Some Natural Medicines May Alter Laboratory Test Results

Chris D. Meletis, N.D.

Practitioners that use natural medicine will freely admit that "just because it's natural doesn't make it safe." It is logical that, because 25–33 percent of conventional prescription medicines originated from natural sources, certain extracts may also have side-effects. Philosophically, some people might argue that there is a difference between an isolated substance used in the form of a drug and using a botanical extract. However, this line of argument for many products has become weakened with the advent and abundant use of standardized products that concentrate isolated active chemicals from plants to create "quasidrugs."

Indeed, the same trends that originally resulted in the creation of pharmaceuticals are beginning to reshape the traditional use of botanical medicines. If an isolated substance in a drug derived from a plant is made into a prescription medicine and can cause side-effects, then, of course, herbal medicines that are dissected and modified to create quasidrugs increases the likelihood of interactions and side-effects. This is especially true when quasidrugs are not used with sufficient knowledge of nature's intended balance. Drug–drug interactions occur and it follows quite logically that drug–natural medicine interactions also happen.

These potentials for side-effects and interactions, however, are not limited to botanical medicines, supplemental forms of vitamins, minerals, and other nutrients when they are taken at doses and durations that do not occur naturally. We have moved beyond the concept of "food as the best medicine" into an arena of actively, and sometimes aggressively, manipulating and changing the biochemical balance of these substances in a broad and global fashion that increases the likelihood of both altered physiologic and chemical functioning, producing both positive and, at times, negative effects.

Because integrative medicine practitioners combine natural therapies with conventional ones, it is vital to have a sophisticated understanding of these medicines, particularly how they interact with conventional drugs. This is a topic that is now receiving more attention in the literature.

Another area of vital importance—one that demands substantial exploration and investigation—is how natural medicines can affect the results of laboratory tests. This article presents a select sampling of these interactions.

Nutraceutical–Laboratory Test Interactions

At this point in time, less than 1 of 10 nutraceuticals appear to have interactions with laboratory tests. This is probably largely because these supplements are generally safe but also because there is no required screening process for all nutraceuticals prior to making them available to consumers. Yet, when an interaction does arise, the result can take the form of an actual alteration of laboratory values resulting from changes in biochemical metabolism in vivo or false laboratory values caused by interference with a given laboratory technique. The tendency for certain nutraceuticals to be used for addressing specific conditions can guide a health provider in determining the potential presence of a culprit that may alter laboratory values.

α-Lipoic Acid

α-Lipoic acid is generally considered to be a fairly targeted nutrient that is used to achieve specific health goals.

- *Glucose level*—A study, conducted by the Department of Internal Medicine, in Frankfurt, Germany, examined the effect of α-lipoic acid, a cofactor of the pyruvate dehydrogenase complex, on insulin sensitivity and glucose effectiveness. The subjects included 10 lean and 10 obese patients with type-2 diabetes and 10 lean and 10 obese healthy controls. Insulin sensitivity and glucose effectiveness were measured after oral glucose loading. A modified, frequently sampled, intravenous (IV) glucose tolerance test was performed after oral treatment with 600 mg of α-lipoic acid, twice per day, for 4 weeks. α-Lipoic acid was associated with increased glucose effectiveness in both groups of patients with diabetes. Higher insulin sensitivity and lower fasting glucose levels were noted in only in the lean patients with diabetes. In addition, lactate and pyruvate, before and after glucose loading, were approximately 45 percent lower in both the lean and obese patients with diabetes.[1]
- *Glycosylated hemoglobin level*—No effect has been observed, although daily glucose levels may be lower on average in patients who take this supplement.[2,3] A 7-month, multicenter, randomized controlled trial examined the effects of α-lipoic acid on polyneuropathy in patients with diabetes. The study involved 509 outpatients who were assigned randomly for 6 months to sequential treatment with 600 mg of α lipoic acid, per day, IV, for 3 weeks, followed by 600 mg of α-lipoic acid, 3 times per day for 6 months. A placebo group received 600 mg of α-lipoic acid, for 3 weeks, followed by placebo, 3 per day, for 6 months. There was no overt effect on glycosylated hemoglobin. The researchers concluded that there was a favorable effect on reducing diabetic neuropathy without adverse reactions.[3]
- *T-helper cell/T-suppressor cell ratio*—α-Lipoic acid may improve

the T-helper/T-suppressor ratio in patients who are infected with human immunodeficiency virus (HIV).[4]

