UPDATES AND ADDITIONS
for

Herbal Contraindications & Drug Interactions
plus Herbal Adjuncts with Medicines

FOURTH EDITION

by Francis Brinker, N.D.

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NOTICE

Information provided in the book or these updates and additions is not intended as recommendations for self treatment or to substitute 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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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 updates or new information* (+) *added.*

Aloe
American ginseng +
Amla ^
Arnica +
Asian ginseng +
Astragalus +
Barberry +
Bilberry +
Bitter orange
Black cohosh
Black cumin +
Black pepper +
Cannabis +
Cassia +
Cayenne
Chamomile
Chili ^
Chinese skullcap +
Cinnamon +
Clove +
Cocoa +
Cola +
Coptis +
Cranberry
Crucifers +
Dong Quai +
Echinacea angustifolia
Echinacea pallida +
Echinacea purpurea +
English plantain +
Fenugreek
Frankincense +
French maritime pine +
Garlic +
Ginger +
Ginkgo
Goldenseal +
Grapefruit ^
Guarana +
Hops +
Horse chestnut +
Kava

Kudzu +
Kutaki +
Larch ^
Licorice ^
Long pepper +
Maitake +
Milk thistle +
Oregon grape +
Passion flower
Pomegranate +
Prickly pear
Psyllium
Schisandra +
Soy +
St. John's wort
Stinging nettle
Sweet annie +
Tea +
Thunder god vine
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.7.4.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 D_3 ^

E.5.9 Potential Herbal Prevention of Dermal Photocarcinogenesis ^

E.5.10 Herbal Prevention of Acute UV-induced Erythema ^

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.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

Contraindications, Drug Interactions and/or Complementary Adjuncts

ALOE p. 34

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

Drug Interactions

Ia. 1) Increased the hypoglycemic effect of **glyburide** [**glibenclamide]** when given twice daily for 42 days (PO in human clinical study).[122]
The juice processed with catalase and removal of anthroquinones and monosaccharides reduced blood glucose levels to normal in type 2 diabetes with diet-induced obesity, apparently by decreasing insulin resistance (PO in mice). Plasma insulin was lowered, as were plasma and liver triglycerides.[2741]

AMERICAN GINSENG p. 37

Panax quinquefolius root

Contraindications

II. 1) Estrogen-independent proliferation of human breast cancer cell with the alcoholic extract (*in vitro*)[1664] suggests avoiding regular consumption with a history of **breast cancer** (speculative).
HOWEVER, a standardized proprietary extract with no effect on the cell cycle significantly inhibited estrogen-receptor positive breast cancer cell proliferation at concentrations of 500 mcg/ml and higher (*in vitro*),[981] as did a water-extract on the same cells (*in vitro*).[3063] A freeze-dried water extract of the root significantly reduced proliferation of these estrogen-sensitive human breast cancer cells, as well as antiproliferation and resistance to stimulated COX-2 expression in estrogen-receptor negative breast cancer cells (*in vitro*).[3062] Though a fresh-root extract had no effect, a 70% ethanol steam-processed root extract with increased ginsenoside Rg3, as well as isolated Rb3, significantly decreased proliferative activity of estrogen-receptor positive and negative human breast cancer cells by arresting the cell cycle in G1-phase (*in vitro*).[3061] In conjunction with the synergistic effect with chemotherapeutic agents against breast cancer cells [See Complementary Adjuncts IIb. 1.], the weight of *in-vitro* evidence now seems to suggest a potential benefit in breast cancer (speculative).

Drug Interactions

Ia. 1) 3 grams root or more reduced blood sugar in type-2 diabetics treated with **sulfonylureas** or a combination with **metformin** (PO in human study).[1114]
Either 1, 2, 3, 6, or 9 grams of the ground root improved glucose tolerance when given 40 minutes prior to a 25-gram glucose challenge in 10 nondiabetics (PO in human studies).[1685,2917]

III. 1) The saponin fraction enhanced **phenylephrine** vasoconstrictor effect (*in vitro*).[1550]
HOWEVER, when 16 hypertensive patients were randomly given 3 grams of root from 6 different farms in Ontario, Canada, for 1 day each, none produced an overall mean change in blood pressure compared to baseline over a period of 160 minutes (PO in human study). Thirteen were taking 1 or more antihypertensive drugs, including 6 on diuretics, 6 on ACE inhibitors, 3 on calcium channel blockers, 2 on beta blockers, and 2 on angiotensin receptor blockers. After monitoring every 10 minutes, increases in mean systolic blood pressure after 140 minutes and diastolic blood pressure after 160 minutes were countered by a lowered mean diastolic pressure at 100 minutes, compared to mean pressures from 2 days on placebo.[2915]

Complementary Adjuncts

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

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

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

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

+ 3) Pretreatment with 100 and 200 mg/kg of ginsenosides Rb_1 or Rg_1 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 Rb_1 or Rg_1, along with inhibition of the accompanying dopamine supersensitivity.[2929,2931]

IIb. + 2) A 70% ethanolic extract of 4-hour steamed roots, with greatly altered ginsenoside content including 78 mg/g Rg3, 25 mg/g 20R-Rg2, 23 mg/g Rg2, 16 mg/g Rb1, and 12 mg/g Rh2, increased apoptosis of HCT116 and SW480 colorectal cancer cells maximally when combined antioxidants **N-acetyl cysteine** or **vitamin C** that lowered the reactive oxygen species generated and increased apoptosis (*in vitro*).[2923]

AMERICAN GINSENG

^ berry

Complementary Adjuncts

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

AMLA NEW

Emblica officinalis = Phyllanthus emblica fruit

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

Complementary Adjuncts

IIa. 1) At 250 and 500 mg/kg, the aqueous extract given for 7 days before a single 40 mg/kg dose of **cyclophosphamide** was shown to inhibit the bone marrow chromosomal mutations induced by the anticancer drug (PO in mice).[2853] At 100 mg/kg the aqueous extract taken for 10 days reduced

immunosuppression of humoral immunity by cyclophosphamide (PO in mice).[2855] This may be due to the reduction of CYP450 levels in the liver, since cyclophosphamide is bioactivated by CYP450, or it may be due to the increased liver and kidney levels of glutathione, glutathione-S-transferase, or other detoxification and antioxidant enzymes as shown in animals with both the aqueous and ethanolic extracts (PO in mice).[2853,2854,2855]

2) When a 50% ethanolic extract was given at 75 mg/kg 4 hours before exposure to 5 g/kg **alcohol** (**ethanol**) was given to induce hepatotoxicity, it significantly reduced serum transaminases ALT and AST and interleukin(IL)-1beta similar to 5 mg/kg silymarin, as compared to controls (PO in rats). Similarly, when 75 mg/kg of the amla extract was given daily for 7 days after 21 days of 4 g/kg/day of ethanol, ALT and IL-1beta were reduced greater than no treatment and slightly better than 5 mg/kg silymarin. In rat liver cells exposed to alcohol, the ALT was also shown to be significantly reduced by the extract at 0.5 mg/ml (*in vitro*).[2856]

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

IIb. 1) Ethanolic extract of the fruit was shown to protect against cardiotoxicity of **doxorubicin** by increasing the IC_{50} 12-fold without impacting its antitumor activity on HeLa cells (*in vitro*).[2859] The aqueous extracts of the dried fruit increased the cytotoxicity of both doxorubicin and **cisplatin** against human liver cancer cells and lung cancer cells (*in vitro*).[2860]

ARNICA p. 41

**Arnica montana* flowers

Complementary Adjuncts

Ia. + 1) A preparation made with 50 g fresh herbal 1:20 tincture in 100 g of gel was compared to a 5% ibuprofen gel for 21 days on hand osteoarthritis in 204 randomized subjects for whom 500 mg **acetaminophen** (**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]

ASIAN GINSENG p. 44

Panax ginseng root

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]

Complementary Adjuncts

Ia. 3) Following surgery for stage III gastric cancer, red ginseng powder doubled survival rates in patients given **5-fluorouracil** and **cisplatin** (PO in human clinical study).[1382]

The aqueous extract of the steamed Korean red ginseng root at a concentration of 2.5 mcg/ml containing ginsenosides Rb_1 and Rg_1 significantly attentuated auditory hair cell damage caused by cisplatin (*in vitro*). This prevention of ototoxicity was due to inhibition of the free radical generation and apoptosis by cisplatin (*in vitro*).[2725]

\+ 5) Just under half of the 61 patients between the ages of 50-80 years with Alzheimer's disease who were being treated with **donepezil**, **galantamine**, **memantine**, or **rivastigmine** were also given 4.5 g/day or 9.0 g/day of Korean red ginseng root powder for 12 weeks and monitored by cognitive tests (PO in human clinical trial). At the open-label study's end, those receiving the higher ginseng dose had significantly lower scores on the Alzheimer's Disease Assessment Scale [ADAS] and its cognitive component and the Clinical Dementia Rating scale.[3059] In a similar 12-week study by the same researchers with Alzheimer's patients ages 47-83 years, 39 active treatment controls and 49 additionally receiving 4.5 g/day Korean white ginseng root powder and 9 given 9 g/day ginseng, significant improvements were shown on the ADAS cognitive subscale and the mini-mental state examination for the ginseng groups (PO in human clinical study). There were no significant differences in scores between the 2 ginseng doses. When the ginseng use was stopped, the improved scores decreased over 12 weeks to control levels.[3060]

IIa. + 3) Pretreatment with 100 and 200 mg/kg of ginsenosides Rb_1 or Rg_1 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 Rb_1 or Rg_1, along with inhibition of the accompanying dopamine supersensitivity.[2929,2931] The inhibition of methamphetamine-induced hyperlocomotion and conditioned place preference by 50 and 150 mg/kg of unspecified ginsenosides was associated with stimulation of adenosine A_{2A} receptors (IP in mice).[2930]

ASTRAGALUS p. 51

Astragalus membranaceus, Astragalus mongholicus root

Complementary Adjuncts

IIa. + 3) Equal quantities of astragalus root and dong quai (*Angelica sinensis*) root were extracted with ethanol and water, the extracts combined, and 2.1 grams daily given with or without the ACE inhibitor **enalapril** to monitor kidney fibrosis and compared to enalapril alone (PO in rats). The tubulointerstitial fibrosis was reduced by the herbal extract and enalapril separately along with transforming growth factor-β1 [TGF-β1], but the herbal-drug combination had the greatest effect by significantly reducing TNF-α, collagen accumulation, fibroblast activation, tubular cell apoptosis more than enalapril alone.[2728] A decoction of equal parts of the 2 roots given at the same dose was previously shown a decrease in TGF-β1 puromucin-induced nephrosis similar to enalapril (PO in rats),[2729] while 3.6 g/kg daily dose of a 5:1 mixture of astraglus 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

Drug Interactions

Ia. 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 transminases ALT and AST (PO in human clinical trial).[2908]

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

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

IIa. + 4) Berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive locomotor activity induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that berberine may help reduce the chronic cocaine psychological dependence (speculative).[2753]

+ 5) When taken with a high cholesterol and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).[2932] When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.[2933] The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);[2932] berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).[2933]

BILBERRY p. 58

Vaccinium myrtillus fruit

Complementary Adjuncts

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

BITTER MELON p. 59

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]

BITTER ORANGE p. 60

Citrus aurantium fruit, juice, or peel

Drug Interactions

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

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

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

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

III. 2) Use of the juice with **substrates of CYP3A4** may increase the absorption (speculative), due a 40% reduction of this isozyme (PO in humans).[1031]
The decoction of the fruit and unripe fruit were slightly inhibitory of **testosterone** metabolism by CYP3A4 (*in vitro*).[1633]

BLACK COHOSH p. 61

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

Contraindications

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

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

Complementary Adjuncts

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

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

BLACK CUMIN p.66

Nigella sativa seed

Complementary Adjuncts

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

In a 3-month randomized study with 29 asthma patients taking inhaled corticosteroids, mostly using **beclomethasone** or **fluticasone** inhalers, and oral corticosteroids, **theophylline**, and **beta-agonists**, wheezing and coughing and asthma severity were significantly improved by the end of the study with 15 using black cumin decoction compared to 14 controls, along with decreased use of all of the drugs by the extract group and no drug reduction by control subjects (PO in human clinical study).[2988] In a group of 15 moderate to severe asthma patients on medications who temporarily and briefly suspended use of theophylline and beclomethasone or fluticasone inhalers but continued with **prednisolone** use, bronchodilation from boiled black cumin extract at 50 or

100 mg/kg was significantly improved compared to the corticosteroid alone, though significantly less when compared to prednisolone with theophylline or salbutamol (PO in human clinical study).[2989]

+ 2) Doses 3 times daily of 250 mg or 500 mg of the powdered seed significantly and dose-dependently reduced acute opiate withrawal symptoms compared to placebo in an open study of 50 **opioid** addicts treated for 12 weeks and as in-patients for the first 12 days (PO in human clinical study). Based on historical controls, craving and relapses were also reduced. Diazepam was used to some to help sleep.[2982]

IIa. 2) The use of thymoquinone at 5 mg/kg daily with **ifosfamide** reduced the severity of the drug-induced Fanconi syndrome with its kidney damage (PO in rats), while the same combination used in treating Ehrlich ascites carcinoma xenograft significantly enhanced antitumor effects, along with lower mortality rate and less weight loss, compared to use of ifosfamide alone (PO in mice).[2431]

+ 3) The hepatotoxicity caused by **acetaminophen** as shown by significant increases in ALT, total nitrate/nitrite, and lipid peroxide and decreased glutathione was prevented by 5 days of 2 mg/kg/day of thymoquinone (PO in mice). The effect was apparently not due to influence on metabolic activation of acetaminophen.[2983]

+ 4) When the seed oil was given at 880 mg/kg for 2 weeks before a 1 ml dose of **ethanol**, it significantly reduced formation of stomach ulcers by increasing mucosal glutathione levels and mucin and decreasing mucosal histamine (PO in rats).[2984] 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]

BLACK PEPPER p. 67

Piper nigrum fruit

Complementary Adjuncts

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]

CANNABIS p. 83

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

Contraindications

I. 3) Avoid **prolonged use** by smoking, since this may cause delirium (empirical)[628] or psychological dependance (empirical, IH in human study).[628,1198]
An 8.4-year follow-up cohort study found that the risk of persistent psychotic symptoms was significantly greater in those with continued cannabis use (IH in human study). This was

independent of an association of cannabis use with pre-existing psychotic symptoms, thus finding no evidence for the risk actually being due to use of cannabis as a self-medication for psychotic symptoms.[2969]

Drug Interactions

Ib. 1) [NOTE: The order of this information has been reversed.] Concurrent abuse of cannabis and other substances is not uncommon (empirical)[628] and results in greater intoxication and impairment when it is combined with **opiates**, **ethanol**, or **barbiturates** (IH in human studies).[1076,1077]

Cannabis use is more common among those prescribed chronic opioid therapy (human studies).[2746] Those who are dependent on **codeine** are more likely to use cannabis than nondependent regular codeine users [23% vs. 5%, respectively] and to use codeine for its pleasurable effects, to relax, or to prevent withdrawal (human study).[2747]

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

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

Complementary Adjuncts

Ia. 1) Vomiting induced by cancer **chemotherapy** agents was relieved by cannabis in 78% of the patients (IH in human clinical study).[1078]

In a randomized, double-blind, crossover trial, when 15 osteogenic sarcoma patients on high-dose **methotrexate**chemotherapy used oral 10 mg/m^2 THC 5 times daily and smoked THC in cannabis after initial vomiting episodes, 14/15 responded and nausea and vomiting were signicantly reduced compared to using placebo and cannabis with no THC (PO and IH in human clinical study). The incidence nausea and vomiting diminished with increasing plasma THC concentrations.[2942] In 14 controlled trials with 681cancer patients using THC for chemotherapy-induced vomiting, THC was as, or more, effective than standard antiemetic drugs (PO in human clinical trials) . In addition, 2 controlled studies showed THC retarded chronic weight loss and stimulated appetite in patients with advanced cancers, and 2 other controlled studies with 46 patients showed THC in doses of 10-20 mg was effective for cancerous pains (PO in human clinical studies).[2944]

HOWEVER, in another trial with the same protocol for oral THC or smoked after a vomiting episode, for 8 cancer patients taking adriamycin and cytoxan only 3/8 had a reduction of nausea and/or vomiting (PO and IH in human clinical study).[2943] A comparative study with 20 cancer patients using oral THC and smoked cannabis for chemotherapy-induced vomiting found efficacy in only 5; overall, 7 preferred THC, 4 preferred cannabis, and 9 had no preference (PO vs IH in human clinical study). Perceptual distortions occurred in 7 including 4 with THC, 2 with cannabis, and 1 with both.[2944]

