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Efficacy and Safety of Common Ingredients in Aphrodisiacs Used for Erectile Dysfunction: A Review

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Abstract

Introduction—Erectile Dysfunction (ED) is the inability to attain or sustain an erection for sexual intercourse. Affected men endorse difficulties with intimacy and feelings of guilt and shame. While medical treatments are available, patients are reluctant to discuss ED with physicians and often utilize dietary supplements to attempt to treat their ED. As such, there is a need to better understand the effects of ingredients used in nutraceuticals for ED treatment.

Aim—To summarize the literature on the efficacy and safety of the most common ingredients used in ED supplements.

Methods—Ten of the most common ingredients in ED supplements were reviewed using PubMed-indexed literature to assess their efficacy and safety in treating ED. Key findings were summarized to include historical use, active ingredients, prior animal studies, human studies, and toxicity.

Main Outcome Measures—Summary of the current literature on the efficacy and safety of common ED supplements.

Results—Nutraceuticals used in ED treatment include a variety of ingredients. While L-arginine is a safe supplement with clinical data supporting improved erectile function, limited data exist on the efficacy of other ingredients in the treatment of ED.

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Conclusion—Despite the growing use of supplements for treatment of sexual dysfunction, ED supplements remain poorly studied, with limited data demonstrating efficacy of individual ingredients. Further study is required to definitively determine the efficacy of nutraceuticals in ED treatment.

Introduction

Medical concerns pertaining to sexual health and erectile dysfunction (ED) are often uncomfortable for men to discuss due to the personal nature of these conditions. However, men with ED endorse feelings of guilt and shame due to difficulty with initiating sexual contact and intimacy[1]. Given that ED is a multidimensional condition with a significant psychogenic component, tools have been developed to set a threshold for which patients with ED can reasonably be considered for psychological treatment in order to mitigate psychologic distress[2,3]. Furthermore, significant advancements in ED treatment have resulted from the development of sildenafil citrate and other phosphodiesterase type 5 (PDE5) inhibitors[4]. Despite these advancements, PDE5 therapy has a 50% discontinuation rate, with no single identifiable factor accounting for the drop-off[5]. Consequently, men with ED often seek non-prescription, alternative therapies due to reluctance to discuss the condition with physicians, poor insurance coverage, and high medication costs[5].

Nutraceuticals and dietary supplements are an accessible alternative that men with ED use to attempt to address their sexual dysfunction. As public awareness of sexual health conditions grows, the demand for dietary supplements to treat these issues is likely to increase. Cui et al. reported that men who seek urologic evaluation often also use dietary supplements to address disorders such as ED, but the use of nutraceuticals for sexual dysfunction is increasingly common regardless of whether men seek medical work-up[7]. Balasubramanian et al. identified that online marketplaces such as Amazon.com are popular avenues for men to acquire nutraceuticals that purport to enhance sexual function[8,9]. The online presence of nutraceuticals highlights the importance for medical practitioners to understand the ingredients commonly contained within these products.

Hundreds of ED supplements are available to consumers online and the sale of these products is likely to expand given that consumers increasingly prefer shopping online[10,11]. Recent work has identified that ginseng, L-arginine, tongkat ali, horny goat weed, tribulus, maca, muira puama, zinc, saw palmetto, and fenugreek are among the most common active ingredients used in ED supplements[9]. Studies characterizing the ingredient profiles of popular online ED supplements have revealed that most of these products are composed of varying quantities and proportions of these common ingredients[7–9]. The ubiquity of these ingredients raises the importance of understanding the evidence supporting their efficacy and inclusion in these products. Here we review the literature on the use of these ingredients and their efficacy and safety as treatments for ED.

Materials and Methods

Prior studies have analyzed ingredients contained within popular supplements available on various online marketplaces [7,9]. We identified the ten most common ingredients in these

studies and reviewed PubMed-indexed literature to assess their efficacy and safety in treating ED. Here we summarize the current literature on mechanism of action, animal studies, randomized clinical trials (RCT), and meta-analyses detailing the use of these ingredients in ED therapy.

Ginseng

Ginseng is an herb derived from the *Panax* genus of plants. *Panax* plants are colloquially named based on their geographical origins, with Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolium*) as the two most commonly studied variants[11].

