Chapter 12
Nutraceuticals for Fertility and Erectile Health: A Brief Overview of What Works and What Is Worthless

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Introduction: Lifestyle Changes Matter

Clinicians should not dismiss the importance of lifestyle changes on overall health and male fertility and sexual function. Most heart unhealthy behaviors also negatively impact almost all other areas of men's health [1], including fertility and erectile health [2, 3]. Thus, improving or encouraging heart healthy changes in patients may improve overall mental and physical health [4], which could provide the optimum scenario to enhance any specific conventional medical options.

Heart healthy recommendations are also arguably the most logical and practical suggestions that simultaneously can also improve quality and perhaps quantity of life for patients across a broad spectrum of specialties [5]. It should be remembered and reiterated that cardiovascular disease (CVD) is the number 1 overall cause of mortality in the USA and in other industrialized countries [6, 7]. CVD is currently the number 1 cause of death worldwide, and is the number 1 cause of death in virtually every region of the world. Cancer is the second leading cause of death in the USA and in most developed countries, and is expected to potentially mirror the number of deaths from CVD in the next several years in various regions of the world.

If cancer becomes the primary cause of mortality, the majority of what is known concerning lifestyle and dietary change for CVD prevention directly appears to apply to cancer prevention [2, 5]. Heart healthy changes are tantamount to overall urologic health improvements regardless of the part of the human anatomy that is receiving focus, including the bladder, kidney, penis, testicles, or prostate. Heart healthy changes need to be advocated in urology clinics because it places probability and the research into perspective.

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If multiple lifestyle changes, or if achieving numerous healthy parameters over time appears to be strongly correlated with some of the largest improvements in health then this theory should have arguably been well tested. And it has been tested over the years and the results are profound and exemplary. For example, data from the National Health and Nutrition Examination Survey (NHANES) was utilized that included 44,959 US adults 20 years of age or older [8]. Mean age was 46–47 years and approximately half of the participants were women. Median follow-up was 14.5 years. A total of only 1–2 % of the participants met all seven of the health parameters. There was a remarkable 51 % reduction in all-cause mortality, 76 % reduction in cardiovascular mortality, and 70 % reduction in ischemic heart disease (IHD) mortality for participants meeting six or more metrics compared to one or fewer. Achieving a higher number of cardiovascular health parameters also appeared to be correlated with a lower risk for all-cancer mortality. These seven basic goals/parameters only achieved by 1–2 % of Americans are listed in Table 12.1.

Reviewing the impact of obesity, high cholesterol, blood pressure and glucose, lack of exercise, improper diet, tobacco use and other potential overall and specific health contributors such as stress and depression, which individually or combined can increase oxidative stress all have some minor or major impact on fertility and erectile health. This is arguably the most holistic approach to changing patient lives and improving overall outcomes [2, 3, 9, 10]. In other words, it is the ultimate two for one beneficial impact on your patients.

Applying comprehensive heart healthy lifestyle data to determine its true objective efficacy in urologic health may not appear to be simple, but in reality it is not difficult. When discussed with patients the observations from this research is quite profound throughout urology. For example, a unique 2-year randomized trial from Italy of vigorous aerobic exercise and diet to improve erectile dysfunction (ED) should have received more clinical attention [11, 12]. It still should change the way health care professionals treat men with ED. A total of 110 obese men (body mass index or BMI of 36–37 = morbidly obese) with ED, waist-to-hip ratio (WHR) of 1.01–1.02, age 43 years, erectile dysfunction score 13–14 out of 25 (IIEF), and without diabetes, high cholesterol, or hypertension were included. A total of 55 men were randomized to an aggressive intervention group that involved caloric restriction and increased physical activity via personalized dietary counseling (Mediterranean-style diet), and regular appointments with a personal trainer. Another group of 55 men were in the control group and were given general educational information about exercise and healthy food choices. After 2 years, the BMI significantly decreased on average from 36.9 to 31.2 in the intervention group, and serum levels of interleukin-6 and C-reactive protein also decreased significantly. The average physical activity level increased significantly from 48 to 195 min per week in the intervention group, and the mean erectile function score increased significantly from 13.9 to 17. A total of 17 men in the intervention group actually reported an erectile score of 22 or higher (normal function). Several changes were independently and significantly correlated with a higher rate of improved erections including a lower BMI or BMI reduction, increased physical

Table 12.1 Seven steps for improved overall, reproductive, and erectile health that only 1–2 % of the US population has been able to achieve

1. Avoiding all tobacco products
2. BMI 25 or less
3. Being physically active almost every day of the week
4. Overall diet that is heart healthy (fruits/veggies/fiber/fish...)
5. Total cholesterol equal to or less than 200 mg/dl[a]
6. Blood pressure equal to or less than 120/80
7. Fasting blood glucose less than 100 mg/dl

[a]An exception is the fact that an unusually high HDL could lead to high total cholesterol, regardless of the fact that an LDL less than 100 mg/dl is another target in these individuals

activity, and a lower C-reactive protein levels. Again, approximately 33 % of the men in this study with E.D. regained normal erectile function after 2 years of following healthy behaviors primarily from exercise, weight reduction, caloric control, and healthy dietary changes. Although a major limitation of this trial was the lack of analysis on psychological factors and social intervention, these lifestyle changes could have improved mood, self-esteem, and reduced depression, and this could have also been a reason for improved erectile function. Still, the combined healthy changes in the intervention group that occurred after 2 years were notable, diverse, and included the following heart healthy and urologic healthy parameters:

- Total caloric reduction of −390 cal per day (2,340–1,950)
- Complex carbohydrate increase and simple sugar reduction
- Fiber consumption increased by 10 g a day (15–25)
- Protein consumption increased significantly (13–16 % of caloric intake)
- No change in the overall percentage of fat in the diet (30 % of calories), but a reduction in saturated fat (14–9 %) and an increased intake in monounsaturated fat (9–14 %)
- Ratios of omega-6 to omega-3 fatty acids was reduced by half (12–6)
- Cholesterol was reduced from dietary sources by 84 mg per day (360–276)
- Exercise time (mainly walking) increased from about 7 min per day to almost 30 min per day
- Average weight loss was 33 lb (226.6–193.6)
- Average BMI decreased by almost 6 points (36.9–31.2)
- WHR decreased by 0.09 (1.02–0.93)
- Erectile function scores increased by 3 points (13.9–17 points)
- Systolic (127–124 mmHg) and diastolic (86–82 mmHg) blood pressure decreased by 3–4 points
- Total cholesterol decreased by 11 mg/dl (213–202), but HDL (good cholesterol) increased by 9 points (39–48 mg/dl)
- Triglycerides decreased by 19 mg/dl (169–150)
- Glucose decreased by 8 mg/dl (103–95) and insulin level also decreased by 7 points (21–14 μU/ml)

– C-reactive protein (CRP) was reduced by1.4 mg/L (3.3–1.9)
– Interleukin 6 was reduced by 1.4 pg/ml (4.5–3.1)
– Interleukin-8 (IL-8, another inflammatory marker) was reduced by 1.2 pg/ml (5.3–4.1)

Additionally, how many more laboratory, cross-sectional, or prospective studies are needed in the area of heart healthy interventions and the potential for improved fertility [13–15], before these recommendations become a part of clinical urologic guidelines? Heart health is tantamount to improved probability of male fertility and erectile health, and this is the theme of this chapter, which includes primarily nutraceutical recommendations.

In addition, clinicians need to keep in mind that lifestyle changes can immediately increase nutrient levels before supplementation with an antioxidant pill is recommended because obesity, substance abuse, insulin resistance, and other heart unhealthy changes accelerate the depletion or dilution of a variety of antioxidants in the serum not only in adults but also in adolescents [2, 16, 17]. For example, there is plenty of discourse of vitamin D supplementation for overall health but there appears to be little discourse on weight loss as a "natural" way to significantly increase serum vitamin D levels without additional supplementation. Lifestyle changes and minimal supplement dosages are more logical, practical, safe, and heart healthy compared to high doses of antioxidants from pills and no lifestyle alterations. In other words, patients that adhere to heart healthy parameters have the highest chance of success in my opinion in combination with conventional medicine as needed. In other words, lifestyle matters!

Nutraceuticals/Dietary Supplements: Fertility

There is a consistent suggestion that up to 80 % of male factor subfertility cases are believed to be the result of "oxidative stress" [18]. Perhaps some of the strongest evidence to espouse the use of dietary supplements for male infertility has been published. A Cochrane Systematic review was arguably one of the most extensive ever published in male fertility and dietary supplements, as it reviewed 34 randomized clinical trials with 2,876 couples in total [19]. Studies used in this analysis were for couples undergoing assisted reproduction technologies (ART), for example in vitro fertilization (IVF), intrauterine insemination (IUI), or intracyclic sperm injection (ICSI). The inclusion criteria were randomized controlled trials that included men as part of a couple with unexplained subfertility or subfertility that were using ART with their own gametes. Trials were excluded in there were non-randomized, included men taking any other fertility-enhancing medications, or men that had used chemotherapy treatment. The primary outcome was the live birth rate per couple randomized. And there were multiple secondary outcomes:

– Pregnancy rate per couple
– Miscarriage rate per couple or spontaneous abortion

- Stillbirth rate per couple
- Level of sperm DNA damage after treatment
- Sperm concentration and sperm motility
- Adverse effects associated with dietary supplements and withdrawals

The overall findings continue to surprise a number of health care professionals and patients, in my opinion, by concluding that antioxidant supplementation in males appears to have a positive role in improving the outcomes of live birth and pregnancy rates in couples participating in ART [19]. In fact, for live births the *p*-value was 0.0008 and for pregnancy rates it was $p < 0.00001$. Critics of this analysis on "live births" will arguably point toward the small number of such events, 20 live births that occurred from a total of 214 couples in only three studies that was used in this part of the analysis, or the "pregnancy rates," which actually was derived from 96 pregnancies in 15 trials that included 964 couples. However, it is still interesting that this is a viable minimal or moderate option for some men given the low cost of most "antioxidants" utilized in these studies. Additionally, acute side effects were similar to a placebo with no serious adverse events reported in any trial.