\+ 2) In 125 patients with peripheral neuropathic pain who remained on stable analgesia including 86 on **opioids** [15 on the stronger **morphine**, **methadone, oxycodone**, or **pethidine** and 71 on the weaker **tramadol, codeine, dihydrocodeine**, and **dextropropoxyphene**] as well as 41 on non-opioid **analgesics** or **anti-inflammatory** drugs, those who received a standardized cannabis extract oromucosal spray with equivalent amounts of THC and cannabidiol for 5 weeks had significantly reduced pain intensity and better sleep than those on placebo (human clinical study). The cannabis group also had greater sedation and GI side effects, and 18% withdrew compared to 3% placebo withdrawals. Extending the study to 1 year maintained pain relief without increased dose or toxicity.[2748] In a crossover trial with 21 neuropathic pain patients, 25 mg of cannabis with

9.4% THC 3 times daily for 5 days compared to cannabis with 0% THC significantly improved average daily pain intensity and sleep; routine medications continued by the patients included opioids by 61%, **antidepressants** by 52%, **anticonvulsants** by 43%, and **NSAIDs** by 43% (IH in human clinical study). Though mild, adverse effects were more frequent with the higher THC dose.[2940]

+ 3) The 28 patients with distal sensory polyneuropathy as an expression of HIV neuropathic pain who completed a randomised crossover trial using cannabis for 1 week (IH in human clinical study) maintained the use of pain-modifying agents including 18 on **opioids** , 18 taking **anticonvulsants**, 10 who used **acetaminophen** or **NSAIDs**, and 8 on **tricyclic antidepressants**. Additional pain relief in daily functioning was significantly greater with cannabis than with a placebo without THC. Changes in morphine equivalent doses and pain severity did not differ between those who used concomitant opioids and those who did not. Changes in aspirin equivalents were minimal.[2848] In 50 HIV patients with chronic painful sensory neuropathy who were randomly assigned to smoke cannabis or an identical placebo 3 times daily for 5 days, the cannabis group had a significantly greater 34% reduction in daily pain, with 52% having over 30% reduced pain compared to 24% with this effect while using placebo (IH in human clinical study). About half used concomitant medications divided similarly between **gabapentin**, opioids, and others. Experimentally induced hyperalgesia from topical **capsaicin** application was also significantly reduced in those subjects smoking cannabis.[2847]

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

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

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

CASSIA p. 86

Cinnamomum cassia = *Cinnamomum aromaticum* bark

Drug Interactions

Ia. 1) A 9:1 cassia extract at 336 mg/day for 4 months significantly reduced serum glucose in type 2 diabetics with poor glycemic control taking **oral hypoglycemics** including **sulfonylureas** and **metformin** or both (PO in human clinical study).[1900]

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

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

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

CAYENNE p. 90

**Capsicum frutescens* fruit

Contraindications

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

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

CHAMOMILE p. 94

Matricaria recutita = Matricaria chamomilla herb or flowers

Contraindications

II. 1) [Clarification: Regular] internal consumption should be avoided in **pregnancy**.[2]

A study of 392 pregnant Italian women found that those 37 who were regular users of chamomile had a 21.6% higher frequency of threatened miscarriages, mostly in the 4th-5th month of gestation, and a 21.6% increase in preterm labors compared to non-users (PO in human study).[3078]

Complementary Adjuncts

Ia. 1) A flower extract as a mouth rinse effectively treated <u>oral mucositis</u> 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]

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.: chilli)

Contraindications

I. 1) Do not use in chronic **irritable bowel**,[24,777] due to neural irritant and intestinal contractile properties of capsaicin (*in vitro*, animal, and human studies).[176]

2) Avoid use with **allergic hypersensitivity**, since this may result in urticaria (empirical).[17]

Drug Interactions

Ia. 1) Intestinal absorption of **iron** (**ferrous sulfate**) as part of fortified fish sauce with vegetables and rice was reduced 38% when it was taken with 4.3 g chili pepper with 25 mg polyphenols (PO in human study). This chili did not affect gastric acid secretion. No effect 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] Dilute capsaicin at 0.1 mcg/kg protected the stomach from mucosal damage by ethanol (PO in rats).[1120]

HOWEVER, at 10-30 mg/kg capsaicin aggravated the damage caused by ethanol (PO in rats).[1120]

CHINESE SKULLCAP p. 100

Scutellaria baicalensis root

Complementary Adjuncts

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

CINNAMON p. 102

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

Drug Interactions

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

CLOVE p. 103

Syzygium aromaticum = *Eugenia caryophyllata* buds

Complementary Adjuncts

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

\+ 2) Pretreatment with 10-100 mg/kg of eugenol an hour before administration of a single 1 ml dose of **ethanol** significantly reduced the alcohol-induced formation of stomach ulcers both in number and degree of damage (PO in rats).[2958]

COCOA p. 104

Theobroma cacao seed

Drug Interactions

III. + 2) Consumption of single doses of 300 ml cocoa containing 897 mg flavanols and 81 mg **aspirin** alone and combined in a crossover trial with 16 subjects demonstrated that these two agents had similar and additive effects inhibiting platelet function and inhibiting platelet activity shown by P-selectin expression induced by collagen with epinephrine, but not collagen with ADP, after 2 and/or 6 hours (*ex vivo*).[2906] When cocoa tablets with 234 mg flavanols and procyanidins were taken daily for 28 days by 13 subjects, the P selectin expression and collagen- and ADP-induced platelet aggregation was significantly reduced compared to the 15 in the placebo group (*ex vivo*).[1447]

Complementary Adjuncts

Ia. + 1) Cocoa that supplied 963 mg flavanols daily to patients with <u>diabetes type 2</u> on **oral hypoglycemics**, **insulin**, **antiplatelet drugs**, **statins**, **beta blockers**, and/or **ACE inhibitors** increased flow-mediated dilation (PO in human clinical study).[2600]
Twelve subjects with type 2 diabetes, 5 using the oral hypoglycemic **metformin**, 8 taking statins, and 3 on **antihypertensives**, consumed daily for 8 weeks each with a 4-week washout 3 chocolate bars of 15 grams each with 16.6 mg epicatechins and 3 chocolate bars with > 2 mg epicatechins; only the high epicatechin bars led to significantly increased HDL and lower ratio of total cholesterol:HCL (PO in human clinical trial). The beneficial changes reverted to baseline values when the high epicatechin chocolate intervention stopped. No changes in weight gain, glycemic control, insulin resistance or the inflammatory marker C-reactive protein were noted with either type of chocolate bar.[2740]

\+ 2) In 20 patients with <u>congestive heart failure</u>, 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 ***<u>Escherichia coli</u>*** 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 p. 113

Coptis chinensis and *Coptis groenlandica* rhizomes

Drug Interactions

Ia. 1) The combination of 1500 mg berberine daily for 3 months in 43 type 2 diabetes patients with one or more **oral hypoglycemic** medications including **sulfonylureas**, **metformin acarbose**, and/or **insulin** resulted in lower blood sugar through week 12 (PO in human clinical study).[2315]
In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered fasting and postload plasma glucose and HbA1c compared to 52 diabetics on placebo, along with significantly reducing the triglycerides, total cholesterol, and LDL-cholesterol, body weight, and systolic blood pressure (PO in human clinical study).[2907] In 50 type 2 diabetic patients randomly selected to use 1 gm berberine daily, the 26% and 18% significant reductions in fasting blood glucose and HbA1c were equivalent to those of the 26 and 21 diabetic patients who used

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

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

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

IIa. + 4) A methanolic extract of *C. chinensis* rhizome at doses of 100, 200, and 400 mg/kg and berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive locomotor activity induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the coptis and berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that coptis and berberine may help reduce the chronic cocaine psychological dependence (speculative), since coptis rhizome has been used in the treatment of substance abuse (empirical).[2753]

\+ 5) When taken with a high cholesterol and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).[2932] When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.[2933] The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);[2932] berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).[2933]

CRANBERRY p. 117

Vaccinium macrocarpon fruit

Drug Interactions

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

HOWEVER, when 30 patients on warfarin with stable INRs of 1.7-3.3 were randomized to 240 ml cranberry juice cocktail or matching placebo daily for 2 weeks, there was no resulting

differences between groups in plasma R- or S-warfarin concentrations (PO in human clinical trial). The only significant difference between groups in mean INRs measured every 3 days was on day 12, when the cranberry group INR value was higher, but by day 15 the groups values were equivalent.[2763] The juice of only 1 of 5 commercial cranberry juice samples tested showed significant inhibitory effects on metabolism of warfarin by CYP2C9 (*in vitro*). When 16 healthy volunteers consumed the inhibitory cranberry juice prior to a single dose of warfarin, its bioavailability and its half-life were not increased (PO in human study). The inhibition (*in vitro*) did not correlate with warfarin clearance (*in vivo*), since warfarin metabolism in the liver of living subjects is remote from the site of exposure to the inhibitory cranberry components in the intestines.[3083]

Complementary Adjuncts

IIa. 1) Cranberry extract at 100 mg/kg daily for 10 days reduced the cardiotoxicity of a single 15 mg/kg IP dose of **doxorubicin** given on the seventh day (PO in rats). The antioxidant extract reduced mortality and ECG changes, while inhibiting glutathione depletion, oxidized glutathione and malondialdehyde accumulation, and elevation of myeloperoxidase and lactose dehydrogenase, among other improvements to doxorubicin cardiotoxic effects.[3080]

CRUCIFERS p. 120

Brassica spp. heads or leaves

Complementary Adjuncts

IIa. + 1) The glucosinolate hydrolysis product indole-3-carbinol from cruciferous vegetables protected against hepatotoxicity from the antitumor drug **trabectidin** when given at 0.5% of the diet for 6 days prior, but it did not interfere with trabectidin's antitumor efficacy (PO in rats). A dietary concentration of only 0.1% indole-3-carbinol was not protective, nor was 0.2% of its acid condensation product, diindolylmethane.[2177]

2) The isothiocyanate sulfurophane, derived mostly from broccoli sprouts, reduced hepatotoxicity activities induced by **cisplatin** when sulforaphane was given at 500 mcg/kg daily for 3 days prior to the cisplatin (IP in rats). The reduced damage was a result of protection of liver mitochondrial function and antioxidant enzymes and prevention of oxidative stress.[2934]

DOG ROSE p. 126

Rosa canina dried fruit (hips)

Complementary Adjuncts

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

DONG QUAI p. 127

Angelica sinensis root

Complementary Adjuncts

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

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

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

IIa. + 4) Equal quantities of astragalus root (*Astragalus membranaceus*) and dong quai root were extracted with ethanol and water, the extracts combined, and 2.1 grams daily given with or without the ACE inhibitor **enalapril** to monitor kidney fibrosis and compared to enalapril alone (PO in rats). The tubulointerstitial fibrosis was reduced by the herbal extract and enalapril separately along with transforming growth factor-β1 [TGF-β1], but the herbal-drug combination had the greatest effect by significantly reducing TNF-α, collagen accumulation, fibroblast activation, tubular cell apoptosis more than enalapril alone.[2728] A decoction of equal parts of the 2 roots given at the same dose was previously shown a decrease in TGF-β1 puromucin-induced nephrosis similar to enalapril (PO in rats),[2729] while 3.6 g/kg daily dose of a 5:1 mixture of astraglus 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]

ECHINACEA ANGUSTIFOLIA p. 129

Echinacea angustifolia roots

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

Contraindications

I. 1) **Allergic hypersensitivity** to plants in the Asteraceae family (empirical).[777,1890]
A man with a long history of asthma and hay fever developed hypereosinophilia and very elevated IgE associated with abdominal cramps and occassional 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]

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 occassional 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 occassional 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

Ia. + 3) The dried juice dose of 500 mg daily together with10 mg zinc, 15 mcg selenium and 50 mg vitamin C given to 37 chronic obstructive pulmonary disease [COPD] patients with acute upper respiratory tract infections treated with **ciprofloxacin** helped to lessen and shorten exacerbations compared with 32 given placebo, in a double-blind, randomized study of mostly male patients with a mean age of 66 years (PO in clinical study).[2796]

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

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

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

ECHINACEA PURPUREA root p. 136

Contraindications

I. 1) **Allergic hypersensitivity** to plants in the Asteraceae family (empirical).[777,1890]
A man with a long history of asthma and hay fever developed hypereosinophilia and very elevated IgE associated with abdominal cramps and occassional 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 trail with 15 HIV patients receiving anti-retroviral treatment with darunavir/rionavir, 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]

Complementary Adjuncts

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

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

ENGLISH PLANTAIN p. 142

Plantago lanceolata leaves

Complementary Adjuncts

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

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

FENUGREEK p. 151

Trigonella foenum-graecum seed

Drug Interactions

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

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

Hypoglycemic activity was also shown in diabetes melitus type 2 with 100 grams defatted seed powder for 10 days with 15 patients taking **glyburide** (**glibenclamide**), **glipizide**, and/or **metformin** (PO in human clinical study).[1645] In 10 type 2 diabetic patients on stable glibenclamide using 25 grams of the powdered seeds daily for 15 days in a crossover design, plasma glucose was significantly lower following an IV glucose tolerance test (PO in human clinical study).[130] In 21 patients taking 15 grams powdered seeds soaked in water, of whom 10 were using glibenclamide and metformin and 7 glibenclamide alone, postprandial levels were significantly reduced (PO in human study).[961] In 20 patients with mild cases of type 2 diabetes, but not in 20 with severe cases, using 5 grams of fenugreek powder daily without oral hypoglycemic drugs significantly reduced fasting and postprandial blood sugar after 1 month (PO in human clinical study).[339]

FRANKINCENSE p. 158

Boswellia serrata resin

Complementary Adjuncts

Ia. 1) In osteoarthritis of the knee, those taking placebo used **ibuprofen** more than subjects using 100 mg/day of extract with 30% 3-O-acetyl-11-keto-beta-boswellic acid [AKBA], but outcomes were significantly better in the extract group (PO in human clinical study).[2483]
A randomized, placebo-controlled, double-blind trial for 90 days with 60 knee osteoarthritis patients using ibuprofen and 100 mg extract with 30% AKBA or 100 mg of 20% AKBA and oil both had significantly less pain and stiffness than placebo, but the AKBA/oil group had a quicker response and significantly better functional ability scores than placebo (PO in human clinical study).[2804]

+ 2) In a randomized double-blind study of 44 brain tumor patients receiving radiotherapy for several weeks, **dexamethasone** was used to control cerebral edema, but those also taking 4200 mg of H15 extract daily had significantly reduced brain swelling at therapy's end compared to baseline than those using placebo (PO in human clinical study). The dexamethasone doses were individualized, but the differences between the groups were not significant. Six patients in the boswellia group, but none in the placebo group, had diarrhea. There were no differences in quality of life or mental functioning between the 2 groups.[2846]

FRENCH MARITIME PINE p. 158

Pinus pinaster = Pinus maritima bark fraction

Complementary Adjuncts

Ia. 1) The polyphenol fraction used in high blood pressure allowed significant reduction of **nifedipine** dosage compared to placebo (PO in human clinical study).[1623]

Also, 150 mg/day Pycnogenol for 8 weeks compared to placebo significantly reduced the capillary filtration leading to tissue edema associated with nifedipin used in the treatment of hypertension in 30 patients (PO in human clinic study). Likewise, the capillary filtration associated with **ACE inhibitors** in 23 patients was also significantly reduced by the same dose after 8 weeks, compared to placebo.[2794]

2) Use of 150 mg of Pycnogenol daily for 3 months in osteoarthritis with concurrent **NSAIDs** and/or **analgesics** led to a significant reduction in inflammation and pain scores and less drug use, compared to baseline and placebo (PO in human clinical study).[2324]

Also, 150 mg/day of Pycnogenol for 3 months in a randomized, double-blind, placebo-controlled trial with 37 knee osteoarthritis patients led to significantly reduced scores for total symptoms, pain, and physical function at 60 and 90 days, while NSAIDs and **COX-2 inhibitors** used were reduced significantly after 30, 60, and 90 days and placebo use increased significantly after 90 days (PO in human clinical study).[2795]

