UPDATES AND ADDITIONS
for
Herbal Contraindications & Drug Interactions
plus Herbal Adjuncts with Medicines
FOURTH EDITION
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Information provided in the book or these updates and additions is not intended as recommendations for self treatment or to substitute for instructions provided by one’s own doctor or health care provider. Combining herbal use with medications should only be done after consultation with a knowledgeable physician. Preliminary research data on potentially beneficial combinations of herbals and drugs is provided to educate pharmacists and physicians and encourage further clinical research. Information provided in the book and in these updates is not intended as recommending self treatment or to replace instructions provided by one’s own doctor or health care provider.

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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-β1 Before, During, &/or After Chemotherapy
E.5 Herbals for Preventing and Healing Radiation Adverse Effects and/or Enhancing Radiotherapy or Photodynamic Therapy
E.5.4. Protection from Adverse Effects by Cobalt 60 or Cesium 137 Gamma Radiation
E.5.5 Enhancing Antineoplastic Effects of Radiation
E.5.7. Reducing Transforming Growth Factor-β1 Before, During, &/or After Radiotherapy
E.6 Herbals and Anti-infection Agents
E.6.1 Botanicals active against antibiotic-resistant strains of bacteria
E.6.2 Botanicals improving antimicrobial efficacy against resistant strains
E.6.3 Botanicals enhancing the ordinary efficacy of antibiotics & antiseptics
E.6.6 Botanicals inhibiting efflux of antimicrobial agents by bacteria
E.6.7 Botanicals enhancing [or reducing] the efficacy of antifungal agents
E.6.9 Botanicals enhancing the efficacy of immunizations against infections

REFERENCES
New references citations from 2709 to 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  
_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). 

   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.

AMERICAN GINSENG  
_Panax quinquefolius_ root

Contraindications

II. 1) Estrogen-independent proliferation of human breast cancer cell with the alcoholic extract (_in vitro_) 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_), as did a water-extract on the same cells (_in vitro_). 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_). 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_). 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).

   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.

   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).

   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).

   HOWEVER, based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low (speculative).
III. 1) The saponin fraction enhanced phenylephrine vasoconstrictor effect \((\textit{in vitro})\).\textsuperscript{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.\textsuperscript{2915}

2) Using 3 digoxin immunoassays, a American ginseng extract increased the digoxin measurement results for the fluorescence polarization immunoassay \((\textit{in vitro})\).\textsuperscript{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 \((\textit{in vitro})\).\textsuperscript{3435}

Complementary Adjuncts

Ia. + 1) In a randomized blinded study with 175 \textit{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.\textsuperscript{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.\textsuperscript{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 \textit{respiratory symptoms} in the community group, compared to the 101 and 21 subjects receiving placebo, respectively (PO in human clinical study).\textsuperscript{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 \textit{genotoxicity} in bone marrow and peripheral blood (PO in mice).\textsuperscript{2922}

+ 2) Ginsenoside Rg3, the main ginsenoside in steamed American ginseng roots,\textsuperscript{2923} when given with cyclophosphamide for 10 days to animals with transplanted SKOV-3 \textit{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).\textsuperscript{2924} In other studies, the \textbf{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)\textsuperscript{2925} and when exposed to the major fresh root ginsenoside Rb1 \((\textit{in vitro})\).\textsuperscript{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)\textsuperscript{2922} and Rb1 \((\textit{in vitro})\).
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).  

3) Pretreatment with 100 and 200 mg/kg of ginsenosides Rb1 or Rg1 caused significant inhibition of hyperactivity induced by methamphetamine of 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.  

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).  

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).  

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).  

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.  

AMERICAN GINSENG  

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).  

AMLA  

Emblica officinalis = Phyllanthus emblica fruit  

(Indian gooseberry; It. & Port.: Mirabolano emblica; Beng.: amlaki; Punj.: olay; Arab.: halilaj; 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). At 100 mg/kg the aqueous extract taken for 10 days reduced immunosuppression of humoral immunity by cyclophosphamide (PO in mice). 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).  

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. Amla aqueous extract at 250 mg/kg/day following chronic alcohol liver damage lowered lipid peroxidation and elevated liver antioxidant enzymes (PO in rats). 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).

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 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).

ARJUNA

*Terminalia arjuna* bark

**Complementary Adjuncts**

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.

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.2286

ARNICA

*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 (paracetemol) 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

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 ashwandha 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 ashwaganda but the drug group the opposite trend.1233

2) The 44 patients with breast cancer who received 6 grams daily of an ashwagandha root extract, 50% of whom received a taxotere, adriamycinc, 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, creatinine, urinary protein and glucose, and significant reductions in body weight and potassium.3253

ASIAN GINSENG p. 44

Panax ginseng root

Contraindications

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

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

Drug Interactions

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

HOWEVER, a 500 mg dose of a standardized extract given twice daily for 28 days to 12 subjects resulted in significant decreases in AUC, half-life and maximum concentration of the CYP 3A4 substrate midazolam, indicative of induction (PO in human study). There was no effect on the Pgp substrate fexofenadine.2965

3) A randomized trial using 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). 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).

**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). 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).

+ 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. 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.

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. 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 A₂A receptors (IP in mice).

**ASTRAGALUS**

*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. 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), 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 leucopenia induced by cancer chemotherapy or radiotherapy, especially when the white blood cell count was not less than 1000/mm^3 from anticancer drugs (PO in human clinical study).

+ 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).

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).

+ 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). 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. The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats); berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).

+ 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).

+ 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.

BILBERRY

Vaccinium myrtillus fruit
Complementary Adjuncts

Ia. + 1) When 80 mg bilberry (Vaccinium myrtillus) extract with 36% anthocyanins and 40 mg Pycnogenol with 70% procyanidins as a standardized combination was given once daily in the morning to 79 ocular hypertension patients either alone or together with latanoprost eye drops and compared to latanoprost alone, the extract combination with the drug was best for lowering intraocular pressure and enhancing retinal blood flow (PO in human clinical study). The extract alone eventually was similarly effective as the drug for lowering intraocular pressure, but it took 24 weeks for the extract compared to only 4 weeks with latanoprost. The only adverse effects were those related to latanoprost.2966

BITTER MELON

Momordica charantia fruit / juice and seeds

Contraindications

I. 1) Avoid in pregnancy due to the emmenogogue 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),393 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

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

*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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{2814}

BLACK CUMIN
\textit{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 cumin extract (PO in human clinical study).\textsuperscript{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 cumin decoction compared to 14 controls, along with decreased use of all of the drugs by the extract group and no drug reduction by control subjects (PO in human clinical study).\textsuperscript{2988} In a group of 15 moderate to severe asthma patients on medications who temporarily and briefly suspended use of theophylline and beclomethasone or fluticasone inhalers but continued with prednisolone use, bronchodilation from boiled black cumin extract at 50 or 100 mg/kg was significantly improved compared to the corticosteroid alone, though significantly less when compared to prednisolone with theophylline or salbutamol (PO in human clinical study).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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

IIa. 2) The use of thymoquinone at 5 mg/kg daily with ifosfamide reduced the severity of the drug-induced Fanconi syndrome with its kidney damage (PO in rats), while the same combination used in treating *Ehrlich ascites carcinorna* 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 Thymoquine 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 peroxidanse, 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

*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).

IIa. + 1) Piperine at 70 µmol/kg increased plasma bioavailability of the chemopreventive agent epigallocatechin gallate [EGCG] in green tea by 1.3-fold when given concurrently compared to EGCG given alone (PO in mice). Piperine also increased the maximum plasma concentration of EGCG by inhibiting glucuronidation in mice intestines by 40%. Likewise, the gluruanidation 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).

+ 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).

+ 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.

+ 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.

BLACK RASPBERRY
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). This includes a reduction of the liver fibrotic markers, improved body weight and circulatory antioxidant status, decreased lipid levels, and reduced plasma AST, ALT, and peroxidative markers.

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.

BURDOCK
Arctium lappa root p. 79
Complementary Adjuncts

IIa. + 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

IIa. + 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, 1372,3275 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 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), 528,1198,3275 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
H O W E V E R, cannabis has been used to ease withdrawal from alcohol and opiates (empirical).  
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. 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.

**Complementary Adjuncts**  
Ia. 1) **Vomiting** induced by cancer chemotherapy agents was relieved by cannabis in 78% of the patients (IH in human clinical study). 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. 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).  
H O W E V E R, 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). 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.  

+ 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. 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. States that have enacted medical cannabis laws have shown on average a 24.8% lower annual opioid overdose mortality rate from 1999-2010.  

+ 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. 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.

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).

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. Cannabidiol 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. States that have enacted medical cannabis laws have shown on average a 24.8% lower annual opioid overdose mortality rate from 1999-2010. 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).

5) A group of 30 multiple sclerosis patients, 60% using the antispasticity 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). 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%].

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.

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). 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).

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 [HbA1C] 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 HbA1C 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.

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

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).

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).

CAT’S CLAW  p. 89
Uncaria tomentosa bark or root
IIa. + 2) After treatment with daily intraperitoneal injections of doxorubicin over 3 days to induce leukopenia, a water extract of the inner and outer bark was given for 16
consecutive days (PO in rats). The animals receiving the extract recovered significantly sooner than controls; those given 80 mg/kg extract daily showed normalized white blood cell counts after 10 days and those given 40 mg/kg had normal white counts after 15 days, but it took 20 days to return to normal for those receiving only the doxorubicin. The increase in white blood cell counts included both lymphocytic and neutrophilic cell fractions, whereas the positive control Neupogen increased only the non-lymphocyte fractions.

**CAYENNE**

*Capsicum frutescens* fruit

**Contraindications**

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

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.\(^\text{2939}\)

**Complementary Adjuncts**

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

**CELANDINE**

*Chelidonium majus* root and herb

**Contraindications**

I. 4) Do not consume following an idiosyncratic hepatotoxicity after using celandine (empirical).\(^\text{1890}\)

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.\(^\text{3304}\)

**CHAMOMILE**

*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).\(^\text{3078}\)

HOWEVER, the authors failed to identify by scientific name whether the chamomile used was German (*Matricaria recutita*) or Roman (*Chamaemelum nobile*) chamomile.\(^\text{3078}\) 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.\(^{205}\)

**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**

*Capsicum anuum* fruit

["Peppers" refers to nonpungent varieties of this species eaten as vegetables; chilis are pungent.]

(chili pepper, Thai chili; Sp.: chile; Mex.: chili)

**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).\textsuperscript{1120} 
2) The \textbf{mineral absorption} of \textit{calcium, iron,} and \textit{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.\textsuperscript{3471}

**CHINESE RHUBARB**

\textit{Rheum officinale, Rheum palmatum} root

\textbf{Drug Interactions}

II. 1) A decoction of \textit{R. palmatum} root of 2 g/kg administered in either a single dose or 7 doses with 200 mg/kg \textit{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).\textsuperscript{5335}

**CHINESE SKULLCAP**

\textit{Scutellaria baicalensis} root

\textbf{Complementary Adjuncts}

IIa. 3) The \textbf{hepatotoxicity} effects of \textit{ethanol} (\textit{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).\textsuperscript{2839}

**CHOKEBERRY**

\textit{Aronia melanocarpa} fruit

\textbf{Drug Interactions}

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

**CINCHONA**

\textit{Cinchona} spp. bark

\textbf{Complementary Adjuncts}

IIa. 3) The antiarrhythmic drug \textit{amiodarone} given intratracheally causes direct \textbf{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).\textsuperscript{3436}

**CINCHONA**

\textit{Cinchona} spp. bark

\textbf{Complementary Adjuncts}

IIb. 1) The inhibition by quinine and/or quinidine of \textit{ethacrynic acid} and 1,3-bis(2-chloroethyl)-1-nitrosourea (\textit{BCNU} or \textit{carmustine}) phase II glutathione S-transferase conjugation by \textit{tumor cells} (in vitro) could lead greater retention of these and increased efficacy of BCNU as an agent against \textit{some cancers} (speculative).\textsuperscript{1547}
CINNAMON  p. 102

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

**Drug Interactions**

I. 1) The extract did not reduce normal blood glucose. In a study of 37 type 2 diabetics taking stable doses of metformin or gliclazide, those taking 3 g/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).

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).

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.

+ 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).

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). 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).

**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).

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.
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

Cola nitida, Cola acuminata seed

Complementary Adjuncts

IIb. 1) The minimum concentration of fluoroquinolone antibiotic drugs ciprofloxacin, perfloxacin, 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 perfloxacin and levofloxacin (in vitro). 3034

COPTIS

Coptis chinensis and Coptis groenlandica rhizomes

Contraindications

II. 1) Do not use in jaundice in newborns or from hemolytic anemia (speculative). 1092

HOWEVER, when coptis rhizome and/or berberine-containing amur cork tree (*Phellodendron amurense*) bark were given in herbal concoctions according to traditional dosage and indication to 20 patients with chronic cytopenic hematological conditions, though 3 patients with thalassemia intermedia had transient elevation of serum bilirubin, there was no associated aggravation of anemia or liver dysfunction (PO in human clinical study). 3108

Drug Interactions

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

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

+ 3) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the bioavailability of CYP 3A4 substrate midazolam by 40% and its maximum plasma concentration by 38%, and significantly decreased its oral clearance by 27% (PO in human study). 3238
4) Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the 8-hour urinary ratio of the CYP 2D6 substrate dextromethorphan to its metabolite dextrorphan by 9-fold (PO in human study).3238

5) Berberine at 900 mg daily in 17 healthy males for 14 days doubled significantly the 8-hour urinary ratio of the CYP 2C9 substrate losartan to its metabolite E-3174 (PO in human study).3228

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).2935 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);2902 berberine and
the combination even significantly reduced plasma ALT concentrations (PO in hamsters).

+ 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).

+ 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.

CORN SILK

\(^\text{NEW}\)

\(^*\) Zea mays stigma

**Complementary Adjuncts**

Ia. 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.

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

CRANBERRY

\(^\text{p. 117}\)

\(^\text{Vaccinium macrocarpon fruit}\)

**Drug Interactions**

Ib. 1) A report on 5 individuals suggested cranberry juice may increase the effects of warfarin (PO in human case series). 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).

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. 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.
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).  

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.

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.  

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.

DAN SHEN  p. 122

Salvia miltiorrhiza root

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 deterpenoid components of dan shen, specifically cryptotanshinone and tanshinone IIA (in vitro).  

+ 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).  

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).  

Testing the extract component diydrotanshinone I showed it inhibits CYP3A, while the dan shen components cryptotanshinone and tanshinone IIA induce CYP3A (in vitro).  

Ib. 1) The effect of anticoagulants can be increased, exemplified by warfarin (PO in human case reports).  

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).

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.

DONG QUAI  
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).

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-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. A decoction of equal parts of the 2 roots given at the same dose was previously shown a decrease in TGF-β1 puromucin-induced nephrosis similar to enalapril (PO in rats), 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).

ECHINACEA ANGUSTIFOLIA  
Echinacea angustifolia roots
(Echinacea, narrow-leaved coneflower, combflower, Sampson root, black Sampson)

Contraindications

1. Allergic hypersensitivity to plants in the Asteraceae family (empirical). 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.
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

**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 antiretroviral 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**
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).

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

ELEUTHERO

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).

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).

ENGLISH PLANTAIN

Plantago lanceolata leaves

Complementary Adjuncts

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

+ 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).

EVENING PRIMROSE

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.

FENUGREEK

Trigonella foenum-graecum seed

Drug Interactions

Ia. 1) Fenugreek hydroalcoholic extract, in type 2 diabetes patients using sulfonylureas or biguanides, or both, significantly decreased HbA1c, lowered fasting and 2-hour postprandial insulin levels, and increased insulin sensitivity, compared to placebo (PO in human clinical study).

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, HbA1c, and clinical symptom scores, compared to controls.

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).
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). 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). 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).

**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.

+ 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.

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). 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.

