Herbs and Immunosuppressive Drugs

Corticosteroids, Methotrexate, and Others

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Abstract

Interactions between immunosuppressive drugs (other than calcineurin inhibitors) and herbs are reviewed. The benefits of combining corticosteroids with *Salvia miltiorrhiza* (Chinese sage), *Allium sativum* (garlic), *Allium cepa* (onion), *Panax notoginseng* (sanchi ginseng), *Tripterygium wilfordii* (thunder duke vine),* and *Zingiber officinale* (ginger) are discussed. The impact of *Citrus* x *paradisi* (grapefruit), *Hypericum perforatum* (St. John's wort), *Glycyrrhiza glabra,* and *G. uralensis* (licorice) on corticosteroid pharmacokinetics is reviewed. Interactions of *Nigella sativa* (black cumin), *Paeonia lactiflora* (white peony) root without bark, thunder duke vine, licorice, and glycyrrhizin with methotrexate (used in immunosuppressive doses, compared to chemotherapeutic doses), positive and negative, are discussed.

Little research is available on interactions with azathioprine, 6-mercaptopurine, sirolimus, cyclophosphamide, and mycophenolate with herbs, but the studies that exist are reviewed, including those on *Artemisia absinthium* (wormwood), thunder duke vine, St. John's wort, silymarin, glycyrrhizin, *Astragalus membranaceus* (astragalus), and the Chinese herbal formula *Qing Re Huo Xue Tang.*

Introduction

Immunosuppressive drugs make organ transplantation possible and are also used to treat many patients with autoimmune diseases. While these agents offer great benefits, there is a high risk of serious adverse effects when the drugs are used, and they rarely effect cures. The previous article on this topic reviewed the interactions—positive and negative—between herbs and the commonly used calcineurin-inhibiting immunosuppressive drugs cyclosporine and tacrolimus.[1] The current article focuses on other immunosuppressive medications, all of which have received less research attention than the calcineurin inhibitors in terms of interactions with herbs.

Corticosteroids: Pharmacodynamic Interactions

Numerous herbs have been investigated in human clinical trials to determine if they can boost the efficacy of corticosteroids. Unlike other immunosuppressive drugs, corticosteroids are used to treat many other inflammatory disorders.

Salvionolic acid B is a complex molecule isolated from *Salvia miltiorrhiza* (Chinese sage, *dān shēn*). In a clinical trial, 42 Chinese subjects with oral submucous fibrosis, a precancerous condition associated with betel-nut chewing, were randomized to receive either 2 mg of triamcinolone or 4 mg of salvianolic acid B or the two combined by intralesional injection (after an application of a topical anesthetic) once weekly for 20 weeks.[2] All participants were asked to stop chewing betel-nuts, stop smoking, avoid ethanol, and stretch their mouths for 15 minutes three times daily. The combination of salvianolic acid B and triamcinolone improved mouth opening and relieved burning sensations significantly better than either agent alone.

There is also some evidence that an injectable extract of Chinese sage is safe and may improve nephroprotective effects of corticosteroids in children with primary nephrotic syndrome.[3] Details of this Chinese-language study are not available, but the outcomes were only serum markers of kidney damage, and the researchers did not assess long-term clinical outcomes that are of greater importance to patients. Nevertheless, it appears that, despite its immunologic effects, Chinese sage may be safe to use with corticosteroids.

*Although this herb is frequently called "thunder god vine," this is a mistranslation, which was confirmed by Dan Bensky, DO (an expert translator and author of one of the most widely used and revered English-language Chinese herbal materia medicas), in a personal communication. While almost all Western literature uses this common name, the current authors believe that it is important to start using a more-correct translation rather than perpetuating what is clearly an error that is being unknowingly propagated.

Alopecia areata is an autoimmune disease causing hair loss. In a double-blinded trial in 40 Iranian patients with alopecia areata, all were treated with betamethasone 0.1% and randomly assigned to additionally use either a 5% gel of *Allium sativum* (garlic; the gel preparation was stated to be " odorless") or a matching placebo.[4] Adding garlic to the steroid resulted in significantly better clinical results (more hair regrowth) than what was produced by the steroid with the placebo.