\+ 5) When 40 mg Pycnogenol with 70% procyanidins and 80 mg bilberry (*Vaccinium myrtillus*) extract with 36% anthocyanins as a standardized combination was given once daily in the morning to 79 ocular hypertension patients either alone or together with **latanoprost** eye drops and compared to latanoprost alone, the extract combination with the drug was best for lowering intraocular pressure and enhancing retinal blood flow (PO in human clinical study). The extract alone eventually was similarly effective as the drug for lowering intraocular pressure, but it took 24 weeks for the extract compared to only 4 weeks with latanoprost. The only adverse effects were those related to latanoprost.[2966]

GARLIC p. 161

Allium sativum cloves

Drug Interactions

Ia. \+ 3) The use of 300 mg garlic tablets with 0.6% allicin 3 times daily together with **metformin** for 24 weeks by 30 patients with diabetes type 2 resulted in significantly lower levels of fasting blood sugar, total cholesterol, LDL-cholesterol, and triglycerides compared to diabetics who took only metformin (PO in human clinical study). HDL-c was significantly increased in the garlic group after 12 weeks. No adverse effects were reported.[3089]

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

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

Complementary Adjuncts

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

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]

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% **chorhexidine** 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]

GINGER p. 166

Zingiber officinale rhizome

Complementary Adjuncts

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

In high emetogenic chemotherapy cycles with cisplatin and **doxorubicin** for bone sarcoma in 25 children and 35 young adults, when ginger capsules or placebos were added to treatment with the antiemetic drugs **ondansetron** and **dexamethasone** to help control the drug-induced nausea and vomiting, compared to placebo the ginger significantly reduced acute moderate to severe nausea [93% vs. 56%, respectively] and vomiting [77% vs. 33%, respectively] (PO in human clinical study). Likewise, compared to placebo the ginger decreased significantly the delayed moderate to severe nausea [73% vs. 26%, respectively] and vomiting [47% vs. 15%, respectively]. For patients weighing 20-40 kg, 3 doses of 334 mg of ginger were used, while those from 40-60 kg received 2 doses of 800 mg each at 1 hour before and 3 after and a 400 mg dose 8 hours after chemotherapy infusions.[2909]

IIa. + 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 serum total 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]

GINKGO p. 170

Ginkgo biloba leaves

Contraindications

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

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

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

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

Drug Interactions

Ib. 5) **Warfarin** use in a 78-year-old woman resulted in intracerebral hemorrhage after the addition of ginkgo for 2 months (human case report).[524]

HOWEVER, in a retrospective population study of about 200,000 ambulatory patients in the Taiwan Longitudinal Health Insurance Database, 7700 using ginkgo extract showed there was not a higher hemorrhage risk associated with the 60 concurrently taking warfarin or antiplatelet drugs [colpidogrel, cilostazol, ticlopidine], though there were significantly higher risks of hemorrhage among males and those ≥ 65 years of age (PO in human study). [2960]

Complementary Adjuncts

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

A review and meta-analysis of 6 randomized studies lasting at least 8 weeks and using standardized ginkgo extract as an add-on therapy for chronic schizophrenia in 466 cases compared to 362 patients on placebo [except in 1 study] found significant improvement in negative symptoms with **chlorpromazine** and **clozapine** and in total symptoms with chlorpromazine (PO in human clinical studies).[2760]

GOLDENSEAL p. 182

**Hydrastis canadensis* roots/rhizome

Drug Interactions

Ia. 1) [Note CORRECTION: 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] Also, 3.97 gram of the root extract delivering 132 mg hydrastine and 77 mg berberine per day for 14 days significantly INCREASED [not "reduced" as in some early copies] midazolam bioavailability in 16 healthy subjects (PO in human study).[2501]]

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 transminases ALT and AST (PO in human clinical trial).[2908]

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

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

IIa. + 4) Berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive locomotor activity induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that berberine may help reduce the chronic cocaine psychological dependence (speculative).[2753]

\+ 5) When taken with a high cholesterol and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).[2932] When the same doses of berberine and plant stanols were used in a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.[2933] The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);[2932] berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).[2933]

GRAPEFRUIT p. 186

Citrus paradisi fruit / juice

Drug Interactions

Ia. ^ 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]

GUARANA p. 194

Paullinia cupana seeds

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 questionaire tools documented significant improvements in global fatigue scores when the extract was used immediately after chemotherapy , when compared to placebo use, while neither anxiety or depression nor insomnia were worsened.[2920]

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

HOPS p. 203

Humulus lupulus strobiles

Complementary Adjuncts

1a. + 1) A combination of 3 herbal hydroethanolic extracts including hops strobiles 4-8:1, valerian (*Valerian officinalis*) root 3-6:1, and passion flower (*Passiflora incarnata*) herb 4-7:1 was found to markedly improve symptoms associated with **benzodiazepine** withdrawal phase in 107 patients of an average age of 54 years (PO in human clinical study). The extracts were begun with

1-2 tablets daily as benzodiazepine dosage was reduced for 2 weeks, and continued for the next 4 weeks after benzodiazepine use was stopped. Improvement was shown for pronounced tiredness in 76% and general unrest in 71%, according to subjective assessment of patients. Sleep improved in 68% by the end of the treatment, and 74% had more motivation and drive than at the beginning. At the end, 62% were calmer and better able to cope. No adverse drug events occurred in any patients.[2634]

HORSE CHESTNUT p. 204

**Aesculus hippocastanum* seeds

Complementary Adjuncts

IIa. + 1) While suboptimal doses of the triterpenoid saponin mixture escin and **corticosterone** individually had no effect on carrageenan-induced paw edema or pleural inflammation, the combination of these agents at the same doses reduced the paw edema and the volume of pleural exudates and the exudate white blood cells (PO in rats). Likewise, alone these agent had no effects on inflammatory factors in macrophages stimulated by lipopolysaccharides, but together they inhibited secretion of nitric oxide, TNF-α, and interleukin 1β (*in vitro*).[2837]

KAVA p. 212

**Piper methysticum* rhizomes and root

Contraindications

II. 4) Consumption of kava products should be avoided in individuals with **jaundice** or past **liver disorders** (speculative).[1232]

Cytotoxicity to liver cells of isolated kavalactones was shown to be mild for kavain and moderate for methysticin at supraphysiological concentrations of 200 mcM each, whereas yangonin was markedly cytotoxic at 25 mcM due primarily to apoptosis but not to glutathione depletion (*in vitro*).[2844] Yangonin had previously been shown to have an 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]

HOWEVER, another hepatotoxic agent in kava root, the chalcone flavokawain B [FKB] has been identified as the active hepatotoxin (*in vitro*) and *in vivo* at 25 mg/kg (PO in mice). FKB is preferentially extracted in lipophilic solvents 160-fold over water; in the dried extracts, FKB was at 0.2 mg/g for water, 32.3 mg/g for 95% ethanol, and 33.7 mg/g for acetone. FKB is a potent hepatotoxin sensitive to reduced glutathione, and its levels in kava-containing preparations should be specifically monitored and controlled.[2709] Mold hepatotoxin contamination has also been raised as a possible explanation of the rare cases of liver damage associated with kava (speculative).[2913,3067]

Drug Interactions

Ia. 1) Intoxication increased when kava was taken with **alcohol** compared to alcohol alone (PO in human study).[1025]

Alcohol is often consumed concurrently with kava in kava-associated hepatotoxicity cases (PO in case series), and there may be a metabolic interaction with ethanol that could facilitate liver damage (speculative).[2710]

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 p. 221

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

Complementary Adjuncts

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

KUTAKI p. 222

Picrorhiza kurroa rhizome/roots

Complementary Adjuncts

IIa. + 4) The iridoid glycoside fraction of the ethanolic fraction of kutaki at 12 mg/kg daily for 15 days with **ethanol** reduced the hepatotoxicity from the concurrent and prior 30 days of ethanol 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]

LARCH

NEW

^ *Larix* spp. bark

Complementary Adjuncts

Ia. 1) A randomized, double-blind parallel group of 45 adults used 4.5 grams of larch arabinogalactan or maltodextrin placebo as a powder in water or juice once daily for 72 days to test antibody response to *Streptococcus pneumoniae* **pneumonia vaccine** (PO in human study). The 23-valent vaccine was given after 30 days, and 21 and 42 days later the pneumococcal antigen-specific IgG antibodies subtypes 18C and 23F were increased significantly more in the larch arabinogalactan group than in the placebo group, while subtypes 4, 6B, 9V, and 19F also were greater with the larch group, but not significantly.[2739] Larch arabinogalactan has been shown to enhance human natural killer cell cytotoxicity indirectly by increasing release of interferon gamma (*in vitro*)[2754] and has reportedly been used clinically to enhance immune

function and thereby reduce the frequency and severity of recurrent pediatric otitis media (empirical).[2755]

LICORICE p. 225

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

Contraindications

4) Avoid use in **pregnancy**,[2,4,6,17,401] especially excessive intake.[1890]

A study of 392 pregnant Italian women found that those 14 who were regular users of licorice had a 35.7% higher frequency of threatened miscarriages, mostly in the 4th-5th month of gestation, and a 16.7%% increase in preterm labors compared to non-users (PO in human study).[3078]

Drug Interactions

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

Complementary Adjuncts

Ia. 2) [Clarifications] After treating stomach ulcers for 12 weeks, DGL with 88% healing was statistically as effective as cimetidine with 94% healing in groups of 50 patients of which 28 in the licorice group consumed **ethanol** and 7 recently used **prednisone** or **NSAIDs** (PO in human clinical study). Though ulcerations and symptoms associated with anti-inflammatory use were more severe, recent anti-inflammatory drugs intake or habitual alcohol consumption did not influence the rate of ulcer healing.[502]

IIa. 3) Coating **ibuprofen** with licorice extracts reduced stomach ulcers and lowered the ulcer index compared to use of ibuprofen alone (PO in rats).[1006]

Similarly, an hour before being given a stomach ulcer-inducing dose of **indomethacin**, licorice extract doses of 12.5,25, and 50 mg/kg were administered; all doses significantly reduced the ulcer index compared to indomethacin alone, while raising the gastric pH (PO in rats).[2976]

LONG PEPPER p. 232

Piper longum fruit

Complementary Adjuncts

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]

LYCIUM p. 234

Lycium barbarum berry

(goji)

Drug Interactions

Ib. 1) After 4 days of drinking a concentrated decoction of 5 g of the fruit 3 to 4 times daily, a 61-year-old woman stabilized on **warfarin** experienced an INR elevation from 2.4 determined 4 weeks prior to 4.1 just after the lycium consumption (PO in human case report). After discontinuing the tea and stopping warfarin for 1 day and restarting it at a lower weekly dose, 7 days later her INR was 2.4 and remained stable for 7 subsequent tests over the next 3 months. After various concentrations of the drug and herb were incubated with microsomes to assess potential inhibition of CYP 2C9 metabolism of warfarin, no inhibition was observed (*in vitro*).[1768]

In another incident, an 80-year-old woman on a chronic stable warfarin dosage had her therapeutic 2-3.5 INR elevated twice after drinking lycium tea (PO in human case report). On the first occasion, 3 cups of tea made from 10 g lycium fruit per cup the first day was followed by 2 cups of tea the second day, raising her INR to 4.97. Two months later after restabilizing the INR, she consumed 4 cups of the tea 1 day prior to testing, and her INR was raised again to 3.86. Other possible interferences with INR were excluded.[3027]

Complementary Adjuncts

IIa. + 1) The ascites, oxidative stress, and cardiotoxicity produced by the **chemotherapy** agent **doxorubicin** weekly for 3 weeks was significantly reduced by prior and ongoing daily consumption of lycium berry decoction (PO in rats). Mortality was lowered from 38% to 13%, the cardiotoxicity showed significant reduction in conduction abnormalities, loss of heart muscle, and arrhythmia, while the significantly increased superoxide dismutase and lowered lipid peroxidation and serum AST demonstrated less oxidative stress in those given lycium extract. Lycium extract did not interfere with doxorubicin cytotoxicity (*in vitro*).[3029]

\+ 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]

MAITAKE p. 236

Grifola frondosa mushroom fruiting bodies

Complementary Adjuncts

Ia. + 1) 750 mg of maitake mushroom powder plus 54 mg of its glycoprotein fraction designated MSX 3 times daily between meals was used by 26 randomized polycystic ovary syndrome patients for up to 12 weeks, while **clomiphene citrate** was given to 31 others; 15 of those who did not respond to these monotherapies were given a combination of the two for up to 16 weeks (PO in human clinical study). The ovulation rates were 77% for maitake/MSX patients and 94% for clomiphene patients. Of those nonresponders given the combination, evidence of ovulation was shown by 7 of 7 of those who failed with maitake/MSX and 6 of 8 of those who failed with clomiphene.[2910]

MILK THISTLE p. 243

Silybum marianum = Carduus marianus seeds

Drug Interactions

Ia. + 3) The inhibition of **losartan** metabolism by treatment with 140 mg of silymarin 3 times daily for 14 days was only significant in the 6 Chinese men with a CYP2C9*1 genotype; it was not significant in the 6 men with a CYP2C9*3 genotype (PO in human study).[2981]

III. 2) S(-)-**warfarin** 7-hydroxylation by CYP 2C9 was competitively inhibited by silybin (*in vitro*).[1297]

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

Complementary Adjuncts

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

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

Silymarin use following **ethanol** hepatotoxicity helps normalize lab indices for transaminases (PO in human clinical studies).[119,1257]
Silymarin at 200 mg/kg given with 5 g/kg ethanol 3 times in 24 hours attenuated the acute elevation in serum ALT, enhance lipid peroxidation, increase in liver TNF production, decrease in glutathione content, and microvesicular steatosis with mild necrosis caused by ethanol given alone (PO in mice).[2901]

IIa. 1) Prevention by silybin of hepatotoxicity from **acetaminophen** protected from glutathione depletion and lipid peroxidation (IV in rats).[117]
Giving 30 mg/kg with, or 4 hours after, a hepatotoxic dose of 150 mg/kg of acetaminophen prevented the associated elevations in serum ALT, AST, ALP, LDH, total and direct bilirubin, and methemoglobin equivalent to the effects of 100 mg/kg of N-acetylcysteine (PO in cats).[2824]
DNA strand breaks in liver cells caused by 25-30 mM acetaminophen were prevented by silybin at 25 mcM, though hepatocellular toxicity of acetaminophen was not affected (*in vitro*).[2902]

OAT p. 252

Avena sativa bran

Drug Interactions

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

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

OLIVE

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 hypertension medications including **atenolol, nifedipine, lisinopril**, **doxazosin**, and **hydrochlorothiazide** (PO in human clinical study).[1773] [Note: listed in book as a Drug Interaction.]

