



Plant-Derived Supplements for Sexual Health and Problems: Part 1—Trends over the Past Decade

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Abstract

Purpose of Review In this update on plant-derived supplements, we provide a general introduction regarding the status and interest in phytochemicals for sexual health, indicating both progress and problems with past and current research.

Recent Findings We summarize the development and current status of two well-known plant-derived supplements, using them as case studies for understanding some of the problems associated with the study of such supplements on sexual health.

Summary We interpret the current situation regarding plant-derived supplements, identify common sources/journals for information about medicinal herbs for sexual health, identify supplements that are garnering increasing attention within the research community, and discuss the larger potential and pitfalls associated with this domain of research.

Keywords Phytochemicals · Herbs · Plant-derived supplements · Sexual health · Sexual dysfunction · Sexual desire · Erectile function

Introduction

Plant-derived dietary supplements for improving health continue to be an expanding business. According to Statistics MRC, the Global Herbal Supplements market reached \$49.1 billion in 2016 and is expected to grow to \$86.7 billion by 2022, increasing at a compound annual growth rate (CAGR) of 9.9%. In the USA and elsewhere, such supplements are typically promoted for physical and mental health, treating disorders, and preventing disease. No longer is this business the domain of smaller, independent manufacturers and retailers; given the continually growing market worldwide, larger pharmaceutical houses and food producers have shown increasing interest in such products.

As sexual problems are estimated to affect about 1/3 of the population worldwide [1], it is not surprising that numerous

and extensive claims have been made about the sexual health benefits of many plant-derived dietary supplements. Yet these claims are often based upon folklore or hearsay. Although such lore is critically important to the initial stages of exploration, identification, and development of potentially new and effective treatments (indeed, phytochemicals have played an important role in both traditional and modern medicine), the rigorous scientific testing that needs to follow is often absent.

Multiple factors may account for the relative paucity of evidence-based reports regarding effects of supplements on sexuality. First, unlike prescription medications that necessarily undergo tests for both safety and efficacy prior to their approval for the general public [2•], dietary supplement manufacturers in the USA have no obligation to demonstrate *efficacy* in their products under the 1994 Dietary Supplement Health and Education Act (DSHEA) [3, 4], eliminating many of the requirements for validating evidence. Second, pharmaceutical companies that support research to bring patented drugs to market have little incentive to test herbal supplements, as the substance itself cannot be patented, but only the preparation and/or delivery method. Third, herbal supplements specifically marketed to improve sexual functioning often fail to differentiate between direct effects on the sexual response cycle—desire, arousal, orgasm—and indirect effects on comorbidities such as lower urinary tract

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symptoms (LUTS) or benign prostate hyperplasia (BPH) that may negatively impact sexual responsivity or otherwise exacerbate sexual dysfunctions [5•]. And fourth, in many cases, the molecular mechanisms through which these supplements are presumed to act have not been thoroughly elucidated. Moreover, even in cases where certain phytochemicals have been evaluated in animal models (e.g., rodent corporal cavernosal tissue), their findings have often not been replicated in human studies.

In 2002/2003, and later in 2007, we reviewed the literature on plant-derived treatments for sexual problems. In the initial review [6], we concluded that methodological problems plagued the research in this field, noting that (a) few studies distinguished clearly among effects on the various components of the sexual response cycle, that is, on desire/arousal, or orgasm; (b) most studies relied on self-reports of global improvements on vaguely defined outcomes such as sexual “performance”; (c) few studies provided a clear assessment of sexual functioning prior to use of the substance or partitioned out placebo effects; (d) studies often did not distinguish between effects on men and women; and (e) studies seldom distinguished general health benefits from those specific to sexual health and function. In retrospect, studies on plant-derived supplements were few and far between at that time, with studies often being preliminary, uncontrolled, and not indexed in major bibliographic databases, limiting both confidence in and access to the research. Nevertheless, our review offered several conclusions regarding specific supplements. Specifically, yohimbine had been extensively investigated and found to have small prosexual effects beyond placebo [7–9]. Both ginkgo and ginseng appeared to impart small prosexual effects, and even though the body of evidence was small, plausible biological explanations were offered or supported—based mainly on facilitated blood flow that might enhance genital response. For botanicals such as maca, damiana, muira puama, and *Tribulus terrestris*, evidence was yet too preliminary to draw conclusions regarding possible efficacy. Given the either low or unsupported efficacy, the potential for adverse effects, and the availability of other well-tested pharmaceutical options (e.g., for erectile dysfunction), there was little justification to recommend such supplements for sexual problems [6, 8, 10].

