

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

FOURTH EDITION

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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. These corrections have been made in recent printings (or will be made in later printings) of the book. It is recommended that if the noted corrections have not already 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.

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.eclecticherb.com/emp 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'.

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
- IIb.** *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

* 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 ^

Arjuna +

Arnica +

Ashwagandha +

Asian ginseng +

Astragalus +

Barberry +

Bilberry +

Bitter melon

Bitter orange

Black cohosh

Black cumin +

Black pepper +

Black raspberry ^

Borage +

Burdock +

Calamus +

Cannabis +

Cassia +

Cat's claw +

Cayenne

Celandine

Chamomile

Chili ^

Chinese rhubarb +

Chinese skullcap +

Chokeberry +

Cinchona

Cinnamon +

Clove +

Cocoa +

Cola +

Coptis +

Corn silk ^

Cranberry

Crucifers +

Dan shen +

Dog rose +

Dong Quai +

Echinacea angustifolia

Echinacea pallida +
Echinacea purpurea +
English plantain +
Evening primrose +
Fenugreek +
Fo-ti
Frankincense +
French maritime pine +
Garlic +
Ginger +
Ginkgo
Goldenseal +
Grapefruit +
Guarana +
Hawthorn +
Hops +
Horse chestnut +
Jujube +
Kava
Kudzu +
Kutaki +
Larch ^
Licorice +
Long pepper +
Lycium +
Maca
Maitake +
Milk thistle +
Oat
Olive +
Oregon grape +
Passion flower
Pau d'Arco +
Pelargonium ^
Peppermint +
Pomegranate +
Prickly pear
Psyllium
Quassia (Surinam) +
Raspberry +
Roman chamomile
Saffron +
Sage +
Sanch ginseng ^
Saw palmetto +
Schisandra +
Silk tree +
Southern schizandra ^
Soy +
St. John's wort
Stinging nettle

Sweet annie +
 Sweet cherry ^
 Tart cherry ^
 Tea +
 Tea tree +
 Thunder god vine
 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.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.

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 Herbs 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 Herbs 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

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REFERENCES

New references citations from 2709 to 3418 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.

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

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

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

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}
- Iia. + 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, a 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

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

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
- 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, cratinine, 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 ginseng doses of 2 grams 3 times daily for 12 weeks in 19 patients with diabetes type 2, in combination with diet alone or diet plus **hypoglycemic drugs** in 14 resulted in reduction in oral glucose tolerance test indices by 8-11% and plasma insulin by 33-38% (PO in human clinical study).²⁰⁴²
- 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

- 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. 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
- 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

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-β1 [TGF-β1], 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-β1 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-β1 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
- 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 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

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

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

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% isopropenolic 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

p.66

Nigella sativa seed

Complementary Adjuncts

- Ia. 1) Chemical war victims from **mustard gas** **inhalation** on **salbutamol** and **corticosteroids** required less of these after taking black cummin extract (PO in human clinical study).²⁴⁸⁹
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 cummin 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 cummin 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
- + 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

- + 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
- Ila. 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

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 μ 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) 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,^{3134,3155} and reduced plasma AST, ALT, and peroxidative markers.³¹⁵⁵

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

p. 79

Arctium lappa root

Complementary Adjuncts

- Ila. + 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

CALAMUS

p. 81

**Acorus calamus* roots/rhizome

Complementary Adjuncts

- Ila. + 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. 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,^{1737,3275} increases the risk of developing schizophrenia and psychotic outcomes,³²⁷²⁻³²⁷⁴ and contributes to a poor prognosis for those with established psychotic disorder (IH in human studies).^{1372,1737,3272} The risks increase dose-dependently^{3273,3274} and with frequency of use (human studies).³²⁷³
- 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}

Drug Interactions

- Ib. 1) [NOTE: The order of this information has been reversed.] 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**, **ethanol**, or **barbiturates** (IH in human studies).^{1076,1077}
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

HOWEVER, cannabis has been used to ease withdrawal from alcohol and opiates (empirical).⁷

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

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 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
- + 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

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

p. 86

Cinnamomum cassia = *Cinnamomum aromaticum* bark

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 HbA_{1c} 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

- Ila. + 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

Complementary Adjuncts

- Ia. 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** after using celandine (empirical).¹⁸⁹⁰

Liver-specific CIOMS analysis of 33 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

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
- Iia. + 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 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

- Ila. + 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 trabectedin 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

- Ila. + 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 transminases 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
- 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

CORN SILK

NEW

^ *Zea mays* stigma

Complementary Adjuncts

- Ila. 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 by gentamicin was 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
- Ilb. 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
 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
- 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

DOG ROSE

p. 126

Rosa canina dried fruit (hips)

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

- 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 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) 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

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

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 alkamides, 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

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

Complementary Adjuncts

- Ila. + 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

ENGLISH PLANTAIN

p. 142

Plantago lanceolata leaves

Complementary Adjuncts

- Ila. + 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

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

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
- + 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

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
- 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 hypertension 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

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

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

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

- 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

- 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
- + 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
- 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