OREGON GRAPE p. 254

Mahonia spp. root bark

Contraindications

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

Drug Interactions

Ia. 3) The combination of 500 mg berberine 3 times daily for 3 months in 43 patients with poorly-controlled type 2 diabetes together with one or more of their regular **oral hypoglycemic** medications including **sulfonylureas** in 28, **metformin** in 20 **acarbose** in 15, and/or **insulin** in 10 resulted in lower fasting and postprandial blood sugar from week 1 through week 12 (PO in human clinical study). Fasting plasma insulin was also lowered by 28% and an index of insulin resistance by 45% of those on medications, while total cholesterol and LDL were likewise reduced. In 31 newly diagnosed type 2 diabetics to whom 15 were given the same dose of berberine and 16 used 500 mg metformin 3 times daily, berberine's hypoglycemic effect was similar to that of metformin on fasting and postprandial blood glucose, as well as reducing glycosylated hemoglobin and plasma triglycerides (PO in human clinical study). Transient gastrointestinal adverse effects were experienced by 35% of the patients, or 20 in total.[2315]

In 58 type 2 diabetic patients, 1 gm daily of berberine significantly lowered fasting and postload plasma glucose and HbA1c compared to 52 diabetics on placebo, along with significantly reducing the triglycerides, total cholesterol, and LDL-cholesterol, body weight, and

systolic blood pressure (PO in human clinical study).[2907] In 50 type 2 diabetic patients randomly selected to use 1 gm berberine daily, the 26% and 18% significant reductions in fasting blood glucose and HbA1c were equivalent to those of the 26 and 21 diabetic patients who used metformin or rosiglitazone, respectively (PO in human clinical trial). Only the berberine group had a significant reduction of triglycerides. Also, in another group of 18 hepatitis C and 17 chronic hepatitis B patients with type 2 diabetes or impaired fasting glucose, 1 gm/day berberine significantly reduced fasting blood glucose, triglycerides, and the transminases ALT and AST (PO in human clinical trial).[2908]

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

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

\+ 5) When taken with a high cholesterol and high fat diet, berberine at 100 mg/kg daily combined with 1% plant **stanols** in the diet for 6 weeks significantly and synergistically reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls (PO in rats).[2932] When the same doses of berberine and plant stanols were used with a normal diet for 4 weeks, the combination significantly reduced plasma total cholesterol, non-HDL cholesterol, and triglycerides compared to controls and significantly more than the plant stanols alone (PO in hamsters). Berberine and stanols synergistically inhibited fractional cholesterol absorption and increased gene expression of CYP7A1 and CYP27A1 that convert cholesterol to bile acids.[2933] The berberine and stanols alone or in combination showed no biochemical toxicity on the liver (PO in rats);[2932] berberine and the combination even significantly reduced plasma ALT concentrations (PO in hamsters).[2933]

IIa. + 3) Berberine at 200 mg/kg given for 10 days with **cocaine** significantly inhibited the excessive locomotor activity induced by an acute dose of cocaine 4 days later (PO in rats). The effect was associated with a significant decrease in tyrosine hydroxylase activity in the ventral tegmental area with the berberine, indicating a reduction in the production of dopamine (PO in rats). This suggests that berberine may help reduce the chronic cocaine psychological dependence (speculative).[2753]

PASSION FLOWER p. 258

Passiflora incarnata herb

Complementary Adjuncts

Ia. 2) [See Ib. 1) in book.] A combination of 3 herbal hydroethanolic extracts including passion flower herb 4-7:1, hops (*Humulus lupulus*) strobiles 4-8:1, and valerian (*Valerian officinalis*) root 3-6:1, was found to markedly improve symptoms associated with **benzodiazepine** withdrawal phase in 107 patients of an average age of 54 years (PO in human clinical study). The extracts were begun with 1-2 tablets daily as benzodiazepine dosage was reduced for 2 weeks, and

continued for the next 4 weeks after benzodiazepine use was stopped. Improvement was shown for pronounced tiredness in 76% and general unrest in 71%, according to subjective assessment of patients. Sleep improved in 68% by the end of the treatment, and 74% had more motivation and drive than at the beginning. At the end, 62% were calmer and better able to cope. No adverse drug events occurred in any patients.[2634]

POMEGRANATE p. 266

Punica granatum fruit

Complementary Adjuncts

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

PRICKLY PEAR p. 269

Opuntia spp. stems/pads and fruit

Drug Interactions

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

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

PSYLLIUM p. 270

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

Complementary Adjuncts

Ia. 2) In diabetes type 2 psyllium reduces glucose concentration in the blood when taken with **glibenclamide** [**glyburide**] (PO in human clinical study).[1448]
In a 3-part randomized crossover study with 7 type 2 diabetic patients using glibenclamide and 5 taking **tolbutamide**, the use of 15 g of psyllium before 90 g of white bread reduced postprandial glucose significantly compared to placebo and similarly to acarbose (PO in human clinical study).[2798] A randomized, double-blind, placebo-controlled 8-week study of 5.1 g psyllium in 250 ml twice daily before breakfast and dinner in 36 type 2 diabetic patients taking glibenclamide or **metformin** led to significant decreases in fasting blood sugar, glycosylated hemoglobin, and LDL/HDL ratio and a significant increase in HDL-cholesterol with psyllium compared to placebo (PO in human clinical trial). Gastric tolerance of metformin was better in the psyllium group.[2799] Another randomized, blinded, placebo-controlled 8-week study with 29 type 2 diabetic patients using diet and oral sulfonylureas or diet only showed significantly reduced all-day and postprandial blood 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]

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 ginsengosides [50% Rg1, 6% Re] and notoginsenoside R1 [11%] was given daily for 4 weeks (PO in human clinical study). Those receiving the extract had significantly better improvement in neurological function involving movement of limbs and in daily living activities compared with aspirin alone. Adverse events were equivalent between groups.[3076]

SCHISANDRA p. 281

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

Drug Interactions

II. + 3) The lignan extract containing 10.9% schisandrol A, 2.4% gomisin C, 1.9% deoxyschizandrin, and 1.8% γ-schizandrin inhibits intestinal CYP 3A4 metabolism of **midazolam** when a single 150 mg/kg dose is given with oral midazolam, but not hepatic metabolism for IV midazolam (PO in rats). The lignan extract also inhibits metabolism of midazolam (*in vitro*).[2832] While gomisins B and G are also active, gomisin C is the most potent inhibitor of CYP3A4 metabolism of erythromycin and testosterone and irreversibly inactivates it in a time- and concentration-dependent manner (*in vitro*).[2946]

HOWEVER, when 150 mg/kg of the lignan extract is given for 14 days, it induces the CYP 3A4 protein expression in the liver 2.5-fold and its intestinal metabolism 4-fold, and thereby increases midazolam metabolism, especially in the small intestines (PO in rats). In those rats that in which the extract and midazolam were co-administered after 14 of the extract, the induction was modified somewhat by concurrent intestinal CYP 3A4 inhibition. Gomisin C was the most potent inhibitor (*in vitro*) and the least concentrated in the liver (PO in rats), while schisadrol A was the least potent (*in vitro*) and the most concentrated in the liver (PO in rats).[2832]

SOY p. 287

Glycine max beans

Complementary Adjuncts

Ib. + 1) In 8 children of ages 6-13 years receiving **chemotherapy** for cancers [including neuroblastoma, Wilms tumor, mesenchymal tumor, adrenocrotical tumor with lung metastasis, and glioma] with combinations of **adriamycin**, **carboplatin**, **cisplatin**, **cyclophosphamide**, **dacarbazine**, **etoposide**, **ifosfamide**, **irinotecan**, **paclitaxel**, **procarbazine**, **temozolamide**, and **vincristine**, in the first cycle they received no soy isoflavones, while in subsequent cycles the chemotherapy was the same except a soy isoflavone extract tablet with 8 mg of genistein was given daily (PO in human case series). In all, 9 cycles were given without soy isoflavones, and in 6 children 57 chemotherapy cycles with the genistein occurred over a period of 12-19 months. During the genistein cycles there was shorter duration of neutropenia and antibiotic use and less oral mucositis.[2813]

ST. JOHN'S WORT p. 289

Hypericum perforatum herb, tops

Contraindications

I. 3) Do not take prior to **surgery**.[1309,1890]

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

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

Drug Interactions

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

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

STINGING NETTLE p. 306

Urtica dioica leaf [not the root]

Contraindications

I. 1) Excessive internal use should be avoided in **pregnancy**,[2,3] especially in early pregnancy, due to its emmenagogue effect when prepared as a decoction of the plant (empirical).[3087] Uterine stimulant activity has been shown with its constituent serotonin (*in vitro*).[3088]

II. 2) Avoid use in brittle **diabetes** (speculative).[893,2250]
A nettle cyclical peptide fraction designated UD-1 enhances glucose uptake by forming unique pores in skeletal muscle cell membranes that are glucose-permeable (*in vitro*).[2998]

Complementary Adjuncts

Ia. 1) Stewed leaf enhanced the effect of **diclofenac** when given to 19 acute arthritis patients (PO in human clinical trial).[386]

Randomized to placebo or a commercial combination of stinging nettle with fish oil, zinc, and vitamin E taken in capsules, 1 in the morning and 2 at night, and taking their usual regular **NSAIDs** and/or **analgesics**, 81 patients with osteoarthritis of the knee or hip were studied for 3 months (PO in human clinical study). Compared to placebo, the defined daily doses of NSAIDs including diclofenac, **celecoxib**, **ibuprofen**, **ketoprofen**, **naproxen**, **piroxicam, sulindac**, and **tenoxicam** and weekly analgesic equivalents to 500 mg tablets of **acetaminophen** [**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.[2722]

SWEET ANNIE p. 307

Artemisia annua herb

Complementary Adjuncts

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

TEA p. 309

Camellia sinensis = Thea sinensis leaves

Contraindications

I. 2) Avoid concentrated aqueous-**ethanolic extract** of green tea for weight loss associated with 13 cases of hepatitis, after use from 9 days to 5 months (PO in human case reports).[1508,1579,1580,2328,2577]
Giving a green tea extract of concentrated catechins [63-65% EGCG, 3-4% EGC, 6-8% ECG, 8-12% epicatechin] in doses of 0, 200, 500, or 800-1000 mg/kg/day to animals that were fasting led to extensive organ morbidity and mortality [0/8, 3/8, 5/8, and 8/8 deaths per dose group, respectively] within 6.5 months with most death before 13 weeks (PO in dogs). In a 13-week follow up trial using 200 mg/kg/day, no deaths occurred and toxicity in fasted dogs was less

severe and included GI irritation, but the same dose given to non-fasted dogs resulted in much less severe reactions. Plasma catechin levels were 2-4 times greater after fasting than after feeding, similar to results shown with humans in a prior study.[2742] Similarly, a dose of 2000 mg/kg/day of EGCG was shown to be lethal (PO in rats), but doses up to 500 mg/kg/day were not toxic (PO in rats and PO in divided doses to pre-fed dogs), though in fasted animals a single-dose of this amount caused morbidity (PO in dogs).[2743] This suggests that use of high doses of concentrated green tea catechins high in EGCG while fasting increases the risk of toxicity.

HOWEVER, the animal bolus dose model used with fasting dogs is considered unrealistic when compared to human tea consumption patterns.[2743] The peak plasma concentration levels in dogs with no observed adverse effect were 4-10 times the plasma levels achieved in humans who consumed catechins equivalent to about 10-16 cups of tea (PO in dogs and humans).[2744]

Drug Interactions

I. + 17) Use of a green tea catechin extract supplying 800 gm 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 inhbition 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]

Complementary Adjuncts

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

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

IIa. + 6) The component catechin given in 2 daily doses of 150 mg/kg with **ciprofloxacin** to mice with chronic bacterial prostatitis significantly reduced the *E. coli* in the prostate compared with use of ciprofloxacin alone (PO in rats).[3038]

THUNDER GOD VINE p. 318

**Tripterygium wilfordii* peeled root

Complementary Adjuncts

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

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

TURMERIC p. 324

Curcuma aromatica, Curcuma longa = Curcuma domestica root

Drug Interactions

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

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.[2721] With half using the same curcuminoid mixture [75% curcumin, 15% demethoxycurcumin, 10% bisdemethoxycurcumin] and dose as the 50-patient 3-month study, an 8-month study with 100 osteoarthritis patients using NSAIDS or **acetaminophen** showed significant improvements compared to the control group in pain, stiffness, and physical functions including walking distance and for inflammatory markers including IL-1b, IL-6, soluble CD40 ligand, and ESR (PO in human clinical study). In addition, the curcumin group used significantly less NSAIDs like **celecoxib** and/or acetaminophen and other drugs and nondrug treatments and had less gastrointestinal complication, distal edema, hospital admissions, and management costs than the control group.[2802]

A comparative study with 91 knee osteoarthritis patients randomized to receive 2 grams daily of turmeric extract [1 gram curcumin] or 800 mg of ibuprofen for 6 weeks found the 45 given turmeric extract had equivalent efficacy, adverse effects, and patient satisfaction as those on ibuprofen after 6 weeks (PO in human clinical study).[2787]

\+ 4) Patients with chronic anterior uveitis, including 56 with autoimmune, 28 with herpetic, and 22 with other or unknown causes, suffering up to 4 relapses in the previous year were given 240 mg daily for 12-18 months of curcumin formulated with phosphatidylcholine together with the standard treatment they had been receiving that involved systemic **steroids**, **immune suppressants**, **antiherpetics**, and **antitoxoplasmic drugs** or eye drops with steroids, **mydriatics**, **cycloplegics**, and **NSAIDs** (PO in human clinical trial). The number of patients with relapses after the curcumin was instituted was 19, and the number of relapses per year for the group was 36, compared to the 275 relapses per year prior to the curcumin.[2803]

\+ 5) In 508 tuberculosis patients with treatment-induced hepatotoxicity, 192 were given **isoniazid, rifampicin**, and **pyrazinamide** along with ethambutol for 2 months, which were continued for 4 more months without the pyrazinamide, while 316 were given the same schedule of drugs together with 1 gm/day of turmeric extract with 25% curcumin and 1 gm/day of *Tinospora cordifolia* powder enriched 50% with its 10:1 hydro-ethanolic extract (PO in human clinical study). The extract concentrates were approximately equivalent to 6 gm/day of each herbal powder. After the 6 months, those using the herbal extracts had significantly lower markers for hepatotoxicity including average serum AST, ALT, and bilirubin levels, significantly less poorly resolved liver parenchymal lesions, and better compliance than the controls. The extract group also had significantly less TB-positive sputum after 4 weeks.[2995]

IIa. + 5) The addition of 2% curcumin to the diet significantly reduced the incidence of lung metastasis with the use of **paclitaxel** following surgical removal of human breast cancer cell tumors, compared to paclitaxel alone (PO in mice). While paclitaxel induces the activation of IκBα kinase, NF-κB, and NF-κB antiapoptotic gene products involved in prolifereation and metastasis of tumor cells, curcumin inhibited these drug-induced effects along with the activation by paclitaxel of COX-2 mRNA and promoter activity (*in vitro*). Curcumin also potentiated paclitaxel cytotoxicity to breast cancer cells (*in vitro*). Curcumin significantly reduced metastasis even when used alone (PO in mice). The anti-metastatic effect of curcumin with the low paclitaxel dosage was equivalent to a high dose of paclitaxel, suggesting the potential for an equally effective and less toxic treatment (speculative).[2781] 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),[2785] though another study showed negligible distribution outside the gut after 7 days at this dose (PO in human clinical study).[2786]

6) Liposomal curcumin enhanced the effects of suboptimal concentrations of **cisplatin** against xenograft head and neck sqamous cell carcinoma [HNSCC tumors], significantly better than either agent alone (IV in mice). Curcumin inhibited IKKβ, leading to NFκB inhibition, a different growth signaling pathway than that of cisplatin. The combination of these 2 agents also suppressed 2 HNSCC cell lines (*in vitro*).[2877] [See IIb. 1) in the book.]

7) Curcumin at 100 mg/kg dosage given 3 times following intramuscular injection of α,β-**arteether**, one day after injection of ***Plasmodium berghei*** to simulate an animal version of malaria, prevented recrdescence with 100% survival in contrast to 100% fatality 5-8 days after arteether monotherapy (PO in mice). Curcumin in combination with **artemisinin** are additive in killing ***Plasmodium falciparum*** (*in vitro*).[2914]

IIb. + 4) Liposomal curcumin has shown synergistic effects of growth inhibition and apoptosis in colorectal cancer cells when combined with **oxaliplatin** at a 4:1 ratio, as curcumin was a better growth inhibitor than oxaliplatin (*in vitro*), though there was no advantage when using oxaliplatin with curcumin for xenographic colon tumors (IV in mice).[2782]

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

VALERIAN p. 328

**Valeriana officinalis* root/rhizome

Complementary Adjuncts

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

WILD YAM p. 334

Dioscorea villosa root

Contraindications

I. 2) Avoid use in **liver disease** such as **viral hepatitis, toxic hepatitis,** or **cirrhosis** (empirical).[777] Use of 0.8 gm/day of a 50:1 extract for 28 days led to some inflammatory and fibrotic changes in the liver (PO in rats).[2979]

II. 3) Avoid long-term use by those with **kidney dysfunction** or taking drugs that alter kidney function (speculative), since use of 0.8 gm/day of a 50:1 extract for 28 days led to fibrotic changes in the kidney (PO in rats).[2979]

YOHIMBE p. 340

**Pausinystalia yohimbe = Corynanthe yohimbe* bark

Contraindications

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

Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 5% involved altered mental status or behavior (empirical).[2766]

3) Avoid use during **anxiety**,[344] due to its exacerbation by the alkaloidal component yohimbine (PO and IV in human clinical studies).[76,79,344]

Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 33% involved anxiety or agitation (empirical).[2766]

4) Do not use in **high blood pressure**,[344] due to its exacerbation by 0.2 mg/kg yohimbine in 9 hypertensive patients, 10 mg in 29 hypertensives, or 21.6 mg in 25 hypertensives (PO in human clinical studies).[534,535,536]

Of the 238 adverse events reported to the California Poison Control System from 2000-2006 in association with yohimbine-containing products, 25% involved hypertension (empirical).[2766]

8) The conditions of **angina pectoris** and other **heart disease** produce greater risk with yohimbine (PO in human studies).[344]

