged consumption by some may cause psychological dependence (empirical, IH in human studies),^{628,1198,3275} and physical withdrawal (IH in human studies).^{2,628,1198,3271}

HOWEVER, even with high doses over prolonged periods, withdrawal symptoms are mild and the risk of dependency is low when compared to tobacco, alcohol, opioids, and benzodiazepines (human studies).³²⁷¹

4) Avoid **motor vehicle** operation, since driving ability can be impaired for up to 8 hours (IH in human studies).^{2,627,268,629}

Driving under the influence of cannabis heightens the risk of motor vehicle accidents dose-dependently, increasing with higher frequency of use (human studies).^{3275,3276} Using a driving simulator in a placebo-controlled study, 7 men and 5 women who were recreational users of cannabis and alcohol were given 13 mg of THC [tetrahydrocannabinol] by smoking and/or alcohol to reach a blood alcohol content level of 0.05% and tested for driving performance, subjective effects, and physiological changes (IH in human study). The combination of cannabis with alcohol led to poorer driving performance such as number of collisions and lane position variability, enhancement of some subjective drug effects including sedation and sleepiness, and increased heart rate, compared to taking either THC or alcohol alone.³⁶²⁹

Drug Interactions

- Ia. + 1) In a study of 200 patients, the total body clearance of **theophylline** was greatest among young adults who smoked 2 or more cannabis cigarettes daily (IH in human study). Since tobacco smoking was also associated with increased theophylline clearance, this may be due to metabolic induction by polycyclic aromatic hydrocarbons present in smoking material and charbroiled foods (speculative).³⁶²⁴ Smoking and charbroiled meat is known to increase CYP 1A2 activity, the hepatic isozyme primarily responsible for metabolizing theophylline (IH and PO in humans).³⁶²⁵
- + 2) In 7 adult male volunteers, smoking 1 gram of cannabis increased heart rate at both low and high THC blood levels, with THC level-dependent increases in mean arterial blood pressure (IH in human study). IV **cocaine** alone increased heart rate dose-dependently, while both low and high doses of cocaine increased blood pressure similarly. When cocaine doses were given 13 minutes after the start of smoking cannabis, the heart rate was greater at about 50 bpm over baseline for all doses than the approximately 33 bpm increase over baseline for the highest levels of either drug alone. The mean arterial pressure of the combinations did not surpass that of using cocaine alone.³⁶²⁸
- + 3) The effective use of cannabidiol [CBD] for seizures³⁶³³ led to an open-label safety study with **antiepileptic drugs** in 39 adults and 42 children, using increasing CBD doses every 2 weeks from 5-50 mg/kg daily, showed a significant increase in N-desmethyloclobazam [nCLB], the active metabolite of **clobazam**, that led to sedation in 6 of 12 adults and 8 of 15 children with the higher nCLB levels (PO in human clinical study). On the other hand, significant increases in serum levels resulted for **rufinamide**, **topiramate** [in adults and children], **eslicarbazepine**, and **zonisamide** [in adults only], but these drugs remained within therapeutic range. These changes in drug levels were believed to be due to modulation of cytochrome P450 [CYP] enzyme activities (speculative). Also, when used concomitantly with **valproate**, CBD was associated with significantly increased levels of the liver enzymes AST and ALT.³⁶³¹

HOWEVER, in 13 pediatric patients with refractory epilepsy, the combination of 20-25 mg/kg CBD with clobazam daily for 8 weeks led to increased clobazam and significantly increased active metabolite nCLB levels at 4 weeks (PO in human clinical study). This resulted in 9 of 13 having more than 50% fewer seizures, even though clobazam doses were reduced in 10 of 13 over the course of treatment due to side effects, including drowsiness in 6. The authors concluded that, with monitoring of drug levels, CBD is both safe and effective in refractory epilepsy treated with clobazam, as shown with ongoing monitoring after 36 weeks.³⁶³²

- Ib. 1) [NOTE: The order of this information has been reversed and alcohol has been given a separate entry.] Concurrent abuse of cannabis and other substances is not uncommon (empirical)⁶²⁸ and results in greater intoxication and impairment when it is combined with **opiates** or **barbiturates** (IH in human studies).¹⁰⁷⁷

Cannabis use is more common among those prescribed chronic opioid therapy (human studies).²⁷⁴⁶ Those who are dependent on **codeine** are more likely to use cannabis than nondependent regular codeine users [23% vs. 5%, respectively] and to use codeine for its pleasurable effects, to relax, or to prevent withdrawal (human study).²⁷⁴⁷ The opioid **oxymorphone**, in an IV dose of 1.0 mg/70 kg, caused sedation and depressed ventilation from 24.9 l/min to 14.1 l/min in 8 volunteers, while THC dose-dependently increased oxymorphone-induced sedation and ventilatory depression to 6.6 l/min after a 134 mcg/kg dose (IV in human study). The combination at this dose also significantly decreased the CO₂-ventilation slope and total peripheral resistance, as well as significantly increasing the heart rate and cardiac index, though oxymorphone alone did not cause significant cardiovascular changes. In one individual, the heart rate exceeded 150 bpm after only 27 mcg/kg THC. Also, **pentobarbital**, at 100 mg/70 kg IV, caused no significant cardiovascular changes but with THC induced anxiety and hallucinations in 5 of 7 volunteers, 4 at IV doses of 90 mcg/kg. While ventilation was not affected, THC given after pentobarbital treatment increased cardiac index, decreased peripheral resistance, and significantly increased the heart rate from 76 to 130 bpm.³⁶³⁰

HOWEVER, cannabis has been used to ease withdrawal from opiates (empirical).^{3270,3545} A 35-year-old man with HIV-related peripheral neuropathy likewise tried multiple medicines for pain, using 360 mg/day of long-acting morphine plus 75 mg 4 times daily of morphine sulphate for breakthrough pain; after using 3-4 puffs of cannabis 3-4 times daily, morphine dosage decreased to 180 mg/day over 4 months and was discontinued after 9 months.²⁷⁴⁵ Cannabidiol, a nonpsychotropic component of cannabis, was found to inhibit cue-induced heroin seeking in doses from 5-20 mg/kg (IP in rats). This was associated with normalization of mesolimbic cannabinoid type-1 and glutamine R1 receptor expressions.²⁹⁷³

- 2) Simultaneous consumption results in additive effects with greater subjective intoxication and behavioral impairment when cannabis is combined with **alcohol (ethanol)** (IH in human studies).¹⁰⁷⁶ Concurrent abuse of cannabis and alcohol is not uncommon (empirical).⁶²⁸

Using a driving simulator in a placebo-controlled study, 7 men and 5 women who were recreational users of cannabis and alcohol were given 13 mg of THC [tetrahydrocannabinol] by smoking and/or alcohol to reach a blood alcohol content level of 0.05% and tested for driving performance, subjective effects, and physiological changes (IH in human study). The combination of cannabis with alcohol led to poorer driving performance such as number of collisions and lane position variability, enhancement of some subjective drug effects including sedation and sleepiness, and increased heart rate, compared to taking either THC or alcohol alone.³⁶²⁹

HOWEVER, cannabis has been used to ease withdrawal from alcohol (empirical).^{3270,3545} Nonetheless, a 36-year-old man on **disulfiram** for a month to avoid alcohol abuse then also substituted smoking cannabis for drinking alcohol (IH in human case report). Immediately, he became confused and disoriented, and within 3 days had manic outbursts, though acting relatively normal between these episodes. After taking chlorpromazine, he became calm in 48 hours and continued taking disulfiram with no cannabis use without further problems.³⁶²⁶ Also, a 28-year-old man with a history of using alcohol, amphetamines, cocaine, and cannabis had been

admitted to the hospital with alcohol intoxication (IH in human case report). He was given disulfuram once daily at bedtime, since a urine test was negative for amphetamines, cocaine, opiates, meperidine, and barbiturates, but THC was not tested. He became euphoric, hyperactive, and unable to sleep; the disulfuram dose was reduced and then stopped. Urinalysis taken during disulfuram use was again negative for drugs previously assessed, but positive for THC. He admitted smoking 2-4 cannabis cigarettes nightly while taking the disulfuram. He stated that the cannabis had never affected him that way before, and it felt like he was taking amphetamines. Within 48 hours of stopping disulfuram he returned to normal, though he continued smoking cannabis.³⁶²⁷

Complementary Adjuncts

- Ia. 1) **Vomiting** induced by cancer **chemotherapy** agents was relieved by cannabis in 78% of the patients (IH in human clinical study).¹⁰⁷⁸
In a randomized, double-blind, crossover trial, when 15 osteogenic sarcoma patients on high-dose **methotrexate** chemotherapy used oral 10 mg/m² THC 5 times daily and smoked THC in cannabis after initial vomiting episodes, 14/15 responded and nausea and vomiting were significantly reduced compared to using placebo and cannabis with no THC (PO and IH in human clinical study). The incidence nausea and vomiting diminished with increasing plasma THC concentrations.²⁹⁴² In 14 controlled trials with 681 cancer patients using THC for chemotherapy-induced vomiting, THC was as, or more, effective than standard antiemetic drugs (PO in human clinical trials). In addition, 2 controlled studies showed THC retarded chronic weight loss and stimulated appetite in patients with advanced cancers, and 2 other controlled studies with 46 patients showed THC in doses of 10-20 mg was effective for cancerous pains (PO in human clinical studies).²⁹⁴⁴
HOWEVER, in another trial with the same protocol for oral THC or smoked after a vomiting episode, for 8 cancer patients taking adriamycin and cytoxan only 3/8 had a reduction of nausea and/or vomiting (PO and IH in human clinical study).²⁹⁴³ A comparative study with 20 cancer patients using oral THC and smoked cannabis for chemotherapy-induced vomiting found efficacy in only 5; overall, 7 preferred THC, 4 preferred cannabis, and 9 had no preference (PO vs IH in human clinical study). Perceptual distortions occurred in 7 including 4 with THC, 2 with cannabis, and 1 with both.²⁹⁴⁴
- + 2) In 125 patients with peripheral **neuropathic pain** who remained on stable analgesia including 86 on **opioids** [15 on the stronger **morphine, methadone, oxycodone, or pethidine** and 71 on the weaker **tramadol, codeine, dihydrocodeine, and dextropropoxyphene**] as well as 41 on non-opioid **analgesics** or **anti-inflammatory** drugs, those who received a standardized cannabis extract oromucosal spray with equivalent amounts of THC and cannabidiol for 5 weeks had significantly reduced pain intensity and better sleep than those on placebo (human clinical study). The cannabis group also had greater sedation and GI side effects, and 18% withdrew compared to 3% placebo withdrawals. Extending the study to 1 year maintained pain relief without increased dose or toxicity.²⁷⁴⁸ In a crossover trial with 21 neuropathic pain patients, 25 mg of cannabis with 9.4% THC 3 times daily for 5 days compared to cannabis with 0% THC significantly improved average daily pain intensity and sleep; routine medications continued by the patients included opioids by 61%, **antidepressants** by 52%, **anticonvulsants** by 43%, and **NSAIDs** by 43% (IH in human clinical study). Though mild, adverse effects were more frequent with the higher THC dose.²⁹⁴⁰ States that have enacted medical cannabis laws have shown on average a 24.8% lower annual opioid overdose mortality rate from 1999-2010.³⁴⁰⁴
- + 3) The 28 patients with distal sensory polyneuropathy as an expression of **HIV neuropathic pain** who completed a randomised crossover trial using cannabis for 1 week (IH in human clinical study) maintained the use of pain-modifying agents including 18 on **opioids**, 18 taking **anticonvulsants**, 10 who used **acetaminophen** or **NSAIDs**, and 8 on **tricyclic antidepressants**. Additional pain relief in daily functioning was significantly greater with cannabis than with a placebo without THC. Changes in morphine equivalent doses and pain severity did not differ

between those who used concomitant opioids and those who did not. Changes in aspirin equivalents were minimal.²⁸⁴⁸ In 50 HIV patients with chronic painful sensory neuropathy who were randomly assigned to smoke cannabis or an identical placebo 3 times daily for 5 days, the cannabis group had a significantly greater 34% reduction in daily pain, with 52% having over 30% reduced pain compared to 24% with this effect while using placebo (IH in human clinical study). About half used concomitant medications divided similarly between **gabapentin**, opioids, and others. Experimentally induced **hyperalgesia** from topical **capsaicin** application was also significantly reduced in those subjects smoking cannabis.²⁸⁴⁷

- + 4) Vaporized cannabis extract given for 3 2/3 days to 21 patients using opioids for **chronic pain**, including 11 taking **morphine** and 10 using **oxycodone**, significantly reduced pain by an average of 27% without significantly altering plasma opioid levels (IH in human clinical study).³¹²⁶

Of 30 chronic pain patients in a pain management center who used 1-5 grams [avg. 2.5 gr] medical cannabis daily for 1-5 years, 93% reported moderate or greater pain relief, and no serious adverse effects were noted (IH in human case series). Of those with adverse effects 70% were able to decrease the medications such as **opiates** and **NSAIDs** that were causing the side effects.²⁷⁵⁰ Cannabis has been shown effective for chronic pain by increasing analgesia when used in combination with morphine (IH in human case series). A 47-year-old woman with chronic multiple sclerosis had inadequate relief from a plethora of medications, including 75 mg/day of long-acting morphine, but with the addition of 2-4 puffs of cannabis at bedtime she was able to reduce her medications and adequately control her pain with 45 mg/day of morphine. Also, a 35-year-old man with HIV-related peripheral neuropathy likewise tried multiple medicines for pain, using 360 mg/day of long-acting morphine plus 75 mg 4 times daily of morphine sulphate for breakthrough pain; after using 3-4 puffs of cannabis 3-4 times daily, morphine dosage decreased to 180 mg/day over 4 months and was discontinued after 9 months. Finally, a 44-year-old man with a lumbar spine injury had low back and leg pain resistant to physiotherapy and several pain medications; he relied on 150 mg/day of long-acting morphine. Smoking cannabis 4-5 times daily for 2 weeks allowed a decrease in morphine to 90 mg/day, then to 60 mg/day after 2 more weeks, after which he was able to resume work with good pain control.²⁷⁴⁵ States that have enacted medical cannabis laws have shown on average a 24.8% lower annual opioid overdose mortality rate from 1999-2010.³⁴⁰⁴

In a systematic review of cannabis use in adults with chronic pain which describes up to 39% of patients prescribed long-term opioid for pain also using cannabis, 27 chronic pain trials were reviewed, and low-strength evidence was found only for cannabis alleviating chronic neuropathic pain (IH or PO in human clinical trials).³⁷²¹

- + 5) A group of 30 **multiple sclerosis** patients, 60% using the antispasmodic agents **baclofen** and **tizanidine** and 7% taking the disease modifying drugs **interferon beta-1a,b** or **glatiramer** had significantly reduced spasticity and pain compared to placebo after treatment with 800 mg smoked once daily for 3 days in a placebo-controlled crossover trial (IH in human clinical study).³³⁰⁵

Another 135 multiple sclerosis patients were randomly treated for **overactive bladder** with a standardized cannabis extract oromucosal spray or placebo for 8 weeks in addition to a stable dose of **anticholinergics** (PO in human clinical study). The dose was individually triturated and found significantly effective for several secondary treatment endpoints including improvements in nocturia, daytime voids, number of voids per day, and patient global impression of change. The tolerance of the cannabis extract was good with the most common adverse effects related to the central nervous system including dizziness [18%], headache [6%], disorientation [6%], dissociation [6%], impaired balance [5%], and paresthesia [3%].²⁷⁵¹

6) In **postoperative pain** in 65 patients following analgesia with **morphine**, the use of an extract of cannabis with 1 part THC to 0.3 parts cannabidiol, doses of 10 mg or 15 mg doses of the extract led to pain relief reflected by rescue analgesia requirements similar to many analgesics routinely used; sedation increased with increasing doses (PO in human clinical study).²⁷⁴⁹

- + 7) Experimentally induced **hyperalgesia** from topical **capsaicin** application was significantly reduced in those subjects smoking cannabis (IH in human clinical study).²⁸⁴⁷
- + 8) The frequency or drug-resistant seizures in 120 young adults and children with **Dravet Syndrome** being treated by **clobazam** (65%), **valproate** (59%), **stiripentol** (42%), **levetiracetam** (28%), and **topiramate** (26%) was reduced by 50% in 43% of 61 patients with the use of cannabidiol, significantly more than the 27% of 59 patients taking placebo (PO in human clinical trial). Of those taking cannabidiol, a significant 5% became seizure free, compared to 0% of those taking placebo. Caregivers indicated improvement in at least 1 of 7 categories of the global impression scale in 62% of the cannabidiol group, compared to only 34% in the placebo group.³⁷¹⁶

CARAWAY

p. 84

Carum carvi seeds

Drug Interactions

- II. 1) A butanolic fraction of the seed increased plasma levels and bioavailability of the antitubercular drugs **rifampicin**, **pyrazinamide**, and **isoniazide** due to increased absorption from enhanced permeation (PO in rats). A 40% reduced dose of these drugs combined with the fraction was equivalent in bioavailability to a normal dose.³⁴⁷⁷

CASSIA CINNAMON

p. 86

Cinnamomum cassia syn. *Cinnamomum aromaticum* bark
(cassia, cassia bark, Chinese cinnamon)

Contraindications

- I. 1) Avoid in large doses in **pregnancy**,^{6,150,401} due to potential abortifacient effects (empirical).⁷⁴ The potential for hepatotoxicity due to its extremely high coumarin content is also a matter of concern in pregnancy (speculative).^{2231,2248}

HOWEVER, in reviewing 129 patients [111 females] of average age of 58 years from 2008-2013 who had used Japanese Kampo medicines with high cassia cinnamon and coumarin content, 98 exceeded the European standard for coumarin of tolerable daily intake of 0.1 mg/kg/day (PO in human clinical case series). While 17 of these 98 [17.3%] had abnormal liver function test values, 6 of 31 [19.4%] of those consuming less than the tolerable amount showed similar results, indicating no significant difference with high coumarin intake. No cases of abnormal liver changes were directly associated with cinnamon bark intake but appeared related to other diseases, concomitant drugs, lifestyle, age, or problems unrelated to the period of Kampo intake.³⁵⁹⁵

Drug Interactions

- Ia. 1) In type 2 diabetes using the **sulfonylurea** drug **glibenclamide**, cassia further reduced fasting glucose (PO in human clinical study).¹⁵⁹² A cassia extract also significantly reduced serum glucose in type 2 diabetics with poor glycemic control taking **oral hypoglycemics** including sulfonylureas and **metformin** or both (PO in human clinical study).¹⁹⁰⁰

In a randomized, double-blind study of 66 patients with type 2 diabetes, along with taking the sulfonylurea drug **gliclazide** for 3 months 23 were also given cassia extract at 120 mg/day, 23 received the extract at 360 mg/day, and 20 took a placebo, as changes from baseline for fasting blood glucose and glycosylated hemoglobin [HbA_{1C}] were compared (PO in human clinical study). Each 120 mg of extract was derived from the water-soluble fraction of 4.8 grams of cassia cinnamon. After 3 months, significant improvements for both parameters were shown in the low- and high-dose groups, but not for the placebo group. The blood sugar and HbA_{1C} reductions were greater in the high-dose group, but only the low-dose group had a significant reduction in triglyceride levels as well. Only the placebo group had a significant elevations of cholesterol and the liver enzyme alanine aminotransferase.³²⁴⁴

In another study of 58 patients with poorly controlled type 2 diabetes, 30 given 2 grams of cassia cinnamon powder daily for 12 weeks had significantly improved mean HbA1c and systolic and diastolic blood pressures, compared to the 28 placebo controls (PO in human clinical study). In addition, the fasting plasma glucose, waist circumference, and body mass index were improved from baseline in the cassia group, of whom 24 treated were treated with metformin, 2 with sulfonylureas, and 4 with both.²⁷⁵⁸

Tests of 2 extracts rich in B-type procyanidin oligomers derived from cassia from 2 different areas of China were both found to be as effective as metformin in reducing extracellular glucose in normal or insulin-resistant HepG2 cells (*in vitro*) and blood glucose in STZ-diabetic animals (PO in rats).²⁸³⁶

- III. + 3) Due to the depression of glutathione levels by cinnamaldehyde (in rats), the oral use of cassia oil should be avoided with concurrent use of **acetaminophen (paracetamol)**.⁴⁰⁰

CAT'S CLAW

p. 89

Uncaria tomentosa bark or root

Drug Interactions

- Ib. 1) A woman with cirrhosis from hepatitis C infection who was HIV positive was receiving protease inhibitor treatment with **atazanavir**, **ritonavir** and **saquinavir** while she was also taking a cat's claw preparation (PO in human case report). After taking the cat's claw for 2 months, it was discovered in preparation for liver transplantation that her serum trough concentrations of all 3 protease inhibitors were greatly elevated above the therapeutic cut-off values. When the cat's claw was withdrawn, the serum trough concentration dropped dramatically to near normal ranges.³⁵²⁰
- II. 1) When cat's claw dried bark containing pentacyclic oxindole alkaloids was given at doses of 3.5 and 7.1 mg/kg, comparable to normal human doses, together with **diazepam**, both doses over a span of 30 minutes enhanced the drug's reduction of spontaneous motor activity. The lower dose also further increased diazepam's inhibition of exploratory ability but reduced diazepam's musculoskeletal relaxant activity (PO in mice).³⁵¹⁹

Complementary Adjuncts

- IIa. + 2) After treatment with daily intraperitoneal injections of **doxorubicin** over 3 days to induce **leukopenia**, a water extract of the inner and outer bark was given for 16 consecutive days (PO in rats). The animals receiving the extract recovered significantly sooner than controls; those given 80 mg/kg extract daily showed normalized white blood cell counts after 10 days and those given 40 mg/kg had normal white counts after 15 days, but it took 20 days to return to normal for those receiving only the doxorubicin. The increase in white blood cell counts included both lymphocytic and neutrophilic cell fractions, whereas the positive control Neupogen® increased only the non-lymphocyte fractions.³³³¹

CAYENNE

p. 90

**Capsicum frutescens* fruit

Contraindications

- I. 7) Avoid local application to areas of **skin damage** (empirical)⁴⁰¹ that may result in an open sore (empirical).^{6,17,150}

The application of 0.1% capsaicin cream for 48 hours to 20 subjects, compared to placebo in 12, resulted in a maximal loss of sensory function by day 6 and autonomic function by day 16 including sudomotor, vasomotor, pilomotor functions and significant loss of nerve fiber densities (TP in human study). Nerve regeneration occurred within 40-50 days for autonomic nerves but 140-150 days for sensory nerve fibers. Caution should be taken in using capsaicin on skin at risk for ulceration, especially neuropathic conditions.²⁹³⁹

Drug Interactions

- Ib. 2) **Antacids** are antagonized and the alimentary mucosa is further irritated (empirical).⁷⁷⁷

HOWEVER, a study of 50 consecutive patients with duodenal ulcers proved by endoscopy who were all being treated with a liquid antacid [containing 61 g/L aluminum hydroxide and 20 g/L magnesium hydroxide] 6 times daily, administered 1 g cayenne powder 3 times daily with the standard meals to half of them (PO in human clinical study). There were no differences in symptomatic relief and 80% of the ulcers healed in each group. No hemorrhage or erosions were shown on endoscopy in the cayenne group, though 2 of the 25 had a mild intolerance to the cayenne.³⁵⁴⁴

- II. 4) The pungent component capsaicin was given at 3, 8, or 25 mg/kg daily for 7 days, when on day 7 a single 80 mg/kg dose of the CYP 3A4 substrate **simvastatin** was given orally (PO in rats). Compared to controls, the capsaicin led to a significant dose-dependent decrease of the bioavailability of cholesterol-lowering simvastatin by 67%-78%. Likewise, the maximum plasma concentration of simvastatin and its acid metabolite were also significantly reduced with capsaicin pretreatment.³⁵⁴⁷

Complementary Adjuncts

- IIa. 1) The **mineral absorption** of **calcium, iron, and zinc** were all significantly improved with the addition of 0.015g% of capsaicin to the diet, compared to the same diet without capsaicin (PO in rats). Calcium absorption was improved the most. Capsaicin increased the uptake of zinc better than either piperine or ginger.³⁴⁷¹

CELANDINE

p. 92

**Chelidonium majus* root and herb

Contraindications

- I. 4) Do not consume following an idiosyncratic **hepatotoxicity** reaction after using celandine (empirical).¹⁸⁹⁰

Liver-specific CIOMS analysis of 22 hepatotoxicity cases in Germany associated with celandine found 2 highly probable, 6 probable, 10 possible, 1 unlikely, and 3 excluded (PO in human cases). The celandine hepatotoxicity cases had patient averages of 56 years of age, use for 36 days, latency until first symptoms of 30 days, and jaundice after 36 days, with a female predominance.³³⁰⁴

Drug Interactions

- III. 2) Celandine may aggravate hepatotoxic reactions to **anesthetics, steroids, estrogen, or chlorpromazine** (speculative), due to its own liver stimulant and toxic effects (empirical).¹⁸⁹⁰

In tests with 1.5 and 3 g/kg daily for 2 to 4 weeks in Wistar rats, no changes occurred in food consumption, body weight, liver enzyme activities, liver cell morphology, and malondialdehyde formation at either dosage level (PO in rats). Glutathione levels at the higher dose and superoxide dismutase activity at both doses decreased significantly, suggesting caution in situations such as pharmacological treatments that could compromise liver function. In contrast, **acetaminophen** at 2 g/kg significantly increased liver enzymes, total bilirubin, and cholebilirubin.³⁷¹³

HOWEVER, when given with a 0.5 g/kg acetaminophen dose that had induced focal liver cell necrosis and significant increases in AST, ALT, and total bilirubin, the addition of 3 ml/kg [derived from 1.5 g/kg of herb] of a 70% ethanolic extract of celandine dried aerial parts twice daily for 2 days before the acetaminophen did not increase these effects in either gender (PO in rats). Given alone in this amount, 50 times the usual human dose, celandine did not alter parameters of liver function in male Wistar rats, but in the female rats it increased fibrinogen levels.³⁷¹²

CHAGA

NEW

^ (*Inonotus obliquus*) mushroom

Complementary Adjuncts

- Ia. 1) An aqueous extract of the fruiting body was freeze-dried and given at a dose of 10 mg daily for 24 days after **immunosuppression** induced by the chemotherapy drug **cyclophosphamide** (PO in mice). By as early as 8 days after extract treatment, the number of granulocyte and macrophage colony-forming units were almost to the level of non-immunosuppressed controls. Serum levels of interleukin-6 were highly increased by the extract, and tumor necrosis factor- α was maintained at a background level, compared to its elevation in controls after the drug treatment.³⁵⁰⁴

CHAMOMILE

p. 94

Matricaria recutita = *Matricaria chamomilla* herb or flowers

Contraindications

- II. 1) [Clarification] ALSO, REGULAR internal consumption should be avoided THROUGHOUT **pregnancy**. A study of 392 pregnant Italian women found that those 37 who were regular users of chamomile had a 21.6% higher frequency of threatened miscarriages, mostly in the 4th-5th month of gestation, and a 21.6% increase in preterm labors compared to non-users (PO in human study).³⁰⁷⁸

HOWEVER, the authors failed to identify by scientific name whether the chamomile used was German (*Matricaria recutita*) or Roman (*Chamaemelum nobile*) chamomile.³⁰⁷⁸ Likewise, scientific species identification was not utilized in describing the association of regular chamomile use in 56 subjects for 3 to 9 months during pregnancy with low birth weight, though the risk did not reach statistical significance (PO in human study). There was no association in this study with chamomile use and preterm birth.³²⁰⁵

Complementary Adjuncts

- Ia. 1) A flower extract as a mouth rinse effectively treated **oral mucositis** from **chemotherapy** in 78 cancer patients (TP in human clinical study).²⁵⁴¹

A major constituent of chamomile, bisabololoxide A, was shown at a 10 mcM concentration to enhance the antiproliferative effects of 3-10 mcM concentrations of 5-fluorouracil on human leukemia K562 cells (*in vitro*).²⁸⁶³

- Ia. + 2) Chamomile hydroalcoholic extract, given at 25 mg/kg for 4 days before and with IV **cisplatin** before an SC formalin injection, reduced the second phase **neuropathic pain** expressions from cisplatin-induced peripheral neuropathy (IP in mice). The chamomile extract given alone reduced the first and second phase formalin-exacerbated pain better than morphine; the pain increased in the first and second phase when cisplatin was given alone (IP in mice).³³⁷⁴

CHILI

NEW

^ * *Capsicum annuum* fruit

["Peppers" refers to nonpungent varieties of this species eaten as vegetables; chilis are pungent.] (chili pepper, Thai chili; Sp.: chile; Mex.: chilli)

Contraindications

- I. 1) Do not use in chronic **irritable bowel**,^{24,777} due to neural irritant and intestinal contractile properties of capsaicin (*in vitro*, animal, and human studies).¹⁷⁶
2) Avoid use with **allergic hypersensitivity**, since this may result in urticaria (empirical).¹⁷

Drug Interactions

- Ia. 1) Intestinal absorption of **iron (ferrous sulfate)** as part of fortified fish sauce with vegetables and rice was reduced 38% when it was taken with 4.3 g chili pepper with 25 mg polyphenols (PO in human study). This chili did not affect gastric acid secretion.²⁸⁰⁷

HOWEVER, the absorption of iron was significantly improved with the addition of capsaicin to the diet, compared to the same diet without capsaicin (PO in rats).³⁴⁷¹ No effect on iron absorption was found when 0.5 g turmeric (*Curcuma longa*) with 50 mg of polyphenols was taken instead.²⁸⁰⁷

Complementary Adjuncts

- Ia. 1) A dose of 20 gm of powdered dry fruit (containing 9.56 mg capsaicin, a concentration of 478 ppm) reduced **stomach damage** to the mucous membrane in 18 subjects when taken half an hour before **aspirin** (PO in human study).²¹¹ Dilute capsaicin at 0.1 mcg/kg protected the stomach from mucosal damage by aspirin (PO in rats).¹¹²⁰
 HOWEVER, capsaicin at 1.0 mg/kg initially protected but then enhanced aspirin stomach mucosal damage. At 10-30 mg/kg capsaicin aggravated the damage caused by aspirin (PO in rats).¹¹²⁰
- IIa. 1) A significant dose-dependent prevention of **stomach ulcers** induced by **ethanol** and acid was shown by giving 3-30 mg/kg of capsaicin, probably due to increase mucosal blood flow and reduced motility (PO in rats).⁵²² Red pepper as 3.0%, and capsaicin as 0.01%, of the diet for 8 weeks followed by an acute exposure to ethanol showed gastroprotective effects by significantly increasing activity of the endogenous antioxidant enzymes superoxide dismutase, glutathione reductase, and glutathion-S-transferase in the stomach and intestinal mucosa and increasing mucin content in stomach mucosa, compared to having no exposure to the spice (PO in rats).³³⁴⁷ Dilute capsaicin at 0.1 mcg/kg protected the stomach from mucosal damage by ethanol (PO in rats).¹¹²⁰
 HOWEVER, at 10-30 mg/kg capsaicin aggravated the damage caused by ethanol (PO in rats).¹¹²⁰
- 2) The **mineral absorption** of **calcium**, **iron**, and **zinc** were all significantly improved with the addition of capsaicin to the diet, compared to the same diet without capsaicin (PO in rats). Calcium absorption was improved the most. Capsaicin increased the uptake of zinc better than either piperine or ginger.³⁴⁷¹

CHINESE HIBISCUS

Hibiscus rosa-sinensis flowers
 (rose of China)

Contraindications

- II. 1) Its excessive internal use should be avoided in early **pregnancy** (speculative),² due to its emmenagogue effects (empirical). [Plant part not identified for abortifacient use.]⁷⁴

CHINESE RHUBARB

p. 99

**Rheum officinale*, **Rheum palmatum* root

Drug Interactions

- II. 1) A decoction of *R. palmatum* root of 2 g/kg administered in either a single dose or 7 doses with 200 mg/kg **phenytoin** after the last dose caused significant reductions in the peak serum concentration and the bioavailability of phenytoin and its metabolites (PO in rats). The efflux of phenytoin by P-gp in human colon cells was significantly increased, though MRP-2 phenytoin transport from renal cells was inhibited (*in vitro*).³³³⁵

CHINESE SKULLCAP

p. 100

Scutellaria baicalensis root

Complementary Adjuncts

- IIa. + 3) The **hepatotoxicity** effects of **ethanol (alcohol)** in conjunction with a 40% fat diet led to elevated serum transaminase enzymes and LDH, as well as elevated triglyceride, LDL-cholesterol, and total cholesterol that were all significantly reversed to near control levels when 100 mg/kg of water extract was given concurrently for 28 days (PO in mice).²⁸³⁹

CHOKEBERRY

p. 101

Aronia melanocarpa fruit

Drug Interactions

- Ib. 1) After his fourth cycle of **trabectedin** as second-line chemotherapy, a man with liposarcoma suddenly developed weakness and diffuse muscle pain, after taking a chokeberry preparation during the last course of trabectin and the subsequent 2 weeks (PO in human case report). Along with increased serum levels of myoglobin, creatinine phosphokinase, and lactate dehydrogenase, there was evidence of pancytopenia and a large increase in liver enzymes. After stopping the chokeberry extract, the markers of myolysis slowly returned to normal and muscle strength progressively recovered. Trabectedin is metabolized by CYP3A4. The evidence indicated that it was probable the adverse event was an interaction of trabectedin and chokeberry, likely through inhibition of CYP3A4 (speculative).³³⁶⁹

Complementary Adjuncts

- IIa. + 3) The antiarrhythmic drug **amiodarone** given intratracheally causes direct **lung damage** resulting in acute toxic pneumonitis, inducing oxidative stress and fibrosis, but these effects and pulmonary inflammation were significantly reduced with chokeberry juice given at 5 ml/kg for up to 10 days after exposure to amiodarone (PO in rats).³⁴³⁶

CINCHONA

p. 101

**Cinchona* spp. bark

Complementary Adjuncts

- IIb. 1) The inhibition by quinine and/or quinidine of **ethacrynic acid** and 1,3-bis(2-chloroethyl)-1-nitrosurea (**BCNU** or **carmustine**) phase II glutathione S-transferase conjugation by [CORRECTION:] **tumor cells** (*in vitro*) could lead greater retention of these and increased efficacy of BCNU as an agent against [CORRECTION:] some cancers (speculative).¹⁵⁴⁷

CINNAMON

p. 102

**Cinnamomum verum* = *Cinnamomum zeylanicum* bark [See also Cassia.]

Drug Interactions

- I. 1) The extract did not reduce normal blood glucose.¹⁷⁶³ In a study of 37 type 2 diabetics taking stable doses of **metformin** or **gliclazide**, those taking 3 gram/day of cinnamon had significantly reduced fasting blood glucose, glycosylated hemoglobin, triglycerides, and weight compared to baseline, but not compared to those taking placebo (PO in human clinical study).³²⁸⁷
- III. + 3) Due to the depression of glutathione levels by cinnamaldehyde (in rats), the oral use of cinnamon oil should be avoided with concurrent use of **acetaminophen** (**paracetamol**).⁴⁰⁰

CLOVE

p. 103

Syzygium aromaticum = *Eugenia caryophyllata* buds

Complementary Adjuncts

- IIa. + 1) Pretreatment with 10 mg/kg of eugenol an hour before administration of a single 30 mg/kg dose of **indomethacin** significantly reduced the indomethacin-induced formation of **stomach ulcers** (PO in rats). This was accompanied by significant reductions in gastric acid and pepsin activity, along with decreased gastric mucosal nitrite and malondialdehyde, and an increase in reduced glutathione and mucin concentration, compared with indomethacin alone.²⁹⁵⁷
- + 2) Pretreatment with 10-100 mg/kg of eugenol an hour before administration of a single 1 ml dose of **ethanol** significantly reduced the alcohol-induced formation of **stomach ulcers** both in number and degree of damage (PO in rats).²⁹⁵⁸

COCOA

p. 104

Theobroma cacao seed

Drug Interactions

- III. + 2) Consumption of single doses of 300 ml cocoa containing 897 mg flavanols and 81 mg **aspirin** alone and combined in a crossover trial with 16 subjects demonstrated that these two agents had similar and additive effects inhibiting platelet function and inhibiting platelet activity shown by

P-selectin expression induced by collagen with epinephrine, but not collagen with ADP, after 2 and/or 6 hours (*ex vivo*).²⁹⁰⁶ When cocoa tablets with 234 mg flavanols and procyanidins were taken daily for 28 days by 13 subjects, the P selectin expression and collagen- and ADP-induced platelet aggregation was significantly reduced compared to the 15 in the placebo group (*ex vivo*).¹⁴⁴⁷

Complementary Adjuncts

- Ia. + 1) Cocoa that supplied 963 mg flavanols daily to patients with **diabetes type 2** on **oral hypoglycemics, insulin, antiplatelet drugs, statins, beta-blockers**, and/or **ACE inhibitors** increased flow-mediated dilation (PO in human clinical study).²⁶⁰⁰ Twelve subjects with type 2 diabetes, 5 using the oral hypoglycemic **metformin**, 8 taking statins, and 3 on **antihypertensives**, consumed daily for 8 weeks each with a 4-week washout 3 chocolate bars of 15 grams each with 16.6 mg epicatechins and 3 chocolate bars with > 2 mg epicatechins; only the high epicatechin bars led to significantly increased HDL and lower ratio of total cholesterol:HCL (PO in human clinical trial). The beneficial changes reverted to baseline values when the high epicatechin chocolate intervention stopped. No changes in weight gain, glycemic control, insulin resistance or the inflammatory marker C-reactive protein were noted with either type of chocolate bar.²⁷⁴⁰
- + 2) In 20 patients with **congestive heart failure**, all of whom were taking **beta-blockers** and **ACE inhibitors** or **angiotensin receptor blockers** and most of whom used **diuretics, statins**, and **oral anticoagulants** the half who ate 40 g twice daily of a commercial dark chocolate with 70% cocoa [providing 1.25 g/day of total polyphenols] had significantly better flow-mediated dilation in the brachial artery after 4 weeks than those taking placebo (PO in human clinical study). This surrogate marker of vascular endothelial function is not improved by statins in congestive heart failure patients. In addition, platelet adhesion was significantly reduced within hours after the chocolate was consumed, but this effect was not sustained after the flavanols were cleared from the blood overnight. Blood pressure, low on average at baseline at 110/66 mmHg due to medication, was not significantly changed, nor were weight gain and blood lipids altered.³⁰⁷⁷

COLA

p. 109

Cola nitida, Cola acuminata seed

Complementary Adjuncts

- IIb. 1) The minimum concentration of **fluoroquinolone** antibiotic drugs **ciprofloxacin, perfloracin**, and **levofloxacin** necessary to inhibit the grow of *Escherichia coli* decreased as the ratio of cola seed methanolic extract to drug increased to 3:2 for ciprofoxacin and 4:1 for perfloracin and levofloxacin (*in vitro*).³⁰³⁴

COPTIS

p. 113

Coptis chinensis and *Coptis groenlandica* rhizomes

Contraindications

- II. 1) Do not use in **jaundice** in **newborns** or from **hemolytic anemia** (speculative).¹⁰⁹² HOWEVER, when coptis rhizome and/or berberine-containing amur cork tree (*Phellodendron amurense*) bark were given in herbal concoctions according to traditional dosage and indication to 20 patients with chronic cytopenic hematological conditions, though 3 patients with thalassemia intermedia had transient elevation of serum bilirubin, there was no associated aggravation of anemia or liver dysfunction (PO in human clinical study).³¹⁰⁸

Drug Interactions

- Ia. 1) The combination of 1500 mg berberine daily for 3 months in 43 type 2 diabetes patients with one or more **oral hypoglycemic** medications including **sulfonylureas, metformin acarbose**, and/or **insulin** resulted in lower blood sugar through week 12 (PO in human clinical study).²³¹⁵

In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered fasting and postload plasma glucose and HbA1c compared to 52 diabetics on placebo, along with significantly reducing the triglycerides, total cholesterol, and LDL-cholesterol, body weight, and systolic blood pressure (PO in human clinical study).²⁹⁰⁷ In 50 type 2 diabetic patients randomly selected to use 1 gm berberine daily, the 26% and 18% significant reductions in fasting blood glucose and HbA1c were equivalent to those of the 26 and 21 diabetic patients who used metformin or rosiglitazone, respectively (PO in human clinical trial). Only the berberine group had a significant reduction of triglycerides. Also, in another group of 18 hepatitis C and 17 chronic hepatitis B patients with type 2 diabetes or impaired fasting glucose, 1 gm/day berberine significantly reduced fasting blood glucose, triglycerides, and the transaminases ALT and AST (PO in human clinical trial).²⁹⁰⁸

- + 3) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the bioavailability of CYP 3A4 substrate **midazolam** by 40% and its maximum plasma concentration by 38%, and significantly decreased its oral clearance by 27% (PO in human study).³²³⁸
- + 4) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the 8-hour urinary ratio of the CYP 2D6 substrate **dextromethorphan** to its metabolite dextrorphan by 9-fold (PO in human study).³²³⁸
- + 5) Berberine at 900 mg daily in 17 healthy males for 14 days doubled significantly the 8-hour urinary ratio of the CYP 2C9 substrate **losartan** to its metabolite E-3174 (PO in human study).³²³⁸
- II. + 2) In doses of 30 mg/kg berberine for 2 weeks, the Pgp substrates **digoxin** and **cyclosporine** had significantly increased maximum serum concentration and bioavailability compared to controls, indicating berberine inhibition of Pgp drug efflux (PO in rats).³¹⁰⁵ Likewise, the oral bioavailability of **ketoconazole** was significantly increased by berberine given at 60 mg/kg (PO in rats). Since ketoconazole is both a substrate and an inhibitor of Pgp and berberine is a Pgp substrate, the pharmacokinetic effect of each on the other may lead to pharmacodynamic synergism against fungal infections (speculative).³¹⁰⁴
- III. 3) [See Complementary Adjuncts Ia. 3) below.]

Complementary Adjuncts

- Ia. + 3) When 500 mg berberine hydrochloride was given twice daily with **simvastatin** 20 mg once daily for 2 months to 23 patients in a randomized trial for **high cholesterol**, the 31.8% reduction in LDL cholesterol was significantly better than the 23.8% with berberine in 24 patients or the 14.3% with simvastatin in 16 patients used alone (PO in human clinical study). For triglycerides, the combinations reduced these by 38.9%, significantly better than 22.1% for berberine or 11.4% for simvastatin alone. Similar results were obtained for total cholesterol. No adverse effects were observed in any group. These results reflected those obtained in animals given 90 mg/kg/day berberine and/or 6 mg/kg/day simvastatin (PO in rats).²⁹⁰⁵ In 58 type 2 diabetic patients, 1 gm daily of berberine derived from *C. chinensis* significantly lowered triglycerides, total cholesterol, and LDL-cholesterol compared to 52 diabetics on placebo, along with significantly reducing the fasting and postload plasma glucose, HbA1c, body weight and systolic blood pressure (PO in human clinical study).²⁹⁰⁷

In human liver-derived cells, berberine was found to have an additive effect with lovastatin (*in vitro*). Since lovastatin did not reduce the effect of berberine, this indicated a different mechanism of action for the two (*in vitro*).¹⁶⁵⁶

- + 4) When 500 mg berberine hydrochloride was given twice daily with **simvastatin** 20 mg once daily for 2 months to 23 patients in a randomized trial for **high cholesterol**, the 31.8% reduction in LDL cholesterol was significantly better than the 23.8% with berberine in 24 patients or the 14.3% with simvastatin in 16 patients used alone (PO in human clinical study). For triglycerides, the combinations reduced these by 38.9%, significantly better than 22.1% for berberine or 11.4% for simvastatin alone. Similar results were obtained for total cholesterol. No adverse effects were

observed in any group. These results reflected those obtained in animals given 90 mg/kg/day berberine and/or 6 mg/kg/day simvastatin (PO in rats).²⁹⁰⁵

In human liver-derived cells, berberine was found to have an additive effect with lovastatin (*in vitro*). Since lovastatin did not reduce the effect of berberine, this indicated a different mechanism of action for the two (*in vitro*).¹⁶⁵⁶

- IIa. + 4) A methanolic extract of *C. chinensis* rhizome at doses of 100, 200, and 400 mg/kg and berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive **locomotor activity** induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the coptis and berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that coptis and berberine may help reduce the chronic cocaine psychological dependence (speculative), since coptis rhizome has been used in the treatment of substance abuse (empirical).²⁷⁵³
- + 5) When taken with a **high cholesterol** and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).²⁹³² When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.²⁹³³ The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);²⁹³² berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).²⁹³³
- + 6) The combination of 1 mg/kg berberine with 0.5 mg/kg **amphotericin B** increased the survival for disseminated **candidiasis** to 36 days from 12 days for controls and 17 days and 14 days, respectively, when these 2 antifungal agents were used separately (IP in mice).³¹⁰⁷
- + 7) Compared to those injected with 2.5 mg/kg **doxorubicin** alone every other day for 14 days, those injected with 60 mg/kg berberine an hour prior to the drug had less **cardiotoxicity** as shown by significantly smaller increases in mortality, LDH activity, myocardial injury, and QRS duration (IP in mice). This indicates a potential protective role of berberine against heart damage by doxorubicin.³¹⁴⁸
- + 8) After treatment of ***Clostridium difficile* infection** with 50 mg/kg **vancomycin** daily for 5 days, the use of berberine at 100 mg/kg for the next 5 days prevented weight loss and improved the disease activity index score and the histopathology score, while decreasing the mortality rate, compared to vancomycin alone (PO in mice). Berberine prevented relapse of *C. difficile* infection and significantly improved survival, while counteracting vancomycin side effects. Berberine appears to be effective by restoring intestinal microbiota and inhibiting expansion of *Enterobacteriaceae* family members.³⁶¹⁹

CORN SILK

NEW

^ *Zea mays* stigma

Complementary Adjuncts

- IIa. 1) The damage from acute **kidney toxicity** with the use of the antibiotic **gentamicin** was reduced by 200 and 300 mg/kg of corn silk given 1 hour before 100 mg/kg of gentamicin was injected intraperitoneally daily for 8 days (IP in rats). Elevations in plasma creatinine induced by gentamicin were significantly reduced by the corn silk, though increased urea was not. Histopathological damage was somewhat decreased, as the corn silk reduced interstitial nephritis but not the acute tubular necrosis or hyaline cast formation, compared to controls receiving only gentamicin.³⁴⁸⁶

- Iib. 1). The major corn silk flavonoid maysin reduces the viability of PC-3 androgen-independent **prostate cancer cells** in a concentration-dependent manner and at 50 mcg/ml acts synergistically with the anti-cancer agents **5-fluorouracil, camptothecin, cisplatin, and etoposide** to inhibit the growth significantly more than the chemotherapy agents alone (*in vitro*).³⁴⁸⁸

CRANBERRY

p. 117

Vaccinium macrocarpon fruit

Drug Interactions

- Ib. 1) A report on 5 individuals suggested cranberry juice may increase the effects of **warfarin** (PO in human case series).¹⁷⁶⁴ In one of several other cases, a man taking warfarin with an INR of 2-3 prior to using 24 oz cranberry juice daily for 2 weeks developed blood in his sputum and stools, low hemoglobin, and an INR of >18 (PO in human case report).²⁵⁰⁵

A 46-year-old woman stabilized on warfarin with a 2.0 INR had it increase to 4.6 after drinking about 48 oz (1420 ml) of cranberry juice cocktail daily for 2 days (PO in human case report). After 14 days with no more cranberry, it had lowered to 2.3 and was maintained for 3 months at an average of 2.1 (1.4-2.5). Then, after about 64 oz (1893 ml) cranberry juice cocktail daily for 3-4 days, her INR was elevated to 6.5. Stopping warfarin for 3 days reduced it to 1.86.³⁶⁹⁶

HOWEVER, when 30 patients on warfarin with stable INRs of 1.7-3.3 were randomized to 240 ml cranberry juice cocktail or matching placebo daily for 2 weeks, there was no resulting differences between groups in plasma R- or S-warfarin concentrations (PO in human clinical trial). The only significant difference between groups in mean INRs measured every 3 days was on day 12, when the cranberry group INR value was higher, but by day 15 the groups values were equivalent.²⁷⁶³ The juice of only 1 of 5 commercial cranberry juice samples tested showed significant inhibitory effects on metabolism of warfarin by CYP2C9 (*in vitro*). When 16 healthy volunteers consumed the inhibitory cranberry juice prior to a single dose of warfarin, its bioavailability and its half-life were not increased (PO in human study). The inhibition (*in vitro*) did not correlate with warfarin clearance (*in vivo*), since warfarin metabolism in the liver of living subjects is remote from the site of exposure to the inhibitory cranberry components in the intestines.³⁰⁸³

Complementary Adjuncts

- Ia. 1) Fifteen patients with **diabetes type 2** taking **oral hypoglycemics** were shown to have decreased total cholesterol and LDL-cholesterol when taking 500 mg capsules of cranberry extract 3 times daily after meals for 12 weeks compared to 15 using placebo (PO in human clinical study).³⁰⁹⁸
- IIa. 1) Cranberry extract at 100 mg/kg daily for 10 days reduced the **cardiotoxicity** of a single 15 mg/kg IP dose of **doxorubicin** given on the seventh day (PO in rats). The antioxidant extract reduced mortality and ECG changes, while inhibiting glutathione depletion, oxidized glutathione and malondialdehyde accumulation, and elevation of myeloperoxidase and lactose dehydrogenase, among other improvements to doxorubicin cardiotoxic effects.³⁰⁸⁰

CRUCIFERS

p. 120

Brassica spp. heads or leaves

Complementary Adjuncts

- IIa. + 1) The glucosinolate hydrolysis product indole-3-carbinol from cruciferous vegetables protected against **hepatotoxicity** from the antitumor drug **trabectedin** when given at 0.5% of the diet for 6 days prior, but it did not interfere with trabectedin's antitumor efficacy (PO in rats). A dietary concentration of only 0.1% indole-3-carbinol was not protective, nor was 0.2% of its acid condensation product, diindolylmethane.²¹⁷⁷
- 2) The isothiocyanate sulforaphane, derived mostly from broccoli sprouts, reduced **hepatotoxicity** activities induced by **cisplatin** when sulforaphane was given at 500 mcg/kg daily

for 3 days prior to the cisplatin (IP in rats). The reduced damage was a result of protection of liver mitochondrial function and antioxidant enzymes and prevention of oxidative stress.²⁹³⁴

DAN SHEN

Salvia miltiorrhiza root

p. 122

Drug Interactions

- Ia. + 1) The bioavailability and maximum plasma concentration of drug **fexofenadine** were reduced by 37.2% and 27.4%, respectively, following consumption of 3 g daily of dan shen extract for 10 days by 12 healthy men; the average clearance of fexofenadine was increased by 104.9% (PO in human study). This effect was due to induction of P-glycoprotein mRNA by diterpenoid components of dan shen, specifically cryptotanshinone and tanshinone IIA (*in vitro*).³⁴²⁴
- + 2) Though a single 1g dose of dan shen extract led to an 87% increase in maximum plasma concentration of **midazolam** after 1 dose of the drug, when 3 g of the extract was given daily for 10 days it decreased the maximum concentration of 1 dose of midazolam by 66.6%, half-life by 43.8%, and bioavailability by 79.9% in 12 healthy subjects (PO in human study).³⁴²⁵ Likewise, when 12 men were given extracts of 12 g of dan shen for 14 days, midazolam oral clearance was increased by 35.4% and the maximum concentration and bioavailability were decreased by 31.1% and 27.0%, respectively, but the half-life was not changed (PO in human study).³⁴⁴³
- A single (IP in rats) or a 3-day dose of 200 mg/kg of dan shen extract increased midazolam bioavailability (IP or PO in rats). The same single dose (IP or PO in rats) and 3-day dose (IP in rats) increased midazolam sleeping time, though a 500 mg/kg 3-day dose did so even more (PO in rats).³⁵⁶¹ Testing the extract component dihydrotanshinone I showed it inhibits CYP3A, while the dan shen components cryptotanshinone and tanshinone IIA induce CYP3A (*in vitro*).³⁴²⁵
- Ib. 1) The effect of **anticoagulants**⁴⁰⁴ can be increased, exemplified by **warfarin** (PO in human case reports).^{202,444,715}
- Dan shen ethyl acetate extract with major tanshinones given at 2 g/kg for 3 days increased oral warfarin steady state plasma concentration by 23% (PO in rats).³⁴⁴⁴

DEVIL'S CLAW

Harpagophytum procumbens roots and tubers

p. 124

Complementary Adjuncts

- IIa. 1) In animals with **neuropathic pain**, a subanalgesic dose of 3 mg/kg **morphine** combined with a 400 mg/kg devil's claw extract doses that had no aninociceptive effect alone led to significant antihyperalgesic and antiallodynic effects that were well-defined (IP in rats). The pain was induced by chronic constriction injury with ligation of the sciatic nerve, signs of sensitization were quantified as decreased paw withdrawal threshold from stimulation and allodynic threshold decrease in the left hindpaw 14 days after surgery. Devil's claw extract had a significant dose-dependent antiallodynic effect at 600 and 800 mg/kg when given alone.³⁷¹⁴

DOG ROSE

Rosa canina dried fruit (hips)

p. 126

Drug Interactions

- Ib. + 2) A 37-year-old man who had received a kidney transplant was given immunosuppressant drugs **cyclosporin** and azathioprin, the latter later replaced by mycophenolate mofetil, while consuming 1-1.5 liters of chamomile tea daily (PO in human case report). Cyclosporin levels were decreased to 150 mg/day until its trough levels were adequately maintained, until he was told to stop consuming chamomile tea, which he replaced with rose hips (*Rosa canina*) tea. In a few weeks, the cyclosporin trough levels decreased markedly until they reached a stable level, at which time the cyclosporin dosage was increased.³⁵⁷¹
- HOWEVER, it was assumed by the authors that the chamomile tea had inhibited CYP 3A4 metabolism of cyclosporin, based on a prior *in vitro* study,⁸⁴⁰ though in theory it could potentially

have been caused by rose hips tea inducing CYP 3A4 metabolism of cyclosporine. On the other hand, no evidence supports rose hips [dog rose] induction of CYP 3A4.