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

Drug Interactions

- Ia. 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 **talinalolol** bioavailability due to inhibition of P-glycoprotein efflux (PO in human study).^{2680,3138} The bioavailability and peak plasma concentration of talinalolol 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
- 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 or more greater than is achieved in the plasma by normal therapeutic doses of 120-240 mg of a 50:1 concentrated ginkgo extract (*in vitro*).¹⁷⁴⁷
- 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
- 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
- + 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. + 5) When ginkgo leaves were decocted and the extract given together with oral **cyclosporine**, the maximum concentration of cyclosporin was reduced by 62%, and its bioavailability decreased by 51%, though no effects was shown when cyclosporin 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 cyclosporin reduced the peak concentration by 60% and the bioavailability of cyclosporin by 68%, but again no effect on IV cyclosporin. 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. 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 time 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 time 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

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

- + 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
- Ila. + 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
 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
- 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
- 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

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

- 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

HOPS

p. 203

Humulus lupulus strobiles

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 agent 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

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
- 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 Mold

hepatotoxin contamination has also been raised as a possible explanation of the rare cases of liver damage associated with kava (speculative).^{2913,3067}

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 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

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

- Ila. + 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 picoside-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

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
- 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
(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

- Ila. + 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

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

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 **talinolol** 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

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

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 spoonful 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

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

PASSION FLOWER

p. 258

Passiflora incarnata herb

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 (*Valerian 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 avellanedae = *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 mcl 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 receiveing **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

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

- Ia. +** 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

- Ia. +** 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

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

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

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** 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

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 had 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 **talinolol** bioavailability, due to inhibition of P-glycoprotein efflux (PO in human study). The bioavailability and peak plasma concentration of talinolol 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. Gomisin C was the most potent inhibitor (*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, gomisin 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

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 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
- This 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 A tissue distribution study showed that the tacrolimus was increased in the blood by 3-fold, as well as significantly increased in muscle and 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
- 3) 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

SOY

p. 287

Glycine max beans

Complementary Adjuncts

- Ib. + 1) In 8 children of ages 6-13 years receiving **chemotherapy** for **cancers** [including neuroblastoma, Wilms tumor, mesenchymal tumor, adrenocrotical 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. 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. 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 **dienogesterol** 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

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.

- + 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

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

- Ila. 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

- Ila. 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

- Ila. 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 memol/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 concentrated aqueous-**ethanolic extract** of green tea for weight loss associated with 13 cases of hepatitis, after use from 9 days to 5 months (PO in human case reports).^{1508,1579,1580,2328,2577}

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 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

Drug Interactions

- I. + 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 **bupirone** (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

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
- 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 GOD VINE

p. 318

**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 TFIID 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

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 glycated serum proteins were compared to baseline, a significant 20.8% reduction in blood glucose and 11.2% decrease in glycated 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** [131 I] 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 131 I, and lessened the depletion of reduced glutathione in the liver.³¹⁸⁶ Parotid gland atrophy and lipomatosis from 131 I 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 **talinalolol** (PO in human study). The mechanism was unclear due to the small dose and group and short duration.²⁸⁰⁶

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 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 [75% curcumin, 15% demethoxycurcumin, 10% bisdemethoxycurcumin] 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 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 **offluoxetine** 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

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
- 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

Complementary Adjuncts

- 1a. 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

p

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HERBALS TO BE USED WITH CAUTION

A.8 Bioactivations of Phytochemical Procarcinogens and Potential Toxins ^

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) ^

Phytochemicals Common Herb

<u>Sources</u>	<u>Activators</u>	<u>Metabolite Toxic Effects</u>
aristolochic carcinogens, 150,1357,2818	Aristolochia *(<i>Aristolochia</i> spp.) herbs ²⁸¹⁷	CYPs 1A1/2; ²⁸¹⁶ kidney
acids	Wild ginger *(<i>Asarum canadensis</i>) rhizome ¹⁵⁰	ST
1A ²⁷⁹²	kidney toxins ^{150,1357}	

estragole carcinogen, ^{150,759,760}	Basil (<i>Ocimum basilicum</i>) herb ^{150,400}	CYPs 1A2,2A6,	liver
seeds ^{150,400}	Fennel (<i>Foeniculum vulgare</i>) 2C19,2D6,2E1;	mutagenic ²⁸²⁰	
	Tarragon (<i>Artemisia dracunculus</i>) leaf ^{150,400}	STs ²⁷⁹²	
methyl- eugenol	Asarabacca (<i>Asarum europaeum</i>) rhizome ⁴⁰⁰	CYPs 1A2,2C9,	liver carcinogen ^{759,760}
	Wild ginger *(<i>Asarum canadensis</i>) rhizome ⁴⁰⁰	2C19, 2D6;	
	Am. pennyroyal *(<i>Hedeoma pulegoides</i>) ^{150,2792}	CYPs ⁶⁴³ 1A2,	liver
pulegone toxin ^{642,644,645}	Eur. pennyroyal *(<i>Mentha pulegium</i>) ^{150,2792}	2C19,2E1 ²⁸²¹	
pyrrolizidine 2B6, ²⁷⁹² alkaloids	Borage herb *(<i>Borago officinalis</i>), ¹⁵⁰ liver toxins ^{38,144,236,333,590}	CYPs	
	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 spp.</i>), ²⁷⁹²	3A4 ¹¹⁸³	
	Tansy ragwort herb *(<i>Senecio jabocaea</i>) ²⁷⁹²		
safrole carcinogen, ^{150,759,760,2819} mutagenic ²⁸²⁰	Sassafras *(<i>Sassafras albidum</i>) root bark ¹⁵⁰	CYPs ²⁸¹⁹ 2A6,	liver
		2C9,2D6,2E1;	
		STs ²⁷⁹²	
teucrin A 3A4 ²⁷⁹²	Germander (<i>Teucrium chamaedrys</i>) ²⁸²² liver toxin ^{1516,1517,1518}	CYP	

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.1.1.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 Modifying Intestinal Absorption of Medicines and Phase III Metabolism

B.1.1 Slowed and/or Reduced Absorption by Herbal

Components p. 364

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

Chili fruit (*Capsicum annuum*) – **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

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**, 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*) – **cefactor** (s)²⁶¹⁸

B.1.2 Enhancement of

Absorption

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B.1.2.a General Absorption Enhancement by Pungent Herbs

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 **talinolol** (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*) – **talinolol** (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*) –

talinolol (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
- 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 d (kidney),²⁷⁷⁹ rhodamine-123 (colon)^{2777,2780} [See Note 5.]