Ginseng that is less than 4 years old is classified as fresh ginseng, while white ginseng (4–6 years old) and red ginseng (dried ginseng more than 6 years old) are characterized based upon their longer processing times[12]. Extracts and powders derived from ginseng have historically been used in Asian culture as an aphrodisiac and herbal remedy for enhancing sexual function and satisfaction[13]. Ginseng continues to be used to improve sexual performance and is the most commonly used ingredient in men's health supplements for ED[7].

Ginseng is composed of biologically active compounds called ginsenosides and ginseng saponins. Both compounds are reported to increase nitric oxide (NO) synthase activity and facilitate blood flow to the penile corpora cavernosa [14]. Studies evaluating the mechanism of action of ginseng berry extract in rat models demonstrated that the herb increases intracavernosal pressure in a dose-dependent fashion[15].

Randomized controlled trials (RCTs) employing ginseng have assessed the herb's efficacy in improving erectile function. Jang et al. performed a meta-analysis of ginseng's effects on erectile function, encompassing seven RCTs. Outcome measures included both self-reported symptomatic improvement as well as pre- and post-treatment International Index of Erectile Function (IIEF) scores. Although 6 of the 7 RCTs reported statistically significant improvements in erectile function, the included studies utilized different doses, supplementation regimens, and heterogenous study populations[16–19]. Consequently, the generalizability of these findings is difficult due to a lack of standardized supplementation protocols. Furthermore, mild side effects of headache, insomnia, abdominal pain, and constipation were observed, although no severe adverse reactions were reported[19].

Another key limitation in the use of ginseng for ED includes uneven distribution of ginseng saponins and ginsenosides in the *Panax* plant, which leads to dosing and concentration inconsistencies when nutraceuticals from ginseng extract are made[20]. Nevertheless, ginseng remains the most extensively studied herbal ingredient in products advertised to improve sexual performance and erectile function, with multiple trials conducted on human subjects[9]. Ginseng appears to have some efficacy in treating ED over placebo, but despite its benign side effect profile, the quality of studies examining its effects is low and additional research is needed to evaluate the efficacy of ginseng for the treatment of ED[19].

L-Arginine

The amino acid L-arginine is a precursor to NO and is converted by NO synthase[21]. L-arginine increases the availability of NO and cyclic guanosine monophosphate, thereby leading to improved erectile function, and is a common ingredient in ED supplements.

When given in doses that exceed the body's physiologic production, supplemental L-arginine can increase somatic concentrations of NO. This increased bioavailability of NO is believed to improve erectile function[7]. Studies investigating long-term L-arginine supplementation in rats observed that exogenous L-arginine significantly increases maximal intracavernosal pressures (MIP) from 86 +/− 6 to 104 +/− 4 mm Hg ($p = 0.04$)[22]. Subsequent work by Moody et al. reaffirmed that penile NO synthase activity increases in rats that are fed L-arginine[22]. These improved markers of erectile function in animal models suggest that L-arginine improves penile blood flow and prompted further study in human subjects.

A placebo-controlled RCT conducted by Chen et al. in 50 men with ED demonstrated that 31% of men taking a daily 5 gram (g) dose of L-arginine for a 2 week period reported improved erectile function on O'Leary's sexual function questionnaire. In contrast, only 12% of men in the placebo group reported improved erectile function[23]. Another RCT on a European sexual improvement product, which included L-arginine as a key ingredient, reported that men with ED noted improvement in their erectile function using the IIEF-5 questionnaire from a baseline of 15.2 +/− 6.6 points to 27.1 +/− 2.1 points after six months ($p < 0.05$). This is a significant improvement compared to men treated with the placebo whose IIEF scores improved from a baseline of 15.1 +/− 7.0 points to 19.0 +/− 3.1 points in the same time frame[24].

Chang et al. conducted the first systematic review and meta-analysis on the efficacy of L-arginine supplementation in ED, reporting on 10 RCTs that met inclusion criteria[25]. Arginine supplementation resulted in significant improvements in subjective ratings of erectile function when compared to untreated or placebo-treated men. Furthermore, although higher rates of headaches, itching, and insomnia were noted, the severity of these side effects with L-arginine was minimal[25]. Notably, a high degree of heterogeneity was observed in the meta-analysis, but the data remains significant and the use of L-arginine for ED treatment does not appear to be contraindicated.