Complementary Adjuncts

- Ia. + 2) In 89 **rheumatoid arthritis** patients using **acetaminophen, NSAIDs, steroids** and disease-modifying anti-rheumatic drugs including **methotrexate, leflunomide, chloroquin**, or other biological antirheumatic drugs, those 44 taking 5 grams daily of rose-hip powder a significantly better health assessment disability index after 6 months than those on placebo (PO in human clinical study). The Physicians Global Scale and patient quality of life scores were also significantly better in those on rose-hip than in the placebo group. The drug intake of both groups did not differ at baseline or after 6 months.²⁹⁶²

DONG QUAI

p. 127

Angelica sinensis root

Complementary Adjuncts

- Ib. + 1) Among 31,938 Chinese **breast cancer** survivors who were treated with **tamoxifen**, almost half also used dong quai. The hazard ratio for subsequently developing endometrial cancer in the 157 cases that occurred was reduced significantly by dong quai use (PO in human population study).³⁵¹⁷
- IIa. + 4) Equal quantities of astragalus root (*Astragalus membranaceus*) and dong quai root were extracted with ethanol and water, the extracts combined, and 2.1 grams daily given with or without the ACE inhibitor **enalapril** to monitor **kidney fibrosis** and compared to enalapril alone (PO in rats). The tubulointerstitial fibrosis was reduced by the herbal extract and enalapril separately along with transforming growth factor- β 1 [TGF- β 1], but the herbal-drug combination had the greatest effect by significantly reducing TNF- α , collagen accumulation, fibroblast activation, tubular cell apoptosis more than enalapril alone.²⁷²⁸ A decoction of equal parts of the 2 roots given at the same dose was previously shown a decrease in TGF- β 1 puromycin-induced nephrosis similar to enalapril (PO in rats),²⁷²⁹ while 3.6 g/kg daily dose of a 5:1 mixture of astragalus and dong quai roots, respectively, as a decocted extract also modestly decreased kidney TGF- β 1 mRNA expression following streptozotocin-induced damage, similar to the ACE inhibitor benazepril (PO in rats).²⁷³⁰

ECHINACEA ANGUSTIFOLIA

p. 129

Echinacea angustifolia roots

(Echinacea, narrow-leaved coneflower, combflower, Sampson root, black Sampson)

Contraindications

- I. 1) **Allergic hypersensitivity** to plants in the Asteraceae family (empirical).^{777,1890}
A man with a long history of asthma and hay fever developed hypereosinophilia and very elevated IgE associated with abdominal cramps and occasional nausea and diarrhea for 3 years that began and ended with supplementation of an uncharacterized echinacea supplement (PO in human case report). Treatment with prednisone was finally able to be tapered off after he discontinued the echinacea which was suspected of causing an IgE-mediated allergic response.²⁷⁵⁹
- II. 4) *Echinacea angustifolia* root should be avoided in **autoimmune disorders** (speculative).⁴
HOWEVER, a review on echinacea safety concluded that contraindications in autoimmune disease are questionable (speculative), in that alkamides in lipophilic echinacea preparations suppress cellular immune responses. In some autoimmune cases, beneficial effects have been reported.³⁵⁷⁹

Drug Interactions

- III. 1) *Echinacea* spp. may offset the effects of **immunosuppressive drugs** (speculative).^{777,893}
HOWEVER, a review on echinacea safety concluded that contraindications with immune suppression are questionable (speculative), in that alkamides in lipophilic echinacea preparations

suppress cellular immune responses. In some autoimmune cases, beneficial effects have been reported.³⁵⁷⁹

Complementary Adjunct

- I. 1) In 26 adults of ages 38-79 years with **respiratory disorders** [chronic bronchitis, respiratory insufficiency, and asthma] receiving an autumnal **influenza vaccine** for types A and B, 12 were also given a standardized root extract for 1 month prior and for 2 months after the vaccination (PO in human clinical study). One extract tablet was given twice daily for 15 days, once daily for the next 15 days, then once every other day for 2 months. The hydroalcoholic extract tablet was 100 mg and was standardized to >2% echinacoside, >5% branched galacturonic polysaccharide, and <0.1% alkamides. The number of upper respiratory viral infections that occurred from the time of the vaccination until 4 months afterward was 5 including 3 with respiratory complications in those receiving only the vaccine, while those receiving the extract with the vaccine had only 1 viral respiratory infection with no complications. In 12 others receiving only the extract, 2 respiratory viral infections occurred including 1 with respiratory complications; the total leucocyte count, lymphocyte percentage, and IgG antibody levels all statistically increased in this group between baseline and day 105.³¹⁷⁸

ECHINACEA PALLIDA

p. 132

Echinacea pallida root or whole plant

Contraindications

- I. 1) **Allergic hypersensitivity** to plants in the Asteraceae family (empirical).^{777,1890}
A man with a long history of asthma and hay fever developed hypereosinophilia and very elevated IgE associated with abdominal cramps and occasional nausea and diarrhea for 3 years that began and ended with supplementation of an uncharacterized echinacea supplement (PO in human case report). Treatment with prednisone was finally able to be tapered off after he discontinued the echinacea which was suspected of causing an IgE-mediated allergic response.²⁷⁵⁹
- II. 4) *Echinacea angustifolia* root should be avoided in **autoimmune disorders** (speculative).⁴
HOWEVER, a review on echinacea safety concluded that contraindications in autoimmune disease are questionable (speculative), in that alkamides in lipophilic echinacea preparations suppress cellular immune responses. In some autoimmune cases, beneficial effects have been reported.³⁵⁷⁹

Drug Interactions

- III. 1) *Echinacea* spp. may offset the effects of **immunosuppressive drugs** (speculative).^{777,893}
HOWEVER, a review on echinacea safety concluded that contraindications with immune suppression are questionable (speculative), in that alkamides in lipophilic echinacea preparations suppress cellular immune responses. In some autoimmune cases, beneficial effects have been reported.³⁵⁷⁹

Complementary Adjuncts

- IIb. + 1) The 52% ethanolic extract of the whole plant given in water at a 10% concentration reduced **kidney damage** and **weight loss** caused by the chemotherapy drug **cisplatin** (PO in mice). This effect was due in part to restoring oxygen consumption in the kidneys.²⁷²⁶

ECHINACEA PURPUREA

p. 134

Echinacea purpurea aerial plant or whole plant

Contraindications

- I. 1) **Allergic hypersensitivity** to plants in the Asteraceae family (empirical).^{777,1890}
A man with a long history of asthma and hay fever developed hypereosinophilia and very elevated IgE associated with abdominal cramps and occasional nausea and diarrhea for 3 years that began and ended with supplementation of an uncharacterized echinacea supplement (PO in

human case report). Treatment with prednisone was finally able to be tapered off after he discontinued the echinacea which was suspected of causing an IgE-mediated allergic response.²⁷⁵⁹

Drug Interactions

Ia. + 1) *E. purpurea* whole fresh plant 8:1 extract, standardized to 0.25 mg/ml alkaloids, 2.5 mg/ml cichoric acid and 25.5 mg/ml polysaccharides, was given in 250 mg doses 3 times daily for 28 days to 16 healthy subjects taking lopinavir-ritonavir for the first 14 days (PO in human study). After these 14 days, there was no change in lopinavir bioavailability or peak concentration. After the extract was given 28 days, a single dose of fexofenadine and one dose of **midazolam** were then administered, and the midazolam bioavailability was significantly reduced as its clearance was increased. The fexofenadine pharmacokinetics were not significantly altered. This extract was therefore found to have a modest inducing effect on CYP 3A as shown with midazolam, but not enough to counter the CYP 3A inhibiting effect of ritonavir. It had no effect on Pgp activity as it applies to fexofenadine.³⁰⁹⁹

HOWEVER, when 800 mg of the whole plant extract was given twice daily for 28 days in another study, it had no significant effect on midazolam bioavailability (PO in human study).¹⁵⁸⁹ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²

III. 1) *Echinacea* spp. may offset the effects of **immunosuppressive drugs** (speculative).^{777,893}

HOWEVER, a review on echinacea safety concluded that contraindications with immune suppression are questionable (speculative), in that alkaloids in lipophilic echinacea preparations suppress cellular immune responses. In some autoimmune cases, beneficial effects have been reported.³⁵⁷⁹

Complementary Adjuncts

Ia. + 3) The dried juice dose of 500 mg daily together with 10 mg zinc, 15 mcg selenium and 50 mg vitamin C given to 37 chronic obstructive pulmonary disease [**COPD**] patients with acute upper respiratory tract infections treated with **ciprofloxacin** helped to lessen and shorten exacerbations compared with 32 given placebo, in a double-blind, randomized study of mostly male patients with a mean age of 66 years (PO in clinical study).²⁷⁹⁶

HOWEVER, the dried juice alone at 500 mg/day did not differ from placebo when combined with ciprofloxacin in treating upper respiratory tract infections in 36 subjects with COPD (PO in human clinical study).²⁷⁹⁶

IIa. + 1) A water-soluble polysaccharide complex from this species increased both the antitumor and the antimetastatic effects of **cyclophosphamide** in transplanted **lung carcinoma** (in mice).²⁸⁰⁹

HOWEVER, the tincture of this species, though it did not influence cytostatic therapy or change metastasis, did stimulate lung carcinoma tumor growth (in mice).²⁸⁰⁹

ECHINACEA PURPUREA root

p. 136

Contraindications

I. 1) **Allergic hypersensitivity** to plants in the Asteraceae family (empirical).^{777,1890}

A man with a long history of asthma and hay fever developed hypereosinophilia and very elevated IgE associated with abdominal cramps and occasional nausea and diarrhea for 3 years that began and ended with supplementation of an uncharacterized echinacea supplement (PO in human case report). Treatment with prednisone was finally able to be tapered off after he discontinued the echinacea which was suspected of causing an IgE-mediated allergic response.²⁷⁵⁹

II. 4) *Echinacea purpurea* root use should be avoided in **AIDS** and **HIV infection** (speculative).^{4,17}

HOWEVER, in a 15-day open-label trial with 15 HIV patients receiving anti-retroviral treatment with darunavir/ritonavir, 500 mg of the root extract given every 6 hours for 14 days was well tolerated and did not significantly affect the drug pharmacokinetics (PO in human clinical study).²⁷⁹³

Drug Interactions

- Ia. 1) *Echinacea purpurea* root extract at 1.6 g daily for 8 days reduced overall bioavailability of IV **midazolam** in 12 subjects (PO in human study).¹⁵⁸⁸

HOWEVER, when 15 HIV patients took 500 mg of the root extract every 6 hours for 14 days, the extract did not significantly affect the bioavailability or activity in the group of an oral combination of the CYP 3A4 protease inhibitor substrates darunavir and ritonavir, though a few individuals showed up to 30% less bioavailability for darunavir while a couple showed more (PO in human clinical study).²⁷⁹³ Likewise, the metabolism of CYP 3A4 protease inhibitor substrate etravirine was not significantly impacted by 1500 mg of the root extract daily for 14 days in 15 HIV-infected patients.³⁵³⁸ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²

Complementary Adjuncts

- Iia. + 1) A water-soluble polysaccharide complex from this species increased both the antitumor and the antimetastatic effects of **cyclophosphamide** in transplanted **lung carcinoma** (in mice).²⁸⁰⁹

HOWEVER, the tincture of this species, though it did not influence cytostatic therapy or change metastasis, did stimulate lung carcinoma tumor growth (in mice).²⁸⁰⁹

ELEUTHERO

p. 140

Eleutherococcus senticosus syn. *Acanthopanax senticosus* root

Drug Interactions

- III. 2) Eleuthero association with falsely elevated **digoxin** levels in the absence of toxic effects was presumably due to a digoxin assay interaction (*ex vivo* in human case report).⁹⁰⁷

A new analyzer technology from Abbott Laboratories has led to development of 2 analyzers, iDig and cDig, using specific monoclonal antibody against digoxin for which "Siberian ginseng" does not interfere with detection of digoxin (*in vitro*).³⁴³⁵

Complementary Adjuncts

- Iia. + 1) In alloxan-induced diabetes, **kidney toxicity** and **hepatotoxicity** from **metformin** could be reversed when 200 mg/kg the root polysaccharide (ASP) was combined with 2 mg/kg metformin daily for 28 days (PO in rats). In diabetic rats receiving the ASP with metformin, there were significant decreases in creatinine and urea levels, as well as in total bilirubin, the transaminases AST and AST, and alkaline phosphatase and significantly increased superoxide dismutase, compared to diabetic controls and those receiving only metformin. In addition, in comparison to metformin-only rats, the addition of ASP resulted in reductions, though not significant, in blood glucose, total cholesterol and triglycerides, and oxidative stress marker TBARS and increases in body weight, liver glycogen, glutathione, and glutathione peroxidase.³⁷¹⁸

ENGLISH LAVENDER

p. 141

Lavandula officinalis syn. *Lavandula angustifolia* syn. *Lavandula vera* flowers

Complementary Adjuncts

- Ia. + 2) In randomized, placebo-controlled, double-blind study of 100 patients of ages 19-64 years with **renal colic**, half were given 75 mg IM of the NSAID **diclofenac**, while the other 50 were the same diclofenac treatment combined with aromatherapy with 2% lavender oil (IH in human clinical study). Using a visual analogue scale to assess pain severity, after 30 minutes the combined treatment of the drug with lavender oil inhalation provided significantly greater relief from pain than did the drug alone, especially among female patients.³⁵³³

ENGLISH PLANTAIN

p. 142

Plantago lanceolata leaves

Complementary Adjuncts

- Iia. + 1) An aqueous extract was shown to significantly reduce the score for **stomach ulcers** from **indomethacin** better than the standard drug misoprostol at 280 mcg/kg when the extract was given at 400 mg/kg (PO in mice).²⁸³⁸

- + 2) An aqueous extract was shown to significantly reduce the score for **stomach ulcers** from **cysteamine** when the extract was given at 400 mg/kg, though not as well as the standard drug ranitidine at 70 mg/kg (PO in mice).²⁸³⁸

EUCALYPTUS

p. 146

**Eucalyptus* spp. leaves

Drug Interactions

- II. + 3) When eucalytus (*E. globulus*) dried leaf was given at doses of 3.25 and 6 mg/kg, comparable to normal human doses, together with **diazepam**, both doses after 30 minutes inhibited the drug's depressant mental effects and especially its musculoskeletal relaxant activity (PO in mice).³⁵¹⁹

EUROPEAN PENNYROYAL

p. 148

Mentha pulegium herb

Complementary Adjuncts

- Ia. + 1) In a randomized, placebo-controlled, double-blind study of 100 patients with **functional dyspepsia** taking 40 mg of **famotidine** once daily, 330 mg daily of a 19.4:1 extract made with 30% ethanol was given 3 times daily for 2 months to half of the patients (PO in human clinical trial). Compared to placebo and baseline, the extract significantly reduced the Hong Kong dyspepsia index and the rate of *H. pylori* infection. In addition, significant reductions were seen with upper abdominal bloating and dull ache belching, and total dyspepsia scores, compared to placebo. Quality of life was also improved significantly by the extract, in comparison with the placebo.³⁷¹⁵

EVENING PRIMROSE

p. 148

Oenothera biennis seed oil

Complementary Adjuncts

- Ia. + 4) In a randomized study, 40 acne patients received **isotretinoin** treatment for 8 weeks, with or without 2700 mg of evening primrose oil 3 times daily, providing 240 mg of gamma-linolenic acid, to observe the effect on the isotretinoin adverse effect of **xerotic cheilitis** (PO in human clinical study). After 8 weeks there was a significant reduction in transepidermal water loss of the lips in the patients receiving EPO which improved the xerotic cheilitis.³⁴⁷⁸

FENUGREEK

p. 151

Trigonella foenum-graecum seed

Drug Interactions

- Ia. 1) Fenugreek hydroalcoholic extract, in type 2 diabetes patients using **sulfonylureas** or **biguanides**, or both, significantly decreased HbA_{1c}, lowered fasting and 2-hour postprandial insulin levels, and increased insulin sensitivity, compared to placebo (PO in human clinical study).¹³⁶⁰

In 69 type 2 diabetic patients taking sulfonylureas, 46 were given 6 pills of fenugreek total saponins 3 times daily for 12 weeks, while the others received placebos (PO in human clinical study). The fenugreek group had significantly lower fasting and 2-hour postprandial blood glucose, HbA_{1c}, and clinical symptom scores, compared to controls.²⁸¹⁵

Hypoglycemic activity was also shown in diabetes melitus type 2 with 100 grams defatted seed powder for 10 days with 15 patients taking **glyburide (glibenclamide)**, **glipizide**, and/or **metformin** (PO in human clinical study).¹⁶⁴⁵ In 10 type 2 diabetic patients on stable glibenclamide using 25 grams of the powdered seeds daily for 15 days in a crossover design, plasma glucose was significantly lower following an IV glucose tolerance test (PO in human clinical study).¹³⁰ In 21 patients taking 15 grams powdered seeds soaked in water, of whom 10 were using glibenclamide and metformin and 7 glibenclamide alone, postprandial levels were significantly reduced (PO in human study).⁹⁶¹ In 20 patients with mild cases of type 2 diabetes,

but not in 20 with severe cases, using 5 grams of fenugreek powder daily without oral hypoglycemic drugs significantly reduced fasting and postprandial blood sugar after 1 month (PO in human clinical study).³³⁹

Complementary Adjuncts

- Ia. + 1) In a placebo-controlled, double-blind study of 50 patients with **Parkinson's disease**, 600 mg/day of a standardized extract of fenugreek was given for 6 months as an adjuvant to **L-dopa** (PO in human clinical study). The United Parkinson's Disease Rating Scale total score showed a rise of 0.01%, compared to a 13.36% rise for placebo. In addition, scores of several other tests were around 5 times better with the fenugreek extract than with placebo. Tolerability and safety of the extract were excellent.³³⁹⁴
- + 2) In a randomized, placebo-controlled, double-blind study of 101 university students with moderate to severe primary **dysmenorrhea**, 51 took 2-3 900 mg capsules of fenugreek 3 times daily during the first 3 days of menstruation over 2 menstrual cycles (PO in human clinical study). In addition to having significantly reduced menstrual pain severity and duration for both cycles in comparison to placebo, the fenugreek group also used significantly fewer **NSAID** tablets such as **ibuprofen** and **mefenamic acid** on average. The analgesics were taken an hour or more after the fenugreek or placebo capsules and after recording the pain severity.³⁴¹⁶
- IIa. 1) A 1% aqueous extract of fenugreek seeds with **ethanol** for 60 days reduced **hepatotoxicity** and **brain damage** compared to alcohol alone (PO in rats).¹⁴⁸⁴
- After 30 days of 6 g/kg/day of alcohol alone, using 200 mg/kg/day of a 12.5-16.5:1 methanolic extract dissolved in water for another 30 days in addition to the ethanol led to significant reductions in protein carbonyl content and lipid peroxidation products, increased activity antioxidant enzymes, and restoration of thiol group levels compared to controls (PO in rats). These effects were equivalent to the positive control: 100 mg/kg/day of silymarin.³¹⁵⁶

FO-TI

p. 156

Polygonum multiflorum = *Reynoutria multiflora* root
(Chinese knotweed; Ch: he shou wu)

Contraindications

- I. 1) Avoid in **diarrhea**, due to its irritant properties (empirical)¹⁵⁰ associated with its anthoquinone component emodin.³³⁶⁷

FRANKINCENSE [now see: INDIAN FRANKINCENSE]

p. 158

FRENCH MARITIME PINE

p. 158

Pinus pinaster = *Pinus maritima* bark fraction

Complementary Adjuncts

- Ia. 1) The polyphenol fraction used in **high blood pressure** allowed significant reduction of **nifedipine** dosage compared to placebo (PO in human clinical study).¹⁶²³
- Also, 150 mg/day Pycnogenol for 8 weeks compared to placebo significantly reduced the capillary filtration leading to tissue edema associated with nifedipin used in the treatment of hypertension in 30 patients (PO in human clinic study). Likewise, the capillary filtration associated with **ACE inhibitors** in 23 patients was also significantly reduced by the same dose after 8 weeks, compared to placebo.²⁷⁹⁴
- 2) Use of 150 mg of Pycnogenol daily for 3 months in **osteoarthritis** with concurrent **NSAIDs** and/or **analgesics** led to a significant reduction in inflammation and pain scores and less drug use, compared to baseline and placebo (PO in human clinical study).²³²⁴
- Also, 150 mg/day of Pycnogenol for 3 months in a randomized, double-blind, placebo-controlled trial with 37 knee osteoarthritis patients led to significantly reduced scores for total symptoms, pain, and physical function at 60 and 90 days, while NSAIDs and **COX-2 inhibitors**

- used were reduced significantly after 30, 60, and 90 days and placebo use increased significantly after 90 days (PO in human clinical study).²⁷⁹⁵
- + 5) When 40 mg Pycnogenol with 70% procyanidins and 80 mg bilberry (*Vaccinium myrtillus*) extract with 36% anthocyanins as a standardized combination was given once daily in the morning to 79 **ocular hypertension** patients either alone or together with **latanoprost** eye drops and compared to latanoprost alone, the extract combination with the drug was best for lowering intraocular pressure and enhancing retinal blood flow (PO in human clinical study). The extract alone eventually was similarly effective as the drug for lowering intraocular pressure, but it took 24 weeks for the extract compared to only 4 weeks with latanoprost. The only adverse effects were those related to latanoprost.²⁹⁶⁶
 - + 6) When given to 33 patients with **allergic asthma**, 100 mg daily of Pycnogenol for 6 months decreased the daily dosage of the inhaled **corticosteroid** drug **fluticasone propionate** in 55%, whereas just 6% of those 32 taking only the corticosteroid reduced the dosage (PO in human clinical study). None of the Pycnogenol group increased fluticasone dosage, but 18.8% of the other group did. In addition to reducing or maintaining the drug dose, asthma symptoms were significantly reduced and breathing parameters significantly improved only in the Pycnogenol group, while they also used less of the rescue medication **salbutamol** than those taking only fluticasone.³⁰⁹³

In a randomized, placebo-controlled, double-blind 3-month study of 60 patients ages 6-18 years with **childhood asthma**, the half receiving Pycnogenol at 1 mg/lb of body weight daily, along with the oral medication **zafirlukast** and the rescue inhalant **albuterol**, had significantly better symptom relief and pulmonary function and significantly less albuterol use and urinary leukotrienes after 1, 2, and 3 months than the half who took placebo with their medications (PO in human clinical study).³⁰⁹⁴
 - + 7) In a randomized, placebo-controlled, single-blind trial Pycnogenol mixed in a 50:50 solution of glycerin and water was applied locally at 1 mg/kg/day 3 times daily for 1 week in children ages 6-15 years to **oral mucositis** induced by **chemotherapy** including **mitoxantrone**, **chlorambucil** and **prednisolone** for non-Hodgkin lymphoma or other drugs for acute lymphoblastic leukemia and acute myeloid leukemia; it significantly reduced the WHO grade of the mucositis for Grades I to III, compared to those treated locally only with glycerin (TP in human clinical study). While only 4.2% healed completely and 12.5% improved in the glycerin group, 58.3% healed completely and 37.5% improved in the Pycnogenol in glycerin group.³³³³

GARLIC

p. 161

Allium sativum cloves

Drug Interactions

- Ia. 1) Two garlic caplets per day for 3 weeks in 10 healthy subjects reduced **saquinavir** by 49%-54% compared to baseline (PO in human study).¹²¹⁰

When 600 mg garlic extract with 3.6 mg allicin was taken by 10 healthy males twice daily for 21 days, though it decreased the average saquinavir bioavailability by 15%, it did not change bioavailability of CYP3A4 substrate simvastatin (PO in human study). The CYP3A4 expression was reduced by only 4% in the liver and 13% in the duodenum, but intestinal P-glycoprotein increased by 31%. So, since saquinavir is a substrate of both CYP3A4 and Pgp, the induction of Pgp best explains the decreased saquinavir levels, in spite of less CYP3A4 metabolism.³²²³
- + 3) The use of 300 mg garlic tablets with 0.6% allicin 3 times daily together with **metformin** for 24 weeks by 30 patients with diabetes type 2 resulted in significantly lower levels of fasting blood sugar, total cholesterol, LDL-cholesterol, and triglycerides compared to diabetics who took only metformin (PO in human clinical study). HDL-c was significantly increased in the garlic group after 12 weeks. No adverse effects were reported.³⁰⁸⁹

Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²

- + 4) When 16 subjects given 10 ml of aged garlic extract [derived from 6-7 garlic cloves] daily for 3 months, the peak plasma concentration of **acetaminophen** was significantly increased after 1 month, while after 2 months its bioavailability significantly increased and renal clearance decreased (PO in human study). [Acetaminophen, or **paracetamol**, requires metabolic conversion for its bioactivation.] The extract caused no significant effect after 3 months on CYP 2E1 metabolism of acetaminophen, but the bioavailability of its inactive glucuronide conjugate did significantly increase. The extract used minced garlic incubated in 15-20% alcohol for 8-12 months and had as its major constituent S-allyl-L-cysteine, but very little diallyl sulfide.¹⁸¹⁵

Garlic and its S-allyl components inhibit cytochrome P450 2E1 oxidation of acetaminophen and thereby reduce its bioactivation (*in vitro*).⁵⁴⁰

- IV. [1] May enhance cholesterol-lowering agents due to additive effects (speculative).⁷⁷⁷

900 mg daily of garlic tablets with 0.6% allicin in 30 diabetes type 2 patients for 24 weeks resulted in significantly lower total cholesterol, LDL-cholesterol, and triglycerides compared to 30 controls (PO in human clinical study).^{3089]}

Complementary Adjuncts

- Ia. + 3) Aged garlic extract at 960 mg/day containing 2.4 mg S-allylcysteine was given for 12 weeks to 25 patients with **hypertension** treated with **ACE inhibitors** [24%], **angiotensin II receptor antagonists** [48%], **calcium channel blockers** [44%], **beta-blockers** [40%], and/or **diuretics** [60%] and compared to 25 treated placebo-control subjects in a randomized, double-blind trial (PO in human clinical study). In patients with hypertension uncontrolled by drugs having a systolic blood pressure > 140 mm Hg, the addition of the aged garlic extract lowered the blood pressure significantly compared to controls.²⁷⁵⁷

- + 4) When 60 patients with **tubercular lymphadenitis** were treated with a 4-drug antitubercular therapy of **isoniazid**, **rifampicin**, **ethambutol**, and **pyrazinamide** for 60 days, half were given 3-6 pearls of garlic extract in divided doses on days 31-45 (PO in human clinical study). The garlic relieved the dyspepsia in all the patients receiving it with the drugs, and significantly increased the antitubercular activity of the serum, compared to the drugs alone. Liver function blood tests remained normal in both groups.³¹⁶⁹

An aqueous extract of garlic cloves has been shown to inhibit the growth of 2 strains of multidrug-resistant *Mycobacterium tuberculosis* by 72% each (*in vitro*)³¹⁷⁰ and to reduce the individual minimum inhibitory concentration of the drugs isoniazid and rifampicin (*in vitro*).³¹⁷¹

- Ib. + 1) A woman with chronic symptomatic group B **streptococcus vaginitis** resistant to antibiotics obtained relief with a half clove of freshly cut garlic inserted each night for 1-4 weeks along with local treatment with 0.5 g of 1% **chlorhexidine** gel every 4-7 nights (vaginally). Of 8 other cases lasting from 6 months to 5 years and unsuccessfully treated with one or more 10-14 day courses of antibiotics such amoxicillin or azithromycin, and in most cases also with oral probiotics or local tea tree oil (*Melaleuca leucodendron*), 7 then using only fresh cut garlic obtained symptomatic relief while 1 found the local fresh garlic too irritating to use (vaginally).²⁷¹¹

- IIa. 4) Raw garlic extracts protected from **stomach damage** by 100% **ethanol** (PO in rats).¹²⁶³

The homogenized bulb or leaves at 250 mg/kg for 5 days, when followed by a single **hepatotoxic** dose of **alcohol**, resulted in higher levels of glutathione and ascorbic acid and lower malondialdehyde, while significantly enhancing catalase and glutathione reductase activities, compared to those exposed to ethanol only (PO in rats).³¹⁶⁶

- 5) Aged garlic extract helped protect animals from **cardiotoxicity** by **doxorubicin** (IP in mice).¹²⁷³

In addition, when garlic aqueous extract was given at 125 and 250 mg/kg after doxorubicin damage to heart muscle, it significantly and dose-dependently reduced cardiotoxicity markers in the heart tissue and serum, decreased changes induced in ECG parameters, and increased antioxidant enzyme activity reduced by doxorubicin (PO in rats). The therapeutic effects were enhanced for both doses when combined with 60 mg/kg **atorvastatin**.³³¹³

6) Garlic leaves as 2% of diet¹⁹¹¹ reduced **kidney toxicity** from **gentamicin**, preventing necrosis and oxidative changes (PO in rats).^{1911,1912,1913}

Likewise, powdered dry garlic bulbs fed as 4% of the diet for 27 days before 3 days of gentamicin injections led to significantly reduced AST levels, a marker of liver inflammation, and improved antioxidant status (PO in rats).³³⁸⁷

- + 7) The intake for 3 weeks of fresh garlic homogenate in 125 or 250 mg/kg doses or equivalent amounts of S-allyl cysteine sulfoxide [SACS; 0.111 or 0.222 mg/kg], alone or together with the ACE inhibitor **captopril** in the last week, for fructose-induced **high blood pressure** led significant reductions in systolic blood pressure, heart rate, cholesterol, triglycerides, and glucose compared to the fructose control group (PO in rats). The greatest reductions occurred with the high garlic homogenate dose with captopril, suggesting greater biological activity than SACS alone. SACS demonstrated synergistic effects with captopril for reducing blood pressure (PO in rats) and in ACE inhibition (*in vitro*).²⁷⁵⁶

Before **heart damage** induced by isoproterenol, 250 mg/kg of garlic homogenate was given for 30 days including the last 7 days with captopril (PO in rats). While the garlic and captopril both significantly prevented superoxide dismutase and catalase reductions in heart tissue induced by isoproterenol, the combination was even more effective in protecting the myocardium from injury.³⁵¹⁸

GENTIAN

p. 166

**Gentiana lutea* roots

Complementary Adjuncts

- IIa. 1) The hydroethanolic extract was found to reduce testicular damage induced by **ketoconazole** when given for 3 weeks prior and continued during the 5 days of the drug IP administration (PO in rats).³³⁵³

GINGER

p. 166

Zingiber officinale rhizome

Contraindications

- II. 2) Avoid large doses **prior to surgery** to avoid risk of hemorrhage (speculative),⁴²⁸ due to inhibition of platelet aggregation (*in vitro*).^{292,294}

In a placebo-controlled, crossover study with 30 healthy men, 50 grams of butter given with or without 5 grams of powdered ginger in capsules led to an 18.8% decrease in fibrinolytic activity with only the butter but a 6.7% fibrinolytic activity increase with the butter plus ginger (PO in human study).³⁴⁴⁹

HOWEVER, a 2015 systematic literature review that included 8 clinical trials and 2 observational trials concluded that the evidence is equivocal on whether ginger affects coagulation and platelet aggregation (PO in humans). The results appear dependent upon dosage and subject characteristics such as being healthy or not.³⁵⁴³

Drug Interactions

- II. + 2) The oral administration of **cyclosporine** in conjunction with, or 2 hours after, 5 ml/kg ginger juice led to significantly reduced peak serum concentrations [by 71% and 51%, respectively] and bioavailability [by 63% and 40%, respectively], compared with cyclosporine consumption alone (PO in rats). There was no reduction in peak serum concentration or bioavailability when cyclosporine was injected IV in combination with PO ginger juice, indicating the interaction most likely occurred in the absorption phase. Ginger juice did not alter the efflux of rhodamine 123 from the serosal to the mucosal surface of jejunum or ileum section, demonstrating that it did not increase the activity of P-glycoprotein as a means of reducing cyclosporine absorption.³⁴⁷²
- + 3) In a study of pre-treatment with ginger juice, grapefruit juice, or water, bioavailability of **tacrolimus** was significantly increased by the ginger and grapefruit juice in comparison with

water (PO in rats). Grapefruit juice is a known inhibitor of intestinal CYP 3A4 of which tacrolimus is a substrate.³⁶⁰⁶

Complementary Adjuncts

Ia. 1) When 1.0 gm of powdered ginger was given prior to surgery to 20 women, it reduced **nausea** from anesthetics **thiopental**, **alcuronium**, and/or **vecuronium** compared to 20 controls (PO in human clinical study).⁵⁰⁸

The same 1 gram dose of powdered ginger given 1 hour before surgery with **anesthesia** in a randomized, placebo-controlled, double-blind study with 160 patients resulted in a significantly lower nausea score average and a borderline significant lower frequency of nausea 2 hours after surgery, compared to those receiving placebo (PO in human clinical study). While nausea score and frequency were also lower with ginger than placebo after 4 and 6 hours post operation, the differences were not significant.³⁴¹⁷

2) A study of **osteoarthritis** used extracts from ginger and galangal; **acetaminophen** was allowed for pain (PO in human clinical study). Reduced pain on standing after using the extract was significantly better than for placebo, and stiffness and pain after walking were also improved by the extracts.¹⁴⁰⁹

A 1-month randomized, placebo-controlled, double-blind study using 30 mg/day of a 33.3:1 ginger ethanolic extract or 400 mg ibuprofen 3 times daily or placebo in groups of 40 each of osteoarthritis patients with moderate to severe pain showed that scores for pain and regressive pain after rising were significantly greater for placebo than for the extract or ibuprofen (PO in human clinical study). Acetaminophen was allowed in both groups, and there was no significant difference in pain scores between ginger extract and ibuprofen.³³¹⁴ Twenty knee osteoarthritis patients received a capsule with 250 mg supercritical carbon dioxide extract of ginger 4 times daily or placebo for 12 weeks in a 6-month randomized, placebo-controlled, double-blind, crossover trial and used handicap and the visual analog scale for pain on movement and as outcome measures (PO in human clinical study). Acetaminophen was allowed in both groups, and at the end of the study, the ginger extract group had highly significant decreased handicap and pain on movement compared to placebo.³³¹⁶

A randomized, double-blind, controlled study of 43 osteoarthritis patients with former gastropathy or dyspepsia from NSAIDs compared giving 200 mg/day of a 20:1 ginger extract in 170 mg lipid combined with 500 mg glucosamine to 21 patients to giving 100 mg diclofenac to 22 patients for 4 weeks (PO in human clinical study). Afterward, the diclofenac group had increased severity of dyspepsia pain, stomach mucosa degeneration, and a decrease in stomach prostaglandins (PG), while ginger group had no change in stomach pain and increased levels of PGE1, PGE2, and PGF α indicative of mucosal protection. Both groups had significantly lower osteoarthritis pain on standing and moving.³³¹⁵

3) Ginger before and after chemotherapy controlled **nausea and vomiting** from **cyclophosphamide** (PO in human clinical study).¹⁵⁹⁸

When 500 mg dried and powdered ginger 3 times daily for 4 days was given to advanced breast cancer patients with **nausea** from standard **chemotherapy** of **docetaxel**, **epirubicin**, and cyclophosphamide while being treated with the standard antiemetic regimen of **granisetron** plus **dexamethasone**, those 37 who received ginger had significantly reduced nausea from 6-24 hours postchemotherapy compared to the 41 patients using only standard antiemetics, but not beyond the first day (PO in human clinical study).³⁰⁹² In a randomized, placebo-controlled, double-blind study with 51 patients receiving emetogenic chemotherapy and antiemetics, nausea-related quality of life was assessed through 3 chemotherapy cycles in which 4 capsules each with 300 mg ginger extract standardized to 5% gingerols were given with chemotherapy and for 4 days afterward (PO in human clinical trial). In 84% the chemotherapy was moderately emetogenic and in 16% it was highly emetogenic. In the first chemotherapy cycle there were significant improvements in the global quality of life, chemotherapy-induced nausea [CIN] quality of life, CIN and vomiting quality of life, and less fatigue, compared to placebo. In the third cycle, only

global quality of life and less fatigue were significantly improved in comparison to placebo. Adverse effects with ginger extract were no different than with placebo.³⁷⁰² In a randomized, placebo-controlled, single-blind, crossover study, 60 breast cancer patients were using either high emetic risk chemotherapy, 75% **5-flouracil**, epirubicin, and cyclophosphamide and 11.7% docetaxel, doxorubicin, and cyclophosphamide, or were given low emetic risk docetaxel alone (IH in human clinical study). Ginger essential oil aromatherapy on a necklace was used for 5 days, and the same was done with artificial ginger fragrance placebo. The ginger essential oil led to a significant reduction in the score for acute nausea, but it was not sustained. The essential oil also significantly improved global health status, role functioning, and appetite loss.³⁵³⁷

4) In a randomized crossover study with 48 gynecologic cancer patients receiving **cisplatin** therapy along with the antiemetic drug **metoclopramide** 8 times the first day, 1 gram daily of ginger for the first 5 days after **chemotherapy** was as effective in controlling **nausea and vomiting** as was continuing for 5 days the standard drug metoclopramide which was more associated with restlessness (PO in human clinical study).²⁵³⁴

In high emetogenic chemotherapy cycles with cisplatin and **doxorubicin** for bone sarcoma in 25 children and 35 young adults, when ginger capsules or placebos were added to treatment with the antiemetic drugs **ondansetron** and **dexamethasone** to help control the drug-induced nausea and vomiting, compared to placebo the ginger significantly reduced acute moderate to severe nausea [93% vs. 56%, respectively] and vomiting [77% vs. 33%, respectively] (PO in human clinical study). Likewise, compared to placebo the ginger decreased significantly the delayed moderate to severe nausea [73% vs. 26%, respectively] and vomiting [47% vs. 15%, respectively]. For patients weighing 20-40 kg, 3 doses of 334 mg of ginger were used, while those from 40-60 kg received 2 doses of 800 mg each at 1 hour before and 3 after and a 400 mg dose 8 hours after chemotherapy infusions.²⁹⁰⁹ In highly emetogenic chemotherapy that was mostly **anthracycline-** or **platinum-**based, all 88 patients received ondansetron, metoclopramide, and dexamethasone, and 42 additionally received 10 mg of 6-gingerol from ginger twice daily for 12 weeks, while 46 were given placebo (PO in human clinical study). The gingerol group had a significantly higher complete response to the antiemetics than the placebo group (77% vs. 32%), and a significantly better appetite score and quality of life and significantly less grade 3 fatigue than those on placebo.³⁶²²

- + 7) In a randomized, placebo-controlled, double-blind trial with 41 patients with **diabetes type 2** treated with **oral hypoglycemics**, 22 received 2 grams daily of ginger powder for 12 weeks (PO in human clinical trial). After 12 weeks, the ginger group had significantly reduced fasting blood sugar, glycosylated hemoglobin, apolipoprotein B and malondialdehyde compared to baseline and to the placebo group. Those using ginger also had a significantly increased level of apolipoprotein A.³⁵⁰¹
- + 8) In a randomized, placebo-controlled, double-blind study of 60 tuberculosis [TB] patients being treated with the anti-TB drugs **isoniazid**, **rifampin**, **pyrazinamide**, and **ethambutol** known to induce gastrointestinal [GI] adverse events such as **nausea and vomiting** and **hepatotoxicity** in up to 36% of patients, 500 mg of ginger was given to half of them ½ hour prior to the daily dose of anti-TB drugs for 4 weeks (PO in human clinical study). With nausea as the most common adverse GI event, those 70% with this in the ginger group were significantly fewer and less severe than the 90% with nausea in the placebo group. Vomiting occurred with 9.8% of those taking ginger versus 47.1% of those on placebo. Hepatotoxicity resulted in 16.7% of the ginger group, compared to the 36.7% with liver toxicity in the placebo group.³⁶⁰²
- + 9) In a randomized, controlled, double-blind study of 67 women with **vaginal candidiasis**, a vaginal cream with 1% **clotrimazole** was used by 34 once daily for 7 days, while 33 used a cream with 1% clotrimazole and ginger extract (TP in human clinical study). The group using the cream with ginger had significantly less burning, itching, and cheesy secretion than the other group after 1 week. There was no significant difference in recurrence at the 1-month follow up.³⁷¹⁷

- IIa. 1) Ginger extract significantly reduced mucosal **stomach damage** by 70% **ethanol (alcohol)** by inhibiting reduction of mucin content (PO in rats).⁴⁹⁸
 Ginger as 0.05% of the diet for 8 weeks followed by an acute exposure to ethanol showed gastroprotective effects by significantly increasing activity of the endogenous antioxidant enzymes superoxide dismutase, glutathione reductase, and glutathion-S-transferase in the stomach and intestinal mucosa and increasing mucin content in stomach mucosa, compared to having no exposure to the spice (PO in rats).³³⁴⁷
- + 3) A 50% ethanol extract given at daily doses of 400 mg/kg with 20 or 80 mg/kg of **atorvastatin** for 4 weeks significantly decreased **high cholesterol** more than the atorvastatin doses given alone or the control (PO in rats). Ginger extracts significantly diminished the reductions by atorvastatin of liver superoxide dismutase and catalase levels. In addition, the combinations of ginger extract with the 2 atorvastatin doses significantly reduced the atorvastatin-induced serum **aminotransferase elevations** and increases in liver malondialdehyde and nitric oxide, so that the lower atorvastatin combination dosage no longer caused significant elevations of these levels.²⁸⁴⁹
- + 4) An ethanolic ginger extract, when given at 200 to 600 mg/kg together with 2.5 mg/kg **morphine**, significantly and dose-dependently enhanced the morphine analgesia in reducing the response to **pain** induced by radiant heat, compared to morphine alone (IP in rats).³³²¹
- + 5) The **mineral absorption** of **calcium, iron, and zinc** were all significantly improved with the addition of 0.05g% of ginger to the diet, compared to the same diet without ginger (PO in rats). Calcium absorption was improved the most. Ginger increased the uptake of iron better than either piperine or capsaicin.³⁴⁷¹
- + 6) When given concurrently with a 600 mg/kg IP dose of **acetaminophen** that by itself induces **hepatotoxicity**, 100 mg/kg of powdered ginger as an aqueous suspension significantly reduced liver toxicity markers alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP], along with lowering plasma bilirubin (PO in rats). The marker of oxidative stress malondialdehyde [MDA] was also reduced, while hepatic necrosis and cellular vacuolization were substantially decreased. The effects of ginger were comparable to vitamin E.³⁴⁷⁵ A hydro-alcoholic extract of ginger at 200 mg/kg given 1 hour before a single 3 g/kg oral dose of acetaminophen significantly reduced the activities of serum transaminases and ALP, compared to the acetaminophen dose alone that induced hepatotoxicity (PO in rats). MDA was likewise significantly reduced, while superoxid dismutase and glutathione-S-transferase was significantly increased with the extract before the drug, compared to acetaminophen without it. Centrilobular necrosis from acetaminophen toxicity was greatly diminished with extract use.³⁴⁷³ In a study in which 0.1 ml/kg ginger oil extracted with alcohol was given 2, 6, and 10 hours after a 600 mg/kg hepatotoxic dose of acetaminophen PO, serum AST, ALT, ALP, and sorbitol and glutamate dehydrogenases were all significantly reduced (PO in rats).³⁴⁷⁴
- + 7) The **kidney toxicity** involving tubular and renal cell damage from **gentamicin** was prevented when ginger hydroalcoholic extract was given at 200 mg/kg for either 3 days before, or 3 days before plus 7 days during, gentamicin 80 mg/kg IP administration (PO in rats). When ginger extract was only given for 10 days after the gentamicin 7-day exposure, there was no benefit.³⁶⁵⁹

GINKGO

p. 170

Ginkgo biloba leaves

Contraindications

- I. 2) Avoid or use caution in **bleeding disorders**^{428,1890,2960} due to potential association with hemorrhage (PO in human case reports).^{195,525,1190,1191,1449}

In a retrospective population study of about 200,000 ambulatory patients in the Taiwan Longitudinal Health Insurance Database, 7700 using ginkgo extract showed significantly higher risks of hemorrhage among males and those ≥ 65 years of age (PO in human study).²⁹⁶⁰

HOWEVER, In a randomized, placebo-controlled, double-blind crossover study with 50 healthy male subjects, 120 mg of EGb 761 twice daily for 1 week did not show any evidence of

inhibition of platelet aggregation or blood coagulation, based on 29 parameters assessed (PO in human study).³⁴⁴⁵

- II. 1) Do not use before elective **surgery** (speculative)^{428,703,1309,1310,1782,1890} since ginkgo may contribute to hemorrhage.

In a retrospective population study of about 200,000 ambulatory patients in the Taiwan Longitudinal Health Insurance Database, 7700 using ginkgo extract showed significantly higher risks of hemorrhage among males and those ≥ 65 years of age (PO in human study).²⁹⁶⁰

2) Patients possibly predisposed to **seizures** should avoid or use cautiously (speculative). Two epilepsy patients who had been stabilized with sodium valproate without a seizure for 1.5 and 2.0 years experienced 3 to 4 seizures within two weeks of beginning use of 120 mg daily of ginkgo extract (PO in human case reports). After two days of being off the ginkgo extract, no more seizures occurred over the next 18 and 4 months, respectively.¹²⁴⁷

A fatal breakthrough seizure occurred with a 55-year-old man who was believed to be compliant with seizure medication prescriptions (PO in human case report). It is possible that ginkgo may have increased the metabolic breakdown of his phenytoin and divalproex anticonvulsant medications (speculative).³⁵⁵¹

Drug Interactions

- Ia. 1) When ginkgo extract was taken for 28 days, it reduced the bioavailability of CYP 2C9 substrate **tolbutamide** and its effect on lowering blood glucose (PO in human study).²⁰¹⁵

To animals fed a low protein diet of 7% casein for 3 weeks, along with controls with a normal protein diet with 20% casein, ginkgo extract was given at 100 mg/kg daily for 5 days, combined with the hypoglycemic drug tolbutamide on the last day (PO in rats). In the control rats the ginkgo had little influence on the tolbutamide hypoglycemic effect though the plasma drug concentration tended to be low, but in the low-protein rats the plasma concentration and hypoglycemic effect were both significantly reduced. Ginkgo extract markedly increased CYP 2C activity in both groups, but significantly more so in rats with low protein intake.³⁵²⁹

- 3) 120 mg/day of ginkgo for 18 days increased plasma **nifedipine** 53% (PO in human study).¹⁷²⁸

When 240 mg of standardized extract was given only once to 8 healthy young men simultaneously with nifedipine and compared to nifedipine alone in an open, random crossover trial, there was no significant change in the maximal plasma concentration of nifedipine, though its average value did increase by about 30% with the combination (PO in human study). For 2 of the subjects, the values were about twice as great, and they had more severe and longer headaches with the extract than without it. Also, the average heart rate of the group tended to be additionally faster by 2-9% with the combination than the 5-11% increase with nifedipine alone. So, it was recommended to avoid the combination when possible and to monitor carefully when ginkgo and nifedipine are taken together.³²²⁹

HOWEVER, in a study of 20 patients each taking the hormonal CYP 3A4 substrates anastrozole, letrozole, or tamoxifen, there were no significant changes in trough concentration after taking 240 mg daily of EGb 761 for 3 weeks.³²⁶⁸ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low in doses of the standardized extract of ≤ 240 mg/day (speculative).³²²²

- 4) A dose of 360 mg/day of EGb 761 increased bioavailability of CYP 3A4 substrate **midazolam** by 25% and decreased its oral clearance by 26% (PO in humans study).²⁰¹⁵

HOWEVER, in another study with 14 healthy subjects, 240 mg daily for 4 weeks significantly reduced midazolam bioavailability by 34% and its maximum concentration by 31%, but half-life was not changed, indicative of intestinal, but not hepatic, induction. Still, the same dose for 2 weeks had no effect on the combination of lopinavir and ritonavir, probably due to ritonavir's CYP3A4 inhibiting activity.³¹³⁵ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low in doses of the standardized extract of ≤ 240 mg/day (speculative).³²²²

- 5) Taking 360 mg extract daily for 14 days significantly increased **talinolol** bioavailability due to inhibition of P-glycoprotein efflux (PO in human study).^{2680,3138} The bioavailability and peak

- plasma concentration of talinolol were significantly increased in 12 healthy subjects by ginkgo extract by 21% and 33%, respectively, while its half-life increased of 11% was not significant (PO in human study).³¹³⁸ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low in doses of the standardized extract of ≤ 240 mg/day (speculative).³²²²
- + 8) An extract dose of 120 mg every third day for 14 days in 16 volunteers significantly reduced bioavailability and maximum plasma concentration of **atorvastatin**, but did not impact its cholesterol-lowering efficacy.³⁵⁵³
- Ib. 1) 80 mg extract daily was associated with spontaneous bleeding, following 3-year use of **aspirin** as an antiplatelet drug (PO in human case report).¹⁹⁴
- HOWEVER, a [CORRECTION insert: half-maximal inhibition of] PAF-induced aggregation of human platelets experimentally requires a concentration of 100 times greater or more than is achieved in the plasma by normal therapeutic doses of 120-240 mg of a 50:1 concentrated ginkgo extract (*in vitro*).¹⁷⁴⁷
- 4) Two elderly epilepsy patients stabilized on anticonvulsant therapy with **sodium valproate** experienced seizures after use of ginkgo extract (PO in human case reports).¹²⁴⁷
- A fatal breakthrough seizure occurred with a 55-year-old man who was believed to be compliant with seizure medication prescriptions **phenytoin** and **valproic acid** (PO in human case report). Since phenytoin and valproate are metabolized by CYP2C9 and CYP2C19, and ginkgo has been shown to induce these isozymes (PO in human studies),^{1617,2015,2301,2302} it is possible that ginkgo may have increased the metabolic breakdown of his phenytoin and divalproex anticonvulsant medications (speculative).³⁵⁵¹
- 5) **Warfarin** use in a 78-year-old woman resulted in intracerebral hemorrhage after the addition of ginkgo for 2 months (human case report).⁵²⁴
- Using the Veterans Administration Informatics and Computing Infrastructure, of the 807,399 patients who used warfarin over the period of 2008-2014, 11,003 also used ginkgo at least once; at least one bleeding event occurred in 18.0% of the warfarin-only population, while 22.6% of those who also used ginkgo experienced a bleeding event (PO in human clinical review).³⁵⁸³
- HOWEVER, in a retrospective population study of about 200,000 ambulatory patients in the Taiwan Longitudinal Health Insurance Database, 7700 using ginkgo extract showed there was not a higher hemorrhage risk associated with the 60 concurrently taking warfarin or antiplatelet drugs [colpidogrel, cilostazol, ticlopidine], though there were significantly higher risks of hemorrhage among males and those ≥ 65 years of age (PO in human study).²⁹⁶⁰
- HOWEVER, a preclinical study giving ginkgo extract up to 1000 mg/kg or its components ginkgolide B up to 140 mg/kg for 5 days showed no anticoagulation effects (PO in mice). When 100 mg/kg ginkgo extract or 4.2 mg/kg bilobalide or the vehicle were given for 5 days, with or without warfarin for the last 3 days, the prothrombin time and activated partial thromoplastin time were both significantly reduced by the extract and bilobalide (PO in mice). Bilobalide at 10 mg/kg for 5 days induced CYPs 1A1, 1A2, 2B, 3A, and 2C [warfarin hydroxylase], leading to increased metabolism of warfarin racemers: (R)- moreso than (S)-warfarin (PO in mice).³⁵⁵⁴
- Warfarin hydroxylase induction would increase the tendency to clot, not bleed.
- + 7) The introduction of ginkgo extract at 160 mg/day for 2 weeks after 3 years of uneventful use of **risperidone** resulted in priapism that required emergency hospital treatment (PO in human case report). The ginkgo and risperidone were discontinued, and when the risperidone alone was reintroduced, no further episodes of priapism occurred during the 6 months of follow-up.³²³⁰
 - + 8) A man who was very drug-compliant had been taking **efavirenz** for 2 years in combination with 2 other drugs. A virological failure developed that involved a mutation in the reverse transcriptase gene. Plasma efavirenz levels in blood samples dating back 15 months were shown to steadily decrease over time. The only change in comedication during this time was his taking a ginkgo product for "some months". This was thought to be the probable cause, possibly due to induction of CYP3A4.³³⁹²

- II. 2) Antiplatelet **ticlopidine** was as effective inhibiting platelet aggregation at 50 mg/kg/day with 40 mg/kg/day ginkgo extract as a dose of 200 mg/kg/day alone (PO in rats and mice). The combination increased bleeding time by 150% and improved recovery in acute thrombosis.¹⁰⁹⁰

HOWEVER, in a randomized, open-label, 2-treatment, single-dose crossover study of 24 healthy males with 250 mg ticlopidine alone or in combination with 80 mg ginkgo extract, there was no significant difference in bleeding time, platelet aggregation, or ticlopidine pharmacokinetics between the 2 treatments (PO in human study). Additional adverse effects after combining the ticlopidine with ginkgo were 2 cases of nausea and 1 case of headache.³⁵⁵⁵

- + 5) When ginkgo leaves were decocted and the extract given together with oral **cyclosporine**, the maximum concentration of cyclosporine was reduced by 62%, and its bioavailability decreased by 51%, though no effects was shown when cyclosporine was given IV (PO in rats). When given onion (*Allium cepa*) juice instead, another rich source of quercetin containing 2.5 times that of the ginkgo extract, the combination with oral cyclosporine reduced the peak concentration by 60% and the bioavailability of cyclosporine by 68%, but again no effect on IV cyclosporine. This indicates that the interaction occurred by reducing absorption. No effect was shown by onion juice on Pgp, whereas ginkgo paradoxically inhibits Pgp (*in vitro*) that would result in an increase in cyclosporine absorption.³¹⁹²

Complementary Adjuncts

- Ia. 5) Ginkgo leaf extract given to **schizophrenia** patients together with **haloperidol** increased the effectiveness and reduced the extrapyramidal side effects of the medication (PO in human clinical study).¹²⁸¹

A review and meta-analysis of 6 randomized studies lasting at least 8 weeks and using standardized ginkgo extract as an add-on therapy for chronic schizophrenia in 466 cases compared to 362 patients on placebo [except in 1 study] found significant improvement in negative symptoms with **chlorpromazine** and **clozapine** and in total symptoms with chlorpromazine (PO in human clinical studies).²⁷⁶⁰ In addition, of 157 schizophrenic patients with tardive dyskinesia taking chlorpromazine, those 78 also taking EGb 761 for 12 weeks had a significant decrease in Abnormal Involuntary Movement Scale [AIMS] score, compared to 79 taking placebo, but there was no difference in positive or negative symptoms (PO in human clinical study).³²⁹² In 15 chronic schizophrenic patients given 300 mg/day EGb 761 for 8 weeks together with **olanzapine**, compared with 14 taking olanzapine only, significant improvements in positive symptoms and decreases in superoxide dismutase and catalase levels were found with the ginkgo group (PO in human clinical study).³²⁹¹ A systematic review of ginkgo as an adjunct to **antipsychotics** in treating chronic schizophrenia assessed 8 randomized, placebo-controlled, double-blind studies with 1033 patients enrolled, including 571 using ginkgo extract and 462 taking placebo (PO in human clinical studies). Ginkgo extract with antipsychotics significantly ameliorated total and negative symptoms, compared to placebo, with no distinguishable differences in adverse effects.³⁶²³

- + 7) In two randomized, placebo-controlled, double-blind studies in which **radioiodine** [I-131] was used to treat 25 patients with **Graves' disease**³⁰⁹⁵ and 23 **thyroid cancer** patients postsurgically for thyroid remnant ablation,³⁰⁹⁶ those who received 120 mg EGb 761 daily for 3 days before and a month after the I-131 had less chromosome damage as shown by significantly fewer micronucleated lymphocytes and clastogenic factors than those who received placebo (PO in human clinical study).^{3095,3096}
- + 8) In 828 mild to moderate **Alzheimer's disease** patients receiving conventional therapy with the cholinesterase inhibitors **donepezil**, **galantamine**, or **rivastigmine**, 29 also were taking ginkgo extract EGb 761, most at a dose of 120 mg daily (PO in human clinical study). After a 1-year follow-up, the score on the Mini Mental State Examination [MMSE] was significantly improved for those using the ginkgo extract compared to conventional therapy alone. The MMSE effect seen after 6 months was positive, but not significant.³⁴⁸⁴

- + 9) In a 2-month, randomized, placebo-controlled, double-blind trial involving 111 patients with **acne**, a topical gel with 0.1% **adapalene** was used as the primary treatment after evening facial cleansing, while 55 also used a cream containing ginkgo extract, bakuchiol, and mannitol after morning facial cleansing (TP in human clinical study). Those using the adapalene gel with ginkgo cream had significantly improved inflammatory lesions, IgA, and seborrhea intensity, compared to those using the adapalene gel and placebo cream. Subject perception and global efficacy assessments also indicated superiority of the ginkgo cream. Safety and local tolerance of the ginkgo cream were good.³⁴⁹⁹
- + 10) In a prospective, open-label study to determine maximum dose, efficacy, and tolerance of ginkgo extract when combined with **sorafenib**, the only drug shown to improve overall survival of advanced **hepatocellular carcinoma**, daily ginkgo doses of 60, 120, 240, and 360 mg were initially tested on 27 advanced liver cancer patients being given sorafenib 400 mg twice daily (PO in human clinical study). Ginkgo extract at 240 mg was determined to be the maximum tolerated dose, so an additional 32 new advanced hepatocellular carcinoma patients were treated at this dose together with sorafenib. In these 32 patients, 3 showed a partial positive response, with a stable disease in 21, and a progressive disease in 8 patients. Median overall survival with sorafenib alone in a previous trial was 10.7 months, compared to 7.9 months with placebo; in this study, the mean overall survival was 11.6 months, and no additional toxicities were seen with the ginkgo combination compared to the prior study monotherapy with sorafenib.³⁶⁰³
- IIa. + 2) After **osteoporosis** was induced by administering **dexamethasone** for 5 weeks, ginkgo standardized extract at 14 mg/kg or more daily significantly increased the percentage of alveolar bone of the mandible and at 28 mg/kg or more daily significantly increased the percentage of trabecular bone in the femur, compared to controls (PO in rats).³¹⁴⁷
- + 3) Doses of a standardized extract prepared with phospholipids at 3:1 [phytosome] and given at 100 mg/kg for 30 days helped protect against **heart damage** induced in the last 2 days by 2 doses of subcutaneous **isoproterenol** at 85 mg/kg (PO in rats). The extract significantly increased cardiac levels of glutathione and the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, as well as reducing the lipid peroxidation marker malondialdehyde in the heart and cardiac damage markers AST, LDH, and CPK in the serum.³¹⁸⁵
- + 4) The **ototoxicity** caused by excessive **gentamicin** including auditory brain stem response threshold, cochlear hair cell damage ratio, and apoptosis was prevented with 100 mg/kg of EGb 761 for 2 days prior plus concurrently (PO in guinea pigs). The protection was believed to be due to a reduced formation of reactive oxygen species and nitric oxide-related mechanism as shown in cultured cochlear cells (*in vitro*).³²⁶⁰
- + 5) When 30 mice received 2 mg/kg **cisplatin** twice weekly for 9 doses, half were also given about 100 mg/kg EGb761 daily in the drinking water, and comparisons were made for cisplatin-induced **peripheral neuropathy** (PO in mice). A control and ginkgo-only group were also monitored. The cisplatin plus ginkgo group had significantly less reduction in nerve conduction velocity and dorsal root ganglia growth retardation than the cisplatin-only group. The ginkgo-only group was similar to controls in these outcomes.³³⁷³

GOLDENSEAL

p. 182

**Hydrastis canadensis* roots/rhizome

Contraindications

- II. 1) Do not use in **jaundice** in **newborns** (speculative).^{777,1890}
 HOWEVER, when berberine-containing herbs were given in herbal concoctions according to traditional dosage and indication to 20 patients with chronic cytopenic hematological conditions, though 3 patients with thalassemia intermedia had transient elevation of serum bilirubin, there was no associated aggravation of anemia or liver dysfunction (PO in human clinical study).³¹⁰⁸

Drug Interactions

Ia. 1) A dose of 2.7 gram goldenseal extract daily for 28 days inhibited metabolism of CYP3A4 substrate **midazolam** by 40% in 12 healthy subjects (PO in human study).¹⁸⁰⁷ Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the bioavailability of CYP 3A4 substrate midazolam by 40% and its maximum plasma concentration by 38%, and significantly decreased its oral clearance by 27% (PO in human study).³²³⁸ Also, 3.97 gram of the root extract delivering 132 mg hydrastine and 77 mg berberine per day for 14 days significantly [Note CORRECTION: not "reduced"] INCREASED midazolam bioavailability in 16 healthy subjects (PO in human study).²⁵⁰¹ When tested with plasma of 5 volunteers given different doses of goldenseal extract, the 3 samples with the highest hydrastine and lowest berberine levels caused significant inhibition of midazolam metabolism by CYP 3A4/5 (*ex vivo*). The metabolism of midazolam by human liver microsomes was significantly inhibited in a phosphate buffer solution by berberine and hydrastine at concentrations of 300 and 10 mcM, respectively. At 100 mcM, hydrastine inhibited CYP 3A4/5 by over 80%, whereas berberine had no measurable effect. When tested in plasma, hydrastine and berberine had even greater inhibitory activities, with significant inhibition of midazolam metabolism by human liver microsomes at 3 mcM and 100 mcM, respectively (*in vitro*).³⁶³⁴

Based on clinical relevance, the pharmacokinetic interaction risk with drugs that are substrates of CYP 3A4 or 2D6 has been assessed as high (speculative).³²²²

3) The combination of 1500 mg berberine daily for 3 months in 43 type 2 diabetes patients with one or more **oral hypoglycemic** medications including **sulfonylureas, metformin acarbose,** and/or **insulin** resulted in lower blood sugar through week 12 (PO in human clinical study).²³¹⁵

In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered fasting and postload plasma glucose and HbA1c compared to 52 diabetics on placebo, along with significantly reducing the triglycerides, total cholesterol, and LDL-cholesterol, body weight, and systolic blood pressure (PO in human clinical study).²⁹⁰⁷ In 50 type 2 diabetic patients randomly selected to use 1 gm berberine daily, the 26% and 18% significant reductions in fasting blood glucose and HbA1c were equivalent to those of the 26 and 21 diabetic patients who used metformin or rosiglitazone, respectively (PO in human clinical trial). Only the berberine group had a significant reduction of triglycerides. Also, in another group of 18 hepatitis C and 17 chronic hepatitis B patients with type 2 diabetes or impaired fasting glucose, 1 gm/day berberine significantly reduced fasting blood glucose, triglycerides, and the transaminases ALT and AST (PO in human clinical trial).²⁹⁰⁸

+ 5) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the 8-hour urinary ratio of the CYP 2D6 substrate **dextromethorphan** to its metabolite dextrorphan by 9-fold (PO in human study).³²³⁸

+ 6) Berberine at 900 mg daily in 17 healthy males for 14 days doubled significantly the 8-hour urinary ratio of the CYP 2C9 substrate **losartan** to its metabolite E-3174 (PO in human study).³²³⁸

II. + 2) In doses of 30 mg/kg berberine for 2 weeks, the Pgp substrates **digoxin** and **cyclosporine** had significantly increased maximum serum concentration and bioavailability compared to controls, indicating berberine inhibition of Pgp drug efflux (PO in rats).³¹⁰⁵ Likewise, the oral bioavailability of **ketoconazole** was significantly increased by berberine given at 60 mg/kg (PO in rats). Since ketoconazole is both a substrate and an inhibitor of Pgp and berberine is a Pgp substrate, the pharmacokinetic effect of each on the other may lead to pharmacodynamic synergism against fungal infections (speculative).³¹⁰⁴

+ 3) Goldenseal powder at 300 mg/kg inhibits **acetaminophen** metabolism by CYP2E1, as shown by an increase in the drug's serum levels, and thereby protects the animals from liver toxic effects of this drug, as indicated by serum transaminase levels (PO in rats).³⁶¹⁸

HOWEVER, a goldenseal root extract had no effect on CYP2E1 metabolism of chlorzoxazone (PO in humans).¹⁸⁰⁷

III. 3) [See Complementary Adjuncts Ia. 3) below.]

Complementary Adjuncts

- Ia. + 3) When 500 mg berberine hydrochloride was given twice daily with **simvastatin** 20 mg once daily for 2 months to 23 patients in a randomized trial for **high cholesterol**, the 31.8% reduction in LDL cholesterol was significantly better than the 23.8% with berberine in 24 patients or the 14.3% with simvastatin in 16 patients used alone (PO in human clinical study). For triglycerides, the combinations reduced these by 38.9%, significantly better than 22.1% for berberine or 11.4% for simvastatin alone. Similar results were obtained for total cholesterol. No adverse effects were observed in any group. These results reflected those obtained in animals given 90 mg/kg/day berberine and/or 6 mg/kg/day simvastatin (PO in rats).²⁹⁰⁵ In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered triglycerides, total cholesterol, and LDL-cholesterol compared to 52 diabetics on placebo, along with significantly reducing the fasting and postload plasma glucose, HbA1c, body weight and systolic blood pressure (PO in human clinical study).²⁹⁰⁷
- In human liver-derived cells, berberine was found to have an additive effect with lovastatin (*in vitro*). Since lovastatin did not reduce the effect of berberine, this indicated a different mechanism of action for the two (*in vitro*).¹⁶⁵⁶
- IIa. + 4) Berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive **locomotor activity** induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that berberine may help reduce the chronic cocaine psychological dependence (speculative).²⁷⁵³
- + 5) When taken with a **high cholesterol** and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).²⁹³² When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.²⁹³³ The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);²⁹³² berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).²⁹³³
- + 6) The combination of 1 mg/kg berberine with 0.5 mg/kg **amphotericin B** increased the survival for disseminated **candidiasis** to 36 days from 17 days and 14 days, respectively, when these 2 antifungal agents were used separately, and compared to 12 days for controls (IP in mice).³¹⁰⁷
- + 7) Compared to those injected with 2.5 mg/kg **doxorubicin** alone every other day for 14 days, those injected with 60 mg/kg berberine an hour prior to the drug had less **cardiotoxicity** as shown by significantly smaller increases in mortality, LDH activity, myocardial injury, and QRS duration (IP in mice). This indicates a potential protective role of berberine against heart damage by doxorubicin.³¹⁴⁸
- + 8) After treatment of ***Clostridium difficile* infection** with 50 mg/kg **vancomycin** daily for 5 days, the use of berberine at 100 mg/kg for the next 5 days prevented weight loss and improved the disease activity index score and the histopathology score, while decreasing the mortality rate, compared to vancomycin alone (PO in mice). Berberine prevented relapse of *C. difficile* infection and significantly improved survival, while counteracting vancomycin side effects. Berberine appears to be effective by restoring intestinal microbiota and inhibiting expansion of *Enterobacteriaceae* family members.³⁶¹⁹
- IIb. 1) Berberine reduced **bacterial resistance** to **penicillin** and **chloromycetin** of enteric bacteria previously been unaffected by these **antibiotics** (*in vitro*).⁵⁷⁸

A 1:5 extract [g of goldenseal leaf to ml of 50% ethanolic solvent] with a minimum inhibitory concentration [MIC] of 75 mcg/ml was twice as active against methicillin-resistant *Staphylococcus aureus* [MRSA] as isolated berberine with an MIC of 150 mcg/ml (*in vitro*).³¹³⁰

GOTU KOLA

p. 185

Centella asiatica syn. *Hydrocotyle asiatica* herb

Drug Interactions

- Ib. + 1) When **venlafaxine** was given for depression to a 35-year-old female for 3 months, along with her taking gotu kola and bladderwrack (*Fucus vesiculosus*) for weight loss for 1 year, she developed dyspnea from acute cardiomyopathy and pneumonitis (PO in human case report). After discontinuing the venlafaxine, she rapidly improved. Venlafaxine is metabolized by CYP 2D6 and to a lesser extent CYP 3A4.³⁵⁶⁹ Gotu kola constituents asiatic acid and madecassic acid inhibited CYP 2D6 metabolism of the substrate dextromethorphan, while asiatic acid also inhibited CYP 3A4 metabolism of testosterone (*in vitro*).³⁵⁶⁸ It was suggested that venlafaxine metabolism was inhibited by gotu kola and/or bladderwrack (speculation).³⁵⁶⁹

Complementary Adjuncts

- Ila. + 1) The **myocardial injury** from the chemotherapy drug **adriamycin** due to reactive oxygen species generation and mitochondrial dysfunction was significantly reduced by an aqueous extract of gotu kola at 200 mg/kg given before and with adriamycin administration (PO in rats). The extract improved levels of cardiac marker enzymes, mitochondrial glutathione levels, and mitochondrial antioxidant enzymes included glutathione peroxidase, superoxide dismutase, and catalase, compared to adriamycin alone.³⁶¹⁵

GRAPEFRUIT

p. 186

Citrus paradisi fruit / juice

Drug Interactions

- Ia. 16) [CORRECTION: The interaction and its reference citation #2590 in the text was listed previously as number 8) with citation #1274. Therefore, the following interaction and citation are new.]
- + When grapefruit juice or water was given with the CYP 3A4 substrate **erythromycin** to 6 healthy men, the grapefruit juice significantly increased the maximum plasma concentration and bioavailability of the antibiotic erythromycin, compared to water (PO in human study).²⁵⁹⁰
 - + 21) When 17 patients with Addison's disease receiving **cortisol** were given 200 ml of pink grapefruit juice 3 times daily for 3 days, the juice significantly increased median serum cortisol levels over a 2.6 hour period, with a 19% increased cortisol bioavailability over that time (PO in human clinical study). The median urinary allo- plus tetrahydrocortisol/tetrahydrocortisone ratio was also significantly increased.³⁰²¹
 - + 22) The chemotherapeutic drug **sirolimus** showed 350% greater bioavailability when taken once weekly in conjunction with 240 ml of grapefruit juice once daily in a phase I pharmacokinetic study with 101 advanced cancer patients taking either this combination, sirolimus alone, or sirolimus with ketoconazole (PO in human clinical study). The authors note that lower doses of sirolimus are possible with simultaneous consumption of a consistent source of grapefruit juice to provide equivalent blood levels of the drug.³¹⁴⁴
- Ib. + 4) Following a liver transplant, a 52-year-old man stabilized on **tacrolimus** as part of his medication began after 4 months to experience toxicity symptoms and highly elevated blood levels of the drug (PO in human case report). He had been warned to avoid grapefruit consumption, but a friend had given him orange marmalade he craved that was home-made with half grapefruit to supply the bitter flavor, and he consumed over 3 lbs of it in the week prior to the toxic symptoms.³¹²⁴

GUARANA

p. 194

Paullinia cupana seeds

Drug Interactions

- II. 1) When 821 mg/kg of guarana extract was taken simultaneously with a single dose 50 mg/kg oral **amiodarone**, there were significant reductions in peak plasma levels, tissue levels, and bioavailability of the drug (PO in rats). However, when the same dose of guarana extract was taken for 14 days prior to administration of a single dose of amiodarone, there was no significant effect on its pharmacokinetics. Apparently, the guarana extract interacts with amiodarone in the gastrointestinal tract.³⁴²³

Complementary Adjuncts

- Ia. + 1) The **cancer-related fatigue** in 60 **breast cancer** patients receiving systemic **chemotherapy**, including 81% or more receiving a combination of **doxorubicin** and **cyclophosphamide** with or without **fluorouracil**, was treated using guarana extract at 50 mg twice daily, providing 6.5 mg of caffeine for 21 days in a randomized, placebo-controlled, crossover design trial (PO in human clinical trial). Several questionnaire tools documented significant improvements in global fatigue scores when the extract was used immediately after chemotherapy, when compared to placebo use, while neither anxiety or depression nor insomnia were worsened.²⁹²⁰

HOWEVER, a 75 mg daily dose of guarana was not found effective in relieving fatigue in a randomized, blinded, crossover trial with 36 breast cancer patients undergoing radiation therapy 28 times over 35 days (PO in human clinical study).²⁹²¹

HAWTHORN

p. 199

Crataegus spp. leaves, flowers and/or fruit

Complementary Adjuncts

- Ia. 1) When compared to NYHA class II chronic **heart failure** patients on synthetic drugs only, those class II patients using only *C. oxyacantha* leaf and flower extract or the extract in addition to **cardiac glycosides** such as **digoxin** had significantly less fatigue, stress dyspnea, and palpitations and required significantly fewer cardiac glycosides (PO in human clinical study).²²³⁸

HOWEVER, a study on digoxin immunoassays with 2 hawthorn hydroalcoholic extracts with 12% ethanol, one from the leaf, flower and berry and the other from the berry only, showed no interference with the Tina-Quant assay, but the Digoxin III assay indicated falsely elevated levels of digoxin for both both extracts, both alone and in the presence of digoxin (*in vitro*). Also, rat heart muscle cells had increased intracellular calcium levels with both extracts but showed no additive response with digoxin (*in vitro*). On the basis of these findings, the authors recommend that patients on digitalis should avoid digoxin (speculative).³⁵²⁸

- IIa. + 2) Dose-dependent gastroprotective activity against **stomach ulcers** induced by **ethanol** was comparable to that of ranitidine as shown with hawthorn berry ethanol extract given in a range of 50-200 mg/kg (PO in rats).