**FO-TI**

*Polygonum multiflorum* = *Reynoutria multiflora* root

(Chinese knotweed; Ch: he shou wu)

**Contraindications**

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

**FRANKINCENSE**

*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).

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 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

1a. 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 nifedinip 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.\footnote{3093}

In a randomized, placebo-controlled, double-blind 3-month study of 60 patients ages 6-18 years with \textit{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).\footnote{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 \textit{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.\footnote{3333}

\textbf{GARLIC}

\textit{Allium sativum} cloves

\textbf{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).\footnote{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.\footnote{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.\footnote{3089}

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

IV. 1) May enhance cholesterol-lowering agents due to additive effects (speculative).\footnote{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).\footnote{3089}

\textbf{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 antituberculosis 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), due to inhibition of platelet aggregation (**in vitro**). 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).

**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.

**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).

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.

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

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).

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).

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, glycated 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 significant diminished the reductions by atorvastatin of liver superoxide dismutate 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).³⁶³

+ 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

Ginkgo biloba leaves

Contraindications

I. 2) Avoid or use caution in bleeding disorders due to potential association with hemorrhage (PO in human case reports).

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).

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).

II. 1) Do not use before elective surgery (speculative) 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).

Drug Interactions

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

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.

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. Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low in doses of the standardized extract of ≤ 240 mg/day (speculative).

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).

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. Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low in doses of the standardized extract of ≤ 240 mg/day (speculative).

5) Taking 360 mg extract daily for 14 days 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 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). Based on clinical relevance, the pharmacokinetic interaction risk has been assessed as low in doses of the standardized extract of \( \leq 240 \text{ mg/day} \) (speculative).

**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). 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).

5) **Warfarin** use in a 78-year-old woman resulted in intracerebral hemorrhage after the addition of ginkgo for 2 months (human case report).

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 \( \geq 65 \text{ years of age} \) (PO in human study).

+ 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.

+ 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.

**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.

**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.

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. 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 PGFα 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

IIa. + 2) After osteoporosis was induced by administering dexamethasone for 5 weeks, ginkgo standardized extract at 14 mg/kg or more daily significantly increased the percentage of alveolar bone of the mandible and at 28 mg/kg or more daily significantly increased the percentage of trabecular bone in the femur, compared to controls (PO in rats).3147

+ 3) Doses of a standardized extract prepared with phospholipids at 3:1 [phytosome] and given at 100 mg/kg for 30 days helped protect against heart damage induced in the last 2 days by 2 doses of subcutaneous isoproterenol at 85 mg/kg (PO in rats). The extract significantly increased cardiac levels of glutathione and the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, as well as reducing the lipid peroxidation marker malondialdehyde in the heart and cardiac damage markers AST, LDH, and CPK in the serum.3185

+ 4) The ototoxicity caused by excessive gentamicin including auditory brain stem response threshold, cochlear hair cell damage ratio, and apoptosis was prevented with 100 mg/kg of EGb 761 for 2 days prior plus concurrently (PO in guinea pigs). The protection was believed to be due to a reduced formation of reactive oxygen species and nitric oxide-related mechanism as shown in cultured cochlear cells (in vitro).3260

+ 5) When 30 mice received 2 mg/kg cisplatin twice weekly for 9 doses, half were also given about 100 mg/kg EGb761 daily in the drinking water, and comparisons were made for cisplatin-induced peripheral neuropathy (PO in mice). A control and ginkgo-only group were also monitored. The cisplatin plus ginkgo group had significantly less reduction in nerve conduction velocity and dorsal root ganglia growth retardation than the cisplatin-only group. The ginkgo-only group was similar to controls in these outcomes.3373

GOLDENSEAL p. 182

*Hydrastis canadensis roots/rhizome

Contraindications

II. 1) Do not use in jaundice in newborns (speculative).777,1890

HOWEVER, when berberine-containing herbs were given in herbal concoctions according to traditional dosage and indication to 20 patients with chronic cytopenic hematological conditions, though 3 patients with thalassemia intermedia had transient elevation of serum bilirubin, there was no associated aggravation of anemia or liver dysfunction (PO in human clinical study).3108

Drug Interactions

Ia. 1) A dose of 2.7 gram goldenseal extract daily for 28 days inhibited metabolism of CYP3A4 substrate midazolam by 40% in 12 healthy subjects (PO in human study).1807 Berberine at 300 mg 3 times daily for 14 days in 17 healthy males significantly increased the bioavailability of CYP 3A4 substrate midazolam by 40% and its maximum plasma concentration by 38%, and significantly decreased its oral clearance by 27% (PO in human study).3238 Also, 3.97 gram of the root extract delivering 132 mg hydrastine and 77 mg berberine per day for 14 days significantly [Note CORRECTION: not "reduced"] INCREASED midazolam bioavailability in 16 healthy subjects (PO in human study).2501 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).

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).

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).

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).

II. +

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).

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).2932

+ 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  
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.\textsuperscript{3124}

**GUARANA**

*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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{2921}

**HAWTHORN**

*Cranegus* 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.\textsuperscript{3344}

**HOPS**

*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.\textsuperscript{2634}
HORSE CHESTNUT  
*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 1β (*in vitro*).2837

JUJUBE  
*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 (*Porzia 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  
*Piper methysticum* rhizomes and root

**Contraindications**

I. 1) Avoid operating a motor vehicle following excessive use of kava.244,728

HOEVER, 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 supraphysiologi 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.2706 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 IC_{50} 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**

*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**

*Picrorhiza kurroa* rhizome/roots

**Complementary Adjuncts**
IIa. + 4) The iridoid glycoside fraction of the ethanolic fraction of kutaki at 12 mg/kg daily for 15 days with ethanol reduced the hepatotoxicity from the concurrent and prior 30 days of alcohol consumption, compared to the alcohol consumption alone (PO in rats). The extract group had significant increases in liver acetaldehyde dehydrogenase for alcohol metabolism, as well as the antioxidant enzymes superoxide dismutase, catalase, peroxidase, and glutathione-S-transferase. The extract-fed rats also had significantly lower hepatic GGT, acid phosphatase, lipid peroxides, and bilirubin, among other indicators. Significant reductions in serum enzyme activities for the extract group included ADH, GGT, AlkPhos, GOT, and GPT and serum chemical markers bilirubin and triglycerides.2936

+ 5) The iridoid glycoside fraction of the ethanolic fraction of kutaki, given at 1 mg/kg for 14 days prior to experimental malaria infection with multidrug-resistant Plasmodium yoelii subsequently treated for 3 days with suboptimal intraperitoneal dose of chloroquine, resulted in effective treatment based on survival and parasitic load, compared to treatment failure using chloroquine without the extract pretreatment (PO in mice). Extract use for 14 days was shown to enhance immune response by significantly increasing ovalbumin antigen-induced T-cell proliferation and activation and antigen-specific antibody production, compared to controls.2937

+ 6) The combination of 2 iridoid glycosides, 1 part picroside-I and 1.5 parts kutkoside, given for 7 days at 6 mg/kg blocked the hepatotoxicity of acetaminophen (paracetamol) given after day 7ethinylestradiol 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) 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. 

LICORICE

*Glycyrrhiza glabra [or Glycyrrhiza uralensis] root/rhizome

Contraindications

4) Avoid use in pregnancy, especially excessive intake.

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). 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.

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.

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.

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). [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). 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_\text{A}-\text{BZD} receptor by 98% at 10 mg/ml (in vitro).

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.

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.

IIa. 3) Coating ibuprofen with licorice extracts reduced stomach ulcers and lowered the ulcer index compared to use of ibuprofen alone (PO in rats). 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).

LOBELIA  
*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).

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. 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.

LONG PEPPER  
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).

Complementary Adjuncts

Ia. 1) Piperine increased serum concentrations of curcumin and increased curcumin bioavailability by 2000% (PO in human study). 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).

IIa. 1) Piperine at 70 µmol/kg increased plasma bioavailability of the chemopreventive agent epigallocatechin gallate [EGCG] in green tea by 1.3-fold when given concurrently compared to EGCG given alone (PO in mice). Piperine also increased the maximum plasma concentration of EGCG by inhibiting glucuronidation in mice intestines by 40%. Likewise, the gluruonidation 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

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

IIa. + 1) The ascites, oxidative stress, and cardiotoxicity produced by the chemotherapy agent doxorubicin weekly for 3 weeks was significantly reduced by prior and ongoing daily consumption of lycium berry decoction (PO in rats). Mortality was lowered from 38% to 13%, the cardiotoxicity showed significant reduction in conduction abnormalities, loss of heart muscle, and arrhythmia, while the significantly increased superoxide dismutase and lowered lipid peroxidation and serum AST demonstrated less oxidative stress in those given lycium extract. Lycium extract did not interfere with doxorubicin cytotoxicity (in vitro).3629

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

*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). 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.

MAITAKE

*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.

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.

MILK THISTLE

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

Ib. 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. 

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

III. 2) S(-)-warfarin 7-hydroxylation by CYP 2C9 was competitively inhibited by silybin (in vitro).

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.

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).

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).

Silymarin use following ethanol hepatotoxicity helps normalize lab indices for transaminases (PO in human clinical studies). 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).

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).

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).

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.

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

**OAT**

*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).

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).

**OLIVE**

*Olea europaea* fruit oil

**Complementary Adjuncts**

Ia. 1) Consumption of 3-4 spoonsful of extra virgin olive oil daily for 6 months compared to safflower oil in a crossover study led to significant reductions in the use of high blood pressure medications including atenolol, nifedipine, lisinopril, doxazosin, and hydrochlorothiazide (PO in human clinical study). [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.

**OREGON GRAPE**

*Mahonia* spp. root bark

**Contraindications**

I. 5) [Note CORRECTION: This item should be listed as 3) under DRUG INTERACTIONS la. on the next page (p. 255). See below.]

II. 3) Avoid in jaundice in newborns or from hemolytic anemia or unconjugated hyperbilirubinemia as Gilbert’s syndrome and Crigler-Najjar syndrome (speculative).

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).
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.

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). 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).

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). 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).

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). 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). 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. The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats); berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).

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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). 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). 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. The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats); berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).

+ 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). 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.
PASSION FLOWER  
*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  
*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  
*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 pentobarbiton 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**

*Punica granatum* fruit

**Drug Interactions**

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) and in rats**, 3112, 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, in vitro),** 1920,1923,1925 [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.]**

   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) and in rats, 3112, 3245, when 250 ml of pomegranate juice or a single pomegranate extract capsule 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

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

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

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

   2) **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) 1920,1923,2213 in rats 1920.

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

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

   **HOWEVER,** despite also inhibiting the metabolism of CYP 2C9 drug substrates (in vitro) and in rats, 3112, 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).\textsuperscript{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.\textsuperscript{2602}

HOWEVER, despite inhibiting the metabolism of CYP 2C9 drug substrates (\textit{in vitro} \textsuperscript{3112,3245} and in rats \textsuperscript{3112}), 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).\textsuperscript{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).\textsuperscript{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).\textsuperscript{3153-3155} This includes a reduction of the liver fibrotic markers,\textsuperscript{3153} improved body weight and circulatory antioxidant status,\textsuperscript{3154} decreased lipid levels,\textsuperscript{3154,3155} and reduced plasma AST, ALT, and peroxidative markers.\textsuperscript{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.\textsuperscript{3381}

PRICKLY PEAR p. 269

\textit{Opuntia} spp. stems/pads and fruit

Drug Interactions

Ia. 1) Heated and unheated stems of the species \textit{Opuntia ficus-indica} given at a dose 500 gm to 8 type diabetics receiving glibenclamide (glyburide) lowered blood sugar after 2-3 hours (PO in human clinical study).\textsuperscript{351}

\textit{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).\textsuperscript{2826}

PSYLLIUM p. 270

\textit{Plantago psyllium} = \textit{Plantago afra} and \textit{Plantago ovata} = \textit{Plantago ispaghula} seed or seed husk

Complementary Adjuncts
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)**

*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**

IIa. +

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 H\(_2\) 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**

*Rubus idaeus* leaves

**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, improved body weight and circulatory antioxidant status, decreased lipid levels, and reduced plasma AST, ALT, and peroxidative markers.\(^{3155}\)

**ROMAN CHAMOMILE**

*Chamaemelum nobile* = *Anthemis nobilis* flowers and herb

**Complementary Adjuncts**

IIa. +

1)
**Contraindications**

I. 1) Avoid in pregnancy, due to the emmenogogue and abortifacient effects of the flower and of the plant (empirical) and its volatile oil. 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.\(^{3078}\)

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**ROSEMARY**

*Rosmarinus officinalis* leaves

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**SAFFRON**

*p. 278*

*Crocus sativus* stigma

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**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.\(^{3464}\)

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**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**

IIa. + 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).

**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 ginsengsides [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.

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.

**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.

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. 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.\(^{3419}\) A tablet with 320 mg saw palmetto extract, 200 mg \textit{Lactobacillus sporogenes}, and 100 arbutin was given daily for 30 days to 77 men with \textit{chronic bacterial prostatitis} together with 600 mg/day the antibiotic \textit{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.\(^{3414}\)

\textbf{SCHISANDRA} \hspace{1cm} p. 281

\textit{Schisandra chinensis} fruit

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

\textbf{Drug Interactions}

Ia. 1) When 12 subjects took 600 mg extract daily for 14 days, it significantly increased \textit{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% deoxyxchizandin, and 1.8% \(\gamma\)-schizandrin inhibits intestinal CYP 3A4 metabolism of \textit{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 \textit{(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 \textit{(in vitro)} and the least concentrated in the liver (PO in rats), while schisadrol A was the least potent \textit{(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 \textit{erythromycin} and \textit{testosterone} and irreversibly inactivates it in a time- and concentration-dependent manner \textit{(in vitro)}.\(^{2946}\)

\textbf{SCOTCH BROOM} \hspace{1cm} p. 282

*Cytisus scoparius syn. \textit{Sarothamnus scoparius} tops

\textbf{Complementary Adjuncts}

Ia. 1) In a randomized, placebo-controlled, double-blind trial to stop \textit{smoking tobacco}, placebo or cytisine from \textit{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-HT2C receptor by 88% at 10 mg/ml (*in vitro*).3127

SOUTHERN SCHISANDRA

"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 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.2837

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.

ST. JOHN’S WORT

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

STINGING NETTLE

_Urtica dioica_ leaf [not the root]

Contraindications

I. 1) Excessive internal use should be avoided in pregnancy, especially in early pregnancy, due to its emmenagogue effect when prepared as a decoction of the plant (empirical). Uterine stimulant activity has been shown with its constituent serotonin (in vitro).

II. 2) Avoid use in brittle diabetes (speculative).

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). 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).

Complementary Adjuncts

Ia. 1) Stewed leaf enhanced the effect of diclofenac when given to 19 acute arthritis patients (PO in human clinical trial).

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 [paracetemol] 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.

_Urtica dioica_ root

Complementary Adjuncts

Iia. 1) A hydroalcoholic root extract at 10 mg/kg daily in animals exposed to nicotine for 28 days significantly increased the sperm motility, count, and normal morphology, seminiferous tubule diameter, and testosterone levels compare to nicotine-only controls (IP in mice). At 20 mg/kg daily of root extract with nicotine, the testis weight was also significantly increased in comparision 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.