Notes:

3. 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
5. 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

1. 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

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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

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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**. 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)**. 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), 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 1 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 glycemia. Those botanicals not having strong hypoglycemic properties alone, such as psyllium and milk thistle, likely have an even greater margin of safety.

B.4.1 Hypoglycemic and/or Antihyperglycemic

Herbals

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

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

Chirata herb (*Swertia chirayita*)³²¹⁷

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

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

Gulanha stem (*Tinospora cordifolia*)³²¹⁷

Gymnema leaves (*Gymnema sylvestri*)³²¹⁷

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

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

Ivy gourd herb (*Coccinia indica*)³²¹⁷

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

Kino heartwood (*Pterocarpus marsupium*)³²¹⁷

Moringa stem bark (*Moringa oleifera*)³²¹⁷
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

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 **sulfonylurea**
s^{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**, **glipizide**, **metformin**¹⁶⁰⁹
Milk thistle fruit (*Silybum marianum*) – **glyburide (glibenclamide)**, **metformin**²⁰⁴¹
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
Tulsi seed (*Ocimum tenuiflorum* = *Ocimum sanctum*)
– **chlorpropamide**, **glibenclamide**, **glipizide**, **penformin**³³⁰⁸

B.5 Modifying the Effects of Anticoagulants

p.

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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, 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)**, **heparin (H)**, or **antiplatelet drugs (AP)**.

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*) [**neg W & AP**²⁹⁶⁰]

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

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

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

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

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

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

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

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 praeruptorins 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.a Modulation by Phase I &/or Phase II &/or Phase III

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

7-ethoxyresorufin [1A1/2] – ; Co³²⁹⁰
7-pentoxyresorufin [2B1/2] – ; An,²⁹⁷⁵ Co³²⁹⁰

Drugs: rosuvastatin – bc³²³²
phenytoin – Gc³²⁸⁴ ; Bc, Fg³²⁸⁴
warfarin – ; Co³²⁹⁰

Steroids: dehydroepiandrosterone [OATP-C] – bA, ep mr, nr, si³²²⁴
estradiol – Bl, By, ea³⁰⁸²
testosterone – ; Co³²⁹⁰

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

(Bc) Black cumin seed (*Nigella sativa*) – CYP 2B11, 3A4³²⁸⁴

(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
- (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, 3A4³⁰⁴⁴ [**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.]
- (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 w as 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

- (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

- (lt) 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

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

Probes: 7-methoxyresorufin – cc²⁹³⁸ ; 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*)

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

Isoenzyme Inducers

(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

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[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

Probes: aniline – Am²⁸⁵⁷

Drugs: chlorzoxazone – ts²⁷⁷⁰

Procarcinogens: NMBA (N-nitrosomethylbenzylamine) – Bp²⁴⁶⁰

Isoenzyme Inhibitors

(Am) Amla fruit (*Emblica officinalis*)

(Bp) Black raspberry fruit (*Rubus occidentalis*)

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

Notes:

1. SJW 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

B.7.2.c Influence on CYP 3A Metabolic Conversion of Substrates

Probes: 7-benzyloxy-4-(Fl³Me)coumarin – cc²⁹³⁸
 7-benzyloxyquinoline – cc²⁹³⁸
 7-benzyloxyresorufin – cc²⁹³⁸
 dibenzylfluorescein – cc²⁹³⁸
 luciferin 6'benzyl ether – sc²⁷⁷¹

Drugs: atorvastatin – ; SJ²²⁰⁰
 buspirone – rs,²⁹⁷⁰ Te²⁸¹⁰
 efavirenz – Gb³³⁹²
 erythromycin – Gf,²⁵⁹⁰ sc²⁹⁴⁶
 finasteride – ; SJ³¹³³
 methadone – ; SJ¹⁶⁴¹
 midazolam –
 bb,³²³⁸ cc,²⁷⁷⁸ cc,²²⁷⁹ 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,²
 965 sc,²⁸³²
 nevirapine – pp³¹³² ; SJ¹⁹⁷²
 nicardipine – ep³²⁰⁹
 nifedipine – Gb³²²⁹
 nitrendipine – Pg³¹¹¹
 paclitaxel –
 Eu,²⁵⁶⁸ Fr,²⁶⁶⁴ Gb,²¹⁴⁵ Gf,²⁵⁶⁸ Go,²¹⁴⁵ is,²⁸³³ kb,²⁶⁶⁴ Kv,²⁵⁶⁸ Mt,²¹⁴⁵ Po,²⁵
 68 qu,²⁸³⁵ Ss²⁸²⁷
 sirolimus – Gf³¹⁴⁴
 tacrolimus – Gf,³¹²⁴ Ss,²⁸³⁰ Ss,^{2828,2830} Ss²⁸²⁹
 tamoxifen – ep³²⁰⁶

Steroids: testosterone – cm,²⁷⁶⁸ sc,²⁹⁴⁶ ts²⁷⁷⁰ ; Co³²⁹⁰
 cortisol – Gf^{3021,3426}

Procarcinogens: aflatoxin B₁ – ep³²⁰¹

Isoenzyme Inhibitors

- (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*)
 (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*)
 (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.]