- + 3) The **testicular toxicity** caused by **cyclophosphamide** was partially ameliorated by a water extract of *C. monogyna* berries given 4 hours after the drug at a dose of 20 mg/kg daily for 28 days (PO in rats). The weights of the testes and epididymides had lower weights and spermatogenic activities were not as severe as with exposure to cyclophosphamide only.³³⁴⁴ Likewise, adverse effects including reduced spermatogenesis, decrease in sperm count and motility, increased abnormal and dead spermatozoa, and increased concentrations of follicle stimulating hormone [FSH] and luteinizing hormone [LH] induced by the chemotherapy drug **doxorubicin**, when given in 5 doses IP at 4 mg/kg weekly for 4 weeks, were partially prevented when hawthorn berry aqueous extract was administered simultaneously at 20 mg/kg daily (PO in rats).³⁶¹³

HIBISCUS

NEW

^ (*Hibiscus sabdariffa*) flowers [for *Hibiscus rosa-sinensis*, now see Chinese hibiscus]

Drug Interactions

- Ia. 1) When 1 L of a sweetened aqueous extract made with 30 g/L dried flowers was consumed 1.3 hours before **acetaminophen (paracetamol)** was taken by 6 healthy male subjects, the urinary clearance was increased by 11.7%, thereby significantly reducing its terminal elimination half-life by 47%, compared to consumption of water beforehand (PO in human study). The study authors recommend that hibiscus extract be consumed 3-4 hours before acetaminophen to avoid shortening its therapeutic effects (speculative).³⁵¹¹
- 2) A hibiscus beverage was taken with 600 mg tablets of the malarial drug **chloroquine** by 6 healthy men on an empty stomach after an overnight fast to assess its effect on the drug absorption in comparison with water and lemonade (PO in human study). The bioavailability and maximum plasma concentration were both significantly reduced by the hibiscus beverage and the lemonade. This was believed to be due to their acidity (speculative).³⁵¹²
- 3) A water infusion made from 30 g of dried flower per liter of boiled water was given in doses of 300 ml daily for 3 days to 12 healthy subjects, and on the third day the beverage was taken with 25 mg of **diclofenac** (PO in human study). In this randomized crossover study, compared to taking diclofenac with water, the hibiscus infusion led to a significant reduction in excretion of the drug during the 8 hours after its administration.³⁵¹³

HOPS

p. 203

Humulus lupulus strobiles

Drug Interactions

- II. 1) A hop extract dose-dependently increased the sleeping time induced by the **pentobarbital** (IP in mice).⁵⁷

HOWEVER, 10 ml/kg of a 0.5% aqueous solution of 70% ethanolic extracts of cultivated Magnum and Aroma genotypes showed a dose-dependent suppression of the sleeping time induced by 40 mg/kg pentobarbital when given before administration of the drugs (IP in mice). Tert-butanolic extracts of these genotypes reduced the sleeping time of the drugs to a lesser extent, but the Magnum tert-butanolic extract did reduce the sleep induction time of pentobarbital. Tert-butanolic extract of wild hops genotype significantly reduced pentobarbital-induced sleeping time (IP in mice). Likewise, with 3 mg/kg **diazepam** the tert-butanolic extracts of the 2 cultivated genotypes and the ethanolic extract of the Magnum genotype significantly increased the time on the rotarod compared to diazepam alone, antagonizing its effects, while the wild genotype ethanolic extract reduced the time on the rotarod, though not significantly (IP in mice).³⁶²¹

Complementary Adjuncts

- Ia. + 1) A combination of 3 herbal hydroethanolic extracts including hops strobiles 4-8:1, valerian (*Valerian officinalis*) root 3-6:1, and passion flower (*Passiflora incarnata*) herb 4-7:1 was found to markedly improve symptoms associated with **benzodiazepine withdrawal** phase in 107 patients of an average age of 54 years (PO in human clinical study). The extracts were begun with 1-2 tablets daily as benzodiazepine dosage was reduced for 2 weeks, and continued for the next 4 weeks after benzodiazepine use was stopped. Improvement was shown for pronounced tiredness in 76% and general unrest in 71%, according to subjective assessment of patients. Sleep improved in 68% by the end of the treatment, and 74% had more motivation and drive than at the beginning. At the end, 62% were calmer and better able to cope. No adverse drug events occurred in any patients.²⁶³⁴

HORSE CHESTNUT

p. 204

**Aesculus hippocastanum* seeds

Complementary Adjuncts

- IIa. + 1) While suboptimal doses of the triterpenoid saponin mixture escin and **corticosterone** individually had no effect on carrageenan-induced paw **edema** or pleural **inflammation**, the

combination of these agents at the same doses reduced the paw edema and the volume of pleural exudates and the exudate white blood cells (PO in rats). Likewise, alone these agents had no effects on inflammatory factors in macrophages stimulated by lipopolysaccharides, but together they inhibited secretion of nitric oxide, TNF- α , and interleukin 1 β (*in vitro*).²⁸³⁷

HORSETAIL

p. 206

**Equisetum arvense* plant

Drug Interactions

- I.b. + 1) A 49-year-old woman effectively treated for 6 years with an antiviral combination, then one drug was altered for another 6 years of the viral suppressive regimen of **zidovudine**, **lamivudine**, and **efavirenz**, when she had 2 consecutive detectable viral loads beginning 2 months after she started supplementing with horsetail powder (PO in case report). Likewise, a 75-year-old man on the same regimen was switched after 9 years to the fixed-dose combination of **emtricitabine**, **tenofovir**, and efavirenz when detectable viral loads occurred after 4 and 9 months, beginning after he started horsetail powder supplementation (PO in case report). In both cases, viral load suppression was shown to be effective 1 month after the patients ceased taking horsetail.³⁶²⁰

INDIAN FRANKINCENSE [formerly listed as FRANKINCENSE] p. 158

Boswellia serrata resin

Complementary Adjuncts

- Ia. 1) In **osteoarthritis** of the knee, those taking placebo used **ibuprofen** more than subjects using 100 mg/day of extract with 30% 3-O-acetyl-11-keto-beta-boswellic acid [AKBA], but outcomes were significantly better in the extract group (PO in human clinical study).²⁴⁸³
- A randomized, placebo-controlled, double-blind trial for 90 days with 60 knee osteoarthritis patients using ibuprofen and 100 mg extract with 30% AKBA or 100 mg of 20% AKBA and oil both had significantly less pain and stiffness than placebo, but the AKBA/oil group had a quicker response and significantly better functional ability scores than placebo (PO in human clinical study).²⁸⁰⁴
- In a comparative, randomized, placebo-controlled, double-blind trial with 201 osteoarthritis patients of ages 40-70 years, the effects of 333 mg **curcuminoids** with turmeric (*Curcuma longa*) volatile oil was assessed with and without 150 mg boswellic acid extract when taken 3 times daily for 12 weeks (PO in human clinical study). After 3 months the curcuminoid complex extract showed significant efficacy over placebo in physical performance tests, whereas the addition of boswellic acid resulted in significantly improved physical performance tests and WOMAC joint pain index. The efficacy of the combination was superior, and both treatments were well tolerated.³⁷¹⁰
- + 2) In a randomized double-blind study of 44 brain tumor patients receiving radiotherapy for several weeks, **dexamethasone** was used to control **cerebral edema**, but those also taking 4200 mg of H15 extract daily had significantly reduced brain swelling at therapy's end compared to baseline than those using placebo (PO in human clinical study). The dexamethasone doses were individualized, but the differences between the groups were not significant. Six patients in the boswellia group, but none in the placebo group, had diarrhea. There were no differences in quality of life or mental functioning between the 2 groups.²⁸⁴⁶
- + 3) In a randomized, placebo-controlled, double-blind study of 71 patients with **diabetes type 2** treated with **metformin** but having fasting blood sugar levels of 140-200 mg/dl, 400 mg gum resin capsules or placebo were given twice daily for 12 weeks (PO in human clinical study). The 37 patients given the gum resin had significantly lowered fasting blood sugar, glycosylated hemoglobin, insulin, total cholesterol, LDL, and triglyceride levels compared with the 34 in the placebo group, but no significant effects on liver and kidney function tests.³⁴¹³
- + 4) Of 32 patients with **asthma** and stabilized on 1 inhalation twice daily of **corticosteroids** (**fluticasone + sameterol**, **beclomethasone + formoterol**, or **budesonide + formoterol**), along

with long-acting oral **beta-agonists**, 18 were randomized to receive 4 weeks of additional treatment with 500 mg/day of boswellia standardized extract in a phospholipid base and 14 did not (PO in human clinical study). During the 4 weeks they could reduce the number of corticosteroid inhalations and kept track of the total number. Compared to the 14 controls, the number of inhalations was significantly lowered with the boswellia extract by 26% in week 2, 28% in week 3, and 42% in week 4. By week 4 the boswellia group were using on average 8 inhalations per week compared to 13.8 inhalations in the group without boswellia.³⁵⁴²

JUJUBE

p. 211

Ziziphus spinosa seeds

Drug Interactions

- II. 1) Three fractions of the hexane extract were shown to potentiate sleeping time anesthesia from **hexobarbital** and produce sedative effects (in mice).¹²⁵⁴

As part of an alcoholic extract combination with 7.5 parts jujube, 2 parts each of the nonsedative Szechuan lovage (*Ligusticum chuanxiong*) and the fungus fu-lin (*Poria cocos*), and 1 part each of the nonsedatives anemarrhena (*Anemarrhena asphodeloides*) and Chinese licorice (*Glycyrrhiza uralensis*), 60 subjects with sleep disorders given 1 gram of this combination extract suanzaorentang nightly for 2 weeks had significant improvements in sleep and well-being compared to 1-week placebo period before active treatment (PO in human clinical study). Sleep latency, sleep time number of awakenings, sleep quality and subjective feeling on arising were all significantly enhanced. No side effects were noted.¹²¹⁹

KAVA

p. 212

**Piper methysticum* rhizomes and root

Contraindications

- I. 1) Avoid operating a **motor vehicle** following excessive use of kava.^{244,728}
HOWEVER, using a driving simulator, an acute therapeutic dose of kava water-soluble extract with 180 mg kavalactones showed no impairment on driving outcomes when compared to placebo in a crossover trial with 22 adults (PO in human study). On the other hand, the benzodiazepine drug oxazepam significantly reduced braking reaction time and increased lapses in concentration when compared to kava. Significantly decreased alertness over time was found with oxazepam but not with kava or placebo.³²⁵¹
- II. 4) Consumption of kava products should be avoided in individuals with **jaundice** or past **liver disorders** (speculative).¹²³²

Mold hepatotoxin contamination has also been raised as a possible explanation of the rare cases of liver damage associated with kava (speculative).^{2913,3067} Cytotoxicity to liver cells of isolated kavalactones was shown to be mild for kavain and moderate for methysticin at supraphysiological concentrations of 200 mcM each, whereas yangonin was markedly cytotoxic at 25 mcM due primarily to apoptosis but not to glutathione depletion (*in vitro*).²⁸⁴⁴ Yangonin had previously been shown to have an IC₅₀ of 14-16 mcM, greater than desmethoxyyangonin at 53-59 mcM, levels over 100 mcM for methysticin, and 49-53 mcg/mL for kava ethanolic extract (*in vitro*).¹⁶⁴³

HOWEVER, another hepatotoxic agent in kava root, the chalcone flavokawain B [FKB] has been identified as the active hepatotoxin (*in vitro*) and *in vivo* at 25 mg/kg (PO in mice). FKB is preferentially extracted in lipophilic solvents 160-fold over water; in the dried extracts, FKB was at 0.2 mg/g for water, 32.3 mg/g for 95% ethanol, and 33.7 mg/g for acetone. FKB is a potent hepatotoxin sensitive to reduced glutathione, and its levels in kava-containing preparations should be specifically monitored and controlled.²⁷⁰⁹ The combination of using organic solvents including acetone and ethanol to extract "2-day" [rather than "noble"] cultivars of kava higher in the lipophilic FKB, dihydromethysticin, yangonin, and desmethoxyyangonin is a probable

explanation for many of the cases of liver toxicity possibly or probably due to kava extract consumption (speculative).³⁵⁰⁷

Drug Interactions

Ia. 1) Intoxication increased when kava was taken with **alcohol** compared to alcohol alone (PO in human study).¹⁰²⁵
Alcohol is often consumed concurrently with kava in kava-associated hepatotoxicity cases (PO in case series), and there may be a metabolic interaction with ethanol that could facilitate liver damage (speculative).²⁷¹⁰ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²

III. 1) Kavalactone-concentrated products equivalent to those associated with adverse effects on the liver should be avoided in individuals taking any **liver-toxic drugs** (speculative); cases of liver toxicity associated with acetone and ethanolic standardized extracts have been reported in Germany and Switzerland.¹²³²

HOWEVER, the chalcone flavokawain B [FKB] has been identified as the active hepatotoxin (*in vitro*) and *in vivo* at 25 mg/kg (PO in mice). FKB is preferentially extracted in lipophilic solvents 160-fold over water; in the dried extracts, FKB was at 0.2 mg/g for water, 32.3 mg/g for 95% ethanol, and 33.7 mg/g for acetone. FKB is a potent hepatotoxin sensitive to reduced glutathione, and its levels in kava-containing preparations should be specifically monitored and controlled.²⁷⁰⁹ The combination of using organic solvents including acetone and ethanol to extract "2-day" [rather than "noble"] cultivars of kava higher in the lipophilic FKB, dihydromethysticin, yangonin, and desmethoxyyangonin is a probable explanation for many of the cases of liver toxicity possibly or probably due to kava extract consumption (speculative).³⁵⁰⁷ Cytotoxicity to liver cells of isolated kavalactones was shown to be mild for kavain and moderate for methysticin at supraphysiological concentrations of 200 mcM each, whereas yangonin was markedly cytotoxic at 25 mcM due primarily to apoptosis but not to glutathione depletion (*in vitro*).²⁸⁴⁴ Yangonin had previously been shown to have an IC₅₀ of 14-16 mcM, greater than desmethoxyyangonin at 53-59 mcM, levels over 100 mcM for methysticin, and 49-53 mcg/mL for kava ethanolic extract (*in vitro*).¹⁶⁴³

KUDZU

p. 221

Pueraria lobata = *Pueraria montana* var. *lobata* = *Pueraria thunbergiana* root

Complementary Adjuncts

I. 1) When kudzu root was used by **alcohol** abusers, about 80% no longer experienced **alcohol craving** after 2-4 weeks (empirical).⁵⁴⁶

When 1200 mg daily was given to 10 healthy adults prior to drinking sessions in a double-blind, placebo-controlled crossover trial, beer consumption was significantly reduced from 3.5 to 2.4 beers per session, and those on puerarin took smaller sips, drank more slowly, and waited longer between beers (PO in human study).³²²¹

In addition, in a randomized, placebo-controlled, double-blind study of 17 young men consuming about 28 alcoholic drinks weekly and not seeking treatment but diagnosed with **alcohol abuse** or dependence, a 2-week run-in for baseline values was followed by 4 weeks of treatment with 250 mg of kudzu isoflavones 3 times daily for 10 men and placebo for 7 men, and then 2 weeks of follow-up (PO in human clinical study). There were no adverse events or changes in blood chemistry, and adherence was excellent. The men taking the kudzu isoflavones in comparison to placebo significantly reduced the number of drinks per week by 34-57%, the percent of days abstinent, and the consecutive number of days abstinent, and also decreased the number of days of heavy drinking. In the follow-up stage, the reductions in the kudzu group remained significantly less than baseline values.³⁵⁰⁹

Puerarin at 30-120 mg/kg significantly and dose-dependently increased serum levels of alcohol dehydrogenase (ADH) and ALDH and subsequently decreased liver levels of CYPs 1A2, 2E1, and 3A induced by ethanol intake (PO in rats). It also reduced hepatocellular lesions.³²⁸³

- IIb. + 1) The ethanolic extract of the root at concentrations from 5-100 mcg/ml prevented **auditory hair cell damage** caused by the chemotherapy drug **cisplatin** (*in vitro*). This effect was due to inhibition of lipid peroxidation and enhanced scavenging of free radicals (*in vitro*).²⁷²⁴

KUTAKI

p. 222

Picrorhiza kurroa rhizome/roots

Complementary Adjuncts

- IIa. + 4) The iridoid glycoside fraction of the ethanolic fraction of kutaki at 12 mg/kg daily for 15 days with **ethanol** reduced the **hepatotoxicity** from the concurrent and prior 30 days of **alcohol** consumption, compared to the alcohol consumption alone (PO in rats). The extract group had significant increases in liver acetaldehyde dehydrogenase for alcohol metabolism, as well as the antioxidant enzymes superoxide dismutase, catalase, peroxidase, and glutathione-S-transferase. The extract-fed rats also had significantly lower hepatic GGT, acid phosphatase, lipid peroxides, and bilirubin, among other indicators. Significant reductions in serum enzyme activities for the extract group included ADH, GGT, AlkPhos, GOT, and GPT and serum chemical markers bilirubin and triglycerides.²⁹³⁶
- + 5) The iridoid glycoside fraction of the ethanolic fraction of kutaki, given at 1 mg/kg for 14 days prior to experimental malaria infection with multidrug-resistant *Plasmodium yoelii* subsequently treated for 3 days with suboptimal intraperitoneal dose of **chloroquine**, resulted in effective treatment based on survival and parasitic load, compared to treatment failure using chloroquine without the extract pretreatment (PO in mice). Extract use for 14 days was shown to enhance immune response by significantly increasing ovalbumin antigen-induced T-cell proliferation and activation and antigen-specific antibody production, compared to controls.²⁹³⁷
- + 6) The combination of 2 iridoid glycosides, 1 part picroside-I and 1.5 parts kutkoside, given for 7 days at 6 mg/kg blocked the **hepatotoxicity** of **acetaminophen (paracetamol)** given after day 7 **ethinylestradiol** given on days 5-7 as indicated by its anticholestatic effect (PO in rats and guinea pigs).³¹⁶⁰ The same results were shown with the 12 mg/kg of the combination when given concurrently for 6 days with the hepatotoxin **rifampicin** (PO in rats and guinea pigs).³¹⁶¹ The changes in bile volume and the content of bile salts and bile acids caused by the 3 drugs in untreated animals were antagonized by both doses of the iridoid glycosides, and the effects were greater in all of these parameters than those achieved with 20 mg/kg of silymarin.^{3160,3161} The reduced viability of hepatocytes and reduction in oxygen uptake rate induced by rifampicin was also reversed more effectively by the 12 mg/kg of the glycoside combination than by 20 mg/kg silymarin (*in vitro*).³¹⁶¹

LARCH

NEW

^ *Larix* spp. bark

Complementary Adjuncts

- Ia. 1) A randomized, double-blind parallel group of 45 adults used 4.5 grams of larch arabinogalactan or maltodextrin placebo as a powder in water or juice once daily for 72 days to test antibody response to ***Streptococcus pneumoniae* pneumonia vaccine** (PO in human study). The 23-valent vaccine was given after 30 days, and 21 and 42 days later the pneumococcal antigen-specific IgG antibodies subtypes 18C and 23F were increased significantly more in the larch arabinogalactan group than in the placebo group, while subtypes 4, 6B, 9V, and 19F also were greater with the larch group, but not significantly.²⁷³⁹ Larch arabinogalactan has been

shown to enhance human natural killer cell cytotoxicity indirectly by increasing release of interferon gamma (*in vitro*)²⁷⁵⁴ and has reportedly been used clinically to enhance immune function and thereby reduce the frequency and severity of recurrent pediatric otitis media (empirical).²⁷⁵⁵

2) A randomized, placebo-controlled, double-blind 60-day study with 75 healthy adults used 1.5 g/day larch arabinogalactans with 27, 4.5 g/day arabinogalactans with 25, and placebo with 23 and then administered an influenza vaccine and **tetanus vaccine** after 30 days (PO in human clinical study). The *Clostridium tetani* toxoid IgG levels were significantly greater 30 days after the vaccine for the 1.5 g/day dose than for placebo. There were no significant immunoglobulin or adverse events differences between groups following the influenza vaccine.³³⁵¹

LICORICE

p. 225

**Glycyrrhiza glabra* [or *Glycyrrhiza uralensis*] root/rhizome

Contraindications

4) Avoid use in **pregnancy**,^{2,4,6,17,401} especially excessive intake.¹⁸⁹⁰

A study of 392 pregnant Italian women found that those 14 who were regular users of licorice had a 35.7% higher frequency of threatened miscarriages, mostly in the 4th-5th month of gestation, and a 16.7% increase in preterm labors compared to non-users (PO in human study).³⁰⁷⁸ In Korea, 185 women taking Chinese licorice (*G. uralensis*) at a maximum dose of 2.1 g/day during the first through 25th weeks of pregnancy to treat conditions such as coughs or colds had a significantly higher rate of stillbirths, compared to 370 age-matched controls and to the general population (PO in human study). Other outcomes between the 2 groups were similar, suggesting Chinese licorice is not teratogenic.³³³²

A study of children born in Helsinki, Finland, in 1998 to 327 mothers with <250 mg/week glycyrrhizin intake and 51 mothers with >500 mg/week glycyrrhizin consumption showed that the children in 2009-2011 exposed in utero to high glycyrrhizin scored 7 points lower on IQ tests, had poorer memory, and had higher risk of ADHD problems (PO in human etiological study). The girls exposed to high glycyrrhizin in utero were also taller, heavier, had higher BMI for age, and more advanced pubertal development than girls exposed to low glycyrrhizin.³⁵⁸⁵

Drug Interactions

Ia. ^ 3) When 17 patients with Addison's disease receiving **cortisol** were given 24 grams daily for 3 days of commercial licorice containing about 150 mg glycyrrhizin, the licorice significantly increased median serum cortisol levels for 2.6 hours after licorice ingestion, with a 5.7% increase of cortisol bioavailability over that time (PO in human clinical study). The median urinary cortisol/cortisone ratio was also significantly increased.³⁰²¹

Ib. + 5) An 80-year-old woman on **warfarin** twice developed elevated INR and black tarry stools after eating a pound of licorice candy (PO in human case report). Her INR was raised from a baseline of 2.1 to 5.5 after licorice consumption; 2 weeks after being advised to restrict licorice, her INR decreased to 1.2.³⁴⁴⁶

Decreased coagulation following excessive licorice consumption may be possible due to inhibition of thrombin by glycyrrhizin, shown to prolong plasma thrombin and fibrinogen clotting times and to inhibit thrombin-induced platelet aggregation (*in vitro*).³⁴⁴⁷ [This seems likely, since enhanced metabolic breakdown of S-warfarin was induced by 500 mg/kg of an aqueous extract equivalent to 3 gm/kg dried root (PO in rats), probably through activation of pregnane X receptor as shown by an ethanolic extract of *G. uralensis* (*in vitro*).¹⁹²⁶ Such an impact on warfarin metabolism would actually lower the INR.]

II. + 3) The ethanolic extract of *G. uralensis* root at 1000 mg/kg with a hypnotic dose of **pentobarbital** significantly increased sleep duration and at 500 and 1000 mg/kg decreased sleep latency (PO in mice). The extract showed no sleep inducing effects of its own at 1000 mg/kg in any of 15 animals but induced sleep in 80% given a subhypnotic dose of pentobarbital (PO in

mice). It also displaced flumazenil from the GABA_A-BZD receptor by 98% at 10 mg/ml (*in vitro*).³¹²⁷

- + 4) When the methanolic extract of licorice as given for 6 days at a dose of 1 g/kg before IV administration of 150 mg/kg **acetaminophen**, the biliary and urinary excretions of the acetaminophen-glucuronide was significantly increased by 156% and 132%, respectively (PO in rats). The enzymatic activity of UDP-glucuronosyltransferase (UGT) was shown to increase by 111% at the same licorice extract dose, while concentration of UGT was increased 257%. This indicates that licorice extract could increase liver detoxification of xenobiotics.⁵⁵⁸

Complementary Adjuncts

- Ia. 2) [Clarifications] After treating **stomach ulcers** for 12 weeks, DGL with 88% healing was statistically as effective as cimetidine with 94% healing in groups of 50 patients of which 28 in the licorice group consumed **ethanol** and 7 recently used **prednisone** or **NSAIDs** (PO in human clinical study). Though ulcerations and symptoms associated with anti-inflammatory use were more severe, recent anti-inflammatory drugs intake or habitual alcohol consumption did not influence the rate of ulcer healing.⁵⁰²
- + 4) A randomized, placebo-controlled, double-blind, crossover study with 6 men and 6 women evaluated the **hepatotoxicity** from consuming 40% **ethanol** to achieve a blood alcohol level of 0.12% for 12 consecutive days and the protective effect of taking 0.1-0.3% glycyrrhizin from licorice mixed with the alcohol (PO in human study). After 12 days of alcohol consumption and no glycyrrhizin, liver function enzymes AST, ALT, and GGT significantly increased from baseline, but not when glycyrrhizin was consumed concurrently, indicative of a protective effect. With glycyrrhizin use, plasma alkaline phosphatase decreased significantly.³⁶⁶⁰
- IIa. 3) Coating **ibuprofen** with licorice extracts reduced **stomach ulcers** and lowered the ulcer index compared to use of ibuprofen alone (PO in rats).¹⁰⁰⁶
Similarly, an hour before being given a stomach ulcer-inducing dose of **indomethacin**, licorice extract doses of 12.5, 25, and 50 mg/kg were administered; all doses significantly reduced the ulcer index compared to indomethacin alone, while raising the gastric pH (PO in rats).²⁹⁷⁶

LOBELIA

p. 231

**Lobelia inflata* herb or seeds

Complementary Adjuncts

- Ia. 1) A lobelia alkaloid mixture or 8 mg lobeline reduces **tobacco** consumption as a **cigarette smoking** deterrent (PO in human clinical study).⁵⁵⁴
In a study of 22 smokers who smoked on average 31.5 cigarettes daily, tablets with either 2.5, 5.0, or 7.5 mg were given sublingually 3, 6, 9, or 12 times daily beginning the day after stopping smoking at noon (PO in human clinical study). Withdrawal symptoms were significantly reduced with increasing cumulative dosage, with maximum effectiveness with 7.5 mg taken either 9 or 12 times per day. Adverse effects were not clinically significant.³⁴⁵³ In a randomized, placebo-controlled, double-blind trial with 180 healthy smokers, 90 were given 7.5 mg of lobeline sublingually 9 times daily for 6 weeks (PO in human clinical study). Among smokers who were highly dependent on tobacco that completed the trial, there was a greater tendency to cease smoking among those who used lobelia versus placebo.³⁴⁵⁴

LONG PEPPER

p. 232

Piper longum fruit

Drug Interactions

- Ia. + 4) A single dose of the potent non-nucleoside inhibitor of HIV-1 reverse transcriptase, **nevirapine** [a CYP 3A substrate] had 120% greater maximum concentration and 170% increased bioavailability in 8 healthy subjects when taken after 6 days of piperine compared to placebo in a crossover trial (PO in human study).³¹³²

Complementary Adjuncts

- Ia. 1) Piperine increased serum concentrations of **curcumin** and increased curcumin **bioavailability** by 2000% (PO in human study).¹⁵³³
The significant improvements by 200 mg/kg oral curcumin of chronic stress impaired memory performance and serum cortisone, along with oxidative stress parameters including elevated malondialdehyde and decreases in reduced glutathione, superoxide dismutase and catalase, were significantly enhanced with the addition of 20 mg/kg piperine (PO in rats).³³⁹⁶
- IIa. + 1) Piperine at 70 $\mu\text{mol/kg}$ increased plasma **bioavailability** of the chemopreventive agent epigallocatechin gallate [**EGCG**] in green tea by 1.3-fold when given concurrently compared to EGCG given alone (PO in mice). Piperine also increased the maximum plasma concentration of EGCG by inhibiting glucuronidation in mice intestines by 40%. Likewise, the glucuronidation of EGCG was inhibited in human HT-29 colon adenocarcinoma cells (*in vitro*). Piperine also increased EGCG transit time in the intestines (PO in mice).²⁹³⁵
- + 2) The **mineral absorption** of **calcium**, **iron**, and **zinc** were all significantly improved with the addition of 0.02g% of piperine to the diet, compared to the same diet without piperine (PO in rats). Calcium absorption was improved the most. Piperine increased the uptake of calcium better than either capsaicin or ginger.³⁴⁷¹

LYCIUM

p. 234

Lycium barbarum berry

(Barbary wolfberry, Chinese wolfberry, goji)

Drug Interactions

- Ib. 1) After 4 days of drinking a concentrated decoction of 5 g of the fruit 3 to 4 times daily, a 61-year-old woman stabilized on **warfarin** experienced an INR elevation from 2.4 determined 4 weeks prior to 4.1 just after the lycium consumption (PO in human case report). After discontinuing the tea and stopping warfarin for 1 day and restarting it at a lower weekly dose, 7 days later her INR was 2.4 and remained stable for 7 subsequent tests over the next 3 months. After various concentrations of the drug and herb were incubated with microsomes to assess potential inhibition of CYP 2C9 metabolism of warfarin, no inhibition was observed (*in vitro*).¹⁷⁶⁸ In another incident, an 80-year-old woman on a chronic stable warfarin dosage had her therapeutic 2-3.5 INR elevated twice after drinking lycium tea (PO in human case report). On the first occasion, 3 cups of tea made from 10 g lycium fruit per cup the first day was followed by 2 cups of tea the second day, raising her INR to 4.97. Two months later after restabilizing the INR, she consumed 4 cups of the tea 1 day prior to testing, and her INR was raised again to 3.86. Other possible interferences with INR were excluded.³⁰²⁷ A third case involved a 71-year-old woman taking warfarin who was hospitalized with a greatly elevated INR and prothrombin time >120 seconds after drinking goji juice for 4 days (PO in human case report). She was experiencing a bloody nose, bruising, and rectal bleeding. After 2 days off of warfarin and goji juice, along with phytonadione treatment, her INR was reduced to 2.6. The Naranjo probability scale indicated the INR elevation was due to a probable interaction between the juice and warfarin.³⁴⁴⁸

Complementary Adjuncts

- IIa. + 1) The ascites, oxidative stress, and **cardiotoxicity** produced by the **chemotherapy** agent **doxorubicin** weekly for 3 weeks was significantly reduced by prior and ongoing daily consumption of lycium berry decoction (PO in rats). Mortality was lowered from 38% to 13%, the cardiotoxicity showed significant reduction in conduction abnormalities, loss of heart muscle, and arrhythmia, while the significantly increased superoxide dismutase and lowered lipid peroxidation and serum AST demonstrated less oxidative stress in those given lycium extract. Lycium extract did not interfere with doxorubicin cytotoxicity (*in vitro*).³⁰²⁹
- When goji polysaccharides were given at 200 mg/kg for 7 days before and 3 days after 10 mg/kg intravenous doxorubicin, the drug's **testicular toxicity** was dramatically reduced compared to controls given water (PO in rats). The polysaccharides reduced oxidation markers and increased plasma testosterone levels. Compared to controls, the severe degenerative changes to

seminiferous tubules and abnormal sperm rate was attenuated, and reductions of testicular weight, sperm concentrations, and mobile sperm percentage were ameliorated.³¹¹⁰

- + 2) The polysaccharide fraction given at a dose of 200 mg/kg daily for 6 days following 2 days of **myelosuppression** by **mitomycin C** injections led to significantly enhanced recovery of platelet counts and volume and peripheral red blood cell counts, hemoglobin, and hematocrit from 10 to 21 days following the drug (SC in mice).³⁰³⁰

MACA

p. 235

Lepidium meyenii root
(Peruvian ginseng)

Complementary Adjuncts

- Ia. 1) In a randomized double-blind 12-week trial on 14 women and 2 men with **sexual dysfunction** resulting from use of **SSRIs** to treat depression, the 9 taking 3 gr/day of maca had increased sexual function scores (PO in human clinical trial).²⁴⁸⁶

A 12-week, placebo-controlled, double-blind study of 30 premenopausal and 12 postmenopausal women with sexual dysfunction induced by SSRIs or **venlafaxine** (a serotonin and norepinephrine re-uptake inhibitor [**SNRI**]) utilized 3 grams daily maca root in half (PO in human clinical study). Remission rates were almost twice as high for maca as placebo in the Arizona Sexual Functioning Scale [score ≤ 10] and the Massachusetts General Hospital Sexual Function Questionnaire [score ≤ 8]. The higher remission rates occurred primarily in postmenopausal women.³⁴⁸³

MAITAKE

p. 236

Grifola frondosa mushroom fruiting bodies

Drug Interactions

- Ia. + 1) Type II diabetes patients using **glyburide (glibenclamide)**, **glipizide**, or **metformin** further lowered their fasting blood glucose with maitake mushroom powder in caplets (PO in human clinical trial).¹⁶⁰⁹

A 44-year-old man and 75-year-old woman with type 2 diabetes, treated with the oral hypoglycemic drug glibenclamide, were given 500 mg caplets of maitake polysaccharides 3 times daily, and within 10-14 days the fasting blood sugar was further reduced 50% and 21%, respectively, and remained so for 2.5-3 months (PO in human case reports). Glibenclamide doses were reduced by half, and the lowered fasting blood sugar levels were sustained with the new drug doses. After 2 more months, the man stopped using glibenclamide, and maintained his lowered blood sugar level with only 2 caplets daily of the maitake polysaccharides over an additional 13-month monitoring period. The man and woman both lost weight, 7 kg and 2 kg, respectively, during the trial.³⁵⁷⁶

- Ib. + 1) A 79-year-old man with atrial fibrillation was prescribed **warfarin** and maintained an international normalized ratio [INR] between 2-3 for 2 months, until he began taking a maitake D-fraction product 3 times daily to impact his bladder cancer, since it was not treated by chemotherapy (PO in human case report). A week later his INR was elevated to 5.1, though no other changes were made in medication or diet. Warfarin dosage was adjusted downward in stages, since he persisted in using the maitake product. Both warfarin and maitake were discontinued when he began comfort care due to his terminal cancer.³⁵⁷⁵

Complementary Adjuncts

- Ia. + 1) 750 mg of maitake mushroom powder plus 54 mg of its glycoprotein fraction designated MSX 3 times daily between meals was used by 26 randomized **polycystic ovary syndrome** patients for up to 12 weeks, while **clomiphene citrate** was given to 31 others; 15 of those who did not respond to these monotherapies were given a combination of the two for up to 16 weeks (PO in human clinical study). The ovulation rates were 77% for maitake/MSX patients and 94% for clomiphene patients. Of those nonresponders given the combination, evidence of ovulation was

shown by 7 of 7 of those who failed with maitake/MSX and 6 of 8 of those who failed with clomiphene.²⁹¹⁰

- Ib. + 1) When 4 patients with **liver carcinoma** were given 40-150 mg of maitake MD-fraction and 4-6 g of whole maitake powder in conjunction with **5-fluorouracil** chemotherapy and/or after treatment with **cisplatin** and/or **adriamycin**, in all 4 cases the cancer either disappeared, improved, or stabilized with the addition of the maitake (PO in human case series). Similar outcomes were reported with single cases of breast and lung cancers with metastases. These 6 cases were described as representative of 36 cancer patients in which significant symptom improvement or regression was observed for 11/16 with breast cancer, 7/12 with liver cancer, and 5/8 with liver cancer with maitake use. Immune function improvements with interleukin (IL)-2 production and CD4+ count were noted in these cancer after addition of maitake and its MD-fraction, compared to a lack of improvement in these factors in 3 leukemia patients.³³⁴¹

MANGO

Mangifera indica bark

Complementary Adjuncts

- Ia. 1) In a randomized, controlled trial of 20 patients with **rheumatoid arthritis**, all subjects were had been receiving 12.5 mg/week of **methotrexate** associated with NSAIDs (**diclofenac**, **ibuprofen**, and **naproxen**) and/or **prednisone** for 1 year (PO in human clinical study). Then, after baseline assessments, 10 of these continued on the same regimen, while the other 10 were also taking the same plus 300 mg of bark extract 3 times daily before meals for 180 days. Only the extract group had significant improvement in the disease activity score-28 (DAS 28) parameters compared to baseline, though the differences between groups was not significant. Improvements in the American College of Rheumatology criteria after 90 days were also only significant in the extract group at 80%. All of the patients taking the extract had significantly reduced intake of NSAIDs, and of these a significant 70% had no further gastrointestinal side effects.³⁷¹¹

MILK THISTLE

p. 243

Silybum marianum = *Carduus marianus* seeds

Drug Interactions

- Ia. + 3) The inhibition of **losartan** metabolism by treatment with 140 mg of silymarin 3 times daily for 14 days was only significant in the 6 Chinese men with a CYP2C9*1 genotype (PO in human study). Though it was not significant in the 6 men with a CYP2C9*3 genotype, the active metabolite E-3174 was reduced in both genotypes, so it had the effect of potentially diminishing the therapeutic efficacy of taking losartan as an antihypertensive for both genotypes.²⁹⁸¹ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²
- + 4) In a single-blind, placebo-controlled, randomized crossover trial, silymarin at 420 mg daily for 14 days inhibits Pgp efflux of 1 dose of **talinalolol** in 18 healthy subjects, 6 each of which were homozygous (CC, TT) and heterozygous (CT) for MDR1 3435 (PO in human study). The peak plasma concentration and bioavailability were both significantly higher after silymarin by 36.2% and 36.5%, respectively, while the oral clearance was significantly lowered by 23.1%, compared with placebo.³¹³⁷
- HOWEVER, when tested with the Pgp substrate digoxin in 16 healthy humans 440 mg silymarin given as 900 mg of standardized extract daily for 14 days did not significantly alter the drug bioavailability. There was a tendency toward reducing digoxin levels, suggesting potential Pgp induction.¹⁸⁰⁶ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).³²²²
- III. 2) S(-)-**warfarin** 7-hydroxylation by CYP 2C9 was competitively inhibited by silybin (*in vitro*).¹²⁹⁷

Silybin B with an IC₅₀ of 8.2 μM was a more potent inhibitor of human liver microsome CYP2C9 warfarin metabolism than silybin A with an IC₅₀ of 18 μM (*in vitro*). Isosilybins A and B were less potent still with respective IC₅₀s of 74 and >100 μM. Silybin B also significantly inhibited recombinant CYP 2C9*1 and its recombinant polymorphisms 2C9*2 and 2C9*3 more than silybin A (*in vitro*). Both silybins inhibited CYP2C9*3 significantly more than the CYP2C9 of human liver microsomes pooled from 50 donors.²⁹⁸⁰

- + 3) The metabolism of **tolbutamide** by human liver microsome with isozyme CYP 2C9 was significantly inhibited in a phosphate buffer solution by silybin A and B at concentrations of 3 and 1 μM, respectively (*in vitro*). When tested in plasma, a 30 μM concentration of silybin A and B was required before the isozyme was significantly inhibited (*in vitro*).³⁶³⁴

HOWEVER, the metabolism by human liver microsomes of the CYP 2C9 substrate tolbutamide was not inhibited when exposed to the plasma of 5 donors who had taken milk thistle extract and had high levels of silybin A and B in the plasma (*ex vivo*). This indicates the value of testing plasma after consumption and absorption of complex botanical preparations, which is more representative of systemic human tissue exposure, in contrast to testing the extract as it exists before consumption, disproportionate absorption, and binding to plasma components.³⁶³⁴

Complementary Adjuncts

- Ia. 2) 420 mg silymarin daily given to **alcohol cirrhosis** patients for several years reduced the mortality rate (PO in human clinical studies).^{495,1256}

HOWEVER, in randomized, multicenter, double-blind trial with 200 alcoholics with cirrhosis, 450 mg of silymarin did not improve survival time compared with placebo (PO in human clinical study).²⁸²⁵

Silymarin use following **ethanol hepatotoxicity** helps normalize lab indices for transaminases (PO in human clinical studies).^{119,1257}

Silymarin at 200 mg/kg given with 5 g/kg ethanol 3 times in 24 hours attenuated the acute elevation in serum ALT, enhance lipid peroxidation, increase in liver TNF production, decrease in glutathione content, and microvesicular steatosis with mild necrosis caused by ethanol given alone (PO in mice).²⁹⁰¹ Silymarin at 60 mg/kg for 24 weeks concurrently with ethanol significantly and dose-dependently increased serum levels of alcohol dehydrogenase (ADH) and ALDH and decreased liver levels of CYPs 1A2, 2E1, and 3A induced by ethanol taken without silymarin (PO in rats).³²⁸³

4) Silymarin given to **diabetes type 2** patients taking **metformin** and **glibenclamide** significantly decreased glycosylated hemoglobin, fasting blood sugar, total cholesterol, LDL, triglycerides, and SGOT and SGPT levels, compared to placebo (PO in human clinical study).²⁰⁴¹

A randomized, placebo-controlled, triple-blind parallel trial with 40 type 2 diabetes patients receiving metformin and/or glibenclamide utilized 140 mg of silymarin 3 times daily with 20 patients for 45 days to observe the impact on oxidative stress and inflammatory markers (PO in human clinical study). Those receiving the silymarin increased significantly their total antioxidant capacity and superoxide dismutase and glutathione peroxidase activities by 8.4%, 12.9%, and 30.3%, respectively, compared to those receiving placebo, along with a significant 26.8% reduction in high sensitivity C-reactive protein. In addition, fasting blood sugar was decreased significantly by the silymarin treatment, compared to placebo.³⁴⁷⁹

- Iia. 1) Prevention by silybin of **hepatotoxicity** from **acetaminophen** protected from glutathione depletion and lipid peroxidation (IV in rats).¹¹⁷

Giving silymarin 30 mg/kg with, or 4 hours after, a hepatotoxic dose of 150 mg/kg of acetaminophen prevented the associated elevations in serum ALT, AST, ALP, LDH, total and direct bilirubin, and methemoglobin equivalent to the effects of 100 mg/kg of N-acetylcysteine (PO in cats).²⁸²⁴ When silymarin was given at 100 mg/kg body weight after acetaminophen-induced hepatotoxicity, improvements in albumin globulin ratio and serum alkaline phosphatase and transaminases AST and ALT were significantly better (PO in rats). Also, the histopathologic damage to the liver was less and signs of regeneration were greater than with no treatment.³¹⁸¹

DNA strand breaks in liver cells caused by 25-30 mM acetaminophen were prevented by silybin at 25 mcM, though hepatocellular toxicity of acetaminophen was not affected (*in vitro*).²⁹⁰²

3) Silybin helps prevent **kidney damage** from nephrotoxic **cisplatin** at doses of 200 mg/kg (IV in rats).^{186,187}

HOWEVER, in a randomized, placebo-controlled, double-blind trial silymarin at 420 mg daily beginning 24-48 hours before and continuing through three 21-day cisplatin chemotherapy courses did not reduce acute kidney injury or renal wasting of magnesium and potassium electrolytes in 12 patients, compared to 12 patient controls (PO in human clinical study). No adverse effects were associated with silymarin use.³⁵³⁶

MYRRH root

p. 249

Commiphora molmol

Drug Interactions

Ib. + 1) A 57-year-old man with a prosthetic mitral valve, regularly taking 3 mg/day **warfarin** to reduce blood coagulation and increase his International Normalized Ratio [INR], began taking an aqueous extract of myrrh roots 3 times daily for acute bronchitis together with his warfarin (PO in human case report). One week later, after a 2.4 INR finding, his INR tested as only 0.9. He stopped the extract and was given IV heparin for 3 days to raise the INR to an acceptable level and was told to completely avoid all herbal medications. The myrrh aqueous extract was believed to have induced hepatic microsomal enzymes that rapidly metabolized the warfarin (speculative).³⁵²³

HOWEVER, there is no evidence that water-soluble myrrh components induce the CYP 2C9 enzyme that metabolized warfarin, and 7 days is not long enough to allow for induction of CYP enzymes. It may be possible that the myrrh root extract interfered with warfarin absorption by some unidentified mechanism (speculative).

NIGELLA [formerly listed as BLACK CUMIN]

p.66

Nigella sativa seed

(black cumin, black caraway, black seed; Arab.: kalonji)

Complementary Adjuncts

- Ia. 1) Chemical war victims from **mustard gas inhalation** on **salbutamol** and **corticosteroids** required less of these after taking black cumin extract (PO in human clinical study).²⁴⁸⁹
- + 2) Doses 3 times daily of 250 mg or 500 mg of the powdered seed significantly and dose-dependently reduced acute **opiate withdrawal** symptoms compared to placebo in an open study of 50 **opioid** addicts treated for 12 weeks and as in-patients for the first 12 days (PO in human clinical study). Based on historical controls, craving and relapses were also reduced. Diazepam was used to some to help sleep.²⁹⁸²
- + 3) In 40 females with **rheumatoid arthritis** taking the antirheumatic drugs **methotrexate**, **hydroxychloroquine**, **diclofenac**, and **folic acid**, 500 mg of seed oil given twice daily for a month significantly decreased disease scores, along with fewer swollen joints and shorter morning stiffness duration, compared with results after 1 month of placebo (PO in human clinical study).³¹¹⁴ In a randomized, placebo-controlled, double-blind trial investigating 1000 mg of black cumin oil daily for 8 weeks, all 39 women had rheumatoid arthritis and received methotrexate, hydroxychloroquine, and **prednisone**, but no NSAIDs, while 23 of them took the oil and 16 received placebo (PO in human clinical study). Those using the oil had significantly increased levels of the anti-inflammatory serum cytokine interleukin (IL)-10 and significantly lower levels of the inflammatory marker nitric oxide and lipid peroxidation marker malondialdehyde.³⁵⁹⁴
- + 4) In 21 patients with non-ulcer ***Helicobacter pylori* dyspepsia** who were receiving **omeprazole**, 2 grams of seed powder daily for 4 weeks was effectively in eradicating the *H. pylori* in 66.7% (PO in human clinical study). The difference between this outcome and the 82.6% eradication

- from use of triple therapy with clarithromycin, amoxicillin, and omeprazole was not statistically significant.³³¹²
- + 5) In a 3-month randomized study with 29 **asthma** patients taking inhaled **corticosteroids**, mostly using **beclomethasone** or **fluticasone** inhalers, and oral corticosteroids, **theophylline**, and **beta-agonists**, wheezing and coughing and asthma severity were significantly improved by the end of the study with 15 using black cumin decoction compared to 14 controls, along with decreased use of all of the drugs by the extract group and no drug reduction by control subjects (PO in human clinical study).²⁹⁸⁸ In a group of 15 moderate to severe asthma patients on medications who temporarily and briefly suspended use of theophylline and beclomethasone or fluticasone inhalers but continued with **prednisolone** use, bronchodilation from boiled black cumin extract at 50 or 100 mg/kg was significantly improved compared to the corticosteroid alone, though significantly less when compared to prednisolone with theophylline or salbutamol (PO in human clinical study).²⁹⁸⁹

In a randomized, placebo-controlled, single-blind study with 76 patients with partially-controlled asthma, black cumin seeds were given as powder in capsules in doses of 1 or 2 grams daily for 3 months, along with maintenance inhalation therapy with **budesonide** or fluticasone (PO in human clinical study). The percent predicted forced expiratory volume at 1 second [FEV₁ % predicted] and forced expiratory flow were both increased significantly with the 2 g dose, and peak expiratory flow variability (PEF) was improved significantly at both doses after 6 and 12 weeks, in comparison to controls. The asthma control test score was improved significantly with both doses after 6 and 12 weeks, compared to baseline. Serum IgE significantly decreased and interferon- γ significantly increased at both doses after 12 weeks, compared to baseline values.³⁶⁰⁰
 - + 6) Children of ages 2-18 years with **brain tumors** receiving **chemotherapy** were randomized into 2 groups of 40 to receive 5 grams of nigella seeds daily for 3-9 months or not (PO in human clinical study). Significantly fewer episodes of febrile neutropenia were experienced by the nigella group with only 2.2%, compared to the 19.3% in the control group. As a result, the length of hospital stay was significantly less for the nigella group, 2.5 days versus 5 days for the control group.³⁶⁶⁹
 - + 7) In 80 patients with **metabolic syndrome** and poor glycemic control while taking 500 mg **metformin** twice daily and 10 mg **atorvastatin** once daily, 500 mg of nigella powder daily was given to half of them for 8 weeks (PO in human clinical study). After 2 months those receiving the powder had significantly reduced fasting blood glucose, postprandial glucose, glycated hemoglobin, and LDL-cholesterol, in comparison to controls.³⁶⁹⁵
 - Iia. 2) The use of thymoquinone at 5 mg/kg daily with **ifosfamide** reduced the severity of the drug-induced **Fanconi syndrome** with its **kidney damage** (PO in rats), while the same combination used in treating **Ehrlich ascites carcinoma** xenograft significantly enhanced antitumor effects, along with lower mortality rate and less weight loss, compared to use of ifosfamide alone (PO in mice).²⁴³¹
 - + 3) The **hepatotoxicity** caused by **acetaminophen** as shown by significant increases in ALT, total nitrate/nitrite, and lipid peroxide and decreased glutathione was prevented by 5 days of 2 mg/kg/day of thymoquinone (PO in mice). The effect was apparently not due to influence on metabolic activation of acetaminophen.²⁹⁸³
 - + 4) When the seed oil was given at 880 mg/kg for 2 weeks before a 1 ml dose of **ethanol**, it significantly reduced formation of **stomach ulcers** by increasing mucosal glutathione levels and mucin and decreasing mucosal histamine (PO in rats).²⁹⁸⁴ Thymoquinone given at 20 mg/kg reduced ethanol-induced stomach ulcers and the associated lipid peroxidation and glutathione depletion (PO in rats).²⁹⁸⁷
 - + 5) The **cardiotoxicity** induced by **doxorubicin** as indicated by elevated serum lactate dehydrogenase and creatine phosphokinase was prevented with 5 days of pretreatment and 2 days of concurrent treatment with 10 mg/kg daily of thymoquinone (PO in rats). This protection is

likely due to thymoquinone's demonstrated superoxide radical scavenger potency and its inhibition on lipid peroxidation (*in vitro*).²⁹⁸⁵

- + 6) The antitumor effect of **gemcitabine** and/or **oxaliplatin** for 2 weeks against orthotopic **pancreatic cancer** was significantly increased by 25 days of treatment before, during, and after with 3 mg thymoquinone, based on tumor weight, while also reducing local invasion and nodal metastasis (PO in mice). The effect of pretreatment with thymoquinone also reduced pancreatic cancer cell growth in 3 cell cultures due in part to chemosensitization from down-regulation of NF-κB (*in vitro*).²⁹⁸⁶

7) Injections of 80 mg/kg **gentamicin** for 8 days resulted in **kidney toxicity** with significant increases in serum creatinine, BUN, TBARs, and total nitrate/nitrite and decreases in kidney glutathione, glutathione peroxidase, catalase, and ATP levels were noted, but giving the drug together with 50 mg/L thymoquinone in drinking water for 8 days completely reversed all of the changes and kept the damage markers control levels (PO in rats).³²⁵⁹

NONI

p. 251

Morinda citrifolia fruit

Drug Interactions

- Ib. 1) A 49-year-old man taking **phenytoin** for 10 years to control epilepsy developed sub-therapeutic blood levels and poor seizure control when noni juice was taken daily (PO in human case report). Since the patient refused to discontinue the noni juice, the addition of clobazam for seizures and a reduction of noni juice intake led to control of the seizures, with only some auras and minor partial seizures occurring.³⁶⁶³

Complementary Adjuncts

- Ia. 1) The precipitates from adding ethanol to the juice given with **doxorubicin (adriamycin)**, **cisplatin**, **5-fluorouracil**, or **vincristine** for Lewis lung **carcinomatosis**, increased the survivors and life span significantly (IP in mice).¹⁷⁵⁸

A similar polysaccharide-rich fraction was co-administered at doses of 25, 50, 100, and 200 mg/kg daily with doxorubicin to assess its impact on immune function and antioxidant status (PO in rats). The 25 and 50 mg/kg doses significantly increased TCD8+ cell proliferation when given with doxorubicin, indicative of immune enhancement. Catalase levels decreased following the 100 mg/kg dose, suggesting that noni fraction provides antioxidant protection.³⁶⁶⁴

OAT

p. 252

Avena sativa bran

Drug Interactions

- Ib. 1) 50-100 gm daily in 2 patients taking **lovastatin** resulted in elevated LDL that decreased after oat bran was withdrawn (PO in human case reports).¹⁸⁴¹

HOWEVER, in randomized hypercholesterolemic subjects, consumption of only 6 gm oat bran concentrate with 54% beta-glucan twice daily with meals for 6 weeks significantly lowered LDL in 35 adults, compared to 40 controls (PO in human clinical trial).²⁹⁷²

OLIVE

p. 253

Olea europaea fruit oil

Complementary Adjuncts

- Ia. 1) Consumption of 3-4 spoonsful of extra virgin olive oil daily for 6 months compared to safflower oil in a crossover study led to significant reductions in the use of **high blood pressure** medications including **atenolol**, **nifedipine**, **lisinopril**, **doxazosin**, and **hydrochlorothiazide** (PO in human clinical study).¹⁷⁷³ [CORRECTION Note: listed in early printings of the book as a Drug Interaction.]
- + 2) In 34 type 2 diabetes patients with a single **diabetic foot ulcer**, olive oil was used on 17 patients in conjunction with routine care received by the other 17 patients that consisted of local

debridement, oral **antibiotics**, and daily cleansing and sterile dressing (TP in human clinical study). The oil was poured on the ulcer surface with a syringe and then a gauze bandage soaked with the oil was applied to the ulcer daily for 4 weeks. After 4 weeks the olive oil group had significant improvements in degree of ulceration, color, surrounding tissue, and total ulcer status, compared to the control group. The ulcer area and depth were also significantly improved in comparison to controls. Complete healing of ulcers occurred in 73.3% of olive oil users versus 13.3% of non-users, a significantly greater percentage.³⁵⁰⁰

OLIVE leaf

Complementary Adjuncts

- Ia. 1) A dry extract given to 8 early and 16 long-term phase **rheumatoid arthritis** patients together with **methotrexate** for 6 weeks was compared to 8 early phase patients receiving methotrexate treatment alone (PO in human clinical study). While in early phase methotrexate alone did not impact catalase and significantly reduced lipid peroxidation and DNA damage after 6 weeks, when combined with the olive leaf extract there was high catalase activity, decreased protein damage and lipid peroxidation, and significantly reduced DNA damage and IL-6 levels after only 3 weeks. Long-term effects only showed modest cell damage alterations after 6 weeks with the combination.³⁶⁶⁸

OREGON GRAPE

p. 254

Mahonia spp. root bark

Contraindications

- I. 5) [Note CORRECTION: This item should be listed as 3) under DRUG INTERACTIONS Ia. on the next page (p. 255). See below.]
- II. 3) Avoid in **jaundice** in **newborns**^{777,1890} or from **hemolytic anemia** or unconjugated hyperbilirubinemia as **Gilbert's syndrome** and **Crigler-Najjar syndrome** (speculative).⁷⁷⁷
HOWEVER, when berberine-containing herbs were given in herbal concoctions according to traditional dosage and indication to 20 patients with chronic cytopenic hematological conditions, though 3 patients with thalassemia intermedia had transient elevation of serum bilirubin, there was no associated aggravation of anemia or liver dysfunction (PO in human clinical study).³¹⁰⁸

Drug Interactions

- Ia. 1) [CORRECTION: See appropriate listing for berbamine under Complementary Adjuncts Ia. 3.] Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the bioavailability of CYP 3A4 substrate **midazolam** by 40% and its maximum plasma concentration by 38%, and significantly decreased its oral clearance by 27% (PO in human study).³²³⁸
- 3) The combination of 500 mg berberine 3 times daily for 3 months in 43 patients with poorly-controlled type 2 diabetes together with one or more of their regular **oral hypoglycemic** medications including **sulfonylureas** in 28, **metformin** in 20 **acarbose** in 15, and/or **insulin** in 10 resulted in lower fasting and postprandial blood sugar from week 1 through week 12 (PO in human clinical study). Fasting plasma insulin was also lowered by 28% and an index of insulin resistance by 45% of those on medications, while total cholesterol and LDL were likewise reduced. In 31 newly diagnosed type 2 diabetics to whom 15 were given the same dose of berberine and 16 used 500 mg metformin 3 times daily, berberine's hypoglycemic effect was similar to that of metformin on fasting and postprandial blood glucose, as well as reducing glycosylated hemoglobin and plasma triglycerides (PO in human clinical study). Transient gastrointestinal adverse effects were experienced by 35% of the patients, or 20 in total.²³¹⁵
- In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered fasting and postload plasma glucose and HbA1c compared to 52 diabetics on placebo, along with significantly reducing the triglycerides, total cholesterol, and LDL-cholesterol, body weight, and systolic blood pressure (PO in human clinical study).²⁹⁰⁷ In 50 type 2 diabetic patients randomly selected to use 1 gm berberine daily, the 26% and 18% significant reductions in fasting blood glucose and HbA1c were equivalent to those of the 26 and 21 diabetic patients who used

metformin or rosiglitazone, respectively (PO in human clinical trial). Only the berberine group had a significant reduction of triglycerides. Also, in another group of 18 hepatitis C and 17 chronic hepatitis B patients with type 2 diabetes or impaired fasting glucose, 1 gm/day berberine significantly reduced fasting blood glucose, triglycerides, and the transaminases ALT and AST (PO in human clinical trial).²⁹⁰⁸

- + 4) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the 8-hour urinary ratio of the CYP 2D6 substrate **dextromethorphan** to its metabolite dextrorphan by 9-fold (PO in human study).³²³⁸
- + 5) Berberine at 900 mg daily in 17 healthy males for 14 days doubled significantly the 8-hour urinary ratio of the CYP 2C9 substrate **losartan** to its metabolite E-3174 (PO in human study).³²³⁸
- II. + 2) In doses of 30 mg/kg berberine for 2 weeks, the Pgp substrates **digoxin** and **cyclosporine** had significantly increased maximum serum concentration and bioavailability compared to controls, indicating berberine inhibition of Pgp drug efflux (PO in rats).³¹⁰⁵ Likewise, the oral bioavailability of **ketoconazole** was significantly increased by berberine given at 60 mg/kg (PO in rats). Since ketoconazole is both a substrate and an inhibitor of Pgp and berberine is a Pgp substrate, the pharmacokinetic effect of each on the other may lead to pharmacodynamic synergism against fungal infections (speculative).³¹⁰⁴
- III. 3) [See Complementary Adjuncts Ia. 4) below.]