The common question that will result from this or any other positive analysis for male fertility and antioxidants is which specific nutraceuticals and at what dosage and frequency? Interestingly, this Cochrane review could not identify one specific antioxidant or combination product from these trials [5], so readers and patients are left with multiple questions. Thus, a summary of antioxidant supplements used in past well-designed placebo-controlled trials is needed with an overall cost, safety, and health perspective to determine which products should be recommended and perhaps avoided by patients. This was a primary weakness of the Cochrane review and other reviews in male fertility [19], which is the overall lack of specific recommendations based on overall safety and efficacy of these agents long-term for overall health and fertility maintenance. This chapter will attempt to provide clarity on this issue of which supplements to recommend or avoid based on heart healthy and overall heath sensitivity and recommendations. And the specific end-points of past studies matter so that clinicians need to constantly ask themselves in which of the following areas does this supplement impact:

- Oxidative stress reduction/markers
- Total Sperm Number
- Sperm concentration
- Sperm morphology
- Sperm motility (% motility and/or forward progression)
- Pregnancy rate
- Live births
- Short and long-term safety
- Miscellaneous (ejaculate volume, pH, viscosity, sperm agglutination, other parameters...)

The impact on pregnancy and live birth rates along with overall safety are the more important variables and are in need of more results in these areas for all of the dietary supplements mentioned in this chapter. And it is also of interest that if some supplements may improve male infertility when dealing with ART then it may impact those with motility issues (asthenospermia) or idiopathic oligoasthenoteratozoospermia (OAT) because of the overlap in those that use ART and men with this condition.

First Do No Harm Specific Supplementation for Infertility

Coenzyme Q10 (CoQ10, Also Known as "Ubiquinone")

CoQ10 appears to be a safe dietary supplement that requires a low and realistic dose for male fertility preservation. CoQ10 (also known as "ubiquinone") supplements have a consistent overall safety profile, and actually have some clinical data to suggest that they may reduce blood pressure, but primarily in those with some form of hypertension, and these supplements might have some role in reducing myalgia from statin therapy [20, 21], but these results have been inconsistent yet still at least proven to be safe at a variety of dosages [22]. The role of CoQ10 in the respiratory pathway as a method to improve energy production and reduce oxidative stress has been well known in basic human physiology. It is for this reason that there is interest in utilizing this dietary supplement for oxidative stress reduction.

Seminal fluid also contains a measurable quantity of CoQ10 that appear to be correlated with sperm count and motility. Patients with idiopathic asthenozoospermia may benefit in terms of spermatozoa motility when consuming 200 mg per day of CoQ10 for 6 months [23]. Another study of 212 infertile men taking 300 mg over 26-weeks found significant improvements in multiple parameters including sperm density, motility, and acrosome reaction [24]. Serum levels of FSH and LH were significantly reduced. However, in a randomized trial of men with oligoasthenoteratozoospermia at a dosage of 200 mg per day compared to placebo, it appeared to reduce markers of oxidative stress but did not demonstrate significant impacts on sperm concentration, motility, and morphology [25].

CoQ10 can be a costly nutraceutical so patients should compare prices from multiple commercial resources to determine the most cost effective product. I have not observed profound differences in clinical effects with low cost compared to high cost CoQ10 products. CoQ10 appears to be a heart healthy or safe supplement [20], except it does have the rare potential to reduce the impact of warfarin because of vitamin K-like properties [26], but ironically its minimal anti-platelet effects may increase bleeding when combined with aspirin or clopidogrel. Regardless, it is a supplement that could be encouraged for fertility improvement in most men at a dosage of 200–300 mg per day for a trial period of 3–6 months.

The biggest reservation about CoQ10 is not adverse effects, or locating a low cost product, but its true efficacy over time. This is due to the initial promise and then slight to moderate disappointment in this product in other areas of medicine. For example, the impact on statin induced myalgia reduction was interesting initially [21], but is not an absolute solution today [22], and this is also true for this product in terms of its antihypertensive [27] and Parkinson's disease research [28]. In other words, the excitement and hype on this supplement was initially tremendous, but more rigorous trials in other areas of medicine have proven adequate consistent safety but efficacy was disappointing. For example, the National Institute of Neurological Disorders and Stroke (NINDS) stopped the QE3 phase 3 study of CoQ10 for the treatment of early stage Parkinson's disease, acting on the recommendation of the study's safety board [28]. An interim analysis showed minimal likelihood of benefit at dosages of 1,200 and 2,400 mg per day for up to 16 months. All subjects also received vitamin E at a dosage of 1,200 IU per day. The study enrolled 600 patients at 67 clinical trial sites and the reason CoQ10 was utilized was due to the close association of oxidative stress and mitochondrial dysfunction as contributors to Parkinson's disease and some past positive data from a Cochrane Database of Systematic Review of four randomized past trials [29], so CoQ10 became a logical treatment choice. This is somewhat similar to the theory and origins of utilizing CoQ10 to improve fertility parameters [30]. Still, the benefit outweighs the risk, so it should be a part of the current dietary supplement discussion for men with subfertility.

L-Carnitine

The story of L-carnitine for male fertility arguably mirrors that for CoQ10 in terms of initial excitement, safety and then some controversy over the lack of impact in other areas of medicine. L-Carnitine is a potential amino acid dietary supplement for male fertility, but large dosages may be needed, and it is not a low cost product. L-Carnitine transports fatty acids from the cytosol to the mitochondria for energy production in each cell of the body [31], which is arguably why there has always been interest in this compound. Humans can produce carnitine de novo in the liver from lysine and methionine (25 %), but dietary intake is the primary source of carnitine (75 %). Foods high in carnitine include dairy and meat and a plant-based diet is in general a poor source of carnitine. Excretion of carnitine occurs from the kidneys, but reabsorption is also efficient so that vegans are still able to maintain close to normal blood levels of this amino acid despite only 10 % or less the consumption of carnitine compared to omnivores.

L-Carnitine had preliminary research that it may slightly reduce fatigue in some cancer patients in higher dosages, but a phase 3 trial demonstrated 2,000 mg per day worked no better than placebo for this specific situation over a 4-week testing period [32]. Even subset analysis revealed that those individuals that had lower blood levels of carnitine at baseline experienced no benefit. The future of L-

carnitine in terms of energy production for patients with fatigue is now questionable, but there is still adequate data in other areas of medicine, for example, the ability of this product to increase the body weight or nutritional status of high-risk cachetic patients [33], improve peripheral artery disease [34], and the impact of this supplement on male fertility—primarily motility [31].

It is of interest that vitamin C (ascorbic acid) is needed to synthesize carnitine in the human body [31]. The highest concentration of carnitine apart from supplements occurs in red meat and dairy products so vegetarians that are trying to maintain fertility would potentially be better candidates for this supplement. There are several minimally different forms of L-carnitine available for purchase utilized in clinical trials including L-carnitine, acetyl-L-carnitine (ALC), and propionyl-L-carnitine (PLC). These other types of L-carnitine have been tested because L-carnitine itself tends to be unstable. Yet these other forms of L-carnitine do not necessarily have better fertility data, especially when compared to each other at 3,000 mg per day [35], and are more costly for the patient. Some clinical trials have suggested that the combination of these supplements may improve motility [36], but again this is not my interpretation from these same studies with similar authors [36, 37]. Thus, multiple clinical trials have demonstrated the ability of L-carnitine, or other forms of carnitine to improve primarily sperm motility and potentially pregnancy rates [35–43]. Yet there has been inconsistent or minimal evidence that it can impact sperm concentration and morphology. A small US randomized, double-blind placebo-controlled study in men with idiopathic asthenospermia has challenged the potentially positive results with carnitine [44]. Male patients with sperm motility of 10–50 % were utilized and over 24 weeks 2,000 mg of L-carnitine and 1,000 mg of L-acetyl-carnitine per day were ingested compared to placebo ($n = 12$ vs. $n = 9$). No significant differences in motility or total motile sperm counts occurred at 12 or 24 weeks. These researchers called into question the clinical significance of the effect of L-carnitine for infertile men, but in terms of objectivity their trial was well executed but the small number of participants was a methodological limitation. They also reviewed past studies and suggested several methodology issues such as exclusion of some patients from final analysis as an issue [37], and also found carnitine to cause statistical significance in the past, but the clinical significance of the results are questionable. Another concern is lack of improvement in seminal plasma or sperm carnitine levels following supplementation [37, 44], which could be the result of adequate baseline levels or simply no ability to improve these concentrations with these supplements [44]. After this critical publication a systematic review of nine clinical trials was published by independent researchers on the impact of L-carnitine for male infertility [45], and thus far a significant improvement in pregnancy rates ($p < 0.0001$), total and forward sperm motility ($p = 0.04$), and atypical sperms cell ($p < 0.00001$), but no impact was found for sperm concentration or semen volume. Therefore, again clinicians and patients are left to decide on this controversial supplement. L-Carnitine causes an unpredictable change or minimal to moderate increase in sperm motility without a consistent change in sperm morphology and concentration or increase in seminal plasma carnitine levels, but there

is a potential increase in pregnancy without any current consistent safety issues. Is this adequate to endorse the utilization of high doses of carnitine for male infertility? It should not be endorsed for preventive measures to preserve fertility, but its other features (especially safety) make it a controversial option at least.

Adverse events using L-carnitine or serious drug interactions have not been identified. Yet a recent concern over L-carnitine utilization by potentially heart disease producing flora received attention [46], but so did a meta-analysis demonstrating a lower risk of cardiovascular events with L-carnitine from secondary prevention studies [47]. Another recent phase 3 trial in cancer to reduce chemotherapy induced neuropathy actually found an increase in neuropathy with this supplement at 3,000 mg per day [48]. Therefore, the controversy of whether or not this supplement could be beneficial will continue. I am not that concerned about toxicity in healthy patients but similar to CoQ10 the question of whether or not it can improve fertility parameters is open.

Doses of 2–4 g (2,000–4,000 mg per day, divided doses two to three times a day) on average have been used in clinical trials. L-Carnitine or acetyl-L-carnitine or a combination of both was used in these past studies. There was no commentary as to whether L-carnitine was ingested with or without a meal so it seems there is flexibility in regard to this issue.