Patients (N = 27) with hypertrophic scars or keloids were all treated with intralesional injections of 40 mg/mL of triamcinolone once per month for 4 months. Fourteen of these patients were randomly assigned to also receive concomitant injections with an extract of 10% *Allium cepa* (onion), 50 U/g of heparin, and 1% allantoin.[5] Treatment allocation was not concealed; thus, the study was not blinded. The combination therapy resulted in significantly better outcomes in terms of reducing pain, itching, and elevation, compared to the effect of the steroids alone, with no differences noted in erythema and induration. There were no adverse effects associated with either treatment.

A group of 84 patients with rheumatoid arthritis (RA) all treated with diclofenac, leflunomide, and prednisone were randomized to this treatment alone or with the addition of a total saponin extract of the immunomodulating *Panax notoginseng* (sanchi ginseng) root.[6] The trial lasted 28 days. Symptoms were reduced in both groups of patients, compared to baseline, but the reductions were significantly greater in the sanchi ginseng saponin group, compared to the drug-only group. Platelet count, and serum ceruloplasmin, α1-acid glycoprotein, and C-reactive protein (CRP) levels fell significantly more in the saponin group compared to the drug-only group.

In the article in the previous issue of this journal,[1] *Tripterygium wilfordii* (thunder duke vine) was discussed more extensively, as a well-characterized immunosuppressive herbal medicine.* This herb should be used with great caution as it can have very serious adverse effects, including hepatotoxicity, myelosuppression, and infertility.

In a trial of 68 patients with myasthenia gravis all taking prednisone, half were randomly assigned to also receive an extract of the root of thunder duke vine. However, details of the dose, duration of the trial, and additional parameters were not available in English in this Chinese-language article.[7] Reductions of symptoms and decreases in serum IL-6 and peripheral B-lymphocyte levels were superior in the herb with prednisone group, compared to the prednisone-only group. Adverse effects were not reported.

In a trial of 121 American patients with RA, 28% of whom were taking prednisone, researchers randomized the patients to also take 180 mg daily of a thunder duke vine ethanol/ethyl acetate extract standardized to triptolide and tripdiolide content or to take 2 g of sulfasalazine daily.[8] Blinding was not clearly described, but, apparently, the study was at least single blinded. After 24 weeks, a significantly greater number of patients taking thunder duke vine extract achieved a 20%, 50%, or 70% reduction in their symptom scores, compared to the patients in the sulfasalazine group. A significantly greater number of the patients taking sulfasalazine withdrew from the study because of adverse effects, compared to the patients who were taking thunder duke vine. There was a nonsignificant trend toward greater reduction of radiographically noted progression in the thunder duke vine group, compared to the drug group.

Corticosteroids are also used for patients with general anesthetic- and chemotherapy-induced nausea and vomiting. Although these potent drugs are often effective, sometimes they do not work, even when they are combined with potent serotonin-receptor antagonist antiemetic drugs. In a double-blinded trial, 120 Turkish patients undergoing thyroidectomy (and thus receiving general anesthesia with its attendant risk of emesis) all received 10 mg of diazepam and intravenous dexamethasone and were randomized to receive either 500 mg of *Zingiber officinale* (ginger) 1 hour before surgery or placebo.[9] There was no difference between the groups in rates of nausea and vomiting. While it is possible that ginger simply does not work in this context, it is also possible that the dose used was insufficient.

Table 1. Preclinical Studies on Herbs for Reducing Hepatotoxicity of Azathioprine

Herb or constituent	Model	Reference
Ficus hispida (fig) leaf extract	Rats	[a]
Glycyrrhiza uralensis (Chinese licorice) root aqueous extract	Human & rat hepatocytes	[b]
Glycyrrhizin	Human & rat hepatocytes	[b]
Hibiscus sabdariffa (hibiscus, *karkade*) flower aqueous extract	Rats	[c]
Rosmarinus officinalis (rosemary) leaf aqueous extract	Rats	[c]
Salvia miltiorrhiza (Chinese sage, *dān shēn*) root aqueous extract	Rats	[d]
Salvia officinalis (sage) leaf aqueous extract	Rats	[c]

[a]Shanmugarajan TS, Devaki T. Hepatic perturbations provoked by azathioprine: A paradigm to rationalize the cytoprotective potential of *Ficus hispida* Linn. *Toxicol Mech Methods* 2009;19:129–134; [b]Wu YT, Shen C, Yin J, et al. Azathioprine hepatotoxicity and the protective effect of liquorice and glycyrrhizic acid. Phytother Res 2006;20:640–645; [c]Amin A, Hamza AA. Hepatoprotective effects of *Hibiscus*, *Rosmarinus* and *Salvia* on azathioprine-induced toxicity in rats. Life Sci 2005;77:266–278; [d]Sun C, Chen D, Qu Z, et al. Protective effects of radix *Salviae miltiorrhizae* on azathioprine hepatotoxicity in rats [in Chinese]. Zhongguo Zhong Yao Za Zhi 1996;21:496–498,512.