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

APPENDICES

Appendix A

HERBALS TO BE USED WITH CAUTION

A.8 Bioactivations of Phytochemical Procarcinogens and Potential Toxins

^

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

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

Major references: 150, 2792

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

Phytochemicals	*Common Herb Sources*	*Activators*	*Metabolite Toxic Effects*
aristolochic acids	Aristolochia *(*Aristolochia* spp.) herbs[2817] Wild ginger *(*Asarum canadensis*) rhizome[150]	CYPs 1A1/2;[2816] ST 1A[2792]	kidney carcinogens,[150,1357,2818] kidney toxins[150,1357]
estragole	Basil (*Ocimum basilicum*) herb[150,400] Fennel (*Foeniculum vulgare*) seeds[150,400] Tarragon (*Artemisia dracunculus*) leaf[150,400]	CYPs 1A2,2A6, 2C19,2D6,2E1; STs[2792]	liver carcinogen,[150,759,760] mutagenic[2820]
methyl-eugenol	Asarabacca (*Asarum europeum*) rhizome[400] Wild ginger *(*Asarum canadensis*) rhizome[400]	CYPs 1A2,2C9, 2C19, 2D6; STs[2792]	liver carcinogen[759,760]
pulegone	Am. pennyroyal *(*Hedeoma pulegoides*)[150,2792] Eur. pennyroyal *(*Mentha pulegium*)[150,2792]	CYPs[643] 1A2, 2C19,2E1[2821]	liver toxin[642,644,645]
pyrrolizidine alkaloids	Borage herb *(*Borago officinalis*),[150] Comfrey plant *(*Symphytum officinale*),[150,2792] Common groundsel herb *(*Senecio vulgaris*),[2792] Gravel root *(*Eupatorium purpureum*),[150]	CYPs 2B6,[2792] 3A4[1183]	liver toxins[38,144,236,333,590]

	Rattlebox herb *(*Crotalaria* spp.),[2792] Tansy ragwort herb *(*Senecio jabocaea*)[2792]		
safrole	Sassafras *(*Sassafras albidum*) root bark[150]	CYPs[2819] 2A6, 2C9,2D6,2E1; STs[2792]	liver carcinogen,[150,759,760,2819] mutagenic[2820]
teucrin A	Germander (*Teuchrium chamaedrys*)[2822]	CYP 3A4[2792]	liver toxin[1516,1517,1518]

Appendix B
HERBAL-DRUG INTERACTIONS

[Note CORRECTIONS: In Appendices B and E in the first l00 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 B the other herbs that may be missing the * include: Aloes, Black cohosh, Cayenne, Celandine, Chaparral, Chinese rhubarb, Cinchona, Coffee, Cubeb, Garlic, Juniper, Kava, Licorice, Madagascar periwinkle, Sage, Sassafras, Thuja, and Valerian.]

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

p. 361

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

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

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

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

Apple fruit juice (*Malus domestica*) – **aliskiren** (2B1),[3069] **fexofenadine** (2B1)[3068]

Blueberry fruit (*Vaccinium* spp.) – glibenclamide[3084]

Milk thistle seeds pc silymarin (*Silybum marianum*) – rosuvastatin (oocytes-1B1)[2963] [**not rosuvastatin**[2963]]

Orange fruit juice (*Citrus sinensis*) – **aliskiren** (2B1)[3069]

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

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

B.1.2 Enhancement of Absorption

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

Ginger rhizome c 6-gingerol (*Zingiber officinale*) – digoxin (colon, kidney)[2279]

Mulberry twigs pc morin (*Morus alba*) – *paclitaxel* (intestine)[2834]

Nan wu wei zi fruit (*Schisandra sphenanthera*) – **tacrolimus** (intestine),[2829] *paclitaxel* (intestine),[2827] *tacrolimus* (intestine),[2828,2830] tacrolimus (colon)[2830]

Onion bulbs c quercetin (*Allium cepa*) – *paclitaxel* (intestine)[2835]

Schisandra fruit c schisandrin B (*Schisandra chinensis*) – daunorubicin (leukemia, epidermoid carcinoma, breast cancer MCF-7 & Bcap37), doxorubicin (leukemia, epidermoid carcinoma), epirubicin (leukemia, epidermoid carcinoma), homoharringtonine (leukemia, epidermoid carcinoma), hydroxycamptothecin (leukemia, epidermoid carcinoma), mitoxantrone (leukemia, epidermoid carcinoma), taxol (leukemia, epidermoid carcinoma, breast cancer MCF-7 & Bcap37), vincristine (leukemia, epidermoid carcinoma, breast cancer MCF-7 & Bcap37)[2831]

Soy beans pc genistein (*Glycine max*) – *paclitaxel* (intestine)[2833]

Turmeric root tincture or pc curcumin (*Curcuma longa*) – calcein-AM (colon),[2777] *celiprolol* (intestine),[2778] daunorubicin (colon),[2777] digoxin (colon),[2779,2780] and (kidney),[2779] rhodamine-123 (colon)[2777,2780] [See Note 5.]

Notes:

5. While curcumin has consistently shown inhibition to Pgp *in vitro*[2777,2779,2780] and in an *in vivo* study in rats,[2778] and hydroethanolic extracts of *Curcuma longa* and of other *Curcuma* spp. inhibits Pgp *in vitro*,[2777] methanolic extracts of *C. longa* and of other *Curcuma* spp. increased Pgp activity *in vitro*.[2780]

B.3 Potentiating Sedative or Tranquilizing Medicines

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

Passion flower herb (*Passiflora incarnata*)[2879]
Purple passion fruit leaves (*Passiflora edulis*) B[2952]

B.4 Modifying Blood Sugar In Diabetics p. 374

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

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.4.1 Hypoglycemic and/or Antihyperglycemic Herbals

Cayenne fruit *(*Capsicum frutescens*) – **h**(**hl**)[2808]
Fenugreek [Note CORRECTION: the superscript in the second line after **h**(**t1**) should be "1646", not 1645.]
Gynostemma herb (*Gynostemma pentaphyllum*) – **e(t2)**[2811]
Prickly pear stems (*Opuntia* spp.)[2826]

B.4.2 Antihyperglycemic Botanicals Enhancing Oral Hypoglycemic Drugs in Humans

Cassia bark extract (*Cinnamomum cassia*) – **metformin** and/or **sulfonylureas**[1900,2758]
Fenugreek seeds (*Trigonella foenum-graecum*) – **glyburide**(**glibenclamide**)[130] and/or **metformin**[961,1645] and/or **glipizide**;[1645] **sulfonylureas**[1360,2815] and/or **biguanides**[1360]
Garlic cloves (*Allium sativum*) – **metformin**[3089]
Maitake mushroom fruiting bodies (*Grifola frondosa*) – **glyburide**, **glipizide**, **metformin**[1609]
Psyllium seed husks (*Plantago ovata*) – **glyburide (glibenclamide)**,[2798] **metformin**,[2799] **oral hypoglycemics**,[2801] **sulfonylureas,**[2800] **tolbutamide**[2798]
Royal sun agaricus mushrooms (*Agaricus blazei*) – **gliclazide, metformin**[2215]

B.5 Modifying the Effects of Anticoagulants

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. This has been shown to occur in both *in vitro* and *in vivo* when the polysaccharide components are injected. These active polysaccharides have not been shown to be systemically active after oral consumption, but local anticoagulant effects in the gut may be possible. The research on marine algae is mostly studies using platelet-rich plasma ***in vitro*** **(I)** to test an **extract/fraction (e)** or one or more isolated **components (c)**. ***In vivo*** **(V)** studies use injections in animals test

these derivatives for enhancement of bleeding time or protective effects against a clot-inducing agent.

B.5.1.c In association with simultaneous consumption, several herbs have been inferred from *in vivo* studies or human case reports to possibly induce a reduction in the metabolism and/or enhancement of the effect of **warfarin (W)**, **heparin (H)**, or **antiplatelet drugs (AP)**.

B.5.1 Increasing Potential for Hemorrhage

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

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

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.]

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

Lycium [Gobi] fruit (*Lycium barbarum*) **We**[1768,3027]

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

Chokeberry fruit (*Aronia melanocarpa*) Ie,[2961,2964] **Ee**[2964]

Cocoa seed (*Theobroma cacao*) **Ee**[1447,2906]

Grape seed (*Vitis vinifera*) Ie[2961]

B.7 Modifying Enzyme Activities in Metabolic Conversions p. 387

B.7.1 Unspecified Influences of Herbal Agents on Substrate Pharmacokinetics

Note: CORRECTION of the web address listing CYP isozyme substrates, inhibitors, and inducers is:

http://medicine.iupui.edu/clinpharm/DDIs

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.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 MDR1[2680] and inhibited,[1728,2015] had no effect,[1328,1824,2301] or slightly induced[1840] 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.7.3 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. 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.

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

Probes: benzyloxyresorufin [2B1/2/6] – cc[2938]
7-ethoxyresorufin [1A1/2, 1B1] – ; *An*[2975]
7-pentoxyresorufin [2B1/2] – ; *An*[2975]
Steroids: estradiol – *Bl, By, ea*[3082]

Conversion/clearance Inhibitors

(Ao) Aloe gel (*Aloe vera*) – *2C11*[2947]
(Bl) Blueberry fruit (*Vaccinium corymbosum*) – *1A1, 1B1*[3082]
(By) Black raspberry fruit (*Rubus occidentalis*) – *1A1, 1B1*[3082]
(cc) curcumin in turmeric root (*Curcuma longa, Curcuma aromatica*) – 1A2, 2B6, 2C9, 2D6, 3A4[2938]
(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]
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – [**not CYP2B6** (**bupropion**)[2762]]

Conversion/clearance Inducers

(An) Andrographis leaves (*Andrographis paniculata*) − *1A1, 2B*[2975] [See Note 9.]
(Ep) Echinacea purpurea tops (*Echinacea purpurea*) − *1A1, 2D1*[2978]
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – [**not CYP2B6** (**bupropion**)[2762]]

Notes:

9. Though andrographis has shown inhibition of the metabolism of probe substrate 7-ethoxyresorufin for CYP 1A1/2 *in vitro*,[2035] it induces metabolism of this probe *in vivo* in rats. No effect was shown on the *in vivo* metabolism of the CYP 1A2 probe substrate methoxyresorufin.[2975]

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

Receptor activators

(Gb) ginkgo leaf extract (*Ginkgo biloba*) − (liver)[3044]
(go) ginkgolides from ginkgo leaf (*Ginkgo biloba*) − (liver)[3044]

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

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

Probes:7-methoxyresorufin – cc[2938]
Drugs: caffeine – ; **rs**,[2970] **SJ**[1328]
phenacetin – ts[2770]

Isoenzyme Inhibitors

(cc) curcumin in turmeric root (*Curcuma longa, Curcuma aromatica*)
(ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)

Isoenzyme Inducers

(rs) resveratrol as in dark-skin grapes (*Vitis vinifera*), mulberry fruit (*Morus* spp.), blueberry fruit (*Vaccinium* spp.)
(SJ) St John's wort herb (*Hypericum perforatum*)

No Effect in Human Studies with Isoenzyme CYP 1A2 substrates

[Note CORRECTION: (SJ) St John's wort herb (*Hypericum perforatum*) – caffeine superscript '1328' should be deleted, since a significant mean 26% increase in metabolite to caffeine ratio was observed in the group of 6 men and 6 women. Also, apply this CORRECTION to Note 3.]
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – caffeine[1328,1808,2302,3091] [See Note 4.]
(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[2857]
Drugs: chlorzoxazone – ts[2770]
Procarcinogens: NMBA (N-nitrosomethylbenzylamine) – *Bp*[2460]
Isoenzyme Inhibitors
(Am) Amla fruit (*Emblica officinalis*)
(Bp) Black raspberry fruit (*Rubus occindentalis*)
(ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)
Notes:
1. SJW extract (0.3% hypericin) at 900 mg daily for 28 days in 6 men and 6 women in good health increased chlorzoxazone CYP2E1 metabolism by 110%,[1328] but in 12 healthy elderly the same preparation and dosage increased chlorzoxazone metabolism by only 28%.[1808]

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

Probes: 7-benzyloxy-4-(Fl^{3}Me)coumarin – cc[2938]
7-benzyloxyquinoline − cc[2938]
7-benzyloxyresorufin – cc[2938]
dibenzylfluorescein – cc[2938]
luciferin 6'benzyl ether – sc[2771]
Drugs: buspirone – **rs**,[2970] **Te**[2810]
erythromycin − sc[2946]
midazolam – *cc*,[2778] cc, gn[2779] sc,*sc*,[2832] Sf,[1923] Wg[1885] ; **Gs**,[2965] *sc*,[2832]
paclitaxel – Eu,[2568] Fr,[2664] Gb,[2145] Gf,[2568] Go,[2145] *is*,[2833] kb,[2664] Kv,[2568] Mt,[2145] *Nw*,[2827] Po,[2568] *qu*[2835]
tacrolimus – Nw,[2830] *Nw*,[2828,2830] **Nw**[2829]
Steroids: testosterone – cm,[2768] sc,[2946] ts[2770]
cortisol – **Gf**[3021]
Isoenzyme Inhibitors
(cc) curcumin in turmeric root (*Curcuma longa, Curcuma aromatica*)
(cm) curcumenol from zedoary rhizomes (*Curcuma zedoaria*)
(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.]
(Nw) Nan wu wei zi fruit (*Schisandra sphenanthera*)
(Po) Pomelo fruit juice (*Citrus grandis*)

(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.]
(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) [See Note 19.]
(ts) tanshinones from dan shen roots (*Salvia miltiorrhiza*)

Isoenzyme Inducers

(Gs) Asian ginseng root (*Panax ginseng*) [See Note 11.]
(sc) schisandrol A/gomisin A lignans from schisandra fruit (*Schisandra chinensis*) [See Note 20.]

No Effect in Human Studies with Isoenzyme CYP 3A substrates

(Ca) Cannabis tops infusion *(*Cannabis sativa, Cannabis indica*) – docetaxel, irinotecan[2941]
(Ep) Echinacea purpurea root or entire plant (*Echinacea purpurea*) – darunavir/ritonavir[2793]
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – midazolam[1328,1808,3091] [See Note 15.]

Notes:

3. CYP3A1/2 in rats was inhibited by 50 mg/kg of a 60% ethanolic extract of *E. purpurea* herb after 3 days.[2978]
11. Daily doses for 28 days of 1.0 gm Asian ginseng standardized to 5% ginsenosides induced metabolism of the CYP3A4 substrate midazolam,[2965] while 1.5 gm failed to alter the 1-hour postdose ratio of metabolite to drug for midazolam in 2 human studies.[1328,1808] However, 200 mg/day of uncharacterized "ginseng" for 18 days inhibited metabolism of CYP3A4 substrate nifedipine, as indicated by increased peak plasma concentrations of 29%.[1728]
15. Concerning ginkgo, 360 mg/day EGb 761 increased midazolam bioavailability by 25% and decreased its oral clearance 26%,[2015] but 240 mg standardized ginkgo failed to alter the metabolism of CYP3A4 substrate midazolam in humans.[1328,1808,3091]
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 gm 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]
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.

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

Drugs: diclofenac – Cb,[3085] cc[2938]
losartan − **rs**,[2970] **si**[2981]
tolbutamide – pt,[3043] ts[2770]
warfarin − si[2980]

Isoenzyme Inhibitors

(Cb) Cranberry fruit/juice (*Vaccinium macrocarpon*)

(cc) curcumin in turmeric root (*Curcuma longa, Curcuma aromatica*)
(pt) polysacchacaride 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*)
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.]
(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – losartan[2810]
Notes:
3. Though ginkgo extract acts as a CYP 2C9 inhibitor *in vitro,*[2011,2145,2151] 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.