- (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 fruit (*Schisandra chinensis*) [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*)

Isoenzyme Inducers

- (Ds) Dan shen root (*Salvia miltiorrhiza*) [See Note 22.]
- (Ep) Echinacea purpurea tops (*Echinacea purpurea*) [See Note 3.]
- (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

- (Ca) Cannabis tops infusion *(*Cannabis sativa*, *Cannabis indica*) – docetaxel, irinotecan²⁹⁴¹
- (Ep) Echinacea purpurea root or entire plant (*Echinacea purpurea*) – darunavir/ritonavir,²⁷⁹³ lopinavir/ritonavir³⁰⁹⁹ [See Note 3.]
- (Ga) Garlic bulbs (*Allium sativum*) – simvastatin³²²³ [See Note 7.]
- (Gb) Ginkgo leaf extract (*Ginkgo biloba*) – anastrozole, letrozole,³²⁶⁸ lopinavir,³¹³⁵ midazolam,³⁰⁹¹ ritonavir,³¹³⁵ tamoxifen,³²⁶⁸ ticlopidine³²²⁷ [See Note 15.]
- (La) English lavender flowers (*Lavandula angustifolia*) – midazolam³³⁰³

Notes:

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 affect after 14 days of the extract when given in combination with the CYP 3A inhibitor ritonavir.³⁰⁹⁹ 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 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 therefor 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 schisadrol 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
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} Tested *in vitro* the component dihydrotanshinone I inhibits CYP3A, while cryptotanshinone and tanshinone IIA induce CYP3A.³⁴²⁵

B.7.2.d Influence on CYP 2C9 Metabolic Conversion of Substrates

Drugs: diclofenac – Cb,³⁰⁸⁵ cc,²⁹³⁸ Pg³¹¹²
 flurbiprofen – am,¹⁹⁵⁴ Pg,³²⁴⁵ qu¹⁹⁵⁴

losartan – bb,³²³⁸ rs,²⁹⁷⁰ si²⁹⁸¹
 phenprocoumon – ; SJ⁶⁰⁵
 rosiglitazone – ; SJ²⁶³⁸
 tolbutamide – Pg,³¹¹² pt,³⁰⁴³ ts²⁷⁷⁰
 warfarin – si²⁹⁸⁰ ; Co³²⁹⁰

Isoenzyme Inhibitors

- (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*)
 (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

- (Co) Coleus root (*Coleus forskohlii*)
 (SJ) St. John's wort herb (*Hypericum perforatum*)

No Effect in Human Studies with Isoenzyme CYP 2C9 substrates

- (Cb) Cranberry fruit/juice (*Vaccinium macrocarpon*) – diclofenac³⁰⁸⁵ [See Note 9.]
 (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:

- Though ginkgo extract acts as a CYP 2C9 inhibitor *in vitro*,^{2011,2145,2151} at 360 mg/day EGb 761 in humans²⁰¹⁵ and as 0.5% of the diet in rats it was shown to induce this isozyme.¹⁹⁵² Normal therapeutic doses do not produce either effect in humans.^{1433,1774,1842,2011,3091}
- 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.
- 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
- 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.
- 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

B.7.2.e Influence on CYP 2C19 Metabolic Conversion of Substrates

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*) – 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

Drugs: dextromethorphan – **bb**,³²³⁸ **cc**,²⁹³⁸ **rs**²⁹⁷⁰
 metoprolol – **sa**²⁷⁶⁷

Isoenzyme Inhibitors

- (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*)
 (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 p.426

- (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

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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 cinerea*) – 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
 (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

- (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) bladder,³⁴⁰¹ skin,^{2895,2896,3037} skin^{2895,2896}
- (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) tigloylgomisin 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

- (By) 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

p. 433

(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
- (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 (Cyanocobalamin) / 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 Herbs with Drugs

E.1.1 Herbs and Those Drugs Which May Potentially Be

Complemented

p. 484

Amla fruit (*Embllica 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 **chemotherapy,**^{2916,3293} **influenza vaccine,**^{2918,2919} *cyclophosphamide,*^{2924,2925} *mitomycin C,*²⁹²² N-acetyl cysteine, vitamin C²⁹²³

berry – 5-fluorouracil²⁹²⁷

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 **taxotere,**³²⁵² *gentamicin*³²⁵³