Androstenedione

Whenever a hormonal intervention is utilized to produce altered physiologic activity or to alter biochemical processes, a myriad of potential effects can arise. All too often, patients will take over-the-counter hormones, not realizing that they are supplements that should be listed on patient intake forms as such or not telling providers about such use. Although this supplement is taken by many patients to enhance wellness, androstenedione can actually alter important cardiovascular indices.

- *High-density lipoprotein*—Androstenedione may suppress high-density lipoprotein (HDL) levels.[15] Young men that consumed

Natural Medicine–Laboratory Test Interaction Summary

Natural medicine	Common names	Reasons for use	Possible effects on laboratory values (text reference)
Nutraceuticals			
α-lipoic acid	a-lipoic acid, ALA, lipoic acid, thioctacid, thioctan	Antioxidant; prevent diabetes, retinopathy, cataracts, or glaucoma; support patients with HIV, Wilson's disease, or lactic acidosis resulting from altered metabolism	*Blood glucose:* may lower serum glucose levels in patients with type 2 diabetes by reducing insulin resistance and enhanced glucose utilization (1) *Glycosylated hemoglobin:* none (2,3) *T-helper/T-suppressor ratio:* improves ratio of T-helper cells relative to T-suppressor cells (4)
Androstenedione	Andro, androstene	Replace low endogenous levels or lowered androgen levels; increase athletic performance; enhance exercise endurance; decrease recuperative time; support sexual function	*HDL:* lowers HDL levels (5) *Estrone, estradiol, testosterone, dihydrotestosterone:* elevates estrone, free testosterone, dihydrotestosterone (5,6); and estradiol (6) levels. *Nandrolone:* urine tests positive for nandrolone marker because of contamination with 19-norandrostenedione *Testosterone:* free and total testosterone levels may become elevated initially but may then normalize (5,6)
β-Glucan	Beta-glucan, beta-glycan, gifolan, schizophyllan	Support patients with high cholesterol, cancer, HIV, diabetes, allergies, and other conditions	*WBC counts:* WBC counts may be elevated (8)
Boron	Borate, boric acid, sodium borate	Promote bone health; treat OA; enhance mental functioning; increase muscle mass, (illustrates benefits of using trace minerals therapeutically)	*Estrogen:* theoretically, may elevate estrogen levels (9) *Bone-mineral density:* increases in female athletes (10) *Phosphorus:* decreases serum phosphorus (10)
Glucosamine sulfate	D-Glucosamine, glucosamine sulphate (British spelling)	Support patients with OA and other joint conditions, including TMJ disease	*Glucose:* may elevate blood glucose (11,12) *Insulin:* potential ability to increase insulin level
Botanicals			
Goldenseal (*Hydrastis canadensis*)	Goldenroot, hydrastis, Indian turmeric, yellow root	Antibacterial; treat nasal congestion, flatulence, and URIs	Increases bilirubin level (14)
Grapefruit)	Grapefruit, pomelo, toronja	Weight loss, anticancer agent; cholesterol reduction; potassium, vitamin C, and fiber source	Increases serum levels of numerous drugs, including amlodipine, nifedipine, nisoldipine, felodipine, nimodipine, nicardipine, dlitiazem, verapamil, buspirone, midazolam, triazolam, diazepam, carbamazepine, cisapride, cyclo-sporin, estradiol, lovastatin, saquinavir, simivastatin, atorvastatin, terfenadine, losartan (4)
Botanical component			
Indole	Indole-3-carbinol, 3-indolyl-cabinol, I3C, (common sources include broccoli, cauliflower, other cruciferous vegetables, and several botanicals)	Prevent breast or colon cancer, support patients with SLE; liver detoxification	Increases levels of ALT/SGPT (19)

Note: These possible laboratory interactions represent a select sampling of available literature. Additional data becomes available continuously and keeping up to date is important.