Complementary Adjuncts

- Ia. + 4) When 500 mg berberine hydrochloride was given twice daily with **simvastatin** 20 mg once daily for 2 months to 23 patients in a randomized trial for **high cholesterol**, the 31.8% reduction in LDL cholesterol was significantly better than the 23.8% with berberine in 24 patients or the 14.3% with simvastatin in 16 patients used alone (PO in human clinical study). For triglycerides, the combinations reduced these by 38.9%, significantly better than 22.1% for berberine or 11.4% for simvastatin alone. Similar results were obtained for total cholesterol. No adverse effects were observed in any group. These results reflected those obtained in animals given 90 mg/kg/day berberine and/or 6 mg/kg/day simvastatin (PO in rats).²⁹⁰⁵ In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered triglycerides, total cholesterol, and LDL-cholesterol compared to 52 diabetics on placebo, along with significantly reducing the fasting and postload plasma glucose, HbA1c, body weight and systolic blood pressure (PO in human clinical study).²⁹⁰⁷

In human liver-derived cells, berberine was found to have an additive effect with lovastatin (*in vitro*). Since lovastatin did not reduce the effect of berberine, this indicated a different mechanism of action for the two (*in vitro*).¹⁶⁵⁶

- + 5) When taken with a **high cholesterol** and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).²⁹³² When the same doses of berberine and plant stanols were used with a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.²⁹³³ The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);²⁹³² berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).²⁹³³
- IIa. + 3) Berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive **locomotor activity** induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the berberine, indicating a reduction in the production of dopamine (PO in rats). This

suggests that berberine may help reduce the chronic cocaine psychological dependence (speculative).²⁷⁵³

- + 5) When taken with a **high cholesterol** and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).²⁹³² When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.²⁹³³ The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);²⁹³² berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).²⁹³³
- + 6) The combination of 1 mg/kg berberine with 0.5 mg/kg **amphotericin B** increased the survival for disseminated **candidiasis** to 36 days from 12 days for controls and 17 days and 14 days, respectively, when these 2 antifungal agents were used separately (IP in mice).³¹⁰⁷
- + 7) Compared to those injected with 2.5 mg/kg **doxorubicin** alone every other day for 14 days, those injected with 60 mg/kg berberine an hour prior to the drug had less **cardiotoxicity** as shown by significantly smaller increases in mortality, LDH activity, myocardial injury, and QRS duration (IP in mice). This indicates a potential protective role of berberine against heart damage by doxorubicin.³¹⁴⁸
- + 8) After treatment of ***Clostridium difficile* infection** with 50 mg/kg **vancomycin** daily for 5 days, the use of berberine at 100 mg/kg for the next 5 days prevented weight loss and improved the disease activity index score and the histopathology score, while decreasing the mortality rate, compared to vancomycin alone (PO in mice). Berberine prevented relapse of *C. difficile* infection and significantly improved survival, while counteracting vancomycin side effects. Berberine appears to be effective by restoring intestinal microbiota and inhibiting expansion of *Enterobacteriaceae* family members.³⁶¹⁹

PASSION FLOWER

p. 258

Passiflora incarnata herb

Drug Interactions

- Ia. + 1) A patient with generalized anxiety disorder being treated with **lorazepam** experienced dizziness, throbbing, handshaking, and muscular fatigue after he began self-medicating with passion flower and valerian (*Valeriana officinalis*) for 4 consecutive nights. The first 2 nights he used passionflower dried herb and valerian infusion, while the last 2 nights he took combination solid extract tablets with about 1 gram of each extract at hourly intervals. (PO in human case report). The adverse effects from the combinations appeared to be an additive or synergistic effect due to binding to GABA receptors (speculative).³⁵⁵⁷

Complementary Adjuncts

- Ia. 2) [See Ib. 1) in book.] A combination of 3 herbal hydroethanolic extracts including passion flower herb 4-7:1, hops (*Humulus lupulus*) strobiles 4-8:1, and valerian (*Valeriana officinalis*) root 3-6:1, was found to markedly improve symptoms associated with **benzodiazepine withdrawal** phase in 107 patients of an average age of 54 years (PO in human clinical study). The extracts were begun with 1-2 tablets daily as benzodiazepine dosage was reduced for 2 weeks, and continued for the next 4 weeks after benzodiazepine use was stopped. Improvement was shown for pronounced tiredness in 76% and general unrest in 71%, according to subjective assessment of patients. Sleep improved in 68% by the end of the treatment, and 74% had more motivation and drive than at the beginning. At the end, 62% were calmer and better able to cope. No adverse drug events occurred in any patients.²⁶³⁴

PAU D'ARCO

Tabebuia avellaneda = *Tabebuia impetiginosa* bark

Drug Interactions

- III. + 3) Though not genotoxic itself, the bark potentiated the genotoxicity of the chemotherapy mutagenic drug **doxorubicin** (*in vitro*).³²⁹⁶

PELARGONIUM

NEW

^ *Pelargonium sidoides* root

Complementary Adjuncts

- Ia. 1) Of 200 adult patients with chronic obstructive pulmonary disease [**COPD**] using **salmeterol** as regular inhalant therapy, or this combined with **budesonide**, along with **ipratropiumbromide** and **fenoterol** as needed, 99 were also given 30 drops 3 times daily for 24 weeks a 1:8-10 hydroethanolic root extract while 100 received a matched placebo (PO in human clinical study). The extract group on average significantly went a longer time before the first exacerbation, had fewer exacerbations, used less of the antibiotics **augmentin** or **ofloxacin** and for shorter periods, lost fewer work days, and had great patient satisfaction than did the placebo group. Aside from more mild gastrointestinal disorders, the extract caused no more adverse effects than placebo.³²⁶⁹

PEPPERMINT

p. 261

Mentha x piperita leaves

Drug Interactions

- II. 3) Acute pretreatment with 0.2 ml/kg peppermint oil increased gut motility and significantly prolonged **pentobarbitone** sleeping time, while 5-day pretreatment with the same dose significantly shortened it (PO in mice). This could be due to short term inhibition and long-term induction of pentobarbitone metabolism by the oil (speculative).³¹¹³
- 4) Chronic intake of 0.1-0.2 ml/kg peppermint oil significantly decreased the analgesic effect of **codeine** (PO in mice). This could possibly be due to an inhibition of codeine conversion to morphine by CYP 2D6 (speculative), but there was no acute effect.³¹¹³
- 5) Chronic intake of 0.2 ml/kg peppermint oil significantly prolonged and enhanced the impaired coordination effect of **midazolam** (PO in mice). This was probably due to CYP 3A inhibition over time (speculative), since there was no acute effect.³¹¹³

Complementary Adjuncts

- Ia. 1) When combined with the antiemetic drugs **granistron**, **dexamethasone**, or **metoclopramide**, 2 drops of peppermint or spearmint (*Mentha spicata*) oils given in capsules with sugar a half-hour before and 4 and 8 hours after chemotherapy significantly reduced **nausea and vomiting** induced by **chemotherapy**, compared to the drugs alone or the drugs with placebo, in a randomized double-blind trial with 200 cancer patients (PO in human clinical study).³²⁸⁵

POMEGRANATE

p. 266

Punica granatum fruit

Drug Interactions

- Ib. 1) A man using **ezetimibe** daily and **rosuvastatin** every other day developed rhabdomyolysis after beginning pomegranate juice (PO in human case report).¹⁹⁸²
- HOWEVER, prior to statin treatment he had elevated creatinine kinase, and taking atorvastatin and simvastatin previously caused myalgia. All 3 statins additionally increased the creatine kinase levels. Unlike atorvastatin and simvastatin that are metabolized by CYP 3A4, rosuvastatin is metabolized by CYP 2C9 and 2C19.¹⁹⁸² Despite inhibiting the metabolism of CYP 2C9 drug substrates (*in vitro*^{3112,3245} and in rats³¹¹²), when 250 ml of pomegranate juice or a single capsule with 1 gram pomegranate extract containing 689 mg of polyphenols was given in a crossover trial to 12 subjects along with the CYP 2C9 substrate flurbiprofen, no change in its metabolism was noted when compared with placebo control and the positive control inhibitor

fluconazole (PO in human study).³²⁴⁵ Also, though pomegranate juice has been shown to inhibit CYP 3A (PO in rats,¹⁹²⁰ *in vitro*^{1920,1923}), [Note CORRECTION as follows.] it does not inhibit metabolism of midazolam by CYP 3A4 (PO in humans).²²¹³

2) [Note CORRECTION: this item is properly found as item IV. 1.]

II. + 2) Pomegranate juice given at 3 ml/kg/day as a pretreatment for 1 week led to significantly increased absorption 5-fold of the calcium channel blocker **nitrendipine** (PO in rats). The drug's peak plasma concentration and oral bioavailability also were significantly increased 1.8-fold when the juice was administered 1 hour before nitrendipine. The effect is likely due to inhibition of Pgp and CYP3A in the gut, but not in the liver. The elimination half-life was not altered by pretreatment or concurrent use of the juice.³¹¹¹

+ 3) When 3 ml pomegranate juice was given 1 hour before **tolbutamide**, the bioavailability significantly increased 1.2-fold, but the elimination half-life was not altered (PO in rats). This suggests that intestinal metabolism by CYP 2C9 was inhibited, but not its liver metabolism.³¹¹²

HOWEVER, despite also inhibiting the metabolism of CYP 2C9 drug substrates (*in vitro*^{3112,3245}), when 250 ml of pomegranate juice or a single pomegranate extract capsule with 689 mg of polyphenols was given in a crossover trial to 12 subjects along with the substrate flurbiprofen, no change in its metabolism was noted when compared with placebo control and the positive control inhibitor fluconazole (PO in human study).³²⁴⁵

III. 1) Pomegranate juice strongly inhibited the metabolism of the CYP 3A substrate **midazolam** (*in vitro*).¹⁹²³ Pomegranate juice was shown in other studies to inhibit CYP3A (*in vitro*,^{1920,2123,2213} in rats¹⁹²⁰).

HOWEVER, 2 doses of 8 oz juice each given about 12 hrs and 1 hr prior to midazolam had no effect on IV or oral midazolam clearance (PO in human study).²²¹³

+ 2) Pomegranate juice almost completely inhibits **diclofenac** metabolism by human liver microsomes in a 5% concentration when 25 ml is added (*in vitro*), indicative of CYP 2C9 inhibition.³¹¹²

HOWEVER, despite also inhibiting the metabolism of CYP 2C9 drug substrates (*in vitro*³²⁴⁵ and in rats³¹¹²), when 250 ml of pomegranate juice or a single pomegranate extract capsule with 689 mg of polyphenols was given in a crossover trial to 12 subjects along with the substrate flurbiprofen, no change in its metabolism was noted when compared with placebo control and the positive control inhibitor fluconazole (PO in human study).³²⁴⁵

IV. [1] A woman was stabilized on warfarin dosage for 5 months while consuming pomegranate juice 2-3 times/week (PO in human case report) . She began to have subtherapeutic INRs for 4 months after skipping a couple of doses, but returned to normal dosing and INRs. After referral to an anticoagulation clinic, she stopped the juice and had 2 normal INRs, but then 2 subnormal INRs though any potential CYP inhibition by the juice would have been eliminated. Another dose increase resulted in normal INRs.²⁶⁰²

HOWEVER, despite inhibiting the metabolism of CYP 2C9 drug substrates (*in vitro*^{3112,3245} and in rats³¹¹²), when 250 ml of pomegranate juice or a single pomegranate extract capsule with 689 mg of polyphenols was given in a crossover trial to 12 subjects along with the substrate flurbiprofen, no change in its metabolism was noted when compared with placebo control and the positive control inhibitor fluconazole (PO in human study).³²⁴⁵

Complementary Adjuncts

Ia. 1) Use of 10 ml daily of a pomegranate juice concentrate, with a polyphenol content of 1300 mg equivalent to 200 ml of juice, for 12 weeks by 6 **rheumatoid arthritis** patients taking the disease-modifying anti-rheumatic drugs **methotrexate** and **hydroxychloroquine** [plus **sulfazine** in 2], along with **prednisone** in 5 and **NSAIDs** in 4, resulted in significantly fewer tender joints that decreased by 62% (PO in human clinical study).³⁰²⁴

Iia. 1) The component ellagic acid at 60 mg/kg has been shown to reduce effects of **alcohol hepatotoxicity** induced by 7.9 g/kg **ethanol** daily for 45 days (PO in rats).³¹⁵³⁻³¹⁵⁵ This includes a reduction of the liver fibrotic markers,³¹⁵³ improved body weight and circulatory antioxidant

status,³¹⁵⁴ decreased lipid levels,^{3154,3155} and reduced plasma AST, ALT, and peroxidative markers.³¹⁵⁵

2) After 12 weeks, in groups inoculated in the tibial bone with **metastatic prostate cancer cells** and treated with either the 50% DMSO vehicle as controls, or with 5 mg/kg docetaxel once weekly, pomegranate fruit extract 60 mg/kg 3 times per week, or a combination of the **docetaxel** and pomegranate extract treatments, the PSAs levels in these groups were 60.5, 54.1, 40.4, or 11.6 ng/ml, respectively (IP in mice). Besides the extract and combination groups having significantly lower PSAs than the control or docetaxel groups, radiographically the extract and combination groups also showed inhibitory effects of prostate cancer tumor growth in bones compared to controls.³³⁸¹

PRICKLY PEAR

p. 269

Opuntia spp. stems/pads and fruit

Drug Interactions

Ia. 1) Heated and unheated stems of the species *Opuntia ficus-indica* given at a dose 500 gm to 8 type diabetics receiving **glibenclamide (glyburide)** lowered blood sugar after 2-3 hours (PO in human clinical study).⁹⁵¹

O. ficus-indica water extract of the stems and a proprietary skin blend of the 3 parts stem to 1 part fruit both significantly reduced blood glucose and increased insulin in a 120 minute glucose tolerance test in normal animals at doses of 6 mg/kg, while the skin blend also significantly increased basal insulin levels (PO in rat study).²⁸²⁶

Ib. 1) A 58-year-old man with type 2 diabetes who had maintained normoglycemic control with **metformin** plus 10 mg **glipizide** daily, as indicated by fasting blood glucose readings and hemoglobin A_{1c} values, experienced 4 hypoglycemic events following use of crude prickly pear pads daily for a month (PO in human case report). Glipizide was discontinued and his blood sugar normalized, while he continued the prickly pear consumption for another month, before his use of the pads was revealed during consultation with a pharmacist.³⁵⁶⁵

Complementary Adjuncts

Ia. 1) Freeze-dried pads given before 90% **ethanol** to assess **stomach ulcer** formation significantly reduced hyperemia and lesions (PO in rats).²⁶⁹⁶

When 5 mg/kg of prickly pear mucilage was given after chronic gastric damage from ethanol, the enzymatic changes and mucosal erosion were promptly corrected by its anti-inflammatory effect (PO in rats).³⁵⁰⁵

PSYLLIUM

p. 270

Plantago psyllium = *Plantago afra* and *Plantago ovata* = *Plantago ispaghula* seed or seed husk

Complementary Adjuncts

Ia. 2) In **diabetes type 2** psyllium reduces glucose concentration in the blood when taken with **glibenclamide [glyburide]** (PO in human clinical study).¹⁴⁴⁸

In a 3-part randomized crossover study with 7 type 2 diabetic patients using glibenclamide and 5 taking **tolbutamide**, the use of 15 g of psyllium before 90 g of white bread reduced postprandial glucose significantly compared to placebo and similarly to acarbose (PO in human clinical study).²⁷⁹⁸ A randomized, double-blind, placebo-controlled 8-week study of 5.1 g psyllium in 250 ml twice daily before breakfast and dinner in 36 type 2 diabetic patients taking glibenclamide or **metformin** led to significant decreases in fasting blood sugar, glycosylated hemoglobin, and LDL/HDL ratio and a significant increase in HDL-cholesterol with psyllium compared to placebo (PO in human clinical trial). Gastric tolerance of metformin was better in the psyllium group.²⁷⁹⁹ Another randomized, blinded, placebo-controlled 8-week study with 29 type 2 diabetic patients using diet and oral sulfonylureas or diet only showed significantly reduced all-day and postprandial blood glucose, total cholesterol, and LDL-cholesterol with 5.1 g psyllium before the morning and evening meals compared to placebo (PO in human clinical trial).²⁸⁰⁰ In 12

type 2 diabetics taking unspecified **oral hypoglycemic** drugs and 6 treating with diet alone, 6.8 g psyllium twice daily before the first and last meal reduced maximum postprandial glucose elevation significantly after all 3 meals (PO in human clinical study). There was no significant difference in this effect from those who used the drugs compared to those who did not.²⁸⁰¹

QUASSIA (SURINAM)

p. 272

Quassia amara bark, wood, root

(bitterwood, Surinam wood; Sp.: amargo, cuassia, hombre grande, palo muneco, ruda, Simaruba; Port.: pau amarelo, guabo, pau quassia, wewe gifi)

Complementary Adjuncts

Ila. + 1) For preventing **gastric ulcers** induced by 40 mg/kg i.p. **indomethacin**, 200-800 mg/kg of a quassia methanolic extract was found to significantly reduce the incidence by 77-85% (PO in rats). Gastric acidity also decreased dose-dependently. Quassia extract at 20 mg/kg inhibits basal and histamine-induced gastric acid secretion which is accentuated by cimetidine. Quassia probable acts through histamine H₂ receptor.³³⁸² Gastric ulcers induced by either indomethacin or by **ethanol** were significantly reduced by doses of 4.9-48.9 mg/kg daily for 1 week of an extract containing quassinoids (PO in rats).³³⁸³ In gastric ulcers induced by a combination of indomethacin with the cholinomimetic bethanechol, 100 mg/kg of extracts made with either 70% or 100% ethanolic, dichloromethane, or hexane reduced ulcer incidence by 22.5%, 23.4%, 50.5% and 46.8%, respectively (PO in mice). For ulcers induced by combined **hydrochloric acid** and ethanol the same 4 extracts significantly reduced ulcer formation at doses of 25 (except 70% ethanolic extract), 50, 75, and 100 mg/kg and significantly increased free mucus.³³⁸⁴

RASPBERRY

p. 273

Rubus idaeus leaves

Complementary Adjuncts

Ila. + 1) The component ellagic acid at 60 mg/kg has been shown to reduce effects of **alcohol hepatotoxicity** induced by 7.9 g/kg **ethanol** daily for 45 days (PO in rats).³¹⁵³⁻³¹⁵⁵ This includes a reduction of the liver fibrotic markers,³¹⁵³ improved body weight and circulatory antioxidant status,³¹⁵⁴ decreased lipid levels,^{3154,3155} and reduced plasma AST, ALT, and peroxidative markers.³¹⁵⁵

RHODIOLA

Rhodiola rosea root

Drug Interactions

IV. 1) Concerns about rhodiola interactions with drugs administered concomitantly led to a standardized extract of the roots being studied separately in combination with **theophylline** and **warfarin** (PO in rats). No significant interference was found with theophylline or warfarin pharmacokinetics or warfarin coagulation activity.³⁵⁵⁰

ROMAN CHAMOMILE

p. 276

Chamaemelum nobile = *Anthemis nobilis* flowers and herb

Contraindications

I. 1) Avoid in **pregnancy**, due to the emmenagogue and abortifacient effects of the flower and of the plant (empirical)^{74,150,1125} and its volatile oil.⁷⁴ Regular internal consumption should be avoided throughout **pregnancy**, based on a study of 392 pregnant Italian women that found the 37 who were regular users of chamomile had a 21.6% higher frequency of threatened miscarriages and a 21.6% increase in preterm labors, compared to non-users (PO in human study).³⁰⁷⁸

HOWEVER, the authors failed to identify by scientific name whether the chamomile used was German (*Matricaria recutita*) or Roman (*Chamaemelum nobile*) chamomile.³⁰⁷⁸

ROOT OF GOLD

NEW

^ *Heliopsis longipes* root
(Sp.: chilcuan)

Complementary Adjuncts

IIa. 1) In a thermal **inflammatory pain** test using an ethanolic extract of the dry root separately and combined with the NSAID **diclofenac**, a dose-dependent analgesic effect was shown for each agent alone and combined (PO in mice). The combination showed a synergistic effect, with lower doses of each resulting in greater analgesia than the simply by adding the effects of each at that dose.³⁵⁶² Testing the acetone extract and the component affinin demonstrated dose-dependent antinociceptive effects for both each in capsaicin and acetic acid tests (IP in mice).³⁵⁶³

ROSEMARY

p. 276

Rosmarinus officinalis leaves

Complementary Adjuncts

IIa. 1) Aqueous and ethanolic extracts of the aerial parts reduced the **withdrawal** syndrome of **morphine** when given at 1.7 g/kg and 1.0 g/kg, respectively (IP in mice). Only the aqueous extract contained an alkaloid. The extracts also reduced the analgesic activity of morphine.³⁴⁶⁴

SAFFRON

p. 278

**Crocus sativus* stigma

Complementary Adjuncts

Ia. + 1) In a randomized, prospective, comparative pilot study with 34 patients with stable primary **open-angle glaucoma** receiving treatment with **timolol** and **dorzolamide** eye drops, 17 also received 30 mg aqueous saffron extract daily for 1 month (PO in human clinical study). During, at the end of, and after a 1-month washout following the trial, intraocular pressure was measured and compared between the 2 groups. The saffron group had a significant reduction of intraocular pressure after 3 and 4 weeks compared to control group, but at the end of the was washout period, both groups had returned to baseline levels. No adverse effects were encountered.³⁴³⁷

+ 2) A randomized, placebo-controlled, double-blind trial with 34 women with **sexual dysfunction** from treatment of depression with **fluoxetine** used 30 mg of saffron daily with half of them for 4 weeks (PO in human clinical study). Those taking saffron had significant improvements after 4 weeks in the Female Sexual Function Index total score and subscore domains for arousal, lubrication, and pain. Side effects for the 2 groups were similar.³⁴⁸⁰ Similarly, a randomized, double-blind, placebo-controlled study of 30 men with **erectile dysfunction** from treatment of depression with fluoxetine utilized 30 mg daily of saffron with 15 of these men for 4 weeks (PO in human clinical study). After 2 weeks and 4 weeks, there were significant improvements in the total score for the International Index of Erectile Function scale as well as with the domains for erectile function and sexual satisfaction. A total of 60% of the men using saffron regained normal erectile function, compared to 7% of the men on placebo; side effects were similar in both groups.³⁴⁸¹

In a pilot study for men with idiopathic erectile dysfunction, 20 men with ED took a 200 mg tablet of saffron each morning for 10 days (PO in human clinical study). After 10 days there was significant improved nocturnal rigidity and tumescence of both the tip and base of the penis, along with significantly higher scores in the International Index of Erectile Function questionnaire, both total score and in all domains: erectile function, sexual desire, intercourse, orgasmic function, and satisfaction.³⁴⁸²

IIa. 1) The aqueous and ethanolic extracts of the stigma reduced the **withdrawal** syndrome from **morphine** at doses of 80 and 800 mg/kg, respectively, whereas the constituent crocin did not (IP in mice).³⁴⁶⁵

SAGE

p. 279

**Salvia officinalis* leaves

Complementary Adjuncts

Ila. + 2) Sage hydroalcoholic extract, given at 100 mg/kg after and with IV **vincristine** for 10 of 12 days before formalin injection, reduced the second phase **neuropathic pain** expressions from vincristine-induced peripheral neuropathy (IP in mice). The sage extract given alone also reduced the formalin-exacerbated pain that was increased when vincristine was given alone (IP in mice).³³⁷²

SANCHI GINSENG

NEW

^ *Panax notoginseng*
(tienchi ginseng; Ch.: san qui ginseng.)

Complementary Adjuncts

- Ia. 1) In 140 patients with acute or subacute anterior cerebral **ischemic stroke**, 50 mg **aspirin** with or without 100 mg of panaxatriol saponin extract standardized to ginsenosides [50% Rg1, 6% Re] and notoginsenoside R1 [11%] was given daily for 4 weeks (PO in human clinical study). Those receiving the extract had significantly better improvement in neurological function involving movement of limbs and in daily living activities compared with aspirin alone. Adverse events were equivalent between groups.³⁰⁷⁶
- 2) In a randomized study of 84 **rheumatoid arthritis** patients receiving **diclofenac**, **leflunomide**, and **prednisone** for 28 days, 43 also received a total saponin fraction from sanchi ginseng (PO in human clinical study). The clinical improvement were significantly better in the saponin group for joint pain, tenderness, and swelling and time of morning stiffness compared to using only drugs, even though the improvements were significant for the drugs alone. Also, laboratory findings for the saponin group that were significantly better than for drugs-only included lowered platelet count, ceruloplasmin, alpha1-acid glycoprotein, and C-reactive protein; these were also lowered significantly for drugs alone, along with other rheumatoid arthritis markers in both groups.³⁴¹⁸
- 3) In a review of randomized, controlled studies on unstable **angina pectoris** patients maintained on their medications, 2 soft capsules of sanchi ginseng extract were used twice daily for 4 weeks in 2 separate placebo-controlled studies published in Chinese, one with 90 subjects in each group and the other with 50 subjects in each group (PO in human studies). In the larger study, patients were taking **nitrates**, **beta-blockers**, **calcium channel blockers**, and low molecular weight **heparin**, while the smaller study patients used the same except for **aspirin** in place of heparin. Risk ratios showed the extract outcome was more favorable than placebo in both studies for symptoms of angina pectoris and improvement of ECG, while the larger study also indicated improved outcomes for frequency and duration of angina pectoris and the smaller study had fewer cardiovascular events than placebo (0 vs. 2, respectively).³⁷⁰¹
- Ila. + 1) Mice receiving 100 mg/kg of saponins from the dried rhizomes for 5 days prior to a 20 mg/kg intraperitoneal **doxorubicin** injection had significantly less **cardiotoxicity** from the chemotherapy drug, compared to doxorubicin given without the saponin pretreatment (PO in mice). This was shown by improved ventricular contraction, minimal morphology changes in the heart, and lower lactate dehydrogenase, creatine kinase, and creatine kinase isoenzyme levels in heart tissue, as well as normalized antioxidant enzyme activities, in those receiving the saponins. In addition, the saponins did not compromise the inhibition of cancer cell proliferation by doxorubicin (*in vitro*).³⁵⁶⁶
- Ilb. + 1) The saponins of sanchi ginseng at 50-200 mcg/ml for 4 hours in a transfected HeLa cell line increased the **cytotoxicity** of the cancer chemotherapeutic agent **cisplatin** by enhancing functional gap junction activity (*in vitro*).³⁵⁷²

SAW PALMETTO

p. 280

Serenoa repens fruit

Complementary Adjuncts

Ia. + 1) A product with 320 mg saw palmetto extract, 5 mg lycopene and 50 mcg selenium was given for 1 year with or without 0.4 mg of the adrenergic alpha-blocker drug **tamsulosin** and compared with the effects of 0.4 mg tamsulosin alone in 219 men with **benign prostatic hyperplasia** [BPH] and lower urinary tract symptoms (PO in human clinical study). Those receiving the saw palmetto extract/nutrients/drug combination had significantly greater improvement for International Prostate Symptom Score [IPSS] and in maximum urinary flow than with tamsulosin alone or the extract/nutrients alone after a year. The combination extract/nutrients/drug also improved erectile dysfunction symptoms better than tamsulosin alone after 1 year.³⁴¹¹ A randomized, open-label study with 103 men with BPH using the same doses of tamsulosin alone or combined with saw palmetto extract found significantly improved storage symptoms with the combination after 12 months, though the difference in IPSS, prostate volume, voiding subscore, maximal flow rate, post-voiding retention, and PSA were not significantly changed (PO in human clinical study).³⁶⁷⁵

However, a prospective study comparing 320 mg daily of saw palmetto extract with 0.4 mg per day of tamsulosin or a combination of the 2 agents in groups of 20 patients each found no statistical differences between the groups in IPSS or maximal flow rates (PO in human clinical study). The saw palmetto group showed no adverse treatment effects.³⁴³⁴ Also, in a 6-month randomized trial with patients with benign prostatic hyperplasia having lower urinary tract symptoms in which 87 received 0.4 mg tamsulosin, 97 took 320 mg saw palmetto ethanolic extract, and 81 used a combination of both, there were no statistical differences in outcomes between the 3 groups (PO in human clinical study). All groups had significant improvements in IPSS and maximal flow rates, with the saw palmetto group having the greatest decrease in IPSS and the combination showing the greatest increase in flow rate. Treatment-related adverse effects occurred in 23% given tamsulosin alone and in 21% given the combination, but none were observed in the group taking saw palmetto extract alone.³⁴¹⁹

+ 2) A tablet with 320 mg saw palmetto extract, 200 mg *Lactobacillus sporogenes*, and 100 arbutin was given daily for 30 days to 77 men with **chronic bacterial prostatitis** together with 600 mg/day the antibiotic **prulifloxacin** given for 21 days and compared with a prulifloxacin-only regimen (PO in human clinical study). After 2 months, those who only received antibiotic had a 27.6% recurrence, compared to only 7.8% of those who also took the saw palmetto combination. After 2, 4, and 6 months the prostatitis symptoms were significantly less among those receiving saw palmetto combination with prulifloxacin, compared to those receiving prulifloxacin alone.³⁴¹⁴

SCHISANDRA

p. 281

Schisandra chinensis fruit

(northern schizandra Ch.: bei wu wei zi [Mand.]

Drug Interactions

Ia. 1) When 12 subjects took 600 mg extract daily for 14 days, it significantly increased **talinalolol** bioavailability, due to inhibition of P-glycoprotein efflux (PO in human study). The bioavailability and peak plasma concentration of talinalolol were significantly increased by schisandra extract by 47% and 51%, respectively.³¹³⁸ Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as high (speculative).³²²²

II. + 3) The lignan extract containing 10.9% schisandrol A, 2.4% gomisin C, 1.9% deoxyschizandrin, and 1.8% γ -schizandrin inhibits intestinal CYP 3A4 metabolism of **midazolam** when a single 150 mg/kg dose is given with oral midazolam, but not hepatic metabolism for IV midazolam (PO in rats). The lignan extract also inhibits metabolism of midazolam (*in vitro*).²⁸³²

HOWEVER, when 150 mg/kg of the lignan extract is given for 14 days, it induces the CYP 3A4 protein expression in the liver 2.5-fold and its intestinal metabolism 4-fold, and thereby increases midazolam metabolism, especially in the small intestines (PO in rats). In those rats that

in which the extract and midazolam were co-administered after 14 of the extract, the induction was modified somewhat by concurrent intestinal CYP 3A4 inhibition. Gomisins B and G were the most potent inhibitors (*in vitro*) and the least concentrated in the liver (PO in rats), while schisadrol A was the least potent (*in vitro*) and the most concentrated in the liver (PO in rats).²⁸³²

- III. 1) While gomisins B and G are also active, gomisins C is the most potent inhibitor of CYP3A4 metabolism of **erythromycin** and **testosterone** and irreversibly inactivates it in a time- and concentration-dependent manner (*in vitro*).²⁹⁴⁶

SCOTCH BROOM

p. 282

**Cytisus scoparius* syn. *Sarothamnus scoparius* tops

Complementary Adjuncts

- Ia. 1) In a randomized, placebo-controlled, double-blind trial to stop **smoking tobacco**, placebo or cytisine from *Cytisus* spp. was given to 370 smokers each for 25 days (PO in human clinical study). With minimal counseling while using 6 tablets with 1.5 mg cytisine each for 3 days, 5 for 9 days, 4 for 4 days, 3 for 4 days, and 2 tablets for the last 5 days, day 5 was the target quit day. After 12 months from the end of treatment, significantly more [8.4%] of those receiving cytisine were still abstaining, compared to the placebo group [2.4%]. The relative inexpense of cytisine over other methods to stop smoking add to its appeal.³⁴⁰⁵

SEA BUCKTHORN

p. 283

Hippophae rhamnoides fruit

Complementary Adjuncts

- IIa. + 2) Pretreatment with 20 ml/kg of sea buckthorn oil daily for 30 days significantly modulated **cardiotoxicity** due to free-radical oxidative damage when 85 mg/kg **isoproterenol** was given SC on days 29 and 30 (PO in rats). On day 31, control rats not receiving the oil showed myocardial necrosis, edema, and inflammation, along with cardiac dysfunction, depleted marker enzymes, and increased lipid peroxidation. As a free-radical scavenger, the oil proved to have protective antioxidant activity that mitigated myocardial damage.³⁶⁸⁴
- + 3) When given 50 mg/kg sea buckthorn extract an hour before administering 5 mg/kg **methotrexate** per day orally for a month, **mucositis** was prevented in the cheek, lower lip and tongue that occurred in animals not receiving the extract (PO in rats). In addition, significantly higher levels of malondialdehyde, IL-1b, and TNF-a were seen in those tissues of animals not receiving the extract, compared to those that did, especially in the tongue. The sea buckthorn extract prevented mucositis induced methotrexate.³⁶⁸⁵

SESAME

p. 285

Sesamum indicum seed oil

Complementary Adjuncts

- Ia. 1) When used by 40 **hypertensive diabetics** taking **atenolol** and oral hypoglycemic drug **glibenclamide**, sesame oil reduced blood pressures (PO in human clinical study).²⁰⁵⁰
- When 60 nonhypertensive patients with **diabetes type 2** were given either 5 mg **glibenclamide**, 35 grams sesame oil, or the combination daily for 60 days, those receiving the combination had significant reductions in glucose and glycosylated hemoglobin of 36% and 43%, respectively, in comparison to glibenclamide or sesame oil alone (PO in human clinical study). Also, with sesame oil and the combination, significant decreases occurred in total cholesterol, LDL-cholesterol, triglycerides compared to baseline, and significant increases were found in HDL-cholesterol and enzymatic and non-enzymatic antioxidants. The sesame oil was used in cooking or on salads.³⁶⁵⁸

SHEPHERD'S PURSE

p. 286

Capsella bursa-pastoris herb

Complementary Adjuncts

- Ia. 1) In a randomized, placebo-controlled, single-blind study of reducing **postpartum hemorrhage**, 100 women were administered 20 U of **oxytocin** in 1 L of Ringer's solution immediately after placental expulsion, and half of these were given 10 drops of a hydroalcoholic extract of shepherd's purse, while the other half was given placebo drops (SL in human clinical study). Compared to baseline, both groups had significantly less bleeding after the intervention, but the bleeding decreased significantly more in the extract group than in the placebo group in the first, second, and third hours after administration. The extract group also had significantly higher hematocrit and hemoglobin value 6 hours after delivery than the placebo group. Satisfaction with treatment was also significantly higher in the shepherd's purse group.³⁷¹³

SHIITAKE

NEW

^ *Lentinula edodes* (= *Lentinus edodes*) mycelia

Complementary Adjuncts

- Ia. 1) A mycelial extract at 1.8 grams daily was tested for 4 weeks to see its effect on quality of life and the immune response of 7 cancer patients on chemotherapy, 3 with **breast cancer** receiving **epirubicin** and **cyclophosphamide** and 4 with gastrointestinal (**GI cancer**) treated with **TS-1**, **UFT** or **5-fluorouracil**, **irinotecan**, and **folate** (PO in human clinical study). A first course chemotherapy-only was compared to the second course combined with the extract. After the second course there were significant improvements in quality of life, natural killer cell activity, and immunosuppressive acidic protein levels. No adverse effects were found with the combined extract and chemotherapy.³⁵⁰²
- 2) The mycelia extract was tested in 7 patients with advanced **colorectal cancer** and metastasis and 1 with **gastric cancer** and metastasis during a second round of chemotherapy with irinotecan, UFT, **mitomycin C**, 5-fluorouracil, **levofolinate**, and/or **taxol** (PO in human study). After the first course of chemotherapy without the extract, adverse events of grade 1 or 2 had occurred in 6 of the 8 patients, but none occurred after the second course while using the extract. After the second course there was also a tendency for improved interferon- γ production by CD4+ and CD8+ T cells and CD56+ natural killer T cells.³⁵⁰³

SILK TREE

p. 286

Albizia julibrissin bark

Drug Interactions

- II. + 1) The ethanolic extract of the bark at 500 and 1000 mg/kg with a hypnotic dose of **pentobarbital** increased sleep duration and decreased sleep latency (PO in mice). The extract showed no sleep inducing effects of its own at 1000 mg/kg in any of 15 animals but induced sleep in 67% given a subhypnotic dose of pentobarbital (PO in mice). It also displaced mesulergine from the 5-HT_{2C} receptor by 88% at 10 mg/ml (*in vitro*).³¹²⁷

SOUTHERN SCHISANDRA

NEW

^ *Schisandra sphenanthera* fruit
(southern schizandra; Ch.: nan wu wei zi)

Drug Interactions

- Ia. 1) When 3 capsules of the extract were given twice daily [66.5 mg deoxyschizandrin/day] for 7 days, it significantly increased the oral bioavailability and maximum plasma concentration of **midazolam**, compared to baseline levels (PO in human study). Midazolam half-life was unchanged, but time to maximum concentration of midazolam and its metabolite 1'-hydroxy-midazolam were significantly increased.³¹³⁶
- II. 1) An ethanol fraction of the fruit dose-dependently reduced sleep latency and increased sleeping time induced by **pentobarbital** (PO in mice).²⁰⁷⁴

2) When 0.25 g/kg of an ethanolic extract was given 15 minutes before **paclitaxel**, the drug bioavailability and maximum plasma concentration were significantly increased, moreso when paclitaxel was given orally than IV (PO in rat study). No CNS toxicity or other side effects were observed. Paclitaxel is a substrate of Pgp and CYP3A, suggesting that one or both of these is inhibited by southern schisandra.²⁸²⁷

Complementary Adjuncts

Ia. 1) To examine the potential advantage of southern schisandra ethanol extract [wu-zhi] on **drug-induced hepatitis** from taking **tacrolimus**, 64 renal transplant patients on triple therapy with tacrolimus, mycophenolate mofetil, and prednisone were divided equally to receive wu-zhi capsules twice daily for 6 months or not (PO in human clinical study). Tacrolimus steady-state trough blood concentrations were monitored, and its dosage decreases were allowed. After 6 months using the wu-zhi extract, tacrolimus dosage was decreased by 34%, compared to 14.3% without it; the ratio of concentration/dose of tacrolimus was 220.7% with the extract and 53.8% without it. The liver enzymes ALT and AST that were elevated by the drugs were also significantly reduced in those using wu-zhi extract. The estimated cost saving for tacrolimus was \$6.15 daily, a 38.9% reduction.³⁵⁵⁸

When 12 healthy subjects were given 3 capsules of extract with 11.25 mg deoxyschizandrin per capsule twice daily for 14 days, preceded and followed by a dose of tacrolimus, the bioavailability, maximum blood concentration, and time to maximum concentration of tacrolimus were significantly increased, while apparent oral clearance was significantly decreased (PO in human study).²⁸²⁹

A single dose of wu-zhi increased the maximum plasma concentration and bioavailability 5-fold, and after 12 days of pretreatment prior to tacrolimus the increases were still significant (PO in rats).³⁵⁵⁹ A tissue distribution study showed that the tacrolimus was increased in the blood by 3-fold, as well as significantly increased in muscle and spleen, after 0.25 g/kg/day of the extract was taken for 4 days, compared to no extract intake (PO in rats).²⁸²⁸ The improved bioavailability of tacrolimus was confirmed by examining first-pass metabolism in the intestines and liver, in which oral bioavailability was significantly increased by 2.1-fold, largely due to intestinal first-pass effect (PO in rats). The efflux transport of tacrolimus by Pgp was significantly lower with extract exposure and CYP3A metabolism by rat and human liver microsomes was inhibited by 100 mcM of extract (*in vitro*), indicating Pgp and CYP3A inhibition.²⁸³⁰ Of 6 active lignins of wu-zhi that may inhibit CYP3A and/or Pgp and increase tacrolimus bioavailability, the strongest is schisandrol B (PO in rats). All 6 lignins [schisandrin A, B, and C, schisandrol A and B, and schisantherin A] inhibited tacrolimus metabolism by CYP3A dose-dependently (*in vitro*). In addition, schisandrin A and B and schisandrol B inhibited Pgp efflux of tacrolimus (*in vitro*).³⁵⁶⁰

SOY

p. 287

Glycine max beans

Complementary Adjuncts

Ia. + 2) A black soybean extract high in hull polyphenols given for 2 months to 7 patients with diabetes type 2 and postprandial **hyperlipidemia** who were concurrently taking the antihyperlipidemic drug **fenofibrate** resulted in significant reductions in serum triglyceride levels and LDL-cholesterol concentrations, compared to 11 patients using fenofibrate alone (PO in human clinical study). A group of 18 patients using the soybean extract alone showed no improvement on lipid levels.³⁵¹⁰

Ib. + 1) In 8 children of ages 6-13 years receiving **chemotherapy** for **cancers** [including neuroblastoma, Wilms tumor, mesenchymal tumor, adrenocortical tumor with lung metastasis, and glioma] with combinations of **adriamycin**, **carboplatin**, **cisplatin**, **cyclophosphamide**, **dacarbazine**, **etoposide**, **ifosfamide**, **irinotecan**, **paclitaxel**, **procarbazine**, **temozolamide**, and **vincristine**, in the first cycle they received no soy isoflavones, while in subsequent cycles the

chemotherapy was the same except a soy isoflavone extract tablet with 8 mg of genistein was given daily (PO in human case series). In all, 9 cycles were given without soy isoflavones, and in 6 children 57 chemotherapy cycles with the genistein occurred over a period of 12-19 months. During the genistein cycles there was shorter duration of neutropenia and antibiotic use and less oral mucositis.²⁸¹³

ST. JOHN'S WORT

p. 289

Hypericum perforatum herb, tops

Contraindications

- I. 1) This herb should not be used during **pregnancy**.³

HOWEVER, 38 women using S. John's wort during pregnancy were compared to 90,128 who were not, and no association was found with its use in regard to gestational age, preterm births, and Apgar score. There was a greater percentage of malformations in the St. John's wort group [8.1%], but it was not statistically significant and the 3 cases did not follow a specific pattern.³⁵³⁰

- 3) Do not take prior to **surgery**.^{1309,1890}

Note CORRECTIONS: in the last line of the first paragraph, it should read: [See drug interactions Ib.2 below.], not 'I.10'.

In the third paragraph, the brackets should read: [See drug interactions Ia.4 and Ia.7&8, respectively.], not 'I.6 and I.8 below'.

Drug Interactions

- Ia. 1) After 2 weeks of the **tricyclic antidepressant** drug **amitriptyline**, combining extract LI160 for 2 weeks led to a significant decrease in its bioavailability (PO in human clinical study).¹⁶¹⁴

HOWEVER, in a randomized, placebo-controlled, double-blind study of 40 patients with mild to moderate depression who were taking the tricyclic antidepressants amitriptyline, **imipramine**, or **nortriptyline**, those also taking St. John's wort extract providing 300 mcg total hypericin daily for 6 weeks had significantly greater reduction of the Beck Depression Inventory score after 6 weeks (PO in human clinical study). None complained of sexual side effects, but the extract group had improved sleep quality, increased energy, and reduced impatience and gastrointestinal complications.³⁶⁹¹

- 5) In females taking the **oral contraceptives ethinylestradiol** and **desogestrel** with St. John's wort extract, intracyclic bleeding increased and 3-ketodesogestrel was reduced (PO in human study).¹⁵⁰⁵

A 36-year-old woman taking a contraceptive with combined ethinylestradiol and **dienogestrol** for a year began self-medicating with a St. John's wort extract at 1700 mg daily for about 3 months when she became pregnant (PO in human case report). Four other cases of St. John's wort association with ineffective contraception had been reported in Germany prior to that time.³⁰¹³

- 10) [Note CORRECTION: See Ib. 7) on p. 302 for proper category for nevirapine case series.]

16) St. John's wort together with CYP 3A4 substrate **irinotecan** reduced plasma levels of SN-38 by 42% (PO in human clinical study).¹³⁴² When St. John's wort tablets were given to 17 subjects (11 females) at 600 mg once daily for 15 days, along with CYP3A4 and Pgp substrate boceprevir at 800 mg 3 times daily for the last 5 of these days, there was a nonsignificant change in boceprevir plasma concentration of 9% reduction, compared to when it was given for 5 days alone (PO in human study). The St. John's wort dosage was monitored by hypericin, but not hyperforin, plasma concentration.³⁶⁹⁰

Since irinotecan is a substrate for P-glycoprotein (*in vitro*),³²⁷⁹ inducing Pgp with St. John's wort likely contributes to increased irinotecan efflux and reduced bioavailability (speculation), though this was not true for boceprevir (PO in human study).³⁶⁹⁰

- + 25) When 600 mg of St. John's wort extract with 4% hyperforin was given for 14 days to 12 healthy men, the bioavailability, maximum plasma concentration, and half-life of a single 5 mg

dose of **finasteride** were significantly reduced, compared to dosing with the drug prior to giving the extract (PO in human study).³¹³³

- + 26) In an open crossover study with 20 healthy male subjects, they each received 1 gram of **metformin** twice each day for a week, either with or without 240-294 mg St. John's wort extract capsules twice daily for 21 days preceding and concurrently with the metformin (PO in human study). Comparing pharmacokinetics of metformin alone and with the extract showed no differences except a decrease in metformin renal clearance with the extract. In a glucose tolerance test for both periods in 17 subjects, the area under time-concentration curve [AUC] for glucose was significantly less with the extract. Insulin sensitivity was not affected, but the acute insulin response was significantly increased by the extract.³⁴³⁸
- + 27) In a randomized, placebo-controlled, double-blind, crossover study with 12 healthy subjects, 300 mg St. John's wort extract given 3 times daily for 15 days was followed by a 15 mg dose of **oxycodone** (PO in human study). Compared to placebo, the extract led to significantly reduced bioavailability of oxycodone, as well as significantly reducing the self-reported drug effect.³⁶⁹³
- + 28) In a controlled, open-label, fixed-dose study 14 male subjects were given **zolpidem** before and after receiving 300 mg St. John's wort extract at 3 times daily for 14 days (PO in human study). The extract led to significant reductions in mean bioavailability and maximum plasma concentration and a significant increase in mean oral clearance of zolpidem. In 3 subjects the bioavailability was slightly increased after taking the extract.³⁶⁹⁴
- Ib. + 11) A 41-year-old woman with schizophrenia was treated for 6 months with 500 mg **clozapine** daily and maintained a stable 12-hour trough concentration of 0.46-0.57 mg/l, until she began self-medicating with 900 mg daily of St. John's wort containing 27 mg hyperforin (PO in human case report). Her mental condition deteriorated as her plasma clozapine concentration was reduced to 0.19 mg/l and 3 weeks later to 0.16 mg/l. After discontinuing the St. John's wort for 1 month, her plasma clozapine was elevated to 0.32 mg/l and in another month to 0.41 mg/l. Her psychiatric condition improved as well.³⁵²⁴

Complementary Adjuncts

- Ia. + 1) Of 100 **migraine headache** patients receiving 200 mg **sodium valproate** twice daily, half were given added placebo and half were given 160 mg of St. John's wort extract 3 times daily for 45 days (PO in human clinical trial). Those receiving the extract had significant reductions in the intensity of their migraines and a greater decline in their frequency than those receiving placebo. The use of **indomethacin** as a rescue drug was not significantly different between groups.³²⁴⁸
- + 2) The **glucose tolerance** of 20 healthy men taking **metformin** was improved when St. John's wort was added for 21 days prior and concomitantly, in comparison to metformin alone (PO in human study). The renal clearance of metformin was significantly reduced by the extract, but no other pharmacokinetic indicators were significantly altered. St. John's wort did significantly enhance insulin secretion, compared to metformin use alone.³⁶⁵⁷
- + 3) In a randomized, placebo-controlled, double-blind study of 40 patients with mild to moderate **depression** who were taking the **tricyclic antidepressant** drugs **amitriptyline**, **imipramine**, or **nortriptyline**, those also taking St. John's wort extract providing 300 mcg total hypericin daily for 6 weeks had significantly greater reduction of the Beck Depression Inventory score after 6 weeks (PO in human clinical study). None complained of sexual side effects, but the extract group had improved sleep quality, increased energy, and reduced impatience and gastrointestinal complications.³⁶⁹¹

HOWEVER, after 2 weeks of giving the tricyclic antidepressant drug amitriptyline to 12 patients with depression, combining it with 900 mg/day of extract LII60 for 2 weeks led to a significant decrease in its bioavailability, peak and trough plasma concentrations, and urinary excretion of amitriptyline and most of its metabolites (PO in human clinical study). The effect seems to be largely due to induction of P-glycoprotein, though CYP 2C19 at low amitriptyline concentrations may be involved. Amitriptyline did not significantly affect the metabolism of the

hypericins or hyperforin, nor did individual cytochrome P450 genotypes affect these outcomes at the end of the four weeks.¹⁶¹⁴

- IIa. 2) A freeze-dried decoction of the herb was mixed with saline and at doses of 4 ml/kg and 6 ml/kg was shown to be as or more effective, respectively, than 0.2 mg/kg IP clonidine in reducing the **withdrawal** syndrome from **morphine** (PO in rats).³⁴⁶²

STINGING NETTLE

p. 306

Urtica dioica leaf [not the root]

Contraindications

- I. 1) Excessive internal use should be avoided in **pregnancy**,^{2,3} especially in early pregnancy, due to its emmenagogue effect when prepared as a decoction of the plant (empirical).³⁰⁸⁷ Uterine stimulant activity has been shown with its constituent serotonin (*in vitro*).³⁰⁸⁸
- II. 2) Avoid use in brittle **diabetes** (speculative).^{893,2250} Use of nettle leaf extracts have shown hypoglycemic effects as well as reduced fasting insulin resistance index with 100-200 mg of hydroalcoholic extract (IP in rats).³³⁵² A nettle cyclical peptide fraction designated UD-1 enhances glucose uptake by forming unique pores in skeletal muscle cell membranes that are glucose-permeable (*in vitro*).²⁹⁹⁸

Complementary Adjuncts

- Ia. 1) Stewed leaf enhanced the effect of **diclofenac** when given to 19 acute **arthritis** patients (PO in human clinical trial).³⁸⁶
- Randomized to placebo or a commercial combination of stinging nettle with fish oil, zinc, and vitamin E taken in capsules, 1 in the morning and 2 at night, and taking their usual regular **NSAIDs** and/or **analgesics**, 81 patients with **osteoarthritis** of the knee or hip were studied for 3 months (PO in human clinical study). Compared to placebo, the defined daily doses of NSAIDs including diclofenac, **celecoxib**, **ibuprofen**, **ketoprofen**, **naproxen**, **piroxicam**, **sulindac**, and **tenoxicam** and weekly analgesic equivalents to 500 mg tablets of **acetaminophen [paracetamol]** with or without **opiates** and **aspirin** were both significantly reduced in the nettle group, while the mean scores for pain, stiffness, and function were also significantly improved.²⁷²²

Urtica dioica root

Complementary Adjuncts

- IIa. 1) A hydroalcoholic root extract at 10 mg/kg daily in animals exposed to **nicotine** for 28 days significantly increased the sperm motility, count, and normal morphology, seminiferous tubule diameter, and testosterone levels compare to nicotine-only controls (IP in mice). At 20 mg/kg daily of root extract with nicotine, the testis weight was also significantly increased in comparison to nicotine controls. Nicotine alone significantly **reduced testosterone and sperm** count, motility, and normal morphology, seminiferous tubule diameter, and testis weight compared to no-nicotine controls.³⁴⁵⁶

SWEET ANNIE

p. 307

Artemisia annua herb

Complementary Adjuncts

- IIb. + 1) An artemisinin combination with **curcumin** is additive in killing ***Plasmodium falciparum*** (*in vitro*). In addition, the semisynthetic derivative α,β -arteether given one day after injection of *Plasmodium berghei* to simulate an animal version of malaria and followed for 3 days by oral curcumin at 100 mg/kg dosage prevented recrudescence with 100% survival in contrast to 100% fatality 5-8 days after arteether monotherapy (IM in mice).²⁹¹⁴

SWEET CHERRY

NEW

^ *Prunus avium* fruit

(cherry)

Complementary Adjuncts

Ia. 1) In 633 patients with **gout**, the consumption of cherries or cherry extract for a 2-day period reduced the risk of an acute attack in those 285 taking **allopurinol** by 75%, compared to a 53% reduction in risk when using allopurinol alone (PO in human study). The preventive effect of combining cherry products with **colchicine** enhanced the reduced risk from 39% for colchicine alone to 48% with the combination. Cherry consumption independently reduced the acute attack risk by 35% overall, with 25% less risk after a single serving increasing to 43% reduction with once daily consumption for 2 days prior and up to 54% when 3 servings were taken in the 2 days prior to attack. The effect of the extract intake similarly reducing the risk by 45% overall.³²⁹⁹

Bing sweet cherries given after an overnight fast to 10 healthy women in 2 servings totaling 280 g significantly reduced plasma urate levels, compared to baseline (PO in human study). The urinary urate levels were significantly increased after the cherries, compared to baseline, while plasma C-reactive protein was somewhat reduced, indicative of some inflammatory pathway inhibition.³³²⁹

Anthocyanin pigments from both sweet cherries and tart cherries (*Prunus cerasus*) at a concentration of 125 mcg/ml were shown to inhibit COX-1 by 26% to 29% and COX-2 by 37% to 47%, respectively, likely due to the cyanidin moiety (*in vitro*). The anthocyanins with fewer sugar moieties had the greater antioxidant and COX-inhibiting activities.³³⁰¹

TART CHERRY

NEW

^ *Prunus cerasus* fruit
(sour cherry)

Complementary Adjuncts

Ia. 1) The consumption by 24 patients with gout of 2 tablespoons cherry juice concentrate daily for 4 months or more led to a remission in acute attacks of **gout** in 50%, including a significant 62% of 13 patients who had been receiving **allopurinol** (PO in human clinical study). The average number of flares per year for all 24 patients was reduced from 6.85 to 2.00. The reduction in gout attacks was significant in the total patient group and or patients receiving urate-lowering therapy, even though the average serum urate level of those who were flare-free was still 7.8 mg/dl, higher than the the 6.8 mg/dl saturation point of uric acid. In a related 4-month trial with 14 gout patients, all 5 patients who were taking the NSAIDs **celecoxib** or **indomethacin** discontinued the drugs within 60 days of starting the same dose of cherry juice concentrate, though none of the 3 using allopurinol changed their dosage (PO in human clinical study). The number of flares were reduced in 6 of the 9 patients, compared to the rate prior to the study.³²⁹⁸ The concentrate used in these studies was later revealed to be from tart cherries.³³⁰²

The use of 5 ml/kg of tart cherry juice for 2 weeks significantly reduced hyperuricemia by inhibiting hepatic xanthine oxidase/dehydrogenase activity (PO in rats). It also significantly reduced the oxidative marker MDA and increased antioxidant capacity. Though the reduction of serum uric acid was not as great as 5 mg/kg of the positive control allopurinol, the drug provided no antioxidant protection.³³⁰⁰ Anthocyanin pigments from both tart cherries and sweet cherries (*Prunus avium*) at a concentration of 125 mcg/ml were shown to inhibit COX-1 by 26% to 29% and COX-2 by 37% to 47%, respectively, likely due to the cyanidin moiety (*in vitro*). The anthocyanins with fewer sugar moieties had the greater antioxidant and COX-inhibiting activities.³³⁰¹

Ia. 1) The combination of a tart cherry anthocyanin-rich extract with a suboptimal dose of the NSAID drug **sulindac** used for **cancer chemoprevention** was shown after 19 weeks to have fewer tumors, a smaller total tumor burden in the small intestine, and less body weight loss of >10% than those fed sulindac alone (PO in mice). The combination was more effective in colon cancer protection than the drug by itself.²⁴³²

- Iib. 1) With exposure of adipose stem cells to lipopolysaccharide to induce interleukin-6 (IL-6), an cytokine associated with the **inflammation** processes of chronic diseases such as cardiovascular disease, the combination of 50 mcmmol/L **atorvastatin** with 50 mcl/ml tart cherry extract or 250 mcg/ml freeze-dried cherry anthocyanins significantly reduced IL-6 secretion compared to atorvastatin alone (*in vitro*). The isolated anthocyanin cyanidin-3-O-glucoside at 250 mcg/ml had an effect equivalent to both of these combination (*in vitro*).³¹⁴⁵

TEA

p. 309

Camellia sinensis = *Thea sinensis* leaves

Contraindications

- I. 2) Avoid consuming green tea aqueous-ethanolic solid **extract concentrate of EGCG** [epigallocatechin gallate content $\geq 25\%$] for aiding **weight loss**, due to 13 cases of hepatitis from France and Spain after taking it from 9 days to 5 months (PO in human case reports).^{1508,1579,1580,2328,2577} Resolution occurred after discontinuance in 12 cases; 1 case of liver transplantation also involved alcohol and drug use.^{1951,2577} Causality was determined on the Naranjo scale as possible in 11 cases and probable in 2 cases. Recommendation is to take green tea solid extract with food.²⁵⁷⁷

A review of green tea hepatotoxicity through 2008 found 34 cases with one fatality, featuring positive dechallenges in 29 cases and positive rechallenge in 7 cases. Two newer cases were described as possible associations. The cause was thought to be due to excessive EGCG or its metabolites inducing oxidative stress in the liver, in some cases involving concomitant medications.³⁶³⁵

A 24-year-old woman taking 2 caplets of a green tea weight loss supplement twice daily on an empty stomach for 3 months developed severe liver toxicity that required corticosteroid treatment 3 weeks after stopping the supplement (PO in human case report). The supplement contained 135 mg of EGCG as the main ingredient, also with small amounts of 10 other herbs, 5 vitamins, and the tea alkaloids theanine and caffeine. Liver enzymes were elevated, and biopsy showed liver inflammation with alpha-1 antitrypsin globule deposition. No improvement was occurring before the prednisone, and typical causes of liver inflammation had been ruled out. The woman's alpha-1 antitrypsin MZ phenotype may have been a predisposing factor, but corticosteroid treatment led to rapid clinical improvement.³⁶³⁶ Using the same supplement for 2 days while fasting, 2 weeks later a 52-year-old woman experienced vomiting and progressive jaundice for 1 week (PO in human case report). Her serum liver enzymes were greatly elevated, and liver biopsy showed confluent hepatic necrosis with collapse. Other causes of liver insult had been ruled out. Prednisone was initiated, but the patient deteriorated and required a liver transplantation 2 days later.³⁶³⁷

In 3 cases acute hepatitis was associated with women of ages 31, 56, and 59 years using a product to **stop hair loss** that contained 27-30% green tea catechins, 11% grape seed catechins, 11% taurine, and zinc gluconate (PO in case series). They each took 2 tablets daily for 23 days to 1 month. The woman with malaise, jaundice, choluria, and fecal acholia for 15 days had greatly elevated liver enzymes and signs of severe inflammation on liver biopsy; after 6 months of corticosteroid treatment recovery was complete. The second woman with complaints of malaise, nausea, and hypogastric pain and the third woman whose only symptom was pruritic both had moderately elevated liver enzymes, and their conditions resolved in 3 months without treatment.³⁶³⁸

To help **prevent breast cancer**, 12-month, randomized, placebo-controlled, double-blind study in 1075 postmenopausal women with mammographic density indicating risk of breast cancer utilized green tea extract made by extracting dried leaves with water and ethyl acetate, decaffeinating, and spray-drying (PO in human study). The daily dose of 4 capsules, containing 1315 mg of total catechins including 843 mg of EGCG, was taken by 538 women, while liver function and hepatotoxicity based on serum levels of the liver enzyme alanine aminotransferase

(ALT) was monitored monthly for 6 and 12 months, respectively. ALT elevations occurred in 36 using the extract, significantly more than the 4 taking placebo. ALT elevations were mostly mild and average resolution was 30.2 days, with ALT subsiding after discontinuation dechallenge in all but 1. Positive rechallenge occurred in 12 of these. Results suggest that green tea extract is relatively safe, and liver insult resolves spontaneously, if ALT levels are closely monitored and dosing ended or interrupted if ALT elevation occurs.³⁶³⁹ In a further analysis of the 1021 women (513 on extract, 509 on placebo) with normal liver enzyme values at baseline, both ALT and aspartate aminotransferase (AST) levels were significantly higher in the extract group. In addition, 26 women (5.1%) using the extract developed moderate to severe liver dysfunction, compared to placebo. While ALT normalized after dechallenge, one or more rechallenges led to recurrence of elevated ALT, strongly implicating the high dose of this concentrated extract in the liver enzyme elevation.³⁷⁰⁰

HOWEVER, a systematic review of randomized trials evaluated 34 studies and found liver-related events involving 7 subjects with elevated liver enzymes in 4 trials (PO in human studies). The cases were mostly mild, and no serious liver-related adverse effects were reported and are expected to be rare.³⁵⁸⁶ A 1-year randomized, placebo-controlled, double-blind, study was performed with 400 mg EGCG daily in 97 men having atypical small acinar proliferation and/or high-grade prostatic intraepithelial neoplasia to assess potential hepatotoxicity and dose safety (PO in human clinical study). Taken in 2 divided daily doses with food, this decaffeinated green tea catechin product was well tolerated and not found to cause adverse effects in men.³⁶⁶²

The importance of dosage on green tea polyphenol effects was shown when administered after dextran sulfate sodium (DSS)-induced damage to liver and kidneys (PO in mice). The polyphenols were given in dietary doses of 0.01%, 0.1%, and 1.0% with DSS resulted in significantly lower levels of ALT and AST liver transaminases, compared to DSS-only mice, whereas the 1% polyphenol group had increased kidney weight, serum creatinine, and TBARs in liver and kidneys, compared to DSS-only mice. The polyphenols at 0.01% and 0.1% increased heat shock protein 70 and heme oxygenase-1 mRNA, but the 1% level abolished it. The protective effects of low or moderate doses of green tea polyphenols are lost with high doses when adverse effect can occur.³⁶⁴⁰ Exposure to low levels of 3.2 mg/g diet for 2 weeks prior to a bolus dose of 750 mg/kg daily for 3 days mitigated the hepatotoxicity induced by the bolus dose without pretreatment (PO in mice). The single high dose increased ALA 80-fold, decreased hepatic glutathione, and decreased glutathione reductase mRNA expression. The low dose pretreatment prevented this, while increasing glutathione peroxidase 2, 3, 5, and 7 expression, and reduced plasma and hepatic exposure to EGCG from the bolus dose alone by 57% and 71%, respectively. Regular exposure to low EGCG doses protects from adverse effects of a high dose.³⁶⁴¹

Giving a green tea extract of concentrated catechins [63-65% EGCG, 3-4% EGC, 6-8% ECG, 8-12% epicatechin] in doses of 0, 200, 500, or 800-1000 mg/kg/day to animals that were fasting led to extensive dose-dependent organ morbidity and mortality [0/8, 3/8, 5/8, and 8/8 deaths per dose group, respectively] within 6.5 months with most death before 13 weeks (PO in dogs). In a 13-week follow up trial using 200 mg/kg/day, no deaths occurred and toxicity in fasted dogs was less severe and included GI irritation, but the same dose given to non-fasted dogs resulted in much less severe reactions. Plasma catechin levels were 2-4 times greater after fasting than after feeding, similar to results shown with humans in a prior study.²⁷⁴² Similarly, a dose of 2000 mg/kg/day of EGCG was shown to be lethal (PO in rats), but doses up to 500 mg/kg/day were not toxic (PO in rats and PO in divided doses to pre-fed dogs), though in fasted animals a single-dose of this amount caused morbidity (PO in dogs).²⁷⁴³ This suggests that use of high doses of concentrated green tea catechins high in EGCG while fasting increases the risk of toxicity.

