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ALTERNATIVE MEDICINES UPDATE:
A FOCUS ON THE MOST COMMON PRODUCTS YOUR PATIENTS ARE USING

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Complementary and alternative medicine (CAM) is defined as a group of therapeutic and diagnostic disciplines that usually exist outside the institutions where conventional health care is taught and provided.[1] The National Center for Complementary and Alternative Medicine (NCCAM) developed a similar definition in 2002.[2] That definition was revised in 2005 to include any practices that have greater potential for success and benefit to public health. It divides CAM into 4 categories: mind-body medicine, biologically based practices (herbals, botanicals, and dietary regimens), manipulative and body-based practices, and energy medicine.

Between 1990 and 2000, alternative medicine use and expenditures increased concurrently. In 1997, 18.4% of prescription users were also taking an herbal and/or high-dose vitamin.[3] In 2002, approximately 38.2 million adults in the United States used herbals and supplements.[4] More than half (57.3%) of them used these products to treat specific conditions; however, only 33.4% told a conventional health care provider about their herbal or supplement use. US consumers spent 27 billion in 1997 and over 34 billion in 2000 on CAM therapies, and expenditures continue to rise.[5] One-fourth of adults reported use within the past year.[6] Furthermore, CAM use increases with the number of health conditions and number of physician visits.[2]

Dietary supplements are not regulated by the FDA. Instead, they are defined and marketed under the Dietary Supplement and Health Education Act of 1994 (DSHEA). Products must include proper labeling of all ingredients, which would include the name and quantity of each dietary ingredient. If the ingredient is botanical in origin, the labeling must include the part of the plant that represents the active ingredient. Even though all ingredients must be listed, this act does not require the label to inform consumers of potential risks. A lack of standardization in herbals makes it difficult to understand why a product works or the reasons for its adverse effects, resulting in a product whose safety and efficacy is unknown.[6] The US has a goal of standardization to maintain the same extract and amount of active ingredients in dietary supplements, yet the products are regulated less compared to other countries. In Germany, physicians receive formal accreditation in different specialties relating to CAM. As a result, 73% of Germans greater than 16 years old have used at least 1 form of CAM.[7]

In 2005, NCCAM announced the release of its new 5-year strategic plan to research and educate physicians and patients about the benefits and disad-

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vantages of certain alternative medicines.[2] In 2008, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) reported that of the six most commonly used dietary botanical supplements, ginseng has the most adverse effects, followed by echinacea and garlic.[8] Alternative medicine remains a balancing act between significant benefits, side effects and potential drug interactions.

According to a review in 2004, the ten most commonly used herbal products are echinacea, garlic, ginkgo biloba, saw palmetto, ginseng, grape seed extract, green tea, St. John's wort, bilberry, and aloe.[6] From a 2002 NHIS CAM survey, the top 4 products in the US were echinacea (41%), ginseng (25%), ginkgo biloba (22%), and garlic (20%).[9,10] This article will review the clinical data of the top 4 commonly used products, along with St. John's wort and alpha-lipoic acid.

Echinacea

Echinacea is the most commonly used herbal with the least conclusive evidence. The active component is unknown, but it may be related to the amount of echinacosides. Its proposed mechanism of action involves a stimulatory effect on the immune system. Different echinacea species can have different effects on the immune system and on inflammation. Echinacea has antioxidant activity, anti-inflammatory effects via COX inhibition, and antiviral and antifungal activity via leukocyte stimulation. The most researched benefit of echinacea is its claim to treat and/or prevent the common cold and general upper respiratory tract infections (URI).

Most studies determined that echinacea is no different from placebo. Yale, et al. determined that *Echinacea purpurea* does not effectively reduce symptoms and duration of the common cold.[11] A reason could be that herbals are not standardized due to varying parts of plant composition, extraction method, and formulation. Additionally, studies were not appropriately powered. To account for power inadequacies, a meta-analysis is currently the only tool to assess the clinical use of echinacea. According to a Cochrane review of 15 randomized controlled trials (RCT) by Linde, et al., *Echinacea purpurea* is the only preparation that might be effective in early treatment of colds, but the results are not clear.[12] A meta-analysis of 14 studies by Shah, et al. found echinacea decreased the incidence of developing a common cold by 58% and the duration of a cold by 1.4 days.[13] Early URI intervention with a standardized formulation of echinacea is recommended, and may result in a 23% decrease in symptom severity ($p<0.01$).[14] However, this study used high doses and frequency for one week (10 doses on the first day, followed by four doses per day for six days). The German Commission E has approved *E. purpurea* at a recommended dose of 900 mg a day until symptoms resolve.[13]

