DRUG-SUPPLEMENT INTERACTIONS:
THE GOOD, THE BAD AND THE UNDETERMINED

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INTRODUCTION

Concomitant use of dietary supplements with medication may produce adverse or beneficial effects, which are determined by the specific substances and circumstances of use. In conducting a detailed analysis of the available literature during 2004[1], the author made the following general observations, the details of which will form the basis for this chapter:

1. The number of documented adverse interactions is matched by the number of documented beneficial interactions.
2. Most adverse interactions are pharmacokinetic, *i.e.*, the supplement alters the solubility, absorption, excretion, protein binding or metabolism of the drug, resulting in subtherapeutic or toxic plasma concentrations.
3. Many potential interactions mentioned in reviews or compendia fail to be confirmed when tested in controlled

human studies.

4. Beneficial interactions between drugs and supplements are of 3 major types:
    1. Drugs may deplete or inhibit the actions of individual nutrients or metabolic intermediates like coenzyme Q10; dietary supplements may compensate.
    2. Specific supplements may decrease toxicity or side effects of individual drugs or drug classes, through diverse mechanisms.
    3. A supplement may actually enhance the pharmacodynamic action of a drug.

The goal of this chapter is twofold: to help physicians guide their patients in avoiding hazardous drug-supplement interactions and to help them identify supplements that may improve the performance of medications they are prescribing. Because of the diversity of substances and interactions, the information will be presented according to categories of clinical use specific to the practice of internal medicine. Only the results of clinical trials, controlled human experiments and significant case reports will be included. Space limitation precludes discussion of medications primarily used in psychiatry, neurology, and gynecology.

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1. ANALGESIC/ANTI-INFLAMMATORY

a. Aspirin and NSAIDs

Three areas of potential interaction between aspirin or NSAIDs and dietary supplements have been reported: gastrointestinal toxicity, antiplatelet effects and relief of pain and inflammation. Table 1 lists six supplements that may diminish GI side effects of aspirin or NSAIDs, based upon controlled experiments with healthy humans. The protective effect of vitamin C is noteworthy because regular use of aspirin depletes intragastric vitamin C and suppresses gastric blood flow in humans[2].

Potential interactions involving platelet function are described in section 4.a.

Numerous food components and herbs have anti-inflammatory effects when studied *in vitro*. Degradation by intestinal flora, poor absorption and rapid inactivation by conjugation render most of these ineffective *in vivo*. The only supplements shown to affect the anti-inflammatory activity of NSAIDs in controlled clinical trials are fish oil and evening primrose oil. Of all dietary supplements, omega-3 fatty acids derived from fish oil have demonstrated the greatest range of therapeutic drug enhancement (see Table 2). In patients with active rheumatoid arthritis, fish oil supplying 1710 mg of eicosapentaenoic acid (EPA) and 1140 mg of docosahexaenoic acid (DHA) per day[3] or evening primrose oil supplying 540 mg of gamma-linolenic acid (GLA) per day appear to allow a significant reduction in NSAID use without increasing indices of disease activity. A combination of evening primrose oil and fish oil supplying 450 mg of GLA and 240 mg of EPA per day, may have a similar effect.[4]. The effect of fish oils in reducing NSAID requirements of patients with rheumatoid arthritis is measurable by 12 weeks and persists for at least 12 months.

b. 5-ASA Derivatives

5-ASA derivatives are primarily used to treat colonic inflammation. Drugs of this class, sulfasalazine in particular, can impair folic acid transport[5], creating hyperhomocysteinemia[6], a risk factor for deep vein thrombosis[7], which is an extra-intestinal complication of inflammatory bowel disease. Co-administration of folic acid with 5-ASA derivatives is effective in preventing hyperhomocysteinemia; folic acid may also reduce the incidence of colon cancer in patients with ulcerative colitis[8,9]. One study found that a high dose of folic acid (15 mg/day) reversed sulfasalazine-induced pancytopenia in two patients[10].

Fish oil capsules may reduce requirements for 5-ASA derivatives and improve maintenance of remission for patients with ulcerative colitis receiving 5-ASA therapy (see Table 2).

Two specific probiotic supplements appear to enhance the therapeutic efficacy of 5-ASA derivatives for induction or maintenance of remission in patients with inflammatory bowel disease. **VSL-3**, a proprietary mixture of *Lactobacillus acidophilus, L. bulgaricus, L. casei, L plantarum, Bifidobacteriium brevis, B. infantis, B. longum and Streptococcus salivarius ssp thermophilus*, at a dose of 900 billion CFU twice a day added to therapy with balsalazide, induced faster remission of active ulcerative colitis than balsalazide or mesalazine alone[11]. ***Saccharomyces boulardii*, a yeast with anti-inflammatory and immune stimulating effects, appears to potentiate the effects of mesalamine in inducing remission** in patients with active ulcerative colitis[12] and reducing the frequency of relapse in patients with Crohn's disease[13].

c. Glucocorticoids

Chromium picolinate, 600 mcg/day, may reverse steroid-induced diabetes in humans; one study demonstrated a decrease in mean blood glucose from 250 mg/dL to 150 mg/dL and a 50% reduction in dose requirement for oral hypoglycemics[14]. Similar effects have been described in rats treated with dexamethasone[15].