B.7.2.e Influence on CYP 2C19 Metabolic Conversion of Substrates
No Effect in Human Studies with Isoenzyme CYP 2C19 substrates ^
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – diazepam,[2761] omeprazole,[3091] voriconazole[2679] [See Note 1.]
Notes:
1. In a 12-day study with 18 healthy Chinese men, ginkgo standardized extract at 280 mg daily increased metabolism of omeprazole and mephenytoin.[2301,2302] HOWEVER, EGb 761 given at 120 mg twice daily or 240 mg once daily for 8 days to 18 healthy Caucasian men and women caused no significant effect in the metabolism of a single dose of omeprazole.[3091] Also, in 12 healthy Chinese men 240 mg ginkgo standardized extract daily for 8 weeks did not influence diazepam metabolism by CYP2C19, responsible for 50-60% of its clearance.[2761]

B.7.2.f Influence on CYP 2D6 Metabolic Conversion of Substrates
Drugs: dextromethorphan – cc,[2938] **rs**[2970]
metoprolol – *sa*[2767]
Isoenzyme Inhibitors
(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
(Gb) Ginkgo leaf extract (*Ginkgo biloba*) – debrisoquin,[1328,1808,2302] dextromethorphan[1840,3091]
(SJ) St John's wort herb (*Hypericum perforatum*) – [CORRECTION: debrisoquin superscript '1328' should be deleted]
(Te) Tea (green) leaf catechin extract (*Camellia sinensis*) – dextromethorphan[2810]
Notes

2. [Note CORRECTION: an exception to no significant effect of St. John's wort on CYP 2D6 in human studies is a 23% increased urinary recovery ratio of debrisoquin metabolite in one study,[1328] indicative of weak induction.]
6. The study with 42 healthy humans showing significant inhibition of dextromethorphan metabolism involved taking 1 gm of resveratrol orally once daily for 4 weeks.[2970] Consumption of smaller doses may not have this effect, and this 1 gm/day resveratrol dosage could not reasonably be maintained for a month by eating the whole fruit of grapes, blueberries, and/or mulberries.

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

(Bold indicate human studies (subject criteria noted); organ sources of enzymes identified from *in vitro* and animal studies)

B.7.3.a Influence on Activity and/or Content of Glutathione S-Transferases [GSTs]

Conjugation Inducers

(Am) Amla fruit (*Emblica officinalis*) – *liver*[2853,2854]
(Bp) Black raspberry fruit (*Rubus occindentalis*) – *liver*[2460]
(Br) Broccoli florets (*Brassica oleracea* v. *italica*) –*skin* (A1)[2896]
(cc) curcumin in turmeric root (*Curcuma longa, Curcuma aromatica*) – *liver*[2783]
(Cl) Clove oil (*Syzygium aromaticum*) − *liver, forestomach, small intestine*[2954]
(eg) eugenol as in clove buds (*Syzygium aromaticum*) – *liver*[2959]
(Li) Little ironwood herb (*Vernonia cineraea*) – *liver*[2790]
(Sb) Shrubby basil leaf oil (*Ocimum gratissimum = O. suave*) – *liver*[3014]
(sr) sulforaphane from broccoli sprouts and tops (*Brassica oleracea* v. *italica*) – *skin* (A1)[2896]
(Tl) Tulsi leaves (*Ocimum tenuiflorum = Ocimum sanctum*) – *liver*[3015]

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

Conjugation Inhibitors

(Cb) Cranberry fruit/juice (*Vaccinium macrocarpon*) – liver (1A9)[3079]
(ep) epicatechins [EGCG] from green tea leaves (*Camellia sinensis*) – liver (1A4)[3079]
(Mt) Milk thistle seeds (*Silybum marianum*) – liver (1A6, 1A9)[3079]
(Sp) Saw palmetto fruit (*Serenoa repens*) – liver (1A6)[3079]

Conjugation Inducers

(eg) eugenol as in clove buds (*Syzygium aromaticum*) – *liver*[2959]

No effect in humans

(Ag) American ginseng root extract (*Panax quinquefolius*) – **zidovudine**[2325]

B.7.3.c Influence on NAD(P)H:Quinone Oxidoreductase 1 [NQO1; QR; DT-Diaphorase] Activity and/or Content

Conjugation Inducers

(Ag) American ginseng root (*Panax quinquefolius*) – *heart*[2928]
(Br) Broccoli florets (*Brassica oleracea* v. *italica*) – *skin,*[2895,2896,3037] **skin**[2895,2896]
(iq) isoliquiritigenin from licorice root (*Glycyrrhiza glabra, G. uralensis*), tonka bean seeds (*Dipteryx odorata, D.oppositifolia*), etc. – liver[2971]
(sr) sulforaphane from broccoli sprouts and florets (*Brassica oleracea* v. *italica*) – skin,[3037] *skin,* **skin**[2895,2896]

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

(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.d 11beta-Hydroxysteroid Dehydrogenase type 2 Conversion of Cortisol to Cortisone

Conversion Inhibitors

(gl) glycyrrhetinic acid/glycyrrhizin from licorice root *(*Glycyrrhiza glabra*) – kidney[3022]
(Li) Licorice root *(*Glycyrrhiza glabra*) – **in Addison's disease**[3021]

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

Conversion Inhibitors

(Bl) Blueberry fruit (*Vaccinium corymbosum*) – *mammary*[3082]

(By) Black raspberry fruit (*Rubus occidentalis*) – *mammary*[3082]

(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*[3082]

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[3022]

B.7.4.j Sterol 27-Hydroxylase (CYP27A1) Conversion of Cholesterol to Bile Acids and Bioactivation of Vitamin D_3

Conversion Inducers

(bb) berberine from barberry bark (*Berberis vulgaris*), coptis (*Coptis* spp.), goldenseal *(*Hydrastis canadensis*), and Oregon grape root bark (*Mahonia aquifolium*), etc. − *liver*[2933]

Appendix C
HERBALS CONTRAINDICATED FOR MOTHERS AND CHILDREN

C.1 During Pregnancy p. 439

Substances that interfere with the mother's hormonal balance or fetal genetic expression can disrupt fetal development. In the cases of the gender-specific reproductive organs, plants shown in humans or animals to cause **gonadotropic** or **sex hormone (H)** changes may alter normal expression. **Mutagens (M**) and **genotoxins (G)** may likewise disturb normal growth as shown by *in vitro* studies. **Teratogens (T)** have been shown to interfere with normal development of particular structures, and plants with **fetotoxins (F)** endanger the essential functions of the developing child. In cases where such substances cause these effects to occur *in utero*, birth defects are a possible outcome that otherwise could be avoided.

(Based in part on reference 2791,3056-3058.)

Bitter melon fruit /seeds (*Momordica charantia*) A; T
Feverfew herb (*Tanacetum parthenium*) H
Wormwood tops, leaves *(*Artemisia absinthium*) H

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 D_2 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/MINERA/DRUG INTERACTIONS
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.

References: 2823

D.2.5 Magnesium (as Oxide) / Drug Interactions p. 476

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

Appendix E
HERBALS AS POTENTIAL COMPLEMENTARY ADJUNCTS WITH MEDICINES

[Note CORRECTION: In Appendices B and E in the first l00 copies of the book, asterisks (*) are missing in front of the scientific Latin names for a number of listed herbs designated with * in the main body of the text as containing potentially toxic compounds. (European pennyroyal herb *(*Mentha pulegium*) near the top of page 366 lacks an asterisk in these books.) In Appendix E the other herbs that may be missing the * include: Black cohosh, Bryonia, Cannabis, Cayenne, Chinese rhubarb, Cinchona, Garlic, Goldenseal, Jamaica dogwood, Licorice, Sage, Thuja, Thunder god vine, Valerian, and Wormwood.]

E.1 Potentially Beneficial Combinations of Herbals with Drugs p. 483

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

Amla fruit (*Emblica officinalis*) – **isoniazid**, **pyrazinamide**, **rifampicin**,[2857,2858] *cyclophosphamide*,[2853,2955] cisplatin,[2860] doxorubicin[2859,2860]

American ginseng (*Panax quinquefolius*) root – **chemotherapy,**[2916] **influenza vaccine,**[2918,2919] *cyclophosphamide*,[2924,2925] *mitomycin C*,[2922] N-acetyl cysteine, vitamin C [2923]
berry − 5-fluorouracil[2927]

Arnica flowers *(*Arnica montana*) – **acetaminophen**,[2805] **hydroxyethyl salicylate**[3090]

Asian ginseng root (*Panax ginseng*) – **donepezil**, **galantamine**, **memantine**, **rivastigmine**,[3059] cisplatin[2725]

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

Barberry root bark (*Berberis vulgaris*) – **simvastatin,**[2905] *stanols*[2932,2933]

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

Black cumin seed (*Nigella sativa*) – **corticosteroids**,[2988,2989] **beclomethasone**, **beta-agonists**, **fluticasone**, **theophylline**,[2988] *acetaminophen*,[2983] *doxorubicin*,[2430] *gemcitabine*,[2985] *ifosfamide*,[2431] *oxaliplatin*[2985]

Black pepper fruit (*Piper nigrum*) − *EGCG*[2935]

Cannabis tops *(*Cannabis sativa*) – **anticholinergics**,[2751] **anticonvulsants**, **antidepressants**,[2940] **codeine, dextropropoxyphene**, **dihydrocodeine**, **methadone**,[2748] **methotrexate**,[2942] **morphine**,[2748] **NSAIDs**,[2940] **oxycodone**, **pethidine**, **tramadol**[2748]

Clove buds (*Syzygium aromaticum*) − *indomethacin*[2957]

Cocoa seeds (*Theobroma cacao*) – **ACE inhibitors**,[3077] **angiotensin receptor blockers**,[3077] **antihypertensives**,[2740] **beta blockers**,[3077] **diuretics**,[3077] **metformin**,[2740] **oral anticoagulants**,[3077] **statins**[2740,3077]

Cola (*Cola nitida*) seed – **ciprofloxacin**, **perfloxacin**, **levofloxacin**[3034]

Coptis root (*Coptis* spp.) – **simvastatin,**[2905] *stanols*[2932,2933]

Cranberry fruit (*Vaccinium macrocarpon*) – *doxorubicin*[3080]

Crucifers tops, leaves, sprouts (*Brassica* spp.) − *cisplatin*,[2934] *trabectidin*[2177]

Dog rose hips (*Rosa canina*) − **acetaminophen**, **chloroquin**, **leflunomide**, **methotrexate**, **NSAIDs**, **steroids**[2962]

Dong quai root (*Angelica sinensis*) – *enalapril*[2728]

Echinacea pallida whole plant (*Echinacea pallida*) – cisplatin[2726]

English plantain leaves (*Plantago lanceolata*) – *indomethacin*[2838]

Frankincense resin (*Boswellia serrata*) resin – **ibuprofen**[2804]

French maritime pine bark (*Pinus pinaster*) – **latanoprost**[2966]

Garlic fresh cut clove [# = aged garlic extract] *(*Allium sativum*) – #**ACE inhibitors**, #**angiotensin II receptor antagonists**,[2757] #**beta blockers**,[2757] #**calcium channel blockers**,[2757] **captopril**,[2756] **chorhexidine**,[2711] #**diuretics**[2757]

Ginger root (*Zingiber officinale*) – **cisplatin**, **dexamethasone**, **doxorubicin**, **ondansetron**,[2909] *atorvastatin*[2849]
Goldenseal roots/rhizome *(*Hydrastis canadensis*) – **simvastatin,**[2905] *stanols*[2932,2933]
Guarana seeds **(***Paullinia cupana*) – **cyclophosphamide**, **doxorubicin**, **fluorouracil**[2920]
Hops strobiles (*Humulus lupulus*) − **benzodiazepines**[2634]
Kudzu root (*Pueraria thunbergiana = P. lobata*) – cisplatin[2724]
Kutaki roots/rhizome (*Picrorhiza kurroa*) − *chloroquine*[2937]
Larch bark (*Larix* spp.) – **pneumococcal vaccine**[2739]
Licorice root/rhizome *(*Glycyrrhiza glabra, G. uralensis*) – *indomethacin*[2976]
Long pepper fruit (*Piper longum*) − *EGCG*[2935]
Lycium (= Goji) berry (*Lycium barbarum*) − *doxorubicin*,[3029] *mitomycin C*[3030]
Maitake mushroom (*Grifola frondosa*) – **clomiphene citrate**[2910]
Milk thistle seeds (*Silybum marianum*) – *acetaminophen*[2824]
Olive fruit oil (*Olea europaea*) – **atenolol, doxazosin**, **hydrochlorothiazide**, **lisinopril**, **nifedipine**[1773]
Oregon grape root bark (*Mahonia* spp.) – **simvastatin,**[2905] *stanols*[2932,2933]
Passion flower herb (*Passiflora incarnata*) − **benzodiazepines**[2634]
Pomegranate fruit (*Punica granatum*) − **hydroxychloroquine**, **methotrexate**, **prednisone**, **NSAIDs**, **sulfazine**[3024]
Sanchi ginseng root/rhizome (*Panax notoginseng*) − **aspirin**[3076]
Soy beans (*Glycine max*) – **adriamycin, carboplatin, cisplatin, cyclophosphamide, dacarbazine, etoposide, ifosfamide, irinotecan, paclitaxel, procarbazine, temozolamide, vincristine**[2813]
Stinging nettle leaves (*Urtica* spp.) – **acetaminophen** [**paracetemol**] **aspirin**, **celecoxib**, **diclofenac**, **ibuprofen**, **ketoprofen**, **naproxen**, **opiates**, **piroxicam**, **sulindac**, **tenoxicam**[2722]
Sweet annie herb (*Artemisia annua*) – curcumin[2914]
Tea [green] leaves (*Camellia sinensis*) – *ciprofloxacin*,[3038] *indomethacin*[2752]
Turmeric root (*Curcuma longa, C. aromatica*) – **acetaminophen**,[2802] **antiherpetics**, **antitoxoplasmic drugs**,[2803] **celecoxib**,[2802] **cycloplegics**,[2803] **immune suppressants**,[2803] **isoniazid**,[2995] **mydriatics**,[2803] **NSAIDs**,[2721,2803] **pyrazinamide**, **rifampicin**,[2995] **steroids**,[2803] *arteether*,[2914] *cisplatin*,[2877] *paclitaxel*,[2781] artemisinin[2914]
Valerian root (*Valeriana officinalis*) − **benzodiazepines**[2634]

E.2 Herbal Aids for Modifying Substance Abuse p. 488

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

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).**

American ginseng root (*Panax quinquefolius*) – Amp: (Ac[2929])
Coc: (Ac[2931])
Amla fruit (*Emblica officinalis*) – Alc: (ld Ae[2856])
Asian ginseng root (*Panax ginseng*) – Amp: (Ac[2929,2930])
Coc: (Ac[2931])
Barberry bark (*Berberis vulgaris*) − Coc: Ac[2753]
Black cumin seed (*Nigella sativa*) – Alc: (sd Ae,[2984] Ac[2987])
Opi: **Hh**[2982]
Cannabis tops *(*Cannabis sativa*) – Amp: Ac[2977]
Coc: Ac[2977]
Opi: Ac[2973]
Chinese raisin tree fruit (*Hovenia dulcis*) – Alc: Ae (ld Eh)[2845]
Chinese skullcap root (*Scutellaria baicalensis*) – Alc: (ld Ae[2839])
Clove buds (*Syzygium aromaticum*) − Alc: (sd *c*[2958])
Coptis rhizome (*Coptis chinensis*) − Coc: Ae,c[2753]
Goldenseal roots/rhizome *(*Hydrastis canadensis*) − Coc: Ac[2753]
Kutaki root (*Picrorhiza kurroa*) – Alc: (ld Ae[2937])
Little ironweed herb (*Vernonia cinerea*) – Nic: **He**[2713]
Oregon grape bark (*Mahonia aquifolium*) − Coc: Ac[2753]
Passion flower leaves (*Passiflora incarnata*) – **Se**[2879]
Shrubby basil leaves (*Ocimum gratissimum = O. suave*) − Alc: (sd *e*[2953])
St. John's wort herb (*Hypericum perforatum*) – Nic: [**He**[2797]]

E.3 Complementing Treatment of Inflammations p. 492

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

Frankincense resin extract (*Boswellia serrata*) – **e**[2846]

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

Frankincense resin (*Boswellia serrata*) resin – **e**[2804]
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*) – **c**[2721,2802]

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]
Stinging nettle leaves (*Urtica dioica*) – **h**[2722]
Turmeric root [curcumin] (*Curcuma longa, C. aromatica*) – **c**[2802]

E.3.4 Protecting Against NSAID-induced Ulcers

Clove oil [eugenol] (*Syzygium aromaticum*) − *c* [2957]
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]

E.3.5 Protecting Against Acetaminophen-induced Liver Toxicity

Black cumin seed (*Nigella sativa*) – *c*[2983]
Korean acanthopanax root bark (*Acanthopanax koreanum*) – *c*[2727]
Milk thistle fruit (*Silybum marianum*) – *f*[2824]

E.4 Enhancing Chemotherapy and Chemoprevention or Reducing the Adverse Effects p. 494

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.4.3 **Efflux pumps such as multridrug resistance protein (MDR1, also known as P-glycoprotein), multidrug resistance-associated proteins 1 and 2 (MRP-1 and MRP-2), and breast cancer resistance protein (BCRP, also called ABCG2) are active in removing drugs**. **The inhibition of MDR1, MRP-1 and –2, and/or BCRP activity or their gene expression enhances 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 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 process(es) *in vitro*, for which reference citations are also given.

