

Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part II

Mark A. Moyad, MD, MPH^{a,*}, James H. Barada, MD^b,
Tom F. Lue, MD^c, John P. Mulhall, MD^d,
Irwin Goldstein, MD^e, Ahmed Fawzy, MD^f,
for the Sexual Medicine Society (SMS) Nutraceutical Committee

^a*Department of Urology, University of Michigan Medical Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0330, USA*

^b*Center for Male Sexual Health, Albany Medical College, 43 New Scotland Avenue, Albany, NY 12208, USA*

^c*University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94122, USA*

^d*Sexual Medicine Program, Weill Medical College, Cornell University, 445 East 69th Street, New York, NY 10021, USA*

^e*Institute for Sexual Medicine and Center for Sexual Medicine, Boston University School of Medicine, 715 Albany Street, Boston, MA 02118, USA*

^f*Department of Urology, Louisiana State University School of Medicine, 1532 Tulane Avenue, New Orleans, LA 70112, USA*

L-arginine: an amino-acid supplement and a potential precursor to nitric oxide

The primary neurotransmitter that mediates penile erection is the compound nitric oxide (NO) [1–3], which is released during nonadrenergic, noncholinergic neurotransmission and from the endothelium. Within the muscle, NO activates a guanylyl cyclase, which increases the production of intracellular levels of cyclic guanosine monophosphate (GMP). Cyclic GMP is an intracellular second messenger that mediates smooth muscle relaxation and activates specific protein kinases that phosphorylate specific proteins to cause an opening of potassium channels, a closing of calcium channels, and an overall sequestration of intracellular calcium. The decrease in intracellular calcium relaxes smooth muscle and increases the flow of

penile blood. L-arginine, an amino acid, is a precursor to NO. It is possible that taking this precursor in a concentrated pill may alleviate ED in some men. Large sources of dietary nonconcentrated L-arginine exist in the food supply. Whether these sources improve ED is unknown, but they may improve cardiovascular function [4], which in turn promotes healthy erectile or sexual function. For example, legumes, whole grains, and nuts can provide several grams of L-arginine per day when consumed in moderate-to-large amounts [5].

Three, noteworthy, small, pilot clinical studies of L-arginine versus placebo have been completed. The first study, a placebo-controlled clinical trial that used L-arginine, 2800 mg/d, for 2 weeks, found that 40% of patients had improvement in their erections [6]. Responders were younger and had better overall vascular function by hemodynamic investigation than the nonresponders. The second pilot trial included L-arginine, 1500 mg/d, versus placebo for 2 weeks for men with mixed-type ED. L-arginine at this dosage did not demonstrate a benefit compared with placebo [7]. In the third trial, 50 patients were given a high

This article reviews popular components of the numerous dietary supplements for treatment of erectile dysfunction (ED).

* Corresponding author.

E-mail address: moyad@umich.edu (M.A. Moyad).

dosage of L-arginine (5 g/d) or placebo for 6 weeks for organic ED that was mostly the result of diabetic or arteriogenic etiologies [8]. Approximately 31% of the men in the L-arginine group self-reported an improvement compared with 12% in the placebo group. The difference was statistically significant. Additionally, men who improved had low concentrations of NO in the urine. The primary side effect was a reduction of systolic or diastolic blood pressure of approximately 10% in the L-arginine group. Men secreting low levels of NO who are willing to take fairly large daily dosages of L-arginine may observe a benefit.

Larger randomized clinical trials are needed, but L-arginine seems to be an exception to the observation that dietary supplements provide little to no benefit for men with ED. Recent cardiovascular studies using large oral dosages (12 g/d) of L-arginine versus placebo for 3 weeks in hypercholesterolemic men with normal blood pressures have demonstrated reductions in blood pressure and homocysteine levels [9]. The ability of L-arginine to improve certain types of ED seems plausible given its effects on vascular endothelial function, but whether it is practical to ingest it in expensive megadoses for a long time to prevent or treat ED needs to be addressed in the medical literature.

The anabolic steroid supplements

Why are anabolic steroid supplements available for over-the-counter (OTC) purchase in the United States? This question should be addressed before discussing the benefits and limitations of these substances. Their availability is a result of two federal laws passed in the past 15 years [10]. The 1994 Dietary Supplement and Health Education Act (DSHEA) allows virtually any substance to become a dietary supplement as long as the manufacturer does not make any specific health claims on the container label. More specific to anabolic supplements is the 1990 Anabolic Steroid Control Act, which requires the following four criteria to be met for the removal of an anabolic dietary supplement:

- Molecular structure related to testosterone
- Pharmacology related to testosterone
- Cannot be an estrogen, progestin, or corticosteroid
- Cannot promote muscle growth

Androstenedione and dehydroepiandrosterone (DHEA) have molecular structures and pharmacology similar to testosterone, but are not estro-

gens, progestins, or corticosteroids. These supplements are available for purchase OTC because they have not demonstrated muscle enhancement or growth in clinical trials using smaller dosages. They may promote muscle growth when higher dosages are used, but these trials have not been completed or the findings have not been consistent [11]. Other androgenic-anabolic steroids have demonstrated positive effects on muscle size and strength with certain types of resistance training [12,13]. Therefore, under federal law, manufacturers are allowed to sell these types of supplements.

Androstenedione

Normally, androstenedione is produced by the gonads and adrenal glands, and can be converted to testosterone [14]. Some plants also can produce androstenedione, and it has been touted as a “natural” alternative to anabolic steroid use and as a potential supplement to treat ED.

Several short, randomized trials of androstenedione have been completed to determine its effects on a variety of body functions. In one trial conducted in 1998, 30 healthy young men (19–29 years of age with normal testosterone levels) were assigned randomly androstenedione, 300 mg, or placebo over 8 weeks [15]. Significant increases in testosterone levels did not occur and supplementation had no effect on muscle size and strength. Individuals in the androstenedione group experienced an increase in serum levels of estrone and estradiol. These findings suggest that more aromatization occurred with androstenedione or from increasing testosterone levels. The ingestion of androstenedione also was associated with reduced serum levels of high-density lipoproteins (HDL), or “good cholesterol,” of approximately 10%.

Other clinical studies have found similar and other effects of androstenedione dietary supplements [16–21]. For example, 42 healthy men (20–40 years of age) received androstenedione, 100 mg or 300 mg, daily for 7 days; a similar group received no supplements [18]. The men receiving no supplements or androstenedione, 100 mg, demonstrated no significant mean increases in testosterone levels. The group receiving androstenedione, 300 mg, experienced a mean increase in testosterone levels of 34%. Estradiol levels increased by 42% and 128% for the 100 mg- and 300 mg-groups, respectively.

A short clinical trial of 55 healthy men (30–56 years of age) used androstenedione, 100 mg, or

placebo three times daily for 28 days [20]. Total serum testosterone and prostate-specific antigen (PSA) levels were not affected by supplementation, but increases in free testosterone, estradiol, and dihydrotestosterone (DHT) levels were observed. Decreases in serum HDL cholesterol levels also occurred in the supplemented group. No difference in the perception of mood, health, or libido occurred between treatment and placebo groups, which has been documented in other studies with this and other related supplements [21].

In summary, several randomized trials of androstenedione have demonstrated a good correlation between dosage and estradiol levels and an inverse relationship with HDL levels. Other potential benefits, such as increased muscle mass or improved sexual function, have not been found compared with placebo. This is a concern because these supplements may have an effect opposite to those advertised. Estrogen has been associated with favorable cardiovascular benefits [22], but in men these benefits may increase the risk of cardiovascular disease [23], gynecomastia [24], pancreatic cancer, and other medical conditions [25]. Reductions in HDL also diminish cardiovascular protection [26]. With greater intakes of androstenedione, or in men with low baseline levels of testosterone, these supplements may increase testosterone levels [18,20], but the associated negative effects do not make these supplements an option for most individuals.