Omega-3 Fatty Acids

Omega-3 supplements appear to also mirror the previous description with CoQ10 and carnitine due to the initial hype and now the lack of efficacy in other prominent areas of medicine. Additionally, omega-3 supplements simply lack sufficient clinical data in infertility to be recommended at this time. Therefore, recommending dietary sources of omega-3 compounds containing high quantities of EPA and DHA (principal marine sources of omega-3) should be encouraged in most individuals but not individual supplementation. There are numerous marine or fish sources that contain high levels of omega-3 fatty acids, vitamin D, and protein including salmon, tuna, sardines, and a variety of other baked, broiled, raw, but not fried fish are potentially beneficial [49]. Variety should be encouraged to increase compliance and exposure. The benefit of fish consumption to potentially reduce CVD is encouraging from past studies [50] or utilizing fish oil consumption in patients with a history of heart disease has good safety and some positive data [51, 52]. Still, the overall and most up to date clinical trial data with fish oil supplementation on primary endpoints in cardiovascular medicine has been minimal to controversial and more recently discouraging [53], and in otherwise healthy individuals it is not currently espoused [54]. In fact, during the submission of this chapter, arguably the most rigorous primary prevention trial in cardiovascular medicine thus far found no safety issues, but no impact on primary or secondary endpoints with 1,000 mg per day of omega-3 supplementation in a randomized trial of over 12,500 patients and a median follow-up of 5 years [55]. And in arguably the

longest and most methodologically rigorous clinical trials of omega-3 supplements to reduce the progression of macular degeneration (AREDS2 trial), no benefit was observed with 1,000 mg per day of fish oil with a median follow-up of 5 years [56]. Thus, fish oils supplements should probably be reserved for patients with high triglycerides [49], where they are FDA approved for this purpose.

The data on fish oil for male subfertility is minimal and controversial because of insufficient data. For example, a randomized trial of DHA at 400 or 800 mg per day compared to placebo over 3 months for 28 asthenozoospermic (50 % or less motility) men appeared to increase serum and potentially seminal plasma DHA levels, but without impacting DHA into the spermatozoa phospholipid, which may have explained why it did not impact sperm motility compared to placebo [57]. A later trial of men with idiopathic oligoasthenoteratospermia (OAT) randomized to 1,840 mg of total omega-3 (EPA and DHA) product compared to placebo over 32 weeks found a significant increase in sperm count, concentration, morphology, and motility, which may have been associated with the reductions in markers of oxidative stress in men with low omega-3 fatty acid levels [58]. Several cases of reflux, itching and diarrhea occurred in the omega-3 group, which are known rare side effects of these supplements [49]. Again, until more research is conducted taking one to two omega-3 supplements that equates to 1,000–1,840 mg of EPA and DHA daily could be of some benefit, but this is speculative based on this one clinical trial.

Regardless, dietary sources of healthy fish can be encouraged. Mercury concentrations in specific fish have been reported by the Food and Drug Administration (FDA) and in the overall medical literature, but the preliminary data is controversial and it is not known at this time what kind of clinical impact these mercury levels may have on the individual [49]. Four types of larger predatory fish have been most concerning because these fish (king mackerel, shark, swordfish, and tilefish) have the ability to retain greater amounts of methyl-mercury. Moderate consumption (two to three times per week) of most fish should have minimal impact on overall human mercury serum levels, but more ongoing research in this area should soon provide better clarity. The positive impact of consuming fish seems to outweigh the negative impact in the majority of individuals with the exception of women considering pregnancy or who are pregnant. Table 12.2 is a summary of a variety of fish that have consistently demonstrated low levels of mercury, and this table should also teach patients that a variety of fish and shellfish are healthy [49]. It should be kept in mind that approximately two servings per week of fatty oily low mercury fish is the equivalent to approximately ingesting one 250–500 mg fish oil pill per day. Clinicians that still desire to recommend high-dosages of fish oil supplements must keep in mind that these supplements could increase the risk of internal bleeding at higher dosages and especially in combination with other blood thinners. Although the risk of bleeding events is extremely rare, it has been observed in some clinical trials of healthy individuals and in combination with statins at a dosage of only 1,800 mg per day [52].

It is interesting that low cost small and short lived fish such as anchovies and sardines are low in mercury, and have some of the highest levels of omega-3 oils,

Table 12.2 Seafood with some omega-3 fatty acids demonstrating minimal levels of mercury

Anchovies
Catfish
Cod
Crab
Flounder/sole
Haddock
Herring
Lobster
Mahi-mahi
Ocean perch
Oysters
Rainbow trout
Salmon (farmed and wild)
Sardines
Scallops
Shrimp
Spiny lobster
Tilapia
Trout (farmed)
White fish (Great Lakes)

and are used primarily more than any other fish in the manufacturing of fish oil pills to be utilized by the public and in many clinical trials [49]. Patients that cannot eat fish or do not want to utilize fish oil because of an allergy or a personal belief could be recommended algae based omega-3 oils or regularly consume the largest plant based source of omega-3 fatty acids which are found in plant oils (canola and soy), flaxseed, and chia seed.

*Tonkat Ali (*Eurycoma longifolia*)*

This is an extract derived from a plant or a common shrub found along the slopes of hilly areas in the Malaysian rainforest. It has preliminary human data that shows it could improve various aspects of male health including sex drive, increase testosterone in men with age-related androgen deficiency, and especially improve sperm quality and quantity at 200–300 mg a day [59–61].

Multiple laboratory studies have shown an ability of this herbal product to potentially improve male fertility status [62–65], and there is a history of using this product in Malaysia and other nearby locations to enhance fertility and male sexual health. An open label study involved 75 men with idiopathic infertility that utilized the supplement at 200 mg daily for at least the first 3 months [61]. Significant improvement in all semen parameters occurred and 11 (14.7 %) spontaneous pregnancies occurred. However, multiple methodological issues still need to be resolved in a placebo-controlled trial. For example, the authors claims that 350 men started the trial and only 75 completed one full cycle of supplementation (3 months)

and fulfilled the inclusion criteria, but only 17 men completed all 9 months of supplementation, which is an concerning exclusion and/or non-compliance rate that needs further investigation. The authors also point toward the possibility of a "bioactive peptide" that can increase testosterone levels in animals and humans, and may reduce oxidative stress.

The product that has the most research and only one with real clinical data is the standardized water-soluble extract (Physta) of *Eurycoma longifolia* root from the company Biotropics Malaysia Berhad, Kuala Lumpur, Malaysia. The company has also financially supported most of these studies. Their proprietary standardized water-soluble extract from the root of the plant and other Tongkat Ali studies show that this root has multiple diverse ingredients such as [59–66]:

- Tannins
- High-molecular-weight polysaccharides
- Glycoproteins mucopolysaccharides
- Quassinoid alkaloids
- Amino acid isoleucine
- Calcium, magnesium, and potassium

It is theorized to also benefit in the area of male health via pro-hormone effect or DHEA mimic (yet DHEA supplementation has not been adequately researched for its impact on male fertility), or perhaps it is acting more like a diverse multivitamin for men to increase energy levels and slightly enhancing testosterone production in men and women via SHBG reduction or via some unrecognized pathway [67]. It could be that this product is no better than a really low cost source or another supplement of Tongkat Ali, but the problem is that other brands or just generic Tongkat Ali does not have adequate clinical trials or quality control testing (for lead, arsenic. . .). Therefore, Tongkat Ali does not have enough clinical evidence to recommend its use in men with idiopathic infertility but few herbal supplements have even received adequate laboratory and clinical testing in this area with quality control and standardization measures. Thus, it could be utilized for a trial period if other less costly products appear not to be efficacious.

Vitamin C

There is enough indirect information and long-term safety of vitamin C that this is a supplement may have a small role in improving male subfertility [19]. Some positive preliminary data exists for improving fertility in men consuming 200–1,000 mg of vitamin C supplements per day in combination with other antioxidants [19]. Whether or not vitamin C alone can perform as well as the combination supplement treatments is not adequately known. Vitamin C utilization for potentially improving male fertility has a history, but a lack of adequate placebo controlled trials [68, 69]. One small placebo controlled trial of vitamin C (1,000 mg) in combination with high-dose vitamin E (800 mg) for 31 patients

with asthenospermia showed no difference compared to placebo for 56 days and no pregnancies [70]. Interestingly, prolonged abstinence increased sperm count, concentration, total number of motile spermatozoa, and ejaculate volume. This highlights the difficulty in identifying what is working to improve fertility in some of these antioxidant studies.

Vitamin C supplementation improves seminal plasma vitamin C in nonsmokers and smokers and could be correlated with improved morphology [71–73]. Seminal plasma has concentrations of vitamin C that are several orders of magnitude higher than that found in the bloodstream. Smoking has the ability to profoundly reduce vitamin C concentration [74]. A placebo controlled trial of smokers found improvements in sperm quality at 200 and 1,000 mg per day [75]. Therefore, in smokers, ex-smokers or those that have recently quit or are on smoking cessation regimens and trying to improve subfertility, including vitamin C supplementation up to 1,000 mg per day seems logical. Whether or not it is needed outside of this population is debatable. Perhaps, this is why there was also such early interest in vitamin C years ago as opposed to recently because such a large percentage of the population was smokers. It is also possible that the low cost of this supplement does not lead to much industry support for this product and fertility. Regardless of the reason it still seems appropriate for all patients to be encouraged to eat a healthy diet high in vitamin C.

Some of the best dietary sources of vitamin C are listed in Table 12.3 [49, 76], but keep in one should be careful about getting an excessive amount of calories from them. Regardless, being able to achieve vitamin C concentrations from diet that are similar to the dosage utilized in clinical trials of supplementation is simply unrealistic. Still, a combination of regular vitamin C intake from food and daily dietary supplementation may be one of the best methods of maintaining adequate ascorbic acid and antioxidant blood levels that could improve fertility.

There is some relevant concern about oxalate increases with large dosages of plain vitamin C supplements (1,000 mg and higher) over many years, especially in those with a history of oxalate stones. Recently, this concern has been escalated in a large prospective study of men (COSM or Cohort of Swedish Men) utilizing high dosages (1,000 mg or more) of plain vitamin C over an 11-year follow-up period [77]. There were 436 first incident stone cases, and ascorbic acid was associated with a statistically significant twofold increased risk. This would equate to one new kidney stone per 680 high-dose users per year [78].