Despite the apparently successful use of L-arginine in improving erectile function in animal models and human studies, its use in nutraceuticals should continue to be studied in order to better define its side effect profile and optimize dosing for addition to supplements.

Tongkat Ali

Tongkat ali is an herbal supplement derived from the *Euyrcoma longifolia* plant native to Southeast Asia. Traditionally it has been used as an aphrodisiac due to its ability to increase testosterone levels[26]. A number of its active chemical compounds have been isolated, including canthin-6-one alkaloids, quassinoids, squalene derivatives, and eurycolactone[27].

However, no specific studies on the libido enhancing properties of these chemicals are documented in the literature and little is known about their mechanism of action[26].

Tongkat ali has been investigated in animal models with studies reporting that rats demonstrate increased copulatory behavior and sexual activity in both middle-aged and old subjects[28–30]. Subsequent studies of the effects of tongkat ali on erectile function in men are limited, however. Kotirum et al. reported in a 2015 meta-analysis that two RCTs on the effects of tongkat ali on men with ED suggested that the herbal supplement may have a positive impact on erectile function[26]. Although both studies noted improvement in erectile function, the study conducted by Ismail et al. included patients that reported higher baseline levels of erectile function, with an improvement from 25.37 +/− 0.48 points to 26.79 +/− 0.44 points in total IIEF score ($p < 0.001$)[31]. Udani et al. demonstrated a significant increase in 7 out of 11 categories of the sexual intercourse assessment (SIA) ($p < 0.05$); however, this may be attributed to the overall lower baseline erectile functionality[32].

No adverse effects were noted as a result of the tongkat ali administration in either study[31,32]. Despite the reported improvements in erectile function, further research is needed to investigate and confirm tongkat ali's efficacy in stimulating erectile function. There is currently inadequate evidence to suggest that tongkat ali is an effective treatment for ED.

Horny Goat Weed

Horny goat weed (HGW) extract is derived from the *Epimedium grandiflorum* plant. Named after its aphrodisiac effects on goats who ate the leaves of *E. grandiflorum,* HGW is commonly used in many men's health supplements[33]. The bioactive ingredient in HGW is icariin, which has historically been used as an aphrodisiac and herbal treatment for ED in Chinese men[34]. Icariin has PDE5 inhibitor activity *in vitro* and may mimic some properties of testosterone[7]. Studies suggest icariin also enhances smooth muscle proliferation and has neurotrophic effects that may be beneficial for treatment-refractory ED in the context of hypertension or diabetes-induced endothelial cell damage[35–37].

Shindel et al. examined the effect of varying dosages of icariin (1 mg/kg, 5 mg/kg, and 10 mg/kg) on intracavernosal pressure (ICP) in rats with surgical injury of the cavernous nerve over the course of 4 weeks[35]. Icariin increased intracavernosal pressure, and rats in the 1 mg/kg and 10 mg/kg groups had significantly increased ICP/MAP ratios ($p < 0.05$). Rats treated with 5 mg/kg icariin had higher mean ICP/MAP ratios, but the difference was not statistically significant (confidence interval: −0.8187–0.0313). Icariin also increased penile expression of neuronal NO synthase on Western blots in all treatment groups as compared to rats that did not receive icariin[35]. Though these preliminary studies are promising, further studies on the use of HGW in both animal and human models are scarce. Additionally, no definitive studies have characterized the utility or toxicity of icariin in humans. With a lack of both evidence-based efficacy and an understanding of its side effect profile, further studies on HGW should be performed to assess its application in treatment of ED.

Tribulus Terrestris

Tribulus terrestris is an herbal plant discovered in parts of Greece, China, and India that has been claimed to improve physical performance and sexual activity[38]. Historically, tribulus has been used to alleviate infections and inflammation in addition to enhancing fertility, increasing libido, and improving erectile function[39].