The results of short-term clinical trials should encourage men and women to inquire about testosterone replacement instead of consuming a supplement that provides only a precursor to this and other hormones. For example, a small pilot study randomly assigned postmenopausal women ($n = 30$) to a single oral dose of androstenedione, 0 mg, 50 mg, or 100 mg [27]. Large increases in serum testosterone and estrone levels were observed only with the 50 mg- and 100 mg-doses, which was not surprising given that these women already had lower levels of these two hormones. These supplements tend to produce higher levels of hormones that are initially low, and have a smaller effect on hormone levels in the normal-to-high range. Testosterone replacement may be an attractive option for some women or men, but more research is needed [28–30].

Dehydroepiandrosterone

DHEA supplements are derived from plants such as the wild yam, and must be converted in

a laboratory to produce a DHEA-like structure [31]. Many OTC DHEA supplements have not undergone this conversion, and thus contain minimal to no DHEA-specific activity. In postmenopausal women, active DHEA taken orally increases serum testosterone levels [32–36]. Studies with DHEA also demonstrate increases in estradiol levels in postmenopausal women and women with panhypopituitarism [32,33,37]. Other potentially potent DHEA supplements contain the same estrogen-producing qualities from clinical trials with men [38]. Hypogonadal men, or those receiving androgen suppression or luteinizing hormone-releasing hormone agonist treatment for prostate cancer may experience a subsequent testosterone increase (flare) or transient symptomatic benefit with DHEA, but other associated negative effects make these supplements an unattractive option [39,40]. Receiving a precursor to testosterone does not make clinical sense; testosterone itself (if a patient qualifies) would be more sensible and practical. An analogy would be choosing a precursor to salicylic acid versus aspirin for cardiovascular prophylaxis. One does not substitute necessarily for the other and the precursor may not be as effective for the condition.

An exception to testosterone replacement is in men with normal testosterone levels and potentially low levels of serum DHEA. A small, randomized trial of men ($n = 40$) with DHEA sulfate levels below $1.5 \mu\text{mol/L}$ and normal serum levels of testosterone, DHT, prolactin, and PSA ingested DHEA, 50 mg/d, versus placebo for 6 months [41]. All of the men initially had achieved a full erection with prostaglandin E_1 , 10 μg , and patients with obvious or well-known causes of organic ED were excluded from the study. DHEA treatment was correlated with higher mean scores for all five domains of the International Index of Erectile Function (IIEF), despite no increases in serum levels of hormones or other parameters, except for a significant increase in serum DHEA that began at 8 weeks and remained throughout the treatment duration compared with placebo. An initial increase in testosterone levels also occurred and remained in the DHEA group compared with placebo (at 8 weeks); estrogen levels or lipid markers were not measured.

Some men with early organic or psychogenic ED may benefit from small doses of DHEA. Larger randomized trials of greater duration are required, however. A follow-up to the above study that included more men and more definable etiologies for ED demonstrated that oral DHEA

could benefit men with ED caused by hypertension or without an organic etiology [42]. Men with diabetes mellitus or with neurologic conditions did not benefit from DHEA. In the Massachusetts Male Aging Study, DHEA was the only hormone measured that demonstrated an inverse correlation with ED [43]. Further studies should address whether replacement or pharmacologic doses of DHEA affect ED [11].

Ginkgo biloba: a circulation enhancement supplement good for dementia and erectile function?

Ginkgo biloba for the treatment of ED has gained interest in alternative medicine circles for reasons including the apparent benefits of this herbal product in other areas of medicine. Some clinical evidence demonstrates ginkgo extracts can improve vascular perfusion, but most of these trials have focused on its use in dementia, and a specific extract was used rather than a variety of compounds from the plant [44–46]. Ginkgo has been approved in Germany for dementia and limited clinical data suggest it may improve chronic cerebrovascular insufficiency. No studies have been published on the use of ginkgo for ED following localized or advanced prostate cancer treatment, but there have been other relevant studies.

One study treated 60 patients who did not respond to papaverine injections (50 mg or less) with an extract of *Ginkgo biloba*, 60 mg, for 12 to 18 months [47]. No placebo group was included. Ultrasonography detected an improved blood perfusion after 6 to 8 weeks in some men; after 6 months 50% of the patients regained erectile function; in a smaller number, papaverine injections were later successful. In 1998 the study's authors presented the results of a placebo-controlled, double-blind, randomized, follow-up study using an extract of ginkgo, 240 mg/d, for 24 weeks versus placebo for vasculogenic ED [48]. No significant difference was found between the two groups, which highlights the continuing need for quality randomized studies before recommendations can be made.

Ginkgo needs to be tested alone or in combination with other drugs for patients who experience ED from a variety of etiologies before a conclusion can be drawn, and no current data support its use for patients with any type of ED. Perhaps most important, several studies have suggested that ginkgo may increase bleeding time, increase the

risk for hemorrhages, and enhance the action of anticoagulants [49–52]. Further studies need to be completed to confirm this finding because of ginkgo's widespread use in the population compared with the limited number of adverse effects published [53]; for patients it seems better to be safe than sorry.

A clinical study of sexual dysfunction caused by the use of selective serotonin reuptake inhibitor (SSRI) antidepressants reported a 91% "relative success" in women (n = 33) and 76% in men (n = 30) when ginkgo extract, 209 mg/d, was taken for approximately 1 month [54]. Ginkgo was credited with improving sexual function, including enhanced desire, excitement, orgasm, and resolution. A closer analysis of this manuscript revealed numerous problems [55], however. No placebo group was used, and the overall success rate was either misinterpreted or miscalculated. The article reported a success rate of 84%, but when the numbers are added, the rate is approximately 68%. The authors did not report on other important details, such as the treatment success or benefits of the antidepressant for depression. Other medications that these patients were taking for other comorbidities were not listed. The authors concluded that the sexual side effects "appeared" to be caused by the SSRIs, but no pretreatment evaluation was reported, so the authors' basis for this conclusion is unknown. Finally, although "no adverse side effects were reported," a closer evaluation of the data revealed some adverse effects (eg, headaches).

A similar comparative clinical investigation in similar patients found no improvement with ginkgo compared with a placebo arm [56]. Other recent ginkgo studies using a placebo for other non-ED conditions have failed to observe significant benefits [57]. Thus, any data advocating ginkgo supplements for sexual function or ED improvement are suspect until larger randomized trials are completed. The best approach for a future clinical study for ED would be to use the same ginkgo extract used in clinical trials that demonstrated success for patients with dementia compared with placebo [46].

Korean red ginseng: another potential nitric oxide producer and initial studies

Another potential exception to the lack of promising data regarding the effectiveness of dietary supplements is Korean red ginseng

(*Panax ginseng*). Korean red ginseng is one of the most commonly used ginseng products in the United States; many brands are marketed under the name Panax [58]. Korean red ginseng has been investigated preliminarily against HIV [59], and to reduce severe climacteric symptoms or improve mood in postmenopausal women with limited positive results compared with placebo [60,61]. Other studies with this herbal product have found that it may contain numerous active compounds [62], some with antiplatelet and blood-thinning potential [63]. Korean red ginseng also may improve vascular endothelial abnormalities in hypertensive patients by increasing the concentration of NO [64].