If this concern is accurate, low cost buffered vitamin C or calcium ascorbate may be a safer alternative for these specific patients [79], but this also needs more research. The most practical criticism or real concern I hear from colleagues today about vitamin C is also relevant, which is sperm spends minimal time in seminal secretions before ejaculation. Thus, any true DNA injury would occur before entry in the seminal vesicle and ejaculatory ducts. In other words, vitamin C is more of a protective antioxidant after ejaculation and during transit time in the female reproductive tract. Still, overall, the safety of vitamin C at dosages of 200–1,000 mg maximum on general health is adequate [49], and arguably as adequate as any supplement mentioned in this chapter. And the negative effects of tobacco and

Table 12.3 Sources of vitamin C (foods and beverages)

Fruit	*Portion size*	*Vitamin C amount (in mg)*
Guava	1 (medium)	100
Strawberries	1 cup	95
Papaya	1 cup	85
Kiwi	1 (medium)	75
Orange	1 (medium)	70
Cantaloupe	¼ (medium)	60
Mango	1 cup	45
Cantaloupe melon	1 cup	40
Grapefruit	½ fruit	40
Honeydew melon	1/8 (medium)	40
Lemon	1 (medium)	40
Tangerines or tangelos	1 (medium)	25
Watermelon	1 cup	15
Apple	1 (medium)	10
Avocado	1 (medium)	10
Apricot	1 (medium)	10
Banana	1 (medium)	10
Blueberry	1 cup	10
Crabapple	1 (medium)	10
Grape	1 cup	10
Pawpaw	1 (medium)	10
Pineapple	1 cup	10
Plum	1 (medium)	10
Juice	*Portion size*	*Vitamin C amount (in mg)*
Grape juice	½ cup	120
Apple juice	½ cup	50
Orange (fortified) juice	½ cup	50
Cranberry juice	½ cup	45
Grapefruit juice	½ cup	35
Tomato juice	6 oz	35
Vegetables	*Portion size*	*Vitamin c amount (in mg)*
Pepper (raw red or green)	½ cup	65
Broccoli (cooked)	½ cup	60
Kale (cooked)	1 cup	55
Brussels sprouts (cooked)	½ cup	50
Snow peas (fresh cooked)	½ cup	40
Mustard greens (cooked)	1 cup	35
Potato (sweet or regular baked)	1 (medium)	25–30
Cauliflower (raw or cooked)	½ cup	25
Cabbage (red, raw to cooked)	½ cup	20–25
Plantains (sliced and cooked)	1 cup	15
Tomato (raw)	½ cup	15
Cabbage (raw to cooked)	½ cup	10–15
Asparagus (cooked)	½ cup	10

its relationship to vitamin C levels again make this ideal group to at least consider vitamin C supplementation.

Combination Products

Proxeed (Sigma-Tau) is a popular combination dietary supplement for male infertility in some countries, and in my opinion, appears to have no unsafe amounts of any ingredients. It is a combination of L-carnitine (145 mg), acetyl-L-carnitine (64 mg), fructose (250 mg), citric acid (50 mg), selenium (50 μg), coenzyme Q10 (20 mg), zinc (10 mg), vitamin C (90 mg), B12 (1.5 μg), and folic acid (200 μg) given once a day [80]. In an open trial of 114 men with idiopathic asthenoteratozoospermia (96 men completing the trial) for at least 18 months, the mean sperm progressive motility significantly increased from 18.3 to 42.1 and 16 patients "achieved pregnancy." No significant improvement was noted for sperm density and the rate of morphologically normal forms. Whether or not it works the same, better, or worse compared to other less costly supplements mentioned in this chapter is not known. It will be difficult to get clarity from this anytime soon because these comparison trials are not only lacking, but I cannot visualize how the manufacturers of these products will ever be motivated to conduct such head to head studies. Of course they would be welcomed and provide a unique perspective but personally I am not optimistic these will occur. Currently, it would make sense to follow the plethora of the data and I could argue that the lower cost individual or combined supplements for a trial period is completely logical and if not effective then switching to a more commercial combination product would be the next step. I believe the one advantage to these commercial combination products used by health care professionals is quality control, but the downside is cost and lack of impressive research beyond what has already been potentially observed with other antioxidants.

I could further argue that the simplest compounds used in most studies do not have concerning quality control issues overall. Part of the reason for this is that no herbal products (more notorious for quality control because of the need for standardization) are utilized to any extent in past studies and only single ingredient vitamins, minerals and other simplistic compounds. The only recent exception to this list is *Eurycoma longifolia* (Tonkat Ali). Why not just encourage the use of a daily multivitamin, which has good long-term safety data in men and is heart healthy, safe, and may provide caner preventive impacts when only one pill is used per day [81, 82], and also some minimal infertility data [83]. These unanswered, but logical approaches are for clinicians and their patients to decide.

First Do No Harm: Potentially Harmful Supplementation for Infertility

Folic Acid/Vitamin B9 (High Dose)

Folic acid is not an ideal antioxidant for male fertility in my opinion, and should not be used at this time in certain patients, for example those with a personal history or strong family history of cancer, especially prostate cancer. Folate is a water-soluble B-vitamin, which is also known as vitamin "B9," and it occurs naturally in many healthy foods and multiple diverse beverages and foods [84]. Folic acid is the synthetic, human-produced, or manufactured form of folate that is found in dietary supplements and added to a variety of grain products, which are also known as "fortified foods." Folate from foods and folic acid both assist in the production of DNA, RNA, and other items that are critical for the production and maintenance of cells, especially ones involved in rapid cell division and growth such as in pregnancy and infancy [85]. Humans of all ages need folate to produce normal red blood cells and to prevent macrocytic anemia. Folate is also critical for metabolizing an amino acid known as "homocysteine," which may cause cellular damage in abnormally high amounts and is important for the synthesis of methionine. Folate has diverse roles in the development of a human being, which is why this compound is probably best known for preventing neural tube defects (NTDs) [84].

Green leafy vegetables, fruits, legumes and peas are just some of the natural sources of folate. Still, due to the vital role of folate in the prevention of NTDs, the Food and Drug Administration (FDA) required the addition of folic acid to grain products such as breads, cereals, corn, flours, meals, pastas, and rice. In 1998, the USA and Canada officially began fortifying grain products with folic acid [84]. The recommended daily allowance (RDA) is only 400 μg a day [86]. Table 12.4 is a partial listing of food and other sources of folate and folic acid in order of highest to lowest concentrations [86]. It is important to keep in mind that folic acid is generally added to foods that are labeled "enriched" and/or "fortified" in the USA and other countries. It is for this reason it is easy to find recommended daily allowances of folate for example on many breakfast cereals.

Synthetic folic acid was believed to be more bioavailable compared to folate from food, which may have been one of the many reasons to fortify foods around the world, along with the fact that a deficiency of folate in women of reproductive age can have detrimental consequences. Research has now suggested that folate from foods may be only slightly less absorbable (approximately 20 %) compared to what was previously believed [87].

Critical issues with the overall safety and impact of folic acid on male health now exist. A meta-analysis of the randomized trial data on folic acid and other B-vitamin supplementation to reduce the risk of CVD, cancer, or impact all-cause mortality concluded there was minimal to no impact of these supplements in reducing the risk of these conditions [88]. It does not appear to impact the risk of

Table 12.4 A selected list of beverage/food and other sources of folate and folic acid

Food/beverage or other	Micrograms (μg)
100 % Fortified breakfast cereals	400
Multivitamin (on average-1 pill)	400
B-complex vitamin (on average-1 pill)	400–800
Brewer's yeast (1 tablespoon)	250
Beef liver (cooked, 3-oz)	185
Spinach (cooked, ½ cup)	100
Asparagus (4 spears)	85
Rice (white, enriched, ½ cup)	65
Beans (baked, 1 cup)	60
Green peas (boiled, ½ cup)	50
Avocado (½ cup)	45
Broccoli (2 spears)	45
Lettuce (½ cup)	40
Peanuts (dry roasted, 1 oz)	40
Orange or orange juice (6 oz)	30–35
Tomato juice (6 oz)	35
Bread (white, whole wheat, enriched, 1 slice...)	25
Egg (whole)	25
Banana (medium)	20
Wheat germ (1 tablespoon)	20
Rice (brown, ½ cup)	5–10

most chronic diseases, despite the fact that it can reduce blood homocysteine levels by at least 25 %.

Folic acid supplements may increase or encourage the growth of a variety of common tumors and precancerous lesions or polyps in high-risk individuals with adequate or high baseline folate status [89], but it may reduce adenoma risk in those with baseline deficiency of folic acid [90], especially in countries that do not require mandatory fortification. The cancer receiving the most attention in terms of concern is the potential increased risk in prostate cancer [91, 92]. Serum levels of folic acid also appear to be increasing in the elderly such that unmetabolized folic acid (UMFA) has become a concern in men [93].

The controversy over the clinical significance of a potential increased risk of prostate cancer will and should continue without any resolution in the near future. A meta-analysis of randomized trials found a significant increased risk of prostate cancer [94]. Arguably, another larger meta-analysis of randomized trials in cancer suggested that there was no risk and that past meta-analyses were influenced by a higher rate of cancer from one clinical trial [91, 95], where prostate cancer incidence in the folic acid arm was probably increased due to chance [95]. Although these researchers make a compelling argument, the problem with this theory is that most of the major trials looking at prostate cancer incidence still found at least non-significant increases in risk that cannot be disregarded due to chance, and this is confirmed by other recent meta-analysis [96], including recent population studies [97]. The sum of the data is not demonstrating a neutral or reduced effect, but only

an increased risk overall, and the argument is whether or not it is statistically or clinically significant [98].

Clinicians should not encourage supplemental folic acid use especially in men with a history of cancer concerned about fertility, despite some minimal positive or just non-impressive data in the area of fertility itself [99, 100], because other supplements are safer, just as effective and do not appear to require mega-dosage (like folic acid) for a clinical impact. Some of the early and only clinical trials that involved folic acid were utilizing dosages such as 5 mg per day (along with zinc), which is 12.5 times the recommended daily intake [99]. Only sperm concentration, but not motility or morphology, was improved. Food sources of folate can be recommended, because these have not been concerning overall, but the concentrated nutraceuticals do not follow the mantra right now of benefit exceeding risk.