HIV = human immunodeficiency virus; OA= osteoarthritis; TMJ = tempormandibular joint; URI = upper respiratory infection; SLE = systemic lupus erythematosus; HDL = high-density lipoprotein; WBC = white blood cells; ALT = alanine aminotransferase; SGPT = serum glutamic pyruvic transaminase.

100 mg of androstenedione three times per day, for 28 days, experienced a 10-percent decrease in HDL level.[6]

- *Estrone and estradiol*—Because androstenedione is a precursor of estrone, androstenedione supplements may cause elevations of estrone and estradiol levels.[5,6] The previously described 12-week study of the adverse effects of androstenedione on cholesterol produced a significant increase in the aromatization byproducts estrone and estradiol.[5] In a double-blinded, randomized, 28-day study of 55 men, 28 subjects were given 100 mg of androstenedione, 3 times per day, and 27 were given placebo. Results of serum readings reflected an increase of androstenedione (300 percent), free testosterone (45 percent), dihydrotestosterone (83 percent), and estradiol (68 percent).[26]

Patients' urine may test positive for the presence of nandrolone as a result of trace contamination of androstenedione with 19-norandrostenedione.

- *Nandrolone*—Patients' urine may test positive for the presence of nandrolone as a result of trace contamination of androstenedione with 19-norandrostenedione.[7] Nandrolone is an anabolic steroid that resembles testosterone in chemical structure and biologic activity. It is the subject of concern for athletic oversight committees, which test for illicit use by measuring the urine levels of its metabolite, 19-norandrostenedione. Trace contamination of androstenedione with 19-norandrostenedione could result in the unjust accusation that an athlete has used steroids illicitly. As noted in an insightful paper in the *Journal of the American Medical Association*,[7] it is important that consumers be advised to buy supplements from reputable manufacturers that provide certificates of analysis.

The study discussed in this paper involved 41 healthy men, ages 20–44 who took either 100 mg or 300 mg per day daily of androstenedione for 7 days. All subjects were treated with androstenedione containing 19-norandrostenedione. The authors proved that, if androstenedione that was sold over the counter (OTC) contained 19-norandrostenedione, the nandrolone marker was found in the subjects' urine.

This led the researchers to test seven OTC products randomly for the presence of 19- norandrostenedione. Of seven brands tested, 1 contained no androstenedione, 1 contained 10 mg of testosterone, and 4 more contained 90 percent or less of the amount stated on the product labels. The authors concluded that trace contamination of androstenedione with 19-norandrostenedione is sufficient to cause positive urine results for the presence of 19-androstenedione.

- *Testosterone*—Free and total testosterone levels can become elevated, particularly in the first 2 months of use, although testosterone levels may begin to normalize over the course of time for many patients. This effect is the result of the precursor nature of androstenedione for testosterone production.[35,46]

β-*Glucan*

Use of β-glucan may elevate white blood-cell (WBC) counts (leukocytosis). A phase-II, multicenter, double-blinded, randomized, placebo-controlled study of 3 dosages of β-glucan was conducted in a population of surgical patients. Doses of 0.1 mg/kg, 0.5 mg/kg, or 1.0 or 2.0 mg/kg of the supplement were administered to 67 patients who were at a high risk for developing postsurgical infections after thoracic or abdominal surgery.

Serious infections developed in 4 patients who received placebo, in 3 patients who took the lowest dose of 0.1 mg/kg, and in only one patient who received one of the higher doses. Generalized leukocytosis was observed; however, the researchers concluded that β-glucan was safe, well-tolerated, and may decrease postoperative infection rates.[8]

The elevated WBC counts seen in these patients may have resulted because the body's defenses are rallied by β-glucan. This demonstrates the supplement's therapeutic efficacy. However, if use of β-glucan or other immune-stimulating substances are not reported to clinicians, elevated WBC counts in patients who take the supplement might cause their health providers to believe that such patients have infections or other immunity problems that are actually nonexistent.