SWEET ANNIE

_Artemisia annua_ herb

Complementary Adjuncts

Ilb. 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).
SWEET CHERRY
\( \text{Prunus avium} \) 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 (\( \text{Prunus cerasus} \)) 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 (\textit{in vitro}). The anthocyanins with fewer sugar moieties had the greater antioxidant and COX-inhibiting activities.\(^{3301}\)

TART CHERRY
\( \text{Prunus cerasus} \) 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.\(^{3580}\) Anthocyanin pigments from both tart cherries and sweet cherries (\( \text{Prunus avium} \)) 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 (\textit{in vitro}). The anthocyanins with fewer sugar moieties had the greater antioxidant and COX-inhibiting activities.\(^{3301}\)
IIa. 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 mcmol/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  
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 buspirone (PO in human study).2810

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

+ 18) A randomized, crossover study of consumption of 700 ml green tea or water daily for 14 days by 10 healthy volunteers, followed by a single oral dose of the antihypertensive beta-blocker drug nadolol, led to significant decreases in plasma maximum concentration and bioavailability (PO in human study). In addition, the systolic blood pressure effect of nadolol was significantly reduced by the green tea. Nadolol was shown to be a substrate of organic ion-transporting polypeptide (OATP)1A2 (in vitro), so based on the pharmacokinetics it is likely that green tea inhibits OATP1A2 in the intestines.3388
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).\textsuperscript{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.\textsuperscript{3752}

IIa. 1) Black tea for 7 days reduced stomach ulcers produced by ethanol (alcohol) (PO in rats).\textsuperscript{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.\textsuperscript{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).\textsuperscript{3150}

IIb. + 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).\textsuperscript{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.\textsuperscript{3397}

IIb. + 3) In ER\textsuperscript{a} 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 \textit{(in vitro)}.\textsuperscript{3468}

When 25 \textmu M EGCG was combined with 5 \textmu M raloxifene, ER-negative [ER\textsuperscript{a}] MDA-MV-231 human breast cancer cells were significantly reduced by 96% after 7 days, compared to controls \textit{(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.

TEA TREE

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.

THUNDER GOD VINE

*Tripterygium wilfordii peeled root

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

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

   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.3281

   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 TFIIB 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.

TULSI

*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.

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 polydypsia, 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. 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), 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-amylace (in vitro).

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).

Complementary Adjuncts
Ila. 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.

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.

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.

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. 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.  

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). 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. 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.  

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.  

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).  

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).  

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).  

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 atenolol (PO in human study). The mechanism was unclear due to the small dose and group and short duration.  

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 give 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. 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-1β, 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. 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 that the 19% on placebo. The average naproxen usage with curcuminoids was 250-500 mg daily, compared to 500-750 mg daily with placebo.

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.

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. 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).

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, antitherapeutics, 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.

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.\textsuperscript{2995}

+ 6) When 1 gram of a lecithinized formulation of curcumin was given for 4 weeks to 25 \textit{diabetes type 2} patients on \textit{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).\textsuperscript{3097}

+ 7) In 45 \textit{rheumatoid arthritis} patients, groups were randomly selected to receive 500 mg curcumin, 50 mg of \textit{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.\textsuperscript{3103}

+ 8) In a randomized, observer-masked study of 45 patients with major \textit{depression}, curcumin at 1000 mg daily for 6 weeks with a response rate of 62.5% was equivalent to the response to 20 \textit{mg of fluoxetine} of 64.7%, but the combination was most effective at 77.8%, though the differences were not statistically significant (PO in human clinical study). The investigators ranked responses as good or excellent for 70.5% of those on fluoxetine, 75% on curcumin, and 83.3% on both. The medications were well tolerated.\textsuperscript{3103}

+ 9) When a lecithinized formulation of curcuminoids was given in 100 mg doses 3 times daily with meals to cancer patients with \textit{chemotherapy AE} [adverse effects] from 51% using \textit{5-fluorouracil} for colorectal or gastric cancer, 11% using 5-fluorouracil and \textit{cisplatin} for genitourinary cancers, 6% using \textit{vinblastine} and CCNU for kidney cancer, 23% using cisplatin and \textit{gemcitabine} for lung cancer, and 9% using \textit{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).\textsuperscript{3348}

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\textsuperscript{61.5\%}, the quality of life was significantly increased along with significant decreases in markers of \textit{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 \textit{topotecan-cyclophosphamide-etoposide} or cyclophosphamide-\textit{methotrexate} for breast cancer, \textit{docetaxel-cisplatin}-5-fluorouracil for gastric cancer and breast cancer, and 5-fluorouracil regimens for colorectal cancer.\textsuperscript{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 \textit{oral mucositis} induced by \textit{chemotherapy} with \textit{carboplatin}, \textit{cisplatin}, or \textit{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.\textsuperscript{3485}
IIa. + 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.\textsuperscript{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 IkBα 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).\textsuperscript{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.\textsuperscript{3119} As shown by plasma levels and a reduction in biomarkers such as PGE$_2$, curcumin doses of 3.6 grams daily are recommended for cancers outside of the gastrointestinal tract (PO in human clinical study),\textsuperscript{2785} though another study showed negligible distribution outside the gut after 7 days at this dose (PO in human clinical study).\textsuperscript{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).\textsuperscript{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).\textsuperscript{2877}

+ 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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{3122}
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. 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).

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.

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).

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 xenograftic colon tumors (IV in mice). 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).

In 5 of 15 patients receiving the extract this disease remained radiologically stable for the 2-4 months of treatment. Of those 15 patients receiving the curcumin one became nauseous with 450 mg and another had diarrhea with 900 mg. Curcumin has been found in colon mucosa in levels sufficient to explain its pharmacological activities (PO in rats), including in malignant colorectal tissue after 3.6 grams of curcumin have been taken daily for 7 days (PO in human clinical study). Evidence (in vitro and PO in human clinical trials) suggests curcumin may be useful in colon cancer chemoprevention (speculative).

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**VALERIAN**

*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.\textsuperscript{2634}

**WILD YAM**

*Dioscorea villosa* root

**Contraindications**

I. 2) Avoid use in **liver disease** such as **viral hepatitis**, **toxic hepatitis**, or **cirrhosis** (empirical).\textsuperscript{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).\textsuperscript{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).\textsuperscript{2979}

**YOHIMBE**

*Pausinystalia yohimbe = Corynanthe yohimbe* bark

**Contraindications**

I. 1) Do not use in **schizophrenia**,\textsuperscript{76,184} since psychotic episodes can be induced by its alkaloidal constituent yohimbine (IV in human clinical study).\textsuperscript{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).\textsuperscript{2766}

3) Avoid use during **anxiety**,\textsuperscript{344} due to its exacerbation by the alkaloidal component yohimbine (PO and IV in human clinical studies).\textsuperscript{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).\textsuperscript{2766}

4) Do not use in **high blood pressure**,\textsuperscript{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).\textsuperscript{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).\textsuperscript{2766}

8) The conditions of **angina pectoris** and other **heart disease** produce greater risk with yohimbine (PO in human studies).\textsuperscript{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).\textsuperscript{2766}
HERBALS TO BE USED WITH CAUTION

A.8 Bioactivations of Phytochemical Procancerogens 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 of 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 procancerogens, 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 procancerogens 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)

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Common Herb</th>
<th>Activators</th>
<th>Metabolite Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>aristolochic</td>
<td>Aristolochia *(Aristolochia spp.) herbs</td>
<td>CYPs 1A1/2, 2A6</td>
<td>kidney</td>
</tr>
<tr>
<td>carcinogens,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acids</td>
<td>Wild ginger *(Asarum canadensis) rhizome</td>
<td>1A</td>
<td>kidney toxins</td>
</tr>
<tr>
<td>1A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[1A2792]
estragole \[150,579,760\] Basil (*Ocimum basilicum*) herb \[150,400\] CYPs 1A2,2A6, liver

Basil (*Ocimum basilicum*) herb \[150,400\] CYPs 1A2,2A6, liver

Fennel (*Foeniculum vulgare*) seeds \[150,400\] 2C19,2D6,2E1; mutagenic \[2820\]

Tarragon (*Artemisia dracunculus*) leaf \[150,400\] STs \[2792\]

methyl-

Asarabacca (*Artemisia dracunculus*) leaf \[150,400\] STs \[2792\]

Teucrin A \[3A4 \[2792\]

eugenol Am. pennyroyal *(Asarum canadensis)* rhizome \[150,2792\] CYPs \[643\] 1A2, liver

Eur. pennyroyal *(Mentha pulegium)* \[150,2792\] 2C19, 2D6; pyrrolizidine

Borage herb *(Borago officinalis)*, \[150\] CYPs

alkaloids Comfrey plant *(Symphytum officinale)*, \[150,2792\] 3A4 \[1183\]

Gravel root *(Eupatorium purpureum)*, \[2792\]

Rattlebox herb *(Crotalaria spp.)*, \[2792\]

Tansy ragwort herb *(Senecio jacobaea)* safrole Sassafras *(Sassafras albidum)* root bark \[150\] CYPs \[2819\] 2A6, liver

Sassafras *(Sassafras albidum)* root bark \[150\] CYPs \[2819\] 2A6, liver

mutagenic \[2820\]

STs \[2792\]

teucrin A Germander (*Teuchrium chamaedrys)* \[2822\] CYP

Germander (*Teuchrium chamaedrys*) \[2822\] CYP

liver toxin \[1516,1517,1518\]
Appendix B
HERBAL-DRUG INTERACTIONS
[Note CORRECTIONS: In Appendices B and E in the first 100 copies of the book, asterisks (*) are missing in front of the scientific Latin names for a number of listed herbs designated with * in the main body of the text as containing potentially toxic compounds. (For example, European pennroyal 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 anuum) – iron2807
Tea (green) leaves [EGCG] (Camellia sinensis) – sunitinib3210

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) – saquinavir3223
St. John’s wort flowers/leaves (Hypericum perforatum) – methadone1641

B.1.1.e Selective Inhibition of Absorption likely by Inhibiting OATP-B and/or -A
Apple fruit juice (*Malus domestica*) – **aliskiren** (2B1),

Blueberry fruit (*Vaccinium* spp.) – glibenclamide

Milk thistle seeds pc silymarin (*Silybum marianum*) – rosvastatin (ooocytes-1B1) [not rosvastatin]

Orange fruit juice (*Citrus sinensis*) – **aliskiren** (2B1)

Tea green leaves (*Camellia sinensis*) – **nadolol**, nadolol (kidney - 1A2)

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

Cranberry fruit juice (*Vaccinium macrocarpon*) – **cefator** (s)

**B.1.2 Enhancement of Absorption** p. 368

**B.1.2.a General Absorption Enhancement by Pungent Herbals**

Black pepper fruit (*Piper nigrum*) – calcium, iron, zinc

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

Ginger rhizome (*Zingiber officinale*) – calcium, iron, zinc

Long pepper fruit (*Piper longum*) – calcium, iron, zinc

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

African mistletoe leaves (*Tapinanthus sessilifolius*) – digoxin (intestine)

Barberry bark c berberine [at oral dose of 30-60 mg/kg] (*Berberis* spp.) – cyclosporine, digitalis (intestine), ketoconazole (intestine)

Bitter leaf leaves (*Vernonia amygdalina*) – digoxin (intestine)

Coptis rhizome c berberine [at oral dose of 30-60 mg/kg] (*Coptis chinensis*) – cyclosporine, digitalis (intestine), ketoconazole (intestine)

Garlic clove *(Allium sativum)*

Aged garlic c extract and c S-allyl cysteine – c cisplatin (kidney), saquinavir [opposite for darunavir] (liver), c rhodamine 123, c rhodamine 123, c digoxin, hydrochlorothiazide [opposite for glibenclamide] (intestine)

Ginger rhizome c 6-gingerol (*Zingiber officinale*) – digoxin (colon, kidney)

Ginkgo leaves (*Ginkgo biloba*) – raltegravir (intestine), talinolol (intestine), talinolol (intestine) [not fexofenadine], talinolol (intestine)

Goldenseal roots/rhizome c berberine [at oral dose of 30-60 mg/kg] *(Hydrastis canadensis)* – cyclosporine, digitalis (intestine), ketoconazole (intestine)

Licorice root pc glabridin, c glycyrrhetinic acid (*Glycyrrhiza glabra*) – daunorubicin, vinblastine

Lobelia herb c lobeline (*Lobelia inflata*) – rhodamine-123, doxorubicin (colon, leukemia)

Milk thistle seeds pc silymarin (*Silybum marianum*) – talinolol (intestine) [not digoxin]

Mulberry twigs pc morin (*Morus alba*) – paclitaxel (intestine)

Nan wu wei zi fruit (*Schisandra sphenanthera*)

– **tacrolimus** (intestine), paclitaxel (intestine), tacrolimus (intestine), tacrolimus (colon)

Onion bulbs c quercetin (*Allium cepa*) – fexofenadine, paclitaxel (intestine)

Oregon grape root bark c berberine [at oral dose of 30-60 mg/kg] (*Mahonia* spp.) – cyclosporine, digitalis (intestine), ketoconazole (intestine)

Papaya leaves (*Carica papaya*) – digoxin (intestine)

Schisandra fruit lignans or c schisandrin B (*Schisandra chinensis*) – talinolol (intestine), daunorubicin (leukemia, epidermoid carcinoma, breast cancer MCF-7 & Bcap37), doxorubicin (leukemia, epidermoid carcinoma), epirubicin (leukemia, epidermoid carcinoma), homoharringtonine (leukemia, epidermoid carcinoma), hydroxyamphotericin (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)\textsuperscript{2831}

Soy beans pc genistein (Glycine max) – paclitaxel (intestine)\textsuperscript{2833}

Tea green leaves pc catechins/EGCG (Camellia sinensis) – doxorubicin (intestine), \textsuperscript{3207} nicardipine (intestine), \textsuperscript{3209} tamoxifen (intestine), \textsuperscript{3206} verapamil (in testine), \textsuperscript{208}

Turmeric root tincture or pc curcumin (Curcuma longa) – celiprolol (intestine), \textsuperscript{2777} calcein-AM (colon), \textsuperscript{2777} daunorubicin (colon), \textsuperscript{2777} digoxin (colon), \textsuperscript{2779,2780} tamoxifen (intestine), \textsuperscript{3207} nicardipine (intestine), \textsuperscript{3209} tamoxifen (intestine), \textsuperscript{3206} verapamil (intestine), \textsuperscript{208}

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 \textsuperscript{3435}. 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. \textsuperscript{1806}

5. While curcumin has consistently shown inhibition to Pgp in vitro \textsuperscript{2777,2779,2780} and in an in vivo study in rats, \textsuperscript{2777} daunorubicin (colon), \textsuperscript{2777} digoxin (colon), \textsuperscript{2779,2780} an and (kidney), \textsuperscript{2779} rhodamine-123 (colon) \textsuperscript{2777,2780} [See Note 5.]