Selenium and Vitamin E

Selenium or vitamin E supplements should not be recommended to improve fertility in subfertile men strictly based entirely on their overall safety issues and not on efficacy. For example, the initiation and even the final results of the SELECT trial of selenium and/or vitamin E to prevent prostate cancer were concerning for a multitude of reasons [101, 102]. Both agents failed to prevent prostate cancer, and there were multiple past and current safety issues with these nutritional supplement agents. Selenium had a history of potentially increasing the risk of skin cancer recurrence [103], and there were concerns over an increased risk of type-2 diabetes [104]. Interestingly, SELECT observed a non-significant increased risk of type 2 diabetes when the trial was terminated [101]. And there was a non-significant increase in the risk of aggressive (Gleason 7–10) prostate cancer with vitamin E and/or selenium [102].

Vitamin E supplements were also replete with some similar but even more concerning issues compared to selenium during the SELECT trial. Past meta-analysis of other clinical trials found a potential increased risk of all-cause mortality with higher doses of vitamin E supplements [105]. Other large clinical trials found a significant increased risk of heart failure in those with vascular disease or diabetes [106]. A significant increased risk of hemorrhagic stroke was found for vitamin E supplements in another major chemoprevention trial of healthy male physicians (Physicians' Health Study II) that was concurrently being conducted during the time of SELECT [107]. And again SELECT found a non-significant ($p = 0.06$) increased risk of prostate cancer in the vitamin E arm when the study was terminated, and a significantly higher risk with greater follow-up after termination [101, 102]. Thus, both of these supplements have no impressive overall or heart health research unless there is a deficiency in these compounds [108–112], and multiple past and ongoing concerns abound [113, 114], as also outlined earlier. There needs to be more clinician and patient awareness over the multiple serious safety issues with vitamin E and selenium, and these supplements should not be encouraged for

any healthy individual attempting to improve fertility despite past trials in infertility demonstrating some benefit [115–117]. It is also interesting that all of the past trial of vitamin E and/or selenium that have suggested benefit in male subfertility have also been at dosages equivalent or actually larger than past clinical trials in other areas of health that found large concerns [101, 102, 105–107]. Since these supplements have not been found to have profound benefits beyond what has been observed with other supplements discussed in this chapter [19], then it would be prudent again to not recommend this particular compounds with such as negative and nebulous history.

Zinc

The excitement for the use of zinc with or without other supplements is supported by some older clinical trials. For example, over 100 subfertile and fertile men experienced a large improvement in sperm counts (74 % significant increase) over 24 weeks, which was not observed in the placebo group [99]. This older study was published in 2002, and 66 mg of zinc sulfate (six times the recommend daily dietary intake) was used alone or combined with 5 mg of folic acid (over 12 times the recommend dietary intake). Additionally, there was no difference in the serum or seminal plasma level of zinc between the subfertile and fertile men in this study, and zinc supplements did not increase those levels, and the study did not include pregnancy as a clinical endpoint.

Another older clinical trial of 100 men with asthenozoospermia was randomized to 250 mg twice daily (over 45 times the recommended dietary intake) of zinc for 3 months compared to no treatment [118]. Significant improvement in sperm quality, sperm count, motility, fertilizing capacity, and the incidence of anti-sperm antibodies was observed in the zinc group. After 12 months of follow-up, there were 11 pregnancies (22.5 %) in the zinc group and 2 (4.3 %) in the control group ($p < 0.03$). There were no hormonal differences found between the groups. Other studies have methodology issues including a lack of controls or short treatment periods [119].

The issue with zinc currently is that the recommended dietary intake is only 11 mg [120], and mega-doses of zinc supplements are replete with issues especially in urology [121]. One of the largest prospective studies to look at high-dose zinc supplement intake found an increased risk of advanced prostate cancer [122]. And arguably the largest dietary supplement study to use high-dose zinc (macular degeneration) found an increased risk of hospital admissions from this exact same trial (Age Related Eye Disease Study or AREDS) in regard to genitourinary complications (BPH, stones, and UTI) in the 80 mg zinc arm [123, 124]. Thus, whether or not this will be further confirmed is not the issue because at this time zinc supplements in high doses like the ones needed in the fertility trials are too concerning, short and long-term. In fact, some countries such as Canada now discourages the sale of high-dose zinc supplements (40 mg or more) unless research

suggests a specific benefit otherwise and proven safety simply because of these issues [125, 126]. Some major clinical trials (AREDS 2) tested lower zinc dosages compared to the older effective higher dosage based on this history of adverse events [127].

First Do No Harm Specific Supplementation for Improved Erectile Function

L-Arginine or L-Arginine Aspartate + Pycnogenol

Nitric oxide (NO) is produced from L-arginine by nitric oxide synthase (NOS) [22], thus the idea of utilizing L-arginine supplements to enhance the treatment of ED appears logical and is an option for some patients. In fact, L-arginine with its ability to increase NO and lower blood pressure makes it a potential preventive or treatment option in other areas of medicine such as hypertension and preeclampsia [128–130].

However, three serious problems with L-arginine supplementation in terms of metabolism include:

- The potential for extensive first pass liver metabolism (arginase enzyme) that occurs when ingesting this compound [131–133].
- The additional intestinal enzymes (gut arginases) that also exist in the GI tract to further potentially deactivate this agent [131–133].
- The presence of an endogenous inhibitor of NOS, which is known as ADMA (asymmetrical dimethylarginine) [134, 135].

Thus, large dosages of L-arginine will usually needed to achieve some success in general medicine and in the area of ED and FSD, and this can be daunting for the patient. For example, 3–6 g of L-arginine would require 6–12 large pills or capsules per day.

Perhaps, this is one reason large intakes of dietary arginine or supplemental arginine have not been proven beneficial in other areas of medicine such as athletic performance [136, 137]. And this is also the case with erectile function where moderate dosages of L-arginine alone (1,500 mg per day) do not appear to work better compared to placebo [138] for ED. Other studies of high-dosages of L-arginine (5 g per day, $n = 50$) over 6 weeks appear to work mildly to moderately better than placebo in terms of subjective (not objective) outcomes, especially for those that with organic ED that may produce or secrete low amounts of nitrite and nitrate (metabolites of nitric oxide that are fairly stable) from urinary measurements [139]. Urinary nitric oxide metabolites appear to double when taking 5 g per day. One area that needed better research was whether L-arginine efficacy could be enhanced when combining it with other agents.

An impressive amount of clinical data has been garnered for the use of L-arginine aspartate at a lower dosage (2,800–3,000 mg) when used with pycnogenol (80 mg) [140–142]. The most commonly tested supplement in this form is Prelox (Horphag Research Ltd, London, UK). Perhaps, this solves part of the metabolism problem when utilizing L-arginine alone.

A randomized, double-blind, placebo-controlled crossover study of 50 participants with moderate ED (IIEF score of 11–17) and a mean age of 37 years was conducted [141]. The total daily dose of Prelox was 3,000 mg of L-arginine aspartate and 80 mg of pycnogenol. This total dosage was divided into four tablets, two taken between 7 and 9 a.m. and two between 7 and 9 p.m. with 200 ml of water. IIEF scores from 11 to 17 at baseline approximately doubled to 26–30 ($p > 0.001$) after 1 month. The earliest improvement was 1 day and the latest response was after 9 days (mean 4.9 days). IIEF domains including orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction and percent sexual response also approximately doubled ($p > 0.001$). Systolic and diastolic blood pressure also dropped significantly ($p < 0.001$), and side effects were similar to placebo. It should be kept in mind that men with severe CVD or hypertension were excluded from this study.

The clinical trial that has established Prelox as a definite nutraceutical option for men with mild to moderate ED in my opinion and arguably one of the better nutraceutical options for ED was based on a 6-month randomized, double blind trial, placebo-controlled parallel-arm study ($n = 124$, mean age 44 years) [142]. Men in this trial had IIEF scores at baseline of 11–17, and diabetics and those with severe hypertension were excluded. Again, two tablets were utilized in the morning and evening and each table contained 700 mg L-arginine aspartate and 20 mg of pycnogenol (total daily dose was 2,800 mg L-arginine aspartate and 80 mg pycnogenol). The erectile domain of the IIEF (questions 1–5 and 15) improved from a baseline of 15–25 after 3 months and 27 after 6 months compared to placebo where an increase of 15–19 was observed ($p < 0.05$). These results are in the same range of prescription PDE-5 inhibitors. There was an insignificant drop in blood pressure in the Prelox group from a systolic of 139–131 and a diastolic from 86 to 82 (6 point drop in the placebo arm). Total testosterone also increased significantly ($p < 0.05$) from 15.9 to 18.9 nmol/l in the Prelox group (16.9–17.3 nmol/l with placebo). It is plausible that testosterone increased from increased sexual activity and/or another mechanism, and this should be followed in patients to answer this question because it would be an ancillary benefit for some men if this was the case. Increases in the domain of orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction were all significantly improved over placebo ($p < 0.05$) with Prelox. A total of 13 men were lost to follow-up in this trial, so 111 men completed the trial. The question is whether or not the data was analyzed based on intention to treat principle, which is important because all significant values reached the minimum of $p < 0.05$? Regardless, there is adequate efficacy with Prelox and it should be offered as an option for healthy men with mild to moderate ED and no significant co-morbidity and no hepatic or renal abnormalities. The number of pills needed per day (four) could be problematic long-term along

with cost, and whether or not those with CVD should utilize it are questionable. Two clinical trials demonstrated potential adverse events or worse outcomes in those with a previous myocardial event or existing peripheral artery disease (PAD) [143, 144], but other clinical studies have challenged the merit of these findings [145, 146]. Still, the overall efficacy is still notable and again makes it one of the best over the counter options available based on the scientific evidence for men with mild to moderate ED.