Tribulus is composed of the biologically active compounds saponins and tannins[39]. Saponins are known to increase NO activity[14]. Adaikan et al. reported pro-erectile effects in rabbit corpora cavernosa when treated with tribulus over an 8 week course[40]. Tribulus has also been reported to increase libido and serum testosterone in rat models of sexual dysfunction[41]. Despite the promising nature of these animal studies, Qureshi et al. reported in a systematic review of the performance enhancing effects of tribulus that although animal models have increased serum testosterone, no increase in testosterone was observed in men[42].

Fewer studies on the effects of tribulus on erectile function have been conducted in humans. Santos et al. found no improvement in ED symptoms or IIEF scores in men treated with tribulus when compared to a placebo in an RCT [43]. However, a more recent double-blinded RCT conducted by Kamenov et al. reported that although treatment with 1500 mg of tribulus terrestris over the course of 12 weeks did not increase serum testosterone levels, IIEF scores were 2.7 points higher in men treated with tribulus compared with those in the placebo group[44]. No difference in adverse effects was noted between the two groups.

No other human studies on the effects of tribulus on sexual function have been conducted, so inadequate evidence exists to define its utility in treating ED. Furthermore, though no definitive studies have been conducted on the side effect profile of tribulus, case reports of renal failure and liver failure have been documented following its consumption[45,46]. Given the lack of evidence supporting its efficacy in ED treatment and the potential for toxic side effects, further research is required to assess ED supplements containing tribulus.

Maca

Maca is a vegetable derived from the *Lepidium meyenii* plant and has been historically used as both a nutritional supplement and fertility enhancer[33]. Studies on the usage of maca for sexual enhancement are limited, and to date there is no clearly understood mechanism of action. When studied in animal models, a lipid extract derived from the *Lepidium meyenii* plant demonstrated increased sexual behavior in male mice and rats as measured by the number of complete intromissions over a 3-hour time period[47]. No specific studies on maca's effects on ED in animals have been reported in the literature.

Although there is still limited data on maca's use in human trials, Shin et al. conducted a systematic review of the literature to identify studies evaluating maca's effects on humans[48]. Four RCTs successfully met the inclusion criteria, of which three discussed effects of maca on healthy men, postmenopausal women, and athletes[49–51]. One trial discussed the effect of 2400 mg of maca for 12 weeks on men with erectile dysfunction using the IIEF-5 score and reported that patients treated with both maca and a placebo

observed an increase in erectile function at the end of the treatment period. However, patients taking maca reported a greater improvement in IIEF scores than patients treated with the placebo (1.6 +/− 1.1 versus 0.5 +/− 0.6 points, $p < 0.001$)[52]. Despite these findings, Shin et al. concluded that there is not enough evidence to establish a relationship between the usage of maca and improved sexual function due to the limited number of trials, small sample size, and varying supplementation regimens[48].

Only one study has reported that maca improves erectile function in men with ED[52]. There is limited additional literature to suggest maca is an effective supplement in ED treatment. Furthermore, no studies have been conducted on the adverse effects of maca and its side effect profile remains unknown; as such further research is required to determine its role in the management of ED[48].

Muira Puama

Muira puama is most commonly found in Brazil. In Amazonian folk medicine, the plant has a reputation for increasing sexual desire and function in men and women, but little is known about its mechanism of action[11]. Very limited literature exists on the effects of muira puama on erectile function. A 2015 animal study involving use of muira puama in conjunction with L-citrulline, ginger, and *Paullinia cupana* demonstrated improvement in age-related erectile function and NOS expression comparable to that observed with PDE5 inhibitor therapy in rat models[53]. Human studies, however, are more scarce. One study on muira puama assessed the efficacy of a commercially available supplement containing muira puama and gingko in improving libido and anorgasmia in 202 postmenopausal women. Of the women who participated, 65% reported increase in frequency and intensity of sexual thoughts and improved ability to achieve orgasm[54].

More recently, the dietary supplement Revactin®, which is primarily composed of muira puama extract, L-citrulline, ginger extract, and guarana extract, has become an increasingly popular option for ED treatment in affected men. Nguyen et al. studied its safety profile and efficacy in treating ED in 54 middle-aged men given Revactin® twice daily, with erectile function assessed every month using the IIEF. Over the course of three months, men treated with Revactin® reported an IIEF score of 21, 22, and 19 points as compared to a baseline of 16, 15.5, and 14.5, with only 5 patients reporting minor side effects such as sleeplessness, headaches, and heartburn[55]. However, the results of this study are limited by the fact that Revactin® contains multiple ingredients that may positively impact erectile function. Thus, further studies are needed to more definitively determine the effects of muira puama alone on erectile function.