In an open trial of 100 Iranian women with advanced breast cancer receiving docetaxel, epirubicin, and cyclophosphamide chemotherapy (associated with a high risk of nausea and vomiting), all received granisetron and dexamethasone, with or without 500 mg ginger added, t.i.d.[10] The groups were randomized as to whether or not they received the added ginger, but treatment was not blinded and the comparison group received drug therapy alone without a placebo. During the 6–24 hours after chemotherapy was given, the ginger + drugs group had significantly less nausea and vomiting than the drugs-alone group. There was no difference between the groups prior to 6 hours and after 24 hours.

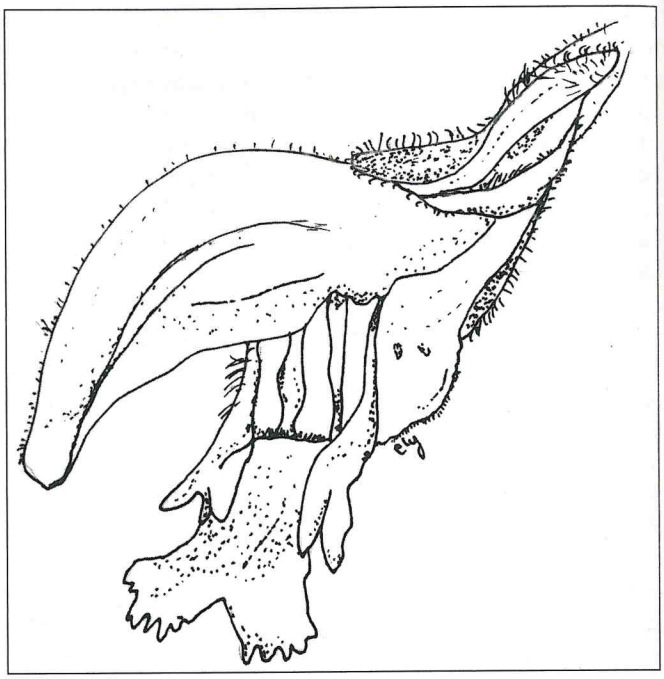
In a double-blinded trial of 60 East Indian children with sarcoma undergoing cisplatin and doxorubicin chemotherapy, all were treated with ondansetron and dexamethasone and then randomly assigned to receive ginger or placebo.[11] In children weighing 20–40 kg (44–88 lbs), the ginger dose was 333 mg t.i.d. of ginger powder. In children weighing 41–60 kg (89–132 lbs), the ginger dose was 800 mg t.i.d. Acute and delayed nausea and vomiting were significantly reduced in the drugs + ginger group, compared to the drugs + placebo group.

Preliminary evidence suggests there may be benefits to adding ginger to drugs for controlling chemotherapy emesis.

This preliminary evidence suggests there may be benefits to adding ginger to these drugs for controlling chemotherapy emesis but also that more research is needed (particularly more rigorously controlled trials) to determine the optimal dose and extraction of ginger. It is notable that, in the three trials on ginger with corticosteroids and other drugs for nausea and vomiting, there was no sign of interference with the drugs in question or any of the chemotherapy drugs being used.

Corticosteroids: Pharmacokinetic Interactions

Budesonide is a corticosteroid normally used for treating gut or lung inflammatory diseases (such as ulcerative colitis or asthma) because the drug is not well-absorbed, thus reducing its potential adverse affects. Budesonide absorption is, in part, limited by gut cytochrome P450 3A4 (CYP3A4) in the gut, breaking it down before it passes into the portal blood. Grapefruit juice, containing multiple constituents, including furanocoumarins, that inhibit gut P450CYP3A4, in a dose of 200 mL t.i.d. for 4 days doubled absorption of budesonide in 8 healthy men in one trial.[12] Therefore, grapefruit juice should not be combined with budesonide to avoid causing systemic adverse effects that would result from overabsorption of the drug.