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

Chinese rhubarb root (Rheum palatum) – phenytoin (kidney MRP2) \textsuperscript{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. \textsuperscript{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) – fexofenadine \textsuperscript{3099}

Ginkgo leaf extract (Ginkgo biloba) – digoxin, \textsuperscript{3225} fexofenadine \textsuperscript{3228}

B.1.3.b No Effect on OATP transport

Garlic clove c allicin *(Allium sativum) – pravastatin \textsuperscript{3223}

B.3 Potentiating Sedative or Tranquilizing Medicines p. 373

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

B.3.1 Hypnotic and/or Anxiolytic Drug Enhancement

Licorice root (Glycyrrhia uralensis) B, BDZ \textsuperscript{3127}

Passion flower herb (Passiflora incarnata) \textsuperscript{2879} \textsuperscript{3207}

Peppermint leaf oil (Mentha piperita) B \textsuperscript{3113}

Purple passion fruit leaves (Passiflora edulis) B \textsuperscript{3052}

Southern schisandra fruit (Schisandra sphenanthera) B \textsuperscript{2074}
Silk tree bark (Albizia julibrissin) B, A, O
Tulsi leaves (Ocimum tenuiflorum = Ocimum sanctum) B

B.4 Modifying Blood Sugar In Diabetics p. 374

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

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. 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 Herbs p. 375

Bitter melon fruit (Momordica charantia) j(t2)
Cayenne fruit *(Capsicum frutescens) – h(h1)
Chirata herb (Swertia chirayita)
Fenugreek seeds (Trigonella foenum-graecum) – h(t1)
[Note CORRECTION: the superscript after h(t1) is "1646", not 1645.]
Gulancha stem (Tinospora cordifolia)
Gymnema leaves (Gymnema sylvestre)
Gynostemma herb (Gynostemma pentaphyllum) – e(t2)
Indian stinging-nettle herb (Tragia involucrata)
Ivy gourd herb (Coccinia indica)
Jambolan seeds (Syzygium cumini = Eugenia jambolana)
Kino heartwood (Pterocarpus marsupium)
Moringa stem bark \((\textit{Moringa oleifera})\)\(^{3217}\)
Prickly pear stems \((\textit{Opuntia} \text{ spp.})\)\(^{3226}\)
Tulsi herb \((\textit{Ocimum tenuiflorum} = \textit{Ocimum sanctum})\)\(^{3187,3188,3189,3219}\)

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

Cassia bark extract \((\textit{Cinnamomum cassia})\) – **metformin** and/or **sulfonylureas**\(^{1900,2758}\) including **gliclazide**\(^{3244}\)
Fenugreek seeds \((\textit{Trigonella foenum-graecum})\) – **glyburide** (glibenclamide)\(^{130}\) and/or **metformin**\(^{961,1645}\) and/or **glipizide**; \(^{1645}\) **sulfonylureas** and/or **biguanides**\(^{1360}\)
Garlic cloves \((\textit{Allium sativum})\) – **metformin**\(^{3089}\)
Gynostemma herb \((\textit{Gynostemma pentaphyllum})\) – **gliclazide**\(^{3237}\)
Maitake mushroom fruiting bodies \((\textit{Grifola frondosa})\) – **glyburide**, **glipizide**, **metformin**\(^{1609}\)
Milk thistle fruit \((\textit{Silybum marianum})\) – **glyburide** (glibenclamide), **metformin**\(^{2041}\)
Psyllium seed husks \((\textit{Plantago ovata})\) – **glyburide** (glibenclamide), \(^{2798}\) **metformin**, \(^{2799}\) oral **hypoglycemics**, \(^{2803}\) **sulfonylureas**, \(^{2808}\) **tolbutamide**\(^{2798}\)
Royal sun agaricus mushrooms \((\textit{Agaricus blazei})\) – **gliclazide**, **metformin**\(^{2215}\)
Tulsi seed \((\textit{Ocimum tenuiflorum} = \textit{Ocimum sanctum})\)
– **chloropropamide**, **glibenclamide**, **glipizide**, **penformin**\(^{3308}\)

**B.5 Modifying the Effects of Anticoagulants** p. 379

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 \textit{in vitro} and \textit{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 \textit{in vitro} \((\text{I})\) to test an extract/fraction \((\text{e})\) or one or more isolated components \((\text{c})\). \textit{In vivo} \((\text{V})\) 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 \textit{in vivo} studies or human case reports to possibly induce a reduction in the metabolism and/or enhancement of the effect of **warfarin** \((\text{W})\), **heparin** \((\text{H})\), or **antiplatelet drugs** \((\text{AP})\).

**B.5.1 Increasing Potential for Hemorrhage** p. 382
**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\(^{3450}\)
- Ma-kombu thallus (*Laminaria japonica*) Ic, 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, 2961,2964,3128,3258,3257, 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*) Ic\(^{3128}\)
- Ginger root (*Zingiber officinale*) HSh\(^{3449}\)
- Grape seed (*Vitis vinifera*) Ie\(^{3128}\)

**B.5.2 Increasing Potential for Coagulation**

p. 385

**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**

p. 387

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 4α determines the liver’s PXR and CAR induction of CYP3A4. Known CAR-mediated inducers of CYP3A4 are the praeeruptorins 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 1A (bilirubin, estradiol, etoposide), 1A4 (imipramine, midazolam, trifluoperazine), 1A6 (naphthol, serotonin), 1A9 (propofol, phenylbutazone), 2B7 (morphine, 3'-azidothymidine, naloxone), and 2B15 (S-oxazepam).

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 5α-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] – cc3298

7-ethoxyresorufin [1A1/2] – ; Co3290

2B1/2/6

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

**Drugs**: rosuvastatin –

phenytoin – Gc3284

warfarin – be3232

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

estradiol – Bl, By, ea3082

testosterone – Co3290

**Procarcinogens**: benzo[alpyrene [1A1] – ep3201

Conversion/Clearance Inhibitors (Increase Bioavailability)

(Ao) Aloe gel (Aloe vera) – 2C113947

(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, 3A43208

(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-C3224 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, 3A43204
myricetin as in tea (black and green) leaves (Camellia sinensis), parsley leaves (Petroselinum sativum), cranberry fruit/juice (Vaccinium macrocarpon), etc. – OATP-C3224

myristicin from parsley leaf oil (Petroselinum sativum), nutmeg seed (*Myristica fragrans), etc. – 1A1, 1A2, 2B1, 329

naringenin as in grapefruit fruit juice (Citrus paradisi) – OATP-C3224

silymarin/silibinin from milk thistle seeds (Silybum marianum) – OATP-C3224

Conversion/Clearance Inducers (Reduce Bioavailability)

Andrographis leaves (Andrographis paniculata) – 1A1, 2B2975

baicalin/baicaelein and other Chinese skullcap flavones (Scutellaria baicalensis) – OATP-1B1(*1b/*1b or*1b/*15)3232

Coleus root (Coleus forskohlii) – CYP 1A1/2, 2B, 2C, 3A1290; GST3290

Echinacea purpurea tops (Echinacea purpurea) – OATP-B; 1A1, 2D12978

Fenugreek seed (Trigonella foenum-graecum) – CYP 2B11, 3A43284

Ginkgo leaf extract (Ginkgo biloba) – OATP-B; 1B1(*1b/*1b or*1b/*15); PXR; 2B6, 3A4; UGT3192

ginkgo flavonol aglycones in ginkgo leaves (Ginkgo biloba) – CYP 1A2; UGT1A1; CYP2B6 (bupropion)762; GST-P1, 3226; UGT-1A1; 3044

ginkgo flavonol aglycones in ginkgo leaves (Ginkgo biloba) – liver; 3044

Ginkgo flavonol aglycones in ginkgo leaves (Ginkgo biloba) – liver; 3044

ginkgolides from ginkgo leaf (Ginkgo biloba) – liver; 3044

Kava root (Piper methysticum) – 1A2, 2B1, 3A13362 [Note 10.]

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,7035 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, 1327,1733 1733 1327,1733 2C19, 2568 2D6, 1327, 3A4, 1327,1475,1577,1733 4A9/11 1327 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) – liver

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

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

Receptor inhibitors

Qian hu (Peucedanum praeruptorum) root3334

Guggul (Commiphora mukul) resin2111,2112
B.7.2 Influences of Herbal Agents in Phase I on Specific Cytochrome P450 Isozymes  p. 405

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

**Probes:** 7-methoxyresorufin – cc\(^{2938}\) ; Co\(^{3290}\), gi, pi\(^{3129}\)

**Drugs:** caffeine – ; rs\(^{2970}\), SJ\(^{1328}\)

**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  p. 408

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

(bb) berberine as in barberry (*Berberis vulgaris*), coptis (*Coptis spp.*), goldenseal *(Hydrastis canadensis)*, and Oregon grape (*Mahonia spp.*) roots/barks – caffeine\(^{3238}\)

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

(La) English lavender flowers (*Lavandula angustifolia*) – caffeine\(^{3303}\)

(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – caffeine\(^{2810}\)

**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 – Am\(^ {2887}\)

**Drugs:** chlorzoxazone – ts\(^{2770}\)

**Procarcinogens:** NMBA (N-nitrosomethylbenzylamine) – Bp\(^{2460}\)

**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%, but in 12 healthy elderly the same preparation and dosage increased chlorzoxazone metabolism by only 28%.

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

**Probes:**
- 7-benzyloxy-4-(Fl1Me)coumarin – cc2938
- 7-benzyloxyquinoline – cc2938
- 7-benzyloxyresorufin – cc2938
- dibenzylfluorescein – cc2938
- luciferin 6’benzyl ether – sc2771

**Drugs:**
- atorvastatin – r2070 Tc2810
- buspirone – rs9070
- efavirenz – Gb3392
- erythromycin – Gf2540 sc2946
- finasteride – ; SJ3113
- midazolam – ; SJ1641
- nevirapine – pp3132
- nicardipine – ep3209
- nifedipine – Gb3229
- tamoxifen – Pp3111
- paclitaxel – ; SJ1972
- sirolimus – ; SJ3144
- tacrolimus – Gf3124 Ss,2830 Ss,2828,2830 Ss,2829
- tamoxifen – ep3206

**Steroids:**
- testosterone – cm,2778 cc,2279 Ds,3425 ep,3201 gn,2779 Pm,3113 Sc,Sc,2832 Sl,1923 Ss,3136 Tc,3202 Wg,1885 ;
- Ds,3425,3443 Ep,3099 Gb,3135 Gs,2

**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’swort 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
CYP3A41210
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 CYP3A4,3233
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, while 1.5 gm failed to alter the 1-hour postdose ratio of metabolite to drug for midazolam in 2 human studies. 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%. However, 240 mg standardized ginkgo failed to alter the metabolism of CYP3A4 substrate midazolam in humans. 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. 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, 2 doses prior to midazolam had no effect on midazolam clearance in healthy humans.2213

19. Though a green tea catechin extract supplying 844 mg catechin daily for 14 days to 11 healthy humans did not affect alprazolam metabolism,1710 use of a green tea catechin extract supplying 800 mg EGCG daily for 4 weeks to 42 healthy human subjects led to a 20% increase in buspirone bioavailability, but this change was not deemed clinically significant.2810 The inhibition effect of green tea extract with 60%+ catechins on oral midazolam metabolism in rat intestines was opposite its induction effect on IV midazolam in the liver of rats; the strong inhibitory effect using human liver microsomes in vitro is therefore not reliable for predicting the in vivo effect.3202

20. The lignan extract of schisandra containing schisandrol A, gomisin C, deoxyschizandrin, and γ-schizandrin inhibits CYP 3A4 metabolism of midazolam in vitro and when 1 dose is given to rats with oral midazolam, but not IV midazolam, indicating inhibition of intestinal but not hepatic metabolism. However, when the lignan extract is given long-term it induces the CYP 3A4 protein expression in the liver 2.5-fold and its intestinal metabolism 4-fold, and thereby increases midazolam metabolism, especially in the small intestines. Gomisin C was the most potent inhibitor in vitro and the least concentrated in the liver, while 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
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*) – diclofenac *3085* [See Note 9.]

(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – tolbutamide *2011,3091* [See Note 3.]

(La) English lavender flowers (*Lavandula angustifolia*) – tolbutamide *3303*

(Pg) Pomegranate fruit (*Punica granatum*) – flurbiprofen *3245*

(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – losartan *3810*

Notes:

3. Though ginkgo extract acts as a CYP 2C9 inhibitor *in vitro*, at 360 mg/day EGb 761 in humans *2015* 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*

7. The study with 42 healthy humans showing significant inhibition of losartan metabolism involved taking 1 gm of resveratrol orally once daily for 4 weeks. *2970* Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.

8. The inhibition of losartan metabolism by a 14-day treatment with 140 mg of silymarin 3 times daily was only significant in the 6 Chinese men with a CYP2C9*1* genotype; it was not significant in the 6 men with a CYP2C9*3* genotype. *2981*

9. Cranberry juice inhibited the metabolism of diclofenac by human liver microsomes *in vitro*, but repeated consumption failed to do some in human subjects. *3085* Likewise, both flurbiprofen *1947* and S-warfarin *2316* metabolism were unaffected in humans.

10. Despite inhibiting the metabolism of CYP 2C9 drug substrates *in vitro* *3112,3245* and in rats, *3112* when 250 ml of pomegranate juice or a single 1 gram capsule of pomegranate extract with 689 mg polyphenols was given in a crossover trial to 12 human subjects along with the substrate flurbiprofen, no change in its metabolism was noted when compared with placebo control and the positive control inhibitor fluconazole. *3245*

**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 – omeprazole *3238*
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – diazepam, omeprazole, ticlopidine, voriconazole [See Note 1.]

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

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. 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. 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.

B.7.2.f Influence on CYP 2D6 Metabolic Conversion of Substrates

Drugs: dextromethorphan – metoprolol – 
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, dextromethorphan, dextromethorphan, dextromethorphan

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

(SJ) St John's wort herb (*Hypericum perforatum*) – [CORRECTION: debrisoquin superscript '1328' should be deleted]

(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – dextromethorphan

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.]

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. Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.

B.7.3 Specific Enzyme Influences of Herbal Agents on Phase II Conjugation p. 426

(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

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

(Br) Broccoli florets or sprouts [e water extract] (*Brassica oleracea v. italica*) – (e) bladder

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

(Chb) Chokeberry fruit [juice] (*Aronia melanocarpa*) – liver
Clove oil (Syzygium aromaticum) – liver, forestomach, small intestine
(Co) Coleus root (Coleus forskohlii) – liver
(eg) eugenol as in clove buds (Syzygium aromaticum) – liver
(Gb) Ginkgo leaves (Ginkgo biloba) – liver (P1)
(Li) Little ironwood herb (Vernonia cineraea) – liver
(os) organosulfides in garlic cloves (Allium sativum) – kidneys
(Sb) Shrubby basil leaf oil (Ocimum gratissimum = O. suave) – liver
(sr) sulforaphane from broccoli sprouts and tops (Brassica oleracea v. italica) – skin
(Tl) Tulsi leaves (Ocimum tenuiflorum = Ocimum sanctum) – liver, skin

B.7.3.b Influence on Activity and/or Content of UDP-Glucuronosyl Transferases

Conjugation Inhibitors
(Cb) Cranberry fruit/juice (Vaccinium macrocarpon) – liver (1A9)
(cy) chrysin from passion flower leaves (Passiflora incarnata, Passiflora coerulea) – liver (1A9)
(ep) epigallocatechin gallate [EGCG] from green tea leaves (Camellia sinensis) – liver (1A9)
(Ep) Echinacea purpurea root (Echinacea purpurea) – liver (1A1)
(Gb) Ginkgo leaf extract (Ginkgo biloba) – liver (1A9), intestine (1A8,1A9) [not liver (1A1)]
(kf) kaempferol as in tea (black and green) leaves (Camellia sinensis), kale leaves (Brassica oleracea v. acaulis), etc. – liver (1A9), intestine (1A8,1A9)
(Mt) Milk thistle seeds (Silybum marianum) – liver (1A1), (1A6, 1A9) [not liver (1A1)]
(qu) quercetin as in onion bulbs (Allium cepa), tea leaves (Camellia sinensis), cranberry fruit/juice (Vaccinium macrocarpon), etc. – liver (1A9), intestine (1A8,1A9)
(Sp) Saw palmetto fruit (Serenoa repens) – liver (1A1), (1A6) [not liver (1A1)]
(tn) tangeretin as in citrus fruit/juice (Citrus spp.) – liver (1A1)

Conjugation Inducers
(cc) curcumin in turmeric root (Curcuma longa, Curcuma aromatica) – colon, intestine
(cn) coumarin as in sweet clover (Melilotus officinalis), etc.
(Cr) Crucifers, specifically Brussels sprouts and/or cabbage (Brassica oleracea) – intestine, liver
(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. – liver
(eg) eugenol as in clove buds (Syzygium aromaticum) – liver
(Gb) Ginkgo leaf extract (Ginkgo biloba) – liver (1A1)
(go) ginkgolides A&B in ginkgo leaves (Ginkgo biloba) – liver (1A1)
(qu) quercetin as in onion bulbs (Allium cepa), tea leaves (Camellia sinensis), cranberry fruit/juice (Vaccinium macrocarpon), etc. – intestine, liver

No effect in humans
(Ag) American ginseng root extract (Panax quinquefolius) – zidovudine