Zinc

Few studies have evaluated the impact of zinc supplementation on improving erectile function[7]. Zinc, however, is commonly included in dietary supplements targeted at improving overall sexual function. Mild zinc deficiency is associated with decreased serum testosterone levels and oligospermia in men[56]. Moderate zinc deficiency has been associated with more severe hypogonadal symptoms[56,57]. Supplemental zinc can both

boost serum testosterone levels and improve hypogonadal symptoms in men with zinc-poor diets[58]. Although zinc supplementation may confer benefits for certain patients, the element is abundantly present in the standard American diet. Thus far, limited evidence exists that zinc supplementation increases testosterone levels or overall sexual function in men with adequate zinc intake.

Althoughzinc can improve sexual desire in rats in a dose-dependent fashion, no studies have evaluated its efficacy in the treatment of ED[59]. Given the limited body of literature evaluating this ingredient, further work is required to assess its impact on overall sexual function. Although many nutraceuticals claiming to improve erectile function contain zinc, the lack of literature supporting its use highlights how ingredients included in these products are often done so without adequate scientific support.

Saw Palmetto

Saw palmetto is an herbal supplement prevalent in southern regions of North America. It is extracted from the American palm tree, and its use in the treatment of lower urinary tract symptoms is well documented[60,61]. Saw palmetto's mechanism of action remains unknown, despite it being one of the best-studied supplements in the urologic literature. These studies have shown that saw palmetto has a benign side effect profile when used to treat urinary symptoms, with the only documented adverse effect being mild gastric distress[62].

The effects of saw palmetto on sexual function, however, are poorly studied. Yang et al. reported that saw palmetto has PDE5 inhibitor properties and noticed an increase in inducible NO synthase mRNA expression on Western blot in rat and rabbit corpus cavernosa muscle tissue[63]. However, such studies have yet to be replicated in human trials. The paucity of data examining the effects of saw palmetto on erectile function highlights the importance of undertaking further research to assess whether or not it should be included in ED-oriented nutraceuticals. Until the body of literature on saw palmetto expands, physicians should counsel patients that further work is required to assess its mechanism of action as well as the ingredient's influence on sexual health and erectile function.

Fenugreek

Fenugreek is derived from the *Trigonella foenum-graecum* plant, and has been used extensively in Ayurvedic, Chinese, and Unani medicine. Fenugreek seed extract is reported to improve libido, glucose control, cholesterol levels, and circadian rhythm[7]. The extract is composed of numerous enzymes, amino acids (including arginine), vitamins, and lipids[7,64].

Prior studies have examined the relationship between fenugreek and sexual health. Aswar et al. compared the effects of fenugreek extract on testicular development in sexually immature rats. Though the authors observed that fenugreek increased anabolic activity resulting in increased muscle mass, it did not affect testosterone levels or testicular architecture at a histologic level[65]. Only two RCTs have studied the use of fenugreek in treatment of sexual dysfunctions. Steels et al. reported that men treated with oral fenugreek observed increased

libido as measured by DISF-SR scores compared to men receiving placebo, but that serum testosterone parameters were unaffected [66]. Another RCT reported that use of 200 mg of fenugreek for 8 weeks significantly improved hypogonadal symptoms as well as IIEF scores; patients treated with fenugreek had an increase in IIEF scores from baseline by 4.66 +/− 10.30 points ($p = 0.015$). By contrast, patients treated with placebo had a IIEF score decrease of 3.82 +/− 9.15 points from baseline ($p = 0.008$)[67]. Both studies noted no significant adverse effects associated with fenugreek use.

Despite its aphrodisiacal and medicinal properties, consumption of fenugreek can have toxic effects. Ouzir et al. reported teratogenic, anti-fertility, and neuropathological effects in conjunction with fenugreek consumption in various animal models[68]. Ouzir et al. more specifically reported significant spermatotoxic effects and decreased testicular weight in rat, mouse, and rabbit models[68]. The data on fenugreek's utility in improving sexual function are sparse and sometimes conflicting, and no studies have been conducted specifically on its application in ED treatment. Taken together, these data underscore the need for further studies to assess both the safety and efficacy of fenugreek therapy.