***Salvia miltiorrhiza* (Chinese sage). Drawing © 2014, by Eric Yarnell, ND, RH (AHG).**

Methylprednisone is a potent corticosteroid that is also a CYP3A4 substrate. It is used systematically. A single dose of 200 mL of grapefruit juice modestly increased absorption of methylprednisone in 10 healthy adults, compared to water. The increase was not enough to be clinically relevant for most people, but the researchers pointed out that highly sensitive patients might experience increased activity and toxicity if they combined grapefruit juice and methylprednisone.[13] This also suggests that grapefruit juice might be used intentionally to allow use of lower doses of methylprednisone without compromising the drug's efficacy. The pharmacokinetics of two related drugs, prednisone and prednisolone, were not affected by grapefruit in one study of 12 patients with kidney transplants.[14]

Hypericum perforatum (St. John's wort) contains hyperforin that can ultimately induce intestinal CYP3A4 and P-glycoprotein (P-gp), which can greatly reduce absorption of medications that are substrates for these molecules. In a group of 8 healthy men who took a St. John's wort extract for 1 month, there was no interference with prednisone or prednisolone after single doses of these drugs.[15]

Glycyrrhiza glabra (licorice) and *G. uralensis* (Chinese licorice, gān cǎo) are the main sources of glycyrrhizin, a glycoside containing the triterpenoid glycyrrhetinic acid, which inhibits 11β-hydroxysteroid dehydrogenase (11βHSD). This enzyme is critical to deactivation of most corticosteroids. 11βHSD type 1 occurs in the liver and adipose tissue; this substance is responsible for inactivating most exogenous steroids, while 11βHSD type 2 occurs in the kidney and acts primarily to prevent endogenous cortisol from acting like a mineralocorticoid. It has been shown that taking licorice with prednisolone increases systemic exposure to this drug in humans.[16]

It is therefore important that corticosteroid doses be decreased when a patient is taking licorice, or that this combination be avoided. This usually might be an argument for intentionally combining the two to achieve a dose-sparing effect. However, given that steroids are inexpensive and the current authors presently cannot determine safely the right combination dose, it is best to simply avoid the combination.

Methotrexate

Methotrexate is a dihydrofolate-reductase inhibitor used in low doses as an immunosuppressive drug and in much higher doses as a chemotherapy agent. This discussion focuses solely on the former use, and nothing indicated here should be automatically considered applicable when the drug is used for chemotherapy. Though not botanical, ongoing folate supplementation has been shown to alleviate the gastrointestinal (GI) upset caused by low-dose methotrexate, and it is standard procedure to combine folinic acid with this drug as a result.[17]

A group of 40 Egyptian women with RA were all treated with diclofenac, methotrexate, and hydroxychloroquine plus placebo for 30 days, followed by *Nigella sativa* (black cumin) for 30 days.[18] Symptoms were reduced significantly during the black cumin phase, compared to the placebo phase. Black cumin has many other beneficial properties besides being immune- and inflammation-modulating, as the current authors have noted in a previous article.[19]

An ethanol extract of *Paeonia lactiflora* (white peony, *bái sháo*) root without bark, described as a "total glucoside extract," was studied as an adjunct to 1.8 g of methotrexate daily in 260 Chinese patients with RA.[20] Patients were randomly assigned to this combination or methotrexate plus sulfasalazine for 24 weeks. Doses of the herbal extract given are unknown, as the full text of the original article is available only in Chinese. Symptomatic reduction was faster and, in several parameters, better, while adverse effects were significantly lower in the peony + methotrexate group, compared to the control group. A similar trial in 61 Chinese patients with RA comparing methotrexate alone to methotrexate plus this same white peony extract over 12 weeks led to similar conclusions.[21]

In one randomized clinical trial involving 70 Chinese patients with RA, 10 mg t.i.d. of a thunder duke vine polyglycoside extract with 7.5 mg of methotrexate weekly was compared to 15 mg of methotrexate weekly.[22] Severity of signs and symptoms, erythrocyte sedimentation rate (ESR, a marker of inflammation), and rheumatoid factor titer all fell significantly more in the thunder duke vine + methotrexate group, compared to what occurred in the control group. The number of patients achieving "markedly effective" results did not differ between the groups. There were significantly more adverse reactions in the higher-dose methotrexate group, compared to the thunder duke vine + lower-dose methotrexate group.