Asian ginseng root (*Panax ginseng*) –

donepezil, galantamine, memantine, rivastigmine,³⁰⁵⁹ cisplatin²⁷²⁵

Astragalus root (*Astragalus membranaceus*) – *enalapril*²⁷²⁸

Barberry root bark (*Berberis vulgaris*) – **simvastatin,**²⁹⁰⁵ *amphotericin*

*B,*³¹⁰⁷ *doxorubicin,*³¹⁴⁸ *stanols*^{2932,2933}

Bilberry fruit (*Vaccinium myrtillus*) – **latanoprost**²⁹⁶⁶

Black cumin seed (*Nigella sativa*) – **beclomethasone, beta-**

agonists,²⁹⁸⁸ **corticosteroids,**^{2988,2989} **diclofenac,**³¹¹⁴ **fluticasone,**²⁹⁸⁸ **folic acid, hydroxychloroquine, methotrexate,**³¹¹⁴ **omeprazole,**³³¹² **theophylline,**²⁹⁸⁸ *acetaminophen,*²⁹⁸³ *doxorubicin,*²⁴³⁰ *gemcitabine,*²⁹⁸⁵ *gentamicin,*³²⁵⁹ *ifosfamide,*²⁴³¹ *oxaliplatin*²⁹⁸⁵

Black pepper fruit (*Piper nigrum*) – **calcium,**³⁴⁷¹ *EGCG,*²⁹³⁵ **emodin,**³⁴⁵⁹ **iron, zinc**³⁴⁷¹

Calamus rhizome (*Acorus calamus*) – *vincristine*³³⁷⁵

Cannabis tops *(*Cannabis sativa*) –

anticholinergics,²⁷⁵¹ **anticonvulsants, antidepressants,**²⁹⁴⁰ **baclofen,**³³⁰⁵ **codeine, dextropropoxyphene, dihydrocodeine,**²⁷⁴⁸ **glatiramer, interferon beta-1a,b,**³³⁰⁵ **methadone,**²⁷⁴⁸ **methotrexate,**²⁹⁴² **morphine,**^{2748,3126} **NSAIDs,**²⁹⁴⁰ **oxycodone,**²⁷⁴⁸ *pethidine,*²⁷⁴⁸ *tizanidine,*³³⁰⁵ **tramadol**²⁷⁴⁸

Cat's claw bark (*Uncaria tomentosa*) – *doxorubicin*³³³¹

Cayenne fruit (*Capsicum frutescens*) – **calcium, iron, zinc**³⁴⁷¹

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, levofloxacin³⁰³⁴

Coptis root (*Coptis* spp.) – simvastatin,²⁹⁰⁵ amphotericin B,³¹⁰⁷ doxorubicin,³¹⁴⁸ stanols^{2932,2933}

Corn silk/stigma (*Zea mays*) – gentamicin,³⁴⁸⁶ camptothecin, cisplatin, etoposide, 5-fluorouracil³⁴⁸⁸

Cranberry fruit [CORRECTION: NOT leaves] (*Vaccinium macrocarpon*) – oral hypoglycemics,³⁰⁹⁸ doxorubicin³⁰⁸⁰

Crucifers tops, leaves, sprouts (*Brassica* spp.) – cisplatin,²⁹³⁴ trabectedin²¹⁷⁷

Dog rose hips (*Rosa canina*) – acetaminophen, chloroquin, leflunomide, methotrexate, NSAIDs, steroids²⁹⁶²

Dong quai root (*Angelica sinensis*) – enalapril²⁷²⁸

Echinacea angustifolia root (*Echinacea angustifolia*) – influenza vaccine³¹⁷⁸

Echinacea pallida whole plant (*Echinacea pallida*) – cisplatin²⁷²⁶

English plantain leaves (*Plantago lanceolata*) – indomethacin²⁸³⁸

Evening primrose seed (*Oenothera biennis*) – isotretinoin³⁴⁷⁸

Fenugreek seeds (*Trigonella foenum-graecum*) – ibuprofen,³⁴¹⁶ L-dopa,³³⁹⁴ mefenamic acid, NSAIDs³⁴¹⁶

Frankincense resin (*Boswellia serrata*) resin – ibuprofen,²⁸⁰⁴ metformin³⁴¹³

French maritime pine bark (*Pinus pinaster*) – albuterol,³⁰⁹⁴ chlorambucil,³³³³ fluticasone,³⁰⁹³ latanoprost,²⁹⁶⁶ mitoxantrone, prednisolone,³³³³ salbutamol,³⁰⁹³ zafirlukast³⁰⁹⁴

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 gentamicin³³⁸⁷

Ginger root (*Zingiber officinale*) – acetaminophen,^{3314,3316} cisplatin,²⁹⁰⁹ cyclophosphamide,³⁰⁹² dexamethasone,^{2909,3092} docetaxel,³⁰⁹² doxorubicin,²⁹⁰⁹ epirubicin,³⁰⁹² granisetron,³⁰⁹² ondansetron,²⁹⁰⁹ oral hypoglycemics,³⁵⁰¹ acetaminophen,^{3473,3474,3475} atorvastatin,²⁸⁴⁹ calcium,³⁴⁷¹ captopril,²⁷⁵⁶ iron,³⁴⁷¹ morphine,³³²¹ zinc³⁴⁷¹

Ginkgo leaves (*Ginkgo biloba*) – adapalene,³⁴⁹⁹ donepezil, galantamine,³⁴⁸⁴ olanzapine,³²⁹¹ radioiodine,^{3095,3096} rivastigmine,³⁴⁸⁴ cisplatin,³³⁷³ dexamethasone,³¹⁴⁷ gentamicin,³²⁶⁰ isoproterenol³¹⁸⁵

Goldenseal roots/rhizome *(*Hydrastis canadensis*) – simvastatin,²⁹⁰⁵ amphotericin B,³¹⁰⁷ doxorubicin,³¹⁴⁸ stanols^{2932,2933}

Guarana seeds (*Paullinia cupana*) – cyclophosphamide, doxorubicin, fluorouracil²⁹²⁰