HOWEVER, the animal bolus dose model used with fasting dogs is considered unrealistic when compared to human tea consumption patterns.²⁷⁴³ The peak plasma concentration levels in dogs with no observed adverse effect were 4-10 times the plasma levels achieved in humans who

consumed catechins equivalent to about 10-16 cups of tea (PO in dogs and humans).²⁷⁴⁴ EGCG liver toxicity was shown to be dependent on differences in sensitivity when given in high doses of 50 mg/kg daily for 3 days (IP in mice). This equal exposure led to severe hepatotoxicity in 16% [43/272] with 10-86,8% liver necrosis, analogous to isolated clinical cases. The genetically heterogeneous population was suggest the hepatotoxic responses were due to genetic differences.³⁶⁴² Another possible association with green tea extract, EGCG, and hepatotoxicity may be an underlying interaction between redox-active copper found in dithiocarbamates (DTC), agents used widely in agriculture, industry, and medicine; an example in medicine is disulfiram, that, when given with EGCG at tolerable levels, is lethal (PO in mice). DTCs can act as copper ionophore in the liver and protomote EGCG auto-oxidation to produce toxicity. Co-administration dramatically increases lipid peroxidation, cell apoptosis, and DNA damage that involves deleterious transcriptional responses in the antioxidant systems in the liver. This indicates that a DTC exposure can reduce green tea polyphenol toxic threshold and vice versa.³⁶⁴³

Drug Interactions

- Ia. + 17) Use of a green tea catechin extract supplying 800 mg EGCG daily for 4 weeks by 42 healthy subjects led to a 20% increase in bioavailability of the CYP 3A4 substrate **buspirone** (PO in human study).²⁸¹⁰

HOWEVER, this inhibition of CYP 3A4 was not deemed clinically significant.²⁸¹⁰ A green tea decaffeinated extract providing 844 mg mixed catechins daily for 14 days did not affect alprazolam metabolism in 11 healthy subjects (PO in human study).¹⁷¹⁰

- + 18) A randomized, crossover study of consumption of 700 ml green tea or water daily for 14 days by 10 healthy volunteers, followed by a single oral dose of the antihypertensive beta-blocker drug **nadolol**, led to significant decreases in plasma maximum concentration and bioavailability (PO in human study). In addition, the systolic blood pressure effect of nadolol was significantly reduced by the green tea. Nadolol was shown to be a substrate of organic ion-transporting polypeptide [OATP]1A2 (*in vitro*), so based on the pharmacokinetics it is likely that green tea inhibits OATP1A2 in the intestines.³³⁸⁸

In a single-dose animal study, 400 mg/kg green tea extract or 150 mg/kg epigallocatechin gallate [EGCG] were compared with oral saline in the effects on 10 mg/kg oral nadolol when taking them 30 minutes beforehand (PO in rat study). The extract reduced nadolol maximum concentration and bioavailability by 85% and 74%, respectively; EGCG also significantly reduced these 2 parameters. Urinary excretion of nadolol was decreased with the extract and EGCG pretreatments, though its terminal half-life was unaffected, suggesting that intestinal absorption by uptake transporters may have been inhibited.³⁵³¹

- Ib. + 2) A 61-year-old man with primary hypercholesterolemia, unable to use statins like **simvastatin** due to early muscle intolerance and increased liver enzymes, revealed that he usually drank 3 cups of green tea daily for his health (PO in human case report). To assess whether this interfered with statin tolerance, simvastatin bioavailability was assessed while he drank tea and again a month after he stopped consuming the tea, giving the drug for 6 days with or without the tea. The results showed that when taken with the tea, simvastatin lactone bioavailability and maximum plasma concentration were significantly elevated compare to its use without the tea. Then the man, after stopping consumption of the tea, was able to take 20 mg of simvastatin daily for 3 months with only minor leg discomfort. By halving this dose, he was asymptomatic with normal liver enzymes and lowered his LDL-cholesterol after 6 months. The cause of the interaction was undetermined.³⁶⁹⁷

- II. + 2) When **acetaminophen (paracetamol)** was given for 1 week at 2 g/kg body weight, with or without green tea extract with 30% polyphenols given at the therapeutic dose of 8.5 mg/kg for 1 month afterward, it led to changes indicative of liver toxicity such as significantly increased liver enzymes AST and ALT, hepatocellular degeneration and necrosis with inflammation, hemorrhage, congestion, and fibrosis (PO in rats). While the hepatotoxic changes by acetaminophen alone were further significantly increased when the green tea extract was added,

but mortality during treatment and in the recovery phase with acetaminophen was eliminated by the addition of the extract. Increased oxidative stress as indicated by significantly elevated malondialdehyde [MDA] and decreased liver catalase and glutathione was also in evidence when each was used alone, and these were made significantly worse when combined.³⁶⁵³

HOWEVER, when given EGCG at 0.54% of the diet for a week before IP injection of acetaminophen at 1 g/kg, 12 hours after the drug injection the plasma levels of ALT and AST were significantly lower than with no EGCG given prior, and histological damage was less (PO in rats). EGCG also inhibited CYP2E1, and this may have reduced the bioactivation of acetaminophen hepatotoxicity.³⁶⁵⁴ When green tea extract was given before acetaminophen, it reduced the increase in serum transaminases and hepatocellular necrosis, but when given after the drug the extract potentiated the hepatotoxicity (PO in mice).³⁶⁵⁵ Also, green tea extract provides a liver-protective effect against the hepatotoxicity of carbon tetrachloride [CCl₄], as shown by reduced liver damage, MDA, total cholesterol, LDL, and triglycerides and increased liver glutathione when given access to 10% extract daily, compared to daily CCl₄ alone by gavage (PO in hamsters).³⁶⁵⁶

- III. + 5) The green tea catechin epigallocatechin gallate [EGCG] was shown to reduce the transport of **folic acid** by the proton-coupled folate transporter [PCFT] in Caco-2 cells and human PCFT-expressing HEK293 cells (*in vitro*). EGCG competitively inhibited folic acid uptake. The drug **methotrexate** is also a PCFT substrate, and its uptake was likewise competitively inhibited by EGCG. This suggested that if folic acid or methotrexate is ingested with green tea, it may result in reduced efficacy.³⁵³²

Complementary Adjuncts

- Ia. 3) Black tea for seven days prior to **aspirin, indomethacin** and **reserpine** reduced the incidence of **stomach ulcers**, probably by altering prostaglandin metabolism and in the case of indomethacin reducing peptic activity (PO in rats).⁴⁹²

Indomethacin-induced ulcers also were healed significantly better with black tea aqueous extract at 40 mg/kg or theaflavins at 1 mg/kg after 3 days by 74-76% (PO in mice). Stomach acid secretion was not modulated, but gastric COX-1 and -2 and PGE were increased.²⁷⁵²

- Iia. 1) Black tea for 7 days reduced **stomach ulcers** produced by **ethanol (alcohol)** (PO in rats).⁴⁹²

Furthermore, **hepatotoxicity** induced by a diet with 15% ethanol by volume for 30 days was reduced when co-administered with 10 ml/kg 2.5% aqueous extract of black tea (PO in rats). This was shown by significant reductions in serum AST, ALT, and GGT and in malondialdehyde and increases in SOD and catalase activities compared to ethanol alone, presumably by decreasing oxidative stress.³¹⁵¹ In addition, after 28 days of intoxication with ethanol the reduction of enzymatic and non-enzymatic antioxidants in the liver, serum, and brain were considerably prevented by consumption of black tea for 1 week prior and concurrently (PO in rats).³¹⁵⁰

An aqueous extract of green tea was given in doses of 5 or 10 mg/kg body weight along with 50% ethanol for 5 weeks, and compared to alcohol consumption alone (PO in rats) Alcohol alone led to significant increases in serum transaminases ALT and AST, alkaline phosphatase, MDA, GST, cholesterol, and triglycerides and decreased activity of superoxide dismutase and other cellular antioxidant enzymes. Reactive oxygen species and loss of antioxidant protection caused histological damage to liver cells. The green tea extract at 10 mg/kg normalized the damage to hepatic cells, the enzymatic markers of liver damage and oxidative stress, blood lipids, and lipid peroxidation.³⁶⁴⁴

- 4) Green tea extract increased apoptosis in ER⁺ MCF-7 **breast cancer cells** when combined with **tamoxifen** compared to tamoxifen alone and decreased MCF-7 graft tumor size and suppressed angiogenesis more than either agent alone (PO in mice).²⁰³⁹

In ER⁺ MCF-7 cells epigallocatechin gallate [EGCG] inhibits growth, decreases Skp2, and increases p27-Kip1 in a dose- and time-dependent fashion; both tamoxifen synergistically enhance EGCG inhibition of MCF-7 cells and further down-regulate Skp2 (*in vitro*).³⁴⁶⁸

In mice implanted with ER-negative [ER⁻] MDA-MV-231 human breast cancer cells, when given 75 µg/kg tamoxifen, 25 mg/kg EGCG, or the combination, only the combination significantly reduced tumor growth, 80% less compared to controls (IP in mice). This was likely due to the concomitant 85% reduction in epidermal growth factor receptor and 78% decrease in mammalian target of rapamycin, compared to controls.³⁴⁶⁷ In ER⁻ MDA-MV-231 breast cancer cells, cell growth was significantly and synergistically inhibited by the combination of EGCG at 25 µM and tamoxifen at 1 µM after 7 days, compared to either individual treatment (*in vitro*).³⁴⁶⁹

- + 6) The component catechin given in 2 daily doses of 150 mg/kg with **ciprofloxacin** to mice with **chronic bacterial prostatitis** significantly reduced the *E. coli* in the prostate compared with use of ciprofloxacin alone (PO in rats).³⁰³⁸
- + 7) Theanine at 4 and 8 mg/kg was shown to significantly attenuate **opioid withdrawal** symptoms after 90-150 minutes and 30-150 minutes, respectively, when given after **morphine** dependence was established (SC in monkeys). The withdrawal signs reduced by theanine included fighting, pacing, retching, shaking, rigid abdominal muscles, and masturbation.³³⁹⁷
- Iib. + 3) In ER⁺ MCF-7 human **breast cancer cells** epigallocatechin gallate [EGCG] inhibits growth, decreases Skp2, and increases p27-Kip1 in a dose- and time-dependent fashion; **paclitaxel** synergistically enhances EGCG inhibition of MCF-7 cells and further down-regulate Skp2 (*in vitro*).³⁴⁶⁸

When 25 µM EGCG was combined with 5 µM **raloxifene**, ER-negative [ER⁻] MDA-MV-231 human breast cancer cells were significantly reduced by 96% after 7 days, compared to controls (*in vitro*). After 48 hours the reduction in cell numbers by the combination was significantly greater than from exposure to either agent alone, along with 21.2% and a 31.5% reductions in the phosphorylation of epidermal growth factor receptor and protein kinase B, respectively, after only 18 hours.³⁴⁷⁰

TEA TREE

p. 317

Melaleuca alternifolia leaf oil

Complementary Adjuncts

- Ia. 1) In a placebo-controlled trial a microemulsion formulation of tea tree oil, **diclofenac**, and **minoxidil** used by 11 men was compared with minoxidil alone for 11 men and placebo for 10 men, applied twice daily for 32 weeks for the treatment of androgenic **alopecia** (TP in human clinical study). Based on average hair count, weight, and thickness and patient self-assessment, the combination was significantly better than placebo and minoxidil alone.³³⁷¹

THUNDER DUKE VINE

p. 318

[formerly Thunder god vine]

**Tripterygium wilfordii* peeled root

Complementary Adjuncts

- Ia. 1) An extract given to 10 **rheumatoid arthritis** patients using **NSAIDs**, 8 also taking **prednisone**, found 8 of 9 had improved clinical and laboratory findings at doses over 360 mg (PO in human clinical study).¹⁴¹⁷

External use in a 6-week randomized, placebo-controlled, double-blind trial involved 31 applying the tincture 5-6 times daily and 30 using placebo (TP in human clinical study). Concurrent **methotrexate**, NSAID, and **auranofin** stable doses were allowed. Response rate with the tincture was 58% versus 20% with the placebo. Compared to placebo, significant improvements were found with tincture clinically for tender joint and swollen joint counts, grip strength, and morning stiffness, along with laboratory measurements of erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and rheumatoid factor [RF] levels, as well as patient and physician global assessments.³²⁸¹

In a trial of 146 rheumatoid arthritis patients given 40-60 mg/day chloroform/methanol extract plus **methotrexate** for 12 months, 39 had used disease-modifying anti-rheumatic drugs prior; 23 had been on methotrexate alone, while 19 used a combination including methotrexate (PO in human clinical study). Significant reductions were found clinically with tender joint and swollen joint counts, and morning stiffness, and in laboratory measures of ESR and CRP after 3 months and 12 months. During the study, 10 withdrew due to adverse events, but most adverse effects were mild. Menstrual irregularity occurred in 16 of the 22 premenopausal women in the study.³²⁸⁰

The unique diterpene triepoxide component triptolide inhibits T-cell transcriptional activation of NF-κB and IL-2 (*in vitro*).²⁸⁶¹ Triptolide has been shown to bind to human transcription factor TFIIH subunit XPB, inhibiting DNA-dependent ATPase activity and RNA polymerase II-mediated transcription (*in vitro*).²⁸⁶²

- Ib. 1) The dry extract was used at 60 mg daily for 6 weeks in 12 patients with **ankylosing spondylitis**, 8 of whom were also using **methotrexate**, **sulfasalazine**, or a combination of both (PO in human case series). Compared to baseline assessments, after 3 and 6 weeks there were significant improvements in disease activity and functional index scores, global score, and physician assessments. No liver enzyme or blood count changes were found.³²⁸²

TIBETAN RHODIOLA

NEW

^ *Rhodiola crenulata* root
(Chin.: hong jing tian)

Complementary Adjuncts

- Ia. 1) In a randomized, placebo-controlled, double-blind study with 57 patients with moderate to severe chronic obstructive pulmonary disease [**COPD**], 38 were given a 250 mg Tibetan rhodiola root capsule twice daily for 12 weeks, while 19 received placebo, in addition to their standard treatment(s) (PO in human clinical trial). Of those receiving the root, 23% were taking **xanthines**, 17% used long-acting muscarinic antagonists [**LAMA**], 22% took long-acting beta-2 agonists [**LABA**] with inhaled **corticosteroids**, while 12% used the LABA plus corticosteroids together with LAMA. Additionally, 6% used LABA alone, 11% used a combination of short-acting MA and BA [**SAMA+SABA**], and 9% took **antihistamines**. Those taking the root capsules had significant improvements in forced expired volume in 1 second [FEV1] and workload compared to baseline, and significantly improved tidal volume and ventilation-CO2 output ratio at peak exercise compared to placebo. The tidal breathing and ventilation efficiency were also significantly improved with taking the root.

TULSI

NEW

^ *Ocimum tenuiflorum* = *Ocimum sanctum* leaves
(holy basil, sacred basil; Sans.: tulasi)

Drug Interactions

- Ia. 1) When powdered leaf was given in 1 gram doses each morning for 30 days to 17 diabetes type 2 patients taking **chlorpropamide**, **glibenclamide**, **glipizide**, or **penformin** and fasting blood sugar and glyated serum proteins were compared to baseline, a significant 20.8% reduction in blood glucose and 11.2% decrease in glyated proteins was found (PO in human clinical study). In addition, total cholesterol, LDL-cholesterol, and VLDL-cholesterol were also significantly decreased. By way of further comparison, the blood sugar and lipid values in 10 diabetic control patients were slightly increased in 1 month.³³⁰⁸

When 30 male type 2 diabetics were given 2 grams of powdered leaf daily for 3 months, significant reductions were found in the numbers of those with polydipsia, polyphagia, and headaches, as well as lower blood pressures (PO in human clinical study). These effects were all greater when the same dose of equal parts tulsi and neem (*Azadirachta indica*) powders were given to 30 other type 2 diabetic patients.³³⁰⁹ The leaf ethanolic extract has been shown to increase the secretion of insulin from perfused pancreas, isolated islet cells and a clonal beta-cell

line taken from rats (*in vitro*),³³¹⁰ while the aqueous, methanolic, and chloroform extracts all inhibited pancreatic and small intestinal glucosidases from mice, similar to acarbose (*in vitro*). The chloroform extract also inhibited alpha-amylase (*in vitro*).³³¹¹

- II. 1) When 20 mg of ethanolic extract derived from 100 mg of leaf was given twice daily for 5 days prior to an injection of **pentobarbital**, the sleeping time was significantly prolonged (PO in mice).³²²⁰

Complementary Adjuncts

- IIa. 1) After peripheral **neuropathic pain** was induced by injection of **vincristine** sulfate for 10 days, 100 or 200 mg/kg of tulsi methanolic extract or its saponin fraction were given for 14 days (PO in rats). Both the extract and fraction at both doses significantly reduced the vincristine-induced pain associated with hind paw pin pricks, paw cold from acetone, and paw heat from hot plate, compared to the effects of no treatment, beginning on day 2 for the pin pricks and acetone cold effects and day 6 for the heat. The fraction was significantly more effective when compared to the extract for these measures over the same time periods, and 200 mg was significantly better than 100 mg of the fraction for all 3 measures after 6 days, as was pain from tail immersion in cold water. The same pattern of significant comparative results were found with the reduction of markers of oxidative stress.³¹⁷⁹
- 2) When the tulsi ethanolic extract was given at 200 mg/kg body weight after **hepatotoxicity** had been induced by **acetaminophen**, improvements in albumin globulin ratio and serum alkaline phosphatase and transaminases AST and ALT were significantly better with the extract (PO in rats). Also, the histopathologic damage to the liver was less and signs of regeneration were greater than with no treatment.³¹⁸¹
- 3) An aqueous extract of tulsi given at 200 mg/kg body weight prevented diarrhea, **stomach ulceration**, and **intestinal damage** caused by 2.4 mg/kg of the NSAID drug **meloxicam** (PO in rats). The same dose of extract also helped alleviate **hepatotoxicity** and maintain hemoglobin levels after 1.2 mg/kg meloxicam, but did not protect the kidney or heart at the higher NSAID dose.³¹⁸³
- 4) Doses of a tulsi hydroalcoholic extract given at 50 or 75 mg/kg for 30 days helped protect against **heart damage** induced by 2 doses in 2 days of subcutaneous [SC] **isoproterenol** at 85 mg/kg (PO in rats). The extract significantly increased cardiac levels of antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, as well as reducing the lipid peroxidation marker malondialdehyde in the heart and cardiac damage markers AST, LDH, and CPK in the serum.³¹⁸⁵ With 50 mg/kg fresh tulsi leaf homogenate daily for 30 days, heart damage from a single dose of 85 mg/kg SC isoproterenol was prevented (PO in rats). After tulsi only, the amount of superoxide dismutase [SOD] and catalase increased significantly in the heart. Without the tulsi, the isoproterenol significantly decreased heart SOD and glutathione peroxidase and produced evidence of cardiac necrosis. After tulsi and isoproterenol, only slight myocardial damage was detected.³²³⁹
- 5) The **salivary gland damage** caused by high-dose **radioiodine** [¹³¹I] was reduced when the tulsi aqueous extract was given for 5 or 15 days prior at 40 mg/kg (PO in mice).^{3184,3186} The extract prevented the increase in lipid peroxidation in the salivary glands and kidneys after 24 hours, compared to those treated with ¹³¹I, and lessened the depletion of reduced glutathione in the liver.³¹⁸⁶ Parotid gland atrophy and lipomatosis from ¹³¹I was shown after 3 months when exposed once or after 6 months with 2 exposures [3 months apart], while those receiving the tulsi extract before the radioiodine had salivary tissue similar to controls.³¹⁸⁴
- 6) The **hepatotoxicity** and **immunosuppressant** effects of the antituberculosis combination of **isoniazid**, **rifampicin** and **pyrazinamide** were significantly reduced by powdered tulsi given at 200 mg/kg for 21 days (PO in guinea pigs). Specifically, the serum AST and alkaline phosphatase were significantly reduced and normalized, respectively, and the phagocytic percentage and other parameters of neutrophilic function were normalized or enhanced, compared to these parameters of those receiving only the antituberculosis drugs.³¹⁹⁸

7) The ethanolic extract of the leaves given at 100 mg/kg for 3 days prior to **aspirin** being used to induce **stomach ulcers** resulted in a significant 63% reduction in ulcers, associated with a 34.6% increase in mucin secretion and a 58% reduction in total acidity and peptic activity (PO in rats). Similarly, stomach ulcers induced by **alcohol (ethanol)** were reduced by 54%, significantly better than from using 10 mg/kg omeprazole (PO in rats). When given for 20 days after a 3-day induction of ulcers by **acetic acid**, the extract significantly healed ulcerations after 5 and 10 days and completely healed them after 20 days, equivalent to omeprazole (PO in rats).³²¹⁸

8) When 20 mg of ethanolic extract derived from 100 mg of leaf was given twice daily for 5 days prior to an injection of **amphetamine**, it significantly and completely prevented **amphetamine toxicity** from resulting in death (PO in mice).³²²⁰

- Iib. 1) The genotoxic **chromosomal damage** to human lymphocytes induced by the synthetic progestin drug **cyproterone** acetate was reduced dose-dependently by a water extract of tulsi (*in vitro*). This effect may help reduce the risk of carcinogenesis from cyproterone use in patients as an antiandrogen for prostate cancer (speculative).³¹⁹⁶

TURMERIC

p. 324

Curcuma aromatica, *Curcuma longa* = *Curcuma domestica* root

Drug Interactions

- Ia. + 1) When curcumin was given at 300 mg daily for 6 days to 12 healthy subjects, it reduced the bioavailability, peak plasma concentration and increased total clearance of a single dose of **talinolol** (PO in human study). The mechanism was unclear due to the small dose and group and short duration.²⁸⁰⁶

- Ib. + 1) A 56-year-old man with an orthotopic liver transplantation was maintained on a low-dose regimen of the anti-rejection drug **tacrolimus** within the desired blood range, when he began taking 15+ spoonful of turmeric daily with his food (PO in human case report). After 10 days, he was hospitalized with tacrolimus levels elevated about 300%, along with elevated potassium and creatinine and worsening edema of the legs, abdomen, and scrotum that were indicative of nephrotoxicity from the excessive drug level. After withholding the medication for 4 days, he was released for the hospital with reduced edema and lower serum creatinine.³⁶⁰⁵

In a study of pre-treatment with turmeric juice, grapefruit juice, or water, bioavailability of tacrolimus was significantly increased by the turmeric and grapefruit juice in comparison with water (PO in rats). Grapefruit juice is a known inhibitor of intestinal CYP 3A4 of which tacrolimus is a substrate.³⁶⁰⁶ The turmeric component curcumin, when given at 60 mg/kg for 4 days, increased the bioavailability of midazolam, also a CYP 3A4 substrate (PO in rats).²⁷⁷⁸

HOWEVER, when given at a dose of 4 grams twice daily for 2 days, along with 24 mg of piperine to enhance its absorption, curcumin failed to impact midazolam metabolism in 8 healthy human volunteers (PO in human study).³⁶⁸¹

Complementary Adjuncts

- Ia. + 3) In 50 patients with **osteoarthritis** of the knees, for 3 months along with prescription nonsteroidal anti-inflammatory drugs (**NSAIDs**), half were given 200 mg curcumin mixture [75% curcumin, 15% demethoxycurcumin, 10% bisdemethoxycurcumin] formulated with phosphatidylcholine and half were given placebo (PO in human clinical study). Those using curcumin had significant improvements in median scores for pain, stiffness, physical function, walking ability, edema, and plasma C-reactive protein levels compared to placebo. NSAID use was decreased by 63% in the curcumin group, significantly more than the 12% reduction with placebo.²⁷²¹ With half using the same curcuminoid mixture and dose as the 50-patient 3-month study, an 8-month study with 100 osteoarthritis patients using NSAIDs or **acetaminophen** showed significant improvements compared to the control group in pain, stiffness, and physical functions including walking distance and for inflammatory markers including IL-1 β , IL-6, soluble CD40 ligand, and ESR (PO in human clinical study). In addition, the curcumin group used significantly less NSAIDs like **celecoxib** and/or acetaminophen and other drugs and nondrug

treatments and had less gastrointestinal complication, distal edema, hospital admissions, and management costs than the control group.²⁸⁰² In a 6-week randomized, placebo-controlled, double-blind study of 40 patients with knee osteoarthritis using the NSAID **naproxen**, 19 were given 1500 mg curcuminoid daily (PO in human clinical study). By the end of the study, those taking curcuminoids had significant improvements in scores for pain and physical function compared to placebo. In addition, 84% of those taking curcuminoids were taking less naproxen, significantly better than the 19% on placebo. The average naproxen usage with curcuminoids was 250-500 mg daily, compared to 500-750 mg daily with placebo.³⁴³³ In a randomized, placebo-controlled, double-blind study of 160 patients with osteoarthritis of the knee, 1000 mg turmeric extract [95% curcuminoids mixed in turmeric powder] to 78 or placebo to 82 subjects were given along with 100 mg **diclofenac** daily for 4 months (PO in human clinical study). By study's end, the extract group had significantly lower WOMAC and pain and physical function VAS scores and lower IL-1 β levels than the placebo group. Reduced oxidative stress in patients taking turmeric was shown with significantly lower reactive oxygen species and malondialdehyde than those taking placebo.³⁶⁸⁰

In addition, in patients with knee osteoarthritis taking a non-curcuminoid extract fraction with 12.6% polysaccharides, those 29 taking 1000 mg daily of the fraction for 42 days used significantly less acetaminophen to control pain during this time than the 29 subjects who were using placebo (PO in human clinical trial). Those taking the extract fraction also had significantly less pain, better function, and greater improvement in orthopedic examinations than those taking placebo. The significant improvements included a higher percentage of elimination of joint tenderness, effusion, crepitation, and limitations of joint movement compared to placebo. Extract adverse events involved 2 cases of mild dyspepsia.³²⁴⁷

A proprietary curcuminoid product with 42 mg of curcumin per capsule in a matrix to maximize absorption was used in doses of 4-6 capsules daily for 6 months by 820 patients with painful osteoarthritis, 54.3% using NSAIDs and 64.7% taking **analgesics**. After 6 months patients were able to discontinue analgesics and NSAIDs by more than half, while also obtaining significantly reduced pain and increased flexibility. Tolerance was excellent.³⁴¹⁵ A comparative study with 91 knee osteoarthritis patients randomized to receive 2 grams daily of turmeric extract [1 gram curcumin] or 800 mg of ibuprofen for 6 weeks found the 45 given turmeric extract had equivalent efficacy, adverse effects, and patient satisfaction as those on ibuprofen after 6 weeks (PO in human clinical study).²⁷⁸⁷

- + 4) Patients with chronic anterior **uveitis**, including 56 with autoimmune, 28 with herpetic, and 22 with other or unknown causes, suffering up to 4 relapses in the previous year were given 240 mg daily for 12-18 months of curcumin formulated with phosphatidylcholine together with the standard treatment they had been receiving that involved systemic **steroids, immune suppressants, antiherpetics, and antitoxoplasmic drugs** or eye drops with steroids, **mydriatics, cycloplegics, and NSAIDs** (PO in human clinical trial). The number of patients with relapses after the curcumin was instituted was 19, and the number of relapses per year for the group was 36, compared to the 275 relapses per year prior to the curcumin.²⁸⁰³
- + 5) In 508 tuberculosis patients with treatment-induced **hepatotoxicity**, 192 were given **isoniazid, rifampicin, and pyrazinamide** along with ethambutol for 2 months, which were continued for 4 more months without the pyrazinamide, while 316 were given the same schedule of drugs together with 1 gm/day of turmeric extract with 25% curcumin and 1 gm/day of *Tinospora cordifolia* powder enriched 50% with its 10:1 hydro-ethanolic extract (PO in human clinical study). The extract concentrates were approximately equivalent to 6 gm/day of each herbal powder. After the 6 months, those using the herbal extracts had significantly lower markers for hepatotoxicity including average serum AST, ALT, and bilirubin levels, significantly less poorly resolved liver parenchymal lesions, and better compliance than the controls. The extract group also had significantly less TB-positive sputum after 4 weeks.²⁹⁹⁵

- + 6) When 1 gram of a lecithinized formulation of curcumin was given for 4 weeks to 25 **diabetes type 2** patients on **oral hypoglycemics**, significant improvements from baseline levels of foot and ankle edema and other signs of microangiopathy were shown, along with significant improvement in Karnofsky scale scores for general health compared to the 25 control subjects (PO in human clinical study).³⁰⁹⁷
- + 7) In 45 **rheumatoid arthritis** patients, groups were randomly selected to receive 500 mg curcumin, 50 mg of **diclofenac**, or both for 8 weeks to monitor scores in disease activity, joint swelling, and tenderness, along with safety outcomes (PO in human clinical study). All 3 groups had significant improvements in these 3 disease outcomes, but the combination and curcumin alone showed better scores than diclofenac alone, while diclofenac had more adverse events than the combination and curcumin alone had none.³¹⁰³
- + 8) In a randomized, observer-masked study of 45 patients with major **depression**, curcumin at 1000 mg daily for 6 weeks with a response rate of 62.5% was equivalent to the response to 20 mg of **fluoxetine** of 64.7%, but the combination was most effective at 77.8%, though the differences were not statistically significant (PO in human clinical study). The investigators ranked responses as good or excellent for 70.5% of those on fluoxetine, 75% on curcumin, and 83.3% on both. The medications were well tolerated.³³⁴⁸
- + 9) When a lecithinized formulation of curcuminoids was given in 100 mg doses 3 times daily with meals to cancer patients with **chemotherapy AE** [adverse effects] from 51% using **5-fluorouracil** for colorectal or gastric cancer, 11% using 5-fluorouracil and **cisplatin** for genitourinary cancers, 6% using **vinblastine** and **CCNU** for kidney cancer, 23% using cisplatin and **gemcitabine** for lung cancer, and 9% using **MOPP/ABVD/COPP** for hematological malignancies, the adverse effects of nausea and vomiting, diarrhea or constipation, malnutrition or weight loss, memory or cognitive dysfunction, infections, neutropenia, and cardiotoxicity were all significantly reduced in the 40 patients receiving curcuminoids, compared to 40 control patients (PO in human clinical study).³³⁶³

In addition, in a randomized, placebo-control, double-blind trial with 180 mg of lecithinized curcuminoids daily for 8 weeks together with standard chemotherapy in 40 cancer patients with solid tumors, mostly colorectal, gastric, and breast cancers[61.5%], the quality of life was significantly increased along with significant decreases in markers of **systemic inflammation** including TNF-a, TGFb, IL-6, substance P, hs-CRP, CGTP, and MCP-1 compared to 40 patients with comparable cancer and chemotherapy who received placebo (PO in human clinical trial). Chemotherapy commonly used in these patients included **topotecan-cyclophosphamide-etoposide** or cyclophosphamide-**methotrexate** for breast cancer, **docetaxel-cisplatin-5-fluorouracil** for gastric cancer and breast cancer, and 5-fluorouracil regimens for colorectal cancer.³⁴⁰⁷
- + 10) A mouthwash with 0.004% curcumin, diluted 1:5 for use for 1 minute 3 times daily for 20 days, was utilized for treating **oral mucositis** induced by **chemotherapy** with **carboplatin**, **cisplatin**, or **taxol** and radiotherapy in 10 cancer patients (PO in human clinical study). After 20 days the pain, ulceration, and severity of mucositis based on the WHO mucositis scale were all significantly improved, compared to standard treatment with a 0.2% chlorhexidine diluted 1:1 for 10 cancer patients.³⁴⁸⁵
- + 11) In a randomized, placebo-controlled, double-blind study completed by 49 **psoriasis** patients using **topical steroids** [**methylprednisolone ointment**], an additional 2 grams daily of curcumin with a lecithin-based delivery system was given to 25 subjects for 12 weeks (PO in human clinical study). Both groups had a significant reduction in Psoriasis Area Severity Index [PASI] values, but the reduction was significantly greater with the curcumin than without it. This PASI improvement remained significantly better in the curcumin group at the 4-week follow-up. Also, IL-22 was significantly reduced in the group using curcumin, but not with use of topical steroids alone.³⁶⁸²

Ila. + 5) In combination with weekly IP **paclitaxel**, curcumin given at 100 mg/kg daily for 5 weeks significantly inhibited MDA-MB-231 tumor cell proliferation, increased apoptosis (PO in mice, *in vitro*) and inhibited **breast cancer** tumor size, compared to paclitaxel alone (PO in mice). This was associated with a decrease in MMP-9 and inhibition of paclitaxel-induced NF-κB activation.³¹¹⁷ The addition of 2% curcumin to the diet significantly reduced the incidence of **lung metastasis** with the use of paclitaxel following surgical removal of human breast cancer cell tumors, compared to paclitaxel alone (PO in mice). While paclitaxel induces the activation of IκBα kinase, NF-κB, and NF-κB antiapoptotic gene products involved in proliferation and metastasis of tumor cells, curcumin inhibited these drug-induced effects along with the activation by paclitaxel of COX-2 mRNA and promoter activity (*in vitro*). Curcumin also potentiated paclitaxel cytotoxicity to breast cancer cells (*in vitro*). Curcumin significantly reduced metastasis even when used alone (PO in mice). The anti-metastatic effect of curcumin with the low paclitaxel dosage was equivalent to a high dose of paclitaxel, suggesting the potential for an equally effective and less toxic treatment (speculative).²⁷⁸¹

Based on a Phase I trial with standard docetaxel dosing in 14 patients with advanced and metastatic breast cancer, a 6-gram curcumin daily dose for 7 consecutive days every 3 weeks is recommended (PO in human clinical study). Of 8 evaluable patients receiving a maximum of 8g/day curcumin, 5 showed a partial response and 3 had stable disease.³¹¹⁹ As shown by plasma levels and a reduction in biomarkers such as PGE₂, curcumin doses of 3.6 grams daily are recommended for cancers outside of the gastrointestinal tract (PO in human clinical study),²⁷⁸⁵ though another study showed negligible distribution outside the gut after 7 days at this dose (PO in human clinical study).²⁷⁸⁶

- + 6) Liposomal curcumin enhanced the effects of suboptimal concentrations of **cisplatin** against xenograft head and neck squamous cell carcinoma [**HNSCC tumors**], significantly better than either agent alone (IV in mice). Curcumin inhibited IKKβ, leading to NFκB inhibition, a different growth signaling pathway than that of cisplatin. The combination of these 2 agents also suppressed 2 HNSCC cell lines (*in vitro*).²⁸⁷⁷ [See Iib. 1) in the book.]
- + 7) Curcumin at 100 mg/kg dosage given 3 times following intramuscular injection of α,β-**arteether**, one day after injection of **Plasmodium berghei** to simulate an animal version of malaria, prevented recrudescence with 100% survival in contrast to 100% fatality 5-8 days after arteether monotherapy (PO in mice). Curcumin in combination with **artemisinin** are additive in killing **Plasmodium falciparum** (*in vitro*).²⁹¹⁴
- + 8) Curcumin at 1gm/kg daily in combination with thrice-weekly IP **gemcitabine** significantly reduced **bladder cancer** tumor volume and microvessel density, compared to gemcitabine alone, while also blocking activation of NF-κB and inducing apoptosis (PO in mice, *in vitro*), and decreasing cyclin D1, VEGF, COX-2, and proliferation marker Ki-67 in the bladder cancer tissue (PO in mice).³¹¹⁸

Doses of curcuminoids [90% curcumin] of 8 g/day in treating advanced pancreatic cancer in a Phase II trial with 17 patients were not tolerated by 5 patients and needed to be reduced to 4 g/day in 2 others when used with IV gemcitabine given in 3 of 4 weeks until toxicity, disease progression, or death occurred (PO in human clinical study). Of 11 evaluable patients, disease stabilized in 4 and partially improved in 1.³¹²⁰

- + 9) Curcumin given at 200 mg/kg 30 minutes after a dose of **acetaminophen** that produces **kidney toxicity** resulted in normalized kidney tissue structure and significantly lower malondialdehyde marker of oxidative damage and increased antioxidant enzyme activity compared to those receiving only acetaminophen (IP in rats).³¹²²
- + 10) After 9.9 g/kg/day of **ethanol** was given for 30 days, 80 mg/kg of curcumin was given concurrently with the 25% **alcohol** to one group that then showed significantly reduction in signs of **hepatotoxicity** compared to those receiving only the alcohol (PO in rats). These signs included elevated serum AST, alkaline phosphatase, total cholesterol, phospholipids, free fatty acids, and

lipid peroxides called thiobarbiturics acid reactive substances.¹⁸³² In another study of alcoholic liver disease, those given only ethanol for 4 weeks developed fatty liver, inflammation, and necrosis accompanied by NF-κB activation and induction of COX-2, iNOS, cytokines, and chemokines, whereas those give 75 mg/kg/day of curcumin with the alcohol avoided these biochemical and pathological changes by blocking the NF-κB activation (PO in rats).³¹⁵⁹

- + 11) The **hepatotoxicity** and **immunosuppressant** effects of the antituberculosis combination of **isoniazid**, **rifampicin** and **pyrazinamide** were significantly reduced by powdered turmeric given at 200 mg/kg for 21 days (PO in guinea pigs). Specifically, the serum AST and alkaline phosphatase were significantly reduced and normalized, respectively, and the phagocytic percentage and other parameters of neutrophilic function were normalized or enhanced, compared to these parameters of those receiving only the antituberculosis drugs.³¹⁹⁸
- + 12) The use of 15 mg/kg curcumin in conjunction with 10 mg/kg **docetaxel** to treat A549-xenograft of non-small cell **lung cancer** showed a synergistic effect that was significantly better than docetaxel alone (IV in mice). A normalization of the significantly elevated alanine aminotransferase from docetaxel alone was achieved by its combination with curcumin, indicating a prevention of hepatotoxicity. The same synergy was shown for enhancing cytotoxicity against the A549 **lung cancer cells** (*in vitro*).³³¹⁹
- + 13) After receiving daily 150 mg/kg curcumin for 15 days prior to **lung infection** with *Klebsiella pneumoniae* and/or 30 mg/kg oral **clarithromycin** 12 hour post infection, comparisons of outcomes of these 3 groups with controls were made (PO in mice). The clarithromycin alone decreased bacterial load and inflammation, whereas curcumin alone had no impact on bacterial load, but alone and combined with the antibiotic curcumin had a more significant reduction in inflammatory parameters including neutrophil influx. The combination led to control of both infection and inflammation, reducing lung damage more than each individually.³⁵¹⁶
- Iib. + 4) Liposomal curcumin has shown synergistic effects of growth inhibition and apoptosis in **colorectal cancer cells** when combined with **oxaliplatin** at a 4:1 ratio, as curcumin was a better growth inhibitor than oxaliplatin (*in vitro*), though there was no advantage when using oxaliplatin with curcumin for xenographic colon tumors (IV in mice).²⁷⁸²

Doses of turmeric extract from 440 mg to 2.2 grams [36-180 mg curcumin] daily and even curcumin doses of 450 mg to 1.8 grams daily have been shown to have poor oral bioavailability systemically but is retained in the gut with good safety, serving as an advantage for application in colorectal cancer patients refractory to chemotherapy (PO in human trial).^{2488,2785} In 5 of 15 patients receiving the extract this disease remained radiologically stable for the 2-4 months of treatment.²⁴⁸⁸ Of those 15 patients receiving the curcumin one became nauseous with 450 mg and another had diarrhea with 900 mg.²⁷⁸⁵ Curcumin has been found in colon mucosa in levels sufficient to explain its pharmacological activities (PO in rats),²⁷⁸³ including in malignant colorectal tissue after 3.6 grams of curcumin have been taken daily for 7 days (PO in human clinical study).²⁷⁸⁶ Evidence (*in vitro* and PO in human clinical trials) suggests curcumin may be useful in colon cancer chemoprevention (speculative).²⁷⁸⁴

VALERIAN

p. 328

**Valeriana officinalis* root/rhizome

Drug Interactions

- Ib. 1) Valerian seems helpful in withdrawal from **benzodiazepine** drugs (empirical).¹⁶⁶ Withdrawal symptoms after valerian discontinuation following many years of regular use were relieved by **midazolam** (PO in human case report).⁸⁹²

A patient with generalized anxiety disorder being treated with **lorazepam** experienced dizziness, throbbing, handshaking, and muscular fatigue after he began self-medicating with valerian and passion flower (*Passiflora incarnata*) for 4 consecutive nights. The first 2 nights he used valerian infusion and passionflower dried herb, while the last 2 nights he took combination

solid extract tablets with about 1 gram of each extract at hourly intervals. (PO in human case report). The adverse effects from the combinations appeared to be an additive or synergistic effect due to binding to GABA receptors (speculative).³⁵⁵⁷

- II. + 4) Though 30 mg/kg valerian combined with **isoflurane** did not increase the emergence time in coming out of general anesthesia, whereas isoflurane with 2 mg/kg **midazolam** injection significantly increased it, when the valerian was given along with the combination of isoflurane and midazolam the emergence time was significantly greater than after using the only the 2 drugs together (PO in rats).³⁵⁵⁶

Complementary Adjuncts

- Ia. 1) A combination of 3 herbal hydroethanolic extracts including valerian root 3-6:1, hops (*Humulus lupulus*) strobiles 4-8:1, and passion flower (*Passiflora incarnata*) herb 4-7:1 was found to markedly improve symptoms associated with **benzodiazepine withdrawal** phase in 107 patients of an average age of 54 years (PO in human clinical study). The extracts were begun with 1-2 tablets daily as benzodiazepine dosage was reduced for 2 weeks, and continued for the next 4 weeks after benzodiazepine use was stopped. Improvement was shown for pronounced tiredness in 76% and general unrest in 71%, according to subjective assessment of patients. Sleep improved in 68% by the end of the treatment, and 74% had more motivation and drive than at the beginning. At the end, 62% were calmer and better able to cope. No adverse drug events occurred in any patients.²⁶³⁴

WILD YAM

p. 334

Dioscorea villosa root

Contraindications

- I. 2) Avoid use in **liver disease** such as **viral hepatitis, toxic hepatitis, or cirrhosis** (empirical).⁷⁷⁷ Use of 0.8 gm/day of a 50:1 extract for 28 days led to some inflammatory and fibrotic changes in the liver (PO in rats).²⁹⁷⁹
- II. 3) Avoid long-term use by those with **kidney dysfunction** or taking drugs that alter kidney function (speculative), since use of 0.8 gm/day of a 50:1 extract for 28 days led to fibrotic changes in the kidney (PO in rats).²⁹⁷⁹

YOHIMBE

p. 340

**Pausinystalia yohimbe* = *Corynanthe yohimbe* bark

Contraindications

- I. 1) Do not use in **schizophrenia**,^{76,184} since psychotic episodes can be induced by its alkaloidal constituent yohimbine (IV in human clinical study).⁷⁶ Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 5% involved altered mental status or behavior (empirical).²⁷⁶⁶
- 3) Avoid use during **anxiety**,³⁴⁴ due to its exacerbation by the alkaloidal component yohimbine (PO and IV in human clinical studies).^{76,79,344} Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 33% involved anxiety or agitation (empirical).²⁷⁶⁶
- 4) Do not use in **high blood pressure**,³⁴⁴ due to its exacerbation by 0.2 mg/kg yohimbine in 9 hypertensive patients, 10 mg in 29 hypertensives, or 21.6 mg in 25 hypertensives (PO in human clinical studies).^{534,535,536} Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 25% involved hypertension (empirical).²⁷⁶⁶
- 8) The conditions of **angina pectoris** and other **heart disease** produce greater risk with yohimbine (PO in human studies).³⁴⁴

Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 43% included tachycardia and 12% involved chest pain (empirical).²⁷⁶⁶

APPENDICES

Appendix A

HERBALS TO BE USED WITH CAUTION

A.2 Due to Potential Photosensitizing Effect

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A.2.2 Other plants not in the carrot family can also act as photosensitizers. Oftentimes the utilized parts and photoactive components these plants, including citrus peels and their essential oils, are most sensitizing following topical exposure.

Ingestion of citrus, on a daily basis has been associated with a significantly increased risk of malignant melanoma of the skin, independent of age and other dietary and lifestyle factors. In particular, half of a grapefruit once or more per week or a 6-ounce glass of orange juice 5-6 times or more per week (but not 6 oz. grapefruit juice or an orange consumed with the same frequency, respectively) significantly increased the hazard ratio for melanoma. This is based on analysis of 63,810 women (Nurses' Health Study 1984 to 2010) and 41,622 men (Health Professionals Follow-Up Study, 1986 to 2010), most of whom are Caucasian. Such "positive association seemed to be more apparent" in those with susceptibility to sunburn as children, more blistering sunburns, more time in direct sunlight, and residences with higher annual flux in ultraviolet light, due in part to significant associations between consumption of grapefruit with melanomas only on body areas with continual higher sun exposure.³⁵⁰⁶

A.2.2 Rutaceae – Rue Family

Grapefruit fruit or peel (*Citrus paradisi*)

Orange fruit juice (*Citrus sinensis*)

A.7 Due to Potential Adverse Effects

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A.7.1 Herbs With Toxic Potential

Commonly used plants are generally safe, but some can have a greater potential for adverse side effects when taken in excessive doses, and these are marked throughout this text with an asterisk (*). The plants listed in this section are all preceded with asterisks and are considered safe only in appropriately small doses (in some cases, extremely small doses and/or for a limited time), so excessive doses for these herbs are by comparison quite small, even in relation to what would be considered normal doses for more commonly used herbs.

Relative doses (therapeutic, toxic and/or lethal), adverse effects, contraindications and antagonistic drug interactions (as antidotes) for most of the potentially toxic plants of the Euro-American traditions can be found in reference 2 (*The Toxicology of Botanical Medicines*).

A.8 Bioactivations of Phytochemical Procarcinogens and Potential Toxins ^

A.8.1 Metabolism of phytochemicals can sometimes lead to the bioactivation of metabolites into toxins or carcinogens. This typically occurs in the liver and often involves Phase I cytochrome P450 (CYP) isozymes or less frequently Phase II conjugating enzymes, especially sulfotransferases. In both cases, with continual exposure to significant doses the end-products of metabolism show enhanced organ toxicities, compared to exposure to the native compounds found in the plant itself. Conversions by intestinal bacteria also have the potential to produce new toxins, as does the exogenous conversion, e.g., transformation of coumarin by molds or fungus to anticoagulant 4-hydroxycoumarins. (See Appendix B.5.1.) Production in some foods such as peanut and corn products of liver carcinogenic aflatoxins by *Aspergillus flavus* or other *Aspergillus*

species of fungus is another cause of concern. However, only those toxic activations that result primarily as a consequence of human metabolism will be considered here.

A number of herbs and extracts should not be taken internally unless appropriately processed to remove the potentially toxic or carcinogenic compounds, such as those containing aristolochic acids or pyrrolizidine alkaloids. For some phytochemicals, such as teucrin A, one of the furano neoclerodane diterpenoids in *Teucrium* spp., the toxicity can be increased in the presence of an appropriate CYP inducer (in this case, one like St. John's wort containing hyperforin). In contrast, its toxicity could theoretically be diminished when exposed to the isozyme-specific CYP 3A4 inhibitor (such as a CYP 3A4 inhibitor like grapefruit juice to help diminish toxicity from exposure to teucrin A). Reducing toxin activation by this approach is intriguing and would be most effective if a single isozyme or metabolic pathway has been identified and can be manipulated. However, *in vivo* research is necessary to confirm this potential. In regard to procarcinogens, the use of certain herbal inhibitors of CYPs may function as an important type of chemoprevention. On the other hand, it is important to avoid combining herbs that could induce enzymes involved in activating potential toxins or procarcinogens with herbs or other sources of these compounds. (See Appendix B.7.)

Major references: 150, 2792

A.8.1 Bioactivations by Cytochrome P450 Isozymes (CYPs) and Sulfotransferases (STs) ^

<i>Phytochemicals</i>	<i>Common Herb Sources</i>	<i>Activators</i>	<i>Metabolite Toxic Effects</i>
aristolochic acids	Aristolochia *(<i>Aristolochia</i> spp.) herbs ²⁸¹⁷ Wild ginger *(<i>Asarum canadensis</i>) rhizome ¹⁵⁰	CYPs 1A1/2; ²⁸¹⁶ ST 1A ²⁷⁹²	kidney carcinogens, ^{150,1357,2818} kidney toxins ^{150,1357}
estragole	Basil (<i>Ocimum basilicum</i>) herb ^{150,400} Fennel (<i>Foeniculum vulgare</i>) seeds ^{150,400} Tarragon (<i>Artemisia dracuncululus</i>) leaf ^{150,400}	CYPs 1A2, 2A6, 2C19, 2D6, 2E1; STs ²⁷⁹²	liver carcinogen, ^{150,759,760} mutagenic ²⁸²⁰
methyl-eugenol	Asarabacca (<i>Asarum europeum</i>) rhizome ⁴⁰⁰ Wild ginger *(<i>Asarum canadensis</i>) rhizome ⁴⁰⁰	CYPs 1A2, 2C9, 2C19, 2D6; STs ²⁷⁹²	liver carcinogen ^{759,760}
pulegone	Am. pennyroyal *(<i>Hedeoma pulegoides</i>) ^{150,2792} Eur. pennyroyal *(<i>Mentha pulegium</i>) ^{150,2792}	CYPs ⁶⁴³ 1A2, 2C19, 2E1 ²⁸²¹	liver toxin ^{642,644,645}
pyrrolizidine alkaloids	Borage herb *(<i>Borago officinalis</i>), ¹⁵⁰ Comfrey plant *(<i>Symphytum officinale</i>), ^{150,2792} Common groundsel herb *(<i>Senecio vulgaris</i>), ²⁷⁹² Gravel root *(<i>Eupatorium purpureum</i>), ¹⁵⁰ Rattlebox herb *(<i>Crotalaria</i> spp.), ²⁷⁹² Tansy ragwort herb *(<i>Senecio jacobaea</i>) ²⁷⁹²	CYPs 2B6, ²⁷⁹² 3A4 ¹¹⁸³	liver toxins ^{38,144,236,333,590}
safrole	Sassafras *(<i>Sassafras albidum</i>) root bark ¹⁵⁰	CYPs ²⁸¹⁹ 2A6, 2C9, 2D6, 2E1; STs ²⁷⁹²	liver carcinogen, ^{150,759,760,2819} mutagenic ²⁸²⁰
teucrin A	Germander (<i>Teucrium chamaedrys</i>) ²⁸²²	CYP 3A4 ²⁷⁹²	liver toxin ^{1516,1517,1518}

Appendix B

HERBAL-DRUG INTERACTIONS

[Note CORRECTIONS: In Appendices B and E in the first 100 copies of the book, asterisks (*) are missing in front of the scientific Latin names for a number of listed herbs designated with * in the main body of the text as containing potentially toxic compounds. (For example, European pennyroyal herb *(*Mentha pulegium*) near the top of page 366 lacks an asterisk in these books.) In Appendix B the other herbs that may be missing the * include: Aloes, Black cohosh, Cayenne, Celandine, Chaparral, Chinese rhubarb, Cinchona, Coffee, Cubeb, Garlic, Juniper, Kava, Licorice, Madagascar periwinkle, Sage, Sassafras, Thuja, and Valerian.]

B.1 Modifying Intestinal Absorption of Medicines and Phase III Metabolism

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B.1.1.b.i & B.1.1.b.ii Even black tea with its known high tannin content and astringency does not completely block iron absorption, if taken with ascorbic acid or an iron supplement providing pharmacological doses or if iron is consumed as the “heme” component of hemoglobin and myoglobin from meat, poultry or fish (40% heme iron, 60% non-heme iron). In addition, tea does not affect non-heme iron absorption as much when the two are consumed separately by rats, with between 60-70% inhibition when tea is taken with meals versus about 20% with tea is taken between meals, since rats synthesize ascorbic acid in the gut. In humans, taking tea with food inhibited non-heme iron absorption from 68% with 0.5 g tea with 40 mg flavonoids per cup to 91% with 5.25 g tea with 420 mg flavonoids per cup.³⁴⁰⁶

B.1.1.d & B.1.2.b P-glycoprotein (Pgp), also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette B1 (ABCB1), in cells of the intestinal mucosa in humans is a major factor in reducing the absorption of some drugs. Pgp is a cell membrane efflux transport protein that pumps certain hydrophobic substrates, including some carcinogens, out of cells lining the intestine and back into the intestinal lumen.

B.1.1.e The **organic anion transporting polypeptide (OATP)** also mediates drug uptake at the intestinal level. OATP-1A2 (OATP-A) is predominantly expressed in the brain rather than the intestine, and OATP-1B1 (OATP-C) is a liver-specific uptake transporter, whereas OATP-2B1 (OATP-B) is more like involved with aiding in intestinal absorption.

B.1.1 Slowed and/or Reduced Absorption by Herbal Components

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B.1.1.b.ii Precipitation by Non-tannin Phenols

Chili fruit (*Capsicum anuum*) – **iron**²⁸⁰⁷

Tea (green) leaves [EGCG] (*Camellia sinensis*) – *sunitinib*³²¹⁰

B.1.1.d Selective Efflux of Drugs or Carcinogens by Inducing P-Glycoprotein

Chinese rhubarb root (*Rheum palmatum*) – *phenytoin* (intestine)³³³⁵

Dan shen root (*Salvia miltiorrhiza*) – **fexofenadine** (intestine)³⁴²⁴

Garlic bulbs (*Allium sativum*) – **saquinavir**³²²³

St. John's wort flowers/leaves (*Hypericum perforatum*) – **methadone**¹⁶⁴¹ [See Note 3.]

Note 3. Though St. John's wort products have more consistently been shown to induce Pgp and reduce absorption for a variety of Pgp substrates in a number of human studies, this was not true for boceprevir. When St. John's wort tablets were given to 17 subjects (11 females) at 600 mg once daily for 15 days, along with boceprevir at 800 mg 3 times daily for the last 5 of these days, there was a nonsignificant change in boceprevir plasma concentration (9% reduction), compared to when it was given for 5 days alone. The St. John's wort dosage was monitored by hypericin, but not hyperforin, plasma concentration.³⁶⁹⁰

B.1.1.e Selective Inhibition of Absorption likely by Inhibiting OATP-B and/or -A

Apple fruit juice (*Malus domestica*) – **aliskiren** (2B1),³⁰⁶⁹ **fexofenadine** (2B1)³⁰⁶⁸
Blueberry fruit (*Vaccinium* spp.) – glibenclamide³⁰⁸⁴
Milk thistle seeds pc silymarin (*Silybum marianum*) – rosuvastatin (oocytes-1B1)²⁹⁶³ [**not rosuvastatin**²⁹⁶³]

Orange fruit juice (*Citrus sinensis*) – **aliskiren** (2B1)³⁰⁶⁹
Tea green leaves (*Camellia sinensis*) – **nadolol**,³³⁸⁸ *nadolol*,³⁵³¹ nadolol (kidney - 1A2)³³⁸⁸

B.1.1.f Slows and/or Decreases Active Intestinal Transport by hPepT1 and/or Others

Cranberry fruit juice (*Vaccinium macrocarpon*) – **cefaclor** (s)²⁶¹⁸

B.1.2 Enhancement of Absorption

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B.1.2.a General Absorption Enhancement by Pungent Herbals

Black pepper fruit (*Piper nigrum*) – calcium, iron, zinc³⁴⁷¹
Cayenne fruit *(*Capsicum frutescens*) – calcium, iron, zinc³⁴⁷¹
Ginger rhizome (*Zingiber officinale*) – calcium, iron, zinc³⁴⁷¹
Long pepper fruit (*Piper longum*) – calcium, iron, zinc³⁴⁷¹

B.1.2.b Selective Retention of Drugs by Inhibiting P-Glycoprotein Drug Efflux

African mistletoe leaves (*Tapinanthus sessilifolius*) – digoxin (intestine)³¹⁹⁷
Barberry bark c berberine [at oral dose of 30-60 mg/kg] (*Berberis* spp.) – cyclosporine, digitalis (intestine),³¹⁰⁵ ketoconazole (intestine)³¹⁰⁴
Bitter leaf leaves (*Vernonia amygdalina*) – digoxin (intestine)³¹⁹⁷
Coptis rhizome c berberine [at oral dose of 30-60 mg/kg] (*Coptis chinensis*) – cyclosporine, digitalis (intestine),³¹⁰⁵ ketoconazole (intestine)³¹⁰⁴
Garlic clove *(*Allium sativum*)
Aged garlic e extract and c S-allyl cysteine – c cisplatin (kidney),³¹⁴⁰ e saquinavir [opposite for darunavir] (liver),³¹⁴¹ c rhodamine 123,^{3142,3143} e rhodamine 123,³¹⁴³ e digoxin, hydrochlorothiazide [opposite for glibenclamide] (intestine)³¹⁴²
Ginger rhizome c 6-gingerol (*Zingiber officinale*) – digoxin (colon, kidney)²²⁷⁹
Ginkgo leaves (*Ginkgo biloba*) – **raltegravir** (intestine),³¹⁹⁰ **talinalol** (intestine),³¹³⁸ [**not fexofenodine**³¹³⁵], rhodamine-123 (intestine)³¹⁹²
Goldenseal roots/rhizome c berberine [at oral dose of 30-60 mg/kg] *(*Hydrastis canadensis*) – cyclosporine, digitalis (intestine),³¹⁰⁵ ketoconazole (intestine)³¹⁰⁴
Licorice root pc glabridin, c glycyrrhetic acid (*Glycyrrhiza glabra*) – daunorubicin, vinblastine³³⁶⁸
Lobelia herb c lobeline (*Lobelia inflata*) – rhodamine-123, doxorubicin (colon, leukemia)³⁴⁴²
Milk thistle seeds pc silymarin (*Silybum marianum*) – **talinalol** (intestine)³¹³⁷ [**not digoxin**¹⁸⁰⁶] [See Note 3.]
Mulberry twigs pc morin (*Morus alba*) – paclitaxel (intestine)²⁸³⁴
Nan wu wei zi fruit (*Schisandra sphenanthera*) – **tacrolimus** (intestine),²⁸²⁹ paclitaxel (intestine),²⁸²⁷ *tacrolimus* (intestine),^{2828,2830} tacrolimus (colon)²⁸³⁰
Onion bulbs c quercetin (*Allium cepa*) – **fexofenadine**,³¹³⁴ paclitaxel (intestine)²⁸³⁵
Oregon grape root bark c berberine [at oral dose of 30-60 mg/kg] (*Mahonia* spp.) – cyclosporine, digitalis (intestine),³¹⁰⁵ ketoconazole (intestine)³¹⁰⁴
Papaya leaves (*Carica papaya*) – digoxin (intestine)³¹⁹⁷
Schisandra fruit lignans or c schisandrin B (*Schisandra chinensis*) – **talinalol** (intestine),³¹³⁸ daunorubicin (leukemia, epidermoid carcinoma, breast cancer MCF-7 & Bcap37), doxorubicin (leukemia, epidermoid carcinoma), epirubicin (leukemia, epidermoid carcinoma), homoharringtonine (leukemia, epidermoid carcinoma), hydroxycamptothecin (leukemia, epidermoid carcinoma), mitoxantrone (leukemia, epidermoid carcinoma), taxol (leukemia, epidermoid carcinoma, breast

cancer MCF-7 & Bcap37), vincristine (leukemia, epidermoid carcinoma, breast cancer MCF-7 & Bcap37)²⁸³¹
 Southern schisandra fruit lignans (*Schisandra sphenanthera*) – tacrolimus (colon)^{2830,3560}
 Soy beans pc genistein (*Glycine max*) – paclitaxel (intestine)²⁸³³
 Tea green leaves pc catechins/EGCG (*Camellia sinensis*) – doxorubicin (intestine),³²⁰⁷ nicardipine (intestine),³²⁰⁹ tamoxifen (intestine),³²⁰⁶ verapamil (intestine),³²⁰⁸
 Turmeric root tincture or pc curcumin (*Curcuma longa*) – calcein-AM (colon),²⁷⁷⁷ celiprolol (intestine),²⁷⁷⁸ daunorubicin (colon),²⁷⁷⁷ digoxin (colon),^{2779,2780} and (kidney),²⁷⁷⁹ rhodamine-123 (colon)^{2777,2780} [See Note 5.]