Echinacea is usually well tolerated. General side effects associated with echinacea are rash and dyspnea. Hepatotoxicity has been reported in rare cases. The immunostimulant property of echinacea combined with immunosuppressants or corticosteroids counteract each other and should not be taken concurrently.

Ginseng

Ginseng's (*Panax ginseng*) major active components are the ginsenosides. Animal studies have shown that ginseng can stimulate hepatic ribosomes and protein synthesis, inhibit platelet aggregation, possibly increase natural killer cell activity and enhance the production of interferons. The clinical significance of these mechanisms may be prolonged exercise time, prevention of stress-induced ulcers, and increased activity of the immune system. Ginseng has also been used for its alleged sedative, hypnotic, demulcent, aphrodisiac, antidepressant, and diuretic activity. These benefits may translate to improved stamina, concentration, vigilance, and well-being. A hypoglycemic effect is due to increased lipogenesis and glycogen storage.[15] A systematic review of 16 trials sought to determine the efficacy of ginseng on physical performance, psychomotor performance and cognitive function, immunomodulation, diabetes mellitus and herpes simplex type-II infections.[16] Results indicate that ginseng root extract has no compelling evidence for any of these indications.

Side effects are uncommon, but in rare cases can cause insomnia, diarrhea, vaginal bleeding, severe headache, psychosis, and Stevens–Johnson syndrome.[15] Siberian ginseng is reported to have the most adverse effects, especially neurologic symptoms such as dizziness and fatigue.[8] Ginseng may inhibit CYP3A4, thereby inhibiting the metabolism of 3A4 substrates, such as certain calcium channel blockers and statins. Pharmacodynamic interactions include potentiation of ethanol's and warfarin's ef-

fects, an induction of mania and psychoactive effects when used concomitantly with phenelzine, and an increased efficacy of influenza vaccination.[17] There is contrasting data for the pharmacokinetic interaction between ginseng and warfarin. Jiang, et al. did not show an effect on the metabolism or clearance of warfarin[18], whereas at least three separate trials did show a decrease in warfarin's AUC.[19,20,21] In either instance, ginseng exerts antiplatelet effects;thus, it should be used cautiously with warfarin, NSAIDs, and other supplements with antiplatelet or anticoagulant effects. Other common dietary supplements that exhibit antiplatelet effects or anticoagulant activity are feverfew, garlic, ginger, green tea, horse chestnut, willow bark, danshen, and dong quai. Adverse effects worsen when ginseng is taken continuously at doses greater than 400 mg daily.[15]

Ginkgo biloba

The flavonoids in gingko biloba increase antioxidant activity, cerebral blood flow (by increasing prostaglandins and norepinephrine release), and anti-inflammatory effects (through inhibition of platelet binding). As a result, it may improve memory deficits and concentration in Alzheimer's patients. Off-labeled uses of *Ginkgo biloba* extract (GBE) include relief of intermittent claudication, tinnitus and vertigo of vascular origin, premenstrual syndrome, and antidepressant-induced sexual dysfunction.[22]

A meta-analysis of 4 RCTs before 1998 revealed a small but statistically significant difference with ginkgo use on cognitive function in patients with Alzheimers.[23] The dose of GBE used was 120—240 mg/day PO divided into 2 to 3 doses for at least 4 - 6 weeks. The most recent Cochrane review from April 2007 identified 33 RCTs that assessed safety and efficacy of ginkgo in cognitive decline.[24] Clinical global improvement (CGIC) showed benefit when more than 200 mg ginkgo each day is used for 24 weeks (OR 1.66, 95% CI 1.12 to 2.46, P=0.01). Cognitive function and activities of daily living, measured by the Crichton Geriatric Scale (CRS), displayed benefit for ginkgo (dose less than 200 mg) at 12 weeks (MD -5.0, 95% CI -7.88, -2.12, p=0.0007) and 24 weeks (SMD -0.16, 95% CI -0.31 to -0.01, p=0.03). Although ginkgo has a modest effect in the treatment of cognitive impairment and dementia, effect sizes were small and may not be clinically significant.[24] The Hawthorne effect may be responsible for any proposed benefit if the subjects were not properly blinded.[25]