Calcium plus vitamin D is effective at preventing steroid-induced reduction of lumbar spine density in patients receiving steroids for less than three years[16,17]. Two reasons for adding calcium and vitamin D supplementation to a glucocorticoid regimen are: (1) glucocorticoids increase calcium excretion, and (2) glucocorticoids induce resistance to the enhancement of intestinal calcium absorption by calcitriol (1,25-dihydroxyvitamin D).[18]

DHEA (dehydroepiandrosterone) may augment the effects of therapy with corticosteroids and diminish side effects. In steroid-treated patients with severe systemic lupus (SLE), DHEA, 200 mg/day for 6 months, improved the SLE-disease activity index and prevented steroid-induced bone loss, when compared to placebo[19]. DHEA also allowed reduction of prednisone dose to less than 7.5 mg/day in a larger proportion of patients than did placebo[20]. In patients with Addison's disease, addition of DHEA, 50 mg/day, to usual steroid replacement therapy, improved energy and mood, compared to placebo[21].

Herbal preparations can alter metabolism of endogenous and exogenous glucocorticoids. Glycyrrhetinic acid (the aglycone of glycyrrhizin), a component of licorice, increases the half-life and area under the curve (AUC) of orally

administered prednisolone, presumably by inhibiting renal 11 beta-hydroxysteroid dehydrogenase and hepatic enzymes involved in beta-hydroxysteroid metabolism[22]. Despite equal content of glycyrrhizin, however, three separate formulas used in traditional Chinese and Japanese kampo medicine had qualitatively different effects on 11 beta-hydroxysteroid dehydrogenase. Sho-saiko-to (xiao chai hu tang), used in Asia for treatment of chronic hepatitis and now available in the U.S., was found to reduce prednisolone AUC by 17%, through an unknown mechanism[23].

d. Acetaminophen

Acetaminophen toxicity results from production of N-acetyl-p-benzoquinone imine (NAPQI) by hepatic cytochrome P450 2E1. NAPQI is usually detoxified by conjugation with glutathione (GSH). The amino acid N-acetylcysteine (NAC), a glutathione precursor, protects against this toxicity[24] and, orally or intravenously, is the treatment of choice for acetaminophen overdose[25]. Several supplements prevent acetaminophen toxicity in laboratory animals; no human studies of these have been reported.

e. Narcotics

Administration of St. John's wort (*Hypericum perforatum*) to four patients on maintenance methadone reduced methadone bioavailability by 47%, producing symptoms of methadone withdrawal in two[26]. St. John’s wort has shown clinically significant adverse interactions with more medications than any other dietary supplement (see Table 3). What makes St. John’s wort so problematic is its ability with chronic use to induce enzymes of drug metabolism and detoxification, especially the cytochrome P450 isozyme CYP3A4, which metabolizes about 50% of all drugs commonly used in the United States, and the P-glycoprotein (P-gp) transport protein.[27] P-gp ejects a variety of xenobiotics from cells. Drugs that are slowly absorbed and also are substrates for intestinal P-gp may have their plasma levels significantly reduced by St. John’s wort. Variability of pharmacokinetic interactions with St. John's wort may reflect the variability of hyperforin content in St. John's wort preparations. Hyperforin appears to be the component of St. John's wort responsible for CYP induction[28]

Yohimbine, an alkaloid derived from yohimbe bark, which is used to enhance sexual function, elicited signs and symptoms of opioid withdrawal in patients receiving methadone maintenance therapy[29]. Yohimbine inhibits central alpha 2-adrenergic receptors that enhance narcotic effects[30].

2. ANTIARRHYTHMIC/ANTIHYPERTENSIVE

a. **Digoxin**

The earliest antiarrhythmic drug, digitalis, and the earliest hypotensive agent, reserpine, were derived from herbal extracts. Numerous herbs contain cardiac glycosides with structural similarity to digitalis[31], but published interactions in humans are limited to alterations in the measurement of digoxin concentration in serum, without clinical effect, caused by ginseng preparations[32 33]. Licorice may cause pseudoaldosteronism and hypokalemia[34], which can promote digoxin

toxicity.

Magnesium supplementation enhances the anti-arrhythmic effect of digoxin and helps to protect against digitalis toxicity[35]; digoxin increases renal magnesium losses, contributing to hypomagnesemia, which lowers the threshold for the development of digitalis toxicity[36]. Magnesium supplementation may be beneficial for patients with normal renal function receiving digoxin therapy.

Gum guar, wheat bran and St. John's wort may decrease plasma digoxin concentration by decreasing intestinal absorption[37].

b. Beta-blockers

Adverse clinical interactions between beta-blockers and dietary supplements have not been published, although herbal preparations containing caffeine or ephedra would be expected to counteract the pharmacodynamic properties of beta-blockers.