L-Citrulline

The major source of L-arginine within the endothelial cell is from L-citrulline, and both L-arginine and L-citrulline raise vascular NO levels [147]. In some individuals L-citrulline may be at least twice as efficient at increasing nitric oxide levels compared to L-arginine, which could solve some of the dosage and other issues mentioned with L-arginine. In a double-blind, randomized, placebo-controlled crossover study, 20 (mean age 57 years) healthy volunteers received six different dosing regimens of placebo, citrulline, and arginine. L-Citrulline was significantly more effective at increasing L-arginine plasma levels compared to L-arginine itself ($p < 0.01$). At a dosage of only 1.5 g per day of oral L-citrulline, L-arginine blood levels were raised to a similar degree as 3.2 g per day of oral L-arginine. L-Citrulline raised the ratio of L-arginine to ADMA, and the arginine/ADMA ratio is again thought to determine substrate availability of arginine to the endothelium. The correlation observed in this study between increases in the arginine/ADMA ratio and forearm flow-mediated vasodilatation indicated a dose–response relationship with NO production. The highest dose of L-citrulline (3 g twice a day or 6 g total) was the most effective at raising nitric oxide levels compared to L-arginine ($p < 0.01$). Urinary nitrate (a marker of NO) and cGMP (another potential indicator of systemic NO production and bioactivity) were significantly ($p = 0.01$, $p = 0.04$) increased over arginine. Neither blood urea nitrogen (BUN) nor serum creatinine was changed, and there were no safety issues over placebo.

It is of interest that the 1.5 g of L-citrulline used as one dosage in the previously mentioned study was the same daily dosage found to be effective in 1-month crossover trial of men with mild to moderate ED [148]. A total of 24 men (mean age is 56.5 $\pm$ 9.8 years) took 1.5 g of L-citrulline a day or placebo for 1 month. An improvement in erection hardness score (validated ED instrument) was found after 1 month in the L-citrulline group compared to placebo ($p < 0.01$). No adverse events occurred over placebo, and 37.5 % of participants had hypertension, 21 % high cholesterol, 12.5 % BPH, and 12.5 % had diabetes. This is preliminary but potentially exciting research suggesting that L-citrulline could be one of the better nutraceutical options for ED and should also be researched as ancillary supplementation to conventional ED options.

The question of short and long-term safety with L-citrulline needs to be addressed. High dosages of L-citrulline have been utilized in some short-term clinical trials with good safety [149, 150]. Citrulline can be used to increase arginine availability without affecting urea excretion and may enhance nitrogen balance. It does appear that adequate renal function is needed for maximum citrulline conversion into arginine and this should be considered.

Citrulline from synthetic or watermelon extract supplements have not been known to cause acute side effects and is another source of citrulline and arginine, but blood pressure reductions could occur, especially in prehypertensive and hypertensive patients and this has to be noted to anyone before starting citrulline supplementation [151]. Citrulline from dietary sources only are difficult if not impossible to obtain, since watermelon is the only source and the rind contains the majority of this compound, but excessive quantities would need to be consumed to equate to several hundred milligrams of this amino acid. Thus, nutraceutical sources of citrulline are the only realistic option for patients recommended more citrulline for erectile health.

Since nitric oxide (NO) production inhibits platelet aggregation as demonstrated from L-arginine infusion studies [152], it should be expected that L-citrulline can do the same but needs more research. And more short and long-term studies are needed in the area of ED to determine the best potential use of this interesting amino acid from watermelon. Since citrulline has the potential to be heart healthy this also makes it a potential ideal candidate in the area of ED in the future [153].

Panax ginseng *and Ginsenosides (Korean Red Ginseng and Others)*

Ginseng actually refers to the root of several species in the genus *Panax*, of which *Panax ginseng* is one of the most widely utilized species and is native to Asian countries such as China and Korea [154–157]. Ginsenosides, which are also known as ginseng saponins or glycosylated steroidal saponins, are unique to the *Panax* species, and are the primary active ingredients in ginseng. More than 30 different ginsenosides have been isolated from the root of *Panax ginseng*, and although ginseng contains other diverse compounds, the individual and collective ginsenosides appear to be the generally agreed upon active ingredients from basic science and clinical trials.

Ginsenosides have multiple mechanisms of action, and each ginsenoside may have tissue-specific impacts [158–161]. The backbone of each ginsenoside is similar and consists of a common four-ring steroid-like structure that includes multiple carbon atoms with attached sugar moieties. Each ginsenoside has a different type, position, and number of sugar moieties attached by a glycosidic bond at C-3 and C-6. Each type of ginsenoside also has at least three side chains at the C-3, C-6, or C-20 position. These side chains are free or are attached to

monomers, dimers, or trimers of sugars. It is these sugar compounds that may provide the cellular-specific or receptor effects of each ginsenoside. The ginseng species, age, part of the plant, harvest season, preservation, and extraction method can all impact the compounds found in ginseng and even alter somewhat the ginsenoside content.

Over several decades, the content of ginsenoside standardized extracts utilized in clinical trials has varied, from approximately 4 % ginsenosides in the 1990s to 4–7 % ginsenosides in the mid-2000s, and higher standardized extracts are offered today (>8 % for example) [162, 163]. The ginsenoside content should be considered when comparing different efficacy doses from clinical trials. When the ginsenoside concentration is isolated, it appears to elicit the same or better results than the sum of the total ginseng components [163], which again supports the accepted general philosophy that ginsenosides are the active medical components of *Panax ginseng*.

One of the more influential evidence based endorsements for ginseng and male sexual function was a clinical evidence guideline of conventional and alternative medicines [164]. The authors used *Panax ginseng* data from six randomized trials conducted over a period of approximately 15 years that included a total of 349 men. The investigators found that ginseng significantly ($p < 0.00001$) improved erectile function compared with placebo over 4–12 weeks. Approximately 58 % of men experienced an improvement in some aspect of sexual function compared with 20 % of men who received the placebo. No other dietary or truly CAM supplement was recommended. Ginseng was found to have "moderate-quality evidence" and the investigators concluded that ginseng is "likely to be beneficial" in men with erectile dysfunction of any etiology (organic and psychogenic causes). The final clinical evidence-based guideline provided in this review stated "Ginseng is a traditional Asian remedy with rare adverse effects in the recommended dose of 0.5–2.0 g daily." What was not mentioned in this review and any other to date to my knowledge is that these dosages recommended were for older less concentrated form of ginseng (4–7 % ginsenosides). And, in this same systematic review [164], the authors mentioned that they still needed to evaluate a more concentrated ginsenoside randomized trial by Park and colleagues that was published in Korean in the Korean Journal of Urology [165], but that the article was being translated. Interestingly, the author of this chapter had this study by Park and colleagues translated into English, and it arguably provides some of the best preliminary clinical data to date for a dietary supplement compared with placebo over 8 weeks for men with ED. This was a multicenter, randomized, double-blind, placebo-controlled study of 69 participants that used a highly concentrated ginsenoside product (800 mg per day) [165]. The primary endpoint was the response to the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire at baseline and 8 weeks. The other domains of the IIEF were secondary endpoints, and safety was monitored. Every single sexual health domain from the IIEF-15 was significantly improved by Korean ginseng compared with placebo: erectile function (primary endpoint), sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction. Additionally, every

question on the IIEF (15 out of 15) was improved significantly in this specific clinical trial. The sexual desire domain, frequency, and degree of sexual desire were all also significantly increased ($p < 0.001$). In other words, both the primary and the secondary endpoints significantly favored ginseng over placebo. No significant differences in adverse events have been reported for ginseng compared with placebo. The results of this trial will strengthen the clinical evidence for *Panax ginseng* and the evidence that highly concentrated ginsenosides are the active or effective ingredients in ginseng [165]. The product used was from a Korean Ginseng Company (BT Gin). Still, the current and future cost of this and other products need to be discussed because again they can be quite high depending on the source and time of year.

The onset of action or efficacy of ginseng could arguably occur within days to months [164–166]. The time period is variable and requires further elucidation, but at least 4–8 weeks should be attempted on a *Panax ginseng* supplement before deciding upon efficacy. The onset of action will not be as rapid on average as PDE-5 inhibitors, but the impact on libido, lower cost in some cases, and safety affords ginseng its own set of advantages for certain patients. In addition, the potential for combining ginseng with conventional ED treatments should be explored since PDE-5 inhibitors have no significant effect on libido.

In terms of *Panax ginseng* the laboratory data for ginsenosides suggest multiple mechanisms of action. In cultured bovine endothelial cells, ginsenosides were shown to stimulate the conversion of [14C]L-arginine to [14C]L-citrulline and to promote vasorelaxation [167]. More specific studies in rabbit corpus cavernosum tissue continue to support the potential of increasing endogenous nitric oxide (NO) concentrations via the addition of ginsenosides [168]. Other basic laboratory investigations and reviews support this thought and mechanism whereby the stimulation of nitric oxide synthase may produce higher quantities of NO and peripheral neurophysiologic enhancement may also occur [169–172].

Ginsenosides also compete with agonists for binding to GABA-A and GABA-B receptors [173, 174], which could also explain a central mechanism of action impacting desire or arousal. Anxiolytic effects have also been demonstrated in mice and maze models. Ginseng and ginsenosides have been shown to positively impact striatal dopaminergic activity and dopamine receptors [175], which could translate to a minimal apomorphine like effect. Ginseng may exert a direct effect on the hypothalamus or pituitary to also suppress prolactin secretion, but these hormonal changes I believe are minor at best because past clinical trials measuring hormonal changes in men did not find significant or consistent increases in prolactin or testosterone [176].

A rare but still surprising issue with some herbal preparations in my opinion is the chance for them to be inappropriately and falsely tagged with an acute safety issue on the basis of isolated case reports or uncontrolled investigation without an examination of the totality of the objective laboratory and clinical evidence. One perpetuated example is a 1979 observational series in a notable medical journal that associated the self-reported utilization of ginseng products with hypertension in 14 individuals after 3 months of use [177]. Yet despite no control group, and other

basic methodology quality-control issues, which included a lack of correction for other confounders (such as high intake of caffeine and potentially other stimulants) the investigation was used by some as proof of cause and effect [178–180]. These hypertensive effects have not been replicated since 1979 in a controlled setting. Randomized trials of hypertensive and non-hypertensive individuals have demonstrated no impact or a partial reduction in blood pressure with *Panax* or American ginseng and isolated ginsenosides, regardless of dose utilized and time period (up to 3 months) [181–186].