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 strobes (Humulus lupulus) – breast
Conjugation Inducers
(Ag) American ginseng root (Panax quinquefolius) – heart
(Bl) Blueberry fruit (Vaccinium spp.) – liver
(Br) Broccoli florets or sprouts [e water extract] (Brassica oleracea v. italica) – (e) bladder, skin, [2895,2896,3037] skin
(Chb) Chokeberry fruit [juice] (Aronia melanocarpa) – liver
(Hp) Hops strobiles (Humulus lupulus) – liver
(iq) isoliquiritigenin from licorice root (Glycyrrhiza glabra, G. uralensis), tonka bean seeds (Diptyeryx odorata, D. oppositifolia), etc. – liver
(sr) sulforaphane from broccoli sprouts and florets (Brassica oleracea v. italica) – mammary epithelium, skin, [2895,2896] skin
(tg) tigloylgomisin H lignan from schisandra fruit (Schisandra chinensis) – liver
(xh) xanthohumol and/or isoxanthohumol in hops strobiles (Humulus lupulus) – liver

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

Conjugation Inhibitors

(By) Blueberry fruit juice (Vaccinium corymbosum) – colon
(Chb) Chokeberry fruit juice (Aronia melanocarpa) – colon
(Cof) Coffee roasted seed infusion (Caffea arabica) – colon
(Pm) Peppermint leaf infusion (Mentha piperita) – colon

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. – breast

(Dm) Damiana leaves (Turnera diffusa) – liver

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

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

(Gw) Grape red wine (Vitis vinifera) – systemic

(iq) isoliquiritigenin from licorice root (Glycyrrhiza glabra, G. uralensis), tonka bean seeds (Diptyeryx odorata, D. oppositifolia), etc. – breast

(is) isoflavone [genistein] in soy beans (Glycine max) – liver

(ms) γ-mangostin in mangosteen (Garcinia mangostana) pericarp – breast

(thc) tetrahydrocannabinol in cannabis (Cannabis sativa) – breast

(Wb) White button mushroom (Agaricus bisporus) – breast

B.7.4.b 5alpha-Reductase Conversion of Testosterone to Dihydrotestosterone

Conversion Inhibitors

(Am) Amla fruit (Phyllanthus emblica) – liver

(Ft) Foti root [emodin] (Polygonum multiflorum) – prostate, epididymis

(Gg) Greater galangal rhizomes (Alpinia galanga) – liver

(gp) gossypol in cotton root bark (Gossypium herbaceum, G. hirsutum) – prostate (types 1 & 2)

(Gr) Ginger rhizomes (Zingiber officinale) – liver

(gs) ginsenosides [Ro, Rd] (Panax ginseng) – epididymis, hair follicle

(Gs) Asian ginseng rhizomes/ root (Panax ginseng) – epididymis, hair follicle

(Hg) Horny goat weed leaf (Epimedium grandiflorum) – epididymus
(is) isoflavones as in soy beans (Glycine max), red clover flowers (Trifolium pratense), etc. – prostate (type 2)

(Jg) Japanese ginseng rhizomes (Panax japonicus) – epididymis

(kf) kaempferol as in tea (black and green) leaves (Camellia sinensis), kale leaves (Brassica oleracea v. acephala), etc. – prostate (type 2)

(Kz) Kudzu flower (Pueraria thomsonii) – epididymis, hair follicle

(Lg) Lesser galangal rhizomes [diarylheptanoids] (Alpinia officinarum) – prostate

(Ls) Lemongrass herb (Cymbopogon citratus) – liver

(na) nordihydroguaiaretic acid in chaparral (Larrea tridentata) – prostate (types 1 & 2)

(Oy) Oyster mushroom (Pleurotus ostreatus) – liver (type 1), prostate (type 2)

(Rs) Reishi mushrooms (Ganoderma lucidum) – prostate, prostate (type 2), liver (type 1)

(Sh) Shiitake mushroom (Lentinula edodes) – liver (type 1), prostate (type 2)

(Sw) Safflower flowers (Carthamus tinctorius) – liver, hair follicle

**B.7.4.d 11beta-Hydroxysteroid Dehydrogenase type 1 or 2 Conversion of Cortisol to Cortisone**

**Conversion Inhibitors**

(gl) glycyrrhetinic acid/glycyrrhizin from licorice root *(Glycyrrhiza glabra, Glycyrrhiza uralensis) – (t1, t2) liver, (t2) kidney

(Li) Licorice root *(Glycyrrhiza glabra) – in Addison’s disease

**B.7.4.g 17beta-Hydroxysteroid Dehydrogenase type 1 Conversion of Estrone to Estradiol**

**Conversion Inhibitors**

(Bl) Blueberry fruit (Vaccinium corymbosum) – mammary

(By) Black raspberry fruit (Rubus occidentalis) – mammary

(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. – mammary

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

**Conversion Inhibitors**

(gl) glycyrrhetinic acid/glycyrrhizin from licorice root *(Glycyrrhiza glabra) – liver

**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. – liver
Appendix C
HERBALS CONTRAINDICATED FOR MOTHERS AND CHILDREN

C.1 During Pregnancy

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/seed (Momordica charantia) A; T
California mugwort herb (Artemisia douglasiana) A
Feverfew herb (Tanacetum parthenium) H
Horsetail herb (Equisetum spp.) A
Pennroyal (See: American pennyroyal, European pennyroyal) E, A
Saw palmetto fruit (Serenoa repens) H
Wormwood tops, leaves *(Artemisia absinthium) H
Yerba mansa (Anemopsis californica) A

C.2 While Breast Feeding

Some herbal preparations are given safely as galactogogues to increase milk production. For example, micronized silymarin given to 25 women with borderline levels of lactation significantly increased milk production after 30 and 63 days compared to placebo. No evidence of silymarin was found in the breast milk of 5 women after 5 days.2898 This micronized standardized silymarin extract was shown after 14 days in female rats to increase prolactin levels that remained significantly elevated another 66 days, likely involving dopamine D₂ receptors.2967 A granular herbal tea formula containing fenugreek was also shown to significantly enhance milk production of a group of 22 mothers, compared to placebo apple tea granules in 22 new mothers or no intervention in 22 others, during the first week of life for their newborns. No maternal or neonatal adverse effects were reported.2899 The fenugreek formula also contained among other herbs goat's rue, fennel, and fennel essential oil, the latter made up almost entirely of the estrogenic component anethole.14 However, in a report of 2 cases of mothers consuming more than 2 liters daily of herbal tea mixtures with extracts of goat's rue, fennel, licorice, and anise for 15-20 days after birth, the breast-fed infants failed to thrive and showed nervous system symptoms after the first week. When the teas were stopped, the infants recovered and did well.1141 Some active constituents of medicinal plants can be excreted in breast milk intact or as metabolites that maintain much of the activity of the original compounds, and problems are more likely when large quantities of the herbal extracts are consumed for extended periods.
Infants under 6 months of age should optimally be given only breast milk and not be given herbal teas or other extracts or medicinal preparations unless prescribed by a recognized health expert. Giving even safe herbal teas to an infant can reduce its milk consumption and vital nutrient intake. As regards a nursing mothers consuming unnecessary herbal products, unless the specific intent is to treat the child by this means, it is preferable to not expose the breast feeding infant to potent medicinal compounds. Especially when particular plant compounds are known to inadvertently produce their unintended pharmacologic effect in the nursing child, caution should be used in taking herbals that contain these.
Appendix D
VITAMIN/MINERAL/DRUG INTERACTIONS

D.1 Drug and Mineral Interactions with Vitamin Supplements p. 457

Interference between vitamins and drugs or prescription mineral supplements can work both ways. In some cases drugs will lower vitamin (LV) oral absorption and/or serum levels or increase excretion or metabolism, while in other cases medications can raise vitamin (RV) bioavailability or increase their effects. In cases where drugs reduce vitamin levels, consumption of plant sources of the vitamin would be highly desirable. Vitamins may also raise drug (RD) or mineral (RM) serum levels or increase their effects, or they may lower drug (LD) or mineral (LM) levels or reduce their effects. Vitamin/drug or vitamin/mineral interactions listed below have caused either toxicity (t) or insufficient (i) effects for one or the other. Clinical findings for humans are emphasized in bold. Other interactions listed have produced observable changes without clinically-apparent adverse effects, but monitoring is advisable.

References: 3243, 3278

D.1.6 Vitamin B12 (Cyanocobalamine) / Drug Interactions p. 462

Esomeprazole - LV
Lansoprazole - LV
Omeprazole - LV
Pantoprazole - LV
Rabeprazole - LV

D.1.8 Vitamin C (Ascorbic Acid, Ascorbates) / Drug Interactions p. 464

Esomeprazole - LV
Lansoprazole - LV
Omeprazole - LV
Pantoprazole - LV
Rabeprazole - LV

D.1.9 Vitamin D (Calciferol) / Drug Interactions p. 465

Efavirenz - LV

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  

Esomeprazole - LM  
Lansoprazole - LM  
Omeprazole - LM  
Pantoprazole - LM  
Rabeprazole - LM  

D.2.4 Iron (as Ferrous Sulfate) / Drug Interactions  

Esomeprazole - LM  
Lansoprazole - LM  
Omeprazole - LM  
Pantoprazole - LM  
Rabeprazole - LM  

D.2.5 Magnesium (as Oxide) / Drug Interactions  

Bumetanide - LM  
Dexlansoprazole - LM  
Esomeprazole - LM  
Indapamide - LM  
Lansoprazole - LM  
Metolazone - LM  
Omeprazole - LM  
Pantoprazole - LM  
Rabeprazole - LM  
Torsemide - LM  

p. 470  
p. 474  
p. 476
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

Amla fruit (*Emblica officinalis*) –
isoniazid, pyrazinamide, rifampicin, cyclophosphamide, cisplatin, doxorubicin

American ginseng (*Panax quinquefolius*) root – ACE inhibitors, beta-blockers, calcium channel blockers, chemotherapy, influenza vaccine, cyclophosphamide, mitomycin C, N-acetyl cysteine, vitamin C

Arboreal blackberry – 5-fluorouracil

Arjuna bark (*Terminalia arjuna*) – isosorbide dinitrate

Arnica flowers (*Arnica montana*) – acetaminophen, hydroxyethyl salicylate

Ashwagandha (*Withania somnifera*) root

– adriamycin, cyclophosphamide, epirubicin, ethambutol, 5-fluorouracil, isoniazid, pyrazinamide, rifampicin, taxotere, gentamicin

Asian ginseng root (*Panax ginseng*) –
donepezil, galantamine, memantine, rivastigmine, cisplatin

Astragalus root (*Astragalus membranaceus*) – enalapril

Barberry root bark (*Berberis vulgaris*) – simvastatin, amphotericin B, doxorubicin, simvastatin, stanols

Bilberry fruit (*Vaccinium myrtillus*) – latanoprost

Black cumin seed (*Nigella sativa*) – beclomethasone, beta-agonists, corticosteroids, diclofenac, fluticasone, folic acid, hydroxychloroquine, methotrexate, omeprazole, theophylline, acetaminophen, doxorubicin, gemcitabine, gentamicin, ifosfamide, oxaliplatin

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

Calamus rhizome (*Acorus calamus*) – vincristine

Cannabis tops (*Cannabis sativa*) –
anticholinergics, anticonvulsants, antidepressants, baclofen, codeine, dextropropoxyphene, dihydrocodeine, glatiramer, interferon beta-1a, methadone, methotrexate, morphine, NSAI, oxycodone, pethidine, tizanidine, tramadol

Cat’s claw bark (*Uncaria tomentosa*) – doxorubicin

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

Chamomile flowers (*Matricaria recutita*) – cisplatin

Chokeberry fruit (*Aronia melanocarpa*) – amiodarone

Clove buds (*Syzygium aromaticum*) – indomethacin

Cola (*Cola nitida*) seed – **ciprofloxacin**, **perflaxacin**, **levoflaxacin**

Coptis root (*Coptis spp.*) – **simvastatin**, **amphotericin B**, **doxorubicin**, **stanols**

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

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

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

Dog rose hips (*Rosa canina*) – **acetaminophen**, **chloroquin**, **lefunomide**, **methotrexate**, **NSAIDs**, **steroids**

Echinacea pallida whole plant (*Echinacea pallida*) – **influenza vaccine**

Echinacea angustifolia root (*Echinacea angustifolia*) – **ACE inhibitors**

Evening primrose leaves (*Plantago lanceolata*) – **indomethacin**

French maritime pine resin (# = aged garlic extract) – **calcium channel blockers**, **cholexedion**, **diuretics**

Ginkgo seeds (*Trigonella foenum-graecum*) – **ibuprofen**, **L-dopa**, **mefenamic acid**, **NSAIDs**

Frankincense resin (*Boswellia serrata*) resin – **ibuprofen**, **metformin**


Goldenseal roots/rhizome *(Hydrastis canadensis*) – **simvastatin**, **amphotericin B**, **doxorubicin**, **stanols**

Guarana seeds (*Paulinia cupana*) – **cyclophosphamide**, **doxorubicin**, **fluorouracil**

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

Hops strobiles (*Humulus lupulus*) – **benzodiazepines**

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

Kutaki root (*Picrohiza kurroa*) – **acetaminophen**, **chloroquine**, **ethinylestradiol**, **rifampicin**

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

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

Long pepper fruit (*Piper longum*) – **calcium**, **EGCG**, **iron**, **zinc**

Lycium (= Goji) berry (*Lycium barbarum*) – **doxorubicin**, **mitomycin C**

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

Maitake mushroom (*Grifola frondosa*) – **clomiphene citrate**, **adriamycin**, **cisplatin**, **5-fluorouracil**
Milk thistle seeds (Silybum marianum) – glibenclamide, metformin, acetaminophen
Olive fruit oil (Olea europaea) – antibiotics, atenolol, doxazosin, hydrochlorothiazide, lisinopril, nifedipine
Oregon grape root bark (Mahonia spp.) – simvastatin, amphotericin B, doxorubicin, statins, stanols
Passion flower herb (Passiflora incarnata) – benzodiazepines
Pelargoniun root (Pelargonium sidoides) – augmentin, budesonide, fenoterol, ipratropiumbromide, ofloxacin, salmeterol
Peppermint leaves (Mentha x piperita) – granisetron, dexamethasone, metoclopromide
Pomegranate fruit (Punica granatum) – hydroxychloroquine, methotrexate, prednisone, NSAIDs, sulfazine, docetaxel
Quassia (Surinam) bark (Quassia amara) – hydrochoric acid, indomethacin
Saffron stigmas (Crocus sativa) – dorzolamide, fluoxetine, timolol
Sage leaves *(Salvia officinalis) – vincristine
Sanchi ginseng root/rhizome (Panax notoginseng) – aspirin, diclofenac, leflunomide, prednisone
Saw palmetto fruit (Serenoa repens) – prulifloxacin, tamsulosin
Soy beans (Glycine max) – adriamycin, carboplatin, cisplatin, cyclophosphamide, dacarbazine, etoposide, ifosfamide, irinotecan, paclitaxel, procarbazine, temozolomide, vincristine
St. John's wort herb (Hypericum perforatum) – indomethacin, sodium valproate
Stinging nettle leaves (Urtica spp.) – acetaminophen [paracetamol] aspirin, celecoxib, diclofenac, ibuprofen, ketoprofen, naproxen, opiates, piroxicam, sulindac, tenoxicam
Sweet annie herb (Artemisia annua) – curcumin
Sweet cherries (Prunus avium) – allopurinol, colchicine
Tart cherry fruit (Prunus cerasus) – allopurinol, celecoxib, indomethacin, sulindac, atorvastatin
Tea [green] leaves (Camellia sinensis) – ciprofloxacin, indomethacin
Tea tree leaf oil (Melaleuca alternifolia) – diclofenac, minoxidil
Thunder god vine peeled root *(Tripterygium wilfordii) – auranofin, methotrexate, NSAIDs, sulfasalazine
Tulsi leaves (Ocimum tenuiflorum = Ocimum sanctum) – acetaminophen, acetic acid, aspirin, isoproterenol, meloxicam, radioiodine, vincristine, ciprofloxacin, pyroterone acetate
Turmeric root (Curcuma longa, C. aromatica) – acetaminophen, analgesics, antihypertetics, antitoxoplastic drugs, carboplatin, CCNU, celecoxib, cisplatin, cyclophosphamide, cycloplegics, diclofenac, docetaxel, etoposide, 5-fluorouracil, fluoxetine, gemcitabine, immune suppressants, isoniazid, methotrexate, MOPP/ABVD/COPP, mydriatics, naproxen, NSAIDs, oral hypoglycemics, pyrazinamide, rifampicin, steroids, taxol, topotecan, v inblastine, arteether, cisplatin, docetaxel, gemcitabine, paclitaxel, artemisinin
Valerian root (Valeriana officinalis) – benzodiazepines
E.2 Herbal Aids for Modifying Substance Abuse