Fish oils may enhance the antihypertensive effects of beta-blockers. (see Table 2). Although fish oils show antiarrhythmic effects, they do not appear to have antiarrhythmic synergy with beta-blockers.[38]

In patients receiving propranolol, coenzyme Q10 60 mg bid may reduce the incidence of cardiac arrhythmia, angina and heart failure during the first 28 days post-myocardial infarction[39] and of cardiac events over the subsequent year[40]. At 90 mg bid, coenzyme Q10 appears to diminish the negative chronotropic and inotropic effects of ocular timolol, used for treatment of glaucoma, without impairment of therapeutic response[41].

Chromium picolinate 600 mcg/day may raise serum HDL-cholesterol in men taking beta-blockers, without affecting total cholesterol[42].

c. Calcium channel blockers

The dihydropyridine calcium channel blockers are substrates for CYP3A and are potentially subject to pharmacokinetic interactions with numerous herbs that inhibit or induce CYP3A isozymes[43]. This interaction was demonstrated in human volunteers when nifedipine and felodipine were taken with peppermint oil, a CYP3A inhibitor[44]. Although garlic extracts may induce CYP3A (and were shown to reduce bioavailability of saquinavir in human volunteers[45]), no interaction between garlic and calcium channel blockers has yet been reported.

Pycnogenol (an extract of bark of the French maritime pine), 100 mg/day for 12 weeks, reduced blood pressure in hypertensive patients taking nifedipine, allowing reduction in drug dosage in a double-blind, placebo-controlled trial[46]. In vitro, pycnogenol stimulates endothelial nitric oxide synthesis, an effect that appears to rest with the oligomeric proanthocyanidin fraction[47].

d. ACE inhibitors

ACE inhibitors, captopril in particular, have metal-binding sites. Co-administration of iron (and possibly other

metals) with ACE inhibitors may significantly reduce drug absorption, impairing the antihypertensive response[48].

ACE inhibitors decrease potassium excretion, so that administration of potassium to patients taking ACE inhibitors may cause severe hyperkalemia[49].

The addition of NAC 600 mg t.i.d. to captopril or enalapril treatment of hypertensive male smokers enhanced the antihypertensive effect of the drug, presumably by protecting vascular nitric oxide from oxidation.[50]

3. ANTIBIOTIC

a. Tetracyclines, quinolones

Chelation of minerals by tetracycline and quinolone antibiotics significantly reduces intestinal absorption and may lead to therapeutic failure. Studies in rats have demonstrated that common herbs like dandelion[51] and fennel[52] can be so rich in minerals that they inhibit absorption of these antibiotics.

b. Metronidazole

Silymarin, a group of flavonoids found in milk thistle, was shown to reduce the bioavailability and blood levels of metronidazole by 30% among healthy volunteers,[53] an effect that may lead to therapeutic failure. None of the suspected mechanisms for this interaction are consistent with other known effects of milk thistle.

Vitamin C (250 mg bid) plus vitamin E (200 IU bid), impaired the effectiveness of metronidazole in the treatment of *H. pylori* infection[54], again through an unidentified mechanism.

Saccharomyces boulardii 250 mg t.i.d. enhanced therapeutic efficacy of metronidazole and diiodoquinol in treatment of acute amebic colitis, reducing the duration of diarrhea by 75% and of fever and abdominal pain by 50% and reducing the prevalence of post-treatment amebic cystosis from 18% to 0[55]. *S. boulardii* (1000 mg/day) appears to enhance therapeutic efficacy of metronidazole[56] and vancomycin[57] in the treatment of recurrent *Clostridium difficile* colitis, but may not be beneficial for a first attack of *C. difficile* colitis.

c. Nitrofurantoin

Deglycyrrhizinated licorice (DGL) administered along with nitrofurantoin to patients with urinary tract infection may increase the urinary concentration of nitrofurantoin, possibly enhancing efficacy[58]. One early controlled study found that combining DGL with nitrofurantoin improved outcome of patients being treated for pyelonephritis[59].

d. Trimethoprim

Although used as an antibiotic, trimethoprim is also a potassium-sparing diuretic, similar in action to amiloride. Concomitant use of trimethoprim with potassium salts may contribute to hyperkalemia[60].

e. Antibiotic-associated diarrhea (AAD)

Probiotic supplements are effective in reducing the incidence of AAD in children[61,62] and adults[63], although the magnitude of the effect varies considerably. The majority of positive studies have been done with *Lactobacillus*

rhamnosus GG and *S. boulardii.*

4. ANTITHROMBOTIC

a. Aspirin and other inhibitors of platelet function

Numerous dietary supplements inhibit platelet function in laboratory experiments. [ref 31, Ulbrect et al]. Many of these, however, do not manifest antiplatelet effects when taken orally by human volunteers. Turmeric[64], flaxseed oil,[65] borage oil (a source of GLA)[66] and primrose oil[67] are notable examples of substances identified as antithrombotic that have no demonstrable effect on hemostatic parameters in controlled human experiments. Others, like resveratrol, only inhibit the function of platelets that are washed *ex vivo* and have no effect on platelets suspended in whole blood, rendering any clinical effect unlikely[68]. Dietary supplements that inhibit human platelet function after oral administration are listed in Table 4. These might act in an additive fashion with antiplatelet drugs, but few actual interactions have been reported. Vitamin E (alpha-tocopherol) is an exception.