Boron

Present in virtually all supplement regimes for the treatment for osteoporosis, this trace mineral can have substantial effects that can serve as an adjunctive therapy to optimize bone-mineral density. The mineral can also affect estrogen and phosphorus levels.

- *Estrogen*—Concomitant use with estrogenic drugs may increase serum estrogen levels.[9] Current knowledge of this potential interaction is based predominantly on the theoretical synergy that could arise from boron's ability enhance estrogenic effects within the body. Thus, boron should be used cautiously, if at all, for patients with estrogen-dependent disease processes or who have risks for such conditions because of this potential to affect estrogenic properties physiologically.
- *Bone mineral density*—Boron may increase bone-mineral density measurements in female athletes.[10] In a clinical trial, 17 female athletes had a slight increase in bone-mineral density over the period of the year-long study, whereas the sedentary control subjects actually demonstrated a slight decrease.
- *Phosphorus*—Boron may also decrease serum phosphorus concentrations in some patients.[10] Female college students who took the mineral in a study had lowered serum phosphorus levels. Subjects in the study's boron-treated group also had lower magnesium levels, which apparently correlated with participating in exercise.[10]

Glucosamine Sulfate

One of the most popular nutrients on the market for relieving the discomfort and debilitating effects of degenerative arthritis, glucosamine sulfate, is generally considered to be safe. However, there is some preliminary evidence that, in some susceptible patients, glucose levels may become elevated. Thus it is important to ask patients with recalcitrant glucose-control problems or arthritis if this supplement is being used.

- *Blood glucose*—It has been posited that glucosamine may elevate blood glucose levels by increasing insulin resistance or diminishing insulin production.[11,12] Rats who were infused with glucosamine had impaired early activation of phosphoinositide (PI) 3-kinase by insulin in skeletal muscle. Prolonged insulin infusion produced a blunting of the PI 3-kinase response to insulin.[12]
- *Insulin*—According to the results of one study glucosamine may cause impairment in glucose-induced insulin secretion.[13] This finding was discovered in a research model that used glucosamine infusion and the study researchers concluded that glucosamine causes severe impairment in glucose-induced insulin secretion. They also concluded that glucosamine-induced beta-cell secretory dysfunction extends to nonglycemic stimuli such as arginine. This pattern of insulin secretion dysfunction mirrors that seen in patients with noninsulin–dependent diabetes mellitus (NIDDM). Thus, the data indicated that glucosamine may contribute to potential pathogenesis of glucose toxicity at the level of the beta-cell in NIDDM.

Although these potential side-effects are yet to be broadly proven and have, in part, been based on glucosamine infusion or animal-model projections, clinically I have noted that occasionally, a patient will experience similar effects with oral intake of glucosamine sulfate. Yet, in another study, it was found that glucosamine sulfate, taken at 1500 mg per day, for 12 weeks, increased blood insulin levels in a group of patients.

Botanical–Laboratory Test Interactions

Botanical medicines can have many potential interactions with pharmaceuticals. The complex, and frequently abundant, active chemical constituents that produce therapeutic benefits can alter the accuracy of laboratory results and/or effect true changes in the body's biochemical pathways, either positively or negatively.

Goldenseal

Goldenseal (*Hydrastis canadensis*) has become best known for its antibacterial properties. It also can affect bilirubin levels.

Goldenseal may increase bilirubin levels. Although this has been shown with berberine isolates, it has not been proven conclusively when whole goldenseal has been used. Actual increases in total and unbound bilirubin levels can become elevated with berberine use because bilirubin is displaced from albumin.

This effect was confirmed in a study of rats that produced the potential physiologic effects. Using a peroxidase kinetic method, protein binding of bilirubin was studied. Berberine was found, in vitro, to have a tenfold superior displacing effect compared to phenylbutazone, a known potent bilirubin displacer. In the same study, berberine was also approximately 100-fold more effective for displacing bilirubin than papaverine, a berberine-like alkaloid.[14] The researchers said that neonates who suffer from kernicterus should not be given berberine-containing preparations. These also include Oregon grape (*Berberis vulgaris*) and other botanicals.