Notes:

- Silymarin at 420 mg daily for 14 days inhibits Pgp efflux of talinolol in 18 healthy humans equal in numbers for homozygous (CC, TT) and heterozygous (CT) MDR1 3435.³¹³⁷ However, when tested with the Pgp substrate digoxin in 16 healthy humans 440 mg silymarin in 900 mg standardized extract daily for 14 days did not significantly alter the drug bioavailability. There was a tendency toward reducing digoxin levels, suggesting potential Pgp induction.¹⁸⁰⁶
- While curcumin has consistently shown inhibition to Pgp *in vitro*^{2777,2779,2780} and in an *in vivo* study in rats,²⁷⁷⁸ and hydroethanolic extracts of *Curcuma longa* and of other *Curcuma* spp. inhibits Pgp *in vitro*,²⁷⁷⁷ methanolic extracts of *C. longa* and of other *Curcuma* spp. increased Pgp activity *in vitro*.²⁷⁸⁰

B.1.2.c Enhanced Retention of Drugs by Inhibiting MRPs

Chinese rhubarb root (*Rheum palmatum*) – phenytoin (kidney MRP2)³³³⁵ [Note 1.]

Notes

- The induction of Pgp by Chinese rhubarb root in rats led to significant reduction in phenytoin bioavailability, in spite of the inhibition of MRP2 in kidney cells that would increase reabsorption of phenytoin.³³³⁵

B.1.3 No Influence on Drug Absorption in Humans

B.1.3.a No Effect on P-glycoprotein Efflux

Echinacea whole plant (*Echinacea purpurea*) – fexofenadine³⁰⁹⁹
 Ginkgo leaf extract (*Ginkgo biloba*) – digoxin,³²²⁵ fexofenadine³²²⁸

B.1.3.b No Effect on OATP transport ^

Garlic clove c allicin *(*Allium sativum*) – pravastatin³²²³

B.3 Potentiating Sedative or Tranquilizing Medicines

p. 373

Some sedative herbs or extracts have shown sedative and/or anxiolytic effects in animal or human research that did not involve potentiating barbiturates, as indicated by reference citations following their scientific names. On this basis there exists a potential interaction with other pharmaceutical sedatives, tranquilizers, hypnotics, or depressants.

B.3.1 Hypnotic and/or Anxiolytic Drug Enhancement

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Licorice root (*Glycyrrhiza uralensis*) B, BDZ³¹²⁷

Passion flower herb (*Passiflora incarnata*)²⁸⁷⁹

Peppermint leaf oil (*Mentha piperita*) B³¹¹³

Purple passion fruit leaves (*Passiflora edulis*) B²⁹⁵²

Southern schisandra fruit (*Schisandra sphenanthera*) B²⁰⁷⁴

Silk tree bark (*Albizia julibrissin*) B, A, O³¹²⁷

Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) B³²²⁰

B.4 Modifying Blood Sugar In Diabetics

p. 374

In the United States from 2007 to 2009, nearly a quarter of an estimated 100,000 emergency hospitalizations annually from adverse drug events in patients over 65 years of age involved insulin (13.9%) or oral hypoglycemic agents (10.7%). These were two of the top four categories of drugs associated with elderly emergency hospitalization due to medications, along with warfarin (33.3%) and oral antiplatelet agents (13.3%).³⁰²³

B.4.1 Insulin-dependent diabetics (type I) must monitor their blood sugar carefully to not only prevent high blood sugar but to avoid causing hypoglycemic episodes as well. The combined effect of large doses of hypoglycemic herbs with insulin treatment may lower blood sugar levels excessively and could potentially result in insulin shock. **The plants listed here** have a documented ability to lower blood sugar levels through a variety of mechanisms when they or their components **are given orally to humans and/or animals**, including enhancement of **hypoglycemic drugs (hd)** in animals. The reduction of blood sugar by the botanicals listed below has been documented for the **herb (h)**, its **juice (j)**, other **extracts (e)**, and/or its **components (c)** or **metabolites (m)**. Only the antihyperglycemic or hypoglycemic **effects shown in humans** are specifically **designated in bold, affecting diabetics of undetermined type (db), type I (t1), type II (t2), prediabetes (pd), or healthy (hl) individuals.**

B.4.2 The hypoglycemic and/or antihyperglycemic herbs are usually administered in type II diabetes (non-insulin-dependent) to help control blood sugar which does not respond well to insulin or oral hypoglycemic treatment. Certain **botanicals taken orally with oral hypoglycemic drugs** have been shown to reduce blood sugar in humans with type II diabetes more than by using the drug alone. While the risk of severe hypoglycemia is greater with insulin use for type I diabetes, severe hypoglycemia can also occur in type II diabetes, especially in association with multiple diabetic medications.³²⁸⁹ Therefore, the use of hypoglycemic botanical preparations by diabetics taking insulin and/or oral hypoglycemic drugs carries a risk, along with a potential for benefitting poorly controlled high blood sugar. Those botanicals not having strong hypoglycemic properties alone, such as psyllium, nigella, sesame oil, and milk thistle, likely have an even greater margin of safety.

B.4.1 Hypoglycemic and/or Antihyperglycemic Herbals

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Aloe leaf gel (*Aloe vera*)²⁷⁴¹ – **j(t2)**³⁶⁰⁸

Asian ginseng roots (*Panax ginseng*) – m(hd)³⁶⁷¹

Bitter melon fruit (*Momordica charantia*)³²¹⁷ – **j(t2)**³⁴⁷⁶

Cayenne fruit *(*Capsicum frutescens*) – **h(hl)**²⁸⁰⁸

Chirata herb (*Swertia chirayita*)³²¹⁷

Eleuthero root (*Eleutherococcus senticosus*)³⁷¹⁹

Fenugreek seeds (*Trigonella foenum-graecum*)³²¹⁷ – **h(t1)**¹⁶⁴⁶

[Note CORRECTION: the superscript after **h(t1)** should be "1646", not 1645.]

Gulantha stem (*Tinospora cordifolia*)³²¹⁷

Gymnema leaves (*Gymnema sylvestre*)³²¹⁷

Gynostemma herb (*Gynostemma pentaphyllum*) – **e(t2)**²⁸¹¹

Indian stinging-nettle herb (*Tragia involucrata*)³²¹⁷

Ivy gourd herb (*Coccoloba indica*)³²¹⁷

Jambolan seeds (*Syzygium cumini* = *Eugenia jambolana*)³²¹⁷

Kino heartwood (*Pterocarpus marsupium*)³²¹⁷

Maitake mushroom fruiting bodies (*Grifola frondosa*)^{3577,3578} – **c(t2)**³⁵⁷⁶

Moringa stem bark (*Moringa oleifera*)³²¹⁷

Mulberry leaves or twigs (*Morus* spp.) – **f(t2)** [tw],³⁵⁹⁸ **e(pd)** [lf]³⁵⁹⁹

Prickly pear stems (*Opuntia* spp.)²⁸²⁶

Tulsi herb (*Ocimum tenuiflorum* = *Ocimum sanctum*)^{3187,3188,3189,3219}

B.4.2 Antihyperglycemic Botanicals Enhancing Oral Hypoglycemic Drugs in Humans p. 378

Aloe leaf juice (*Aloe vera*) – **glyburide** with **metformin**^{3609,3610}

Bitter melon fruit (*Momordica charantia*) – **glibenclamide**, **metformin**³⁶⁷⁰

Cassia bark extract (*Cinnamomum cassia*) – **metformin** and/or **sulfonylureas**^{1900,2758} including **gliclazide**³²⁴⁴

Fenugreek seeds (*Trigonella foenum-graecum*) – **glyburide**(**glibenclamide**)¹³⁰ and/or **metformin**^{961,1645} and/or **glipizide**,¹⁶⁴⁵ **sulfonylureas**^{1360,2815} and/or **biguanides**¹³⁶⁰

Garlic cloves (*Allium sativum*) – **metformin**³⁰⁸⁹

Gynostemma herb (*Gynostemma pentaphyllum*) – **gliclazide**³²³⁷

Maitake mushroom fruiting bodies (*Grifola frondosa*) – **glyburide** (**glibenclamide**),^{1609, 3576} **glipizide**, **metformin**¹⁶⁰⁹

Milk thistle fruit (*Silybum marianum*) – **glyburide** (**glibenclamide**), **metformin**²⁰⁴¹

Nigella seed (*Nigella sativa*) – **metformin**³⁶⁹⁵

Prickly pear pads (*Opuntia* spp.) – **glipizide**, **metformin**³⁵⁶⁵

Psyllium seed husks (*Plantago ovata*) – **glyburide** (**glibenclamide**),²⁷⁹⁸ **metformin**,²⁷⁹⁹ **oral hypoglycemics**,²⁸⁰¹ **sulfonylureas**,²⁸⁰⁰ **tolbutamide**²⁷⁹⁸

Royal sun agaricus mushrooms (*Agaricus blazei*) – **gliclazide**, **metformin**²²¹⁵

Sesame seed oil (*Sesamum indicum*) – **glibenclamide**³⁶⁵⁸

St. John's wort flowering tops (*Hypericum perforatum*) – **metformin**³⁶⁵⁷

Tulsi seed (*Ocimum tenuiflorum* = *Ocimum sanctum*) – **chloropropamide**, **glibenclamide**, **glipizide**, **penformin**³³⁰⁸

B.4.3 Botanicals Impacting Metabolism of Oral Hypoglycemic Drugs in Humans NEW

B.4.3.a Decreasing Hypoglycemic Activity by Inducing Cytochrome P450 Drug Metabolism

Ginkgo leaf [extract] (*Ginkgo biloba*) – **tolbutamide** [CYP2C9]²⁰¹⁵

St. John's wort flowering tops (*Hypericum perforatum*) – **gliclazide** [CYP2C9],²⁶²⁴ **rosiglitazone** [CYP2C9]²⁶³⁸

B.5 Modifying the Effects of Anticoagulants

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In the United States from 2007 to 2009, almost half of an estimated 100,000 emergency hospitalizations annually from adverse drug events in patients over 65 years of age involved warfarin (33.3%) or oral antiplatelet agents (13.3%). These were two of the top three categories of drugs associated with elderly emergency hospitalization due to medications, along with insulin (13.9%).³⁰²³

B.5.1.b Anticoagulant effects can be produced by a variety of marine algae polysaccharides. Red algae containing certain sulphated polysaccharides, especially lambda-carrageenan which has 1/10 the potency of heparin, inhibit thrombin both directly and indirectly. Carrageenan, though antipeptic, is contraindicated in the treatment of peptic ulcer, and carrageenan sources should be avoided in any GI bleeding to avoid exacerbating the hemorrhaging. Brown algae contain various fucan sulphated polysaccharides (fucoidans) that form tertiary complexes with ATIII-Xa and ARIII-IIa, based on a high degree of sulfation, and inactivate thrombin directly or indirectly by heparin co-factor II.³³⁴⁵ This has been shown to occur in both *in vitro* and *in vivo* when the polysaccharide components are injected. These active polysaccharides have not been shown to be systemically active after oral consumption, but local anticoagulant effects in the gut may be possible. The research on marine algae is mostly studies using platelet-rich plasma *in vitro* (I) to test an **extract/fraction** (e) or one or more isolated **components** (c). *In vivo* (V) studies use injections in animals test these derivatives for enhancement of bleeding time or protective effects against a clot-inducing agent.

B.5.1.c In association with simultaneous consumption of the common anticoagulant, several herbs have been inferred from *in vivo* studies or human case reports to possibly induce a reduction in the metabolism and/or enhancement of the effect of **warfarin (W)** or **antiplatelet drugs (AP)**, leading to increased risk of hemorrhage. Decreased plasma neutralization of **heparin (H)** has also been documented. Risk of hemorrhage is considered possible when combining these drugs with certain herbs such as garlic, Asian ginseng, and/or ginkgo.^{3525,3526} However, this is not supported by *in vivo* evidence in regard to their effects on platelet function.²²⁶²

B.5.1 Increasing Potential for Hemorrhage

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B.5.1.a Additive Effect Due To Content of Potential Prothrombinopenic Components

Sanchi ginseng steamed roots (*Panax notoginseng*) **Vh**³⁴⁵⁰

B.5.1.b Commonly Consumed Marine Algae with Antithrombin Polysaccharides

Bladderwrack brown algae (*Fucus vesiculosus*) **Ic**^{735,737,3345}

Ma-kombu thallus (*Laminaria japonica*) **Ie, Ve**²⁸⁴⁰

Sugar kelp brown algae (*Saccharina latissima* = *Laminaria saccharina*) **Ic**³³⁴⁵

B.5.1.c Warfarin or Heparin Metabolism Inhibitors and/or Anticoagulant Adjuvants

[Note CORRECTION: Cocoa seed (*Theobroma cacao*)¹⁴⁴⁷ belongs in B.5.1.d., rather than B.5.1.c.]

Ginkgo leaves (*Ginkgo biloba*) **W**³⁵⁸³ [**neg W & AP**²⁹⁶⁰]

Lycium [Gobi] fruit (*Lycium barbarum*) **We**^{1768,3027,3448}

Maitake mushroom (*Grifola frondosa*) **We**³⁵⁷⁵

B.5.1.d Platelet Aggregation &/or Adhesion Inhibitors

Asian ginseng root (*Panax ginseng*) [**neg Ee + aspirin**³⁷⁰⁸]

Chokeberry fruit (*Aronia melanocarpa*) **Ie,**^{2961,2964,3128,3258} **Ee**^{2964,3257}

Cocoa seed (*Theobroma cacao*) **Ee**^{1447,2906}

Dong quai root (*Angelica sinensis*) [**neg Ee + aspirin**³⁷⁰⁸]

Grape seed (*Vitis vinifera*) **Ie**^{2961,3128}

Sanchi ginseng steamed roots (*Panax notoginseng*) **Ic,**³⁴⁵¹ **Ie,**^{3450,3451} **Eh**³⁴⁵⁰

Turmeric root (*Curcuma longa, Curcuma aromatica*) [**neg Ee + aspirin**³⁷⁰⁸]

B.5.1.e Fibrin Formation Inhibitors or Fibrinolysis Promoters

Chokeberry fruit (*Aronia melanocarpa*) **Ie**³¹²⁸

Ginger root (*Zingiber officinale*) **HSh**³⁴⁴⁹

Grape seed (*Vitis vinifera*) **Ie**³¹²⁸

B.5.2 Increasing Potential for Coagulation

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B.5.2.b Warfarin Antagonism by Inducing Its Metabolism and/or Modifying Its Effect

American ginseng root (*Panax quinquefolius*) **HS**¹⁶⁰⁰

Avocado fruit (*Persea americana*) **CR**³¹²³

Myrrh root aqueous extract (*Commiphora molmol*) **CR**³⁵²³

B.7 Modifying Enzyme Activities in Metabolic Conversions

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Phase II conjugation and rate of clearance of conjugates can be reduced by liver diseases and vary with their severity. For example, hepatitis C virus cirrhosis and nonalcoholic fatty liver disease (NAFLD) patients show significant 4.7-fold and 3.3-fold higher total (unconjugated and conjugated as glucuronides or sulfates) silymarin flavonolignan blood levels, respectively, than healthy subjects.³⁰²⁵ NAFLD patients have significantly higher unconjugated flavonolignan levels than those with noncirrhotic hepatic C. Metabolism of individual flavonolignans also varies between disease conditions, and this leads to disproportionate bioavailability in comparison with the oral dosage concentrations.³⁰²⁶

B.7.1.a The testing of botanical effects on metabolic conversions both *in vitro* and *in vivo* almost never involves use of the whole powdered herb. *In vitro* evaluation requires extraction of the herb for adequate cellular and enzymatic exposure. *In vivo* tests, whether human (in bold) or animal (in italics), also involves dosing in forms that are typically liquid or solid extracts or fractionated derivatives of the herb. There are many different types of extracts for each herb, and these vary in composition and activity. Since each separate form cannot be individually designated in this table format, they are simply described by the common and scientific **names of the herbs (which are capitalized)**. The specific form used for *in vivo* studies will usually be described in the main body of the text under the common name of that herb, especially for human studies. When chemical fractions or **isolated derivatives (indicated with only small letters)** are studied, this noncapitalized term for the fraction or isolated constituent is given along with the names of the herb(s) from which it can be derived.

A preliminary outline of substrates, i.e., drugs, hormones, and procarcinogens, is initially listed. Following each substrate, the abbreviations of those herbs or their components are listed alphabetically in one of the two groups, depending on whether they increase (inhibit metabolism or efflux) or decrease (induce metabolism or efflux or reduce transport) that substrate. The inhibitors are to the left and inducers are to the right. If both inhibitors and inducers are listed for a drug, hormone, or procarcinogen substrate, these groupings are separated with a semicolon. The specific type of pharmacokinetic interactions covered in this section are those for which the mechanism is not definitely known. So, the isozymes and conjugating enzymes shown to inhibited or induced are noted following the herbs or components in those lists. Efflux or transport proteins/polypeptides like Pgp or OATP-C alter bioavailability; inhibiting intestinal Pgp increases intestinal absorption and thereby increases bioavailability, whereas inhibiting OATP-C (OATP-1B1) reduces hepatic uptake which decreases substrate metabolism and increases bioavailability. On the other hand, inhibiting intestinal OATP-B (OATP-2B1) reduces intestinal absorption and bioavailability. Studies in which contradictory results with herbals were **negative [neg] for inhibiting enzymes conversions in humans are shown in brackets**, while other findings that contradict each other based on types of studies or differences in preparations are discussed in the "Notes" at the end of this section.

B.7.1.b **Gene activation via the nuclear transcription factor pregnane X receptor (PXR) regulates phase I isozymes CYPs 1A2, 2B6, 2C8,9,19, and 3A4,5,7, phase II enzymes UGTs (1A1, 1A3, 1A4, 1A6, 1A9),³⁰⁴⁵ GSTs (A1, A2), and STs, and phase III drug transporter proteins Pgp (MDR1), MRP-2 and OATP.**¹⁹²⁸ However, ginkgo extract and ginkgolides A and B were shown to be potent activators of PXR and induce CYP2B6, CYP3A4, UGT1A1, MRP2, and MDR1 in human primary hepatocytes *in vitro*,³⁰⁴⁴ but in human studies oral ginkgo extract inhibited MDR1²⁶⁸⁰ and inhibited,^{1728,2015} had no effect,^{1328,1824,2301} or slightly induced¹⁸⁴⁰ CYP3A4, while other *in vitro* found CYP3A4 inhibition.^{1823,2145,2151,2292,2608} Human studies and the particular parameters that they investigate (e.g., preparation, dose, duration) remain the most clinically relevant for providing data on pertinent metabolic impacts.³⁰⁴⁵

B.7.1.d Another transcription factor acting as a nuclear receptor gene activator that impacts xenobiotic metabolism is the **constitutive androstane receptor (CAR)**. CAR regulates expression of CYPs 2A6, 2B6, 2C9,19 and 3A4, phase II UGTs (1A1, 2B1)³⁰⁴⁵ and GST-A & -M, and phase III MDR-1. The hepatic nuclear factor 4 α determines the liver's PXR and CAR induction of CYP3A4. Known CAR-mediated inducers of CYP3A4 are the praeuptorins A, C and D from qian hu (*Peucedanum praeruptorum*) root.³³³⁴

B.7.2 [Note: CORRECTION of the web address listing CYP isozyme substrates, inhibitors, and inducers is: <http://medicine.iupui.edu/clinpharm/DDIs/table.aspx> .¹⁵⁶⁷]

B.7.3 Inducers or inhibitors of phase II conjugation reactions are listed along with organ sources of the enzymes that have been used in the cited research studies. Genetic polymorphisms are also found in humans for phase II enzymes such as glutathione S-transferases (GSTs) that exist in the primary classes alpha, pi, mu, theta, and zeta (A, P, M, T, and Z, respectively). UDP-glucuronosyltransferase (UGT) is made up of three main subfamilies with 18 enzyme polymorphisms, UGT1A (1,3-10), UGT2A (1,2), and UGT2B (4,7,10,11,15,17,28), most expressed in the liver but some (1A7, 1A8, 1A10) only in the intestines. The influence by inducers and inhibitors on the specific classes and families of these conjugating isozymes are noted when known. Specific probe substrates are used for UGT 1A1 (bilirubin, estradiol, etoposide), 1A4 (imipramine, midazolam, trifluoperazine), 1A6 (naphthol, serotonin), 1A9 (propofol, phenylbutazone), 2B7 (morphine, 3'-azidothymidine, naloxone), and 2B15 (S-oxazepam).³³²²

B.7.4 Herbal influences on steroid metabolism are included to indicate both potential interactions with pharmaceuticals as well as possible modulation of endogenous hormones that impact systemic function. Therapeutic application of modified steroid conversion is illustrated by herbs that reduce the estrogen to testosterone ratio through inhibition of the enzyme **aromatase** [CYP 19; B.7.4.a] and have effectively been used in the treatment of benign prostatic hyperplasia (BPH), while pharmaceutical aromatase inhibitors are used to treat postmenopausal hormone-dependent breast cancer. Similar approaches have been used in other hormone-dependent conditions typified by imbalanced hormone ratios, such as using **5 α -reductase inhibitors (type 1 or type 2)** [B.7.4.b] to treat BPH and/or help prevent prostate cancer for those in whom it has not yet been detected. The influence on **sterol 27-hydroxylase** [CYP27A1; B.7.4.j] in the liver for cholesterol conversion to bile acids and for vitamin D₃ bioactivation also has important implications, as this enzyme is regulated by a variety of endocrine hormones.

B.7.1 Unspecified Influences of Herbal Agents on Substrate Pharmacokinetics p. 394

B.7.1.a Modulation by Phase I &/or Phase II &/or Phase III

Probes: benzyloxyresorufin [2B1/2/6] – cc²⁹³⁸

7-ethoxyresorufin [1A1/2] – ; *bl*,³⁵⁵⁴ *Co*³²⁹⁰
 7-pentoxyresorufin [2B1/2] – ; *An*,²⁹⁷⁵ *bl*,³⁵⁵⁴ *Co*³²⁹⁰

Drugs: rosuvastatin –

phenytoin – *Gc*³²⁸⁴ ; *Fg*, *Ni*³²⁸⁴
 warfarin – ; *Co*,³²⁹⁰ *Gb*³⁵²⁹

Steroids: dehydroepiandrosterone [OATP-C] – bA, ep mr, nr, si³²²⁴

estradiol – *Bl*, *By*, *ea*³⁰⁸² ; *Co*³²⁹⁰
 testosterone – ;

Procarcinogens: benzo[a]pyrene [1A1] – ep³²⁰¹

Conversion/Clearance Inhibitors (Increase Bioavailability)

(Ao) Aloe gel (*Aloe vera*) – 2C11²⁹⁴⁷

(bA) biochanin A from red clover leaves, flowers (*Trifolium pratense*), etc. – OATP-C³²²⁴

(Bl) Blueberry fruit (*Vaccinium corymbosum*) – 1A1, 1B1³⁰⁸²

(By) Black raspberry fruit (*Rubus occidentalis*) – 1A1, 1B1³⁰⁸²

(cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*) – 1A1,²⁰³⁵ 1A2, 2B6, 2C9, 2D6, 3A4²⁹³⁸

(ea) ellagic acid as in strawberry leaves and seeds (*Fragaria* spp.), raspberry seeds and leaves (*Rubus* spp.), black walnut leaves and nuts (*Juglans nigra*), etc. – 1A1,³⁰⁸²

- (ep) epigallocatechin gallate [EGCG] from green tea leaves (*Camellia sinensis*) – OATP-C;³²²⁴
1A1/1A2,^{1998,3201} 2A6,2C19, 2E1, 3A4³²⁰¹
- (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – [not CYP2B6 (bupropion)²⁷⁶²]; UGT-1A9³¹⁹¹
- (Gc) Garden cress seed (*Lepidium sativum*) – CYP 2B11, 3A4³²⁸⁴
- (mr) myricetin as in tea (black and green) leaves (*Camellia sinensis*), parsley leaves (*Petroselinum sativum*), cranberry fruit/juice (*Vaccinium macrocarpon*), etc. – OATP-C³²²⁴
- (my) myristicin from parsley leaf oil (*Petroselinum sativum*), nutmeg seed *(*Myristica fragrans*), etc. –
1A1, 1A2, 2B1,³¹²⁹
- (nr) naringenin as in grapefruit fruit juice (*Citrus paradisi*) – OATP-C³²²⁴
- (si) silymarin/silibinin from milk thistle seeds (*Silybum marianum*) – OATP-C³²²⁴
- Conversion/Clearance Inducers (Reduce Bioavailability)
- (An) Andrographis leaves (*Andrographis paniculata*) – 1A1, 2B²⁹⁷⁵ [See Note 9.]
- (bc) baicalin/baicalein and other Chinese skullcap flavones (*Scutellaria baicalensis*) – OATP-
1B1(*1b/*1b or*1b/*15)³²³²
- (bl) bilobalide from ginkgo leaf (*Ginkgo biloba*) – CYP 1A1, 1A2, 2B, 2C, 3A³⁵⁵⁴
- (Co) Coleus root (*Coleus forskohlii*) – CYP 1A1/2, 2B, 2C, 3A³²⁹⁰; GST³²⁹⁰
- (Ep) Echinacea purpurea tops (*Echinacea purpurea*) – OATP-B;¹⁸⁸³ 1A1, 2D1²⁹⁷⁸
- (Fg) Fenugreek seed (*Trigonella foenum-graecum*) – CYP 2B11, 3A4³²⁸⁴
- (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – OATP-B;¹⁸⁸³ PXR; 2B6, 3A4,³⁰⁴⁴ 2B, 2C³⁵²⁹ [not CYP2B6
(bupropion)²⁷⁶²]; GST-P1,³²²⁶ UGT-1A1³⁰⁴⁴
- (gf) ginkgo flavonol aglycones in ginkgo leaves (*Ginkgo biloba*) – CYP 1A2; UGT1A1³⁰⁴⁴
- (gi) glucobrassicin indole metabolites in specific crucifers (*Brassica oleracea*) – 1A1, 1A2, 2B,³¹²⁹
- (go) ginkgolides A&B in ginkgo leaves (*Ginkgo biloba*) – PXR; 2B6, 3A4; UGT³¹⁹²
- (Kv) Kava root (*Piper methysticum*) – 1A2, 2B1, 3A1³³⁶² [Note 10.]
- (Ni) Nigella seed (*Nigella sativa*) – CYP 2B11, 3A4³²⁸⁴
- (pi) phenethyl isothiocyanate from watercress herb (*Nasturtium officinale*), crucifers (*Brassica* spp.) –
1A1, 1A2, 2B,³¹²⁹

Notes:

9. Though andrographis has shown inhibition of the metabolism of probe substrate 7-ethoxyresorufin for CYP 1A1/2 *in vitro*,²⁰³⁵ it induces metabolism of this probe *in vivo* in rats. No effect was shown on the *in vivo* metabolism of the CYP 1A2 probe substrate methoxyresorufin.²⁹⁷⁵
10. While *in vitro* metabolism by CYP of substrates of CYP 1A1,¹⁷³³ 1A2, 2C19,^{1327,1733} 2C8,²⁵⁶⁸ 2C9,^{1327,1577,1733} 2C19,²⁵⁶⁸ 2D6,¹³²⁷ 3A4,^{1327,1475,1577,1733} 4A9/11¹³²⁷ was inhibited, when 1.0 or 2.0 g/kg of kava extract was administered to rats daily for 14 weeks, CYPs 1A2, 2B1, and 3A1 showed increased expression in both males and females. No effect on CYP isozymes or GGT activity was seen below the 1.0 g/kg. No adverse effects were seen at 0.25 mg/kg.³³⁶²

B.7.1.b Influence on Pregnane X Receptor (PXR)

Receptor activators

- (Cf) California poppy aerial parts [ethanolic extract] (*Eschscholzia californica*) – (liver)³⁵⁴⁶
- (ez) escholtzine from California poppy aerial parts [ethanolic extract] (*Eschscholtzia californica*) – (liver)³⁵⁴⁶
- (Gb) ginkgo leaf extract (*Ginkgo biloba*) – (liver)³⁰⁴⁴
- (gf) ginkgo flavonol aglycones in ginkgo leaves (*Ginkgo biloba*) – liver³⁰⁴⁴
- (go) ginkgolides from ginkgo leaf (*Ginkgo biloba*) – (liver)³⁰⁴⁴

B.7.1.c Influence on Aryl hydrocarbon Receptor (AhR)

Receptor inhibitors

- (It) luteolin as in thyme herb (*Thymus* spp.), asparagus stem (*Asparagus officinalis*), etc. – liver, breast³³⁶⁶

Receptor activators

- (gf) ginkgo flavonol aglycones in ginkgo leaves (*Ginkgo biloba*) – liver³⁰⁴⁴

B.7.1.d Influence on Constitutive Androstane Receptor (CAR)

Receptor inhibitors

Guggul (*Commiphora mukul*) resin^{2111,2112}

Receptor activators

Qian hu (*Peucedanum praeruptorum*) root³³³⁴

B.7.2 Influences of Herbal Agents in Phase I on Specific Cytochrome P450 Isozymes p. 405

B.7.2.a Influence on CYP 1A2 Metabolic Conversion of Substrates

Probes: 3-cyano-7-ethoxy-coumarin – fp³⁵⁷⁰

7-methoxyresorufin – cc²⁹³⁸ ; bl,³⁵⁵⁴ Co,³²⁹⁰ gi, pi³¹²⁹

Drugs: caffeine –

; rs,²⁹⁷⁰ SJ¹³²⁸

phenacetin – ts²⁷⁷⁰

Procarcinogens: 2-amino-1-Me-6-Ph-Imidazo-[4,5b]Pyridine (PhIP) – ep³²⁰¹

Isoenzyme Inhibitors

(cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*)

(ep) epigallocatechin gallate [EGCG] from green tea leaves (*Camellia sinensis*)

(fp) fucophlorethols from bladderwrack (*Fucus vesiculosus*)

(ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)

Isoenzyme Inducers

(bl) bilobalide from ginkgo leaf (*Ginkgo biloba*)

(Co) Coleus root (*Coleus forskohlii*)

(gi) glucobrassicin indole metabolites in certain crucifers (*Brassica oleracea*)

(pi) phenethyl isothiocyanate from watercress herb (*Nasturtium officinale*), crucifers (*Brassica* spp.)

(rs) resveratrol as in dark-skin grapes (*Vitis vinifera*), mulberry fruit (*Morus* spp.), blueberry fruit (*Vaccinium* spp.)

(SJ) St John's wort herb (*Hypericum perforatum*)

No Effect in Human Studies with Isoenzyme CYP 1A2 substrates

[Note CORRECTION: (SJ) St John's wort herb (*Hypericum perforatum*) – caffeine superscript '1328' should be deleted, since a significant mean 26% increase in metabolite to caffeine ratio was observed in the group of 6 men and 6 women. Also, apply this CORRECTION to Note 3.]

(bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape (*Mahonia* spp.) roots/barks – caffeine³²³⁸

(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – caffeine^{1328,1808,2302,3091} [See Note 4.]

(La) English lavender flowers (*Lavandula angustifolia*) – caffeine³³⁰³

(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – caffeine²⁸¹⁰

Notes:

4. Ginkgo extract is a CYP1A2 inducer at low concentrations (2.2 mcg/ml) but an inhibitor at higher concentrations (22 and 220 mcg/ml) *in vitro*.²²⁹² At 100 mg/kg orally and as 0.5% of the diet in rats it was shown to induce this isozyme,^{1952,2278} but normal therapeutic doses do not produce this effect in humans.^{1328,1808,2302,3091}

7. The study with 42 healthy humans showing significant induction of caffeine metabolism involved taking 1 gm of resveratrol orally once daily for 4 weeks.²⁹⁷⁰ Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.

B.7.2.b Influence on CYP 2E1 Metabolic Conversion of Substrates

p. 408

Probes: aniline – Am²⁸⁵⁷

Drugs: chlorzoxazone – ts²⁷⁷⁰

acetaminophen – Go³⁶¹⁸

Procarcinogens: NMBA (N-nitrosomethylbenzylamine) – Bp²⁴⁶⁰

Isoenzyme Inhibitors

- (Am) Amla fruit (*Emblca officinalis*)
 (Bp) Black raspberry fruit (*Rubus occindentalis*)
 (Go) Goldenseal root (*Hydrastis canadensis*)
 (ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)

Notes:

1. St. John's wort extract (0.3% hypericin) at 900 mg daily for 28 days in 6 men and 6 women in good health increased chlorzoxazone CYP2E1 metabolism by 110%,¹³²⁸ but in 12 healthy elderly the same preparation and dosage increased chlorzoxazone metabolism by only 28%.¹⁸⁰⁸
4. Goldenseal powder at 300 mg/kg inhibits acetaminophen metabolism by CYP2E1 in rats and thereby protects these animals from liver toxic effects of this drug.³⁶¹⁸ However, in humans a goldenseal root extract had no effect on CYP2E1.¹⁸⁰⁷

B.7.2.c Influence on CYP 3A Metabolic Conversion of Substrates

p. 411

Probes: 7-benzoyloxy-4-(Fl³Me)coumarin – cc,²⁹³⁸ Cf,³⁵⁴⁶ ez,³⁵⁴⁶

7-benzoyloxyquinoline – cc²⁹³⁸
 7-benzoyloxyresorufin – cc²⁹³⁸
 dibenzylfluorescein – cc²⁹³⁸
 luciferin 6'benzyl ether – sc²⁷⁷¹

Drugs: atazanavir – Cc³⁵²⁰

atorvastatin – ; Gb,³⁵⁵³ SJ²²⁰⁰

bupirone – Gf,³⁶⁰¹ rs,²⁹⁷⁰ Te²⁸¹⁰

celiprolol – cc²⁷⁷⁸

chlorzoxazone – rs³⁵⁹³

cyclosporine – Ch³⁵⁷¹

diazepam – Cc³⁵¹⁹ ; Eu³⁵¹⁹

efavirenz – Gb³³⁹²

erythromycin – Gf,²⁵⁹⁰ sc²⁹⁴⁶

finasteride – ; SJ³¹³³

methadone – ; SJ¹⁶⁴¹

midazolam – bb,³²³⁸ cc,²⁷⁷⁸ cc,²²⁷⁹ Ds,³⁵⁶¹ Ds,³⁴²⁵ ep,³²⁰¹ gn²⁷⁷⁹ Pm,³¹¹³ sc,sc,²⁸³² Sf,¹⁹²³ Ss,³¹³⁶

Te,³²⁰² Wg¹⁸⁸⁵ ; Ds,^{3425,3443} Ep,³⁰⁹⁹ Gb,³¹³⁵ Gs,²⁹⁶⁵ sc,²⁸³²

nevirapine – pp³¹³² ; SJ¹⁹⁷²

nicardipine – ep³²⁰⁹

nifedipine – Gb³²²⁹

nitrendipine – Pg³¹¹¹

oxycodone – SJ³⁶⁹³

paclitaxel – Eu,²⁵⁶⁸ Fr,²⁶⁶⁴ Gb,²¹⁴⁵ Gf,²⁵⁶⁸ Go,²¹⁴⁵ is,²⁸³³ kb,²⁶⁶⁴ Kv,²⁵⁶⁸ Mt,²¹⁴⁵ Po,²⁵⁶⁸ qu,²⁸³⁵

Ss²⁸²⁷

ritonavir – Cc³⁵²⁰

saquinavir – Cc³⁵²⁰

sirolimus – Gf³¹⁴⁴

tacrolimus – Gf,³⁶⁰⁶ Gf,³¹²⁴ Gr, Po,³⁶⁰⁶ sc,³⁵⁶⁰ Ss,²⁸³⁰ Ss,^{2828,2830,3559} Ss,^{2829,3558} Tu,³⁶⁰⁶ Tu³⁶⁰⁵

tamoxifen – ep³²⁰⁶

zolpidem – SJ³⁶⁹⁴

Steroids: testosterone – aa,³⁵⁶⁸ cm,²⁷⁶⁸ sc,²⁹⁴⁶ ts²⁷⁷⁰ ; bl,³⁵⁵⁴ Co³²⁹⁰

cortisol – Gf^{3021,3426}

Procarcinogens: aflatoxin B₁ – ep³²⁰¹

Isoenzyme Inhibitors

(aa) asiatic acid in Gotu kola leaf (*Centella asiatica*)

(bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape (*Mahonia* spp.) roots/barks [See Note 10.]

- (Bo) Bitter orange fruit juice (*Citrus aurantium*)
- (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*)
- (Cc) Cat's claw bark (*Uncaria tomentosa*)
- (Cf) California poppy aerial parts [ethanolic extract] (*Eschscholzia californica*)
- (Ch) Chamomile (*Matricaria recutita*)
- (cm) curcumenol from zedoary rhizomes (*Curcuma zedoaria*)
- (Co) Coleus root (*Coleus forskohlii*)
- (Ds) Dan shen root (*Salvia miltiorrhiza*) [See Note 22.]
- (ep) epigallocatechin gallate [EGCG] from green tea leaves (*Camellia sinensis*)
- (Ep) Echinacea purpurea tops (*Echinacea purpurea*) [See Note 3.]
- (Eu) Eucalyptus leaf oil (*Eucalyptus globulus*)
- (ez) escholtzine from California poppy aerial parts [ethanolic extract] (*Eschscholtzia californica*)
- (Fr) Frankincense resin (*Boswellia* spp.)
- (Gb) Ginkgo leaf extract (*Ginkgo biloba*) [See Note 15.]
- (Gf) Grapefruit fruit/juice (*Citrus paradisi*) [in humans, intestinal CYP3A4 only] [See Note 14.]
- (gn) 6-gingerol in ginger root/rhizome (*Zingiber officinale*)
- (Go) Goldenseal root and herb *(*Hydrastis canadensis*) [See Note 10.]
- (Gr) Ginger root/rhizome (*Zingiber officinale*)
- (is) isoflavones as in soy beans (*Glycine max*), kudzu plant (*Pueraria lobata*), red clover herb (*Trifolium pratense*), etc.
- (kb) keto boswellic acids from frankincense resin (*Boswellia* spp.)
- (Kv) Kava root *(*Piper methysticum*) [See Note 9.]
- (Mt) Milk thistle seeds (*Silybum marianum*) [See Note 1.]
- (Pg) Pomegranate fruit (*Punica granatum*) [See Note 16.]
- (Pm) Peppermint leaf (*Mentha piperita*)
- (Po) Pomelo fruit juice (*Citrus grandis*)
- (pp) piperine in black pepper fruit (*Piper nigrum*), long pepper fruit (*Piper longum*)
- (qu) quercetin as in onion bulbs (*Allium cepa*), tea leaves (*Camellia sinensis*), cranberry fruit/juice (*Vaccinium macrocarpon*), etc.
- (rs) resveratrol as in dark-skin grapes (*Vitis vinifera*), mulberry fruit (*Morus* spp.), blueberry fruit (*Vaccinium* spp.)
- (sc) schisandrol/gomisin lignans from schisandra or southern schisandra fruit (*Schisandra chinensis*, *S. sphenanthera*) [See Note 20.]
- (Ss) Southern schisandra fruit (*Schisandra sphenanthera*)
- (Te) Tea (green) leaf catechin extract (*Camellia sinensis*) [See Note 19.]
- (ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)
- (Tu) Turmeric root (*Curcuma longa*, *Curcuma aromatica*) [See Note 23.]

Isoenzyme Inducers

- (bl) bilobalide from ginkgo leaf (*Ginkgo biloba*)
 - (Ds) Dan shen root (*Salvia miltiorrhiza*) [See Note 22.]
 - (Ep) Echinacea purpurea tops (*Echinacea purpurea*) [See Note 3.]
 - (Eu) Eucalyptus leaf oil (*Eucalyptus globulus*)
 - (Gb) Ginkgo leaf extract (*Ginkgo biloba*) [See Note 15.]
 - (Gs) Asian ginseng root (*Panax ginseng*) [See Note 11.]
 - (sc) schisandrol A/gomisin A lignans from schisandra fruit (*Schisandra chinensis*) [See Note 20.]
 - (SJ) St. John's wort herb (*Hypericum perforatum*)
- No Effect in Human Studies with Isoenzyme CYP 3A substrates
- (Bl) Blueberry fruit/juice (*Vaccinium* spp.) – buspirone³⁶⁰¹
 - (Ca) Cannabis tops infusion *(*Cannabis sativa*, *Cannabis indica*) – docetaxel, irinotecan²⁹⁴¹
 - (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*) – midazolam³⁶⁸¹ [See Note 23.]

(Ep) Echinacea purpurea root or entire plant (*Echinacea purpurea*) – darunavir/ritonavir,²⁷⁹³ etravirine,³⁵³⁸ lopinavir/ritonavir³⁰⁹⁹ [See Note 3.]

(Ga) Garlic bulbs (*Allium sativum*) – simvastatin³²²³ [See Note 7.]

(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – anastrozole,³²⁶⁸ cilostazol,³⁵⁵² letrozole,³²⁶⁸ lopinavir,³¹³⁵ midazolam,³⁰⁹¹ ritonavir,³¹³⁵ tamoxifen,³²⁶⁸ ticlopidine³²²⁷ [See Note 15.]

(La) English lavender flowers (*Lavandula angustifolia*) – midazolam³³⁰³

(SJ) St. John's wort herb (*Hypericum perforatum*) – boceprevir,³⁶⁹⁰ repaglinide³⁵⁶⁴ [See Note 2.]

Notes:

2. A randomized crossover study with 15 healthy humans used 325 mg of a St. John's wort product 3 times daily for 14 days before taking the glucose-lowering CYP3A4 and 2C8 substrate repaglinide, and no pharmacokinetic or pharmacodynamic changes were detected. However, the product's hyperforin content was not reported.³⁵⁶⁴ When St. John's wort tablets were given to 17 subjects (11 females) at 600 mg once daily for 15 days, along with boceprevir at 800 mg 3 times daily for the last 5 of these days, there was a nonsignificant change in boceprevir plasma concentration (9% reduction), compared to when it was given for 5 days alone. The St. John's wort dosage was monitored by hypericin, but not hyperforin, plasma concentration.³⁶⁹⁰
3. While midazolam metabolism was induced by 750 mg daily for 28 days of an 8:1 standardized fresh whole plant extract, lopinavir metabolism was not affected after 14 days of the extract when given in combination with the CYP 3A inhibitor ritonavir.³⁰⁹⁹ Etravirine metabolism was not significantly impacted by 500 mg of the root extract every 8 hours for 14 days in 15 HIV-infected patients on a stationary 400 mg daily drug dosage.³⁵³⁸ CYP3A1/2 in rats was inhibited by 50 mg/kg of a 60% ethanolic extract of *E. purpurea* herb after 3 days.²⁹⁷⁸
7. 7. Garlic caplets reduced plasma content of saquinavir by 50% possibly by induction of CYP3A4.¹²¹⁰ However, when 600 mg garlic extract was taken by 10 men twice daily for 21 days, though it decreased the average saquinavir bioavailability by 15%, it did not change bioavailability of CYP3A4 substrate simvastatin. The CYP3A4 expression was reduced by only 13%, but intestinal P-glycoprotein increased by 31%. So, since saquinavir is a substrate of both CYP3A4 and Pgp, the induction of Pgp best explains the decreased saquinavir levels, in spite of 13% less metabolism by CYP3A4.³²²³
10. Goldenseal extract at 2.7 gram daily inhibited midazolam metabolism in 12 men and women.¹⁸⁰⁷ Likewise, 0.9 grams of berberine daily for 14 days significantly increased single-dose midazolam bioavailability and half-life in 17 healthy men.³²³⁸
11. Daily doses for 28 days of 1.0 gm Asian ginseng standardized to 5% ginsenosides induced metabolism of the CYP3A4 substrate midazolam,²⁹⁶⁵ while 1.5 gm failed to alter the 1-hour postdose ratio of metabolite to drug for midazolam in 2 human studies.^{1328,1808} However, 200 mg/day of uncharacterized "ginseng" for 18 days inhibited metabolism of CYP3A4 substrate nifedipine, as indicated by increased peak plasma concentrations of 29%.¹⁷²⁸
15. Concerning ginkgo, 360 mg/day EGb 761 increased midazolam bioavailability by 25%.²⁰¹⁵ However, 240 mg standardized ginkgo failed to alter the metabolism of CYP3A4 substrate midazolam in humans.³⁰⁹¹ An extract dose of 120 mg every third day for 14 days in 16 volunteers significantly reduced bioavailability and maximum plasma concentration of atorvastatin, but did not impact its cholesterol-lowering efficacy.³⁵⁵³ In a study of 20 patients each taking the hormonal CYP 3A4 substrates anastrozole, letrozole, or tamoxifen, there were no significant changes in trough concentration after taking 240 mg daily of EGb 761 for 3 weeks.³²⁶⁸ Yet, in another study 240 mg daily significantly reduced midazolam bioavailability by 34% and its maximum concentration by 31%, but half-life was not changed, indicative of intestinal, but not hepatic, induction. Still, the same dose for 2 weeks had no effect on the combination of CYP3A4 substrates lopinavir and ritonavir, possibly due to ritonavir's CYP3A4 inhibiting activity.³¹³⁵
16. Though pomegranate juice inhibits CYP3A in rats,^{1920,3111} 2 doses prior to midazolam had no effect on midazolam clearance in healthy humans.²²¹³

19. Though a green tea catechin extract supplying 844 mg catechin daily for 14 days to 11 healthy humans did not affect alprazolam metabolism,¹⁷¹⁰ use of a green tea catechin extract supplying 800 mg EGCG daily for 4 weeks to 42 healthy human subjects led to a 20% increase in buspirone bioavailability, but this change was not deemed clinically significant.²⁸¹⁰ The inhibition effect of green tea extract with 60%+ catechins on oral midazolam metabolism in rat intestines was opposite its induction effect on IV midazolam in the liver of rats; the strong inhibitory effect using human liver microsomes *in vitro* is therefore not reliable for predicting the *in vivo* effect.³²⁰²
20. The lignan extract of schisandra containing schisandrol A, gomisin C, deoxyschizandrin, and γ -schizandrin inhibits CYP 3A4 metabolism of midazolam *in vitro* and when 1 dose is given to rats with oral midazolam, but not IV midazolam, indicating inhibition of intestinal but not hepatic metabolism. However, when the lignan extract is given long-term it induces the CYP 3A4 protein expression in the liver 2.5-fold and its intestinal metabolism 4-fold, and thereby increases midazolam metabolism, especially in the small intestines. Gomisin C was the most potent inhibitor *in vitro* and the least concentrated in the liver, while schisandrol A was the least potent and the most concentrated in the liver.²⁸³² Though gomisins B and G are also active, gomisin C is the most potent inhibitor of CYP3A4 metabolism of erythromycin and testosterone *in vitro* and irreversibly inactivates it in a time- and concentration-dependent manner.²⁹⁴⁶ Six lignans from southern schisandra, i.e., schisandrin A, B, and C, schisandrol A and B, and schisantherin A, when tested *in vitro* with human and rat liver microsomes, inhibited tacrolimus metabolism by CYP3A dose-dependently.³⁵⁶⁰
21. The study with 42 healthy humans showing significant inhibition of buspirone metabolism involved taking 1 gm of resveratrol orally once daily for 4 weeks.²⁹⁷⁰ Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.
22. Though a single dose of dan shen extract led to an 87% increase in midazolam maximum plasma concentration,³⁴²⁵ when the extract was given for 10 or 14 days it decreased the maximum concentration, half-life, and bioavailability in 12 healthy men.^{3425,3443} In rats, a single i.p. dose or a 3-day i.p. or oral dose of 200 mg/kg of dan shen extract increased midazolam bioavailability.³⁵⁶¹ Tested *in vitro* the component dihydrotanshinone I inhibits CYP3A, while cryptotanshinone and tanshinone IIA induce CYP3A.³⁴²⁵
23. Though curcumin had been shown to inhibit midazolam metabolism by CYP3A *in vivo*²⁷⁷⁸ and *in vitro*,²⁷⁷⁹ when given orally at a dose of 4 grams twice daily for 2 days, along with 24 mg of piperine to enhance its absorption, it failed to impact midazolam metabolism in 8 healthy human volunteers.³⁶⁸¹ On the other hand, turmeric inhibited the metabolism of CYP3A substrate tacrolimus in rats³⁶⁰⁶ and appeared to do so in single human case report after 10 days of oral use.³⁶⁰⁵

B.7.2.d Influence on CYP 2C9 Metabolic Conversion of Substrates

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Drugs: diclofenac – Cb,³⁰⁸⁵ cc,²⁹³⁸ Pg,³¹¹² rs³⁶⁰⁴
 flurbiprofen – am,¹⁹⁵⁴ Pg,³²⁴⁵ qu¹⁹⁵⁴
 losartan – bb,³²³⁸ rs,²⁹⁷⁰ si²⁹⁸¹
 phenprocoumon – ; SJ⁶⁰⁵
 rosiglitazone – ; SJ²⁶³⁸
 tolbutamide – aa, Gk³⁵⁶⁸ Pg,³¹¹² pt,³⁰⁴³ ts²⁷⁷⁰
 warfarin – si²⁹⁸⁰ ; bl,³⁵⁵⁴ Co,³²⁹⁰ Gb^{3529,3554}

Isoenzyme Inhibitors

- (aa) asiatic acid/madecassic acid in Gotu kola leaf (*Centella asiatica*)
- (bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape (*Mahonia* spp.) roots/barks
- (Cb) Cranberry fruit/juice (*Vaccinium macrocarpon*)
- (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*)

- (Gk) Gotu kola leaf (*Centella asiatica*)
 (Pg) Pomegranate fruit (*Punica granatum*)
 (pt) polysaccharide peptides from turkey tail (*Coriolus versicolor*)
 (rs) resveratrol as in dark-skin grapes (*Vitis vinifera*), mulberry fruit (*Morus* spp.), blueberry fruit (*Vaccinium* spp.) [See Note 8.]
 (si) silymarin/silybin from milk thistle seeds (*Silybum marianum*) [See Note 8.]
 (ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)

Isoenzyme Inducers

- (bl) bilobalide from ginkgo leaf (*Ginkgo biloba*)
 (Co) Coleus root (*Coleus forskohlii*)
 (Gb) Ginkgo leaf extract (*Ginkgo biloba*) [See Note 3.]
 (SJ) St. John's wort herb (*Hypericum perforatum*)

No Effect in Human Studies with Isoenzyme CYP 2C9 substrates

- (Bl) Blueberry fruit/juice (*Vaccinium* spp.) – flurbiprofen³⁶⁰¹
 (Cb) Cranberry fruit/juice (*Vaccinium macrocarpon*) – diclofenac³⁰⁸⁵ [See Note 9.]
 (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*) – flurbiprofen³⁶⁸¹ [See Note 11.]
 (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – tolbutamide^{2011,3091} [See Note 3.]
 (La) English lavender flowers (*Lavandula angustifolia*) – tolbutamide³³⁰³
 (Pg) Pomegranate fruit (*Punica granatum*) – flurbiprofen³²⁴⁵
 (Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – losartan²⁸¹⁰

Notes:

3. Though ginkgo extract acts as a CYP 2C9 inhibitor *in vitro*,^{2011,2145,2151} at 360 mg/day EGb 761 in humans²⁰¹⁵ and in rats and mice it was shown to induce this isozyme.^{1952,3529,3554} Normal therapeutic doses do not produce either effect in humans.^{1433,1774,1842,2011,3091}
7. The study with 42 healthy humans showing significant inhibition of losartan metabolism involved taking 1 gm of resveratrol orally once daily for 4 weeks.²⁹⁷⁰ Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.
8. The inhibition of losartan metabolism by a 14-day treatment with 140 mg of silymarin 3 times daily was only significant in the 6 Chinese men with a CYP2C9*1 genotype; it was not significant in the 6 men with a CYP2C9*3 genotype.²⁹⁸¹
9. Cranberry juice inhibited the metabolism of diclofenac by human liver microsomes *in vitro*, but repeated consumption failed to do so in human subjects.³⁰⁸⁵ Likewise, both flurbiprofen¹⁹⁴⁷ and S-warfarin²³¹⁶ metabolism were unaffected in humans.
10. Despite inhibiting the metabolism of CYP 2C9 drug substrates *in vitro*^{3112,3245} and in rats,³¹¹² when 250 ml of pomegranate juice or a single 1 gram capsule of pomegranate extract with 689 mg polyphenols was given in a crossover trial to 12 human subjects along with the substrate flurbiprofen, no change in its metabolism was noted when compared with placebo control and the positive control inhibitor fluconazole.³²⁴⁵
11. Though curcumin had been shown to inhibit diclofenac metabolism by CYP2C9 *in vitro*,²⁹³⁸ when curcuminoids were given orally at a dose of 4 grams twice daily for 2 days, along with 24 mg of piperine to enhance its absorption, they failed to impact CYP2C9 metabolism of flurbiprofen in 8 healthy human volunteers.³⁶⁸¹

B.7.2.e Influence on CYP 2C19 Metabolic Conversion of Substrates

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No Effect in Human Studies with Isoenzyme CYP 2C19 substrates ^

- (bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape (*Mahonia* spp.) roots/barks – omeprazole³²³⁸
 (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – cilostazol,³⁵⁵² diazepam,²⁷⁶¹ omeprazole,³⁰⁹¹ ticlopidine,³²²⁷ voriconazole²⁶⁷⁹ [See Note 1.]
 (La) English lavender flowers (*Lavandula angustifolia*) – omeprazole³³⁰³

Notes:

1. In a 12-day study with 18 healthy Chinese men, ginkgo standardized extract at 280 mg daily increased metabolism of omeprazole and mephenytoin.^{2301,2302} HOWEVER, EGb 761 given at 120 mg twice daily or 240 mg once daily for 8 days to 18 healthy Caucasian men and women caused no significant effect in the metabolism of a single dose of omeprazole.³⁰⁹¹ Also, in 12 healthy Chinese men 240 mg ginkgo standardized extract daily for 8 weeks did not influence diazepam metabolism by CYP2C19, responsible for 50-60% of its clearance.²⁷⁶¹

B.7.2.f Influence on CYP 2D6 Metabolic Conversion of Substrates

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Drugs: dextromethorphan – **bb**,³²³⁸ **cc**,²⁹³⁸ **aa**,³⁵⁶⁸ **rs**²⁹⁷⁰
metoprolol – **sa**²⁷⁶⁷
venlafaxine – **Gk**³⁵⁶⁹

Isoenzyme Inhibitors

- (aa) asiatic acid/madecassic acid in Gotu kola leaf (*Centella asiatica*)
- (bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape (*Mahonia* spp.) roots/barks
- (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*)
- (Gk) Gotu kola leaf (*Centella asiatica*)
- (rs) resveratrol as in dark-skin grapes (*Vitis vinifera*), mulberry fruit (*Morus* spp.), blueberry fruit (*Vaccinium* spp.)
- (sa) salvianolic acid B from dan shen roots (*Salvia miltiorrhiza*)

No Effect in Human Studies with Isoenzyme CYP 2D6 substrates

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- (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – debrisoquin,^{1328,1808,2302} dextromethorphan^{1840,3091}
- (La) English lavender flowers (*Lavandula angustifolia*) – dextromethorphan³³⁰³
- (SJ) St John's wort herb (*Hypericum perforatum*) – [CORRECTION: debrisoquin superscript '1328' should be deleted]
- (Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – dextromethorphan²⁸¹⁰

Notes

2. [Note CORRECTION: an exception to no significant effect of St. John's wort on debrisoquin in human studies is a 23% increased urinary recovery ratio of debrisoquin metabolite in one study, indicative of possible Pgp induction.¹³²⁸]
6. The study with 42 healthy humans showing significant inhibition of dextromethorphan metabolism involved taking 1 gm of resveratrol orally once daily for 4 weeks.²⁹⁷⁰ Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.