Other Common Ingredients

Numerous other ingredients are found in popular dietary supplements and nutraceuticals marketed for improvement in sexual function. Though our review focuses on the top ten ingredients identified in a prior study, the current literature on several other common ingredients is presented here[9].

Yohimbine is one of the most well-studied ingredients in urology, with reported improvement in sexual dysfunction[20]. Yohimbine serves as an alpha-2 antagonist and was commonly used as an enhancer of sexual function prior to the availability of commercial PDE5 inhibitors[69]. Though no recent reviews of yohimbine's effects on sexual dysfunction have been published, a 1998 meta-analysis reported that yohimbine is a generally effective treatment for ED as compared with placebo[70]. Furthermore, adverse effects are limited and it is considered a safe natural ingredient for ED. However, without studies analyzing the efficacy of yohimbine compared with conventional PDE5 inhibitor therapy, yohimbine is not recommended as a first-line ED treatment.

Another ingredient commonly used in aphrodisiacs is *turnera diffusa*, (also known as *Damania aphrodisiaca*) which is commonly found throughout Central and South America. Turnera is a well-regarded aphrodisiac throughout Latin American culture and is commonly thought to stimulate sexual desire and performance[71]. Benelli et al. reported that turnera increases copulatory behavior in sexually impotent rats, indicating the potential for its use in ED[72]. No studies have thus far been conducted in humans, however, and turnera's efficacy as treatment for ED remains unclear.

Though it is more frequently used to treat patients with hypertension and dementia, *ginkgo biloba* is also commonly included in ED supplements[20]. Although one study with ginkgo reported improvement in erectile function of men with SSRI-induced ED, further analysis of the study demonstrated poor methodology and no conclusions can be drawn from the

results[73]. Two subsequent RCTs reported that ginkgo did not improve erectile function as compared with placebo, making it a poor agent in ED treatment[74,75].

Future Directions

PDE5 inhibitors such as sildenafil are a mainstay in the treatment of ED[4]. Although PDE5 inhibitors are FDA approved, several factors drive men to seek alternative therapies to improve erectile function[3,5]. Insurance reimbursement policies for ED treatments often lack transparency and are limited in coverage, and men are often reluctant to visit healthcare practitioners. As such, men are led to consider dietary supplements and nutraceuticals[76]. Supplements targeting ED emerge as popular options owing to ease of access, high consumer interest, and lower cost than prescription drugs[9]. The present review focused on analyzing ingredients commonly used in popular ED supplements[9].

L-arginine is the only ingredient in ED-oriented nutraceuticals to reproducibly demonstrate significant improvements in erectile function across multiple human trials[25]. Its efficacy is likely driven by the increased bioavailability of NO, which may enhance erectile function[7]. Ginseng was the most commonly used herbal ingredient in ED supplements[7]. However, despite ginseng's reported improvements in erectile function, enthusiasm about this ingredient is tempered by the fact that RCTs evaluating its efficacy suffer from poor methodology and inconsistent dosing regimens, suggesting the need for significant additional study prior to making conclusions[19]. As such, healthcare practitioners should counsel patients seeking to use ginseng products about this lack of consistency among studies examining its influence on erectile function. Additionally, the uneven distribution of ginseng's active ingredients throughout the plant are another concern due to challenges with standardizing ginseng's concentration in supplements. Despite these limitations, ginseng remains a potentially promising supplement that could be recommended to men with ED in the future.

Many other ingredients in nutraceuticals, including tongkat ali, HGW, tribulus, maca, muira puama, zinc, saw palmetto, and fenugreek have limited studies assessing their efficacy in treating ED in men. While many of these ingredients may demonstrate efficacy in enhancing erectile tissues when administered individually and under controlled *in vitro* conditions, nutraceuticals often feature a mix of many of these ingredients at high dosages. Many supplements also have active ingredients that are incompletely tested and potentially unsafe[77]. Further research is required to define efficacy of key ingredients and optimum doses of each ingredient; while individual ingredients and dosages may be safe in isolation, supplements that incorporate multiple ingredients may have detrimental effects.