A laboratory investigation of Korean red ginseng on rabbit corpus cavernosal smooth muscle found that it can cause a dose-dependent relaxation by increasing the release of NO from corporal sinusoids and may increase intracellular sequestration of calcium [65]. A recent laboratory study confirmed this finding and found that this product may enhance peripheral neurophysiologic mechanisms [66]. Two small clinical trials of Korean red ginseng have provided encouraging results [67,68]. A trial published in 1995 divided 90 patients with ED into three groups of 30 that were given Korean red ginseng, placebo, or trazodone, respectively [67]. No significant changes in the frequency of intercourse, premature ejaculation, and morning erections occurred posttreatment in any group. The group taking Korean red ginseng experienced significant positive changes in other erectile parameters such as penile rigidity, penile girth, libido, and patient satisfaction versus the other groups. Approximately 60% of the patients taking ginseng experienced a therapeutic benefit versus 30% for the placebo and drug groups. No complete remissions of ED were recorded. Because penile hemodynamic changes did not occur after administration of this form of ginseng, it is difficult to determine whether it had an effect without further investigations. Korean red ginseng's apparent ability to increase NO levels or reduce fatigue, insomnia, or depression demonstrates that specific compounds from this herb may benefit some types of ED or sexual dysfunction [60,66].

A double-blind, placebo-controlled, crossover, preliminary trial of Korean red ginseng enrolled 45 patients with ED without previous treatment from a urology clinic in Korea in 8 weeks of treatment, a 2-week washout period, and another 8 weeks of treatment [68]. The dose of oral

ginseng was 900 mg three times daily. The mean patient age was 54 years, 70% of the men had moderate or severe ED as measured by a Korean version of the IIEF, and over 50% of the men had organic comorbidities (eg, hypertension, diabetes mellitus, dyslipidemia). Exclusion criteria included men with a history of radical prostatectomy, neurologic problems, hormonal and chemotherapy treatment, Peyronie's disease, substance abuse, and drugs that interfere with sexual function. All patients had baseline evaluations including IIEF self-assessment, measurement of rigidity and tumescence experienced during audiovisual sexual stimulation, penile duplex ultrasound, and response to an intrapenile injection of papaverine, phentolamine, and prostaglandin E₁. Patients were assessed every 4 weeks during the two 8-week treatment intervals. Improvement was measured by self-report on the IIEF and its subscales and by objective assessments of penile blood flow, size, and rigidity. Follow-up was complete at 16 weeks of treatment.

The study was underpowered to find statistically significant improvement in some clinical outcomes, such as improvement in orgasmic function or overall satisfaction for men and their partners. Nonetheless, mean IIEF scores were significantly higher in the ginseng-treated patients (38.1 ± 16.6 , from baseline 28.0 ± 16.7) compared with placebo (30.9 ± 15.7 , from baseline 28.0 ± 16.7), as were the parameters of penetration and maintenance. When analyzed individually, scores for erectile function, sexual desire, and intercourse satisfaction were improved significantly with ginseng. Approximately 60% of treated patients experienced an improvement in erection compared with 20% with placebo. This yields a number needed to treat of 2.5, but this is a small study, and no data were reported for partner satisfaction. Penile-tip rigidity (measured by RigiScan, Timm Medical Technologies, Eden Prairie, Minnesota) also improved significantly with ginseng compared with placebo. In addition, there was no significant difference recorded in orgasmic function and overall satisfaction between the two treatments.

The authors commented that the mechanism of action for ginseng probably was not related to testosterone levels, which did not change significantly during the study, although serum testosterone normalized after ginseng in four of the seven patients with a decreased baseline level; more research is needed to resolve this issue. Other potential mechanisms of action, such as an inhibitory effect on the uptake of gamma-aminobutyric

acid, glutamate, dopamine, and other neurotransmitters and increased production of NO were proffered from animal data [69,70]. This small trial supports ginseng for some subjective symptoms of ED and enhanced penile-tip rigidity, but this supplement needs a larger placebo trial to determine its overall role for ED treatment. Regardless, this trial has generated positive attention in primary care medicine, which may be in part due to the low cost of Korean Red Ginseng (approximately 6 cents per 500-mg capsule) compared to FDA-approved, prescribed oral agents [71].

In another small trial, researchers from Brazil included 60 men with mild-to-moderate ED (mean age 53.4 years, range 26–74 years) in a double-blind trial of Korean red ginseng, 3 g/d, compared with placebo for 3 months [72]. Compared with the placebo group, the ginseng group reported significant improvement in the IIEF erectile domain score and on all questions of this domain individually, with maintained response during the 3 months of follow-up. A significantly higher percentage of men (66.6%) believed the ginseng treatment improved their erections and sexual intercourse compared with placebo (18.5%, $P < 0.001$). The baseline and 3-month glucose, cholesterol (total cholesterol and triglycerides), and hormone (testosterone and prolactin) levels were similar for both agents. Side effects observed in the treatment arm (3.7%) included headache, insomnia, drowsiness, and spontaneous regression during the first month. Two patients (7.4%) noted delayed ejaculations during the second and third month of treatment. This small trial may indicate that Korean red ginseng may benefit some men with ED, but the presentation did not mention the etiology of ED in these men.

Yohimbine: a drug copycat that is difficult to find in most dietary supplements

Yohimbine is an indole alkaloid extracted from the bark of West African yohim trees [73]. It is a prescription drug that obtained FDA approval for pupillary dilation. Yohimbine seems to produce blood-vessel dilation and increase perfusion; thus, researchers began to test its ability to improve erectile function. Yohimbine contains some compounds similar to an alpha-2 adrenoceptor antagonist with central and peripheral effects. It functions primarily at receptors in brain centers associated with libido and erections. A meta-analysis of seven randomized

trials of over 400 men with ED from a variety of etiologies found that yohimbine (15–43 mg/d) was better versus placebo for all forms of ED combined, but its most apparent improvement occurred with nonorganic ED [74]. The most common adverse effects are palpitations, fine tremor, elevation of diastolic blood pressure, anxiety, and nausea. Yohimbine is not recommended for individuals with organic ED because there are more effective ED agents and its overall effect seems minimal [1].

Yohimbe is available as an OTC supplement, but it is questionable whether such supplements have value or contain the active ingredient found in yohimbine [75–77]. In 1995, the FDA found little or no yohimbine in most (11 of 18) of yohimbine supplements brands tested [77]. None of the other seven brands contained amounts of yohimbine similar to those used in clinical trials. Thus, there seems no justification for purchasing a dietary supplement that claims to contain yohimbine. If a patient expresses interest in this compound or in combining it with other ED treatments, the possibility of using the prescription drug should be the focus of the conversation.

Zinc: hype, hope, minimal medical evidence, and a major health concern for many individuals

Approximately 15% of the United States population uses dietary supplements containing zinc [78]. It may surprise some people, however, that the current recommended dietary intake of zinc is low, as listed in Table 1 with dietary levels of copper. Because large doses of zinc can decrease the concentration of copper in the body, a proper balance or intake between the two is important [79].

The recommended daily allowance (RDA) of zinc is 11 mg for men, but some individuals may ingest far more zinc daily [80]. The reasons for this

Table 1
Current government guidelines for daily recommended dietary allowance and appropriate intake levels of zinc and copper

Age	Zinc (mg)	Copper (μ g)
0–6 mo	2	200
7–12 mo	3	220
1–3 y	3	340
4–8 y	5	440
9–13 y	8	700
14–18 y	11 (boys), 9 (girls)	890
19 or more y	11 (men), 8 (women)	900

discrepancy are not understood, but may include highly publicized reports in alternative medicine publications that advocate the use of zinc supplements to treat everything from the common cold to ED. Another potential reason for greater zinc intake is the observation from several laboratory studies that zinc may inhibit the growth and progression of prostate cancer [81–85].