Concomitant intake of grapefruit juice increases the concentration of many drugs in humans.

Grapefruit

Grapefruit became quite famous because of the acclaimed Hollywood grapefruit diet; yet, this fruit can cause dramatic increases drops in blood levels of many substances, including a number of pharmaceuticals, because it inhibits the liver-metabolism pathway, cytochrome 450.

Because of this effect on cytochrome 450, many levels of pharmaceuticals may be increased and will affect serum/plasma measurements. Among the drugs for which levels may become elevated are amlodipine, nifedipine, nisoldipine, felodipine, nimodipine, nicardipine, dlitiazem, verapamil, buspirone, midazolam, triazolam, diazepam, carbamazepine, cisapride, cyclosporin, estradiol, lovastatin, saquinavir, simivastatin, atorvastatin, terfenadine, losartan.[4]

Concomitant intake of grapefruit juice increases the concentration of many drugs in humans.[15] The predominant effect seems to be mediated mainly by suppression of the CYP3A4 in the small intestine and, to a degree, the liver. This results in a decreased first-pass metabolism with enhanced bioavailability and increased maximal plasma concentrations.

The drugs that are most affected by this phenomenon are those with a typical high first-pass degradation. Among these are felodipine, nitrendipine, nisoldipine, and saquinavir. In these cases, the interaction was most marked with median increases of area under the curve and/or the peak plasma drug concentration after a single dose (Cmax) values exceeding 70 percent of respective controls. Increases for nifedipine, nimodipine, verapamil, cyclosporin, midazolam, traizolam and terfenadine are less pronounced but are still probably clinically relevant.

The grapefruit juice components that are most likely to be the cause of these interactions are psoralen derivatives and the flavonoid naringenin. Because the effect is so pronounced when patients drink grapefruit juice with some drugs, the researcher who conducted the study on grapefruit's effects concluded that patients should refrain from drinking grapefruit juice they take drugs that are extensively metabolized by the CYP3A4 pathway.[15]

Another study demonstrated that consumption of 250 mL of grapefruit juice caused a Cmax of 115 percent for a single oral dose of 5 mg of amlodipine taken with the juice.[16]

Yet, another trial indicated that the mean felodipine bioavail-

ability with grapefruit juice was 284 (range 164–469 percent) of that with water.[17] The effects of the juice on buspirone were tested in a randomized, phase-2 crossover study. For this study, 10 healthy volunteers took either 200 mL of double-strength grapefruit juice or water, 3 times per day, for 2 days. On the third day, each subject was given 10 mg of buspirone with either 200 mL of grapefruit juice or water and an additional 200 mL was ingested one half-hour and 1.5 hours after the buspirone was administered. The mean increase resulting from the grapefruit juice consumption was 4.3-fold (range 2 –15.6-fold).[17]

Indole: A Botanical Component

Scientific validation has now demonstrated that broccoli, cauliflower and their relatives can prevent serious disease states. When taken in supplement form though they too can alter laboratory values because of their indole content. Some patients who take indoles therapeutically may experience a slight increase in alanine aminotransferase (ALT).[19]

In a study of 60 women who were at an increased risk for developing breast cancer, subjects were given either 50, 100, 200, 300, or 400 mg doses of indole-3-carbinol. The minimum effective dose per day as a possible chemopreventive agent against breast cancer was 300 mg. Although this study needs to be replicated on a much larger basis, it demonstrated that indoles can be used safely. However, a small minority of patients may experience a slight increase of ALT but the reason for this is not yet known.