B.7.3 Specific Enzyme Influences of Herbal Agents on Phase II Conjugation

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(Bold indicate human studies (subject criteria noted); organ sources of enzymes identified from *in vitro* and animal studies)

B.7.3.a Influence on Activity and/or Content of Glutathione S-Transferases (GSTs)

Conjugation Inducers

- (Am) Amla fruit (*Emblica officinalis*) – liver^{2853,2854}
- (Bp) Black raspberry fruit (*Rubus occidentalis*) – liver²⁴⁶⁰
- (Br) Broccoli florets or sprouts [e water extract] (*Brassica oleracea* v. *italica*) – (e) bladder,³⁴⁰¹ skin (A1)²⁸⁹⁶
- (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*) – liver²⁷⁸³
- (Chb) Chokeberry fruit [juice] (*Aronia melanocarpa*) – liver (A)³⁴²⁹
- (Cl) Clove oil (*Syzygium aromaticum*) – liver, forestomach, small intestine²⁹⁵⁴
- (Co) Coleus root (*Coleus forskohlii*) – liver³²⁹⁰
- (eg) eugenol as in clove buds (*Syzygium aromaticum*) – liver²⁹⁵⁹

- (Gb) Ginkgo leaves (*Ginkgo biloba*) – liver (P1)³²²⁶
 (Li) Little ironwood herb (*Vernonia cineraria*) – liver²⁷⁹⁰
 (os) organosulfides in garlic cloves (*Allium sativum*) – kidneys³¹⁴⁰
 (Sb) Shrubby basil leaf oil (*Ocimum gratissimum* = *O. suave*) – liver³⁰¹⁴
 (sr) sulforaphane from broccoli sprouts and tops (*Brassica oleracea* v. *italica*) – skin (A1)²⁸⁹⁶
 (Tl) Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – liver,^{3015,3364} skin³²¹³

B.7.3.b Influence on Activity and/or Content of UDP-Glucuronosyl Transferases (UGTs)

Conjugation Inhibitors

- (Cb) Cranberry fruit/juice (*Vaccinium macrocarpon*) – liver (1A9)³⁰⁷⁹
 (cy) chrysin from passion flower leaves (*Passiflora incarnata*, *Passiflora coerulea*) – liver (1A1)³²⁴²
 (ep) epigallocatechin gallate [EGCG] from green tea leaves (*Camellia sinensis*) – liver (1A1),³²⁴¹
 (1A4)³⁰⁷⁹
 (Ep) Echinacea purpurea root (*Echinacea purpurea*) – liver (1A1)³²⁴¹
 (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – liver (1A9), intestine (1A8,1A9)³¹⁹¹ [not liver (1A1)³¹⁹⁰]
 (kf) kaempferol as in tea (black and green) leaves (*Camellia sinensis*), kale leaves (*Brassica oleracea* v. *acephala*), etc. – liver (1A9), intestine (1A8,1A9)³¹⁹¹
 (Mt) Milk thistle seeds (*Silybum marianum*) – liver (1A1),³²⁴¹ (1A6, 1A9)³⁰⁷⁹
 (qu) quercetin as in onion bulbs (*Allium cepa*), tea leaves (*Camellia sinensis*), cranberry fruit/juice (*Vaccinium macrocarpon*), etc. – liver (1A9), intestine (1A8,1A9)³¹⁹¹
 (si) silymarin/silybin from milk thistle seeds (*Silybum marianum*) – intestinal microsomes, kidney cell lysates (1A1, 1A8, 1A10; raloxifene)³⁵⁶⁷
 (Sp) Saw palmetto fruit (*Serenoa repens*) – liver (1A1),³²⁴¹ (1A6)³⁰⁷⁹
 (tn) tangeretin as in citrus fruit/juice (*Citrus* spp.) – liver (1A1)³²⁴²

Conjugation Inducers

- (cc) curcumin in turmeric root (*Curcuma longa*, *Curcuma aromatica*) – colon, intestine³²⁴⁰
 (cn) coumarin as in sweet clover (*Melilotus officinalis*), etc.
 (Cr) Crucifers, specifically Brussels sprouts and/or cabbage (*Brassica oleracea*) – intestine, liver³²⁴⁰
 (ea) ellagic acid as in strawberry leaves and seeds (*Fragaria* spp.), raspberry leaves and seeds (*Rubus* spp.), black walnut leaves and nuts (*Juglans nigra*), etc. – liver³²⁴⁰
 (eg) eugenol as in clove buds (*Syzygium aromaticum*) – liver²⁹⁵⁹
 (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – liver (1A1)³¹⁹²
 (go) ginkgolides A&B in ginkgo leaves (*Ginkgo biloba*) – liver (1A1)³¹⁹²
 (qu) quercetin as in onion bulbs (*Allium cepa*), tea leaves (*Camellia sinensis*), cranberry fruit/juice (*Vaccinium macrocarpon*), etc. – intestine, liver³²⁴⁰

No effect in humans

- (Ag) American ginseng root extract (*Panax quinquefolius*) – zidovudine²³²⁵

B.7.3.c Influence on NAD(P)H:Quinone Oxidoreductase 1 (Quinone Reductase [QR]) or DT-Diaphorase Activity and/or Content

Conjugation Inhibitors

- (fp) fucophloretols from bladderwrack (*Fucus vesiculosus*) – liver³⁵⁷⁰
 (8pn) 8-prenylnaringenin from hops strobiles (*Humulus lupulus*) – breast³⁴⁵⁷

Conjugation Inducers

- (Ag) American ginseng root (*Panax quinquefolius*) – heart²⁹²⁸
 (Bl) Blueberry fruit (*Vaccinium* spp.) – liver³²⁶¹
 (Br) Broccoli florets or sprouts [e water extract] (*Brassica oleracea* v. *italica*) – (e) oral,³⁵³⁴ skin,^{2895,2896}
 skin,^{2895,2896,3037} (e) bladder³⁴⁰¹
 (Chb) Chokeberry fruit [juice] (*Aronia melanocarpa*) – liver³⁴²⁹
 (Hp) Hops strobiles (*Humulus lupulus*) – liver³⁴⁵⁷
 (iq) isoliquiritigenin from licorice root (*Glycyrrhiza glabra*, *G. uralensis*), tonka bean seeds (*Dipteryx odorata*, *D. oppositifolia*), etc. – liver²⁹⁷¹

- (sr) sulforaphane from broccoli sprouts and florets (*Brassica oleracea* v. *italica*) – mammary epithelium,³⁴⁰⁰ skin,³⁰³⁷ skin, **skin**^{2895,2896}
- (tg) tigloylgomis H lignan from schisandra fruit (*Schisandra chinensis*) – liver³¹³⁹
- (xh) xanthohumol and/or isoxanthohumol in hops strobiles (*Humulus lupulus*) – liver³⁴⁵⁷

B.7.3.f Influence on Activity of Estrogen Sulfotransferases (SULT1E1)

NEW

Conjugation Inhibitors

- (Bl) Blueberry fruit juice (*Vaccinium corymbosum*) – colon³⁴²⁷
- (Chb) Chokeberry fruit juice (*Aronia melanocarpa*) – colon³⁴²⁷
- (Cof) Coffee roasted seed infusion (*Coffea arabica*) – colon³⁴²⁷
- (Pm) Peppermint leaf infusion (*Mentha piperita*) – colon³⁴²⁷

B.7.4 Specific Enzyme Influences of Herbal Agents on Steroid Metabolism

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(Bold abbreviations indicate human studies with subject criteria noted; organ enzyme sources identified for *in vitro* tissue studies [non-italicized] and animal studies [italicized])

B.7.4.a Aromatase (CYP 19) Conversion of Androstenedione to Estrone and Testosterone to 17beta-Estradiol

Conversion Inhibitors

- (bA) biochanin A from red clover leaves, flowers (*Trifolium pratense*), etc. – breast³³⁹³
- (Dm) Damiana leaves (*Turnera diffusa*) – liver³²³¹
- (bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape (*Mahonia* spp.) roots/barks – breast³³⁹³
- (ep) epigallocatechin gallate [EGCG] from green tea leaves (*Camellia sinensis*) – cervix³³⁹³
- (fp) fucophlorethols from bladderwrack (*Fucus vesiculosus*)³⁵⁷⁰
- (Gw) Grape red wine (*Vitis vinifera*) – **systemic**³¹⁷⁵
- (iq) isoliquiritigenin from licorice root (*Glycyrrhiza glabra*, *G. uralensis*), tonka bean seeds (*Dipteryx odorata*, *D. oppositifolia*), etc. – breast³³⁹³
- (is) isoflavone [genistein] in soy beans (*Glycine max*) – liver³³⁹³
- (ms) γ -mangostin in mangosteen (*Garcinia mangostana*) pericarp – breast³³⁹³
- (thc) tetrahydrocannabinol in cannabis (*Cannabis sativa*) – breast³³⁹³
- (Wb) White button mushroom (*Agaricus bisporus*) – breast, breast³⁴⁵⁸

B.7.4.b 5alpha-Reductase Conversion of Testosterone to Dihydrotestosterone

Conversion Inhibitors

- (Am) Amla fruit (*Phyllanthus emblica*) – liver³⁴⁹¹
- (Ft) Foti root [emodin³³⁶⁷] (*Polygonum multiflorum*) – prostate,³³⁶⁷ epididymis³⁴⁹⁰
- (Gg) Greater galangal rhizomes (*Alpinia galanga*) – liver³⁴⁹¹
- (gp) gossypol in cotton root bark (*Gossypium herbaceum*, *G. hirsutum*) – prostate (types 1 & 2)³⁴⁹⁵
- (Gr) Ginger rhizomes (*Zingiber officinale*) – liver³⁴⁹¹
- (gs) ginsenosides [Ro, Rd] (*Panax ginseng*) – epididymis, hair follicle³⁴⁸⁹
- (Gs) Asian ginseng rhizomes/ root (*Panax ginseng*) – epididymis, hair follicle³⁴⁸⁹
- (Hg) Horny goat weed leaf (*Epimedium grandiflorum*) – epididymus³⁴⁹⁰
- (is) isoflavones as in soy beans (*Glycine max*), red clover flowers (*Trifolium pratense*), etc. – prostate (type 2)³⁴⁹⁵
- (Jg) Japanese ginseng rhizomes (*Panax japonicus*) – epididymis³⁴⁸⁹
- (kf) kaempferol as in tea (black and green) leaves (*Camellia sinensis*), kale leaves (*Brassica oleracea* v. *acephala*), etc. – prostate (type 2)³⁴⁹⁵
- (Kz) Kudzu flower (*Pueraria thomsonii*) – epididymis, hair follicle³⁴⁹⁰
- (Lg) Lesser galangal rhizomes [diarylheptanoids] (*Alpinia officinarum*) – prostate³⁴⁹⁴
- (Ls) Lemongrass herb (*Cymbopogon citratus*) – liver³⁴⁹¹
- (na) nordihydroguaiaretic acid in chaparral *(*Larrea tridentata*) – prostate (types 1 & 2)³⁴⁹⁵

- (Oy) Oyster mushroom (*Pleurotus ostreatus*) – liver (type 1), prostate (type 2)³⁴⁹²
 (Rs) Reishi mushrooms (*Ganoderma lucidum*) – prostate, prostate (type 2), liver (type 1)³⁴⁹²
 (Sf) Saffron pistil (*Crocus sativus*) – epididymis³⁴⁹⁰
 (Sh) Shiitake mushroom (*Lentinula edodes*) – liver (type 1), prostate (type 2)³⁴⁹²
 (Sw) Safflower flowers (*Carthamus tinctorius*) – liver, hair follicle³⁴⁹¹

B.7.4.d 11beta-Hydroxysteroid Dehydrogenase type 1 or 2 Conversion of Cortisol to Cortisone Conversion Inhibitors

- (gl) glycyrrhetic acid/glycyrrhizin from licorice root *(*Glycyrrhiza glabra*, *Glycyrrhiza uralensis*) – (t1, t2) liver,^{559,3455} (t2) kidney,³⁰²²
 (Li) Licorice root *(*Glycyrrhiza glabra*) – in Addison's disease³⁰²¹

B.7.4.g 17beta-Hydroxysteroid Dehydrogenase type 1 Conversion of Estrone to Estradiol Conversion Inhibitors

- (Bl) Blueberry fruit (*Vaccinium corymbosum*) – mammary³⁰⁸²
 (By) Black raspberry fruit (*Rubus occidentalis*) – mammary³⁰⁸²
 (ea) ellagic acid as in strawberry leaves and seeds (*Fragaria* spp.), raspberry seeds and leaves (*Rubus* spp.), black walnut leaves and nuts (*Juglans nigra*), etc. – mammary³⁰⁸²

B.7.4.i 11beta-Hydroxysteroid Dehydrogenase type 1 Conversion of Cortisone to Cortisol Conversion Inhibitors

- (gl) glycyrrhetic acid/glycyrrhizin from licorice root *(*Glycyrrhiza glabra*) – liver³⁰²²

B.7.4.j Sterol 27-Hydroxylase (CYP27A1) Conversion of Cholesterol to Bile Acids and Bioactivation of Vitamin D₃

Conversion Inducers

- (bb) berberine from barberry bark (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape root bark (*Mahonia aquifolium*), etc. – liver²⁹³³

Appendix C

HERBALS CONTRAINDICATED FOR MOTHERS AND CHILDREN

C.1 *During Pregnancy*

p. 439

Substances that interfere with the mother's hormonal balance or fetal genetic expression can disrupt fetal development. In the cases of the gender-specific reproductive organs, plants shown in humans or animals to cause **gonadotropic** or **sex hormone (H)** changes may alter normal expression. **Mutagens (M)** and **genotoxins (G)** may likewise disturb normal growth as shown by *in vitro* studies. **Teratogens (T)** have been shown to interfere with normal development of particular structures, and plants with **fetotoxins (F)** endanger the essential functions of the developing child. In cases where such substances cause these effects to occur *in utero*, birth defects are a possible outcome that otherwise could be avoided.

(Based in part on reference 2791, 3056-3058, 3377, 3496.)

American mistletoe leaves, stems *(*Phoradendron macrophyllum*) A

Bitter melon fruit /seeds (*Momordica charantia*) A; T

California mugwort herb (*Artemisia douglasiana*) A

Feverfew herb (*Tanacetum parthenium*) H

Horsetail herb (*Equisetum* spp.) A

Pennyroyal (See: American pennyroyal, European pennyroyal) E, A

Saw palmetto fruit (*Serenoa repens*) H

Wormwood tops, leaves *(*Artemisia absinthium*) H

Yerba mansa (*Anemopsis californica*) A

C.2 *While Breast Feeding*

Some herbal preparations are given safely as galactogogues to increase milk production. For example, micronized silymarin given to 25 women with borderline levels of lactation significantly increased milk production after 30 and 63 days compared to placebo. No evidence of silymarin was found in the breast milk of 5 women after 5 days.²⁸⁹⁸ This micronized standardized silymarin extract was shown after 14 days in female rats to increase prolactin levels that remained significantly elevated another 66 days, likely involving dopamine D₂ receptors.²⁹⁶⁷ A granular herbal tea formula containing fenugreek was also shown to significantly enhance milk production of a group of 22 mothers, compared to placebo apple tea granules in 22 new mothers or no intervention in 22 others, during the first week of life for their newborns. No maternal or neonatal adverse effects were reported.²⁸⁹⁹ The fenugreek formula also contained among other herbs goat's rue, fennel, and fennel essential oil, the latter made up almost entirely of the estrogenic component anethole.¹⁴ However, in a report of 2 cases of mothers consuming more than 2 liters daily of herbal tea mixtures with extracts of goat's rue, fennel, licorice, and anise for 15-20 days after birth, the breast-fed infants failed to thrive and showed nervous system symptoms after the first week. When the teas were stopped, the infants recovered and did well.¹¹⁴¹ Some active constituents of medicinal plants can be excreted in breast milk intact or as metabolites that maintain much of the activity of the original compounds, and problems are more likely when large quantities of the herbal extracts are consumed for extended periods.

Infants under 6 months of age should optimally be given only breast milk and not be given herbal teas or other extracts or medicinal preparations unless prescribed by a recognized health expert. Giving even safe herbal teas to an infant can reduce its milk consumption and vital nutrient intake. As regards a nursing mothers consuming unnecessary herbal products, unless the specific intent is to treat the child by this means, it is preferable to not expose the breast feeding infant to

potent medicinal compounds. Especially when particular plant compounds are known to inadvertently produce their unintended pharmacologic effect in the nursing child, caution should be used in taking herbals that contain these.

Appendix D

VITAMIN/MINERAL/DRUG INTERACTIONS

D.1 Drug and Mineral Interactions with Vitamin Supplements p. 457

Interference between vitamins and drugs or prescription mineral supplements can work both ways. In some cases drugs will **lower vitamin (LV)** oral absorption and/or serum levels or increase excretion or metabolism, while in other cases medications can **raise vitamin (RV)** bioavailability or increase their effects. In cases where drugs reduce vitamin levels, consumption of plant sources of the vitamin would be highly desirable. Vitamins may also **raise drug (RD)** or **mineral (RM)** serum levels or increase their effects, or they may **lower drug (LD)** or **mineral (LM)** levels or reduce their effects. Vitamin/drug or vitamin/mineral interactions listed below have caused either **toxicity (t)** or **insufficient (i)** effects for one or the other. **Clinical findings for humans are emphasized in bold.** Other interactions listed have produced observable changes without clinically-apparent adverse effects, but monitoring is advisable.

References: 3243, 3278

D.1.6 Vitamin B₁₂ (Cyanocobalamine) / Drug Interactions

p. 462

Esomeprazole - LV

Lansoprazole - LV

Omeprazole - LV

Pantoprazole - LV

Rabeprazole - LV

D.1.8 Vitamin C (Ascorbic Acid, Ascorbates) / Drug Interactions

p. 464

Esomeprazole - LV

Lansoprazole - LV

Omeprazole - LV

Pantoprazole - LV

Rabeprazole - LV

D.1.9 Vitamin D (Calciferol) / Drug Interactions p. 465

Efavirenz - LV_i

D.2 Drug and Vitamin Interactions with Mineral Supplements p. 467

Interference between minerals administered orally together with drugs or prescription vitamin or mineral supplements can work both ways. In some cases drugs will **lower mineral (LM)** oral absorption and/or serum levels or increase their excretion, while in other cases medications can **raise mineral (RM)** bioavailability or increase their effects. The mineral forms listed below are those that have most commonly been shown to interact with the drugs. In cases where drugs affect the mineral levels, they usually act independently of the form of the mineral consumed, affecting dietary as well as supplementary sources. Adverse interactions are noted by emphasizing the drug **in bold if documented in human studies.**

References: 2823,3278

D.2.1 Calcium (as Carbonate) / Drug Interactions p. 470

Esomeprazole - LM

Lansoprazole - LM

Omeprazole - LM

Pantoprazole - LM

Rabeprazole - LM

D.2.4 Iron (as Ferrous Sulfate) / Drug Interactions

p. 474

Esomeprazole - LM

Lansoprazole - LM

Omeprazole - LM

Pantoprazole - LM

Rabeprazole - LM

D.2.5 Magnesium (as Oxide) / Drug Interactions

p. 476

Bumetanide - LM

Dexlansoprazole - LM

Esomeprazole - LM

Indapamide - LM

Lansoprazole - LM

Metolazone - LM

Omeprazole - LM

Pantoprazole - LM

Rabeprazole - LM

Torsemide - LM

Appendix E

HERBALS AS POTENTIAL COMPLEMENTARY ADJUNCTS WITH MEDICINES

[Note CORRECTION: In Appendices B and E in the first 100 copies of the book, asterisks (*) are missing in front of the scientific Latin names for a number of listed herbs designated with * in the main body of the text as containing potentially toxic compounds. (European pennyroyal herb *(*Mentha pulegium*) near the top of page 366 lacks an asterisk in these books.) In Appendix E the other herbs that may be missing the * include: Black cohosh, Bryonia, Cannabis, Cayenne, Chinese rhubarb, Cinchona, Garlic, Goldenseal, Jamaica dogwood, Licorice, Sage, Thuja, Thunder god vine, Valerian, and Wormwood.]

E.1 Potentially Beneficial Combinations of Herbals with Drugs p. 483

E.1.1 Herbs and Those Drugs Which May Potentially Be Complemented

- Aloe gel (*Aloe vera*) – **chemotherapy**³⁵⁸⁴
- Amla fruit (*Emblica officinalis*) – **isoniazid, pyrazinamide, rifampicin,**^{2857,2858} *cyclophosphamide,*^{2853,2955} **cisplatin,**²⁸⁶⁰ **doxorubicin**^{2859,2860}
- American ginseng (*Panax quinquefolius*) root – **ACE inhibitors, beta-blockers, calcium channel blockers,**^{3420,3704} **chemotherapy,**^{2916,3293} **influenza vaccine,**^{2918,2919} *cyclophosphamide,*^{2924,2925} **mitomycin C,**²⁹²² **N-acetyl cysteine, vitamin C**²⁹²³
- berry – **5-fluorouracil**²⁹²⁷
- Arjuna bark (*Terminalia arjuna*) – **isosorbide dinitrate**^{2661,3286}
- Arnica flowers *(*Arnica montana*) – **acetaminophen,**²⁸⁰⁵ **hydroxyethyl salicylate**³⁰⁹⁰
- Ashwagandha (*Withania somnifera*) root – **adriamycin, cyclophosphamide, epirubicin,**³²⁵² **ethambutol,**³²³³ **5-fluorouracil,**³²⁵² **isoniazid, pyrazinamide, rifampicin,**³²³³ **SSRI's,**³⁵⁴⁸ **taxotere,**³²⁵² **gentamicin**³²⁵³
- Asian [red] ginseng root (*Panax ginseng*) – **adefovirdipivoxil,**³⁶⁶¹ **carboplatin, cisplatin, docetaxel,**³⁷²⁵ **donepezil,**³⁰⁵⁹ **entecavir,**³⁶⁶¹ **galantamine,**³⁰⁵⁹ **lamivudine,**³⁶⁶¹ **memantine,**³⁰⁵⁹ **paclitaxel,**³⁷²⁵ **rivastigmine,**³⁰⁵⁹ **tenofovir,**³⁶⁶¹ *cyclosporine,*³⁵²² **cisplatin**²⁷²⁵
- Astragalus root (*Astragalus membranaceus*) – **enalapril**²⁷²⁸
- Barberry root bark (*Berberis vulgaris*) – **simvastatin,**²⁹⁰⁵ **amphotericin B,**³¹⁰⁷ **doxorubicin,**³¹⁴⁸ **stanols,**^{2932,2933} **vancomycin**³⁶¹⁹
- Bayberry bark (*Myrica cerifera*) – **doxorubicin**³⁷²⁴
- Bilberry fruit (*Vaccinium myrtillus*) – **latanoprost,**²⁹⁶⁶ **doxorubicin**^{3514,3515}
- Black cumin [see *Nigella*]
- Black pepper fruit (*Piper nigrum*) – **calcium,**³⁴⁷¹ **EGCG,**²⁹³⁵ **emodin,**³⁴⁵⁹ **iron, zinc**³⁴⁷¹
- Burdock root (*Arctium lappa*) – **acetaminophen, glucosamine,**³⁵³⁹ **acetic acid, alcohol (ethanol)**³⁵⁴¹
- Calamus rhizome (*Acorus calamus*) – **vincristine**³³⁷⁵
- Cannabis tops *(*Cannabis sativa*) – **anticholinergics,**²⁷⁵¹ **anticonvulsants, antidepressants,**²⁹⁴⁰ **baclofen,**³³⁰⁵ **clobazam,**³⁷¹⁶ **codeine, dextropropoxyphene, dihydrocodeine,**²⁷⁴⁸ **glatiramer, interferon beta-1a,b,**³³⁰⁵ **levetiracetam,**³⁷¹⁶ **methadone,**²⁷⁴⁸ **methotrexate,**²⁹⁴² **morphine,**^{2748,3126} **NSAIDs,**²⁹⁴⁰ **oxycodone,**^{2748,3126} **pethidine,**²⁷⁴⁸ **stiripentol,**³⁷¹⁶ **tizanidine,**³³⁰⁵ **topiramate,**³⁷¹⁶ **tramadol,**²⁷⁴⁸ **valproate**³⁷¹⁶
- Cat's claw bark (*Uncaria tomentosa*) – **doxorubicin**³³³¹
- Cayenne fruit (*Capsicum frutescens*) – **calcium, iron, zinc**³⁴⁷¹
- Chaga mushroom (*Inonotus obliquus*) – **cyclophosphamide**³⁵⁰⁴
- Chamomile flowers (*Matricaria recutita*) – **cisplatin**³³⁷⁴
- Chokeberry fruit (*Aronia melanocarpa*) – **amiodarone,**³⁴³⁶
- Clove buds (*Syzygium aromaticum*) – **indomethacin**²⁹⁵⁷

Cocoa seeds (*Theobroma cacao*) – **ACE inhibitors**,³⁰⁷⁷ **angiotensin receptor blockers**,³⁰⁷⁷ **antihypertensives**,²⁷⁴⁰ **beta-blockers**,³⁰⁷⁷ **diuretics**,³⁰⁷⁷ **metformin**,²⁷⁴⁰ **oral anticoagulants**,³⁰⁷⁷ **statins**^{2740,3077}

Cola (*Cola nitida*) seed – **ciprofloxacin**, **perfloracin**, **levofloxacin**³⁰³⁴

Coptis root (*Coptis* spp.) – **simvastatin**,²⁹⁰⁵ **amphotericin B**,³¹⁰⁷ **doxorubicin**,³¹⁴⁸ **stanols**,^{2932,2933} **vancomycin**³⁶¹⁹

Corn silk/stigma (*Zea mays*) – **gentamicin**,³⁴⁸⁶ **camptothecin**, **cisplatin**, **etoposide**, **5-fluorouracil**³⁴⁸⁸

Cranberry fruit [CORRECTION: NOT leaves] (*Vaccinium macrocarpon*) – **oral hypoglycemics**,³⁰⁹⁸ **doxorubicin**³⁰⁸⁰

Crucifers tops, leaves, sprouts (*Brassica* spp.) – **cisplatin**,²⁹³⁴ **trabectidin**²¹⁷⁷

Dog rose hips (*Rosa canina*) – **acetaminophen**, **chloroquin**, **leflunomide**, **methotrexate**, **NSAIDs**, **steroids**²⁹⁶²

Dong quai root (*Angelica sinensis*) – **tamoxifen**,³⁵¹⁷ **enalapril**²⁷²⁸

Echinacea angustifolia root (*Echinacea angustifolia*) – **influenza vaccine**³¹⁷⁸

Echinacea pallida whole plant (*Echinacea pallida*) – **cisplatin**²⁷²⁶

Eleuthero root (*Eleutherococcus senticosus*) – **metformin**³⁷¹⁸

English lavender (*Lavandula officinalis*) – **diclofenac**³⁵³³

English plantain leaves (*Plantago lanceolata*) – **indomethacin**²⁸³⁸

European pennyroyal leaf (*Mentha pulegium*) – **famotidine**³⁷¹⁵

Evening primrose seed (*Oenothera biennis*) – **isotretinoin**³⁴⁷⁸

Fenugreek seeds (*Trigonella foenum-graecum*) – **ibuprofen**,³⁴¹⁶ **L-dopa**,³³⁹⁴ **mefenamic acid**, **NSAIDs**³⁴¹⁶

Frankincense [see Indian frankincense]

French maritime pine bark (*Pinus pinaster*) – **albuterol**,³⁰⁹⁴ **chlorambucil**,³³³³ **fluticasone**,³⁰⁹³ **latanoprost**,²⁹⁶⁶ **mitoxantrone**, **prednisolone**,³³³³ **salbutamol**,³⁰⁹³ **zafirlukast**³⁰⁹⁴

Garlic fresh cut clove [# = aged garlic extract] *(*Allium sativum*) – **ACE inhibitors**, **angiotensin II receptor antagonists**,²⁷⁵⁷ **atorvastatin**,³³¹³ **beta-blockers**,²⁷⁵⁷ **calcium channel blockers**,²⁷⁵⁷ **chorhexidine**,²⁷¹¹ **diuretics**,²⁷⁵⁷ **ethambutol**, **isoniazid**, **pyrazinamide**, **rifampicin**,³¹⁶⁹ **captopril**,^{2756,3518} **isoproterenol**,³⁵¹⁸ **gentamicin**³³⁸⁷

Ginger root (*Zingiber officinale*) – **acetaminophen**,^{3314,3316} **chemotherapy**,^{2909,3092,3537,3622,3702} **cisplatin**,²⁹⁰⁹ **clotrimazole**,³⁷¹⁷ **cyclophosphamide**,^{3092,3537} **dexamethasone**,^{2909,3092,3622} **docetaxel**,^{3092,3537} **doxorubicin**,^{2909,3537} **epirubicin**,³⁰⁹² **ethambutol**,³⁶⁰² **5-flouracil**,³⁵³⁷ **granisetron**,³⁰⁹² **isoniazid**,³⁶⁰² **metoclopramide**,³⁶²² **ondansetron**,^{2909,3622} **oral hypoglycemics**,³⁵⁰¹ **pyrazinamide**, **rifampin**,³⁶⁰² **acetaminophen**,^{3473,3474,3475} **atorvastatin**,²⁸⁴⁹ **calcium**,³⁴⁷¹ **gentamicin**,³⁶⁵⁹ **iron**,³⁴⁷¹ **morphine**,³³²¹ **zinc**³⁴⁷¹

Ginkgo leaves (*Ginkgo biloba*) – **adapalene**,³⁴⁹⁹ **donepezil**, **galantamine**,³⁴⁸⁴ **olanzapine**,³²⁹¹ **radioiodine**,^{3095,3096} **rivastigmine**,³⁴⁸⁴ **sorafenib**,³⁶⁰³ **cisplatin**,³³⁷³ **dexamethasone**,³¹⁴⁷ **gentamicin**,³²⁶⁰ **isoproterenol**³¹⁸⁵

Goldenseal roots/rhizome *(*Hydrastis canadensis*) – **simvastatin**,²⁹⁰⁵ **amphotericin B**,³¹⁰⁷ **doxorubicin**,³¹⁴⁸ **stanols**,^{2932,2933} **vancomycin**³⁶¹⁹

Gotu kola leaf (*Centella asiatica*) – **adriamycin**³⁶¹⁵

Guarana seeds (*Paullinia cupana*) – **cyclophosphamide**, **doxorubicin**, **fluorouracil**²⁹²⁰

Hawthorn leaves/flowers (*Crataegus* spp.) – **cyclophosphamide**,³³⁴⁴ **doxorubicin**³⁶¹³

Hops strobiles (*Humulus lupulus*) – **benzodiazepines**²⁶³⁴

Indian frankincense gum resin (*Boswellia serrata*) – **beclomethasone**, **budesonide**,³⁵⁴² **curcuminoids**,³⁷¹⁰ **fluticasone**, **formoterol**,³⁵⁴² **ibuprofen**,^{2483,2804} **metformin**,³⁴¹³ **sameterol**³⁵⁴²

Kudzu root (*Pueraria thunbergiana* = *P. lobata*) – **cisplatin**²⁷²⁴

Kutki root (*Picrorhiza kurroa*) – **acetaminophen**,³¹⁶⁰ **chloroquine**,²⁹³⁷ **ethinylestradiol**,³¹⁶⁰ **rifampicin**³¹⁶¹

Larch bark (*Larix* spp.) – **pneumococcal vaccine**,²⁷³⁹ **tetanus vaccine**³³⁵¹

Licorice root/rhizome *(*Glycyrrhiza glabra*, *G. uralensis*) – **indomethacin**²⁹⁷⁶

Long pepper fruit (*Piper longum*) – **calcium**,³⁴⁷¹ **EGCG**,²⁹³⁵ **iron**, **zinc**³⁴⁷¹

Lycium (= Goji) berry (*Lycium barbarum*) – doxorubicin,^{3029,3110} mitomycin C³⁰³⁰
 Maca root (*Lepidium meyenii*) – SNRI, SSRI, venlafaxine³⁴⁸³
 Maitake mushroom (*Grifola frondosa*) – clomiphene citrate,²⁹¹⁰ adriamycin, cisplatin, 5-fluorouracil³³⁴¹
 Mango stem bark (*Mangifera indica*) – diclofenac, ibuprofen, methotrexate, naproxen, prednisone³⁷¹¹
 Milk thistle seeds (*Silybum marianum*) – glibenclamide, metformin,³⁴⁷⁹ acetaminophen^{2824,3181}
 Nigella seed (*Nigella sativa*) – atorvastatin,³⁶⁹⁵ beclomethasone, beta-agonists,²⁹⁸⁸ chemotherapy,³⁶⁶⁹ corticosteroids,^{2988,2989} diclofenac,³¹¹⁴ fluticasone,²⁹⁸⁸ folic acid,³¹¹⁴ hydroxychloroquine, methotrexate,^{3114,3594} omeprazole,³³¹² prednisolone,³⁵⁹⁴ theophylline,²⁹⁸⁸ acetaminophen,²⁹⁸³ doxorubicin,²⁴³⁰ gemcitabine,²⁹⁸⁵ gentamicin,³²⁵⁹ ifosfamide,²⁴³¹ oxaliplatin²⁹⁸⁵
 Noni fruit (*Morinda citrifolia*) – doxorubicin (adriamycin)³⁶⁶⁴
 Olive fruit oil; leaf (*Olea europaea*) – antibiotics,³⁵⁰⁰ atenolol, doxazosin, hydrochlorothiazide, lisinopril, nifedipine¹⁷⁷³; methotrexate³⁶⁶⁸
 Oregon grape root bark (*Mahonia* spp.) – simvastatin,²⁹⁰⁵ amphotericin B,³¹⁰⁷ doxorubicin,³¹⁴⁸ stanols,^{2932,2933} vancomycin³⁶¹⁹
 Passion flower herb (*Passiflora incarnata*) – benzodiazepines²⁶³⁴
 Pelargonium root (*Pelargonium sidoides*) – augmentin, budesonide, fenoterol, ipratropiumbromide, ofloxacin, salmeterol³²⁶⁹
 Peppermint leaves (*Mentha x piperita*) – granistron, dexamethasone, metoclopramide³²⁸⁵
 Pomegranate fruit (*Punica granatum*) – hydroxychloroquine, methotrexate, prednisone, NSAIDs, sulfazine,³⁰²⁴ docetaxel³³⁸¹
 Quassia (Surinam) bark (*Quassia amara*) – hydrocholic acid,³³⁸⁴ indomethacin³³⁸²⁻³³⁸⁴
 Root of Gold root (*Heliopsis longipes*) – diclofenac³⁵⁶²
 Saffron stigmas (*Crocus sativa*) – dorzolamide,³⁴³⁷ fluoxetine,^{3480,3481} timolol³⁴³⁷
 Sage leaves *(*Salvia officinalis*) – vincristine³³⁷²
 Sanchi ginseng root/rhizome (*Panax notoginseng*) – aspirin,^{3076,3701} beta-blockers, calcium channel blockers,³⁷⁰¹ diclofenac,³⁴¹⁸ heparin,³⁷⁰¹ leflunomide, prednisone,³⁴¹⁸ doxorubicin,³⁵⁶⁶ cisplatin³⁵⁷²
 Saw palmetto fruit (*Serenoa repens*) – prulifloxacin,³⁴¹⁴ tamsulosin^{3411,3675}
 Sea buckthorn fruit (*Hippophae rhamnoides*) – isoproterenol,³⁶⁸⁴ methotrexate³⁶⁸⁵
 Sesame seed oil (*Sesamum indicum*) – glibenclamide³⁶⁵⁸
 Shepherd's purse herb (*Capsella bursa-pastoris*) – oxytocin³⁷¹³
 Shiitake mycelia *Lentinula edodes* (= *Lentinus edodes*) – cyclophosphamide, epirubicin,³⁵⁰² 5-fluorouracil,^{3502,3503} folate,³⁵⁰² irinotecan,^{3502,3503} levofolinate, mitomycin C, taxol,³⁵⁰³ TS-1,³⁵⁰² UFT^{3502,3503}
 Southern schisandra fruit (*Schisandra sphenanthera*) – tacrolimus³⁵⁵⁸
 Soy beans (*Glycine max*) – adriamycin, carboplatin, cisplatin, cyclophosphamide, dacarbazine, etoposide, fenofibrate,³⁵¹⁰ ifosfamide, irinotecan, paclitaxel, procarbazine, temozolamide, vincristine²⁸¹³
 St. John's wort herb (*Hypericum perforatum*) – amitriptyline, imipramine,³⁶⁹¹ indomethacin,³²⁴⁸ metformin,³⁶⁵⁷ nortriptyline,³⁶⁹¹ sodium valproate³²⁴⁸
 Stinging nettle leaves (*Urtica* spp.) – acetaminophen [paracetamol] aspirin, celecoxib, diclofenac, ibuprofen, ketoprofen, naproxen, opiates, piroxicam, sulindac, tenoxicam²⁷²²
 root – nicotine³⁴⁵⁶
 Sweet annie herb (*Artemisia annua*) – curcumin²⁹¹⁴
 Sweet cherries (*Prunus avium*) – allopurinol, colchicine³²⁹⁹
 Tart cherry fruit (*Prunus cerasus*) – allopurinol, celecoxib, indomethacin,^{3298,3302} sulindac,²⁴³² atorvastatin³¹⁴⁵
 Tea [green] leaves (*Camellia sinensis*) – ciprofloxacin,³⁰³⁸ indomethacin²⁷⁵²
 Tea tree leaf oil (*Melaleuca alternifolia*) – diclofenac, minoxidil³³⁷¹

Thunder duke vine peeled root *(*Tripterygium wilfordii*) – **auranofin**,³²⁸¹ **methotrexate**,³²⁸⁰⁻³²⁸² **NSAIDs**,³²⁸¹ **sulfasalazine**³²⁸²

Tibetan rhodiola (*Rhodiola crenulata*) – **antihistamines**, **corticosteroids**, **LABA**, **LAMA**, **SAMA+SABA**, **xanthines**³⁵⁰⁸

Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – **acetaminophen**,³¹⁸¹ **acetic acid**, **aspirin**,³²¹⁸ **isoproterenol**,^{3185,3239} **meloxicam**,³¹⁸³ **radioiodine**,^{3184,3186} **vincristine**,³¹⁷⁹ **cyproterone acetate**³¹⁹⁶

Turmeric root (*Curcuma longa*, *C. aromatica*) – **acetaminophen**,^{2802,3247} **analgesics**,³⁴¹⁵ **antiherpetics**, **antitoxoplasmic drugs**,²⁸⁰³ **carboplatin**,³⁴⁸⁵ **CCNU**,³³⁶³ **celecoxib**,²⁸⁰² **cisplatin**,^{3363,3407,3485} **cyclophosphamide**,³⁴⁰⁷ **cycloplegics**,²⁸⁰³ **diclofenac**,^{3103,3680} **docetaxel**,³⁴⁰⁷ **etoposide**,³⁴⁰⁷ **5-fluorouracil**,^{3363,3407} **fluoxetine**,³³⁴⁸ **gemicitabine**,³³⁶³ **immune suppressants**,²⁸⁰³ **isoniazid**,²⁹⁹⁵ **methotrexate**,³⁴⁰⁷ **methylprednisolone**,³⁶⁸² **MOPP/ABVD/COPP**,³³⁶³ **mydriatics**,²⁸⁰³ **naproxen**,³⁴³³ **NSAIDs**,^{2721,2803,3415} **oral hypoglycemics**,³⁰⁹⁷ **pyrazinamide**, **rifampicin**,²⁹⁹⁵ **steroids**,²⁸⁰³ **taxol**,³⁴⁸⁵ **topical steroids**,³⁶⁸² **topotecan**,³⁴⁰⁷ **vinblastine**,³³⁶³ **arteether**,²⁹¹⁴ **cisplatin**,²⁸⁷⁷ **clarithromycin**,³⁵¹⁶ **docetaxel**,³³¹⁹ **gemicitabine**,³¹¹⁸ **paclitaxel**,^{2781,3117} **artemisinin**²⁹¹⁴

Valerian root (*Valeriana officinalis*) – **benzodiazepines**²⁶³⁴

E.2 Herbal Aids for Modifying Substance Abuse

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Studying cannabis use for withdrawal symptoms by opiate or other hard-drug addicts or alcoholics may be a reasonable subject for controlled research, since the benefits of overcoming these self-destructive addictions outweighs the limited risks of short-term marijuana use.³⁵⁴⁵ One potential adverse effect associated with use of cannabis by addicted individuals outside of rarely-approved clinical studies includes the legal consequences, even though some states that have approved its limited medical use. Ironically, the deterrence associated with concern for its federal illegal status may be more prevalent among those who would want to utilize it therapeutically than those who simply exploit it recreationally. On the other hand, concurrent use of cannabis with opiates or alcohol results in additive effects and enhanced impairment.^{1076,1077} Therefore, though cannabis has been used successfully to some extent to help reduce opioid or alcohol dependence,^{3270,3545} personal use of cannabis to reduce alcohol intake should not be considered an appropriate rationale, since concurrent abuse of both together not unusual.⁶²⁸ However, recent animal and human research on the nonpsychotropic cannabis component cannabidiol demonstrated a reduction in cue-induced heroin craving,^{3580,3581} suggesting that cannabidiol may become an appropriate treatment for opioid addiction.³⁵⁸²

Simply substituting one form of drug dependence for another necessarily fails to address the underlying cause(s).

E.2.1 The drugs whose dependence or adverse effects may potentially be alleviated by certain herbs or their derivatives include **alcohol (Alc)**, **amphetamines (Amp)**, **benzodiazepines (Bzd)**, **cocaine (Coc)**, **nicotine (Nic)**, and **opiates (Opi)**. Herbal facilitators of acute withdrawal or beyond may function pharmacologically as mild **anxiolytics (X)**, **sedatives (S)**, **relaxants (R)** for muscle tension and cramps, or **antidepressants (D)**. These types of herbal agents have been shown in animal or human studies to impact dopamine pathways, improve sleep, diminish pain, and/or in other ways help make the withdrawal process less uncomfortable. In some instances, studies show that herbal extracts or isolated components **specifically bind to receptor sites of the drug or alter its enzymatic conversions in vitro (V)**. Reports of **animal studies (A)**, **empirical reports (E)**, or **human studies (H)** document that some herbal agents facilitate specific drug withdrawal or reduce its adverse effects. The studies may involve the powdered **herb (h)**, its **extracts (e)**, or a **component (c)** or a **combination (C)** of several herbal preparations.

Scientific human withdrawal trials are indicated in bold for emphasis. Negative studies are in brackets; counterproductive results are indicated by "not." Reduction of drug adverse effects only is indicated by closure within parentheses. In the case of nicotine, some compounds can help prevent **endothelial injury (ei)** from inhalation of tobacco smoke, though they do not impact the activity of nicotine per se. In regard to alcohol dependence, some herbal preparations provide **amelioration of some of ethanol's adverse effects such as stomach damage (sd) [ulceration] and liver damage (ld).**

E.2.1 Botanical Adjuncts for Reducing Recreational Drug Use and/or Damage

American ginseng root (*Panax quinquefolius*) – Amp: Ac²⁹²⁹

Coc: (Ac²⁹³¹)

Amla fruit (*Embllica officinalis*) – Alc: (ld Ae,^{2856,3152} Ac^{3153,3154,3155})

Anise fruit/seed (*Pimpinella anisum*) – Alc: (sd Ah³⁷⁰³)

Apricot fruit (*Prunus armeniaca*) – Alc: (ld Ah³¹⁵⁷)

Ashwagandha root (*Withania somnifera*) – Opi: Ae³⁴⁶⁶

Asian ginseng root (*Panax ginseng*) – Amp: Ac^{2929,2930}

Coc: Ac²⁹³¹

Barberry bark (*Berberis vulgaris*) – Coc: Ac²⁷⁵³

Belleric myrobalan fruit (*Terminalia bellirica*) – Alc: (sd Ae³¹⁶⁸)

Bishop's weed fruit (*Trachyspermum ammi* syn. *T. copticum*) – Opi: Ae³⁴⁶¹

Black pepper fruit (*Piper nigrum*) – Alc: (sd Ah, Ac³³⁴⁷)

Black raspberry fruit/seeds (*Rubus occidentalis*) – Alc: (ld Ac^{3153,3154,3155})

Blackberry fruit/seeds (*Rubus* spp.) – Alc: (ld Ac^{3153,3154,3155})

Borage seed (*Borago officinalis*) – Alc: Af³²³⁴

Burdock root (*Arctium lappa*) – Alc: (ld Ae³¹⁵⁸)

Cannabis tops *(*Cannabis sativa*) – Amp: Ac²⁹⁷⁷

Coc: Ac²⁹⁷⁷

Opi: Ac,^{2973,3580} **Hc**³⁵⁸¹

Chaparral leaves (*Larrea tridentata*) – Alc: (sd Ac³²⁴⁶)

Chili fruit *(*Capsicum annuum*) – Alc: (sd Ah, Ac³³⁴⁷)

Chinese raisin tree fruit (*Hovenia dulcis*) – Alc: Ae (ld Eh)²⁸⁴⁵

Chinese skullcap root (*Scutellaria baicalensis*) – Alc: (ld Ae²⁸³⁹)

Clove buds (*Syzygium aromaticum*) – Alc: (sd c²⁹⁵⁸)

Coptis rhizome (*Coptis chinensis*) – Coc: Ae,c²⁷⁵³

Coriander fruit (*Coriandrum sativum*) – Alc: (sd Ah³²⁶⁴)

Fenugreek seeds (*Trigonella foenum-graecum*) – Alc: (ld Ae³¹⁵⁶)

Garlic bulbs *(*Allium sativum*) – Alc: (ld Ah,³¹⁶⁶ Ae,f³¹⁴⁹)

Gentian root (*Gentiana lutea*) – Nic: (ei Ae,f,c³⁷⁰⁶)

Ginger rhizome (*Zingiber officinale*) – Alc: (sd Ah, Ac³³⁴⁷)

Goldenseal roots/rhizome *(*Hydrastis canadensis*) – Coc: Ac²⁷⁵³

Grape red wine (*Vitis vinifera*) – Alc: Ae,³¹⁶² Ac^{3163,3164} [not Ac³¹⁶⁵]

Hawthorn berries (*Crataegus laevigata*, *C. monogyna*) – Alc: (sd Ae³³⁴³)

Jambolan seeds (*Syzygium cumini*) – Alc: (ld Ae³¹⁶⁷)

Kudzu root (*Pueraria lobata*) – Alc: Ac,³²⁸³ **He**,³⁵⁰⁹ **Hc**³²²¹

Kutki root (*Picrorhiza kurroa*) – Alc: (ld Ae²⁹³⁶)

Lemon balm herb (*Melissa officinalis*) – Opi: Ae³⁴⁶¹

Licorice root *(*Glycyrrhiza glabra*, *Glycyrrhiza uralensis*) – Alc: (ld **Hc**³⁶⁶⁰)

Little ironweed herb (*Vernonia cinerea*) – Nic: **He**²⁷¹³

Lobelia herb *(*Lobelia inflata*) – Amp: Ac^{3439, 3440, 3441}

Nic: **Hc**^{3453,3454}

Milk thistle seeds (*Silybum marianum*) – Alc: (ld Ae^{3156,3283})

Nigella seed (*Nigella sativa*) – Alc: (sd Ae,²⁹⁸⁴ Ac²⁹⁸⁷)
Opi: **Hh**²⁹⁸²
Oregon grape bark (*Mahonia aquifolium*) – Coc: Ac²⁷⁵³
Passion flower leaves (*Passiflora incarnata*) – Se²⁸⁷⁹
Peppermint herb (*Mentha piperita*) – Opi: Ae³⁴⁶¹
Pomegranate fruit/seeds (*Punica granatum*) – Alc: (ld Ac^{3153,3154,3155})
Prickly pear pads (*Opuntia* spp.) – Alc: (sd Ah³⁵⁰⁵)
Quassia (Surinam) bark (*Quassia amara*) – Alc: (sd Ae^{3383,3384})
Raspberry fruit/seeds, leaves (*Rubus idaeus*) – Alc: (ld Ac^{3153,3154,3155})
Rhodiola root (*Rhodiola rosea*) – Nic: Ae³³¹⁷
Rosemary herb (*Rosmarinus officinalis*) – Alc: (sd Ae³⁶⁷⁶)
Opi: Ae³⁴⁶⁴
Saffron stigma (*Crocus sativus*) – Opi: Ae³⁴⁶⁵
Scotch broom tops (*Cytisus scoparius*) – Nic: **Hc**³⁴⁰⁵
Shrubby basil leaves (*Ocimum gratissimum* = *O. suave*) – Alc: (sd e²⁹⁵³)
St. John's wort herb (*Hypericum perforatum*) – Nic: [**He**^{2797,3378,3379}]
Opi: Ae^{3462,3692}
Strawberry fruit/seeds, leaves (*Fragaria* spp.) – Alc: (ld Ac^{3153,3154,3155})
Summer savory herb (*Satureja hortensis*) – Opi: Ae³⁴⁶¹
Tea black leaves (*Camellia sinensis*) – Alc: (ld Ae^{3150,3151})
green leaves – Alc: (ld Ae,^{3149,3644} c³¹⁴⁹)
Opi: Xc, Ac³³⁹⁷
Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – Alc: (sd Ae³²¹⁸)
Amp: (Ae³²²⁰)
Turmeric rhizome (*Curcuma longa*) – Alc: Ac,³³⁹⁵ (ld Ac^{1832,3159})
Valerian root *(*Valeriana officinalis*) – Bzd: **H**³⁷²⁰
Opi: Ae³⁴⁶¹
Winter melon fruit (*Benincasa hispida*) – Opi: Aj³⁴⁶³

E.3 Complementing Treatment of Inflammations

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E.3.1-3.5 Drug treatments have advantages and drawbacks that differ, depending on the type of drug. **Drugs considered here in interactions with herbs are grouped as corticosteroids** (cortisone, dexamethasone, hydrocortisone, prednisone), **NSAIDs** (acemetacin, aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, metamizol, naproxen, piroxicam, phenylbutazone, rofecoxib, salicylates), and **analgesics** (acetaminophen [paracetamol], codeine, morphine, propoxyphene HCl, propyphenazone, tramadol).

Herbs (h) and their **extracts (e), fractions (f), and components (c) or smoke (s)** are considered here as anti-inflammatory and analgesic adjuvants when they enhance the clinical effects of these drugs, reduce their adverse effects, or reduce their use (frequency or dose) by **humans (in bold)** or **in animals (italicized)**. Some botanical derivatives or components produce additional anti-inflammatory and/or analgesic effects if used with drugs when applied **topically (t)**.

E.3.1 Enhancing the Effects of Corticosteroids

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Indian frankincense resin extract (*Boswellia serrata*) – e²⁸⁴⁶
Nigella seed (*Nigella sativa*) – e^{2988,2989}

E.3.2 Enhancing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

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Fenugreek seed (*Trigonella foenum-graecum*) – h³⁴¹⁶
French maritime pine bark (*Pinus pinaster*) – f²⁷⁹⁵

Indian frankincense resin (*Boswellia serrata*) resin – e²⁸⁰⁴
 Nigella seed (*Nigella sativa*) – f³¹¹⁴
 Purple passion fruit peel (*Passiflora edulis*) – e²⁹⁵¹
 Root of Gold root (*Heliopsis longipes*) – e³⁵⁶²
 Stinging nettle leaves (*Urtica dioica*) – h²⁷²²
 Turmeric root [curcumin] (*Curcuma longa*, *C. aromatica*) – c^{2721,2802,3103,3433}

E.3.3 Enhancing Outcomes When Using Analgesics

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Arnica flowers (*Arnica montana*) – te²⁸⁰⁵
 Cannabis leaves/tops *(*Cannabis sativa*) – e,^{2748,2749} s^{2745,2750}
 Ginger root/rhizome (*Zingiber officinale*) – e³³²¹
 Stinging nettle leaves (*Urtica dioica*) – h²⁷²²
 Turmeric root [curcumin] (*Curcuma longa*, *C. aromatica*) – c,²⁸⁰² f³²⁴⁷

E.3.4 Protecting Against NSAID-induced Ulcers

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African basil leaves (*Ocimum gratissimum* = *O. suave*) – e²⁹⁵³
 Anise fruit/seed (*Pimpinella anisum*) – h³⁷⁰³
 Chaparral leaves (*Larrea tridentata*) – c³²⁴⁶
 Clove oil [eugenol] (*Syzygium aromaticum*) – c²⁹⁵⁷
 Coconut milk (*Cocos nucifera*) – e³³⁹¹
 Coriander seeds (*Coriandrum sativum*) – h³²⁶⁴
 English plantain leaves (*Plantago lanceolata*) – e²⁸³⁸
 Licorice root (*Glycyrrhiza glabra*) – e²⁹⁷⁶
 Rosemary herb (*Rosmarinus officinalis*) – e³⁶⁷⁶
 Sea buckthorn fruit (*Hippophae rhamnoides*) – e¹⁹⁵⁹
 Tea leaves (*Camellia sinensis*) – e,^f²⁷⁵²
 Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – e^{3183,3218}

E.3.5 Protecting Against Acetaminophen-induced Liver Toxicity

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Garlic cloves (*Allium sativum*) – e³³⁸⁶
 Ginger rhizome (*Zingiber officinale*) – h,³⁴⁷⁵ e^{3473,3474}
 Korean acanthopanax root bark (*Acanthopanax koreanum*) – c²⁷²⁷
 Kutaki rhizome/roots (*Picrorhiza kurroa*) – f³¹⁶⁰
 Milk thistle fruit (*Silybum marianum*) – f^{2824,3181}
 Nigella seed (*Nigella sativa*) – c²⁹⁸³
 Red creeper root (*Ventilago maderaspatana*) – c³⁷⁰⁵
 Schisandra fruit (*Schisandra chinensis*) – c⁶⁹⁶
 Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – e³¹⁸¹

E.4 Enhancing Chemotherapy and Chemoprevention

or Reducing the Adverse Effects

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A systematic review of studies implicating risks of herb and food supplement interactions with cancer drugs found 5 acceptable papers that surveyed a total of 806 cancer patients, of which 433 (53.7%) were combining supplements and drugs. Of these, 167 potential risks were identified in 60 patients (13.9%), but the risks were mainly theoretical and unsupported by clinical data. None of the studies reported any actual adverse events that were associated with the combinations.³⁴⁹⁷ Much of the research thus far has been done on an isolated phytochemical component or components. When only isolated components are shown to enhance outcomes with chemotherapy drugs by the research cited in this appendix section, especially with *in vitro* studies, they often are not discussed with the associated herb(s) in the main body of this text.

E.4.1 & E.4.2 To differentiate the types of *in vivo* studies, **human cases are in bold** and **studies in animals are italicized**, while the *in vitro* tests on cells are in regular type-face. Herbal

preparations used in the studies are noted in parentheses as a **combination (C)**, the powdered **herb (h)**, its pyrogenic **smoke (s)**, a complex solvent **extract (e)**, an extract **fraction (f)** or an isolated **component [c] or components [cs]**. **Extracts may be further designated as aqueous (ea), ethanolic (ee), or methanolic (em), etc.** The main component (and chemopreventive preparations in E.4.4) is named in brackets [component name] with the herb or identified by abbreviation [c] with the drug, while abbreviations of other derivatives are named in the parentheses (e.g., f for fraction) with the interacting drug.

E.4.3 ATP-binding cassette (ABC) transporter family is greatly involved with resistance to chemotherapy. **Efflux pumps P-glycoprotein (Pgp, or ABCB1) encoded by multidrug resistance gene (MDR1), multidrug resistance-associated proteins 1 and 2 (MRP-1 and MRP-2, or ABCC1 and ABCC2), and breast cancer resistance protein (BCRP, or ABCG2) are active in removing drugs or their conjugates from tumor cells back into the blood. The inhibition of MDR1, MRP-1 and -2, and/or BCRP activity or their gene expression will enhance the retention of chemotherapy drugs.** The retention of antitumor drugs may also be enhanced through inhibition of some subtypes of high-affinity glutamate transporters such as GLAST and GLT-1. The tissue(s) and/or efflux protein(s) are listed along with the drugs that have been shown to be impacted. The effect on chemotherapeutic agents has been demonstrated mostly with isolated components in cell cultures *in vitro*, so the components are identified [in brackets], usually a **polyphenolic component (pc) or amino acid (aa)**.

E.4.4 The abbreviation for the preparation tested, as in E.4.1 & E.4.2, in combination with the chemopreventive drug is followed by the specific type of cancer or precancerous lesion that they have been shown to synergistically reduce. The abbreviation for the preparation tested in combination with the chemopreventive drug is followed by the specific type of cancer or precancerous lesion that they have been shown to synergistically reduce. The types of preparations listed in brackets between the common and scientific names of the botanicals are those forms of the botanical that have been shown by themselves to inhibit some cancer(s) in humans (**cancer types in bold**) or in animals, or various cancerous cell cultures or process(es) *in vitro*, for which reference citations are also given.

E.4.5 The ubiquitous cytokine transforming growth factor-beta1 (TGFβ1) is associated with P-glycoprotein expression in certain cancers, increasing the resistance to some chemotherapeutic agents. TGFβ1 is one of the most potent metastatic inducers. TGFβ1 has been shown to increase A disintegrin and metalloproteinase-12 (ADAM-12) which plays a critical role in cancer growth and metastasis and is upregulated in many cancers including breast, lung, liver, prostate, gastric, and bladder. TGFβ1 activation of NF-κB increases ADAM-12 mRNA expression in breast cancer cells.²⁷³¹ NF-κB is activated by many carcinogens, tumor promoters, and inflammatory agents associated with cancer development, progression, and drug resistance,²⁷⁷⁵ as well as by chemotherapy agents such as paclitaxel.²⁷⁸¹ TGFβ1 has also been associated with decreased natural killer cell cytotoxicity in gastric cancer patients as cancer progresses.²⁷³² In addition, chronic injury to normal tissue following treatment by chemotherapy or radiation appears to involve TGFβ1 overexpression.²⁷³³ [See Appendix E.5.7.] However, since TGFβ1 acts to suppress epithelial and possibly other types of tumorigenesis in early stages and multiple signaling pathways are involved at different stages, TGFβ1 reduction likely should be restricted to later stages of tumor progression, invasion, and metastasis,²⁷³⁶ i.e., as part of cancer treatment but not prevention.

E.4.1 Enhancing therapeutic effects of chemotherapy

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American ginseng root [steamed root ginsenoside Rg3, Rh2] (*Panax quinquefolius*) – cyclophosphamide [c]^{2924,2926}

berry [extract with 25% ginsenoside Rb3] – 5-fluorouracil (e)²⁹²⁷
 Amla fruit (*Emblica officinalis*) – cisplatin, doxorubicin (e)²⁸⁶⁰
 Asian ginseng root (red) [c panaxadiol] (*Panax ginseng*) – 5-fluorouracil [c]³²⁵⁵
 Beet root (*Beta vulgaris*) – doxorubicin (e)³⁵²¹
 Bibhitakhi fruit (*Terminalia bellerica*) – cisplatin, doxorubicin (e)²⁸⁶⁰
 Chamomile flowers [bisabololoxide A] (*Matricaria recutita*) – 5-fluorouracil [c]²⁸⁶³
 Chokeberry fruit (*Aronia melanocarpa*) – gemcitabine (e)³⁴⁰⁹
 Corn silk/stigma [c maysin] (*Zea mays*) – camptothecin [c], cisplatin [c], etoposide [c], 5-fluorouracil [c]³⁴⁸⁸
 Cranberry fruit/juice proanthocyanidins] (*Vaccinium macrocarpon*) – paraplatin (f)³⁰⁸⁶
 Crucifers like Brussels sprouts, cabbage [c I3C from glucobrassicin, cd DIM (dimer of I3C)] (*Brassica oleracea*) – erlotinib, erlotinib [cd]³²⁵⁴
 Echinacea purpurea polysaccharides (*Echinacea purpurea*) – cyclophosphamide²⁸⁰⁹
 Horse chestnut seeds [escin] *(*Aesculus hippocastanum*) – 5-fluorouracil [c]²⁷⁷⁶
 Licorice root [c1 glycyrrhizin aglycone, c2 isoliquiritigenin] (*Glycyrrhiza glabra*, *Glycyrrhiza uralensis*) – doxorubicin, mitomycin c (c1),³⁵⁹⁰ cyclophosphamide, cyclophosphamide [c2]³⁵⁹²
 Milk thistle seeds [silybin(silibinin)] (*Silybum marianum*) – erlotinib [c]^{3354,3355}
 Nigella seed oil [c thymoquinone] (*Nigella sativa*) – gemcitabine [c], oxaliplatin [c]²⁹⁸⁶
 Sanchi ginseng root [e ethanolic/butanolic extract, c panaxadiol] (*Panax notoginseng*) – 5-fluorouracil (e)³²⁵⁶ and [c],³²⁵⁵ irinotecan (e) [not doxorubicin (e)]³²⁵⁶
 Shiitake mushrooms [lentinan] (*Lentinula edodes*) – **cisplatin, fluoropyrimidine, paclitaxel**³¹²⁵
 Tea green leaves [EGCG &/or ECG] – doxorubicin# [c],^{3203,3207} erlotinib [c],³³⁵⁶ tamoxifen [c],³⁴⁶⁷ erlotinib [c],³³⁵⁶⁻³³⁵⁸ 5-fluorouracil [c],²⁹⁴⁸ paclitaxel [c],³⁴⁶⁸ raloxifene [c],³⁴⁷⁰ tamoxifen [c]^{3468,3469}
 Tulsi leaves [c vicenin-2] (*Ocimum tenuiflorum* = *Ocimum sanctum*) – docetaxel [c]³¹⁸²
 Turmeric rhizome [curcumin] (*Curcuma longa*, *C. aromatica*) – capecitabine [c],³¹¹⁵ cisplatin [c],²⁸⁷⁷ docetaxel [c],³³¹⁹ gemcitabine [c],³¹¹⁸ oxaliplatin [c],³⁴³² paclitaxel [c],²⁷⁸¹ bortezomib,³¹¹⁶ capecitabine,³¹¹⁵ cisplatin [c],^{2876,2877} docetaxel [c],³³¹⁹ doxorubicin# (e),²⁸⁵⁹ etoposide [c] or (e) and etoposide/temozolomide [c] or (e),³¹⁷³ gemcitabine (e),³¹⁷⁴ [c],³¹¹⁸ oxaliplatin [c],²⁸⁶⁵ temozolomide [c] or (e) and temozolomide/etoposide [c] or (e)³¹⁷³

E.4.2 Reducing adverse effects of chemotherapy

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Aloe leaf (*Aloe vera*) – **chemotherapy (e)**³⁵⁸⁴
 American ginseng root [ginsenoside Rb1, steamed root ginsenoside Rg3, Rh2] (*Panax quinquefolius*) – **chemotherapy (h)**,^{2916,3293} cyclophosphamide [cs-Rg,Rh],^{2925,2926} mitomycin C (h),²⁹²² cyclophosphamide [c-Rb]³⁰⁶⁴
 Amla fruit (*Emblica officinalis*) – cyclophosphamide (e),^{2853,2955} doxorubicin (e)²⁸⁵⁹
 Ashwagandha root (*Withania somnifera*) – **taxotere/adriamycin/cyclophosphamide (e)** and **cyclophosphamide/epirubicin/5-fluorouracil (e)**³²⁵²
 Asian ginseng root (*Panax ginseng*) – **carboplatin, cisplatin, docetaxel, paclitaxel (h)**,³⁷²⁵ cisplatin (e)²⁷²⁵
 Broccoli sprouts [sulforaphane] (*Brassica* spp.) – cisplatin [c]^{2934,3403}
 Calamus rhizome (*Acorus calamus*) – vincristine (e)³³⁷⁵
 Cat's claw bark (*Uncaria tomentosa*) – doxorubicin (e)³³³¹
 Chamomile flowers (*Matricaria recutita*) – cisplatin (e)³³⁷⁴
 Chokeberry fruit [phenolic-rich extract] (*Aronia melanocarpa*) – cyclophosphamide, doxorubicin³⁴²⁸
 Cranberry fruit (*Vaccinium macrocarpon*) – doxorubicin (e)³⁰⁸⁰
 Echinacea pallida whole plant (*Echinacea pallida*) – cisplatin (e)²⁷²⁶
 French maritime pine bark (*Pinus pinaster*) – **chlorambucil, mitoxantrone and prednisolone**³³³³
 Ginger rhizome (*Zingiber officinale*) – **cyclophosphamide**,^{3092,3537} **docetaxol**,^{3092,3537} **doxorubicin**,³⁵³⁷ **epirubicin**,³⁰⁹² **5-flouracil**³⁵³⁷
 Ginkgo leaves (*Ginkgo biloba*) – cisplatin (e)³³⁷³
 Gotu kola leaf [aqueous extract] (*Centella asiatica*) – adriamycin (e)³⁶¹⁵

Hawthorn fruit [aqueous extract] (*Crataegus monogyna*) – doxorubicin (e)³⁶¹³
 Hibiscus flower [aqueous extract] (*Hibiscus sabdariffa*) – azathioprine (e)³⁶⁷⁷
 Kudzu root (*Pueraria lobata* = *P. thunbergiana*) – cisplatin (e)²⁷²⁴
 Licorice root [c isoliquiritigenin] (*Glycyrrhiza glabra*, *Glycyrrhiza uralensis*) – cisplatin, [c]³⁵⁹¹
 cyclophosphamide, cyclophosphamide [c]³⁵⁹²
 Lycium (= Goji) fruit [polysaccharides] (*Lycium barbarum*) – doxorubicin [c],³¹¹⁰ doxorubicin# (j),³⁰²⁹
 mitomycin C (f)³⁰³⁰
 Mulberry leaf (*Morus alba*) – doxorubicin (e)²⁸⁵⁹
 Olive leaf (*Olea europaea*) – **intensive chemotherapy** (eL)³³⁸⁹
 Peppermint leaf oil (*Mentha x piperita*) – **adriamycin, carboplatin, cisplatin, cyclophosphamide, epirubicin, etoposide, ifosfamide, irinotecan** (f)³²⁸⁵
 Prickly pear cladode (*Opuntia ficus-indica*) – (e)³⁴¹⁰
 Raspberry fruit [ellagic acid] (*Rubus idaeus*) – cisplatin [c]²⁸⁶⁴
 Reishi mushroom (*Ganoderma lucidum*) – cisplatin (e)³³³⁸
 Rosemary leaves [aqueous extract] (*Rosmarinus officinalis*) – azathioprine (e)³⁶⁷⁷
 Sage leaves [ae aqueous extract, he hydroalcoholic extract] *(*Salvia officinalis*) – azathioprine [ae],³⁶⁷⁷
 vincristine [he]³³⁷²
 Sanchi ginseng rhizome [f saponins] (*Panax notoginseng*) – doxorubicin [f]³⁵⁶⁶
 Soy beans [genistein] (*Glycine max*) – **adriamycin, carboplatin, cisplatin, cyclophosphamide, dacarbazine, etoposide, ifosfamide, irinotecan, paclitaxel, procarbazine, temozolamide, vincristine** [c]²⁸¹³
 Spearmint leaf oil (*Mentha spicata*) – **adriamycin, carboplatin, cisplatin, cyclophosphamide, epirubicin, etoposide, ifosfamide, irinotecan** (f)³²⁸⁵
 Temu lawak rhizome [xanthorrhizol] (*Curcuma xanthorrhiza*) – cisplatin [c]²⁹⁵⁰
 Tomato fruit [c lycopene] (*Lycopersicon esculentum*) – cisplatin [c]²⁸⁶⁴
 Tulsi leaves [e methanolic extract] (*Ocimum tenuiflorum* = *Ocimum sanctum*) – vincristine (e)³¹⁷⁹
 Turmeric root [curcumin] (*Curcuma longa*, *C. aromatica*) – **carboplatin,**³⁴⁸⁵ **cisplatin,**^{3363,3407,3485}
cyclophosphamide, docetaxel, etoposide,³⁴⁰⁷ **5-fluoruracil,**^{3363,3407} **gemcitabine,**³³⁶³
methotrexate,³⁴⁰⁷ **MOPP/ABVD/COPP, vinblastine & CCNU,**³³⁶³ **taxol,**³⁴⁸⁵ **topotecan**³⁴⁰⁷

E.4.3 Selective Cell Retention of Drugs by Inhibiting Efflux Transport Proteins p. 500

Asian ginseng [Note: CORRECTION:, citation #2102 is the following: Choi CH, Kang G, Min Y-D. Reversal of P-glycoprotein-mediated multidrug resistance by protopanaxatriol ginsenosides from Korean red ginseng. *Planta Med.*, 69:235-240, 2003.]
 Hops strobules [prenylflavonoids] (*Humulus lupulus*) – mitoxantrone (kidney BCRP)³³⁸⁵
 Licorice root [c glycyrrhetic acid] (*Glycyrrhiza glabra*) – daunorubicin, vinblastine (MDR1), doxorubicin (MRP1)³³⁶⁸
 Milk thistle fruit [pc silymarin] (*Silybum marianum*) – rosuvastatin (kidney BCRP)²⁹⁶³ [**not rosuvastatin**²⁹⁶³]
 Mulberry twigs [pc morin] (*Morus alba*) – paclitaxel (intestine MDR1)²⁸³⁴
 Nan wu wei zi fruit [extract and/or c schisandrin B] (*Schisandra sphenanthera*) – paclitaxel (intestine MDR1),²⁸²⁷ daunorubicin (leukemia, epidermoid carcinoma, breast cancer MDR1), doxorubicin (leukemia, epidermoid carcinoma MDR1), epirubicin (leukemia, epidermoid carcinoma MDR1), homoharringtonine (leukemia, epidermoid carcinoma MDR1), hydroxycamptothecin (leukemia, epidermoid carcinoma MDR1), mitoxantrone (leukemia, epidermoid carcinoma MDR1), taxol (leukemia, epidermoid carcinoma, breast cancer MDR1), vincristine (leukemia, epidermoid carcinoma, breast cancer MDR1)²⁸³¹
 Onion bulbs [c quercetin] (*Allium cepa*) – paclitaxel (intestine MDR1)²⁸³⁵
 Schisandra fruit [lignans or c schisandrin B] (*Schisandra chinensis*) – daunorubicin (leukemia, epidermoid carcinoma, breast cancer MDR1), doxorubicin (leukemia, epidermoid carcinoma MDR1), epirubicin (leukemia, epidermoid carcinoma MDR1), homoharringtonine (leukemia,

epidermoid carcinoma MDR1), hydroxycamptothecin (leukemia, epidermoid carcinoma MDR1), mitoxantrone (leukemia, epidermoid carcinoma MDR1), taxol (leukemia, epidermoid carcinoma, breast cancer MDR1), vincristine (leukemia, epidermoid carcinoma, breast cancer MDR1)²⁸³¹

Soy beans [pc genistein] (*Glycine max*) – paclitaxel (intestine MDR1)²⁸³³

Tea green leaves [pc catechins/EGCG, aa theanine] (*Camellia sinensis*) – doxorubicin and pc (hepatocellular carcinoma MDR1),³²⁰⁷ tamoxifen and pc (intestine MDR1),³²⁰⁶ doxorubicin [adriamycin] and aa (ovary GLAST/GLT-1),²⁹⁴⁹ tamoxifen and pc (breast carcinoma MDR1 & BCRP)³²⁰⁴

Turmeric root [pc curcumin] (*Curcuma longa*) – etoposide (MRP1 kidney)²⁹⁴⁵

E.4.4 Promoting and/or Enhancing Chemoprevention of Selective Cancers p. 501

African basil leaves [f eugenol-rich oil (*topical*)³⁰¹⁴] (*Ocimum gratissimum*)

American ginseng root [4-hour steamed, 70% ethanol extract^{2923,2996}] (*Panax quinquefolius*) – e/N-acetyl cysteine, e/vitamin C (colorectal Ca HCT116 and SW480)²⁹²³

Apple fruit [fresh (**lung and colon**)²⁷⁸⁹] (*Malus domestica*)

Ashwagandha root [hydroalcoholic extract (*skin*)³⁰⁰⁵] (*Withania somnifera*)

Asian ginseng root [Korean red extract (**non-organ-specific in men**),²⁷⁶⁵ red, white powder, fresh, white extract (**lip, oral, pharyngeal, esophageal, stomach, colorectal, liver, pancreatic, laryngeal, lung, ovaries**)³³²⁵] (*Panax ginseng*)

Bilberry fruit [procyanidins³⁶⁸⁹] (*Vaccinium myrtillus*)

Black raspberry fruit [freeze-dried,^{2997,3070,3075} ethanol extract,^{3071,3074,3177} anthocyanins,^{3071,3072} cs ferulic acid, beta-sitosterol³¹⁷⁷] (*Rubus occidentalis*)

Blueberry fruit³⁶⁸⁶ [anthocyanin fraction,³⁶⁸⁷ flavonol and/or procyanidin fractions,^{3687,3689} pterostilbene³⁶⁸⁸] (*Vaccinium angustifolium*, *V. ashei*, *V. corymbosum*)

Broccoli florets/sprouts [sprouts water extract^{2415,3401,3534} (*oral*)³⁵³⁴ and florets glucosinolates/isothiocyanates extract (colon),³¹⁰⁹ sulphoraphane^{3402,3534,3597}] (*Brassica oleracea* var. *italica*)

Coffee beans roasted [water extract (**skin nonmelanoma in white women**,²⁸⁹⁴ **ER-neg postmenopausal breast**,²⁹⁹⁰ **liver**,²⁹⁹¹ **glioma** [coffee/tea]^{2992,2993}), caffeine (**glioma in men**)²⁹⁹²] (*Coffea arabica*)

Cranberry fruit [juice³¹⁰⁰] (*Vaccinium macrocarpon*)

Crucifers leaves, heads [phenethyl isothiocyanate,²⁹⁹⁷ indole-3-carbinol (I3C),³³⁹⁹ sulphoraphane³⁴⁰²] (*Brassica* spp.)