Vitamin E and aspirin have synergistic antiplatelet effects. Aspirin inhibits platelet aggregation; alpha-tocopherol inhibits platelet adhesion to the vascular endothelium. The interaction may be adverse or beneficial, depending upon the clinical circumstances. Use of low doses of alpha-tocopherol (50 IU/day) increased the risk of gingival bleeding by 25% among men taking aspirin, according to an often-cited study.[69] The addition of 400 IU/day of alpha-tocopherol to 325 mg aspirin/day significantly reduced the incidence of transient ischemic attacks (TIAs) in patients with previous TIAs, when compared to aspirin alone.[70]

Fish oils do not show an additive or synergistic antiplatelet interaction with aspirin[71] but may act synergistically to prolong bleeding time[72]. A prospective long-term study, however, found no increase in bleeding episodes or abnormalities of hemostasis attributable to the combination of 300 mg aspirin with 4000 mg fish oil/day[73].

Policosanol, a mixture of primary aliphatic alcohols isolated from sugar cane wax, exerts dose-dependent inhibition of platelet aggregation, with 20 mg of policosanol/day producing an effect similar to 100 mg of aspirin/day. Combination of aspirin and policosanol produces a mild additive effect in healthy volunteers[74].

A single case report describes spontaneous intraocular bleeding associated with the combined use of aspirin and Ginkgo biloba extract [ref 43, Izzo].

b. Warfarin

Although many reviews warn of potential interactions between dietary supplements and warfarin, few have actually been reported (see Table 5) and some
highly publicized case reports have failed confirmation in controlled studies.
Coenzyme Q10 is structurally similar to vitamin K and has been reported to interfere with response to warfarin, based

upon uncontrolled case reports[75,76]; however, no effect of coenzyme Q10, 100 mg/day for 4 weeks, on warfarin effect was seen in a placebo-controlled trial.[77] Similarly, early reports indicated increased bleeding in patients receiving warfarin along with vitamin E,[78] but a controlled study showed no effect of vitamin E on the anticoagulant response to warfarin, as measured by INR, at doses up to 1200 IU/day[79]. Case reports of vitamin C and fish oil[80] increasing warfarin effect have also not been validated in controlled experimental studies[81]. Although two case reports suggest a decreased warfarin effect in patients taking ginseng[82,83], a controlled study showed no interaction[84]. Variations in the ginseng preparations used may account for the differences.

Because of its narrow therapeutic range, extensive binding to plasma protein and extensive hepatic metabolism, warfarin is likely to be sensitive to interactions with numerous drugs and herbs, so that extreme caution should always be used by patients taking warfarin when adding any dietary supplement.

5. ANTILIPEMIC

Most HMG coA reductase inhibitors (statins) are substrates for P-gp and CYP3A, making them candidates for pharmacokinetic interactions with herbs that alter activity of these enzymes (ref 43, Izzo). St. John's wort decreases the serum concentration of simvastatin (see Table 3), but does not affect pravastatin pharmacokinetics, because pravastatin metabolism is less subject to the activity of CYP and P-gp.

Red yeast rice contains monacolin K, which is identical with lovastatin, and yields similar clinical and toxicological effects[85]. Presumably, red yeast rice would have added therapeutic and toxic effects with any statin, although commercial preparations of red yeast rice extract vary considerably in their monacolin content[86].

An antioxidant cocktail consisting of ß-carotene 25 mg, vitamin C 1000 mg, vitamin E 800 mg., and selenium 100 mcg, adversely affected the reduction in cardiovascular events of simvastatin-niacin therapy among 160 patients with coronary artery disease, low HDL-cholesterol (HDL-C <35) levels and normal LDL-cholesterol (mean LDL-C,140) [87]. Further analysis found that the antioxidant cocktail prevented the increase in protective HDL2-C produced by simvastatin-niacin [88]and blunted the protective increase in HDL-C particle size associated with simvastatin-niacin therapy [89]. These adverse effects were reproduced using vitamin E and vitamin C alone[90]. Selenium by itself actually enhanced the simvastatin-niacin increase in HDL-C2[91]. In contrast, a large prospective study of 20, 563 hyperlipidemic individuals receiving simvastatin without niacin, found that a similar antioxidant cocktail (650 IU vitamin E, 250 mg vitamin C and 20 mg beta-carotene) produced no alteration, positive or negative, in in any therapeutic parameter[92]. The adverse effect of vitamins E and C on anti-lipemic therapy may be specific to patients with low HDL-C.