Though cannabis has been used by some successfully to reduce opioid dependence, personal use of cannabis to reduce alcohol intake should not be considered an appropriate rationale, since concurrent abuse of both together not unusual. 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: Ac

Coc: (Ac)

Amla fruit (*Emblica officinalis*) – Alc: (ld Ac, Ac)

Apricot fruit (*Prunus armeniaca*) – Alc: (ld Ac)

Ashwagandha root (*Withania somnifera*) – Opi: Ac

Asian ginseng root (*Panax ginseng*) – Amp: Ac

Coc: Ac

Barberry bark (*Berberis vulgaris*) – Coc: Ac

Belleric myrobalan fruit (*Terminalia bellirica*) – Alc: (sd Ac)

Bishop's weed fruit (*Trachyspermum ammi* syn. *T. copticum*) – Opi: Ac

Black cumin seed (*Nigella sativa*) – Alc: (sd Ac)

Opi: Hh

Black pepper fruit (*Piper nigrum*) – Alc: (sd Ac)

Black raspberry fruit/seeds (*Rubus occidentalis*) – Alc: (ld Ac)

Blackberry fruit/seeds (*Rubus spp.*) – Alc: (ld Ac)

Borage seed (*Borago officinalis*) – Alc: Af

Burdock root (*Arctium lappa*) – Alc: (ld Ac)

Cannabis tops *(Cannabis sativa)* – Amp: Ac

Coc: Ac

Opi: Ac
Chaparral leaves (Larrea tridentata) – **Ale**: (sd Ah, Ac)
Chili fruit *(Capsicum annuum)* – **Ale**: (sd Ah, Ac)
Chinese skullcap root (Scutellaria baicalensis) – **Ale**: (ld Ah, Ac)
Clove buds *(Syzygium aromaticum)* – **Ale**: (sd c)
Coptis rhizome *(Coptis chinensis)* – **Coc**: Ac, c
Coriander fruit (Coriandrum sativum) – **Ale**: (sd Ah)
Fenugreek seeds (Trigonella foenum-graecum) – **Ale**: (ld Ah)
Garlic bulbs *(Allium sativum)* – **Ale**: (ld Ah, Ac, f)
Ginger rhizome (Zingiber officinale) – **Ale**: (sd Ah, Ac)
Goldenseal roots/rhizome *(Hydrastis canadensis)* – **Coc**: Ac
Grape red wine *(Vitis vinifera)* – **Ale**: Ac, c, (not Ac)
Hawthorn berries *(Crataegus laevigata, C. monogyna)* – **Ale**: (sd Ah)
Jambolan seeds *(Syzygium cumini)* – **Ale**: (ld Ah)
Kudzu root *(Pueraria lobata)* – **Ale**: Ac, He
Kutaki root *(Picrorhiza kurroa)* – **Ale**: (ld Ah)
Lemon balm herb *(Melissa officinalis)* – **Opi**: Ac
Little ironweed herb *(Vernonia cinerea)* – **Nic**: He
Lobelia herb *(Lobelia inflata)* – **Amp**: Ac
Milk thistle seeds *(Silybum marianum)* – **Ale**: (ld Ah)
Oregon grape bark *(Mahonia aquifolium)* – **Coc**: Ac
Passion flower leaves *(Passiflora incarnata)* – **Se**
Peppermint herb *(Mentha piperita)* – **Opi**: Ac
Pomegranate fruit/seeds *( Punica granatum)* – **Ale**: (ld Ah)
Quassia (Surinam) bark *(Quassia amara)* – **Ale**: (sd Ah)
Raspberry fruit/seeds, leaves *(Rubus idaeus)* – **Ale**: (ld Ah)
Rhodiola root *(Rhodiola rosea)* – **Nic**: Ac
Rosemary herb *(Rosmarinus officinalis)* – **Opi**: Ac
Saffron stigma *(Crocus sativus)* – **Opi**: Ac
Scotch broom tops *(Cytisus scoparius)* – **Nic**: He
Shrubby basil leaves *(Ocimum gratissimum = O. suave)* – **Ale**: (sd e)
St. John’s wort herb *(Hypericum perforatum)* – **Nic**: [He]
Strawberry fruit/seeds, leaves *(Fragaria spp.)* – **Ale**: (ld Ah)
Summer savory herb *(Satureja hortensis)* – **Opi**: Ac
Tea black leaves *(Camellia sinensis)* – **Ale**: (ld Ah)
Tulsi leaves *(Ocimum tenuiflorum = Ocimum sanctum)* – **Ale**: (sd Ah)
Turmeric rhizome *(Curcuma longa)* – **Ale**: Ac
Valerian root *(Valeriana officinalis)* – **Opi**: Ac
Winter melon fruit *(Benincasa hispida)* – **Opi**: A

**E.3 Complementing Treatment of Inflammations**

**E.3.1-3.5** Drug treatments have advantages and drawbacks that differ, depending on the type of drug. **Drugs considered here in interactions with herbs are grouped as corticosteroids** (cortisone, dexamethasone, hydrocortisone,
prednisone), NSAIDs (acemetacin, aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, metamizol, naproxen, piroxicam, phenylbutazone, rofecoxib, salicylates), and analgesics (acetaminophen [paracetamol], codeine, morphine, propoxyphene HCl, propyphenazone, tramadol).

Herbs (h) and their extracts (e), fractions (f), and components (c) or smoke (s) are considered here as anti-inflammatory and analgesic adjuvants when they enhance the clinical effects of these drugs, reduce their adverse effects, or reduce their use (frequency or dose) by humans (in bold) or in animals (italicized). Some botanical derivatives or components produce additional anti-inflammatory and/or analgesic effects if used with drugs when applied topically (t).

**E.3.1 Enhancing the Effects of Corticosteroids**

Black cumin seed (Nigella sativa) – e^2988,2989
Frankincense resin extract (Boswellia serrata) – e^2846

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

Black cumin seed (Nigella sativa) – f^3114
Fenugreek seed (Trigonella foenum-graecum) – h^3416
Frankincense resin (Boswellia serrata) resin – e^2904
French maritime pine bark (Pinus pinaster) – f^2795
Purple passion fruit peel (Passiflora edulis) – e^2951
Stinging nettle leaves (Urtica dioica) – h^2722
Turmeric root [curcumin] (Curcuma longa, C. aromatica) – e^2721,2802,3103,3433

**E.3.3 Enhancing Outcomes When Using Analgesics**

Arnica flowers (Arnica montana) – te^2805
Cannabis leaves/tops *(Cannabis sativa) – e^2748,2749, s^2745,2750
Ginger root/rhizome (Zingiber officinale) – e^3321
Stinging nettle leaves (Urtica dioica) – h^2722
Turmeric root [curcumin] (Curcuma longa, C. aromatica) – e, f^3247

**E.3.4 Protecting Against NSAID-induced Ulcers**

Chaparral leaves (Larrea tridentata) – c^3246
Clove oil [eugenol] (Syzygium aromaticum) – c^2057
Coconut milk (Cocos nucifera) – e^3391
Coriander seeds (Coriandum sativum) – h^3264
English plantain leaves (Plantago lanceolata) – e^2838
Licorice root (Glycyrrhiza glabra) – e^2976
Sea buckthorn fruit (Hippophae rhamnoides) – e^1959
Shrubby basil leaves (Ocimum gratissimum = O. suave) – e^2953
Tea leaves (Camellia sinensis) – e,f^2752
Tulsi leaves (Ocimum tenuiflorum = Ocimum sanctum) – e^3183,3218

**E.3.5 Protecting Against Acetaminophen-induced Liver Toxicity**

Black cumin seed (Nigella sativa) – c^2983
Garlic cloves (Allium sativum) – e^3386
Ginger rhizome (Zingiber officinale) – h, e^3475,3473,3474
Korean acanthopanax root bark (Acanthopanax koreanum) – e^2727
Kutaki rhizome/roots (*Picrorhiza kurroa*) – f
Milk thistle fruit (*Silybum marianum*) – f
Schisandra fruit (*Schisandra chinensis*) – c
Tulsi leaves (*Ocimum tenuiflorum* = *Ocimum sanctum*) – e

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

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.

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 chemotherapeutic 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.\(^ {2753}\) [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** p. 497

American ginseng root [steamed root ginsenoside Rg3, Rh2] (Panax quinquefolius) – cyclophosphamide [c]\(^ {2924,2926}\) berry [extract with 25% ginsenoside Rb3] – 5-fluorouracil (e)\(^ {2927}\) Amla fruit (Emblica officinalis) – cisplatin, doxorubicin (e)\(^ {2860}\) Asian ginseng root (red) [c panaxadiol] (Panax ginseng) – 5-fluorouracil [c]\(^ {3255}\) Bibhitaki fruit (Terminalia bellerica) – cisplatin, doxorubicin (e)\(^ {2860}\) Chamomile flowers [bisabololoxide A] (Matricaria recutita) – 5-fluorouracil [c]\(^ {2863}\) Chokeberry fruit (Aronia melanocarpa) – gemcitabine (e)\(^ {3409}\) Corn silk/stigma [c maysin] (Zea mays) – camptothecin [c], cisplatin [c], etoposide [c], 5-fluorouracil [c]\(^ {3488}\) Cranberry fruit/ juice proanthocyanidins) (Vaccinium macrocarpon) – paraplatin (f)\(^ {3086}\) Crucifers like Brussels sprouts, cabbage [c I3C from glucobrassicin, cd DIM (dimer of I3C)] (Brassica oleracea) – erlotinib, erlotinib [cd]\(^ {3254}\) Echinacea purpurea polysaccharides (Echinacea purpurea) – cyclophosphamide\(^ {2809}\) Horse chestnut seeds [escin] *(Aesculus hippocastanum) – 5-fluorouracil [c]\(^ {2776}\) Milk thistle seeds [silybin(silibinin)] (Silybum marianum) – erlotinib [c]\(^ {3354,3355}\) Sanchi ginseng root [c ethanolic/butanol 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 vicin-2] (Ocimum tenuiflorum = Ocimum sanctum) – docetaxel [c]\(^ {3182}\) Turmeric rhizome [curcumin] (Curcuma longa, C. aromatic) – capecitabine [c]\(^ {3115}\) cisplatin [c]\(^ {2877}\) docetaxel [c]\(^ {3319}\) gemcitabine [c]\(^ {3118}\) oxaliplatin [c],
E.4.2 Reducing adverse effects of chemotherapy

American ginseng root [ginsenoside Rb1, steamed root ginsenoside Rg3, Rh2] (Panax quinquefolius) – chemotherapy (h), 2916,2923 cyclophosphamide [cs-Rg,Rh], 2925,2926 mitomycin C (h), 2922-cyclophosphamide [c-Rh] 3064

Amla fruit (Emblica officinalis) – cyclophosphamide (e), 2853,2955 doxorubicin (e) 2859

Ashwagandha root (Withania somnifera) –

taxotere/adriamycin/cyclophosphamide (e) and cyclophosphamide/epirubicin/5-fluorouracil (e) 3252

Asian ginseng root (Panax ginseng) – cisplatin (e) 2725

Broccoli sprouts [sulforaphane] (Brassica spp.) – cisplatin (e) 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 piperita) –

adriamycin, carboplatin, cisplatin, cyclophosphamide, epirubicin, etoposide, ifosfamide, irinotecan (f) 285

Prickly pear cladode (Opuntia ficus-indica) – (e) 3410

Raspberry fruit [ellagic acid] (Rubus idaeus) – cisplatin (e) 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, temozolomide, vincristine [c] 2813

Spearmint leaf oil (Mentha spicata) –

adriamycin, carboplatin, cisplatin, cyclophosphamide, epirubicin, etoposide, ifosfamide, irinotecan (f) 285

Temu lawak rhizome [xanthorrhizol] (Curcuma xanthorrhiza) – cisplatin (c) 2950

Tomato fruit [c lycopene] (Lycopersicon esculentum) – cisplatin (c) 2864

Tulsi leaves [c 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-
E.4.3 Selective Cell Retention of Drugs by Inhibiting Efflux Transport Proteins

Hops strobules [prenlflavonoids] (Humulus lupulus) – mitoxantrone (kidney BCRP) 3385
Licorice root [c glycyrrhetinic 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), 3206 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

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) 3923
Apple fruit [fresh (lung and colon)] 2789 [Malus domestica]
Ashwagandha root [hydroalcoholic extract (skin)] 3065 (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, 297,307,3075 ethanol extract, anthocyanins, 307,3072 cs ferulic acid, beta-sitosterol 3177] (Rubus occidentalis)
Broccoli florets/sprouts [sprouts water extract 2415,3401 and florets glucosinolates/isothiocyanates extract (colon), 3109 sulphoraphane 3402] (Brassica oleracea var. italica)
Coffee beans roasted [water extract (nonmelanoma skin cancer in white women), ER-neg postmenopausal breast cancer, liver cancer, glioma (coffee/tea), caffeine (glioma in men)] (Coffee arabica)

Cranberry fruit [juice] (Vaccinium macrocarpon)

Crucifers leaves, heads [phenethyl isothiocyanate, indole-3-carbinol (I3C), sulforaphane] (Brassica spp.)

Cumin seeds [ground] (Cuminum cyminum)

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

Kava root (Piper methysticum) [f kavalactones]

Milk thistle seeds [silymarin] (Silybum marianum)

Prickly pear fruit [water extract] (Opuntia spp.)

Reishi mushroom [c polysaccharides, triterpenoids] (Ganoderma lucidum) – c/liver

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

Soy beans [isoflavones] (Glycine max)

Strawberry fruit [freeze-dried (esophageal)]

Tea (green or white) leaves [water extracts (colorectal & stomach, esophageal in women, ovarian, endometrial, ovarian, breast, colorectal, leukemia)] (Camellia sinensis)

Turmeric rhizome [curcuminoids (enhanced bioavailability)] (Curcuma longa) – cisplatin, cyclophosphamide docetaxel, etoposide, 5-fluorouracil, methotrexate, topotecan
E.5 Herbals for Preventing and Healing Radiation Adverse Effects and/or Enhancing Radiotherapy or Photodynamic Therapy

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."

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 (TGFβ1) overexpression. Increases in TGFβ1 during radiation treatment for non-small cell lung cancer is indicative of significant reduction in survival time, and significant TGFβ1 elevations after radiation therapy have been correlated with symptomatic radiation pneumonitis.

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.