Hawthorn leaves/flowers (*Crataegus* spp.) – cyclophosphamide³³⁴⁴

Hops strobiles (*Humulus lupulus*) – benzodiazepines²⁶³⁴

Kudzu root (*Pueraria thunbergiana* = *P. lobata*) – cisplatin²⁷²⁴

Kutki root (*Picrorhiza kurroa*) – acetaminophen,³¹⁶⁰ chloroquine,²⁹³⁷ ethinylestradiol,³¹⁶⁰ rifampicin³¹⁶¹

Larch bark (*Larix* spp.) – pneumococcal vaccine,²⁷³⁹ tetanus vaccine³³⁵¹

Licorice root/rhizome *(*Glycyrrhiza glabra*, *G. uralensis*) – indomethacin²⁹⁷⁶

Long pepper fruit (*Piper longum*) – calcium,³⁴⁷¹ EGCG,²⁹³⁵ iron, zinc³⁴⁷¹

Lycium (= Goji) berry (*Lycium barbarum*) – doxorubicin,^{3029,3110} mitomycin C³⁰³⁰

Maca root (*Lepidium meyenii*) – SNRI, SSRIs, venlafaxine³⁴⁸³

Maitake mushroom (*Grifola frondosa*) – clomiphene citrate,²⁹¹⁰ adriamycin, cisplatin, 5-fluorouracil³³⁴¹

Milk thistle seeds (*Silybum marianum*) – **glibenclamide, metformin,**³⁴⁷⁹ *acetaminophen*^{2824,3181}

Olive fruit oil (*Olea europaea*) – **antibiotics,**³⁵⁰⁰ **atenolol, doxazosin, hydrochlorothiazide, lisinopril, nifedipine**¹⁷⁷³

Oregon grape root bark (*Mahonia* spp.) – **simvastatin,**²⁹⁰⁵ *amphotericin B,*³¹⁰⁷ *doxorubicin,*³¹⁴⁸ *stanols*^{2932,2933}

Passion flower herb (*Passiflora incarnata*) – **benzodiazepines**²⁶³⁴

Pelargonium root (*Pelargonium sidoides*) – **augmentin, budesonide, fenoterol, ipratropiumbromide, ofloxacin, salmeterol**³²⁶⁹

Peppermint leaves (*Mentha x piperita*) – **granistron, dexamethasone, metoclopramide**³²⁸⁵

Pomegranate fruit (*Punica granatum*) – **hydroxychloroquine, methotrexate, prednisone, NSAIDs, sulfazine,**³⁰²⁴ *docetaxel*³³⁸

Quassia (Surinam) bark (*Quassia amara*) – *hydrochoric acid,*³³⁸⁴ *indomethacin*³³⁸²⁻³³⁸⁴

Saffron stigmas (*Crocus sativa*) – **dorzolamide,**³⁴³⁷ **fluoxetine,**^{3480,3481} **timolol**³⁴³⁷

Sage leaves *(*Salvia officinalis*) – *vincristine*³³⁷²

Sanchi ginseng root/rhizome (*Panax notoginseng*) – **aspirin,**³⁰⁷⁶ **diclofenac, leflunomide, prednisone**³⁴¹⁸

Saw palmetto fruit (*Serenoa repens*) – **prulifloxacin,**³⁴¹⁴ **tamsulosin**³⁴¹¹

Soy beans (*Glycine max*) – **adriamycin, carboplatin, cisplatin, cyclophosphamide, dacarbazine, etoposide, ifosfamide, irinotecan, paclitaxel, procarbazine, temozolamide, vincristine**²⁸¹³

St. John's wort herb (*Hypericum perforatum*) – **indomethacin, sodium valproate**³²⁴⁸

Stinging nettle leaves (*Urtica* spp.) – **acetaminophen [paracetamol] aspirin, celecoxib, diclofenac, ibuprofen, ketoprofen, naproxen, opiates, piroxicam, sulindac, tenoxicam**²⁷²²
root – *nicotine*³⁴⁵⁶

Sweet annie herb (*Artemisia annua*) – *curcumin*²⁹¹⁴

Sweet cherries (*Prunus avium*) – **allopurinol, colchicine**³²⁹⁹

Tart cherry fruit (*Prunus cerasus*) – **allopurinol, celecoxib, indomethacin,**^{3298,3302} *sulindac,*²⁴³² *atorvastatin*³¹⁴⁵

Tea [green] leaves (*Camellia sinensis*) – *ciprofloxacin,*³⁰³⁸ *indomethacin*²⁷⁵²

Tea tree leaf oil (*Melaleuca alternifolia*) – **diclofenac, minoxidil**³³⁷¹

Thunder god vine peeled root *(*Tripterygium wilfordii*) – **auranofin,**³²⁸¹ **methotrexate,**³²⁸⁰⁻
³²⁸² **NSAIDs,**³²⁸¹ *sulfasalazine*³²⁸²

Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – *acetaminophen,*³¹⁸¹ *acetic acid, aspirin,*³²¹⁸ *isoproterenol,*^{3185,3239} *meloxicam,*³¹⁸³ *radioiodine,*^{3184,3186} *vincristine,*³¹⁷⁹ *yproterone 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 **docetaxel,**³⁴⁰⁷ **etoposide,**³⁴⁰⁷ **5-fluorouracil,**^{3363,3407} **fluoxetine,**³³⁴⁸ **gemcitabine,**³³⁶³ **immune suppressants,**²⁸⁰³ **isoniazid,**²⁹⁹⁵ **methotrexate,**³⁴⁰⁷ **MOPP/ABVD/COPP,**³³⁶³ **mydriatics,**²⁸⁰³ **naproxen,**³⁴³³ **NSAIDs,**^{2721,2803,3415} **oral hypoglycemics,**³⁰⁹⁷ **pyrazinamide, rifampicin,**²⁹⁹⁵ **steroids,**²⁸⁰³ **taxol,**³⁴⁸⁵ **topotecan,**³⁴⁰⁷ **v inblastine,**³³⁶³ *arteether,*²⁹¹⁴ *cisplatin,*²⁸⁷⁷ *docetaxel,*³³¹⁹ *gemcitabine,*³¹¹⁸ *paclitaxel,*^{2781,3117} *artemisinin*²⁹¹⁴

Valerian root (*Valeriana officinalis*) – **benzodiazepines**²⁶³⁴

E.2 Herbal Aids for Modifying Substance

Abuse

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Though cannabis has been used by some successfully to reduce opioid dependence,³²⁷⁰ personal use of cannabis to reduce alcohol intake should not be considered an appropriate rationale, since concurrent abuse of both together not unusual.⁶²⁸ 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. Herbal extracts or isolated components may **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 regards 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})

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 cumin seed (*Nigella sativa*) – **Alc:** (sd Ae,²⁹⁸⁴ Ac²⁹⁸⁷)

Opi: **Hh**²⁹⁸²

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: Ac²⁹⁷³

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)
 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 **Hc**³²²¹
 Kutaki root (*Picrorhiza kurroa*) – Alc: (ld Ae²⁹³⁶)
 Lemon balm herb (*Melissa officinalis*) – Opi: Ae³⁴⁶¹
 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})
 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})
 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*) – 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: Ae³⁴⁶²
 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,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*) – 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 ascorticosteroids** (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

p. 493

Black cumin seed (*Nigella sativa*) – e^{2988,2989}

Frankincense resin extract (*Boswellia serrata*) – e²⁸⁴⁶

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

p. 493

Black cumin seed (*Nigella sativa*) – f³¹¹⁴

Fenugreek seed (*Trigonella foenum-graecum*) – h³⁴¹⁶

Frankincense resin (*Boswellia serrata*) resin – e²⁸⁰⁴

French maritime pine bark (*Pinus pinaster*) – f²⁷⁹⁵

Purple passion fruit peel (*Passiflora edulis*) – e²⁹⁵¹

Stinging nettle leaves (*Urtica dioica*) – h²⁷²²

Turmeric root [curcumin] (*Curcuma longa*, *C. aromatica*) – e^{2721,2802,3103,3433}

E.3.3 Enhancing Outcomes When Using

Analgesics

p. 494

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*) – e,²⁸⁰² f³²⁴⁷

E.3.4 Protecting Against NSAID-induced

Ulcers

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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

Sea buckthorn fruit (*Hippophae rhamnoides*) – e¹⁹⁵⁹

Shrubby basil leaves (*Ocimum gratissimum* = *O. suave*) – e²⁹⁵³

Tea leaves (*Camellia sinensis*) – e,f²⁷⁵²

Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – e^{3183,3218}

E.3.5 Protecting Against Acetaminophen-induced Liver

Toxicity

p. 494

Black cumin seed (*Nigella sativa*) – c²⁹⁸³

Garlic cloves (*Allium sativum*) – e³³⁸⁶

Ginger rhizome (*Zingiber officinale*) – h,³⁴⁷⁵ e^{3473,3474}

Korean acanthopanax root bark (*Acanthopanax koreanum*) – c²⁷²⁷

Kutki rhizome/roots (*Picrorhiza kurroa*) – f^{3160}
Milk thistle fruit (*Silybum marianum*) – $f^{2824,3181}$
Schisandra fruit (*Schisandra chinensis*) – c^{696}
Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – e^{3181}

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 [c] or components [cs]**. 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 (*Embllica officinalis*) – cisplatin, doxorubicin (e)²⁸⁶⁰
 Asian ginseng root (red) [c panaxadiol] (*Panax ginseng*) – 5-fluorouracil [c]³²⁵⁵
 Bibhitakhi fruit (*Terminalia bellerica*) – cisplatin, doxorubicin (e)²⁸⁶⁰
 Chamomile flowers [bisaboloxide 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
 Milk thistle seeds [silybin(silibinin)] (*Silybum marianum*) – erlotinib [c]^{3354,3355}
 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], ³³¹
⁹ *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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- 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 (*Embllica 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*) – *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*, *doxorubicin* ³⁴²⁸
- 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, docetaxol, epirubicin,** ³⁰⁹²
- Ginkgo leaves (*Ginkgo biloba*) – *cisplatin* (e) ³³⁷³
- Kudzu root (*Pueraria lobata* = *P. thunbergiana*) – *cisplatin* (e) ²⁷²⁴
- 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
- Sage leaves [luteolin] * (*Salvia officinalis*) – *vincristine* (e) ³³⁷²
- 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 topotecan³⁴⁰⁷