In an open trial, a combination of 20 mg b.i.d.–t.i.d. of a chloroform/methanol extract of thunder duke vine roots and 10–12.5 mg weekly of methotrexate was given to 166 Chinese patients with RA.[23] These patients were followed for 1 year. Tender and swollen joint and morning stiffness counts as well as the overall symptom count (the DAS28) all showed significant improvement by 3 months, which continued to 12 months, compared to baseline. ESR and CRP levels fell significantly. Most adverse effects were mild, but 16 of 22 premenopausal women in the study developed irregular menses. Ultimately, 10 patients withdrew from the study because of adverse effects, and 8 because of a perceived lack of efficacy.

Patients taking thunder duke vine extracts should be monitored monthly for serum transaminases, creatinine, and complete blood counts. These patients should be warned that they can become infertile (both men and women), sometimes irreversibly, while taking the medicine. Frequency of testing can drop to every 3 months once the patients have 3 months of normal results in a row, until and unless the patients develop symptoms suggesting that problems have occurred. However, to put the toxicity of thunder duke vine in perspective, a retrospective analysis of 864 Chinese patients with RA was undertaken.[24] At reasonable doses, 14% of female patients taking thunder duke vine extracts developed menstrual irregularities, compared to 32% of patients taking methotrexate who developed severe GI upset, 39% of those taking sulfasalazine who developed severe GI upset, 21% of those taking penicillamine who developed a rash, and 20% of those taking hydroxychloroquine who developed blurred vision. Thus, thunder duke vine is less toxic than currently accepted disease-modifying antirheumatic drugs.

Glycyrrhizin significantly decreased adverse effects of chemotherapy in patients with breast cancer.

Chinese licorice and glycyrrhizin have been reported to increase absorption of methotrexate significantly in rats.[25] The mechanism of this interaction was not determined. This suggests that licorice and/or glycyrrhizin might be able to be used as a dose-sparing agent with methotrexate. At least one proof-of-concept study supports this idea—rats with autoimmune arthritis fed a product made of methotrexate emulsified with phospholipid nanoparticles stabilized with glycyrrhizin had better effects than when fed free methotrexate.[26]

While no human studies could be located on the interaction of licorice and low-dose methotrexate, one clinical trial investigated the effect of i.v. glycyrrhizin on high-dose methotrexate as part of combination chemotherapy in 137 Japanese patients with breast cancer.[27] The researchers found no increase in absorption of methotrexate but did find that glycyrrhizin significantly decreased adverse effects of the chemotherapy, compared to no additional treatment. While there might be a difference between low- and high-dose methotrexate pharma-

cokinetics, this research suggests that it is at least safe to combine licorice with low-dose methotrexate, despite the results found in the rodent research.

Azathioprine and 6-Mercaptopurine

Azathioprine is a prodrug form of 6-mercaptopurine, and thus both act as purine-synthesis inhibitors and are widely used as immunosuppressive agents. Myelosuppression and hepatotoxicity are fairly common, and diabetes mellitus and acute pancreatitis can also occur, albeit more rarely. There are very few reports of natural products combined with these drugs in the literature.

Because azathioprine's hepatotoxicity is directly related to oxidative damage,[28] antioxidants should offset this problem, which has proven to be true in preclinical reports. See Table 1 for antioxidant herbs reported to offset the hepatotoxicity of azathioprine.

In one double-blinded trial, 40 German patients with Crohn's disease, 14 of whom were taking azathioprine and 6 of whom were taking methotrexate, were randomized to take either 500 mg t.i.d. of standardized extract of *Artemisia absinthium* (wormwood) leaf or a placebo for 10 weeks.[29] There were no adverse interactions with azathioprine. Ninety percent of the participants randomized to wormwood were able to taper off the corticosteroids safely, and 65% of the wormwood group became completely asymptomatic. No patients who were given the placebo became asymptomatic, and 80% had to take steroids again after tapering them off.

Researchers who conducted a rat study reported that a combination of azathioprine and thunder duke vine aggravated the animals' pulmonary fibrosis.[30] These two agents should not be combined in human patients with this condition until more research is done clarifying whether or not this reaction to the combination of the agents occurs in humans.