The concentration of zinc in the prostate gland is greater than that in any other human tissue in the body [86]. Zinc levels in cancerous prostate tissue are reduced substantially compared to normal prostate tissue, which may suggest that prostate cancer is a state of zinc deficiency that may be corrected or prevented by greater zinc intake. Other laboratory and clinical studies suggest that larger intraprostatic or serum zinc concentrations may increase the risk for or progression of prostate cancer. For example, zinc promotes the activity of the enzyme telomerase, which is thought to play a role in the proliferation of cancer cells, and the overall activity of which is increased in prostate cancer tissue [87,88]. Zinc also can abolish the inhibitory activity of bisphosphonate drugs on prostate cancer cell invasion, which is a serious concern [89,90] because these drugs can impact a variety of cancers [91,92]. Human studies also suggest that higher zinc intakes are correlated to circulating levels of insulin-like growth factor-1 [93] and testosterone [94], both of which may be related to an increased risk for prostate cancer.

Several studies have demonstrated the potential for zinc to increase prostate carcinoma risk; one of the most prominent epidemiologic investigations was taken from the Health Professionals Follow-Up Study [80]. Approximately 47,000 American men were included in this prospective investigation. During 14 years of follow-up, 2901 new cases of prostate cancer were found; 434 of these cases were diagnosed as advanced prostate cancer. Researchers found zinc supplement doses of 100 mg/d or less did not correlate to a risk for prostate cancer. Men that ingested more than 100 mg/d of zinc supplements had a significantly higher risk for being diagnosed with advanced prostate cancer (relative risk = 2.29) compared with nonusers, however. Men that consumed zinc supplements for 10 or more years also had a significantly higher risk for being diagnosed with advanced prostate cancer (relative risk = 2.37). In this cohort, approximately 32% of the total zinc intake was from dietary supplements, the largest source of zinc intake. Other sources included beef (11%) and breakfast cereals (5%). Zinc from food sources, however, was

not correlated with prostate cancer risk. Men consuming zinc supplements also consumed more supplemental calcium, multivitamins, vitamin E supplements, lycopene, iron, copper, folate, and fish, but consumed less red meat and were less likely to have a history of PSA screening compared with nonusers of zinc supplements. Researchers attempted to identify confounding factors in this investigation. One analysis restricted the study population to men reporting lower levels of calcium supplement intake and adjusted for intakes of iron, copper, folate, benign prostatic hyperplasia (BPH), and other factors, but this had no impact on the final results. Therefore, zinc supplements were still the most likely etiology from this investigation.

Increased zinc ingestion also may increase the risk of BPH. The impact of dietary zinc intake on subsequent intraprostatic zinc levels is not known, but a case-controlled study from Greece of diet and BPH observed that greater intakes of dietary zinc had the most significant correlation with the overall risk of BPH (odds ratio = 1.89) [95]. Zinc (mostly from meat and seed sources) was correlated more closely with BPH risk than any other evaluated dietary nutrient, and also strongly confounded the relationship of saturated fat with the risk for BPH. Therefore, the conclusion that meat consumption increases the risk for prostatic disease may be too simplistic. Other factors in meat, such as zinc, may have a stronger effect. Zinc concentration increases in BPH tissue [86,96–102]. Testosterone seems to be involved in the development of BPH and prostate cancer, and it significantly increases the concentration of cellular and mitochondrial zinc. Laboratory investigations have observed that androgen uptake by the prostate was increased significantly by the addition of zinc [99]. Zinc also seems to affect the enzyme 5- α -reductase in the prostate [103]. Whether this is a favorable or unfavorable effect has yet to be researched.

Zinc supplements may benefit a variety of medical conditions, including the common cold [104], acne [105], acute diarrhea [106], progressive myoclonic epilepsy [107], and Wilson's disease [108,109]. The negative effects of zinc supplements may outweigh the benefits in many individuals, however, and the benefits of zinc supplements for more benign conditions such as the common cold have been challenged by other investigations [110]. As an example of zinc's negative effects, excess zinc intake must be included in the differential diagnosis of sideroblastic anemia [111]. The diagnosis of zinc-promoted copper deficiency can be established

from reduced serum copper and ceruloplasmin levels along with an increased zinc serum level. Therefore, reducing or ceasing zinc supplementation may reverse anemia and neutropenia in some individuals.

A small, older clinical study raised concerns with the ingestion of larger doses of zinc supplements. Ingestion of elemental zinc, 150 mg, twice a day (300 mg/d total) for 6 weeks in 11 healthy adult men demonstrated general immune dysfunction that began to reverse with the cessation of the zinc supplements [112]. Levels of serum HDL significantly decreased, and levels of low-density lipoproteins (LDL or “bad cholesterol”) were increased in these men. These negative effects on cholesterol may have contributed to the lymphocyte and polymorphonuclear leukocyte abnormalities in this investigation. Zinc supplements in large doses also may decrease antioxidant defense pathways that may be vital to cancer or other disease prevention [113]. Animal studies have found that zinc may inhibit the cancer-protective ability related to selenium ingestion [114].

There is minimal evidence that zinc supplements can affect ED. Several studies have tested zinc supplements on sexual function, but they mostly included men on kidney dialysis. Some studies demonstrated a benefit, but others found none [115,116]. Patients on dialysis may have a zinc deficiency with hyperprolactinemia that consuming supplemental zinc may correct and produce greater levels of male hormone [99,117]. These investigations, however, cannot assess properly what role zinc may have in general ED treatment. Clinicians should explain to patients that the evidence is not available and taking zinc supplements can result in numerous adverse effects.

It is concerning that many of the popular alternative medicine books seem to promote the use of zinc supplements for “prostate health” or “sexual health” with little data to support or refute these claims. Research not only challenges this assertion but seriously questions the advisability of larger intakes of zinc supplements and dietary zinc. More research is required. Health professionals should express to patients concerned with prostate disease, ED, and other conditions that with few exceptions, zinc supplements can produce serious adverse consequences. Zinc in many multivitamins seems to be adequate, especially when the supplement contains the RDA, but larger intakes of individual zinc supplements (eg, 100 mg/d or more) should be discouraged until adequate research resolves this issue.

Other dietary supplements: the present and future

Many dietary supplements have limited clinical data, so it is difficult to evaluate their effect on any form of ED. For example, *Avena sativa* (wild oats, oat bran, or oatstraw) can reduce cholesterol and possibly blood pressure [118–121]. Several dietary supplements for ED contain some concentrations of *Avena sativa*, perhaps because reducing cholesterol levels or blood pressure or altering the male hormone milieu may impact ED favorably. No specific trials of *Avena sativa* and ED have been published, and beyond a potential cardiovascular benefit, no comment can be made regarding its efficacy. Other OTC, soluble-fiber products [122–124] with some cholesterol-lowering ability, such as psyllium, pectin, guar gum, and locust bean gum, may comprise partially some ED supplements with the thought that cholesterol reduction could lead to enhanced erectile function. No clinical trials have used these compounds for ED, however. Other potential cholesterol-lowering products or supplements, such as soy, may be found in some supplements, but it and other OTC products’ minimal-to-moderate ability to decrease cholesterol remains controversial [125–127]. It seems that any product that can affect cholesterol (or weight) has the potential to become a part of an ED supplement, and the limitations of these marketing claims without evidence from clinical trials should be discussed with patients inquiring about these agents.