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

- 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*)
- Black raspberry fruit [freeze-dried,^{2997,3070,3075} ethanol extract,^{3071,3074,3177} anthocyanins,^{3071,3072} c ferulic acid, beta-sitosterol³¹⁷⁷] (*Rubus occidentalis*)
- Broccoli florets/sprouts [sprouts water extract^{2415,3401} and florets glucosinolates/isothiocyanates extract (colon),³¹⁰⁹ sulphoraphane³⁴⁰²] (*Brassica oleracea* var. *italica*)

Coffee beans roasted [water extract (**nonmelanoma skin cancer in white women**,²⁸⁹⁴ **ER-neg postmenopausal breast cancer**,²⁹⁹⁰ **liver cancer**,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*)

Flax seed [whole/ground (**breast Ca in women**)³³²⁸] (*Linum usitatissimum*)

Kava root (*Piper methysticum*) [f kavalactones³³⁴⁶]

Milk thistle seeds [silymarin^{2900,3320}] (*Silybum marianum*)

Prickly pear fruit [water extract³³⁹⁸] (*Opuntia* spp.)

Reishi [c polysaccharides,^{1094,2999} triterpenoids²⁹⁹⁹] (*Ganoderma lucidum*) – c/liver¹⁰⁹⁴

Shrubby basil leaves [f eugenol-rich oil (*topical*)³⁰¹⁴] (*Ocimum gratissimum* = *O. suave*)

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*)

E.4.5. Reducing Transforming Growth Factor-β1 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 Herbas 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)** 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 (TGF β 1) overexpression.²⁷³³ [See AppendixE.4.5 introduction.] Increases in TGF β 1 during radiation treatment for non-small cell lung cancer is indicative of significant reduction in survival time,²⁷³⁴ and significant TGF β 1 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*) – [neg. Lj]^{2772,2773,2774}
- American ginseng root (*Panax quinquefolius*) – Te^{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*) – Oe³²⁶⁶
- Dong quai roots (*Angelica sinensis*) – Of³³⁶⁵
- Frankincense resin extract (*Boswellia serrata*) – Oe,²⁸⁴⁶ Le³⁴⁹⁸
- Ginkgo leaves (*Ginkgo biloba*) – Oe, Ie³¹⁹³
- Gulanha herb (*Tinospora cordifolia*) – Oe³¹⁹³
- Jambolan seeds, leaf (*Syzygium cumini*) – Oe, Ie³¹⁹³
- Long pepper fruit (*Piper longum*) – Ie³¹⁹⁴
- Milk thistle seeds [flavolignan fraction] (*Silybum marianum*) – If, Of²⁹⁰³
- Neem berry [oil] (*Azadirachta indica*) – Le³⁴³⁰
- Peppermint leaf [oil] (*Mentha x piperita*) – Of³¹⁹⁵
- Rajgira leaf (*Amaranthus paniculatus*) – Oe³¹⁹³
- Sea buckthorn fruit [hydroethanolic extract] (*Hippophae rhamnoides*) – Ie³⁰⁰⁰
- Soy bean [f isoflavones, c genistein] (*Glycine max*) – Of,²⁸¹² Of/c²⁸¹³

St. John's wort flower [extract] (*Hypericum perforatum*) – **Le**³⁴³⁰
 Sweet basil leaves (*Ocimum basilicum*) – **Oe**³¹⁸⁰
 Tomato fruit [c lycopene] (*Lycopersicon esculentum*) – **Oc**²⁷⁶⁹
 Tulsi leaves [ea aqueous extract, em methanolic-aqueous extract, c vicenin, orientin] (*Ocimum tenuiflorum* = *Ocimum sanctum*) – **Oc**,³⁴⁰⁸ **Oem**,³¹⁸⁰ **Iea**,³²¹⁴ **Ic**³²¹⁵
 [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-β1 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] – **Oj**,²⁸⁸⁵ **Te**³⁰¹⁶
 Heather herb [e ethanolic extract] (*Calluna vulgaris*) – **Te**³⁰¹⁶
 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} **Oj**^{2880,2881}
 Tea (black) leaves [e aqueous] – **Oe**,^{2892,2893} **Oe**^{2882,2883}
 Turmeric root [pc curcumin] (*Curcuma longa*) – **Tc**²⁸⁷⁸

E.5.10 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
 Grapes fruit [c resveratrol] (*Vitis* spp.) – **Tc**²⁸⁸⁶
 Lycium (= Goji) berries (*Lycium barbarum*) – **Oj**³⁰²⁸

Rhatany root (*Krameria triandra*) – Te³¹⁷⁶

Tea (green) leaves [f polyphenols or catechins] (*Camellia sinensis*) – Tfp,²⁸⁹⁰ Ofc³³⁶¹

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}

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

p. 507

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

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

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

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

Licorice root (*Glycyrrhiza uralensis*) c gancaonin – (c-ga) vancomycin-resistant strains of *Enterococcus faecalis*, *E. faecium*, *E. gallinarum* and MRSA³⁰³²

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

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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
- Kutki 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/erythrocylin & 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/erythrocylin & 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

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- 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, perfloxacin, 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/amoxillin, 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 \leq 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

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

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*³⁰⁵⁵

Moroccan thyme herbs (*Thymus maroccanus*, *T. broussonetii*) f essential oils – f/fluconazol 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 vaccine**²⁷³⁹

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

Black cumin seed oil (*Nigella sativa*) c thymoquinone – c/gentamicin³²⁵⁹

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

Spiny sowthistle herb (*Sonchus asper*) e methanolic extract – *e/gentamicin* (kidney, liver)³⁰¹⁹

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3 CORRECTIONS:

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