Two patients who had heart transplants and simultaneously took St. John's wort had significant interference with their cyclosporine (acute rejection of the transplants) but this problem was not caused by any interaction of the herb with azathioprine immunosuppressive drugs.[31] This highly preliminary evidence suggests that St. John's wort should be safe with azathioprine, which makes sense as this drug is not known to be a substrate for CYP3A4 or P-gp.

Other Immunosuppressive Drugs

There is a relative dearth of information about other immunosuppressive drugs' interactions with herbs. Sirolimus, despite the similarity of its name to tacrolimus, works by a completely different mechanism; attaching to FK-binding protein 12 and inhibiting the mammalian target of rapamycin (the other name for this drug) type 1. Cyclophosphamide is an alkylating agent also used as chemotherapy for treating cancer. Mycophenolate is a guanosine-synthesis inhibitor.

In a study of 36 Chinese patients, who received kidney transplants, with proteinuria caused by sirolimus, the patients were randomized to receive either 80 mg b.i.d. of the angiotensin-receptor blocker drug valsartan or 10 mg daily of a thunder duke vine extract delivering triptolide.[32] All patients were also taking corticosteroids and mycophenolate. After 12 months, 95% of the patients who were taking thunder duke vine had a decline in proteinuria versus 87% of those who were taken valsartan; 20 of 21 who were taking the thunder duke vine ultimately had their proteinuria cleared completely (no patients on valsartan were completely normalized). Adverse effects were higher in the valsartan group, particularly hyperkalemia.

Among 112 Chinese patients who received kidney transplants, concomitant intake of silymarin or glycyrrhizin (doses not stated) was associated with approximately 33% decreased absorption of sirolimus.[33] The herbal extracts were being given to reduce the hepatotoxicity caused by the patients' immunosuppressive drug regimens. There were no obvious adverse effects from this interaction, but it is entirely possible that these agents could impair efficacy of sirolimus; thus they should not be used concomitantly with this medication.

In patients who had kidney transplants, thunder duke vine extract reduced or eliminated sirolimus-induced proteinuria.

Forty-three Chinese patients with systemic lupus erythematosus, who had lupus nephritis treated with i.v. cyclophosphamide, were randomized to either an additional high-dose infusion of *Astragalus membranaceus* (astragalus, *huáng qí*) extract (20 mL daily) for 12 days per month for 3 months.[34] Clinical symptom scores for proteinuria decreased significantly more in the cyclophosphamide + astragalus group, compared to the group who received the drug alone. There were also significantly more infections in the cyclophosphamide-only group compared to the drug + astragalus group.

This directly contradicts a prior rat study suggesting that astragalus injection could increase rejection of transplants under cyclophosphamide immunosuppression.[35] Other rodent research suggested that oral astragalus could decrease the negative effects of cyclophosphamide on male fertility.[36]

In another study, 32 Chinese patients with autoimmune crescentic glomerulonephritis, all taking corticosteroids along with cyclophosphamide or mycophenolate, were randomized to take *Qing Re Huo Xue* herbal decoction once per day or no additional treatment for 3 months.[37] This formula contained 30 g of *Oldenlandia diffusa* = *Hedyotis diffusa* (hedyotis, *shé shé cǎo*) herb, 30 g of *Lonicera japonica* (Japanese honeysuckle, *jīn yín huā*) stem, 30 g of *Viola* spp. (Chinese violet,

dì dīng) herb, 15 g of *Paeonia lactiflora* (red peony, *chì sháo*) root with bark, 15 g of *Rehmannia glutinosa* (rehmannia, *dì huáng*) root, 15 g of *Polygonatum sibiricum* (solomonseal, *huáng jīng*) rhizome, 30 g of *Codonopsis pilosula* (codonopsis, *dǎng shēn*) root, 30 g of Chinese sage root, 12 g of *Rheum palmatum* (rhubarb, *dà huáng*) cooked root, and 12 g of *Agastache rugosa* (Korean mint, *huò xiāng*) herb. Renal function improved significantly more in the drugs + herbs group, compared to the drugs-alone group. Corticosteroid doses were significantly lower in the drugs + herbs group, compared to the drugs-alone group.

Conclusion

Numerous herbs with immune effects have been studied in combination with a range of immunosuppressive drugs. These combinations have largely been shown to be beneficial (increasing efficacy, decreasing toxicity, or both), although a few have been shown to interfere or increase toxicity. More research is needed but, given the high toxicities (and, at times, high costs) of these sometimes essential drugs, these combinations have a good probability of being highly useful. ■

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