Tribulus terrestris is a plant that grows in numerous countries around the world. It contains many unique compounds that have steroid-like or steroid saponin activity [128–130]. A compound called protodioscin can be extracted from some of these plants under appropriate conditions and apparently transformed into DHEA [131]. Some laboratory investigations have found this compound potentially improves erectile function [132, 133]. It has failed in initial studies to change body composition, enhance exercise, or impact testosterone levels in young men, but increases levels of androstenedione or estradiol when combined with other DHEA-like products [17, 134]. Results similar to those observed with androstenedione/DHEA could be expected, but adequate clinical trials addressing its individual impact or other unique effects on hormonal levels in hypogonadal men or those with ED have not been published.

Other ED supplements such as damiana (*Turnera diffusa*) combined with other herbals, vitamins,

Table 2

A summary of alternative therapies and commercially available erectile dysfunction supplements

Alternative/supplement	Overall evidence
Acupuncture	Psychogenic ED; needs a randomized trial.
Androstenedione/DHEA	Increase estradiol and testosterone levels in men with normal testosterone levels; lowers HDL by an average of 10%. May increase testosterone levels dramatically in hypogonadal men. May benefit men with nonorganic and other ED and suboptimal levels of these precursors
Ginkgo biloba	May have a blood-thinning effect. Lacks benefit in a studies with men with ED.
Korean red ginseng (<i>Panax ginseng</i>)	Three preliminary trials suggest a potential benefit for men with ED, but quality control is a serious issue and more randomized trials are needed.
L-arginine	A precursor to NO. High doses may benefit men that secrete low levels of NO. May lower blood pressure. Needs more randomized trials.
Yohimbine	Supplements probably contain little to no yohimbine. Prescription form is best and may benefit some with psychogenic ED. Can cause serious side effects.
Zinc	May benefit those with a severe zinc deficiency. Otherwise, there is a lack of data and high dosages can be dangerous and immunosuppressive.
Other supplements	<i>Avena sativa</i> and other potential cholesterol and blood-pressure reducers, and <i>Tribulus terrestris</i> (precursor to DHEA) need clinical trials. A recent study of a Chinese herbal combination demonstrated no impact on sexual function versus placebo.
Antioxidants in combination with orally approved FDA medications	Folic acid plus vitamin E may enhance the response to sildenafil in men that failed to initially respond to sildenafil. Other oral drugs plus other supplements (eg, yohimbine and arginine) may enhance erectile response. Large placebo-controlled trials are needed to confirm these observations.

minerals, or other plants and their extracts have demonstrated initial promising results in women and men [135,136], but larger randomized trials are required to confirm efficacy and determine their safety profiles and mechanisms of action.

Combining prescription drugs and supplements through adequate clinical research: the new frontier?

A fascinating and exciting potential use of dietary supplements for ED is to enhance available prescription agents for ED. Some preliminary research has shown the potential for a synergistic effect. Recent animal studies suggest that diabetic rats given a combination of sildenafil and vitamin E had lower activities of phosphodiesterase-5 compared to rats given sildenafil alone [137]. Thus, an antioxidant may enhance the response of sildenafil in diabetic men, but clinical studies are needed.

In a recent study, 124 men (mean age 57.2 years) with ED (etiologies not listed) that did not respond to sildenafil took folic acid, 5 mg, and vitamin E, 800 IU, daily, along with sildenafil pro re nata, 50 mg to 100 mg [138]. The response to

this therapy was evaluated at a 6- to 12-week interval. Researchers found that 59 men (89.4%) chose the combined regimen and three chose sildenafil only. Thirty-six (61%) men had a partial or complete response to the combined regimen, with 32 men (88.9%) reporting excellent or satisfactory results. Seventeen men (28.8%) reported a poor response, four men (6.8%) reported a moderate response, and six men (10.2%) did not use the dietary supplement regimen or sildenafil. Among men that did not respond to the supplement regimen with sildenafil, eight responded to further treatments such as intracavernosal injection (six men), testosterone (one man), and a penile implant (one man). Of the original nonresponders, 84.7% were salvaged using the dietary supplement or salvage treatments. No side effects were reported in the vitamin E and folic acid group. A placebo-controlled trial is needed, but the potential for dietary supplements to enhance the response to a conventional drug dose is intriguing.

A recent cardiovascular study of patients postangioplasty found that individuals taking a daily supplement that included 1 mg of folic acid, 400 µg of vitamin B₁₂, and 10 mg of vitamin B₆ had a lower risk for another procedure, death,

and nonfatal myocardial infarctions compared with placebo after 1 year of study [139]. Thus, antioxidants have the potential to improve vessel patency, which can be translated indirectly to studies of men with ED that has a vasculogenic etiology. Other potential combinations of drugs and supplements, such as L-arginine and yohimbin, have demonstrated efficacy for ED patients in a smaller trial [140], but more studies are needed because other combinations of supplements alone have not provided a benefit in some trials [141]. Definite answers will be achieved only through adequate research.

Summary

It seems naïve to believe that some plants or herbs do not contain specific compounds that could benefit patients with ED. Many supplements have not been investigated in a laboratory or clinical research setting before commercial sale, however, which creates a complex situation. If efficacy is or is not demonstrated through adequate research, then the benefit or lack thereof cannot be mentioned on the label. Furthermore, clinicians and the public cannot be made aware of which compounds or supplements are effective because no general standards for sale exist under the current guidelines.

Dietary supplements have received a tremendous amount of publicity. The large and growing market for ED treatment seems to have contributed partly to the promotion of numerous supplements and their apparent benefits. Whether these dietary supplements have merit is questionable. Some supplements may produce results opposite to those advertised. Other supplements may be enjoying the benefits of the placebo effect. Because a placebo response of 25% to 50% has been recorded in clinical trials with effective agents, it is understandable that some supplements enjoy financial success despite the limited research espousing their use. If one to two of four individuals or one of three individuals who try a dietary supplement gain some benefit for their ED, the market for these supplements will remain extraordinary. On a larger scale, of 100,000 men who try a supplement, approximately 25,000 to 50,000 will claim some success. The challenge for clinicians is to discuss the placebo response properly and the need for good research before any intervention, especially supplements, can be advocated for general use. Table 2 summarizes some popular ED supplements and general

conclusions that can be drawn from clinical investigations.

Some dietary supplements may have an active ingredient that benefits patients with certain types of ED. An exciting area of future dietary supplement research is the ability of certain agents to have a synergistic effect with prescription agents for ED, thereby improving response rates in men that have failed approved ED therapy initially, especially with oral agents. Randomized clinical trials are the best method of determining which dietary supplements will become a part of conventional medicine. Therefore, more randomized trials for dietary supplements are needed so that they may have the opportunity to become a part of the mainstream milieu, which means that more funding needs to be made available for ED research. The coming years of research should bring enormous excitement and objectivity to this area of medicine.

References

- [1] Lue TF. Erectile dysfunction. *N Engl J Med* 2000; 342(24):1802–13.
- [2] Saenz de Tejada I, Goldstein I, Azadzoi K, et al. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. *N Engl J Med* 1989;320(16): 1025–30.
- [3] Ignarro LJ, Bush PA, Buga GM, et al. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. *Biochem Biophys Res Commun* 1990;170(2):843–50.
- [4] Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA* 2002; 288(20):2554–60.
- [5] Oomen CM, van Erk MJ, Feskens EJ, et al. Arginine intake and risk of coronary heart disease mortality in elderly men. *Arterioscler Thromb Vasc Biol* 2000;20(9):2134–9.
- [6] Zorngiotti AW, Lizza AF. Effect of large doses of nitric oxide precursor L-arginine, on erectile dysfunction. *Int J Impot Res* 1994;6(1):33–5.
- [7] Klotz T, Mathers MJ, Braun M, et al. Effectiveness of oral L-arginine in the first-line treatment of erectile dysfunction in a controlled crossover study. *Urol Int* 1999;63(4):220–3.
- [8] Chen J, Wollman Y, Chernichovsky T, et al. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. *BJU Int* 1999; 83(3):269–73.