Outside of the ingredients included in these products, it is equally important to discuss the manufacturing processes and online context in which these products are featured. Following passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, supervision of the production and distribution of dietary supplements declined[78]. The impact of this variability in manufacturing is evidenced by the fact that some nutraceutical ED supplements are contaminated by PDE5 inhibitors[79–81]. Given the possibility for

contamination, practitioners should inform patients about the fact that these herbal supplements may contain unreported compounds.

E-commerce and online retailers have provided consumers convenient and anonymous avenues to obtain these products. Given that online reviews are prominently featured on ED supplement product pages, consumers utilize these testimonials to validate the efficacy of the supplements they seek to purchase. Although these product reviews claim that supplements can lead to considerable improvement in ED, recent work has shown that product reviews are of questionable reliability, as vendors may post fake reviews or pay consumers to falsely claim product efficacy[82,83]. Providers should consider counseling patients about the importance of critically evaluating online information about ED supplements and to scrutinize the veracity of consumer reviews associated with these products.

Men with ED will continue to seek cheaper alternatives to conventional medications as well as to refrain from contact with healthcare practitioners. The Italian Society of Andrology and Sexual Medicine (SIAMS) has reported that though there is some evidence for the use of nutraceuticals in sexual medicine, the body of literature remains limited[84]. As such, nutraceuticals and their active ingredients should be studied in order to better understand their safety and efficacy in treating ED and other conditions. In the present we have discussed the efficacy of ingredients commonly included in ED oriented nutraceuticals and our results corroborate the findings of the SIAMS. While L-arginine has been extensively studied and concluded to be safe and efficacious in ED treatment, the majority of other ingredients have a limited pool of studies assessing their efficacy in humans. While these supplements should continue to be studied in order to ensure maximal safety in ED patients who seek alternative therapies, medical providers should counsel patients about the risks associated with purchasing nutraceuticals for ED including the lack of regulation, risk of contamination, and limited efficacy data.

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Conflicts of Interest

Dr. Pastuszak

- Endo Pharmaceuticals – advisor, consultant, speaker, research support

- Boston Scientific – advisor

- Antares Pharmaceuticals – advisor

- Bayer AG- speaker

Dr. Lipshultz

American Medical Systems (Speaker)

AbbVie (Consultant)

Lipocine (Consultant)

Aytu Bioscience (Consultant)

Endo Pharmaceuticals (Speaker/Consultant)

Dr. Hotaling

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Streamdx (Equity)

Andro360 (Equity)

Nanonc (Equity)

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Table 1:

Overview of relevant studies on ginseng and L-arginine in the treatment of ED

Ginseng			
Mechanism of Action (MOA): Increased NOS synthase activity and facilitate blood flow to corpora cavernosa			
Author	**Study Type**	**Outcome Measure**	**Results**
Cho et al. (2013)	In vivo rat model	Rat intracavernosal pressure	Ginseng berry extract increases intracavernosal pressure in a dose-dependent fashion
Jang et al. (2008)	Meta-analysis	IIEF score	Some evidence exists that ginseng improves erectile function; however, low methodological quality makes it difficult to draw definitive conclusions
L-Arginine			
MOA: Increase somatic concentration of NO			
Moody et al. (1997)	In vivo rat model	NOS expression and MIP	Penile NOS and MIP are significantly increased in rats fed L-arginine
Chen et al. (1999)	RCT	O'Leary's sexual function questionnaire	31% of men treated with L-arginine reported improved erectile function compared to 12% of men in the placebo group
Ledda et al. (2010)	RCT	IIEF-5 score	Men treated with L-arginine had improved erectile function on IIEF-5 scores compared to men treated with placebo
Chang et al. (2018)	Meta-analysis	IIEF score	Multiple RCTs provide evidence that arginine supplements can be recommended to patients with mild to moderate ED

Table 2:

Overview of relevant studies on tongkat ali and horny goat weed in the treatment of ED