All statins reduce synthesis of the endogenous antioxidant, coenzyme Q10[93]. Statin-induced coenzyme Q10 depletion may impair mitochondrial function, raising the serum lactate/pyruvate ratio.[94] Supplemental coenzyme-Q10, 100 mg/day, prevents the decline in serum coenzyme Q10 levels without impairment of the hypolipidemic effect of the

statin[95] and may reduce symptoms of statin myopathy, according to a small controlled study[96]. Statin-induced coenzyme Q10 depletion may actually be increased by vitamin E (700 IU/day)[97], possibly because coenzyme Q10 is consumed in the recycling of the oxidative metabolites of vitamin E (tocopheryl quinones) to tocopherols.[98] Co-enzyme Q10 depletion might possibly explain the reversal by vitamin E of the vascular benefits of atorvastatin in patients with heart failure[99].

6. ANTINEOPLASTIC

Because most antineoplastic agents are highly toxic and have a narrow therapeutic range, the use of dietary supplements by cancer patients has generated considerable concern. St. John's wort is a particular problem, not only because of adverse pharmacokinetic interactions due to enzyme induction by one of its components, hyperformin (see Table 3), but also because another component, hypericin, may interfere with a pharmacodynamic mechanism shared by many antineoplastic agents, topoisomerase inhibition[100].

Natural substances other than St. John's wort that induce P-gp or other transport proteins have the potential to diminish effectiveness of cancer chemotherapy. Although studies in vivo are lacking, in vitro studies indicate that the chronic exposure to the flavonoids quercetin, kaempferol, and silibinin (derived from milk thistle) induce P-gp [ref 160]. Other herbal derivatives are being tested for P-gp inhibition, in an effort to find substances that can overcome multi-drug resistance to cancer chemotherapy[101]. Green tea catechins may either inhibit or induce P-gp, depending upon their structure [ref 160]. The use of herbal therapies in conjunction with chemotherapy creates a serious potential risk for adverse interaction. During the course of a clinical trial, self-administration of essiac tea, a polyherbal product specifically marketed for cancer treatment, was associated with markedly elevated levels of exatecan mesylate and significant clinical toxicity, although the mechanism of the interaction has not been established[102].

Other dietary supplements contraindicated with chemotherapy include zinc and high dose vitamin B6 for patients receiving platins. Zinc supplementation induces synthesis of metallothionein, a metal efflux enzyme that can reduce cellular concentration of platinum-derived antineoplastic drugs, inhibiting effectiveness of cisplatin in rodents.[103] An interaction in humans has not been reported, but it seems prudent to avoid zinc supplementation in patients receiving platins. Many commonly used multivitamin preparations contain zinc. Although high dose pyridoxine (300 mg/square meter/day for 3 weeks) decreased toxicity of cisplatin/hexamethylmelamine therapy of patients with advanced ovarian cancer, its use was associated with decreased duration of the treatment response[104].

In contrast, there are several dietary supplements that have been shown to decrease the side effects of chemotherapy without adversely effecting therapeutic outcome, according to small clinical trials (see Table 6). Some of these substances are classified as antioxidants.

A detailed discussion of the controversy concerning co-administration of antioxidants with cancer chemotherapy

is outside the scope of this chapter. The controversy itself is based upon a misunderstanding of the concept of "antioxidant", which is a conditional term, not an absolute one. Almost all antioxidants exist in at least two redox states and function as pro-oxidants under appropriate conditions. The notion that antioxidants protect cancer cells from the effects of chemotherapy is not supported by empirical data; on the other hand, the notion that antioxidants protect normal tissue from the toxicity of antineoplastic agents needs to be established with specific doses of specific supplements used in conjunction with defined chemotherapeutic agents.

7. DIURETIC

Numerous case reports of severe hypokalemia resulting from the combination of various diuretic agents with licorice have appeared[105]. Licorice may also reverse the antihypertensive effects of diuretics. The presumed mechanism for both effects is pseudoaldosteronism, produced by a metabolite of glycyrrhizin that inhibits 11-beta hydroxysteroid dehydrogenase.

A single case report describes hypertension in a patient taking Ginkgo biloba along with a thiazide diuretic[106]. The presence of an interaction was not established.

Several case reports describe symptomatic hypercalcemia resulting from the combination of thiazide diuretics, which inhibit renal calcium excretion, and vitamin D[107] [108] [109] or calcium supplements[110].

Potassium-sparing diuretics decrease magnesium excretion. Severe hypermagnesemia has occurred when magnesium-containing products were taken by patients using amiloride[111]. The interaction has not yet been reported for triamterene; and may not occur with spironolactone; in healthy unsupplemented subjects, spironolactone, in contrast to amiloride, does not elevate serum magnesium concentration[112].