- [9] Likos A, Mariotti F, Brown PH, West SG. Oral L-arginine reduces blood pressure, cardiac output, and homocysteine levels in men with high cholesterol [abstract 3538]. *Circulation* 2003;108(17):iv–784.
- [10] Yesalis CE. Medical, legal, and societal implications of androstenedione use. *JAMA* 1999;281(21):2043–4.
- [11] Dhatariya KK, Nair KS. Dehydroepiandrosterone: is there a role for replacement? *Mayo Clin Proc* 2003;78:1257–73.
- [12] Kuipers H, Wijnen JAG, Hartgens F, Willems SMM. Influence of anabolic steroids on body composition, blood pressure, lipid profile and liver functions in body builders. *Int J Sports Med* 1991;12(4):413–8.
- [13] Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996;335(1):1–7.
- [14] Horton R, Tait JF. Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. *J Clin Invest* 1966;45:301–13.
- [15] King DS, Sharp RL, Vukovich MD, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men. A randomized controlled trial. *JAMA* 1999;281(21):2020–8.
- [16] Ballantyne CS, Phillips SM, MacDonald JR, et al. The acute effects of androstenedione supplementation in healthy young males. *Can J Appl Physiol* 2000;25(1):68–78.
- [17] Brown GA, Vukovich MD, Reifenrath TA, et al. Effects of anabolic precursors on serum testosterone concentrations and adaptations to resistance training in young men. *Int J Sport Nutr Exerc Metab* 2000;10(3):340–59.
- [18] Leder BZ, Longcope C, Catlin DH, et al. Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 2000;283(6):779–82.
- [19] Rasmussen BB, Volpi E, Gore DC, Wolfe RR. Androstenedione does not stimulate muscle protein anabolism in young healthy men. *J Clin Endocrinol Metab* 2000;85(1):55–9.
- [20] Brown GA, Vukovich MD, Martini ER, et al. Endocrine responses to chronic androstenedione intake in 30- to 56-year-old men. *J Clin Endocrinol Metab* 2000;85(11):4074–80.
- [21] Wallace MB, Lim J, Cutler A, Bucci L. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. *Med Sci Sports Exerc* 1999;31(12):1788–92.
- [22] Stevenson JC. Mechanisms whereby oestrogens influence arterial health. *Eur J Obstet Gynecol Reprod Biol* 1996;65(1):39–42.
- [23] Phillips GB, Pinkernell BH, Jing TY. The association of hyperestrogenemia with coronary thrombosis in men. *Arterioscler Thromb Vasc Biol* 1996;16(11):1383–7.
- [24] Berkovitz GD, Guerami A, Brown TR, et al. Familial gynecomastia with increased extraglandular aromatization of plasma carbon 19-steroids. *J Clin Invest* 1985;75(6):1763–9.
- [25] Fyssas I, Syrigos KN, Konstandoulakis MM, et al. Sex hormone levels in the serum of patients with pancreatic adenocarcinoma. *Horm Metab Res* 1997;29(3):115–8.
- [26] Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation* 1989;79(1):8–15.
- [27] Leder BZ, Leblanc KM, Longcope C, et al. Effects of oral androstenedione administration on serum testosterone and estradiol levels in postmenopausal women. *J Clin Endocrinol Metab* 2002;87(12):5449–54.
- [28] Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343(10):682–8.
- [29] Guzik DS, Hoeger K. Sex, hormones, and hysterectomies. *N Engl J Med* 2000;343(10):730–1.
- [30] Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc* 2003;51(1):101–15.
- [31] Araghiniknam M, Chung S, Nelson-White T, et al. Antioxidant activity of dioscorea and dehydroepiandrosterone (DHEA) in older humans. *Life Sci* 1996;59(11):147–57.
- [32] Genazzani AD, Stomati M, Strucchi C, et al. Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women. *Fertil Steril* 2001;76(2):241–8.
- [33] Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol* 2000;14(5):342–63.
- [34] Morales AJ, Haubrich RH, Hwang JY, et al. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol* 1998;49(4):421–32.
- [35] Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 1994;78(6):1360–7.
- [36] Mortola JF, Yen SSC. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metab* 1990;71(3):696–704.
- [37] Young J, Couzinet B, Nahoul K, et al. Panhypopituitarism as a model to study the metabolism of

- dehydroepiandrosterone (DHEA) in humans. *J Clin Endocrinol Metab* 1997;82(8):2578–85.
- [38] Arlt W, Haas J, Callies F, et al. Biotransformation of oral dehydroepiandrosterone in elderly men: significant increase in circulating estrogens. *J Clin Endocrinol Metab* 1999;84(6):2170–6.
- [39] Jones JA, Nguyen A, Straub M, et al. Use of DHEA in a patient with advanced prostate cancer: a case report and review. *Urology* 1997;50(5):784–8.
- [40] Goldberg M. Dehydroepiandrosterone, insulin-like growth factor-I, and prostate cancer. *Ann Intern Med* 1998;129(7):587–8.
- [41] Reiter WJ, Pycha A, Schatzl G, et al. Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. *Urology* 1999;53(3):590–5.
- [42] Reiter WJ, Schatzl G, Mark I, et al. Dehydroepiandrosterone in the treatment of erectile dysfunction in patients with different organic etiologies. *Urol Res* 2001;29(4):278–81.
- [43] Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychological correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151(1):54–61.
- [44] Kleijnen J, Knipschild P. Ginkgo biloba. *Lancet* 1992;340(8828):1136–9.
- [45] Mashour NH, Lin GI, Frishman WH. Herbal medicine for the treatment of cardiovascular disease: clinical considerations. *Arch Intern Med* 1998;158(20):2225–34.
- [46] Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. *JAMA* 1997;278(16):1327–32.
- [47] Sikora R, Sohn MH, Deutz F-J, et al. Ginkgo biloba extract in the therapy of erectile dysfunction [abstract 73]. *J Urol* 1989;141:188A.
- [48] Sikora R, Sohn MH, Engelke B, et al. Randomized placebo-controlled study on the effects of oral treatment with Ginkgo biloba extract in patients with erectile dysfunction [abstract 917]. *J Urol* 1998;159:240A.
- [49] Ang-Lee MK, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* 2001;286(2):208–16.
- [50] Rowin J, Lewis SL. Spontaneous bilateral subdural hematoma associated with chronic Ginkgo biloba ingestion. *Neurology* 1996;46(6):1775–6.
- [51] Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of Ginkgo biloba extract. *N Engl J Med* 1997;336(15):1108.
- [52] Fong KCS, Kinnear PE. Retrobulbar haemorrhage associated with chronic Ginkgo biloba ingestion. *Postgrad Med J* 2003;79:531–2.
- [53] Wong AH, Smith M, Boon HS. Herbal remedies in psychiatric practice. *Arch Gen Psychiatry* 1998;55(11):1033–44.
- [54] Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. *J Sex Marital Ther* 1998;24(2):139–43.
- [55] Balon R. Ginkgo biloba for antidepressant-induced sexual dysfunction? *J Sex Marital Ther* 1999;25(1):1–2.
- [56] Kang BJ, Lee SJ, Kim MD, Cho MJ. A placebo-controlled, double-blind trial of Ginkgo biloba for antidepressant-induced sexual dysfunction. *Hum Psychopharmacol* 2002;17(6):279–84.
- [57] Solomon PR, Adams F, Silver A, et al. Ginkgo for memory enhancement: a randomized controlled trial. *JAMA* 2002;288(7):835–40.
- [58] Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Saf* 2002;25:323–44.
- [59] Cho YK, Sung H, Lee HJ, et al. Long-term intake of Korean red ginseng in HIV-1-infected patients: development of resistance mutation to zidovudine is delayed. *Int Immunopharmacol* 2001;1(7):1295–305.
- [60] Tode T, Kikuchi Y, Hirata J, et al. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. *Int J Gynaecol Obstet* 1999;67(3):169–74.
- [61] Wiklund IK, Mattson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. *Swedish Alternative Medicine Group. Int J Clin Pharmacol Res* 1999;19:89–99.
- [62] Park JD, Lee YH, Kim SI. Ginsenoside Rf2, a new dammarane glycoside from Korean red ginseng (*Panax ginseng*). *Arch Pharm Res* 1998;21(5):615–7.
- [63] Yun Y, Do J, Ko S, et al. Effects of Korean red ginseng and its mixed prescription on the high molecular weight dextran-induced blood stasis in rats and human platelet aggregation. *J Ethnopharmacol* 2001;77(2–3):259–64.
- [64] Sung J, Han KH, Zo JH, et al. Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. *Am J Chin Med* 2000;28(2):205–16.
- [65] Choi YD, Xin ZC, Choi HK. Effect of Korean red ginseng on the rabbit corpus cavernosus smooth muscle. *Int J Impot Res* 1998;10(1):37–43.
- [66] Choi YD, Rha KH, Choi HK. In vitro and in vivo experimental effect of Korean red ginseng on erection. *J Urol* 1999;162(4):1508–11.
- [67] Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. *Int J Impot Res* 1995;7(3):181–6.
- [68] Hong B, Ji YH, Hong JH, et al. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. *J Urol* 2002;168(5):2070–3.
- [69] Chen X, Lee TJ. Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. *Br J Pharmacol* 1995;115(1):15–8.