Recommendations for ginkgo to improve mild-to-moderate dementia and cognitive function symptoms have become more contradictory within the last year. Lovera, et al. found that ginkgo did not statistically improve cognition in multiple sclerosis patients.[26] Dodge, et al. determined that extending the duration of treatment to assess the safety and effectiveness of ginkgo does not delay cognitive decline.[27] Woelk, et al. found that 480 mg of ginkgo extract (EGb761) daily for more than 4 weeks enhances cognitive function, stabilizes mood, and reduces anxiety ($p = 0.003$).[28] Anxiety symptoms improved more with higher doses and higher baseline anxiety scores.

Side effects are rare, but the most common are headache, flatulence, nausea/vomiting/diarrhea, increased risk for bleeding, and possible infertility. One case report found that trazodone use with ginkgo lead to oversedation.[29] Gingko increases the effects of calcium channel blockers by possibly inhibiting their metabolism via CYP3A4. Ginkgo used in dangerously high doses could lead to seizures or loss of consciousness, especially in patients with a history of seizures. The cause could be related to the ginkgo nuts which contain a potent neurotoxin, and/or CYP2C19 induction by ginkgo leading to subtherapeutic levels of phenytoin and valproic acid.[30]

Garlic

Garlic (*Allium sativum* L.) is converted to the active component, allicin, when crushed. Allicin claims to decrease cholesterol by inhibiting hepatic cholesterol biosynthesis[32], enhancing cholesterol turnover to bile acids, and through enhanced bile acid excretion.[33] The net effect on lipids is a proposed decrease in LDL and VLDL, with an increase in HDL. *S*-allyl-cysteine (SAC) is one of the main active and bioavailable components.[34] SAC is the most abundant water-soluble organosulfur compound in aged garlic extract (AGE). ß-chlorogenin contributes to antiplatelet activity.

In the most recent systematic review of 5 studies for hypercholesterolemia, garlic was estimated to decrease total cholesterol levels by 4 to 6% vs. placebo (-0.41 mmol/L, 95% CI, -0.66 to -0.15 mmol/L).[5] An NIH-funded, randomized, clinical trial reported that no form of garlic in reasonable doses has statistically significant effects on LDL.[35] Six months of using 1.8 mg AGE 6 days per week

slightly increased LDL by 0.2 mg/dL vs. placebo (CI −5.3 to 5.7, p = 0.29). Another systematic review stated that the effects were too small to be clinically relevant.[36] Garlic is suggested to have anti-hypertensive, anti-diabetic, antithrombotic and anti-hyperhomocysteinemia effects, along with biological activities including antimicrobial, antioxidant, anti-carcinogenic, antimutagenic, antiasthmatic, immuno-modulatory and prebiotic.[33] It has an anticoagulant effect through inhibition of platelet adhesion.[37] The change in platelet function may contribute to the lipid effect, as well as decrease the progression of colorectal adenomas in humans.[38] Complications of sickle-cell anemia are decreased due to the significant antioxidant activity on sickle RBCs.[39]

The most common side effects associated with garlic are bad breath and body odor.[33] It stimulates CYP enzymes, thus increases metabolism of drugs such as saquinavir. Using a standardized product such as AGE will not stimulate P450 enzymes nor produce severe gastrointestinal toxicity.[34] AGE showed no significant difference in major adverse events (hemorrhage and bleeding) or minor events (headache, fatigue, colds, and dizziness) compared to placebo.[40] Due to its extraction method, AGE has a greater and more consistent efficacy and safety compared with any other form of garlic.[33] AGE may be the only well standardized preparation, and is safe even with high doses.