Numerous herbs are alleged to have diuretic or cathartic effects. Herbs with diuretic action traditionally ascribed to them include buchu, burdock, butcher's broom, celery seed, cornsilk, couch grass, dandelion, elder broom, goldenrod, gravel root, horsetail, parsley, juniper, stinging nettle, uva-ursi and wild carrot. Potentiation of diuretic medication by these herbs is possible, but not demonstrated. Abuse of Cascara segrada has been associated with hypokalemia[113]; concomitant use of an herbal laxative with a diuretic might produce additive depletion of potassium.

8. HYPOGLYCEMIC

Almost all reported interactions between dietary supplements and anti-diabetic agents are pharmacodynamic and result from potentiation of hypoglycemia. In a systematic review of interactions between drugs and herbs in a hospital clinic population, two-thirds of the observed interactions was potentiation of oral hypoglycemics by nopal (prickly pear cactus) [114]. The most frequently prescribed oral hypoglycemic, the biguanide metformin, is itself an herbal derivative, originally found in French lilac (Galega officinalis), used traditionally for treatment of diabetes.

A review of clinical research on the hypoglycemic effect of natural products concluded that the best evidence for efficacy from adequately designed randomized controlled trials is available for Coccinia indica and American ginseng[115]. Table 7 lists supplements demonstrated to reduce blood sugar or improve insulin sensitivity in small clinical trials of diabetic patients. None of these agents appears adequate as stand alone therapy[116], but many of them are in common use among different ethnic groups, creating the potential for clinically significant drug interactions among diabetics who use them. Nopal is the most widely used herbal hypoglycemic among persons of Mexican descent and bitter melon (karela) is more commonly used by persons from Asia[117].

Concerns that glucosamine[118] or fish oil[119] supplementation might impair glycemic control have not been supported in controlled studies

9. IMMUNE MODULATION

Cyclosporine blood levels are subject to control by P-gp and CYP3A activity, creating great potential for pharmacokinetic interactions with natural products. The increase in cyclosporine trough concentration by grapefruit juice is well-known and has been used therapeutically[120]. St. John's wort, conversely, reduces cyclosporine levels (see Table 3). Cyclosporine in its turn inhibits metabolism of statins, increasing blood levels and the potential for toxicity. Rhabdomylosis, a manifestation of statin toxicity, occurred in a renal transplant patient taking cyclosporine and red yeast rice, which contains the natural lovastatin analogue, monacolin K[121].

Cyclosporine nephrotoxicity in transplant patients has been mitigated by fish oils (see Table 2) and in one study by vitamin E (alpha-tocopherol acetate 500 mg/day)[122].

Folic acid, 1 to 5 mg/day, decreases the toxicity of low-dose methotrexate in patients with rheumatoid arthritis[123] or psoriasis[124] without affecting the therapeutic efficacy of methotrexate. At 5 mg/day, folic acid may prevent methotrexate-induced nausea (ref 123) and the rise in homocysteine associated with methotrexate therapy[125]. It also may increase the cellular uptake of methotrexate[126] and perhaps should not be taken on the day methotrexate is injected.

Interferon-alpha, used in the treatment of chronic hepatitis C infection, may have its therapeutic and toxic effects enhanced by dietary supplements. The polyherbal medicine sho-saiko-to, used in Japan to treat chronic hepatitis C, is now available in the United States. Allergic pneumonitis, an uncommon side effect of both sho-saiko-to and interferon alpha, is several times more likely to occur when the medications are administered together[127] Sho-saiko-to's principal ingredient, bupleurum, is thought to owe its anti-fibrotic effects to the flavonoids baicalin and baicalein, which are structurally similar to the antifibrotic flavonoid silibinin, found in milk thistle[128], an herb frequently taken by patients with chronic liver disease. Until more information is available, it seems prudent to advise patients receiving interferon to avoid concomitant use of milk thistle and bupleurum-containing herbs.

On the other hand, the addition of zinc (150 mg/day as zinc carnisonate[129] or 300 mg/day as zinc sulphate[130]) may enhance the response to interferon therapy without increasing toxicity.

10. NITRATES

Three supplements appear to prevent or reverse nitrate tolerance, according to small human studies. NAC, 2400 mg orally, b.i.d. for 2 days increased the exercise tolerance of patients receiving isosorbide mononitrate (ISMN), when compared to ISMN plus placebo[131]. High dose NAC helps to prevent nitrate tolerance in patients with normal left ventricular function, but results are variable in patients with congestive heart failure[132 133 134]. Oral NAC at a dose of 400 mg t.i.d did not prevent nitrate tolerance in patients with normal cardiac function and stable angina pectoris[135].

Organic nitrates release nitric oxide (NO), a step that requires the presence of thiol groups; depletion of thiols by oxidation is thought to be responsible for nitrate tolerance and NAC is used as a source of replacement sulfhydryl groups. NAC not only potentiates the cardioprotective effects of nitrates, but also aggravates nitrate-induced headache[136].