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

<table>
<thead>
<tr>
<th>Herbal Plant</th>
<th>Use</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe leaf gel (Aloe vera)</td>
<td>neg. Lj</td>
<td>2772,2773,2774</td>
</tr>
<tr>
<td>American ginseng root (Panax quinquefolius)</td>
<td>Oe</td>
<td>2065,3066</td>
</tr>
<tr>
<td>Amla fruit [aqueous extract, methanol extract] (Emblica officinalis)</td>
<td>Oe</td>
<td>2850,2851</td>
</tr>
<tr>
<td>Asian ginseng root (Panax ginseng)</td>
<td>Ie, If, Ic</td>
<td>3223,3224</td>
</tr>
<tr>
<td>Bael leaf, fruit (Aegle marmelos)</td>
<td>Oe, Ie</td>
<td>3193</td>
</tr>
<tr>
<td>Cat’s claw bark (Uncaria tomentosa)</td>
<td>Oe</td>
<td>3330</td>
</tr>
<tr>
<td>Corn silk/stigma [ethanolic extract] (Zea mays)</td>
<td>Oe</td>
<td>3487</td>
</tr>
<tr>
<td>Cranberry fruit extract (Vaccinium macrocarpon)</td>
<td>Oe</td>
<td>3266</td>
</tr>
<tr>
<td>Dong quai roots (Angelica sinensis)</td>
<td>Oe</td>
<td>3365</td>
</tr>
<tr>
<td>Frankincense resin extract (Boswellia serrata)</td>
<td>Oe,</td>
<td>2846,3498</td>
</tr>
<tr>
<td>Ginkgo leaves (Ginkgo biloba)</td>
<td>Oe, Ie</td>
<td>3193</td>
</tr>
<tr>
<td>Gulanach herb (Tinospora cordifolia)</td>
<td>Oe</td>
<td>3193</td>
</tr>
<tr>
<td>Jambolan seeds, leaf (Syzygium cumini)</td>
<td>Oe, Ie</td>
<td>3193</td>
</tr>
<tr>
<td>Long pepper fruit (Piper longum)</td>
<td>Ie</td>
<td>3194</td>
</tr>
<tr>
<td>Milk thistle seeds [flavolignan fraction] (Silybum marianum)</td>
<td>If, Of</td>
<td>2903</td>
</tr>
<tr>
<td>Neem berry [oil] (Azadirachta indica)</td>
<td>Le</td>
<td>3430</td>
</tr>
<tr>
<td>Peppermint leaf [oil] (Mentha x piperita)</td>
<td>Of</td>
<td>3195</td>
</tr>
<tr>
<td>Rajgira leaf (Amaranthus paniculatus)</td>
<td>Oe</td>
<td>3193</td>
</tr>
<tr>
<td>Sea buckthorn fruit [hydroethanolic extract] (Hippophae rhamnoides)</td>
<td>Ie</td>
<td>3000</td>
</tr>
<tr>
<td>Soy bean [f isoflavones, c genistein] (Glycine max)</td>
<td>Of,</td>
<td>2812, Of /c</td>
</tr>
</tbody>
</table>
St. John's wort flower [extract] (Hypericum perforatum) – Le
Sweet basil leaves (Ocimum basilicum) – Oe
Tomato leaves [c lycopenes] (Lycopersicon esculentum) – Oc
Turmeric leaves [ea aqueous extract, em methanolic-aqueous extract, c vicenin, orientin] (Curcuma longa = Ocimum sanctum) – Oc, 3408 Oem, 3180 Iea, 3214 le 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
Turmeric root (Curcuma longa) – Le, 3485 Oc, 3359,3363 Oe, 3121 Oc, 3318

E.5.5 Enhancing Antineoplastic Effects of Radiation

p. 504

Black raspberry fruit [methanol extract] (Rubus occidentalis) – Le [breast adenocarc.] 3081
Turmeric leaves (Ocimum tenuiflorum = Ocimum sanctum) – Oe [melanoma] 3180
Turmeric root (Curcuma longa) – Le [ovarian], 2876 Le [colorectal], 2866,2875 Oe [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) – ([c]in rats with Dong quai [c] 2728,2729,2730
Dong quai root [water and/or ethanol extracts] (Angelica sinensis) – ([c]in rats with Astragalus [c] 2728,2729,2730

Magnolia bark [honokioli] (Magnolia officinalis) – ([c] in human renal cells) 2732
Reishi mushroom [13.5% polysaccharides/6% triterpenes extract] (Ganoderma lucidum) – ([c] in human prostate cancer cells) 2737

E.5.9 Potential Herbal Prevention of Dermal Photocarcinogenesis

NEW

Black raspberry fruit [80% ethanol extract] (Rubus occidentalis) – Te [after UVB irradiation] 3073

Bloodroot root [c sanguinarine] (Sanguinaria canadensis) – Te 3008
Broccoli sprouts [c; c sulforaphane] (Brassica oleracea v. italica) – Te, Te,c 3037

Coffee beans (roasted) [c aqueous] (Coffea arabica) – Oe 2894
Ginger rhizome [c 6-gingerol] (Zingiber officinale) – Te, Te 3010

Grapes fruit [c resveratrol] (Vitis spp.) – Te, 2886,2887,2888,2897 Te 2889

Grape seed [c ethanolic extract; f proanthocyanidin] – Of 2885 Te 3016

Heather herb [c ethanolic extract] (Calluna vulgaris) – Te 3016

Olive leaf [c; c oleuropein], fruit [f oil] (Olea europaea) – Oe,c 2868 Tf [after irradiation] 2870
Pomegranate juice/seed [extract, c delphinidin] (Punica granatum) – Tc, Te 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 [c aqueous; f polyphenols; c EGCG] (Camellia sinensis) – Tf 2890,2892,2893 Tc, 2873,2880,2881 Te 2891,3004,3006 Oe 2874,2883,3004 Of 2880,2881

Tea (black) leaves [c aqueous] – Oe, 2892,2893 Oe 2882,2883

Turmeric root [pc curcumin] (Curcuma longa) – Te 2878

E.5.10 Herbal Prevention of Acute UV-induced Erythema

NEW

Broccoli sprouts [c; c sulforaphane] (Brassica oleracea v. italica) – Te, Te,c 2895
Cocoa bean (fermented, roasted) [h/f flavanols] (Theobroma cacao) – Oh,f 2891
Grapes fruit [c resveratrol] (Vitis spp.) – Te 2886

Lycium (= Goji) berries (Lycium barbarum) – Oj 3028
Rhatany root (*Krameria triandra*) – Te$^{3176}$
Tea (green) leaves [f polyphenols or catechins] (*Camellia sinensis*) – Tfp.$^{2895}$ Oef$^{3361}$

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.  

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**

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

Andrographis leaf (Andrographis paniculata) e aqueous extract – (e) MRSA

Arjun tree leaves (Terminalia arjuna) e methanol extract – (e) MDR-Salmonella typhi

Bael fruit pulp (Aegle marmelos) e methanol or aqueous extracts – (e) MDR-Salmonella typhi

Bibhitaki fruit (Terminalia belerica) ee ethanolic extract – (ee) MDR-MRSA

Black cherry bark (Prunus serotina) ee ethanolic extract – (ee) MDR-Neisseria gonorrhoeae

Black nightshade seeds *(Solanium nigrum) e methanol extract – (e) MDR-Salmonella typhi

Cassia (Cinnamomum cassia) c cinnamaldehyde – (c) MDR-Salmonella typhimurium, (c) MDR-E. coli, (c) MDR-Staph. aureus, (e) erythromycin-resistant Strep. pyogenes

Catechu bark (Acacia catechu) e methanol extract – (e) MDR-Salmonella typhi

Celandine herb (Chelidonium majus) cs 8-hydroxydihydroinosine, 8-hydroxydihydrochelerythrine – (cs) MRSA

Chamomile leaf (Matricaria recutita) e methanol extract – (e) methicillin-resistant Staph. epidermidis

Chaparral leaves [c NDGA/lignins] (Larrea tridentata) – (c) MRSA, (c) MDR-Mycobacterium tuberculosis

Chicory leaves (Cichorium intybus) e methanol extract – (e) MDR-Salmonella typhi

Chinese lantern tree fruit (Dichrostachys glomerata) e methanolic extract – (e) MDR-Escherichia coli, (c) MDR-Enterobacter aerogenes, (e) MDR-Klebsiella pneumoniae, (e) MDR-Pseudomonas aeruginosa

Chinese rhubarb root (Rheum palmatum) cs emodin & rhein – (cs) MRSA

Chinese skullcap root (Scutellaria baicalensis) c baicalin – (e) MDR-Acinetobacter baumannii, (c) MRSA, (c) penicillin-resistant Staphylococcus aureus

Cinnamon bark (Cinnamomum verum) c cinnamaldehyde – (c) MDR-Salmonella typhimurium, (e) MDR-E. coli, (c) MDR-Staph. aureus, (c) erythromycin-resistant Strep. pyogenes

Cinnamon beilschmiedia bark (Beilschmiedia cinnamomea) e methanolic extract – (e) MDR-E. coli, (e) MDR-Enterobacter aerogenes, (c) MDR-K. pneumoniae

Clary sage root (Salvia sclarea) e extract, cs salvipisone, aethiopinone – (c) MRSA, (c) MDR-Staph. epidermidis, (c) methicillin-resistant Staph. epidermidis

Clove bud (Syzygium aromaticum) c eugenol – (c) MDR-Salmonella typhimurium, (c) MDR-E. coli, (c) MDR-Staph. aureus, (c) erythromycin-resistant Strep. pyogenes

Coriander seed (Coriandrum sativum) f essential oil – (f) MRSA

Eucalyptus leaf (Eucalyptus globulus) f essential oil – (f) MRSA, (f) Mycobacterium tuberculosis

ferum essential oil, 1,8-cineole &/or aromadendrene – (f, cs, c-a) MRSA, VRE

Garlic bulb *(Allium sativum) e water extract – (e) MDR-Mycobacterium tuberculosis, (c) isoniazid-resistant Mycobacterium tuberculosis

Goldenseal root and rhizome *(Hydrastis canadensis) ee ethanolic extract, c berberine – (ee, c) MDR-Neisseria gonorrhoeae

leaves: e hydroethanolic extract, c berberine – (e, c) MRSA

Gotu kola leaves (Centella asiatica) e methanol extract – (e) MRSA

Haritaki fruit (Terminalia chebula) ee ethanolic extract – (ee) MDR-MRSA

Horseradish root (Armoracia rusticana) c allyl isothiocyanate – (c) MDR-Salmonella typhimurium, (c) MDR-E. coli, (c) MDR-Staph. aureus, (c) erythromycin-resistant Strep. pyogenes

Indian nettle leaves (Acalypha indica) e aqueous extract – (e) MDR-Mycobacterium tuberculosis

Kikar bark (Acacia nilotica) e aqueous extract – (e) MDR-Salmonella typhi
Kutaki leaves (Picrorrhiza kurroa) e methanol or aqueous extracts – (e) MDR-Salmonella typhi
Licorice root (Glycyrrhiza uralensis) c ganeacolin – (c-ga) vancomycin-resistant strains of Enterococcus faecalis, E. faecium, E. gallinarum and MRSA
Magnolia bark (Magnolia officinalis) e extract – (e) MDR-Acinetobacter baumannii
Malabar nut leaves (Adhatoda vasica) c aqueous extract – (e) MDR-Mycobacterium tuberculosis
Mongolian mulberry (Morus mongolica) cs mulberrofurans – (c) vancomycin-resistant strains of Enterococcus faecalis, E. faecium, E. gallinarum and MRSA
Mustard seed (Brassica nigra) c allyl isothiocyanate – (c) MDR-Salmonella typhimurium, (c) MDR-E. coli, (e) MDR-Staph. aureus, (e) erythromycin-resistant Strep. pyogenes
Orange rind (Citrus sinensis) f essential oil – f MRSA, VRSA
Oregano herb (Origanum vulgare ssp. hirsutum) c carvacrol 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
Pomegranate fruit peel (Punica granatum) ee ethanolic extract, em methanol extract – (ee) MDR-MRSA, (e) MDR-Salmonella typhi
Rabdosia (Rabdosia rubescens) – (e) MDR-Acinetobacter baumannii
Rhodiola root (Rhodiola rosea) ee ethanolic extract – (ee) MDR-Neisseria gonorrhoeae
Rugose rose flower (Rosa rugosa) – (e) MDR-Acinetobacter baumannii
Sage leaf (Salvia officinalis) e extracts – (e) methicillin-resistant Staph. epidermidis
Simal bark (Salvia malaariae) c methanol extract – (e) MDR-Salmonella typhi
Southern prickly ash (Zanthoxylum clava-herculis) e alkaloidal extract, f ethyl acetate, c chelerythrine – (ea, fe, c) MDR-MRSA
Sowa seed (Peucedanum graveolens) e methanol extract – (e) MDR-Salmonella typhi
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
Sweet tea fruit (Rubus chingii) – (e) MDR-Acinetobacter baumannii
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, (ea) MDR-Acinetobacter baumannii
Thyme herb (Thymus vulgaris) f essential oil, c thymol or carvacrol – (f) MRSA, (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
Tropical almond fruit (Terminalia chebula) – (e) MDR-Acinetobacter baumannii
Tulsi seed (Ocimum tenuiflorum = Ocimum sanctum) ea aqueous extract, ee ethanolic extract, ec chloroform extract, c eugenol – (ee) MDR-MRSA, (ea) MDR-Salmonella typhi, (ee, ee) MDR-Neisseria gonorrhoeae, (c) MDR-Neisseria gonorrhoeae
Turmeric rhizome (Curcuma longa) e ethyl acetate extract – (e) MRSA
Usnea lichen (Usnea spp.) cs usnic acid – MRSA
Uva ursi leaf (Arctostaphylos uva-ursi) ee ethanolic extract – (ee) MDR-Neisseria gonorrhoeae
Viranga fruit (Embelia ribes) e methanol and aqueous extracts – (e) MDR-Salmonella typhi

E.6.2 Botanicals improving antimicrobial efficacy against resistant strains

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Bibhitaki fruit (Terminalia belerica) ee ethanolic extract – ee/tetracycline & MDR-MRSA
Cassia bark (Cinnamomum cassia) c cinnamaldehyde – c/tetracycline & MDR-E. coli, c/ampicillin or penicillin & MDR-Staph. aureus
Chamomile herb (Matricaria recutita) e extract – c/oxacillin & methicillin-resistant Staph. epidermidis
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*. 

Chinese rhubarb root (*Rheum palmatum*) cs emodin & rhein – cs/ampicillin or oxacillin & MRSA.

Cinnamon bark (*Cinnamomum verum*) e cinnamaldehyde – c/tetracycline & MDR-*E. coli*, c/ampicillin or penicillin & MDR-*Staph. aureus*.

Cinnamon beilschmiedia bark (*Beilschmiedia cinnamomea*) e methanolic extract – (e) MDR-*E. coli*, (e) MDR-Ent. aerogenes*, (e) MDR-*K. pneumoniae*.

Clary sage roots (*Salvia sclarea*) e extract, c salvipisone or aethiopinone – e/oxacillin & methicillin-resistant *Staph. epidermidis*, c-s or c-a/oxacillin, vancomycin, or linezolid & MRSA, MDR-*Staph. epidermidis*.

Clove bud (*Syzygium aromaticum*) e eugenol – c/penicillin & MDR-*Staph. aureus*.

Goldenseal leaves *(*Hydrastis canadensis*) e hydroethanolic extract – c/berberine & MRSA.

Haritaki fruit (*Terminalia chebula*) ee ethanolic extract – ee/tetracycline & MDR-MRSA.

Horseradish root (*Armoracia rusticana*) c allyl isothiocyanate – c/ampicillin or erythromycin & MDR-*Salmonella typhimurium*, c/bacitracin & MDR-*E. coli*, c/bacitracin & MDR-*Staph. aureus*.

Khat leaves (*Catha edulis*) e aqueous extract – c/tetracycline & *Strep. oralis* and *Strep. sanguis*, e/penicillin-G & *Fusobacterium nucleatum*.

Kutaki roots/rhizome (*Picrorhiza kuruoa*) f iridoid glycosides – f/chloroquine & MDR-*Plasmodium yoelli*.

Lesser galangal rhizome (*Alpinia officinarum*) c galangin – c/gentamicin & MRSA.