St John's Wort

St John's wort is the sixth most commonly used product[10] and the herbal with the most drug interactions[7]. The extract *Hypericum perforatum L.* contains hypericin, hyperforin, and flavonoids, all of which may contribute toward the treatment of depression. St. John's wort inhibits serotonin, norepinephrine, and dopamine re-uptake, decreases interleukin-6 levels, and increases corticotropin-releasing hormone.[5]

Randløv, et al. confirmed that hypericum has a clinically significant effect in minor depressed patients (HAM-D score 7 to 17).[41] St. John's wort is equivalent to TCAs (RR 1.03, 95% CI, 0.93-1.14; seven trials) and SSRIs (RR 0.98, 95% CI, 0.85-1.12; six trials) for treating mild to moderate depression.[42] Patients given hypericum extracts were 25% less likely to drop out of trials compared to TCAs (OR 0.25, 95% CI, 0.14-0.45) and 60% compared to SSRIs (OR 0.60, 95% CI, 0.31-1.15). Although there was no standardization of the extract, most RCTs used LI-160 (hypericum perforatum) at an average dose of 900 mg daily for 8 weeks. There is no evidence to support the benefits of hypericum in severe depression.

Side effects are usually minor and uncommon, slightly less than standard antidepressants, and significantly less than older antidepressants.[41] They include gastrointestinal symptoms, dizziness, confusion, tiredness and sedation. High and long-term dosing will increase LFTs and contribute to the adverse effects of other drugs. St. John's wort primarily induces CYP 3A4 and P-glycoprotein (Pgp), which will increases the metabolism of drug substrates. According to Markowitz and colleagues, 3A4 substrates represent approximately 50% of all marketed medications.[43] Concomitant St. John's wort did not affect carbamazepine, dextromethorphan, mycophenolic acid, and pravastatin.[44] Serious and life threatening interactions occur when cyclosporin, anticoagulants, digoxin, antidepressants, and protease inhibitors are taken with St John's Wort. The combination with SSRIs and other agents that potentiate serotonin can cause serotonin syndrome.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is an endogenous, potent antioxidant that has recently been labeled as the only FDA approved supplement indicated for neuropathy.[45] Sola, et al. suggested that the anti-inflammatory effects, when combined with its antithrombotic effects, may improve endothelial dysfunction.[46] This translates to improved neuropathic symptoms, including stabbing pain, burning pain, paresthesia, and sleep numbness, along with a marked decrease in neuropathic deficits in patients diagnosed with distal symmetric polyneuropathy (DSP).[45] Other proposed benefits include decreased blood glucose, increased insulin sensitivity, and neuroprotection, but further studies are warranted.

A dose of 600 mg daily for at least 5 weeks resulted in side effects confined to the gastrointestinal tract. Other doses were studied in the Symptomatic Diabetic Neuropathy 2 trial (SYDNEY2), but 600 mg had a similar efficacy and favorable safety profile to higher doses. Sixty-two percent of patients experienced greater than 50% reduction in neuropathic symptoms after 3 weeks vs 26% of patients receiving placebo ($p<0.05$).[45] Oral formulations are comparable to intravenous. A meta-analysis com-

Table 1. Summary of Clinical Data

Product	Citation	Trials	Population studied	Dose	Author's Conclusions
Echinacea (*E. purpurea*)	Shah, et al. 2007	Meta-analysis	Patients with symptoms of the early common cold	900 mg daily	23% decrease in symptoms, incidence, and duration of cold
Ginseng	Vogler, et al. 1999	systematic review of 16 trials	Physical/psychomotor performance, cognitive function, immunity, DM, HSVII infections	200 - 600 mg extract daily	No indications for use
Ginkgo biloba (GBE, EGb761)	Birks, et al. 2007	Cochrane review of 33 RCTs	Patients with symptoms of dementia and/or cognitive decline	≥ 200 mg daily x 24 weeks	66% improvement in cognitive symptoms and similar SEs vs placebo (p = 0.01)
Garlic (AGE)	Gardner, et al. 2007	RCT	Mild to moderate hypercholesterolemia (LDL: 130 – 190 mg/dl)	4 g clove/day, 6 d/wk x 6 months	No form of garlic significantly decreased LDL-C; up to 4-6% decrease
St. John's wort (hypericum, LI 160)	Linde, et al. 2005	Cochrane review of 37 RCTs	Patients with symptoms of mild - moderate depression	240 – 1800 mg daily x 4-12 weeks	Significantly better than placebo, Similar efficacy to ADs, Less SEs and more drug interactions
α-lipoic acid (ALA)	Ziegler, et al. 2006	RCT	DM type 1 or 2 with neuropathy	600 mg po daily x 5 weeks	Decreased neuropathic pain symptoms and deficits ($p<0.05$)