Cumin seeds [ground³²¹²] (*Cuminum cyminum*)

Fenugreek seeds [extract, diosgenin³⁵⁹⁷] (*Trigonella foenum-graecum*)

Flax seed [whole/ground (**breast in women**)^{3328,3549}] (*Linum usitatissimum*)

Goldenseal [ee ethanolic extract³⁶¹⁷] (*Hydrastis canadensis*) [See Note 1.]

Kava root [f kavalactones³³⁴⁶] (*Piper methysticum*)

Licorice root (*Glycyrrhiza glabra*, *Glycyrrhiza uralensis*)³⁵⁸⁷

Lingonberry fruit [procyanidins³⁶⁸⁹] (*Vaccinium vitis-idaea*)

Mate leaf [water extract (**breast in women**)^{3678,3679}] (*Ilex paraguariensis*)

Milk thistle seeds [he hydroalcoholic extract,³⁶¹⁶ f silymarin^{2900,3320}] (*Silybum marianum*)

Prickly pear fruit [water extract³³⁹⁸] (*Opuntia* spp.)

Reishi [c polysaccharides,^{1094,2999} triterpenoids²⁹⁹⁹] (*Ganoderma lucidum*) – c/liver¹⁰⁹⁴

Soy beans [isoflavones (**prostate cancer**)³³⁹⁰] (*Glycine max*)

Strawberry fruit [freeze-dried (**esophageal**)³³³⁹]

Tea (green or white) leaves [water extracts (**colorectal & stomach, esophageal in women**,³²⁶⁵ **ovarian, endometrial**,³³⁶⁰ **ovarian, breast, colorectal, leukemia**)³³⁸⁰] (*Camellia sinensis*) (black) leaves [water extract ([coffee/tea] **glioma**),^{2992,2993} caffeine (**glioma in men**)²⁹⁹²]

Tulsi leaves [h powder,^{3212,3216} ae aqueous extract,³²¹⁶ ee ethanolic extract,^{3015,3199,3213,3216} em methanolic extract³¹⁸⁰] (*Ocimum tenuiflorum* = *Ocimum sanctum*)

Turmeric root [pc curcumin^{2784,2788,2904}] (*Curcuma longa*)

Wasabi root/rhizome [c 6-(methylsulfonyl)hexyl isothiocyanate^{3698,3699}] (*Wasabia japonica*)

Notes

1. Though goldenseal 90% ethanolic extract (plant part not specified) was found to reduce liver cancer in mice induced by p-dimethylaminoazobenzene (p-DAB),³⁶¹⁷ when goldenseal root powder was given to mice and rats it increased the incidence of liver tumors.³⁶¹⁶

E.4.5. Reducing Transforming Growth Factor- β 1 Before,

During, &/or After Chemotherapy

p. 502

Astragalus root [water and/or ethanol extracts] (*Astragalus membranaceus*)– ([e]in rats with Dong quai [e])^{2728,2729,2730}

Dong quai root [water and/or ethanol extracts] (*Angelica sinensis*) – ([e]in rats with Astragalus [e])^{2728,2729,2730}

Magnolia bark [honokiol] (*Magnolia officinalis*) – ([c] in human renal cells)²⁷³²

Reishi mushroom [13.5% polysaccharides/6% triterpenes extract] (*Ganoderma lucidum*) – ([e] in human prostate cancer cells)²⁷³⁷

Turmeric rhizome [curcuminoids (enhanced bioavailability)] (*Curcuma longa*) – **cisplatin, cyclophosphamide docetaxel, , etoposide, 5-fluoruracil, methotrexate, topotecan**³⁴⁰⁷

E.5 Herbs for Preventing and Healing Radiation Adverse Effects and/or Enhancing Radiotherapy or Photodynamic Therapy

p. 502

Optimal chemoprevention of radiation damage has several features. "A good chemical protector should be able to protect against the deleterious effect of ionizing radiation during therapeutic procedures as well as during nuclear accidents, space flight and background irradiation etc. An ideal radioprotector should be cheap, does not have toxic implications in a wide dose range, orally administered, rapidly absorbed, possesses a reasonably good dose reduction factor and can act through multiple mechanisms. The plant and natural products have all these qualities."³¹⁹³

Herbal agents can reduce radiation adverse effects in a number of ways. Broad antioxidant and anti-inflammatory effects are fairly ubiquitous among efficacious plants. Typically, blood cell parameters are less disrupted by protection of bone marrow progenitor cells, while preservation and improved regeneration of the gastrointestinal epithelium helps alleviate the GI syndrome. As a consequence, mortality may be reduced. Recovery rates can be enhanced as botanical preparations help protect from radiation sickness. One concern about effective systemic protection is that it theoretically may reduce the therapeutic efficacy of radiation, but this has yet to be clinically demonstrated with botanical supplements.

E.5.1-5.4 Post-therapeutic or concurrent **local applications (L)** or **oral herb preparations (O)** are applied to treat topical burns from both heliotherapy and UV lamps and from X-ray and gamma radiation, or to protect or treat mucositis from gamma radiation.

E.5.3-5.4 Pre-therapeutic use of **oral herb preparations (O)** or **injections (I)** has been studied with exposure to ionizing forms of radiant energy. Some botanicals have been shown to help protect normal structures and their functions that receive less direct or concentrated irradiation than the malignant focus.

To differentiate the types of *in vivo* studies, **human cases are in bold** and **studies in animals are italicized**, while the *in vitro* tests on cells are in regular type-face. The type of preparation used is noted. Herbal preparations may be the powdered **herb (h)**, fresh **gel** or **juice (j)**, a solvent **extract (e)**, an extract **fraction (f)** or an isolated **component (c)**. Clinical trials with **negative results [neg.] are shown in brackets**.

E.5.5-5.6 In some instances, the botanical can serve as a synergistic antitumor agent, or it may improve the post-treatment radiation sensitivity and therapeutic response in certain malignant tissues.

E.5.7 Chronic injury to normal tissue following treatment by chemotherapy or radiation appears to involve transforming growth factor-beta 1 (TGFβ1) overexpression.²⁷³³ [See Appendix E.4.5 introduction.] Increases in TGFβ1 during radiation treatment for non-small cell lung cancer is indicative of significant reduction in survival time,²⁷³⁴ and significant TGFβ1 elevations after radiation therapy have been correlated with symptomatic radiation pneumonitis.²⁷³⁵

E.5.9-5.10 ^ Topical and internal herbal preparations that help prevent UV overexposure and the consequent inflammation and aging and increased risk of skin cancer by blocking the radiation or quenching free radicals are covered here in the context of passive exposure to solar radiation. These should not be use when actively exposing skin lesions to UV phototherapy, due to the counterproductive aspect of simultaneously reducing the therapeutic effect. However, internal use of herbal antioxidants shown to protect against UV damage may be useful in some cases.

Damage to the skin from solar radiation is well known following acute or chronic exposure. Ultraviolet (UV)-induced skin damage is associated with inflammation and the generation of reactive oxygen species or free radicals. An imbalance between reactive oxygen

species generation and cellular antioxidant capacity leads to oxidative stress that contributes to carcinogenesis. Excessive skin exposure to UV can cause DNA damage, cell-cycle arrest, apoptosis, depletion of antioxidant defenses, immunosuppression, and proinflammatory cytokine release. Acute sunburn is attributed to the UVB spectrum (280-320 nm) that only penetrates the epidermis and makes up about 5% of solar UV. However, UVB is 1000 times more carcinogenic to the skin than UVA due to free radical damage. Both melanoma and nonmelanoma skin cancers can arise from UVB damage. The aging from chronic solar radiation is largely attributed to the UVA spectrum (320-400 nm), comprising 90-95% of solar UV. Chronic overexposure to UVA radiation leads to increases in skin pigmentation, thickness, wrinkling, and melanoma risk due to its deep penetration into the dermis of the skin.^{2867,3001}

Currently, commercial sunscreens applied topically reduce skin cancer risk by partially blocking UV radiation but are inadequate alone for preventing dermal carcinogenesis. Some sunscreens do not block UVA, so, though helping prevent sunburn, squamous cell carcinoma, and basal cell carcinoma, increased time in the sun and exposure to UVA can lead to higher risk of melanoma, the most virulent form of skin cancer. Since UV creates oxidative stress in the skin, the use of dietary and **herbal antioxidants orally (O) and/or topically (T)** may help reduce the risk of skin cancer as well as inflammation and erythema (sunburn) from solar radiation. *In vitro* studies of UV radiation done on human keratinocyte cultures are designated as topical treatments.

(Based on major references: 2867, 3001, 3193)

E.5.4. Protection from Adverse Effects of Gamma Radiation

p. 504

Aloe leaf gel (*Aloe vera*) – Lj^{3665,3709} [neg. Lj^{2772,2773,2774}]

American ginseng root (*Panax quinquefolius*) – Le^{3065,3066}

Amla fruit [aqueous extract,^{2850,2852} methanol extract²⁸⁵¹] (*Embllica officinalis*) – Oe^{2850,2851,2852}

Asian ginseng root (*Panax ginseng*) – Ie, If,³³²³ Ic³³²⁴

Bael leaf, fruit (*Aegle marmelos*) – Oe, Ie³¹⁹³

Cat's claw bark (*Uncaria tomentosa*) – Oe³³³⁰

Corn silk/stigma [ethanolic extract] (*Zea mays*) – Oe³⁴⁸⁷

Cranberry fruit extract (*Vaccinium macrocarpon*) – Oe^{3266,3431,3614}

Dong quai roots (*Angelica sinensis*) – Of³³⁶⁵

Frankincense resin extract (*Boswellia serrata*) – Oe,²⁸⁴⁶ Le³⁴⁹⁸

Ginger rhizome (*Zingiber officinale*) – Oe³⁷⁰⁷

Ginkgo leaves (*Ginkgo biloba*) – Oe, Ie³¹⁹³

Gulanha herb (*Tinospora cordifolia*) – Oe³¹⁹³

Indian valerian root [aqueous extract] (*Valeriana wallichii*) – Le³⁶⁸³

Jambolan seeds, leaf (*Syzygium cumini*) – Oe, Ie³¹⁹³

Long pepper fruit (*Piper longum*) – Ie³¹⁹⁴

Milk thistle seeds [flavolignan fraction] (*Silybum marianum*) – If, Of,²⁹⁰³ Lf,³⁶⁶⁶ Of³⁶⁶⁷

Neem berry [oil] (*Azadirachta indica*) – Le³⁴³⁰

Peppermint leaf [oil] (*Mentha x piperita*) – Of³¹⁹⁵

Rajgira leaf (*Amaranthus paniculatus*) – Oe³¹⁹³

Saw palmetto berries [extract] (*Serenoa repens*) – Oe³⁶¹²

Sea buckthorn fruit [hydroethanolic extract] (*Hippophae rhamnoides*) – Ie³⁰⁰⁰

Soy bean [f isoflavones, c genistein] (*Glycine max*) – Of,²⁸¹² Of/Ic²⁸¹³

St. John's wort flower [extract] (*Hypericum perforatum*) – Le³⁴³⁰

Sweet basil leaves (*Ocimum basilicum*) – Oe³¹⁸⁰

Tomato fruit [c lycopene] (*Lycopersicon esculentum*) – Oc²⁷⁶⁹

Tulsi leaves [ea aqueous extract, em methanolic-aqueous extract, c vicenin, orientin] (*Ocimum tenuiflorum* = *Ocimum sanctum*) – Oc,³⁴⁰⁸ Oem,³¹⁸⁰ Iea,³²¹⁴ Ic³²¹⁵

[Note CORRECTION: The current scientific name for Tulsi, also identified as Holy basil on p. 377, is *Ocimum tenuiflorum* but was formerly *Ocimum sanctum*.]

Turkey tail mycelia (*Trametes versicolor*) – **Oh**³²¹¹

Turmeric root (*Curcuma longa*) – **Lc**,³⁴⁸⁵ **Oc**,^{3359,3363} **Oc**,³¹²¹ **Oe**³³¹⁸

E.5.5 Enhancing Antineoplastic Effects of Radiation

p. 504

Black raspberry fruit [methanol extract] (*Rubus occidentalis*) – **Lc** [breast adenocarc.]³⁰⁸¹

Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – **Oe** [melanoma]³¹⁸⁰

Turmeric root (*Curcuma longa*) – **Lc** [ovarian],²⁸⁷⁶ **Lc** [colorectal],^{2866,2875} **Oc** [Note CORRECTION: colorectal]²⁶⁷⁶

E.5.7. Reducing Transforming Growth Factor- β 1 Before, During, &/or After Radiotherapy

p. 505

Astragalus root [water and/or ethanol extracts] (*Astragalus membranaceus*)– ([e]in rats with Dong quai [e])^{2728,2729,2730}

Dong quai root [water and/or ethanol extracts] (*Angelica sinensis*)– ([e]in rats with Astragalus [e])^{2728,2729,2730}

Magnolia bark [honokiol] (*Magnolia officinalis*) – ([c] in human renal cells)²⁷³²

Reishi mushroom [13.5% polysaccharides/6% triterpenes extract] *Ganoderma lucidum* – ([e] in human prostate cancer cells)²⁷³⁷

E.5.9 Potential Herbal Prevention of Dermal Photocarcinogenesis

NEW ^

Black raspberry fruit [80% ethanol extract³⁰⁷¹] (*Rubus occidentalis*) – **Te** [after UVB irradiation]³⁰⁷³

Bloodroot root [c sanguinarine] (*Sanguinaria canadensis*) – **Tc**³⁰⁰⁸

Broccoli sprouts [e; c sulforaphane] (*Brassica oleracea* v. *italica*) – **Tc**, **Te**,**c**³⁰³⁷

Coffee beans (roasted) [e aqueous] (*Coffea arabica*) – **Oe**²⁸⁹⁴

Ginger rhizome [c 6-gingerol] (*Zingiber officinale*) – **Tc**, **Tc**³⁰¹⁰

Grapes fruit [c resveratrol] (*Vitis* spp.) – **Tc**,^{2886,2887,2888,2897} **Tc**²⁸⁸⁹

Grape seed [e ethanolic extract; f proanthocyanidin] – **Of**,²⁸⁸⁵ **Te**³⁰¹⁶

Heather herb [e ethanolic extract] (*Calluna vulgaris*) – **Te**³⁰¹⁶

Licorice root [c glycyrrhizin] (*Glycyrrhiza glabra*, *Glycyrrhiza uralensis*) – **Tc**,³⁵⁸⁸ **Oc** [after UVB irradiation]³⁵⁸⁹

Olive leaf [e; c oleuropein], fruit [f oil] (*Oleo europaea*) – **Oe**, **c**²⁸⁶⁸ **Tf** [after irradiation]²⁸⁷⁰

Pomegranate juice/seed [extract, c delphinidin] (*Punica granatum*) – **Tc**, **Tc**,³⁰⁰⁷ **Te**³⁰⁰⁶

Milk thistle seed [f silymarin; c silybin] (*Silybum marianum*) – **Tf**,^{2871,2872,2873} **Tc**^{2891,3009,3010,3011}

Soy beans [c genistein] (*Glycine max*) – **Tc**^{3017,3018}

Tea (green) leaves [e aqueous; f polyphenols; c EGCG] (*Camellia sinensis*) – **Tf**,²⁸⁹⁰ **Tf**,^{2873,2880} **Tc**,^{2884,3003,3016} **Oe**,^{2874,2883,3004} **Of**,^{2880,2881} **Te**³⁶⁴⁸

Tea (black) leaves [e aqueous] – **Oe**,^{2892,2893} **Oe**,^{2882,2883} **Te**³⁶⁴⁸

Tomato fruit (*Lycopersicon esculentum*) – **Oe**³⁶⁷²

Turmeric root [pc curcumin] (*Curcuma longa*) – **Tc**²⁸⁷⁸

E.5.10.a Herbal Prevention of Acute UV-induced Erythema

NEW ^

Broccoli sprouts [e; c sulforaphane] (*Brassica oleracea* v. *italica*) – **Te**, **Te**,**c**²⁸⁹⁵

Cocoa bean (fermented, roasted) [h/f flavanols] (*Theobroma cacao*) – **Oh/f**²⁹¹¹

Ginseng (red) roots [ee enzyme-treated extract; ginsenoside Rh3] (*Panax ginseng*) – **Tee**³⁶⁵²

(white) roots [ee enzyme-treated extract; ginsenoside F2] (*Panax ginseng*) – **Tee**³⁶⁴⁵

Grapes fruit [c resveratrol] (*Vitis* spp.) – **Tc**²⁸⁸⁶

Honeybush leaves, flowers, twigs (*Cyclopia* spp.) – **Te**,³⁶⁴⁷ **Te**³⁶⁴⁶

Lycium (= Goji) berries (*Lycium barbarum*) – **Oj**³⁰²⁸

Rhatany root (*Krameria triandra*) – **Te**³¹⁷⁶

Rooibos leaves/twigs (*Aspalathus linearis*) – **Te**³⁶⁴⁶

Tea (green) leaves [f polyphenols or catechins] (*Camellia sinensis*) – **Te**,³⁶⁴⁶ **Tfp**,²⁸⁹⁰ **Ofc**³³⁶¹

Tomato fruit (*Lycopersicon esculentum*) – **Oe**^{3673,3674}

E.5.10.b Herbal Reduction of UVB-induced Chronic Photoaging

NEW ^

Fennel seed (*Foeniculum vulgare*) – Te, Te³⁶⁵⁰

Ginseng (red, white) roots [ee enzyme-treated extracts] (*Panax ginseng*) – T(w)ee,³⁶⁴⁵ O(r)ee³⁶⁵¹

Honeybush leaves, flowers, twigs (*Cyclopia* spp.) – Te³⁶⁴⁶

Rooibos leaves/twigs (*Aspalathus linearis*) – Te³⁶⁴⁶

Tea (black, green, white) leaves [e aqueous] (*Camellia sinensis*) – Te,³⁶⁴⁹ Te^{3646,3648}

E.5.11 Herbal Protection Against Radioiodine Therapy Adverse Effects

NEW ^

Ginkgo leaf extract (*Ginkgo biloba*) – Oe^{3095,3096}

Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – Oe^{3184, 3186}

E.6 Herbs and Anti-infection Agents

p. 505

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have recently spread from their common occurrence in hospitals to growing prevalence in the community, including schools. **There are now also vancomycin resistant *Staph. aureus* (VRSA) strains.** Other **bacterial strains have become multiple drug-resistant (MDR), such as MDR *Staph. aureus*** varieties resistant to mupirocin and/or other antibiotics as well as to methicillin (MDR-MRSA). **Vancomycin-resistant *Enterococci* (VRE)** are another example of bacterial transformations causing concerns about treating infections for which a commonly used antibiotic is ineffective.

With increasing failures of antibiotic treatment for some bacterial infections, new or alternative agents and practices are being investigated to help address this growing vulnerability. In particular, combinations of antibiotics are necessary to control some infections and prevent epidemics of diseases like tuberculosis. The disadvantage of using single molecule antimicrobial drugs for infectious disease control is now recognized, based on a microbes ability to rapidly develop resistance to the a single compound and its mechanism of activity. While complex plant extracts typically lack the comparative potency of single-molecule antimicrobial drugs, the pluripotent complexity and multiple pharmacodynamic impact on the infectious process offers the advantage, inherently developed in the plants themselves, of resisting infections over the long term. In addition, when combined with conventional antimicrobial medication, they may complement the drug pharmacology or enhance its effects by improving its absorption, half-life, and/or microbial cellular retention. Conversely, it is possible that for certain drugs and/or particular microbes an extract that is beneficial in some circumstances can be a disadvantage in others by antagonizing ordinary pharmacotherapy. Ongoing research is needed to unveil the potential of beneficial combinations and potential disruptions when combining plant preparations with antimicrobial therapeutic agents.³⁰³¹

The normal typeset for the botanical and other antimicrobial agent(s) indicates *in vitro* studies, while italicizing is used for *in vivo* animal studies, and bold type indicates human clinical studies. In the case of combinations with antimicrobial agents, **abbreviations are used for the botanical forms, whether it be the herb (h), an extract (e), a fraction (f), or a component (c) or several components (cs), and for the name of the associated antimicrobial.** ***E.6.11*** Antimicrobial agents including antibiotics are capable of inducing a variety of adverse effects, depending on the agent. This can limit their life-saving potential by restricting the effective dose required for optimal treatment. Botanicals that are capable of reducing antimicrobial toxicity can help in the acute and/or chronic treatment of infections. **The specific herbal preparation, toxic antimicrobial, and protected organ(s) from *in vitro* (plain type), animal (italicized) or human (bold) studies are listed after each botanical.** Probiotic microorganisms are not considered in this category, though they can be of great benefit in reducing adverse enteric effects and recovering from disrupted intestinal flora from antibiotic use.

(Additional major references: 3031)

E.6.1 Botanicals active against antibiotic-resistant strains of bacteria

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Ajowan fruit (*Carum copticum*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Alstonia stem bark (*Alstonia scholaris*) f hexane fraction of methanolic extract – (f) MDR-

Enterobacteriaceae bacterium IK1_01, (f) MDR-*Shigella dysenteriae*, (f) MDR-*Enterobacter cloacae*, (f) MDR-*Serratia marcescens*³²³⁵

Andrographis leaf (*Andrographis paniculata*) e aqueous extract – (e) MRSA²⁹⁷⁴

Arjun tree leaves (*Terminalia arjuna*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Bael fruit pulp (*Aegle marmelos*) e methanol or aqueous extracts – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Bergamot peel (*Citrus bergamia*) eo essential oil – (eo) MRSA³⁵⁹⁶

Bibhitaki fruit (*Terminalia belerica*) ee ethanolic extract – (ee) MDR-MRSA³²⁰⁰

Black cherry bark (*Prunus serotina*) ee ethanolic extract – (ee) MDR-*Neisseria gonorrhoeae*³³²⁶

Black nightshade seeds *(*Solanum nigrum*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Cassia bark (*Cinnamomum cassia*) c cinnamaldehyde – (c) MDR-*Salmonella typhimurium*, (c) MDR-*E. coli*, (c) MDR-*Staph. aureus*, (c) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Catechu bark (*Acacia catechu*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Celandine herb (*Chelidonium majus*) cs 8-hydroxydihydrosanguinarine, 8-hydroxydihydrochelerythrine – (cs) MRSA³³⁷⁰

Celery leaves (*Apium graveolens*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Chamomile herb (*Matricaria recutita*) e extract – (e) methicillin-resistant *Staph. epidermidis*³³²⁷

Chaparral leaves [c NDGA/lignins] (*Larrea tridentata*) – (c) MRSA, (c) MDR-*Mycobacterium tuberculosis*³¹⁰²

Chicory leaves (*Cichorium intybus*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Chinese lantern tree fruit (*Dichrostachys glomerata*) e methanolic extract – (e) MDR-*Escherichia coli*, (e) MDR-*Enterobacter aerogenes*, (e) MDR-*Klebsiella pneumoniae*, (e) MDR-*Pseudomonas aeruginosa*³⁰²⁰

Chinese rhubarb root (*Rheum palmatum*) cs emodin & rhein – (cs) MRSA³³³⁶

Chinese skullcap root (*Scutellaria baicalensis*) c baicalin – (e) MDR-*Acinetobacter baumannii*,²⁷¹⁹ (c) MRSA, (c) penicillin-resistant *Staphylococcus aureus*²³⁵⁸

Cinnamon bark (*Cinnamomum verum*) c cinnamaldehyde – (c) MDR-*Salmonella typhimurium*, (c) MDR-*E. coli*, (c) MDR-*Staph. aureus*, (c) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Cinnamon beilschmiedia bark (*Beilschmiedia cinnamomea*) e methanolic extract – (e) MDR-*E. coli*, (e) MDR-*Enterobacter aerogenes*, (e) MDR-*K. pneumoniae*³⁰²⁰

Clary sage root (*Salvia sclarea*) (e) extract, cs salvipisone, aethiopinone – (c) MRSA, (c) MDR-*Staph. epidermidis*,³⁰³⁶ (e) methicillin-resistant *Staph. epidermidis*³³²⁷

Clove bud (*Syzygium aromaticum*) c eugenol – (c) MDR-*Salmonella typhimurium*, (c) MDR-*E. coli*, (c) MDR-*Staph. aureus*, (c) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Coriander fruit (*Coriandrum sativum*) f essential oil – (f) MRSA³²⁶²

Devil's claw roots/tubers (*Harpagophytum procumbens*) – morphine³⁷¹⁴

Eucalyptus leaf (*Eucalyptus globulus*) f essential oil – (f) MRSA,²⁷¹² (f) ***Mycobacterium tuberculosis***²⁷¹⁴ fruit essential oil, 1,8-cineole &/or aromadendrene – (f, cs, c-a) MRSA, VRE (*Enterococcus faecalis*)²⁷¹³

Garlic bulb *(*Allium sativum*) e water extract – (e) MDR-*Mycobacterium tuberculosis*,³¹⁷⁰ (c) isoniazid-resistant *Mycobacterium tuberculosis*³¹⁷²

Goldenseal root and rhizome *(*Hydrastis canadensis*) ee ethanolic extract, c berberine – (ee, c) MDR-*Neisseria gonorrhoeae*³³²⁶

leaves: e hydroethanolic extract, c berberine – (e,c) MRSA³¹³⁰

Gotu kola leaves (*Centella asiatica*) e methanol extract – (e) MRSA²⁹⁷⁴

Grapefruit peel (*Citrus paradisi*) eo essential oil – (eo) MRSA³⁵⁹⁶

Haritaki fruit (*Terminalia chebula*) ee ethanolic extract – (ee) MDR-MRSA³²⁰⁰

Horseradish root (*Armoracia rusticana*) c allyl isothiocyanate – (c) MDR-*Salmonella typhimurium*, (c) MDR-*E. coli*, (c) MDR-*Staph. aureus*, (c) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Indian nettle leaves (*Acalypha indica*) e aqueous extract – (e) MDR-*Mycobacterium tuberculosis*³¹⁷⁰

Kikar bark (*Acacia nilotica*) e aqueous extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Kutki leaves (*Picrorrhiza kurroa*) e methanol or aqueous extracts – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Lemongrass leaf (*Cymbopogon flexuosus*) eo essential oil – (eo) MRSA³⁵⁹⁶

Licorice root (*Glycyrrhiza uralensis*) c gancaonin – (c-ga) vancomycin-resistant strains of *Enterococcus faecalis*, *E. faecium*, *E. gallinarum* and MRSA³⁰³²

Lime peel (*Citrus aurantifolia*) eo essential oil – (eo) MRSA³⁵⁹⁶

Magnolia bark (*Magnolia officinalis*) e extract – (e) MDR-*Acinetobacter baumannii*²⁷¹⁹

Malabar nut leaves (*Adhatoda vasica*) e aqueous extract – (e) MDR-*Mycobacterium tuberculosis*³¹⁷⁰

Mongolian mulberry (*Morus mongolica*) cs mulberrofurans – (c) vancomycin-resistant strains of *Enterococcus faecalis*, *E. faecium*, *E. gallinarum* and MRSA³⁰³²

Mustard seed (*Brassica nigra*) c allyl isothiocyanate – (c) MDR-*Salmonella typhimurium*, (c) MDR-*E. coli*, (c) MDR-*Staph. aureus*, (c) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Orange rind (*Citrus sinensis*) f essential oil – f MRSA, VRSA³¹⁴⁶

Oregano herb (*Origanum vulgare* ssp. *hirsutum*) c caravcrol or thymol – (c-c&t) MDR-*Salmonella typhimurium*, (c-c&t) MDR-*E. coli*, (c-c&t) MDR-*Staph. aureus*, (c-c&t) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Pomegranate fruit peel (*Punica granatum*) ee ethanolic extract, em methanol extract – (ee) MDR-MRSA,³²⁰⁰ (em) MDR-*Salmonella typhi*³⁰⁴⁶

Rabdosia (*Rabdosia rubescens*) – (e) MDR-*Acinetobacter baumannii*²⁷¹⁹

Rhodiola root (*Rhodiola rosea*) ee ethanolic extract – (ee) MDR-*Neisseria gonorrhoeae*³³²⁶

Rugose rose flower (*Rosa rugosa*) – (e) MDR-*Acinetobacter baumannii*²⁷¹⁹

Sage leaf (*Salvia officinalis*) e extracts – (e) methicillin-resistant *Staph. epidermidis*³³²⁷

Simal bark (*Salmalia malabarica*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Southern prickly ash (*Zanthoxylum clava-herculis*) e alkaloidal extract, f ethyl acetate, c chelerythrine – (ea, fe, c) MDR-MRSA³⁴²¹

Sowa seed (*Peucedanum graveolens*) e methanol extract – (e) MDR-*Salmonella typhi*³⁰⁴⁶

Star anise fruit (*Illicium verum*) e supercritical CO₂ extract, f diethylether fraction, c anethole – (e) MDR-*Acinetobacter baumannii*, (f) MDR-*Acinetobacter baumannii*, (f) MDR-*Pseudomonas aeruginosa*, (f) MRSA, (c) MDR-*Acinetobacter baumannii*³²⁴⁹

Sweet tea fruit (*Rubus chingii*) – (e) MDR-*Acinetobacter baumannii*²⁷¹⁹

Tea leaf (b black, o Oolong and/or g green) leaf (*Camellia sinensis*) ea aqueous extract, ee ethanolic extract, fa acetone fraction, fm methanol fraction – (ee, fa, fm) MDR-MRSA,³²⁰⁰ (ea) MDR-*Acinetobacter baumannii*²⁷¹⁹

Thyme herb (*Thymus vulgaris*) f essential oil, c thymol or caravcrol – (f) MRSA,²⁷¹² (c-t&c) MDR-*Salmonella typhimurium*, (c-t&c) MDR-*E. coli*, (c-t&c) MDR-*Staph. aureus*, (c-t&c) erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Tropical almond fruit (*Terminalia chebula*) – (e) MDR-*Acinetobacter baumannii*²⁷¹⁹

Tulsi seed (*Ocimum tenuiflorum* = *Ocimum sanctum*) ea aqueous extract, ee ethanolic extract, ec chloroform extract, c eugenol – (ee) MDR-MRSA,³²⁰⁰ (ea) MDR-*Salmonella typhi*,³⁰⁴⁶ (ee, ec) MDR-*Neisseria gonorrhoeae*,³³⁰⁷ (c) MDR-*Neisseria gonorrhoeae*³³⁰⁶

Turmeric rhizome (*Curcuma longa*) e ethyl acetate extract – (e) MRSA³²⁵⁰

Usnea lichen (*Usnea* spp.) c usnic acid – MRSA³³⁷⁶

Uva ursi leaf (*Arctostaphylos uva-ursi*) ee ethanolic extract – (ee) MDR-*Neisseria gonorrhoeae*³³²⁶

Viranga fruit (*Embelia ribes*) e methanol and aqueous extracts – (e) MDR-*Salmonella typhi*³⁰⁴⁶

E.6.2 Botanicals improving antimicrobial efficacy against resistant strains p. 508

Bibhitaki fruit (*Terminalia belerica*) ee ethanolic extract – ee/tetracycline & MDR-MRSA³²⁰⁰

Cassia bark (*Cinnamomum cassia*) c cinnamaldehyde – c/tetracycline & MDR-*E. coli*, c/ampicillin or penicillin & MDR-*Staph. aureus*³⁰⁴⁷

Chamomile herb (*Matricaria recutita*) e extract – e/oxacillin & methicillin-resistant *Staph. epidermidis*³³²⁷

Chinese lantern tree fruit (*Dichrostachys glomerata*) e methanolic extract – (e) MDR-*Escherichia coli*, (e) MDR-*Enterobacter aerogenes*, (e) MDR-*Klebsiella pneumoniae*, (e) MDR-*Pseudomonas aeruginosa*³⁰²⁰

Chinese rhubarb root (*Rheum palmatum*) cs emodin & rhein – cs/ampicillin or oxacillin & MRSA³³³⁶

Cinnamon bark (*Cinnamomum verum*) c cinnamaldehyde – c/tetracycline & MDR-*E. coli*, c/ampicillin or penicillin & MDR-*Staph. aureus*³⁰⁴⁷

Cinnamon beilschmiedia bark (*Beilschmiedia cinnamomea*) e methanolic extract – (e) MDR-*E. coli*, (e) MDR-*Ent. aerogenes*, (e) MDR-*K. pneumoniae*³⁰²⁰

Clary sage roots (*Salvia sclarea*) e extract, c salvipisone or aethiopinone – e/oxacillin & methicillin-resistant *Staph. epidermidis*,³³²⁷ c-s or c-a/oxacillin, vancomycin, or linezolid & MRSA, MDR-*Staph. epidermidis*³⁰³⁶

Clove bud (*Syzygium aromaticum*) c eugenol – c/penicillin & MDR-*Staph. aureus*³⁰⁴⁷

Goldenseal leaves *(*Hydrastis canadensis*) e hydroethanolic extract – e/berberine & MRSA³¹³⁰

Haritaki fruit (*Terminalia chebula*) ee ethanolic extract – ee/tetracycline & MDR-MRSA³²⁰⁰

Horseradish root (*Armoracia rusticana*) c allyl isothiocyanate – c/ampicillin or erythromycin & MDR-*Salmonella typhimurium*, c/bacitracin & MDR-*E. coli*, c/bacitracin & MDR-*Staph. aureus*³⁰⁴⁷

Khat leaves (*Catha edulis*) e aqueous extract – e/tetracycline & *Strep. oralis* and *Strep. sanguis*, e/penicillin-G & *Fusobacterium nucleatum*³⁰³³

Kutaki roots/rhizome (*Picrorhiza kurroa*) f iridoid glycosides – f/chloroquine & MDR-*Plasmodium yoelii*²⁹³⁷

Lesser galangal rhizome (*Alpinia officinarum*) c galangin – c/gentamicin & MRSA³⁰³⁹

Mustard seed (*Brassica nigra*) c allyl isothiocyanate – c/ampicillin or erythromycin & MDR-*Salmonella typhimurium*, c/bacitracin & MDR-*E. coli*, c/bacitracin & MDR-*Staph. aureus*³⁰⁴⁷

Oregano herb (*Origanum vulgare* ssp. *hirsutum*) c caravcrol or thymol – c-c/novobiocin, penicillin, or tetracycline & MDR-*Salmonella typhimurium*, c-c/penicillin or tetracycline and c-t/erythromycin & MDR-*E. coli*, c-c&t/ampicillin, bacitracin, or penicillin & MDR-*Staph. aureus*, c-c&t/erythrocyin & erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Pomegranate fruit peel (*Punica granatum*) ee ethanolic extract – ee/tetracycline & MDR-MRSA³²⁰⁰

Sage leaf (*Salvia officinalis*) e extracts, eo essential oil – e, eo/oxacillin & methicillin-resistant *Staph. epidermidis*³³²⁷

Sappan wood (*Caesalpinia sappan*) e methanol extract – e/ampicillin or oxacillin & MRSA²⁷²⁰

Shirazian thyme herb (*Zataria multiflora*) – f/vancomycin & MRSA²⁷¹⁵

Tea (green) leaf (*Camellia sinensis*) ee ethanolic extract, c EGCG – ee/tetracycline & MDR-MRSA,³²⁰⁰ c-E/imipenem & imipenem-resistant *Klebsiella pneumoniae*²⁹⁶⁸

Thyme herb (*Thymus vulgaris*) c thymol or caravcrol – c-c/novobiocin, penicillin, or tetracycline & MDR-*Salmonella typhimurium*, c-c/penicillin or tetracycline and c-t/erythromycin & MDR-*E. coli*, c-t&c/ampicillin, bacitracin, or penicillin & MDR-*Staph. aureus*, c-t&c/erythrocyin & erythromycin-resistant *Strep. pyogenes*³⁰⁴⁷

Turmeric rhizome (*Curcuma longa*) e ethyl acetate extract – e/ β -lactams (oxacillin or ampicillin) & MRSA³²⁵⁰

E.6.3 Botanicals enhancing the ordinary efficacy of antibiotics & antiseptics p. 510

African basil leaves (*Ocimum gratissimum*) ee ethanolic extract – ee/ampicillin & *Escherichia coli*, *Proteus mirabilis*, ee/septrin & *Escherichia coli*³⁵⁷³

Ashwagandha root (*Withania somnifera*) – **h/ethambutol, isoniazid, pyrazinamide, and rifampicin & *Mycobacterium tuberculosis***³²³³

Barberry root bark (*Berberis vulgaris*) c berberine – **c/sulphacetamide & *Chlamydia trachoma***⁵⁷⁷

Bilberry leaves (*Vaccinium myrtillus*) e aqueous acetone, c gallic acid – e,c/linezolid, vancomycin & *Staph. aureus*³⁴²²

Cinnamon (*Cinnamomum* spp.) f essential oil – f/chlorhexidine & *Streptococcus mutans*, *Lactobacillus plantarum*³⁰³⁵

Clary sage roots (*Salvia sclarea*) c salvipisone or aethiopinone – c/oxacillin & *Staph. aureus*, *Staph. epidermidis*³⁰³⁶

Clove oil (*Syzygium aromaticum*) c eugenol – c/ampicillin, chloramphenicol, erythromycin, norfloxacin, oxacillin, penicillin, polymyxin B, rifampin, tetracycline, vancomycin & *Enterobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*²⁹⁵⁶
[methanolic extract antagonized the activity of cefoxitin, ciprofloxacin, and gentamicin against *E. coli*³³⁴⁹]

Cola seed (*Cola nitida*) e methanolic extract – e/ciprofloxacin, perfloracin, levofloxacin & *E. coli*³⁰³⁴

Coptis root (*Coptis* spp.) c berberine – **c/sulphacetamide & *Chlamydia trachoma***⁵⁷⁷

- Coriander fruit (*Coriandrum sativum*) f essential oil – f/chloramphenicol, ciprofloxacin, gentamicin or tetracycline & *Acinetobacter baumannii*³²⁶³
- Garlic clove *(*Allium sativum*) h fresh cut, e water extract – **local h/chorhexidine & group B *Streptococcus*,²⁷¹¹ e/isoniazid/rifampicin/ethambutol/pyrazinamide & *Mycobacterium tuberculosis*,³¹⁶⁹ e/isoniazid or rifampicin & *Mycobacterium tuberculosis*,³¹⁷¹ me/gentamicin & *E. coli*³³⁴⁹**
- Geranium leaf (*Pelargonium graveolens*) f essential oil – f/norfloxacin & *Bacillus subtilis*, *Bac. cereus*, *Staph. aureus* or *E. coli*³⁰⁴¹
- Goldenseal root and rhizome *(*Hydrastis canadensis*) c berberine – **c/sulphacetamide & *Chlamydia trachoma***⁵⁷⁷
- Maitake mushroom (*Grifola frondosa*) f D-fraction – f/vancomycin & *Listeria monocytogenes*³³⁴⁰
- Manuka (*Leptospermum scoparium*) f essential oil – f/chlorhexidine & *Streptococcus mutans*, *Lactobacillus plantarum*³⁰³⁵
- Oregon grape bark (*Mahonia* [or *Berberis*] spp.) c berberine – **c/sulphacetamide & *Chlamydia trachoma***⁵⁷⁷
- Peppermint (*Mentha piperita*) f essential oil, c menthol – f/ciprofloxacin = 1-1.5 & *Klebsiella pneumoniae*, f/ciprofloxacin ≥ 1 & *Staph. aureus*,²⁶⁸⁹ f/oxytetracycline & *E. coli*, c/oxytetracycline and *E. coli*³⁰⁴²
[f/ciprofloxacin < 0.5 or ≥ 4 reduced antibiotic activity against *Klebsiella pneumoniae*; f/amphotericin B reduced antifungal effect *Candida albicans*²⁶⁸⁹]
- Rosemary leaf (*Rosmarinus officinalis*) f essential oil – f/ciprofloxacin < 3 & *Klebsiella pneumoniae*²⁶⁸⁹
[f/ciprofloxacin reduced antibiotic activity against *Staph. aureus*; f/amphotericin B reduced antifungal effect on *Candida albicans*²⁶⁸⁹]
- Star anise fruit (*Illicium verum*) f diethylether fraction – f/amikacin & *Pseudomonas aeruginosa*, f/amoxicillin, ampicillin, clindamycin, or piperacillin & *Staph. aureus*³²⁴⁹
- Tea (green) leaf (*Camellia sinensis*) c catechin EGCG – c/ciprofloxacin & *E. coli*³⁰³⁸
- Tea tree (*Melaleuca alternifolia*) f essential oil – f/tobramycin & *Staph. aureus*, f/tobramycin & *E. coli*,³⁰⁴⁰ f/ciprofloxacin = 1.5 & *Klebsiella pneumoniae*²⁶⁸⁹
[f/ciprofloxacin < 1 reduced antibiotic activity against *Klebsiella pneumoniae*; f/ciprofloxacin reduced antibiotic activity against *Staph. aureus*; f/amphotericin B reduced antifungal effect on *Candida albicans*²⁶⁸⁹]
- Thyme (*Thymus vulgaris*) f essential oil – f/ciprofloxacin = 1-1.5 & *Klebsiella pneumoniae*²⁶⁸⁹
[f/ciprofloxacin ≤ 1.5 reduced antibiotic activity against *Staph. aureus*; f/amphotericin B reduced antifungal effect on *Candida albicans*²⁶⁸⁹]

E.6.6 Botanicals inhibiting efflux of antimicrobial agents by bacteria p. 511

Goldenseal leaves (*Hydrastis canadensis*) cs sideroxylin, 6- and 8-desmethyl-sideroxylin – e/berberine & NorA *Staph. aureus*,³²³⁶ e/berberine & NorA MRSA,³²⁹⁶ cs/berberine NorA MRSA³²⁹⁷

E.6.7 Botanicals enhancing [or reducing] the efficacy of antifungal agents p. 512

African basil leaves (*Ocimum gratissimum*) ee ethanolic extract – ee/nystatin and ketoconazole & *Candida albicans*³⁵⁷³

Agastache herb (*Agastache rugosa*) f essential oil, c estragole – f,c/ketoconazole & *Blastoschizomyces capitatus*³⁰⁵¹

Barberry bark (*Berberis* spp.) c berberine – c/fluconazole & *Candida albicans*,³¹⁰⁶ c/amphotericin B & *Candida albicans*³¹⁰⁷

Coptis rhizome (*Coptis chinensis*) c berberine – c/fluconazole & *Candida albicans*,³¹⁰⁶ c/amphotericin B & *Candida albicans*³¹⁰⁷

Goldenseal roots/rhizome *(*Hydrastis canadensis*) c berberine – c/fluconazole & *Candida albicans*,³¹⁰⁶ c/amphotericin B & *Candida albicans*³¹⁰⁷

Mediterranean spurge stem (*Euphorbia characias*) f latex – f/ketoconazole & *Candida albicans*³¹⁰⁵

Moroccan thyme herbs (*Thymus maroccanus*, *T. broussonetii*) f essential oils – f/fluconazole or amphotericin B & *Candida albicans*²⁷¹⁶

- Myrtle leaves (*Myrtus communis*) f essential oil – f/amphotericin B & *Candida albicans* or *Aspergillus niger*²⁷¹⁸
- Oregano herb (*Origanum vulgare*) f essential oil – f/amphotericin B & *Candida* spp.,³⁰⁵² f/nystatin & *Candida* spp.³⁰⁵³
- Oregon grape root bark (*Mahonia* spp.) c berberine – c/fluconazole & *Candida albicans*,³¹⁰⁶ c/amphotericin B & *Candida albicans*³¹⁰⁷
- Peppermint (*Mentha piperita*) f essential oil, c menthol – [f/amphotericin B reduced antifungal effect *Candida albicans*²⁶⁸⁹]
- Pomegranate fruit peel (*Punica granatum*) e hydroalcoholic extract, f ethyl acetate, c punicalagin – e,f,c/fluconazole & *Candida albicans*, c/ketoconazole & *Candida albicans*³⁰⁴⁹ [not c/nystatin or amphotericin B & *Candida albicans*³⁰⁴⁹]
- Rose geranium leaf (*Pelargonium graveolens*) f essential oil, c geraniol or citronellol – c-g,c-c/ketoconazole & *Aspergillus flavus*,³⁰⁵⁰ f/amphotericin B & *Candida* spp.,³⁰⁵² f/nystatin & *Candida* spp.³⁰⁵³
- Rosemary leaf (*Rosmarinus officinalis*) f essential oil – [f/amphotericin B reduced antifungal activity against *Candida albicans*²⁶⁸⁹]
- Santolina aerial parts (*Santolina chamaecyparissus*) f essential oil – f/clotrimazole & *Candida albicans*³⁰⁵⁴
- Tea (green) leaf (*Camellia sinensis*) [Note: CORRECTION – catechin EGCG in Tea, not in Tea tree leaf] catechin EGCG – c/amphotericin B or fluconazole & *Candida albicans*²³⁶⁶
- Tea tree leaf (*Melaleuca alternifolia*) f essential oil [Note: CORRECTION – catechin EGCG not in Tea tree leaf. See Tea above.] – f/amphotericin B & *Candida* spp.³⁰⁵² [f/amphotericin B reduced antifungal effect on *Candida albicans*²⁶⁸⁹]
- Thyme leaf (*Thymus vulgaris*) f essential oil – [f(uncharacterized chemotype)/amphotericin B reduced antifungal effect on *Candida albicans*²⁶⁸⁹]
- Tulsi leaves (*Ocimum tenuiflorum* = *O. sanctum*) f essential oil (methyl chavicol chemotype), c methyl chavicol or linalool – f,c/fluconazol or ketoconazole & *Candida* spp. or MDR-*Candida* spp.²⁷¹⁷
- E.6.8 Botanicals enhancing efficacy of antiviral agents** p. 512
- Clove oil (*Syzygium aromaticum*) c eugenol – c/acyclovir & herpes simplex virus types 1 & 2²⁹⁵⁵
- E.6.9 Botanicals enhancing the efficacy of immunizations against infections** p. 512
- Larch bark (*Larix* spp.) cs arabinogalactans – pneumococcal vaccine²⁷³⁹
- E.6.10.a Botanicals reducing adhesion of bacteria that cause infections** p. 512
- Black horehound herb (*Ballota nigra*) e aqueous extract – MRSA³³⁵⁰
- Cranberry fruit (*Vaccinium macrocarpon*) j juice, jc juice cocktail, f high molecular weight compounds – jc (*E.coli*),³⁰⁰² j (*Streptococcus criceti*, *Strep. gordonii*, *Strep. mitis*, *Strep. mutans*, *Strep. oralis*, *Strep. sanguinis*, *Strep. sobrinus*);²⁸⁴³ f-hmw (*Porphyromonas gingivalis*),²⁸⁴¹ (*Strep. sobrinus*)²⁸⁴²
- Motherwort leaves (*Leonurus cardiaca*) e aqueous-acetone (30:70) extract, c ursolic acid – e (*Staphylococcus aureus*), c (*Staph. aureus*)³⁴⁶⁰
- Tassel hyacinth bulb (*Leopoldia comosa*) ae aqueous extract, ee ethanolic extract – ae MRSA, ee MRSA³³⁵⁰
- E.6.10.b Botanicals inducing exocytosis of intracellular bacteria that prolong infections**
- NEW ^
- Coleus [formerly Makandi] leaf (*Coleus forskohlii*) c forskolin – c (*Eschericia coli*)³²⁹⁵
- E.6.11 Botanicals reducing adverse effects caused by antimicrobial agents** NEW
- ^
- Ashwagandha root (*Withania somnifera*) – e/gentamicin³²⁵³

Cordyceps (*Cordyceps sinensis*) h mycelium, e water extract – **h/amikacin** (kidney), **h/gentamicin** (kidney), *h/gentamicin* (kidney), *e/kanamycin* (kidney)⁵⁹⁸
Garlic leaves or cloves *(*Allium sativum*) h-c cloves, h-l leaves, e aged extract, c diallyl sulfide or diallyl disulfide – *h/gentamicin*,^{1911,3387} *c-ds* or *c-dd/gentamicin*,^{1912,1913} *e/gentamicin*^{1914,1915}
Gentian root (*Gentiana lutea*) hydroethanolic extract – *e/ketoconazole*³³⁵³
Ginkgo leaf (*Ginkgo biloba*) e standardized extract – *e/gentamicin*, *e/gentamicin*³²⁶⁰
Milk thistle seed (*Silybum marianum*) f silymarin – *f/metronidazole* (stomach, liver, kidney)²²⁶⁷
Nigella seed oil (*Nigella sativa*) c thymoquinone – *c/gentamicin*³²⁵⁹
Spiny sowthistle herb (*Sonchus asper*) e methanolic extract – *e/gentamicin* (kidney, liver)³⁰¹⁹

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CORRECTIONS

These corrections are for the early printing of the book (prior to 2013). They have been corrected in the Kindle ebook version.

GOLDENSEAL p. 183

**Hydrastis canadensis* roots/rhizome

Drug Interactions

Ia. 1) [Note CORRECTION] 3.97 gram of the root extract delivering 132 mg hydrastine and 77 mg berberine per day for 14 days significantly INCREASED [not "reduced" as in some early copies] midazolam bioavailability in 16 healthy subjects (PO in human study).²⁵⁰¹

GRAPEFRUIT p. 186

Citrus paradisi fruit / juice

Drug Interactions

Ia. 16) [CORRECTION: The interaction and its reference citation #2590 in the text was listed previously as number 8) with citation #1274.]

OREGON GRAPE p. 254

Mahonia spp. root bark

Contraindications

I. 5) [Note CORRECTION: This item should be listed as 3) under DRUG INTERACTIONS Ia. on the next page (p. 255). See below.]

POMEGRANATE p. 266

Punica granatum fruit

Drug Interactions

Ib. 1) A man using **ezetimibe** daily and **rosuvastatin** every other day developed rhabdomyolysis after beginning pomegranate juice (PO in human case report).¹⁹⁸²

HOWEVER, though pomegranate juice has been shown to inhibit CYP 3A (PO in rats,¹⁹²⁰ *in vitro*^{1920,1923}), [Note CORRECTION as follows.] it does not inhibit metabolism of midazolam by CYP 3A4 (PO in humans).²²¹³

2) [Note CORRECTION: this item is properly found as item IV. 1.]

ST. JOHN'S WORT p. 290

Hypericum perforatum herb, tops

Contraindications

I. 3) Do not take prior to **surgery**.^{1309,1890}

[Note CORRECTIONS: in the last line of the first paragraph, it should read: [See drug interactions "Ib.2" below.], not 'I.10'.

Five lines below, in the third paragraph, the brackets should read: [See drug interactions Ia.4 and Ia.7&8, respectively.], not 'I.6 and I.8 below'.

Drug Interactions

10) [Note CORRECTION: See Ib. 7) for proper categorization.]

Appendix B

HERBAL-DRUG INTERACTIONS

[Note CORRECTIONS: In Appendices B and E in the first 100 copies of the book distributed early in 2011, asterisks (*) are missing in front of the scientific Latin names for a number of listed herbs designated with * in the main body of the text as containing potentially toxic compounds. (For example, European pennyroyal herb *(*Mentha pulegium*) near the top of page 366 lacks an asterisk in these books.)

In Appendix B the other herbs that may be missing the * include: Aloes, Black cohosh, Cayenne, Celandine, Chaparral, Chinese rhubarb, Cinchona, Coffee, Cubeb, Garlic, Juniper, Kava, Licorice, Madagascar periwinkle, Sage, Sassafras, Thuja, and Valerian.]

B.4.1 Hypoglycemic and/or Antihyperglycemic Herbs p. 376

Fenugreek [Note CORRECTION: the superscript in the second line after **h(t1)** should be "1646", not 1645.]

B.5.1.c Warfarin or Heparin Metabolism Inhibitors and/or Anticoagulant Adjuvants p. 382

[Note CORRECTION: Cocoa seed (*Theobroma cacao*)¹⁴⁴⁷ belongs in B.5.1.d. rather than B.5.1.c.] 88

CORRECTIONS (cont.)

B.5.2.b Warfarin Antagonism by Inducing Its Metabolism and/or Modifying Its Effect p. 385

Avocado fruit (*Persea americana*) CR³¹²³

B.7 Modifying Enzyme Activities in Metabolic Conversions p. 387

B.7.1 Unspecified Influences of Herbal Agents on Substrate Pharmacokinetics

[Note: CORRECTION of the web address listing CYP isozyme substrates, inhibitors, and inducers is: <http://medicine.iupui.edu/clinpharm/DDIs> .]

B.7.2.a Influence on CYP 1A2 Metabolic Conversion of Substrates

No Effect in Human Studies with Isoenzyme CYP 1A2 substrates p. 408

[Note CORRECTION: (SJ) St John's wort herb (*Hypericum perforatum*) – caffeine superscript '1328' should be deleted, since a significant mean 26% increase in metabolite to caffeine ratio was observed in the group of 6 men and 6 women. Also, apply this CORRECTION to Note 3.]

B.7.2.f Influence on CYP 2D6 Metabolic Conversion of Substrates

No Effect in Human Studies with Isoenzyme CYP 2D6 substrates p.426

(SJ) St John's wort herb (*Hypericum perforatum*) – [Note CORRECTION: debrisoquin superscript '1328' should be deleted.] [See Note 2.]

Notes

2. [Note CORRECTION: an exception to no significant effect of St. John's wort on CYP 2D6 in human studies is a 23% increased urinary recovery ratio of debrisoquin metabolite in one study,¹³²⁸ indicative of weak induction.]

Appendix E

HERBALS AS POTENTIAL COMPLEMENTARY ADJUNCTS WITH MEDICINES

[Note CORRECTION: In Appendices B and E in the first 100 copies of the book distributed early in 2011, asterisks (*) are missing in front of the scientific Latin names for a number of listed herbs designated with * in the main body of the text as containing potentially toxic compounds.

In Appendix E, herbs that may be missing the * include: Black cohosh, Bryonia, Cannabis, Cayenne, Chinese rhubarb, Cinchona, Garlic, Goldenseal, Jamaica dogwood, Licorice, Sage, Thuja, Thunder god vine, Valerian, and Wormwood.]

E.1.1 Herbs and Those Drugs Which May Potentially Be Complemented

Cranberry fruit [NOT leaves] (*Vaccinium macrocarpon*) – oral hypoglycemics,³⁰⁹⁸

E.4.3 Selective Cell Retention of Drugs by Inhibiting Efflux Transport Proteins p. 500

Asian ginseng [Note CORRECTION: citation #2102 is the following: Choi CH, Kang G, Min Y-D. Reversal of P-glycoprotein-mediated multidrug resistance by protopanaxatriol ginsenosides from Korean red ginseng. *Planta Med.*, 69:235-240, 2003.]

E.5.4. Protection from Adverse Effects by Cobalt 60 or Cesium 137 Gamma Radiation p. 504

Tulsi [Note CORRECTION: The scientific name for Tulsi, also identified as Holy basil on p. 377, is *Ocimum tenuiflorum* but was formerly *Ocimum sanctum*.]

E.5.5 Enhancing Antineoplastic Effects of Radiation p. 504

Turmeric root (*Curcuma longa*) – Oc [Note CORRECTION: colorectal]²⁶⁷⁶

E.6.7 Botanicals enhancing [or reducing] the efficacy of antifungal agents p. 512

Tea (green) leaf (*Camellia sinensis*) [Note: CORRECTION – catechin EGCG in Tea, not in Tea tree leaf] catechin EGCG – c/amphotericin B or fluconazole & *Candida albicans*²³⁶⁶

Tea tree leaf (*Melaleuca alternifolia*) f essential oil [Note: CORRECTION – catechin EGCG not in Tea tree leaf. See above.]

Reference CORRECTIONS:

1567. WEBSITE IS NOW – <http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx> [updated Nov. 14, 2011]

2582. Abdul MIM, Jiang X, Williams KM, et al. Pharmacokinetic and pharmacodynamic interactions of echinacea and policosanol with warfarin in healthy subjects. *Br. J. Clin. Pharmacol.*, 69(5):508-515, 2010
[This primary article citation replaces a secondary source.]

2590. [Previous citation was redundant.] Kanazawa S, Ohkubo T, Sugawara K. The effects of grapefruit juice on the pharmacokinetics of erythromycin. *Eur. J. Clin. Pharmacol.*, 56:799-803, 2001

2625. Lee YH, Lee BK, Choi YJ, et al. Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. *Int. J. Cardiol.*, 145:275-276, 2010 [Previous citation indicated "2009 (in press)".]

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