Mustard seed (*Brassica nigra*) c allyl isothiocyanate – c/ampicillin or erythromycin & MDR-*Salmonella typhimurium*, c/bacitracin & MDR-*E. coli*, c/bacitracin & MDR-*Staph. aureus*.

Oregano herb (*Origanum vulgare* ssp. *hirsutum*) c carvacrol 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/erythrocycin & erythromycin-resistant *Strep. pyogenes*.

Pomegranate fruit peel (*Punica granatum*) ee ethanolic extract – ee/tetracycline & MDR-MRSA.

Sage leaf (*Salvia officinalis*) e extracts, eo essential oil – e,eo/oxacillin & methicillin-resistant *Staph. epidermidis*.

Sappan wood (*Caesalpinia sappan*) e methanol extract – c/ampicillin or oxacillin & MRSA.

Shirazian thyme herb (*Zataria multiflora*) – f/vancomycin & MRSA.

Tea (green) leaf (*Camellia sinensis*) ee ethanolic extract, c EGCG – ee/tetracycline & MDR-MRSA.

Thyme herb (*Thymus vulgaris*) c thymol or carvacrol – 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/erythrocycin & erythromycin-resistant *Strep. pyogenes*.

Turmeric rhizome (*Curcuma longa*) e ethyl acetate extract – c/β-lactams (oxacillin or ampicillin) & MRSA.

**E.6.3** Botanicals enhancing the ordinary efficacy of antibiotics & antiseptics p. 510

Ashwagandha root (*Withania somnifera*) – h/ethambutol, isoniazid, pyrazinamide, and rifampicin & *Mycobacterium tuberculosis*. 

Barberry root bark (Berberis vulgaris) c berberine – c/sulphacetamide & Chlamydia trachoma

Bilberry leaves (Vaccinium myrtillus) e aqueous acetone, e gallic acid – e,c/limezolid, vancomycin & Staph. aureus

Cinnamon (Cinnamomum spp.) f essential oil – f/chlorhexidine & Streptococcus mutans, Lactobacillus plantarum

Clary sage roots (Salvia sclarea) e salvipisone or aethiopinone – c/oxacillin & Staph. aureus, Staph. epidermidis

Clove oil (Syzygium aromaticum) c eugenol – c/ampicillin, chloramphenicol, erythromycin, norfl Roxacin, oxacillin, penicillin, polymyxin B, rifampin, tetracycline, vancomycin & Enterobacter aerogenes, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium

[methanolic extract antagonized the activity of cefoxitin, ciprofloxacin, and gentamicin against E. coli]

Cola seed (Cola nitida) e methanolic extract – c/ciprofloxacin, perfloxacin, levofloxacin & E. coli

Coptis root (Coptis spp.) c berberine – c/sulphacetamide & Chlamydia trachoma

Coriander fruit (Coriandrum sativum) f essential oil – f/chloramphenicol, ciprofloxacin, gentamicin or tetracycline & Acinetobacter baumannii

Garlic clove *(Allium sativum) h fresh cut, e water extract – local h/chlorhexidine & group B Streptococcus, e/isoniazid/rifampicin/ethambutol/pyrazinamide & Mycobacterium tuberculosis, e/isoniazid or rifampicin & Mycobacterium tuberculosis

Geranium leaf (Pelargonium graveolens) f essential oil – f/norfl Roxacin & Bacillus subtilis, Bac. cereus, Staph. aureus or E. coli

Goldenseal root and rhizome *(Hydrastis canadensis) c berberine – c/sulphacetamide & Chlamydia trachoma

Maitake mushroom (Grifola frondosa) f D-fraction – f/vancomycin & Listeria monocytogenes

Manuka (Leptospermum scoparium) f essential oil – f/chlorhexidine & Streptococcus mutans, Lactobacillus plantarum

Oregon grape bark (Mahonia [or Berberis] spp.) c berberine – c/sulphacetamide & Chlamydia trachoma

Peppermint (Mentha piperita) f essential oil, e menthol – f/ciprofloxacin = 1-1.5 & Klebsiella pneumoniae, f/ciprofloxacin ≥ 1 & Staph. aureus, f/oxytetracycline & E. coli, c/oxytetracycline and E. coli

[f/ciprofloxacin < 0.5 or ≥ 4 reduced antibiotic activity against Klebsiella pneumoniae; f/amphotericin B reduced antifungal effect Candida albicans]

Rosemary leaf (Rosmarinus officinalis) f essential oil – f/ciprofloxacin < 3 & Klebsiella pneumoniae

[f/ciprofloxacin reduced antibiotic activity against Staph. aureus; f/amphotericin B reduced antifungal effect on Candida albicans]

Star anise fruit (Illicium verum) f diethyl ether fraction – f/amikacin & Pseudomonas aeruginosa, f/amoxillin, ampicillin, clindamycin, or pipericillin & Staph. aureus

Tea (green) leaf (Camellia sinensis) c catechin EGCG – c/ciprofloxacin & E. coli

Tea tree (Melaleuca alternifolia) f essential oil – f/tobramycin & Staph. aureus, f/tobramycin & E. coli, f/ciprofloxacin = 1.5 & Klebsiella pneumoniae

[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]

Thyme (Thymus vulgaris) f essential oil – f/ciprofloxacin = 1-1.5 & Klebsiella pneumoniae
[\(\text{f/ciprofloxacin} \leq 1.5\) reduced antibiotic activity against \(\text{Staph. aureus}\); \(\text{f/amphotericin B}\) reduced antifungal effect on \(\text{Candida albicans}^{2689}\)]

E.6.6 Botanicals inhibiting efflux of antimicrobial agents by bacteria

Goldenseal leaves (\(\text{Hydrastis canadensis}\)) cs sideroxylin, 6- and 8-desmethyl-sideroxylin – e/berberine & NorA \(\text{Staph. aureus}^{3226}\); e/berberine & NorA MRSA, \(\text{Candida albicans}^{3296}\) cs/berberine NorA MRSA \(\text{Candida albicans}^{3297}\)

E.6.7 Botanicals enhancing [or reducing] the efficacy of antifungal agents

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Agastache herb (\(\text{Agastache rugosa}\)) f essential oil, c estragole – f,c/ketoconazole & \(\text{Blastoschizomyces capitatus}^{3051}\)

Barberry bark (\(\text{Berberis spp.}\)) c berberine – c/\(\text{fluconazole} & \text{Candida albicans}^{3106}\); c/amphotericin B & \(\text{Candida albicans}^{3107}\)

Coptis rhizome (\(\text{Coptis chinensis}\)) c berberine – c/\(\text{fluconazole} & \text{Candida albicans}^{3106}\); c/amphotericin B & \(\text{Candida albicans}^{3107}\)

Goldenseal roots/rhizome * (\(\text{Hydrastis canadensis}\)) c berberine – c/\(\text{fluconazole} & \text{Candida albicans}^{3106}\); c/amphotericin B & Candida albicans \(\text{Candida albicans}^{3107}\)

Mediterranean spurge stem (\(\text{Euphorbia characias}\)) f latex – f/ketoconazole & \(\text{Candida albicans}^{3055}\)

Moroccan thyme herbs (\(\text{Thymus maroccanus, T. broussonetii}\)) f essential oils – f/\(\text{fluconazole or amphotericin B} & \text{Candida albicans}^{2716}\)

Myrtle leaves (\(\text{Myrtus communis}\)) f essential oil – f/amphotericin B & \(\text{Candida albicans or Aspergillus niger}^{2718}\)

Oregano herb (\(\text{Origanum vulgare}\)) f essential oil – f/amphotericin B & \(\text{Candida spp.}^{3052}\); f/nystatin & \(\text{Candida spp.}^{3053}\)

Oregon grape root bark (\(\text{Mahonia spp.}\)) c berberine – c/\(\text{fluconazole} & \text{Candida albicans}^{3106}\); c/amphotericin B & \(\text{Candida albicans}^{3107}\)

Peppermint (\(\text{Mentha piperita}\)) f essential oil, c menthol – [f/amphotericin B reduced antifungal effect \(\text{Candida albicans}^{2689}\)]

Pomegranate fruit peel (\(\text{Punica granatum}\)) e hydroalcoholic extract, f ethyl acetate, c punicalagin – e,f,c/\(\text{fluconazole} & \text{Candida albicans, c/ketoconazole} & \text{Candida albicans}^{3049}\); [not c/nystatin or amphotericin B & \(\text{Candida albicans}^{3049}\)]

Rose geranium leaf (\(\text{Pelargonium graveolens}\)) f essential oil, c geraniol or citronellol – c-g,c- c/ketoconazole & \(\text{Aspergillus flavus}^{3050}\) f/amphotericin B & \(\text{Candida spp.}^{3052}\); f/nystatin & \(\text{Candida spp.}^{3053}\)

Rosemary leaf (\(\text{Rosmarinus officinalis}\)) f essential oil – [f/amphotericin B reduced antifungal activity against \(\text{Candida albicans}^{2689}\)]

Santolina aerial parts (\(\text{Santolina chamaecyparissus}\)) f essential oil – f/clotrimazole & \(\text{Candida albicans}^{3054}\)

Tea (green) leaf (\(\text{Camellia sinensis}\)) [Note: CORRECTION – catechin EGCG in Tea, not in Tea tree leaf] catechin EGCG – c/amphotericin B or fluconazole & \(\text{Candida albicans}^{2366}\)

Tea tree leaf (\(\text{Melaleuca alternifolia}\)) f essential oil [Note: CORRECTION – catechin EGCG not in Tea tree leaf. See Tea above.] – f/amphotericin B & \(\text{Candida spp.}^{3052}\); [f/amphotericin B reduced antifungal effect on \(\text{Candida albicans}^{2689}\)]

Thyme leaf (\(\text{Thymus vulgaris}\)) f essential oil – [f/uncharacterized chemotype)/amphotericin B reduced antifungal effect on \(\text{Candida albicans}^{2689}\)]
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.\textsuperscript{2717}

**E.6.8 Botanicals enhancing efficacy of antiviral agents** p. 512

Clove oil (*Syzygium aromaticum*) e eugenol – e/acyclovir & herpes simplex virus types 1 & 2\textsuperscript{2955}

**E.6.9 Botanicals enhancing the efficacy of immunizations against infections** p. 512

Larch bark (*Larix* spp.) cs arabinogalactans – pneumococcal vaccine\textsuperscript{2739}

**E.6.10.a Botanicals reducing adhesion of bacteria that cause infections** p. 512

Black horehound herb (*Ballota nigra*) e aqueous extract – MRSA\textsuperscript{3350}

Cranberry fruit (*Vaccinium macrocarpon*) j juice, jc juice cocktail, f high molecular weight compounds – jc (*E.coli*),\textsuperscript{3002} j (Streptococcus criceti, Strep. gordonii, Strep. mitis, Strep. mutans, Strep oralis, Strep. sanguinis, Strep. sobrinus);\textsuperscript{2843} f-hmw (Porphyromonas gingivalis),\textsuperscript{2841} (Strep. sobrinus)\textsuperscript{2842}

Motherwort leaves (*Leonurus cardiaca*) e aqueous-acetone (30:70) extract, c ursolic acid – e (Staphylococcus aureus), c (Staph. aureus)\textsuperscript{3460}

Tassel hyacinth bulb (*Leopoldia comosa*) ae aqueous extract, ee ethanolic extract – ae MRSA, ee MRSA\textsuperscript{3350}

**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*)\textsuperscript{3295}

**E.6.11 Botanicals reducing adverse effects caused by antimicrobial agents** NEW

Ashwagandha root (*Withania somnifera*) – e/gentamicin\textsuperscript{3253}

Black cumin seed oil (*Nigella sativa*) c thymoquinone – c/gentamicin\textsuperscript{3259}

Cordyceps (*Cordyceps sinensis*) h mycelium, e water extract – h/amikacin (kidney), h/gentamicin (kidney), h/gentamicin (kidney), e/kanamycin (kidney)*\textsuperscript{398}

Garlic leaves or cloves *(Allium sativum)* h-c cloves, h-l leaves, e aged extract, c diallyl sulfide or diallyl disulfide – h/gentamicin,\textsuperscript{1911,3387} c-ds or c-dd/gentamicin,\textsuperscript{1912,1913} e/gentamicin\textsuperscript{1914,1915}

Gentian root (*Gentiana lutea*) hydroethanolic extract – e/ketoconazole\textsuperscript{3353}

Ginkgo leaf (*Ginkgo biloba*) e standardized extract – e/gentamicin, e/gentamicin\textsuperscript{3260}

Milk thistle seed (*Silybum marianum*) f silymarin – f/metronidazole (stomach, liver, kidney)\textsuperscript{3267}

Spiny sowthistle herb (*Sonchus asper*) e methanolic extract – e/gentamicin (kidney, liver)\textsuperscript{3619}
References
3 CORRECTIONS:
1567. WEBSITE IS NOW – http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx [updated Nov. 14, 2011]
   [This primary article citation replaces a secondary source.]


2823. FDA Drug Safety Communication: Low magnesium levels can be associated with long term use of proton pump inhibitor drugs (PPIs). http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm; Mar. 2, 2011


3079. Mohamed M-EF, Fry RF. Inhibitory effects of commonly used herbal extracts on UDP-glucuronosyltransferase 1A4, 1A6, and 1A9 enzyme activities. *Drug Metabol. Dispos.*, 39(9):1522-1528, 2011


3121. Akpolat M, Kanter m, Uzal MC. Protective effects of curcumin against gamma radiation-induced iliac mucosal damage. *Arch. Toxicol.*, 83:609-617, 2009


3191. Mohamed M-EF, Frye RF. Inhibition of intestinal and hepatic glucuronidation of mycophenolic acid by Ginkgo biloba extract and flavonoids. Drug Metab. Dispos., 38(2):270-275, 2010
3200. Aqil F, Khan MSA, Owais M, et al. Effect of certain bioactive plant extracts on clinical isolates of β-
lactamase producing methicillin resistant *Staphylococcus aureus*. *J. Basic Microbiol.*, 45(2):106-
114, 2005
3201. Muto S, Fujita K, Yamazaki Y, et al. Inhibition by green tea catechins of metabolic activation of
3202. Nishikawa M, Ariyoshi N, Kotani A, et al. Effects of continuous ingestion of green tea or grape seed
3204. Farabegoli F, Papi A, Bartolini G, et al. (-)-Epigallocatechin-3-gallate downregulates Pg; and PCRP
in a tamoxifen resistant MCF-7 cell line. *Phytomed.*, 17:356-362, 2010
3206. Shin S-C, Choi J-S. Effects of epigallocatechin gallate on the oral bioavailability and
pharmacokinetics of tamoxifen and its main metabolite, 4-hydroxytamoxifen in rats. *Anti-Cancer
Drugs*, 20:584-588, 2009
3209. Choi J-S, Burm J-P. Effects of oral epigallocatechin gallate on the pharmacokinetics of nicardipine in
3211. Torkelson CJ, Sweet E, Martzen MR, et al. Phase 1 clinical trial of *Trametes versicolor* in women
3214. Ganasoundari A, Zare SM, Uma Devi P. Modification of bone marrow radiosensitivity by medicinal
3215. Uma Devi P, Bisht KS, Vinitha M. A comparative study of radioprotection by Ocimum flavonoids
3216. Kathikeyan K, Ravichandran P, Govindasamy S. Chemopreventive effect of *Ocimum sanctum* on
3217. Kar A, Choudhary BK, Bandyopadhyay NG. Comparative evaluation of hypoglycaemic activity of
properties of *Ocimum sanctum* Linn. *J. Ethnopharm.*, 93:197-206, 2004
3219. Vats V, Yadav SP, Grover JK. Ethanolic extract of *Ocimum sanctum* leaves partially attenuates
streptozotocin-induced alterations in glycogen content and carbohydrate metabolism in rats. *J.
Ethnopharm.*, 90:155-160, 2004
3220. Sakina MR, Dandiya PC, Hamdard ME, et al. Preliminary psychopharmacological evaluation of