RCT = randomized controlled trial; DM = diabetes mellitus; HSVII = herpes simplex virus II; SEs = side effects; ADs = antidepressants (TCAs and SSRIs); PO = by mouth

bined data from the four major studies (ALADIN I, ALADIN III, SYDNEY, and NATHAN II) that supplemented 600 mg of parenteral ALA over a period of three weeks. The authors suggested that this regimen of ALA is safe and superior to placebo in clinical treatment of neuropathic symptoms and deficits.[47] A rare side effect of ALA is insulin autoimmune syndrome, which causes hypoglycemia when autoantibodies are produced to insulin.[48] Dose dependent effects such as nausea, vomiting, and vertigo are also uncommon. Drug interactions appear minimal, if any.[45]

Summary

More than 25% of Americans use herbal products, yet patients (and health-care professionals) often lack accurate information about their safety and efficacy. Of the five herbals reviewed, two did not appear to have efficacious data (garlic and ginseng). St John's wort has efficacy data in the treatment for depression, which is one of the leading indications for using CAM. Although there is some evidence that echinacea decreases the severity and/or duration of the common cold, more well-designed trials are needed. Alpha-lipoic acid is the only FDA proven supplement indicated for neuropathy.

Use all herbal supplements with extreme caution in children less than two years of age and in pregnancy or lactation. Since there is no standardization of extracts, and no warning labels to address potential adverse effects, treat herbals as medicinal products with side effect profiles and potential for drug interactions. In the future, highlighting the potential side effects and drug interactions on the product packaging may help prevent inadvertent use in vulnerable individuals.

References

1. Zollman C, Vickers A. What is complementary medicine? BMJ 1999;319:693–696.
2. National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of

Health. (2005). Expanding Horizons of Health Care: Strategic Plan 2005–2009. Retrieved March 17, 2008, from www.nccam.nih.gov/about/plans/2005/
3. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA 1998;280:1569–1575.
4. Kennedy J. Herb and supplement use in the US adult population. Clin Therapeutics 2005; 27:1847-58.
5. MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. Prev Med 2002;35:166-73.
6. Bent S, Ko R. Commonly used herbal medicines in the United States: a review. Am J Med 2004;116:478-85.
7. Nahin RL, Dahlhamer JM, Taylor BL, et al. Health behaviors and risk factors in those who use complementary and alternative medicine. BMC Public Health 2007;7:217.
8. Wallace RB, Gryzlak BM, Zimmerman MB, et al. Application of FDA Adverse Event Report Data to the Surveillance of Dietary Botanical Supplements. Ann Pharmacother 2008;42.
9. Gardiner P, Graham R, Legedza AT, et al. Factors associated with herbal therapy use by adults in the United States. Alternat Therapeutic Health Med 2007;13:22-9.
10. Barnes P, Powell-Griner E, et al. Complementary and alternative medicine use among adults United States, 2002. Advanced Data 2004;343:1–20.
11. Yale SH, Liu K. Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med 2004;164:1237-41.
12. Linde K, Barrett B, Wölkart K, et al. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev 2006; (1):CD000530.
13. Shah SA, Sander S, White CM, et al. Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. Lancet Infect Dis 2007;7:473-80.
14. Goel V, Lovlin R, Barton R, et al. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther 2004;29:75-83.
15. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med 2002;136:42-53.
16. Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol. 1999;55:567-75.
17. Hu Z, Yang X, Ho PC, et al. Herb-drug interactions: a literature review. Drugs 2005;65:1239-82.
18. Jiang X, Williams KM, Liauw WS, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. B J Clin Pharmacol 2004;57:592-9.
19. Heck AM, DeWitt BA, Lukes AL Potential interactions between alternative therapies and warfarin AJHP 2000;57:1221-1230.
20. Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled Trial. Ann Intern Med 2004;141:23-7.
21. Saw JT, Bahari MB, Ang HH, et al. Potential drug–herb interaction with antiplatelet/anticoagulant drugs. Complementary Therapies in Clinical Practice 2006;12:236-241.
22. Clinical Pharmacology Online. Ginkgo, Ginkgo biloba. Revision Date: 1/23/2003. Access Date: 3/17/2008.
23. Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. Arch Neurol. 1998;55(11):1409-15.
24. Birks J, Grimley EJ. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2007;(2):CD003120.
25. McCarney R, Warner J, Iliffe S, et al. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol 2007;7:30.
26. Lovera J, Bagert B, Smoot K, et al. Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial. Mult Scler 2007;13:376-85.
27. Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of ginkgo biloba for the prevention of cognitive decline. Neurology 2008; Epub Feb 27.
28. Woelk H, Arnoldt KH, Kieser M, et al. Ginkgo biloba special extract EGb 761® in generalized