Regardless, long-term studies (several years) are needed to confirm this consistent finding in the acute setting. In my experience, other compounds found with ginseng commercial products such as caffeine or caffeine mimics I believe have the ability to exacerbate the stimulant effects of ginseng itself, or be the sole cause of blood pressure or heart rate increases in rare patients. It is for this reason that a patient with controlled or uncontrolled hypertension should receive some objective education on the past history of ginseng in combination with adulterants that could theoretically change blood pressure values. Ginseng (*Panax quinquefolius*—somewhat similar to *Panax ginseng*) alone has been shown to increase energy levels in cancer patients with fatigue, but again the safety was similar to a placebo in a large phase 3 like randomized trial ($n = 290$) [187]. This again speaks to the safety and another potential mechanism of action of ginseng (reduced fatigue).

Potential interactions with warfarin or hemostatic issues have also been suggested on the basis of case reports [188], but controlled studies have not been able to substantiate any consistent impact of ginseng on warfarin anticoagulation or hemostasis in general (prothrombin time, partial thromboplastin time, and international normalized ratio [INR]) [189]. Still, this needs to be further elucidated based on studies of other types of ginseng that could have some impact on platelet activity and this could explain some cardiovascular benefits. And since ginseng may improve nitric oxide levels (NO), and NO is known, as mentioned earlier in the chapter, to inhibit platelet aggregation, it is plausible that there could be a blood thinning type effect.

Past human studies of ginseng and sexual health have reported gastrointestinal side effects [164, 166], for example, stomach upset, but these were not reported at a rate significantly higher than the rate for placebo. Ingesting ginseng with a meal seems more appropriate because of potential gastrointestinal issues with most dietary supplement interventions or placebo, and there are no reports that ginseng is less or more efficacious in this scenario. More rigorous monitoring of ginseng safety in clinical trials should be conducted to provide some clarity on adverse events. The dose of ginseng and ginsenoside concentration should always be noted in clinical trials and again reviews on this topic have been lacking. Ginsenoside concentrations should be required for publication in any clinical trial of ginseng.

Panax ginseng has arguably the longest and perhaps one of the most impressive nutraceutical records to date for use in men with mild to moderate ED. Approximately ten randomized trials have suggested that *Panax ginseng* and its ginsenosides have potential efficacy in diverse areas of male sexual health [164, 165, 190, 191]. Still, this is not meant to suggest that it is the most effective ED

nutraceutical option because others (arginine combinations and citrulline) have their own advantages and disadvantages, and methodological quality of future clinical trials needs to be improved. The isolation of the more active ginsenosides also needs more research and in my experience quality control is a real problem with many ginseng products. Also, price issues need to be resolved because at the time of this writing Korean Red ginseng and Chinese ginseng with more concentrated ginsenosides were no longer of low cost.

SAM-e for SSRI-Induced Sexual Dysfunction

S-Adenosyl methionine (SAMe) is a naturally occurring compound that functions as a methyl donor in human metabolism may have a individual treatment role for major depressive disorder (MDD), or an ancillary role to enhance conventional treatment [153, 192–196]. A clinical study of 73 serotonin reuptake inhibitor non-responders with MDD over 6 weeks found a benefit in those receiving 800 mg twice daily of SAM-e compared to placebo [193]. A significantly higher response and remission rate occurred with SAM-e over placebo. Side effects were similar to placebo. Gastrointestinal side effects and headaches have occurred in other studies [194], and SAM-e is not a low cost CAM in general.

Preliminary research also suggests that in those with MDD this dietary supplement may have a positive effect on male arousal and ED, such that scores improved in these areas compared to placebo [197]. SSRIs and other antidepressant medications could have a profound impact on male and female sexual function [198]. I am hopeful that research on SAM-e to support its minimal or even positive effect on sexual function (ED or FSD) in those with MDD continues. It is also of interest that SAM-e has been used as a prescription drug, given as an IV or an injectable in numerous European countries since the 1970s and its ability to reduce osteoarthritic pain is also notable, well published, and on par with NSAIDs but with less toxicity at dosages of up to 600 mg per day [199, 200].

First Do No Harm: Potentially Harmful or Ineffective Nutraceuticals for Erectile Function

Androstenedione and/or DHEA

On January 20, 2005 it became illegal to sell androstenedione dietary supplements in the USA [201, 202]. Androstenedione was considered a "prohormone" supplement that some men used in an attempt to build muscle. It was utilized by some notable US professional athletes before being banned, and it created enormous controversy. It was a potentially dangerous supplement because it had been

associated with a reduction in "good cholesterol" or HDL and it had potentially other health consequences such as significantly increasing estrogen (estrone and estradiol) in healthy young men (ages 26–32 years) taking 100 or 300 mg per day for 7 days, and significantly increasing testosterone levels at 300 mg per day (from 526 to 872 ng/dl on average in one study) [203]. Other studies of young men demonstrated just increases in estrogen with these dosages [204], which is why it would not been surprising that some individual reports of ED from these supplements can also occur because of arguable the suppression of the pituitary and gonadal axis [205]. The individual variability in the response is also what is striking about androstenedione (or DHEA) in men and women, except for the estrogen increases in young and older primarily eugonadal men. Men ages 35–65 years taking 200 mg of androstenedione had significant increases in estrogen but not testosterone over 12 weeks [206]. In postmenopausal women a significant increase in estrone occurred but the individual variability in the response was always notable, which is again part of the problem [207]. Regardless of the population studied the variability or unpredictability of the physiologic response should be mentioned to patients. This has also been my experience that men (and women) without overt hormone deficiencies have variable results and men experience dramatic increases in estrogen and potentially a small increase in testosterone the more testosterone deficient the male [153].

Therefore, there were so many concerns with these supplements that eventually the FDA and the US government decided to remove almost all of them, including androstenedione, from the market [201]. Other so-called prohormone supplements like DHEA were not banned, but are still being allowed for sale. Now, if DHEA is similar to androstenedione in that it has similar effects, then why is this supplement still allowed for sale over the counter? This is part of the strange circumstances surrounding some dietary supplements and the inconsistency in the policies that are applied. DHEA supplements enjoy a unique exemption under federal law, because of a bill approved by Congress in late 2004. How did DHEA survive when other similar to identical supplements did not? Sports officials were in favor of an overall ban on steroids and related products, including DHEA. DHEA has been banned by the Olympics, the World Anti-Doping Agency, the National Collegiate Athletic Association, the National Football League, the National Basketball Association, and minor league baseball. The 2005 law that impacts prohormone supplements, passed without objection, also gave the Drug Enforcement Administration more authority to ban new or novel steroids, with one exemption, DHEA. The term "anabolic steroid" is defined now as any drug or hormonal substance, chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids, and DHEA). In my opinion, since such a large percentage of Congressional officials use dietary supplements and some perceived DHEA as unique, the proposal to ban all over the counter pro-hormone supplements in the USA would have not passed Congress if DHEA were included in the proposal. Now, with this pertinent history, what about any new data to support DHEA for men's health or sexual health?

Population studies such as the Massachusetts Male Aging Study have suggested a higher risk of ED with lower blood levels of DHEA-S [208]. Yet what gets missed in referencing these studies is that there were also inverse associations of HDL with ED and a higher risk of ED in those with heart disease, hypertension, smoking and diabetes for example, which is a more tangible and productive conversation. It should be kept in mind that DHEA levels decrease substantially with aging, and this has been utilized in deceptive advertising in my opinion to encourage men and women to purchase this supplement. Other studies suggest that a lower level of DHEA and an increase risk of ED is only an anemic association [209]. DHEA is produced primarily by the adrenal cortex and in smaller amounts by the testes and the ovaries, and then it is quickly sulfated by sulfotransferases into DHEA-S, which is more stable with a longer half-life and its concentrations stay stable most of the day [210]. DHEA is arguably the most abundant steroid in the human body (more than testosterone), thus for this and many other reasons there will always be sufficient physiologic facts to give it some advertising attraction. It does not appear to have a role for androgen deficient or insufficient men because it is not predictable.

Small studies of men utilizing 50 mg for 6 months (DHEAS level <1.5 μmol/l) showed some improvements in function in those with hypertension and ED or those without organic etiology, but not in those with diabetes or neurologic issues [211, 212]. These men were all generally tested with prostaglandin E1 first to ensure that they were capable of having a full erection with pharmacologic intervention. The problem with DHEA is a lack of large studies with good methodology and no really novel findings with DHEA and ED or in the area of male sexual health. DHEA-S levels are also not easy to acutely or chronically predict with lifestyle interventions; for example, in some studies there is minimal or large changes in this hormonal marker for men and women after large reduction in weight [213–215]. Perhaps this is due to the fact that DHEA levels need to be monitored over many years. Obesity appears to attenuate the association or correlation between higher DHEA and lower morbidity [216].

*Fenugreek (*Trigonella foenum-graecum*)*

Fenugreek has been promoted by numerous commercial entities as an option for testosterone replacement, or a testosterone-enhancing supplement via an aromatase inhibitor mechanism of action (blocks the conversion of testosterone to estrogen) [153]. Human studies have failed to demonstrate that this herb/spice supplement increases testosterone consistently, especially in hypogonadal men. In fact, fenugreek has been used as a spice and is utilized in Indian Ayurvedic and in Chinese Medicine as a stimulus for lactation for breastfeeding women [153, 217]. This supplement has a partial notorious history for being touted as a breast enhancement supplement for women without human research to support this claim. Yet allergic reactions to the powder and mild gastrointestinal upset are not uncommon side

effects and increased bleeding can occur beyond what is expected in those on aspirin or anti-inflammatory drugs [217].

In terms of fenugreek as a TRT supplement, in one clinical study, fenugreek (standardized to 70 % trigimannose) actually significantly reduced levels of free testosterone [218]. Men had a 40 ng/ml free testosterone at baseline, reduced to 33 ng/ml at 4 weeks, and then to 36 ng/ml at 8 weeks ($p = 0.02$) when taking 500 mg per day. DHT levels were reduced in the fenugreek group. Other studies demonstrate that fenugreek either causes no change or slightly increases testosterone in men have been for those with an already normal testosterone at baseline [219, 220]. In other words, it is an unpredictable supplement in the area of TRT. One clinical trial of fenugreek of 500 mg per day (standardized for Grecunin) over 8 weeks showed an average increases of 6.6 and 12.3 % for total testosterone and bioavailable testosterone [219]. Even if fenugreek operates as an aromatase inhibitor, as explained earlier in this chapter, I do not recognize this as a positive mechanism of action because it could cause bone loss in healthy men based on some past clinical trials of prescription drugs that have this same mechanism of action.