L-arginine, the amino acid precursor of nitric oxide, at a dose of 700 mg q.i.d. by mouth, attenuated the development of tolerance to transdermal nitroglycerine over a 2 week period in patients with stable angina pectoris, but had no effect on initial response to nitrate[137].

Folic acid 10 mg/day prevented both nitrate tolerance and nitric oxide synthase dysfunction induced by continuous nitroglycerine in the arterial circulation of healthy volunteers[138]. Continuous treatment with nitroglycerin may reduce bioavailability of tetrahydrobiopterin, an essential cofactor for nitric acid synthase. Folate is involved in regeneration of tetrahydrobiopterin.

CONCLUSION

Because clinically significant interactions between dietary supplements and medication exist, physicians must know all the supplements their patients are taking. Extreme caution should be taken by patients using high risk medications like warfarin, cytotoxic agents and anti-retroviral protease inhibitors. The literature on drug-supplement interactions is dominated by reviews that stress potential adverse interactions due to CYP or P-gp induction/inhibition or to additive pharmacodynamic effects. Many of these are not substantiated when tested in controlled human experiments. A number of small clinical trials demonstrate benefits of dietary supplements in augmenting drug effects or decreasing toxicity. Familiarity with these will allow physicians to direct their patients in the use of dietary supplements to enhance the effectiveness of conventional care. Prescribed in this fashion, it may be possible to apply precision to the use of dietary supplements.

TABLE 1. SUPPLEMENTS THAT DECREASE GASTROINTESTINAL TOXICITY OF ASPIRIN OR NON-STEROIDAL ANTIINFLAMMATORY DRUGS

DRUG	SUPPLEMENT	EFFECTS
Aspirin	Vitamin C	Prevents duodenal injury[139] and gastric lesions[140]
Aspirin	Deglycyrrhizinated licorice (DGL)	Reduces fecal blood loss[141]
Aspirin	Cayenne	Pretreatment reduces gastric mucosal damage.[142]
Aspirin	S-adenosylmethionine	Co-administration reduces erosive gastritis.[143]
Indomethacin	L-glutamine	Prevents increased small bowel permeability[144].
Indomethacin	Bovine colostrum	Prevents increased small bowel permeability[145]

TABLE 2. OMEGA-3 FATTY ACID ENHANCEMENT OF CLINICAL RESPONSE TO MEDICATION IN CONTROLLED CLINICAL TRIALS

DRUG/CLASS	DIAGNOSIS	OMEGA-3 DOSE	EFFECT
5-ASA inhibitor	ulcerative colitis	4.2 to 5.1 g/day	Prevent early relapse[146], Permit reduced drug dose[147]
Antidepressant	unipolar depression	6.6 g/day	Improved mood[148]
Beta-blocker	mild hypertension	2.9-3.4 g/day	Reduced blood pressure[149] [150]
Bronchodilator	exercise-induced bronchospasm	5.2 g/day	Improved pulmonary function reduced bronchodilator use[151]
Cyclosporine	liver transplant	4 g/day	Improved renal function[152]
	renal transplant	3 g/day	Improved renal function[153]
	heart transplant	3.4 g/day	Reduced blood pressure[154]
Lithium	bipolar disorder	9.6 g/day	Global clinical improvement[155]
Neuroleptic	schizophrenia	2 g/day of EPA	Improved symptom control[156]
NSAID	rheumatoid arthritis	2.85 g/day	Reduction of NSAID dose[157]
Statin	combined hyperlipidemia	1400-2800mg/day as ethyl esters	Increased HDL-C and decreased postprandial hypertriglyceridemia[158] and hypercoagulability[159] [160]

TABLE 3. DRUGS WITH SIGNIFICANT REDUCTION IN PLASMA LEVELS WHEN CO-ADMINISTERED WITH ST. JOHN'S WORT IN HUMAN STUDIES

Alprazolam*[161]
Amprenavir[162]
Amitriptyline[163]
Benzodiazepines (ref 162)
Cyclosporine[164]
Dextromethorphan[165]
Digoxin*[166]
Fexofenadine[167]
Imatinib[168]
Indinavir[169]
Irinotecan[170]
Lopinavir (ref 162)
Methadone (see text)
Midazolam[171]
Nevirapine[172]
Omeprazole (varies with genetic polymorphism in CYP3A4 and CYP2C19 activity)[173]
Oral contraceptives[174]
Ritonavir (ref 162)
Simvastain (but not pravastatin)[175]
Tacrolimus (but not mycophenalate)[176]
Theophylline (ref 165)
Verapamil[177]
Warfarin[178]

*Interaction occurs only with high hyperforin content St. John's wort.