- [70] Tsang D, Yeung HW, Tso WW, Peck H. Ginseng saponins: influence on neurotransmitter uptake in rat brain synaptosomes. *Planta Med* 1985;3:221–4.
- [71] Price A, Gazewood J. Korean red ginseng effective for treatment of erectile dysfunction. *J Fam Pract* 2003;52(1):20–1.
- [72] Andrade EM, Messina LE, Alarcon G, et al. Korean red ginseng in the treatment of erectile dysfunction: a prospective controlled double-blind clinical trial [abstract 1419]. *J Urol* 2003; 169(Suppl 4):380.
- [73] Goldberg MR, Robertson D. Yohimbine, a pharmacological probe for the study of the alpha2-adrenoreceptor. *Pharmacol Rev* 1983;35(3): 143–80.
- [74] Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. *J Urol* 1998;159(2): 433–6.
- [75] Silverman E. Herbal sex pills thrive on fantasy more than fact. *Newark Star-Ledger*. January 30, 2000.
- [76] Sharlip I. “Herbal sex pills thrive on fantasy more than fact” (headline in the Newark Star-Ledger, January 30, 2000). International Society for Sexual and Impotence Research *newsbulletin*. December 2001;7:17.
- [77] Foster S, Tyler VE. Tyler’s honest herbal. 4th edition. New York: The Haworth Herbal Press; 2000. p. 393–5.
- [78] Briefel RR, Bialostosky K, Kennedy-Stephenson J, McDowell MA, Ervin RB, Wright JD. Zinc intake of the US population: findings from the third National Health and Nutrition Examination Survey, 1988–1994. *J Nutr* 2000;130(Suppl 5S): 1367S–73S.
- [79] Food and Nutrition Board. National Academy of Sciences. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academy Press; 2001. p. 177–204, 351–98.
- [80] Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst* 2003;95(13):1004–7.
- [81] Ishii K, Usui S, Sugimura Y, Yamamoto H, Yoshikawa K, Hirano K. Inhibition of aminopeptidase N (AP-N) and urokinase-type plasminogen activator (uPA) by zinc suppresses the invasion activity in human urological cancer cells. *Biol Pharm Bull* 2001;24:226–30.
- [82] Ishii K, Usui S, Sugimura Y, et al. Aminopeptidase N regulated by zinc in human prostate participates in tumor cell invasion. *Int J Cancer* 2001;92:49–64.
- [83] Iguchi K, Hamatake M, Ishida R, et al. Induction of necrosis by zinc in prostate carcinoma cells and identification of proteins increased in association with this induction. *Eur J Biochem* 1998;253: 766–70.
- [84] Feng P, Liang JY, Li TL, et al. Zinc induces mitochondria apoptogenesis in prostate cells. *Mol Urol* 2000;4:31–6.
- [85] Liang JY, Liu YY, Zou J, Franklin RB, Costello LC, Feng P. Inhibitory effect of zinc on human prostatic carcinoma cell growth. *Prostate* 1999;40: 200–7.
- [86] Zaichick V, Sviridova TV, Zaichick SV. Zinc in the human prostate gland: normal, hyperplastic and cancerous. *Int Urol Nephrol* 1997;29:565–74.
- [87] Nemoto K, Kondo Y, Himeno S, et al. Modulation of telomerase activity by zinc in human prostatic and renal cancer cells. *Biochem Pharmacol* 2000;59:401–5.
- [88] Sommerfeld HJ, Meeker AK, Piatyszek MA, Bova GS, Shay JW, Coffey DS. Telomerase activity: a prevalent marker of malignant human prostate tissue. *Cancer Res* 1996;56:218–22.
- [89] Boissier S, Ferreras M, Peyruchaud O, et al. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. *Cancer Res* 2000; 60:2949–54.
- [90] Hidalgo M, Eckhardt SG. Development of matrix metalloproteinase inhibitors in cancer therapy. *J Natl Cancer Inst* 2001;93(3):178–93.
- [91] Dearnaley DP, Sydes MR, Mason MD, et al. MRC PR05 Collaborators. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst* 2003;95(17):1300–11.
- [92] Saad F, Gleason DM, Murray R, et al. For the Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002; 94(19):1458–68.
- [93] Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor-1 and insulin-like growth factor binding protein 3 concentrations. *Cancer Epidemiol Biomark Prevent* 2002;11:852–61.
- [94] Prasad AS, Mantzoros CS, Beck FW, Hess JW, Brewer GJ. Zinc status and serum testosterone levels of healthy adults. *Nutrition* 1996;12:344–8.
- [95] Lagiou P, Wu J, Trichopoulou A, Hsieh C-C, Adami H-O, Trichopoulos D. Diet and benign prostatic hyperplasia: a study in Greece. *Urology* 1999;54(2):284–90.
- [96] Duzendorfer U, Drahovsky D. C-peptide, testosterone, estrogen, cortisol and zinc in patients with benign prostatic hyperplasia of the prostate. *Urol Int* 1980;35:369–74.
- [97] Wilden EG, Robinson MR. Plasma zinc levels in prostatic disease. *Br J Urol* 1975;47:295–9.
- [98] Tisell LE, Fjelkegard B, Liessner KH. Zinc concentration and content of the dorsal, lateral