One ancillary health advantage of fenugreek is that the natural seeds can be purchased at health food stores and used in most diet plans (soups, yogurt, oatmeal. . .) and they may slightly lower blood sugar and cholesterol because they are a good source of fiber (1 tablespoon = 3 g of fiber) [153, 221].

Tribulus terrestris

This is an herbal product that has been suggested by some commercial entities to have a DHEA or pro-hormone type effects (for ED and TRT), and it had been around for decades but there is simply no positive or adequate evidence to support its use for ED. Human studies have failed to demonstrate that this herb acts like "DHEA" to increase testosterone, or just increases testosterone by an independent mechanism, which is what it is advertised to do in many places [153]. For example, a small clinical trial of elite male rugby players ($n = 22$) were placed on Tribulus or placebo for 5 weeks and no alterations in testosterone or muscle mass occurred [222]. Another small trial of healthy men ages 20–36 years of age with body weights ranging from 60 to 125 kg ($n = 14$) was published [223]. Participants consumed 10 or 20 mg/kg body weight of Tribulus (divided into three daily intakes) for 4 weeks. No significant changes in any parameter occurred in the Tribulus group and this included testosterone, androstenedione, or LH. The authors concluded that this supplement does not contain any indirect or direct testosterone-enhancing properties. In fact, the only adequate clinical trials where a dose of Tribulus (750 mg or more) appears to increase testosterone is when it is combined with 150 mg of DHEA and 300 mg of androstenedione [224–227]. And drops of 5.0 mg/dl in HDL or "good cholesterol" were observed which have to be somewhat concerning [225], but again was probably due to the DHEA and androstenedione

components. Preliminary clinical trials have failed to demonstrate an impact of Tribulus on body composition or exercise performance and no impact on hormone levels.

Yohimbine Hydrochloride (Not Really a Dietary Supplement or CAM)

Yohimbine comes from the West African Yohimbe tree and can be found as a supplement and a prescription drug (Yocon® etc.) [153, 228]. Whether or not it even works is controversial, but what is not controversial is that it is a "alpha-2-adrenoreceptor antagonist," and some of the side effects include headache, sweating, nausea, dizziness, nervousness/agitation, tremors, sleeplessness, antidiuresis, and elevated blood pressure and heart rate [229]. And it cannot be used by individuals with kidney disease, those on anti-depressants, or other mood-altering drugs, and in some individuals with specific cardiovascular, neurological, and psychological issues.

Many media and other credible sources appear to suggest yohimbine is as an alternative medicine or over the counter dietary supplement, but this is really not the case based on its clinical trial efficacy. It is usually characterized as an "alternative medicine" by some individuals and reviews [220], some may assume this is a dietary supplement, and there are many companies that sell "yohimbe" or tout that they sell "yohimbine HCL." The positive data with the drug or compound derived from this tree, yohimbine hydrochloride, came from European and other studies at a total of 5–10 mg per day (divided doses) [230]. Yohimbine HCL is a prescription drug, but many dietary supplements that mimic this drug have quality serious control problems and are dangerous [228, 229]. Again, yohimbine HCL is the active ingredient found in the bark of a West African tree, but many dietary supplements really sell "yohimbe" which in many cases has little to no or variable quantities of the active ingredient "yohimbine HCL" in it. Again, if there is an interest in yohimbine HCL in the area of ED I believe the prescription drug should be utilized because of quality control issues and because the successful clinical trials utilized this version.

Conclusion

Other supplements in the area of fertility and erectile health simply have shown no benefit, such as magnesium [231], or should not be recommended because of the need for more efficacy and/or safety data (for example L-carnitine for ED) [153]. Tongkat ali (*Eurycoma longifolia*) has some initial positive data for fertility and sexual enhancement [60, 61], but the mechanism of action and tangible effects

Table 12.5 Summary of some of the nutraceutical products discussed in this chapter for fertility and erectile function that could be recommended or discouraged

Fertility nutraceuticals	*Commentary/recommendations*
CoQ10	200–300 mg per day has excellent safety but efficacy is mixed
Folic acid	Not recommended beyond the dose found in a multivitamin (200–400 μg). Has controversial ability to potentially increase the growth of colon polyps and prostate cancer in individuals with already high baseline levels of folate
L-Carnitine	2,000–4,000 mg per day has mixed data but overall safety has been adequate
Multivitamin	Minimal clinical data to improve fertility and could be utilized based on the safety of one pill a day
Omega-3 fatty acid (EPA and DHA)	Increasing dietary intake of marine sources of omega-3 fatty acids is recommended over supplementation
Proxeed (commercial product)	Combination nutraceutical product with minimal clinical data but a long history of physician use and can be utilized. Cost could be the only issue
Selenium and/or vitamin E	Not recommended based on the overall safety concerns in men's health with increasing dosages of selenium (type 2 diabetes or skin cancer recurrence) and vitamin E (prostate cancer)
Tongkat Ali (*Eurycoma longifolia*)	One company (Biotropics Malaysia Berhad, Kuala Lumpur, Malaysia) has a standardized extract at 200 mg per day and could be of benefit
Vitamin C	Up to 1,000 mg per day is recommended and generally safe short-term but can increase oxalate levels significantly. Non-buffered or pH neutral vitamin C (also known as "calcium ascorbate") could cause minimal changes in oxalate and appears to be as effective. Smokers, ex-smokers or those that have recently quit or are on smoking cessation regimens and trying to improve subfertility are the best candidates
Zinc	Not recommended based on the potential for urologic toxicity when used in large dosages (80 mg+) over long periods of time
Erectile function/health nutraceuticals	*Commentary/recommendations*
DHEA/androstenedione	Not recommended, can reduce HDL cholesterol, unpredictable testosterone changes and can increase estrogen levels in men
Fenugreek (*Trigonella foenum-graecum*)	Touted to increase testosterone but has not consistently demonstrated a benefit and could potentially reduce free testosterone
L-Arginine	Not generally recommended alone because of the large dosages needed to overcome first pass metabolism and deactivating enzymes (arginases). Blood pressure reductions with this supplement can occur
L-Arginine aspartate + pycnogenol	One of the most clinically researched and efficacious nutraceuticals for men with mild to moderate ED. Dosages of 2,800–3,000 mg of L-arginine aspartate + 80 mg daily of pycnogenol (Prelox is the most commercialized researched product) has demonstrated adequate efficacy. Cost and pill count may be an issue for some individuals and blood pressure reductions are not uncommon

(continued)

Table 12.5 (continued)

L-Citrulline	Dosages as low as 1,500 mg per day can be recommended for ED based on moderate clinical data and an ability to be as efficacious as L-arginine in producing nitric oxide (NO) at lower dosages. Still requires more clinical research for ED, especially whether or not blood pressure reduction occurs rarely or commonly with higher dosages
MACA (*Lepidium meyenii*)	Not enough research but preliminary data in fertility or ED is promising and should continue
Panax ginseng (Korean Red ginseng and others)	Dosages of 800–3,000 mg (lower dosages with more concentrated ginsenoside products) have been used in multiple randomized trials to benefit men with mild to moderate ED. A consistent impact on libido could make this an option with conventional prescription agents. Cost may become an issue with concentrated ginsenoside products
SAM-e (*S*-adenosyl methionine)	May be used for the treatment of major depressive disorder (MDD) with and without SSRIs medication and has not been shown to reduce sexual function and may even provide a benefit, which is unusual for an anti-depressant. Dosages as high as 800 mg bid have been used but cost is an issue with this supplement
Tribulus terrestris	Not recommended. Suppose to act as a DHEA mimic but in general has not demonstrated any impressive testosterone-enhancing properties
Yohimbine hydrochloride	Not a true nutraceutical because all of the positive and adequate clinical trials used a prescription form of this compound. Yohimbe supplements claim to contain adequate amounts of the active compound (yohimbine HCL) but this has not been proven and in fact quality control and safety has been shown to be an issue with these over the counter products

on erectile health need more clinical research. The testosterone increases are statistically significant but arguably not clinically significant as of yet. Horny Goat Weed (Epimedium species) contains a compound(s) known as "icariin" that may have a PDE-5 like effect [232–234], but clinical research is needed because the majority of the impressive research was derived from basic science studies, but still it is also one clinicians should monitor. MACA (*Lepidium meyenii*) has some preliminary positive clinical data in fertility and ED, but needs more consistent research on standardization of active ingredients and efficacy, but is commonly used in other countries such as Peru [235, 236]. An overview of most nutraceutical products that are discussed in this chapter is provided in Table 12.5.

It is time to view fertility and erectile function nutraceuticals with a wider perspective because a plethora of research has been performed on numerous compounds. Large and authoritative meta-analyses actually endorsed the utilization of multiple products for men attempting to maintain or improve fertility and erectile function [19, 164]. However, before endorsement of a specific supplement becomes logical it would seem imperative to teach clinicians and patients about the overall safety and efficacy of these interventions outside of fertility and ED.

Current conventional options are not perfect and have a host of their own issues from side effects, efficacy and especially price as exemplified by the current cost of PDE-5 inhibitors for example or assisted reproductive technology. Thus, if a nutraceutical that is safe and heart healthy and cost effective can be utilized with or without a conventional agent then it should be embraced. This has arguably already occurred in the area of fertility but in the area of ED nutraceuticals the unctuous history of these products, including the highest rate of recall of any supplement category in FDA history [237], makes it difficult for some clinicians to appreciate the few truly efficacious products amongst a sea of ineffective and tainted products. It is my hope this chapter provided more objectivity to this issue and for clinicians and patients to appreciate a better sense of nutraceuticals that are worthwhile and others that are worthless. This is critical in my opinion, because it could be argued that clinicians are one of the last bastions of objectivity for those that require real answers to the questions that currently abound over nutraceuticals.

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