TABLE 4. DIETARY SUPPLEMENTS THAT INHIBIT PLATELET FUNCTION AFTER ORAL ADMINISTRATION TO HUMANS

SUPPLEMENT	COMMENTS
Dong quai	inhibits pathological platelet activation in ulcerative colitis[179]
Fish oil	reduced PAF- and collagen-activated aggregation[180]
Garlic	inhibits thromboxane synthesis[181]
Ginger	may decrease thromboxane synthesis[182]
Gingko biloba	inhibits collagen-activated aggregation[183], effect inconsistent[184]
Licorice	glycyrrhizin exerts *in vivo* effect[185]
Policosanol	decreases thromboxane synthesis[186]
Pycnogenol	only inhibits cigarette-induced aggregation in smokers[187]
Reishi	effect requires high dose extracts[188]
Resveratrol	inhibits ADP[189]- and thrombin-induced[190] aggregation
Saw palmetto	case report of increased bleeding time and hemorrhage[191]
Tocopherols, mixed	mild inhibition of ADP-induced aggregation[192]
Tocotrienols	decrease thromboxane synthesis[193] but not hemostasis[194]
Vitamin E	inhibits platelet adhesion, not aggregation[195]

TABLE 5. DIETARY SUPPLEMENTS WITH DOCUMENTED INTERACTIONS WITH WARFARIN

SUPPLEMENT	COMMENTS

Boldo hemorrhage, single case report[196]

Chlorella vitamin K content may inhibit warfarin effect[197]

Danshen increases INR[198]

Devil's claw purpura, single case report[199]

Dong quai increased INR, single case report[200]

Fenugreek hemorrhage, single case report [boldo ref]

Garlic two case reports of increased INR[201]

Ginkgo biloba intracerebral hemorrhage, case report[202]

Lyceum barbarum case report of increase INR[203]

Panax ginseng increased clearance without effect on hemostasis[204]

Red yeast rice monacolin K, identical with lovastatin, augments the anticoagulant effect of warfarin[205]

St John's wort decreased INR in multiple case reports[206]

Vinpocetin mild reduction in warfarin effect, unknown mechanism[207]

TABLE 6. DIETARY SUPPLEMENTS THAT MAY PREVENT TOXICITY OF ANTINEOPLASTIC CHEMOTHERAPY: CLINICAL TRIALS

SUPPLEMENT	ANTINEOPLASTIC	INTERACTION
coenzyme Q10*	adriamycin	decreased cardiotoxicity[208]
glutamine	various	decreased mucositis[209], anthracycline cardiotoxicity, irinotecan diarrhea, paclitaxel neuropathy[210]
magnesium**	cisplatin	decreased renal tubular damage[211]
melatonin	cisplatin, etoposide	decreased myelosuppression and

neuropathy[212]

interleukin-2 decreased hypotension[213]

N-acetyl cysteine ifosfamide decreased hemorrhagic cystitis[214]

selenium cisplatin reduced myelosuppression and nephrotoxicity[215]

vitamin B6 5-flurouracil reverse palmar-plantar dysesthesia[216]

vitamin E cisplatin decreased neurotoxicity[217]

* Adriamycin inhibits coenzyme Q10 synthesis[218]

**Cisplatin induces severe intracellular magnesium depletion[219]

TABLE 7: DIETARY SUPPLEMENTS WITH HYPOGLYCEMIC OR INSULIN-SENSITIZING EFFECTS DEMONSTRATED IN DIABETIC HUMANS

Supplement	Effect
Aloe vera, dried sap, ½ tsp/day	Reduces fasting blood sugar in NIDDM[220]
Aloe vera, juice, 1 tbsp bid	Potentiates action of glyburide[221]
Alpha lipoic acid (600 mg/day)	Improves insulin sensitivity[222]
	Improves diabetic control and neuropathy[223]
Bitter melon (Momordica charantia)	Weak hypoglycemic action in NIDDM[224]
Chromium	Most extensively studied with inconclusive and conflicting results in NIDDM[225] [226] [227] [228] [229]

Coccinia indica Reduces blood sugar[230]

Fenugreek (25 g/day) Reduces blood sugar in NIDDM[231]

Ginseng, American (3000 mg) Reduces glycemic response to glucose challenge[232] [233]

Ginseng, Asian (200 mg/day) Reduces blood sugar and glycohemoglobin[234]

Gymnema silvestre(400 mg/day) Reduces insulin requirements[235]
Reduces need for oral hypoglycemics[236]

Nopal (Opuntia spp.) Broiled stems (500 g) reduce blood sugar[237] [238]
Capsules are ineffective[239] [240]

Pycnogenol (100 mg/day) Reduces glucose, improves endothelial function[241]
Improves diabetic retinopathy[242]

Saltbush (Atriplex halimus) Hypoglycemic, insulin potentiating[243]

Vanadyl sulfate (100-150 mg/day) Improves glycemia and insulin sensitivity[244] [245] [246] [247]
Small reduction in insulin requirement[248]

Vijayasar(Pterocarpus marsupium) Reduces blood sugar in mild NIDDM[249]

Vitamin D Increases insulin sensitivity in vitamin D deficiency[250]

Vitamin E (600-900 IU/day) Improves glycemic control[251] and insulin action[252]
Reduces glycohemoglobin and plasma insulin[253]

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