Tongkat Ali			
Mechanism of Action (MOA): No clear mechanism of action			
Author	**Study Type**	**Outcome Measure**	**Results**
Kotirum et al. (2015)	Meta-analysis	IIEF-5 score	Herbal extract from tongkat ali may have an effect on erectile function, but further studies are required to establish efficacy in treatment of ED
Ismail et al. (2012)	RCT	IIEF-5 score	Men treated with tongkat ali extract reported improved erectile function on IIEF-5 scores than men treated with placebo
Udani et al. (2014)	RCT	Sexual intercourse assessment (SIA)	Significant improvement was reported in multiple subjective erectile function scores in men treated with tongkat ali extract
Horny Goat Weed			
MOA: PDE5 inhibitor activity			
Shindel et al. (2010)	In vitro rat model	ICP/MAP ratios and NOS expression	Icariin treated rats had higher mean ICP/MAP ratios and penile expression of NOS on Western blot
Zhang et al. (2013)	In vivo rat model	cGMP expression and NOS expression	Icariin increased the expression of cGMP and NOS in diabetic rat models of ED
Long et al. (2018)	In vitro rat model	eNOS coupling	Icariin inhibits eNOS coupling and may be an important mechanism of improving erectile function in rats

Table 3:

Overview of relevant studies on tribulus terrestris and maca in the treatment of ED

Tribulus Terrestris			
Mechanism of Action (MOA): Increased NO activity			
Author	**Study Type**	**Outcome Measure**	**Results**
Adaikan et al. (2000)	In vitro rabbit model	Tissue response to electrical field stimulation	Corpora cavernosa of rabbits treated with tribulus demonstrated pro-erectile function
Qureshi et al. (2014)	Meta-analysis	Serum testosterone	Animal models treated with tribulus have increased serum testosterone but no increase was observed in men
Santos et al. (2014)	RCT	IIEF score	No improvement was noted in men treated with tribulus compared to men treated with placebo
Kamenov et al. (2017)	RCT	IIEF score	Tribulus treatment did not increase serum testosterone levels, but did increase IIEF scores
Maca			
MOA: No clear mechanism of action			
Zheng et al. (2000)	In vitro rat and mouse models	Number of intromissions per 3-hour period	Increased sexual behavior was observed in male mice and rats treated with maca
Zenico et al. (2009)	RCT	IIEF score	Increased erectile function was observed in men treated with maca
Shin et al. (2010)	Meta-analysis	IIEF score	Not enough evidence exists to establish a relationship between maca usage and improved sexual function

Table 4:

Overview of relevant studies on muira puama and zinc in the treatment of ED

Muira Puama			
Mechanism of Action (MOA): Increased NOS expression			
Author	**Study Type**	**Outcome Measure**	**Results**
Ferrini et al. (2015)	In vitro rat model	NOS expression	Rats treated with muira puama had increased age-related erectile function compared with those treated with PDE5i therapy
Waynberg et al. (2000)	Survey	Independent sexual satisfaction questionnaire	Muira puama increased frequency and intensity of sexual thoughts and improved ability to achieve orgasm
Nguyen et al. (2018)	Prospective study	IIEF score	Treatment with Revactin improved erectile function as compared to baseline
Zinc			
MOA: No clear mechanism of action			
Prasad et al. (1995)	Cross-sectional study	Serum testosterone	Supplemental zinc increases serum testosterone levels and improves hypogonadal symptoms in men with zinc-poor diets

Table 5:

Overview of relevant studies on saw palmetto and fenugreek in the treatment of ED

Saw Palmetto			
Mechanism of Action (MOA): Increased NOS expression			
Author	**Study Type**	**Outcome Measure**	**Results**
Yang et al. (2013)	In vitro rat and rabbit model	NOS expression	Saw palmetto increased PDE5 inhibitor properties in rat and rabbit tissues
Fenugreek			
MOA: No clear mechanism of action			
Aswar et al. (2010)	In vitro rat model	Histologic analysis	Fenugreek increased anabolic activity but had no effect on testosterone levels or testicular architecture
Steels et al. (2011)	RCT	DISF-SR scores	Men treated with oral fenugreek had increased libido compared to placebo
Park et al. (2018)	RCT	IIEF score	Fenugreek use resulted in significantly improved IIEF scores as compared to placebo