E.4.5 The ubiquitous cytokine transforming growth factor-beta1 (TGFβ1) is associated with P-glycoprotein expression in certain cancers, increasing the resistance to some chemotherapeutic agents. TGFβ1 is one of the most potent metastatic inducers. TGFβ1 has been shown to increase A disintegrin and metalloproteinase-12 (ADAM-12) which plays a critical role in cancer growth and metastasis and is upregulated in many cancers including breast, lung, liver, prostate, gastric, and bladder. TGFβ1 activation of NF-κB increases ADAM-12 mRNA expression in breast cancer cells.[2731] NF-κB is activated by many carcinogens, tumor promoters, and inflammatory agents associated with cancer development, progression, and drug resistance,[2775] as well as by chemotherapy agents such as paclitaxel.[2781] TGFβ1 has also been associated with decreased natural killer cell cytotoxicity in gastric cancer patients as cancer progresses.[2732] In addition, chronic injury to normal tissue following treatment by chemotherapy or radiation appears to involve TGFβ1 overexpression.[2733] [See Appendix E.5.7.] However, since TGFβ1 acts to suppress epithelial and possibly other types of tumorigenesis in early stages and multiple signaling pathways are involved at different stages, TGFβ1 reduction likely should be restricted

to later stages of tumor progression, invasion, and metastasis,[2736] i.e., as part of cancer treatment but not prevention.

E.4.1 Enhancing therapeutic effects of chemotherapy

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]

Bibhitakhi fruit (*Terminalia bellerica*) – cisplatin, doxorubicin (e)[2860]

Chamomile flowers [bisabololoxide A] (*Matricaria recutita*) –5-fluorouracil [c][2863]

Cranberry fruit/juice proanthocyanidins] (*Vaccinium macrocarpon*) – paraplatin (f)[3086]

Echinacea purpurea polysaccharides (*Echinacea purpurea*) – *cyclophosphamide*[2809]

Horse chestnut seeds [escin] *(*Aesculus hippocastanum*) – 5-fluorouracil [c][2776]

Tea green leaves [EGCG] (*Camellia sinensis*) – 5-fluorouracil [c][2948]

Turmeric rhizome [curcumin] (*Curcuma longa, C. aromatica*) – *cisplatin* [c],[2877] *paclitaxel* [c],[2781] cisplatin [c],[2876,2877] doxorubicin# (e),[2859] oxaliplatin [c][2865]

E.4.2 Reducing adverse effects of chemotherapy

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

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

Asian ginseng root (*Panax ginseng*) – cisplatin (e)[2725]

Broccoli sprouts [sulforaphane] (*Brassica* spp.) − *cisplatin* [c][2934]

Cranberry fruit (*Vaccinium macrocarpon*) – *doxorubicin* (e)[3080]

Echinacea pallida whole plant (*Echinacea pallida*) – cisplatin (e)[2726]

Kudzu root (*Pueraria lobata = P. thunbergiana*) – cisplatin (e)[2724]

Lycium (= Goji) berry (*Lycium barbarum*) − *doxorubicin#* (j),[3029] *mitomycin C* (f)[3030]

Mulberry leaf (*Morus alba*) – doxorubicin (e)[2859]

Raspberry fruit [ellagic acid] (*Rubus idaeus*) – *cisplatin* [c][2864]

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

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

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

E.4.3 Selective Cell Retention of Drugs by Inhibiting Efflux Transport Proteins

[Note: CORRECTION for Asian ginseng, citation #2102 is the following: Choi CH, Kang G, Min Y-D. Reversal of P-glycoprotein-mediated multidrug resistance by protopanaxatriol ginsenosides from Korean red ginseng. *Planta Med.*, 69:235-240, 2003.]

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 [aa theanine] (*Camellia sinensis*) – doxorubicin [adriamycin] aa (ovary GLAST/GLT-1)[2949]

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)[2923]

Apple fruit [fresh (**lung and colon**[2789])] (*Malus domestica*)

Ashwagandha root [hydroalcoholic extract (*skin*[3005]) (*Withania somnifera*)

Asian ginseng root [Korean red extract (**non-organ-specific in men**[2765])] (*Panax ginseng*)

Black raspberry fruit [freeze-dried,[2997,3070,3075] ethanol extract,[3071,3074] anthocyanins[3071,3072]] (*Rubus occidentalis*)

Coffee beans roasted [water extract (**nonmelanoma skin cancer in white women**,[2894] **ER-neg postmenopausal breast cancer**,[2990] **liver cancer**,[2991] **glioma** [coffee/tea][2992,2993]), caffeine (**glioma in men**[2992])] (*Coffea arabica*)

Crucifers leaves, heads, and sprouts [phenethyl isothiocyanate[2997]] (*Brassica* spp.)

Milk thistle seeds [flavonolignan fraction[2900]]

Reishi [c polysaccharides,[1094,2999] triterpenoids[2999]] (*Ganoderma lucidum*) – c/liver[1094]

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

Tea (black) leaves [water extract (**glioma** [coffee/tea][2992,2993]), caffeine (**glioma in men**[2992])] (*Camellia sinensis*)

Tulsi leaves [e ethanolic extract (*topical*)[3015]] (*Ocimum tenuiflorum = Ocimum sanctum*)

Turmeric root [pc curcumin[2784,2788,2904]] (*Curcuma longa*)

E.4.5. Reducing Transforming Growth Factor-β1 Before, During, &/or After Chemotherapy

Astragalus root [water and/or ethanol extracts] (*Astragalus membranaceus*)– ([e]in rats with Dong quai [e])[2728,2729,2730]

Dong quai root [water and/or ethanol extracts] (*Angelica sinensis*) – ([e]in rats with Astragalus [e])[2728,2729,2730]

Magnolia bark [honokiol] (*Magnolia officinalis*) – ([c] in human renal cells)[2732]

Reishi mushroom [13.5% polysaccharides/6% triterpenes extract] *Ganoderma lucidum*) – ([e] in human prostate cancer cells)[2737]

E.5 Herbals for Preventing and Healing Radiation Adverse Effects and/or Enhancing Radiotherapy or Photodynamic Therapy p. 502

E.5.1-5.4 **Local applications (L)** are designated for appropriate *in vivo* and all *in vitro* studies. Pre-therapeutic use of **oral herb preparations (O) or injections (I)** has been studied with exposure to these other forms of radiant energy. Some botanicals have been shown to help protect normal structures and their functions that receive less direct or concentrated irradiation than the malignant focus.

To differentiate the types of *in vivo* studies, **human cases are in bold** and **studies in animals are italicized**, while the *in vitro* tests on cells are in regular type-face. The type of preparation used is noted. Herbal preparations may be the powdered **herb (h)**, fresh **gel** or **juice (j)**, a solvent **extract (e)**, an extract **fraction (f)** or an isolated **component (c)**. Clinical trials with **negative results [neg.] are shown in brackets.**

E.5.5-5.6 In some instances, the botanical can serve as a synergistic antitumor agent, or it may improve the post-treatment radiation sensitivity and therapeutic response in certain malignant tissues.

E.5.7 Chronic injury to normal tissue following treatment by chemotherapy or radiation appears to involve transforming growth factor-beta 1 (TGFβ1) overexpression.[2733] [See Appendix E.4.5 introduction.] Increases in TGFβ1 during radiation treatment for non-small cell lung cancer is indicative of significant reduction in survival time,[2734] and significant TGFβ1 elevations after radiation therapy have been correlated with symptomatic radiation pneumonitis.[2735]

E.5.9-5.10 ^ Topical and internal herbal preparations that help prevent UV overexposure and the consequent inflammation and aging and increased risk of skin cancer by blocking the radiation or quenching free radicals are covered here in the context of passive exposure to solar radiation. These should not be use when actively exposing skin lesions to UV phototherapy, due to the counterproductive aspect of simultaneously reducing the therapeutic effect. However, internal use of herbal antioxidants shown to protect against UV damage may be useful in some cases.

Damage to the skin from solar radiation is well known following acute or chronic exposure. Ultraviolet (UV)-induced skin damage is associated with inflammation and the generation of reactive oxygen species or free radicals. An imbalance between reactive oxygen species generation and cellular antioxidant capacity leads to oxidative stress that contributes to carcinogenesis. Excessive skin exposure to UV can cause DNA damage, cell-cylce 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 than UVA to the skin 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, and wrinkling due to its deep penetration into the dermis of the skin.[2867,3001]

Currently, commercial sunscreens applied topically reduce skin cancer risk by partially blocking UV radiation but are inadequate alone for preventing dermal carcinogenesis. Some sunscreens do not block UVA, so, though helping prevent sunburn, squamous cell carcinoma, and basal cell carcinoma, increased time in the sun and exposure to UVA can lead to higher risk of melanoma, the most virulent form of skin cancer. Since UV creates oxidative stress in the skin, the use of dietary and **herbal antioxidants internally (I) 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**)

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

Aloe leaf gel (*Aloe vera*) – [**neg. Lj**[2772,2773,2774]]
American ginseng root (*Panax quinquefolius*) – Te[3065,3066]
Amla fruit [aqueous extract,[2850,2852] methanol extract[2851]] (*Emblica officinalis*) – *Oe*[2850,2851,2852]
Frankincense resin extract (*Boswellia serrata*) – **Oe**[2846]
Milk thistle seeds [flavolignan fraction] (*Silybum marianum*) – *If, Of*[2903]
Sea buckthorn fruit [hydroethanolic extract] (*Hippophae rhamnoides*) – *Ie*[3000]
Soy bean [f isoflavones, c genistein] (*Glycine max*) – **Of**,[2812] **Of /c**[2813]
Tomato fruit [c lycopene] (*Lycopersicon esculentum*) – *Oc*[2769]
Note CORRECTION: The scientific name for Tulsi, also known as Holy basil, is *Ocimum tenuiflorum* but was formerly *Ocimum sanctum.*

E.5.5 Enhancing Antineoplastic Effects of Radiation

Black raspberry fruit [methanol extract] (*Rubus occidentalis*) – Lc [breast adenocarc.][3081]
Turmeric root (*Curcuma longa*) – Lc [ovarian],[2876] Lc [colorectal],[2866,2875] *Oc* [colorectal][2676]

E.5.7. Reducing Transforming Growth Factor-β1 Before, During, &/or After Radiotherapy

Astragalus root [water and/or ethanol extracts] (*Astragalus membranaceus*)– ([e]in rats with Dong quai [e])[2728,2729,2730]
Dong quai root [water and/or ethanol extracts] (*Angelica sinensis*)– ([e]in rats with Astragalus [e])[2728,2729,2730]
Magnolia bark [honokiol] (*Magnolia officinalis*) – ([c] in human renal cells)[2732]
Reishi mushroom [13.5% polysaccharides/6% triterpenes extract] *Ganoderma lucidum*) – ([e] in human prostate cancer cells)[2737]

E.5.9 Potential Herbal Prevention of Dermal Photocarcinogenesis ^

Black raspberry fruit [80% ethanol extract[3071]] (*Rubus occidentalis*) − *Te* [after UVB irradiation][3073]
Bloodroot root [c sanguinarine] (*Sanguinaria canadensis*) − *Tc*[3008]
Broccoli sprouts [e; c sulforaphane] (*Brassica oleracea* v. *italica*) – Tc, *Te,c*[3037]
Coffee beans (roasted) [e aqueous] (*Coffea arabica*) – **Ie**[2894]
Ginger rhizome [c 6-gingerol] (*Zingiber officinale*) − Tc, *Tc*[3010]
Grapes fruit [c resveratrol] (*Vitis* spp.) – *Tc*,[2886,2887,2888,2897] Tc[2889]
Grape seed [e ethanolic extract; f proanthocyanidin] – *If*,[2885] *Te*[3016]
Heather herb [e ethanolic extract] (*Calluna vulgaris*) − *Te*[3016]
Olive leaf [e; c oleuropein], fruit [f oil] (*Oleo europaea*) – *Ie,c*[2868] *Tf* [after irradiation][2870]
Pomegranate juice/seed [extract, c delphinidin] (*Punica granatum*) – *Tc*, Tc,[3007] Te[3006]
Milk thistle seed [f silymarin; c silybin] (*Silybum marianum*) – *Tf*,[2871,2872,2873] *Tc*[2891,3009,3010,3011]
Soy beans [c genistein] (*Glycine max*) – *Tc*[3017,3018]
Tea (green) leaves [e aqueous; f polyphenols; c EGCG] (*Camellia sinensis*) – **Tf**,[2890] *Tf*,[2873,2880] *Tc*,[2884,3003,3016] *Ie*,[2874,2883,3004] *If*[2880,2881]
Tea (black) leaves [e aqueous] – **Ie**,[2892,2893] *Ie*[2882,2883]
Turmeric root [pc curcumin] (*Curcuma longa*) – Tc[2878]

E.5.10 Herbal Prevention of Acute UV-induced Erythema ^

Broccoli sprouts [e; c sulforaphane] (*Brassica oleracea* v. *italica*) – **Te**, *Te,c*[2895]
Cocoa bean (fermented, roasted) [h/f flavanols] (*Theobroma cacao*) – **Ih/f**[2911]
Grapes fruit [c resveratrol] (*Vitis* spp.) – *Tc*[2886]
Lycium (= Goji) berries (*Lycium barbarum*) − *Ij*[3028]
Tea (green) leaves [f polyphenols] (*Camellia sinensis*) – **Tf**[2890]

E.6 Herbals and Anti-infection Agents p. 505

With increasing failures of antibiotic treatment for some bacterial infections, new or alternative agents and practices are being investigated to help address this growing vulnerability. In particular, combinations of antibiotics are necessary to control some infections and prevent epidemics of diseases like tuberculosis. The disadvantage of using single molecule antimicrobial drugs for infectious disease control is now recognized, based on a microbes ability to rapidly develop resistance to the a single compound and its mechanism of activity. While complex plant extracts typically lack the comparative potency of single-molecule antimicrobial drugs, the pluripotent complexity and multiple pharmacodynamic impact on the infectious process offers the advantage, inherently developed in the plants themselves, of resisting infections over the long term. In addition, when combined with conventional antimicrobial medication, they may complement the drug pharmacology or enhance its effects by improving its absorption, half-life, and/or microbial cellular retention. Conversely, it is possible that for certain drugs and/or particular microbes an extract that is beneficial in some circumstances can be a disadvantage in others by antagonizing ordinary pharmacotherapy. Ongoing research is needed to unveil the potential of beneficial combinations and potential disruptions when combining plant preparations with antimicrobial therapeutic agents.[3031]

The normal typeset for the botanical and other antimicrobial agent(s) indicates *in vitro* studies, while italicizing is used for *in vivo* animal studies, and bold type indicates human clinical studies. In the case of combinations with antimicrobial agents, **abbreviations are used for the botanical forms, whether it be the herb (h), an extract (e), a fraction (f), or a component (c) or several components (cs), and for the name of the associated antimicrobial**.

^*E.6.11* Antimicrobial agents including antibiotics are capable of inducing a variety of adverse effects, depending on the agent. This can limit their life-saving potential by restricting the effective dose required for optimal treatment. Botanicals that are capable of reducing antimicrobial toxicity can help in the acute and/or chronic treatment of infections. **The specific herbal preparation, toxic antimicrobial, and protected organ(s) from *in vitro* (plain type), animal (italicized) or human (bold) studies are listed after each botanical.** Probiotic microorganisms are not considered in this category, though they can be of great benefit in reducing adverse enteric effects and recovering from disrupted intestinal flora from antibiotic use.