- and medial prostatic lobes and of periurethral adenomas in man. *J Urol* 1982;128:403–5.
- [99] Leake A, Chrisholm GD, Busuttill A, et al. Subcellular distribution of zinc in the benign and malignant human prostate: evidence for a direct zinc androgen interaction. *Acta Endocrinol (Copenh)* 1984;105:281–8.
- [100] Feustel A, Wenrich R. Zinc and cadmium in cell fractions of prostatic cancer tissues of different histological grading in comparison to BPH and normal prostate. *Urol Res* 1984;12:147–50.
- [101] Lahtonen R. Zinc and cadmium concentrations in whole tissue and in separated epithelium and stroma from human benign hypertrophic glands. *Prostate* 1985;6:177–83.
- [102] Brys M, Nawrocka AD, Miekos E, et al. Zinc and cadmium analysis in human prostate neoplasms. *Biol Trace Elem Res* 1997;59:145–52.
- [103] Leake A, Chrisholm GD, Habib FK. The effect of zinc on the 5 alpha-reduction of testosterone by the hyperplastic human prostate gland. *J Steroid Biochem* 1984;20:651–5.
- [104] Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000;133:245–52.
- [105] Verma KC, Saini AS, Dhamija SK. Oral zinc sulphate therapy in acne vulgaris: a double-blind trial. *Acta Derm Venereol* 1980;60:337–40.
- [106] Sazawai S, Black RE, Bhan MK, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea—a community-based, double-blind, controlled trial. *Am J Clin Nutr* 1997;66:413–8.
- [107] Humd RW, Wilder BJ, Helveston WR, Uthman BM. Treatment of four siblings with progressive myoclonus epilepsy of the Unverricht-Lundborg type with N-acetylcysteine. *Neurology* 1996;47:1264–8.
- [108] Brewer GJ, Hill GM, Dick RD, Prasad AS, Cossack ZT. Interactions of trace elements: clinical significance. *J Am Coll Nutr* 1985;4(1):33–8.
- [109] El-Youssaef M. Wilson disease. *Mayo Clin Proc* 2003;78(9):1126–36.
- [110] Macknin ML, Piedmonte M, Calendine C, Janosky J, Wald E. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998;279(24):1962–7.
- [111] Irving JA, Mattman A, Lockitch G, Farrell K, Wadsworth LD. Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation. *CMAJ* 2003;169(2):129–31.
- [112] Chandra RK. Excessive intake of zinc impairs immune responses. *JAMA* 1984;252(11):1443–6.
- [113] Samman S, Roberts DC. The effect of zinc supplements on lipoproteins and copper status. *Atherosclerosis* 1988;70:247–52.
- [114] Schrauzer GN, White DA, Schneider CJ. Inhibition of the genesis of spontaneous mammary tumors in C3H mice: effects of selenium and of selenium-antagonistic elements and their possible role in human breast cancer. *Bioinorg Chem* 1976;6:265–70.
- [115] Mahajan SK, Abbasi AA, Prasad AS, et al. Effect of oral zinc therapy on gonadal function in hemodialysis patients. A double-blind study. *Ann Intern Med* 1982;97(3):357–61.
- [116] Brook AC, Johnston DG, Ward MK, et al. Absence of a therapeutic effect of zinc in the sexual dysfunction of haemodialysed patients. *Lancet* 1980;2(8195 pt 1):618–20.
- [117] Mahajan SK. Zinc in kidney disease. *J Am Coll Nutr* 1989;8(4):296–304.
- [118] Bell S, Goldman VM, Bistrrian BR, et al. Effect of beta-glucan from oats and yeast on serum lipids. *Crit Rev Food Sci Nutr* 1999;39(2):189–202.
- [119] Onning G, Wallmark A, Persson M, et al. Consumption of oat milk for 5 weeks lowers serum cholesterol and LDL cholesterol in free-living men with moderate hypercholesterolemia. *Ann Nutr Metab* 1999;43(5):301–9.
- [120] Saltzman E, Das SK, Lichtenstein AH, et al. An oat-containing hypocaloric diet reduces systolic blood pressure and improves lipid profile beyond effects of weight loss in men and women. *J Nutr* 2001;131(5):1465–70.
- [121] Zava DT, Dollbaum CM, Blen M. Estrogen and progesterin bioactivity of food, herbs, and spices. *Proc Soc Exp Biol Med* 1998;217(3):369–78.
- [122] Jensen CD, Haskell W, Whittam JH. Long-term effects of water-soluble dietary fiber in the management of hypercholesterolemia in healthy men and women. *Am J Cardiol* 1997;79(1):34–7.
- [123] Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999;69(1):30–42.
- [124] Anderson JW, Allgood LD, Lawrence A, et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr* 2000;71(2):472–9.
- [125] Moyad MA. Soy, disease prevention, and prostate cancer. *Semin Urol Oncol* 1999;17(2):97–102.
- [126] Dent SB, Peterson CT, Brace LD, et al. Soy protein intake by perimenopausal women does not affect circulating lipids and lipoproteins or coagulation and fibrinolytic factors. *J Nutr* 2001;131(9):2280–7.
- [127] Gerhardt AL, Gallo NB. Full-fat rice bran and oat bran similarly reduce hypercholesterolemia in humans. *J Nutr* 1998;128(5):865–9.
- [128] Yan W, Ohtani K, Kasai R, Yamasaki K. Steroidal saponins from fruits of *Tribulus terrestris*. *Phytochemistry* 1996;42(5):1417–22.

- [129] Bedir E, Khan IA. New steroidal glycosides from the fruits of *Tribulus terrestris*. *J Nat Prod* 2000; 63(12):1699–701.
- [130] Cai L, Wu Y, Zhang J, et al. Steroidal saponins from *Tribulus terrestris*. *Planta Med* 2001;67(2):196–8.
- [131] Adimoelja A. Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunctions. *Int J Androl* 2000; 23(Suppl 2):82–4.
- [132] Acrasoy HB, Erenmemisoglu A, Tekol Y, et al. Effect of *Tribulus terrestris* L. saponin mixture on some smooth muscle preparations: a preliminary study. *Boll Chim Farm* 1998;137(11):473–5.
- [133] Adaikan PG, Gauthaman K, Prasad RN, Ng SC. Proerectile pharmacological effects of *Tribulus terrestris* extract on the rabbit corpus cavernosum. *Ann Acad Med Singapore* 2000;29(1):22–6.
- [134] Antonio J, Uelmen J, Rodriguez R, Earnest C. The effects of *Tribulus terrestris* on body composition and exercise performance in resistance-trained males. *Int J Sport Nutr Exerc Metab* 2000;10(2): 208–15.
- [135] Ito TY, Trant AS, Polan ML. A double-blind placebo-controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. *J Sex Marital Ther* 2001;27(5):541–9.
- [136] Sperling H, Lorenz A, Kregge S, Michel MC. An extract from the bark of the tree *Aspidosperma Quebracho Blanco* inhibits human penile alpha-adrenoceptors [abstract 938]. *J Urol* 2001;165: 227.
- [137] De Young L, Yu D, Freeman D, Brock GB. Effect of PDE5 inhibition combined with free oxygen radical scavenger therapy on erectile function in a diabetic animal model. *Int J Impot Res* 2003;15(5): 347–54.
- [138] Kuan JK, Brock GB. Oral vitamin E and folic acid supplementation during sildenafil therapy for erectile dysfunction improves salvage in non-responders [abstract 1417]. *J Urol* 2003;169(4):379.
- [139] Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention. The Swiss Heart Study: a randomized controlled trial. *JAMA* 2002;288(8):973–9.
- [140] Lebreton T, Herve JM, Gorny P, Worcel M, Botto H. Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction. *Eur Urol* 2002;41(6):608–13.
- [141] Bent S, Xu L, Li-Yung L, et al. A randomized controlled trial of a Chinese herbal remedy to increase energy, memory, sexual function, and quality of life in elderly adults in Beijing, China. *Am J Med* 2003;115:441–7.