anxiety disorder and adjustment disorder with anxious mood: A randomized, double-blind, placebo-controlled trial. J Psych Research 2007;41:472-480.
29. Galuzzi S, Frisoni GB, et al. Coma in a patient with Alzheimer's disease taking low dose trazodone and ginkgo biloba. J Neurol Neurosurg Psychiatry 2000;68:679.
30. Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with Ginkgo biloba. J Anal Toxicol 2005;29:755-8.
31. Jiang X, Williams KM, Liauw WS, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. B J Clin Pharmacol 2005;59:425-32.
32. Singh DK and Porter TD. Inhibition of sterol 4 alpha-methyl oxidase is the principal mechanism by which garlic decreases cholesterol synthesis, J Nutrition 2006;136:759S–764S.
33. Corzo-Martínez M, Corzo N, Villamiel M. Biological properties of onions and garlic. Trends in Food Science & Technology 2007;18:609-625.
34. Amagase H. Clarifying the real bioactive constituents of garlic. J Nutrition 2006;136:716S–725S.
35. Gardner DC, Lawson LD, Block E, et al. Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia. Arch Intern Med 2007;167:346–353.
36. Pittler MH, Ernst E. Clinical effectiveness of garlic (*Allium sativum*). Molecular Nutrition & Food Research 2007;51:1382 – 5.
37. Steiner M, Lin RS. Changes in platelet function and susceptibility of lipoproteins to oxidation associated with administration of aged garlic extract. J Cardiovasc Pharmacol 1998;31:904-8.
38. Tanaka S, Haruma K, Yoshihara M, et. al. Aged garlic extract has potential suppressive effect on colorectal adenomas in humans. J Nutrition. 2006;136:821S-826S.
39. Takasu J, Uykimpang R, Sunga MA, et al. Aged garlic extract is a potential therapy for sickle-cell anemia. J Nutrition 2006;136:821S-826S.
40. Macan H, Uykimpang R, Alconcel M, et al. Aged garlic extract may be safe for patients on warfarin therapy. J Nutrition 2006;136:793S-795S.
41. Randløv C, Mehlsen J, Thomsen CF, et al. The efficacy of St. John's Wort in patients with minor depressive symptoms or dysthymia--a double-blind placebo-controlled study. Phytomedicine 2006;13:215-221.
42. Linde K, Mulrow CD, Berner M, et al. St John's wort for depression. Cochrane Database of Systematic Reviews 2005;2:CD000448.
43. Markowitz JS, Donovan JL, DeVane CL, et al. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA 2003;290:1500-4.
44. Zhou S, Chan E, Pan SQ, et al. Pharmacokinetic interactions of drugs with St John's wort. J Psychopharmacol 2004;18:262-76.
45. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006;29:2365-70.
46. Sola S, Mir MQ, Cheema FA, et al. Irbesartan and lipoic acid improve endothelial function and reduce markers of inflammation in the metabolic syndrome: results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study. Circulation 2005;111:343-8.
47. Ziegler D, Nowak H, Kempler P, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a meta-analysis. Diabet Med 2004;21:114 -121.
48. Ishida Y, Ohara T, Okuno Y, et al. Alpha-lipoic acid and insulin autoimmune syndrome. Diabetes Care 2007;30:2240-1.

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