(Additional major references: 3031)

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

Ajowan fruit (*Carum copticum*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Andrographis leaf (*Andrographis paniculata*) e aqueous extract − (e) MRSA[2974]
Arjun tree leaves (*Terminalia arjuna*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Bael fruit pulp (*Aegle marmelos*) e methanol or aqueous extracts − (e) MDR-*Salmonella typhi*[3046]
Black nightshade seeds (*Solanum nigrum*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Cassia bark (*Cinnamomum cassia*) c cinnamaldehyde − (c) MDR-*Salmonella typhimurium*, (c) MDR-*E. coli*, (c) MDR-*Staph. aureus*, (c) erythromycin-resistant *Strep. pyogenes*[3047]
Catechu bark (*Acacia catechu*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Celery leaves (*Apium graveolens*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Chicory leaves (*Cichorium intybus*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Chinese lantern tree fruit (*Dichrostachys glomerata*) e methanolic extract − (e) MDR-*Escherichia coli*, (e) MDR-*Enterbacter aerogenes*, (e) MDR-*Klebsiella pneumoniae*, (e) MDR-*Pseudomonas aeruginosa*[3020]

Chinese skullcap root (*Scutellaria baicalensis*) c baicalin – (e) MDR-*Acinetobacter baumannii,*[2719] (c) MRSA, (c) penicillin-resistant *Staphylococcus aureus*[2358]
Cinnamon bark (*Cinnamomum verum*) c cinnamaldehyde − (c) MDR-*Salmonella typhimurium,* (c) MDR-*E. coli,* (c) MDR-*Staph. aureus,* (c) erythromycin-resistant *Strep. pyogenes*[3047]
Cinnamon beilschmiedia bark (*Beilschmiedia cinnamomea*) e methanolic extract − (e) MDR-*E. coli,* (e) MDR-*Ent. aerogenes,* (e) MDR-*K. pneumoniae*[3020]
Clary sage roots (*Salvia sclarea*) cs salvipisone, aethiopinone − (c) MRSA, (c) MR-*Staph. epidermidis*[3036]
Clove bud (*Syzygium aromaticum*) c eugenol − (c) MDR-*Salmonella typhimurium,* (c) MDR-*E. coli,* (c) MDR-*Staph. aureus,* (c) erythromycin-resistant *Strep. pyogenes*[3047]
Eucalyptus leaf (*Eucalyptus globulus*) f essential oil – (f) MRSA,[2712] **(f) *Mycobacterium tuberculosis***[2714] fruit essential oil, 1,8-cineole &/or aromadendrene – (f, cs, c-a) MRSA, VRE (*Ent. faecalis*)[2713]
Gotu kola leaves (*Centella asiatica*) e methanol extract − (e) MRSA[2974]
Horseradish root (*Armoracia rusticana*) c allyl isothiocyanate − (c) MDR-*Salmonella typhimurium,* (c) MDR-*E. coli,* (c) MDR-*Staph. aureus,* (c) erythromycin-resistant *Strep. pyogenes*[3047]
Kikar bark (*Acacia nilotica*) e aqueous extract − (e) MDR-*Salmonella typhi*[3046]
Kurchi seed (*Holarrhena antidysenterica*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Kutaki leaves (*Picrorrhiza kurroa*) e methanol or aqueous extracts − (e) MDR-*Salmonella typhi*[3046]
Licorice root (*Glycyrrhiza uralensis*) c gancaonin – (c-ga) vancomycin-resistant strains of *Enterococcus faecalis, E. faecium, E. gallinarum* and MRSA[3032]
Magnolia bark (*Magnolia officinalis*) e extract – (e) MDR-*Acinetobacter baumannii*[2719]
Mongolian mulberry (*Morus mongolica*) cs mulberrofurans − (c) vancomycin-resistant strains of *Enterococcus faecalis, E. faecium, E. gallinarum* and MRSA[3032]
Mustard seed (*Brassica nigra*) c allyl isothiocyanate − (c) MDR-*Salmonella typhimurium,* (c) MDR-*E. coli,* (c) MDR-*Staph. aureus,* (c) erythromycin-resistant *Strep. pyogenes*[3047]
Oregano herb (*Origanum vulgare* ssp. *hirsutum*) c caravcrol or thymol – (c-c&t) MDR-*Salmonella typhimurium,* (c-c&t) MDR-*E. coli,* (c-c&t) MDR-*Staph. aureus,* (c-c&t) erythromycin-resistant *Strep. pyogenes*[3047]
Pomegranate fruit peel (*Punica granatum*) e methanol extract – (e) MDR-*Salmonella typhi*[3046]
Rabdosia (*Rabdosia rubescens*) – (e) MDR-*Acinetobacter baumannii*[2719]
Rugose rose flower (*Rosa rugosa*) – (e) MDR-*Acinetobacter baumannii*[2719]
Simal bark (*Salmalia malabarica*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Sowa seed (*Peucedanum graveolens*) e methanol extract − (e) MDR-*Salmonella typhi*[3046]
Sweet tea fruit (*Rubus chingii*) – (e) MDR-*Acinetobacter baumannii*[2719]
Tea leaf (*Camellia sinensis*) – (e) MDR-*Acinetobacter baumannii*[2719]
Thyme herb (*Thymus vulgaris*) f essential oil, c thymol or caravcrol – (f) MRSA,[2712] (c-t&c) MDR-*Salmonella typhimurium,* (c-t&c) MDR-*E. coli,* (c-t&c) MDR-*Staph. aureus,* (c-t&c) erythromycin-resistant *Strep. pyogenes*[3047]
Tropical almond fruit (*Terminalia chebula*) – (e) MDR-*Acinetobacter baumannii*[2719]
Tulsi seed (*Ocimum sanctum*) e aqueous extract − (e) MDR-*Salmonella typhi*[3046]
Viranga fruit (*Embelia ribes*) e methanol and aqueous extracts − (e) MDR-*Salmonella typhi*[3046]

E.6.2 Botanicals improving antimicrobial efficacy against resistant strains

Cassia bark (*Cinnamomum cassia*) c cinnamaldehyde − c/tetracycline & MDR-*E. coli,* c/ampicillin or penicillin & MDR-*Staph. aureus*[3047]
Chinese lantern tree fruit (*Dichrostachys glomerata*) e methanolic extract − (e) MDR-*Escherichia coli,* (e) MDR-*Enterbacter aerogenes,* (e) MDR-*Klebsiella pneumoniae,* (e) MDR-*Pseudomonas aeruginosa*[3020]
Cinnamon bark (*Cinnamomum verum*) c cinnamaldehyde − c/tetracycline & MDR-*E. coli,* c/ampicillin or penicillin & MDR-*Staph. aureus*[3047]
Cinnamon beilschmiedia bark (*Beilschmiedia cinnamomea*) e methanolic extract − (e) MDR-*E. coli,* (e) MDR-*Ent. aerogenes,* (e) MDR-*K. pneumoniae*[3020]

Clary sage roots (*Salvia sclarea*) c salvipisone or aethiopinone − c-s or d-a/oxacillin, vancomycin, or linezolid & MRSA, MR-*Staph. epidermidis*[3036]

Clove bud (*Syzygium aromaticum*) c eugenol − c/penicillin & MDR-*Staph. aureus* [3047]

Galangal rhizome (*Alpinia officinarum*) c galangin − c/gentamicin & MRSA[3039]

Horseradish root (*Armoracia rusticana*) c allyl isothiocyanate − c/ampicillin or erythromycin & MDR-*Salmonella typhimurium*, c/bacitracin & MDR-*E. coli*, c/bacitracin & MDR-*Staph. aureus*[3047]

Khat leaves (*Catha edulis*) e aqueous extract − e/tetracycline & *Strep. oralis* and *Strep. sanguis*, e/penicillin-G & *Fusobacterium nucleatum*[3033]

Kutaki roots/rhizome (*Picrorhiza kurroa*) f iridoid glycosides − *f/chloroquine & MDR-Plasmodium yoelii*[2937]

Mustard seed (*Brassica nigra*) c allyl isothiocyanate − c/ampicillin or erythromycin & MDR-*Salmonella typhimurium*, c/bacitracin & MDR-*E. coli*, c/bacitracin & MDR-*Staph. aureus*[3047]

Oregano herb (*Origanum vulgare* ssp. *hirsutum*) c caravcrol or thymol – c-c/novobiocin, penicillin, or tetracycline & MDR-*Salmonella typhimurium*, c-c/penicillin or tetracycline and c-t/erythromycin & MDR-*E. coli*, c-c&t/ampicillin, bacitracin, or penicillin & MDR-*Staph. aureus*, c-c&t/erythrocycin & erythromycin-resistant *Strep. pyogenes*[3047]

Sappan wood (*Caesalpinia sappan*) e methanol extract – e/ampicillin or oxacillin & MRSA[2720]

Shirazian thyme herb (*Zataria multiflora*) – f/vancomycin & MRSA[2715]

Tea (green) leaf (*Camellia sinensis*) e aqueous extract, c EGCG – c-E/imipenem & imipenem-resistant *Klebsiella pneumoniae*[2968]

Thyme herb (*Thymus vulgaris*) c thymol or caravcrol – c-c/novobiocin, penicillin, or tetracycline & MDR-*Salmonella typhimurium*, c-c/penicillin or tetracycline and c-t/erythromycin & MDR-*E. coli*, c-t&c/ampicillin, bacitracin, or penicillin & MDR-*Staph. aureus*, c-t&c/erythrocycin & erythromycin-resistant *Strep. pyogenes*[3047]

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

Barberry root bark (*Berberis vulgaris*) c berberine – **c/sulphacetamide & *Chlamydia trachoma***[577]

Cinnamon (*Cinnamomum* spp.) f essential oil − f/chlorhexidine & *Streptococcus mutans, Lactobacillus plantarum*[3035]

Clary sage roots (*Salvia sclarea*) c salvipisone or aethiopinone − c/oxacillin & *Staph. aureus, Staph. epidermidis*[3036]

Clove oil (*Syzygium aromaticum*) c eugenol − c/ampicillin, chloramphenicol, erythromycin, norfloxacin, oxacillin, penicillin, polymyxin B, rifampin, tetracycline, vancomycin & *Enterobacter aerogenes, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium*[2956]

Cola seed (*Cola nitida*) e methanolic extract – e/ciprofloxacin, perfloxacin, levofloxacin & *E. coli*[3034]

Coptis root (*Coptis* spp.) c berberine – **c/sulphacetamide & *Chlamydia trachoma***[577]

Garlic clove *(*Allium sativum*) h fresh cut – **local h/chorhexidine & group B *Streptococcus***[2711]

Geranium leaf (*Pelargonium graveolens*) f essential oil − f/norfloxacin & *Bacillus subtilis, Bac. cereus, Staph. aureus* or *E. coli*[3041]

Goldenseal root and rhizome *(*Hydrastis canadensis*) c berberine – **c/sulphacetamide & *Chlamydia trachoma***[577]

Manuka (*Leptospermum scoparium*) f essential oil − f/chlorhexidine & *Streptococcus mutans, Lactobacillus plantarum*[3035]

Oregon grape bark (*Mahonia* [or *Berberis*] spp.) c berberine – **c/sulphacetamide & *Chlamydia trachoma***[577]

Peppermint (*Mentha piperita*) f essential oil, c menthol − f/ciprofloxacin = 1-1.5 & *Klebsiella pneumoniae*, f/ciprofloxacin ≥ 1 & *Staph. aureus*,[2689] f/oxytetracylcine & *E. coli*, c/oxytetracycline and *E. coli*[3042]
[f/ciprofloxacin < 0.5 or ≥ 4 reduced antibiotic activity against *Klebsiella pneumoniae*; f/amphotericin B reduced antifungal effect *Candida albicans*[2689]]

Rosemary leaf (*Rosmarinus officinalis*) f essential oil – f/ciprofloxacin < 3 & *Klebsiella pneumoniae*[2689]

[f/ciprofloxacin reduced antibiotic activity against *Staph. aureus*; f/amphotericin B reduced antifungal effect on *Candida albicans*[2689]]

Tea (green) leaf (*Camellia sinensis*) c catechin EGCG – *c/ciprofloxacin & E. coli*[3038]

Tea tree (*Melaleuca alternifolia*) f essential oil − f/tobramycin & *Staph. aureus*, f/tobramycin & *E. coli*,[3040] f/ciprofloxacin = 1.5 & *Klebsiella pneumoniae*[2689]
[f/ciprofloxacin < 1 reduced antibiotic activity against *Klebsiella pneumoniae*; f/ciprofloxacin reduced antibiotic activity against *Staph. aureus*; f/amphotericin B reduced antifungal effect on *Candida albicans*[2689]]

Thyme (*Thymus vulgaris*) f essential oil − f/ciprofloxacin = 1-1.5 & *Klebsiella pneumoniae*[2689]
[f/ciprofloxacin ≤ 1.5 reduced antibiotic activity against *Staph. aureus*; f/amphotericin B reduced antifungal effect on *Candida albicans*[2689]]

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

Agastache herb (*Agastache rugosa*) f essential oil, c estragole – f,c/ketoconazole & *Blastoschizomyces capitatus*[3051]

Mediterranean spurge stem (*Euphorbia characias*) f latex − f/ketoconazole & *Candida albicans*[3055]

Moroccan thyme herbs (*Thymus maroccanus, T. broussonetii*) f essential oils – f/fluconazol or amphotericin B & *Candida albicans*[2716]

Myrtle leaves (*Myrtus communis*) f essential oil – f/amphotericin B & *Candida albicans* or *Aspergillus niger*[2718]

Oregano herb (*Origanum vulgare*) f essential oil – f/amphotericin B & *Candida* spp.,[3052] f/nystatin & *Candida* spp.[3053]

Peppermint (*Mentha piperita*) f essential oil, c menthol − [f/amphotericin B reduced antifungal effect *Candida albicans*[2689]]

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

Rose geranium leaf (*Pelargonium graveolens*) f essential oil, c geraniol or citronellol − c-g,c-c/ketoconazole & *Aspergillus flavus*,[3050] f/amphotericin B & *Candida* spp.,[3052] f/nystatin & *Candida* spp.[3053]

Rosemary leaf (*Rosmarinus officinalis*) f essential oil – [f/amphotericin B reduced antifungal activity against *Candida albicans*[2689]]

Santolina aerial parts (*Santolina chamaecyparissus*) f essential oil − f/clotrimazole & *Candida albicans*[3054]

Tea (green) leaf (*Camellia sinensis*) [Note: CORRECTION – NOT Tea tree leaf] catechin EGCG – c/amphotericin B or fluconazole & *Candida albicans*[2366]

Tea tree leaf (*Melaleuca alternifolia*) f essential oil (See CORRECTION above.) – f/amphotericin B & *Candida* spp.[3052] [f/amphotericin B reduced antifungal effect on *Candida albicans*[2689]]

Thyme leaf (*Thymus vulgaris*) f essential oil – [f(uncharacterized chemotype)/amphotericin B reduced antifungal effect on *Candida albicans*[2689]]

Tulsi leaves (*Ocimum tenuiflorum = O. sanctum*) f essential oil (methyl chavicol chemotype), c methyl chavicol or linalool – f,c/fluconazol or ketoconazole & *Candida* spp. or MDR-*Candida* spp.[2717]

E.6.8 Botanicals enhancing efficacy of antiviral agents

Clove oil (*Syzygium aromaticum*) c eugenol − c/acyclovir & herpes simplex virus types 1 & 2[2955]

E.6.9 Botanicals enhancing the efficacy of immunizations against infections

Larch bark (*Larix* spp.) cs arabinogalactans – **pneumococcal vaccine**[2739]

E.6.10 Botanicals reducing adhesion of bacteria that cause infections

Cranberry fruit (*Vaccinium macrocarpon*) j juice, jc juice cocktail, f high molecular weight compounds – **jc (*E.coli*)**,[3002] j (*Streptococcus criceti, Strep. gordonii, Strep. mitis, Strep. mutans, Strep oralis,*

Strep. sanguinis, Strep. sobrinus);[2843] f-hmw (*Porphyromonas gingivalis*),[2841] (*Strep. sobrinus*)[2842]

E.6.11 Botanicals reducing adverse effects caused by antimicrobial agents ^

Cordyceps (*Cordyceps sinensis*) h mycelium, e water extract – **h/amikacin** (kidney), **h/gentamicin** (kidney), *h/gentamicin* (kidney), *e/kanamycin* (kidney)[598]

Garlic leaves or cloves *(*Allium sativum*) h leaves, e aged extract, c diallyl sulfide or diallyl disulfide – *h/gentamicin*,[1911] *c-ds* or *c-dd/gentamicin*,[1912,1913] *e/gentamicin*[1914,1915]

Milk thistle seed (*Silybum marianum*) f silymarin – *f/metronidazole* (stomach, liver, kidney)[2267]

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

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Note: If searching in the book for Black cohosh entries, a complete listing is available under this standard common name. Following the change of scientific binomial from *Cimicifuga racemosa* to *Actaea racemosa*, the main entry in the herb section lists both, but other entries in the herb section and appendix B use only *Cimicifuga*, while in some early printings appendices A, C, and E utilized only the genus name *Actaea*.

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CORRECTION:

1567. WEBSITE IS NOW − http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx [updated Nov. 14, 2011]

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