Conclusions

Natural medicines sustained our ancestors for the millennia required for our very existence. But as Socrates could attest if asked today, not all natural substances are safe and sometimes there is a fine line between helpful and hurtful agents. With the advances in technology and growing interest in natural medicines, there is a trend toward utilizing natural medicines by general consumers who may not realize that they are consuming medicines, even though they are natural in origin. This situation can result in interactions that alter laboratory values, even though the clinical effects of these medicines are sometimes positive and sometimes negative. It is hoped that information provided on these interactions will be used to produce vital literature to guide physicians and consumers on the safest and most prudent ways to use these medicines. ⊓

References

1. Konrad T, Vinci P, Kusterer K. Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. Diabetes 1999;22:280–287.

2. Ziegler D, Hanefeld M, Ruhnau K. Treatment of symptomatic diabetic polyneuropathy with the antioxidant thiotic acid (α-lipoic acid): A 2 year, multicenter, randomized, double blind, placebo controlled trial (ALADIN II). Free Radic Res 1999;13:171–177.

3. Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A 7-month multicenter randomized controlled trial (ALADIN III Study): ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetologia 1995;38:1425–3143.

4. Jellin JM. Natural Medicine Comprehensive Database. Stockton, CA: Therapeutic Research Faculty, 2002.

5. Broeder CE, Quindry J, Brittingham K. The Andro Project: Physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high intensity resistance training program. Arch Intern Med 2000;160:3093-3104.

6. Brown GA, Vukovich MD, Martini ER, Kohut ML, Franke WD. Endocrine responses to chronic androstenedione intake in 30- to 56-year old men. J Clin Endocrinol Metab 2000;85(11):4074-4080.

7. Catlin DH, Leder BZ, Ahrens B. Trace contamination of over the counter androstenedione and positive urine tests results for a nandrolone metabolite. JAMA 2000;284:2618–2621.

8. Babineau TJ, Hackford A, Kenler A. A phase II multicenter, double blind randomized, placebo controlled study of three dosages of an immunomodulator (PGG-glucan) in high risk surgical patients. Arch Surg 1994;129(11):1204–1210.

9. Shils M, Olson A, Shike M. Modern Nutrition in Health and Disease, 8th ed. Philadelphia: Lea and Febiger, 1994.

10. Meacham SL, Taper LJ, Volpe SL. Effects of boron supplementation on bone mineral density and dietary, blood, and urinary calcium, phophorus, magnesium, and boron in female athletes. Environ Health Perspect 1994;102(suppl.7):79–82.

11. Adams ME. Hype about glucosamine. Lancet 1999;354(9176):353.

12. Holmang A, Nilsson C, Nikasson M. Induction of insulin resistance by glucosamine reduces blood but not interstitial levels of either glucose or insulin. Diabetes 1999;48:106–111.

13. Shanker RR, Zhu JS, Baron AD. Glucosamine infusion in rats mimic the beta-cell dysfunction of non–insulin-dependent diabetes mellitus. Metabolism 1998;47(5):573–577.

14. Chan E. Displacement of bilirubin from albumin by berberine. Biol Neonate 1993;63(4):201–208.

15. Fuhr U. Drug interactions with grapefruit juice: Extent, probable mechanism and clinical relevance. Drug Saf 1998;18(4):251–272.

16. Josefson M, Zackrisson AL, Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlopidine in healthy volunteers. Eur J Clin Pharmacol 1996;51(2):189–193.

17. Bailey DG, Spence JD, Munoz C, Arnold JM. Interactions of citrus juices with felopidine and nifedipine. Lancet 1991;337(8736):268-269.

18. Lilja JJ, Kivisto KT. Grapefruit juice substantially increases plasma concentrations of buspirone. Clin Pharmacol Ther 1998;64(6):655-660.

19. Wong GY, Bradlow L, Sepkovic D. Dose-ranging study of indole-3-carbinol for breast cancer prevention. J Cell Biochem 1997;28(suppl.):111–116.

Chris D. Meletis, N.D., serves as the dean of naturopathic medicine/chief medical officer, National College of Naturopathic Medicine, Portland, Oregon.

To order reprints of this article, write to or call: Karen Ballen, *ALTERNATIVE & COMPLEMENTARY THERAPIES,* Mary Ann Liebert, Inc., 2 Madison Avenue, Larchmont, NY 10538-1961, (914) 834-3100.