In a follow-up 5 years later, the number and ingredients of dietary supplements had expanded greatly [5•], and for several supplements, the number and quality of studies had increased. However, the overall findings at that time did not significantly alter the landscape: better research both eliminated supplement candidates and supported them. For men, ginkgo seemed to show little or no effect (although there has been a recent resurgence of interest), saw palmetto was supported primarily as a treatment for BPH/LUTS, and further research on maca, *Tribulus*, muira, damiana, and tongkat ali had either not been conducted or

demonstrated minimal or no positive effects. Only ginseng and horny goat weed (*Epimedium*) demonstrated moderate promise, and both required replication/confirmation in controlled studies using larger samples. For women, most compounds were directed toward relief from premenstrual or menopausal symptoms, with little attention to women’s sexual response.

Again, in retrospect, two developments may have accounted for the increased attention to the field of herbal medicine in the interim between 2002/2003 and 2007. First was the increased participation of emerging nations in the research enterprise (particularly in parts of Asia), where the use of indigenous approaches to illness and disease, including the use of local herbs and roots, has been supported by long-standing cultural traditions [11•, 12]. Second was the proliferation of supplements touted as prosexual, with most claims based on folklore rather than empirical research, thereby opening the door for investigation into the many newly identified supplements [13, 14••].

Since 2007, the number of published works on alternative and complementary medicine has literally mushroomed. Well over 20 journals—some distributed by major publishing houses, most indexed and abstracted, many online, and many purporting high-impact factors—now regularly publish alternative approaches to health/medicine, including the use of indigenous remedies and plant derivatives (see Table 1 for a list and description of relevant journals). While some of these journals have been longstanding (e.g., *American Journal of Chinese Medicine*, founded 1973), others have been part of the large proliferation of new (often online) journals that has occurred over the past two decades (e.g., *Journal of Herbal Medicine*, founded 2011; *International Journal of Herbal Medicine*, founded 2013). It appears that both respectability and opportunity have increased over the past decade for those conducting and publishing research on plant-derived supplements, both for general health and for sexual health in particular.

Case Studies of Two Well-known Herbal Supplements

Herbal supplements have, in some instances, shown initial promise for sexual health and, with ongoing research, demonstrated fairly consistent and positive effects. Other supplements have foundered as better-designed research studies were eventually implemented. In this section, we discuss two such supplements that represent one possible trajectory likely to be repeated by other supplements demonstrating initial promise regarding sexual health. These two—saw palmetto and yohimbine—were initially met with interest and optimism, thus stimulating a body of research that eventually

Table 1 List and description of select journals that publish research on herbal supplements, health, and sexual effects

Title of journal (current)	Publisher (current)	First issue	Approx impact factor	Scope	Papers on sexual health 2005 to current
<i>African Journal of Traditional, Complementary, and Alternative Medicines</i>	African Ethno-medicines Network (Nigeria)	2004	0.55 (2015)	Publish research in all areas of applied medicinal plants, traditional medicines, complementary alternative medicines, etc.	20
<i>Alternative Medicine Review</i>	Thorne Medicine Review	1996	3.00 (2014)	Original articles, abstracts, and literature reviews to the practicing preventive healthcare professional.	0
<i>Alternative Therapies in Health and Medicine</i>	InnoVision Health Media	1995	1.39 (2015)	Promotes the art and science of integrative medicine to promote health, prevent illness, and treat disease.	1
<i>The American Journal of Chinese Medicine: an International Journal of Comparative Medicine East and West</i>	World Scientific	1973	3.12 (2017)	Scientific and clinical research in indigenous medical techniques, therapeutic procedures, medicinal plants, and traditional medical theories/concepts.	4
<i>Asian Journal of Andrology</i>	Shanghai Institute of Materia Medica	1999	3.30 (2018)	Men's health and related interdisciplinary fields. Includes male reproduction; male infertility; male sexual dysfunction; and genetic factors and male health.	14
<i>BMC Complementary and Alternative Medicine</i>	Springer	2001	2.11 (2017)	Resources that complement or replace conventional therapies, with emphasis on research for biological mechanisms, efficacy, safety, costs, patterns of use, and/or implementation.	36
<i>Chinese Journal of Integrative Medicine (formerly Chinese Journal of Integrated Traditional and Western Medicine)</i>	China Academy of Traditional Chinese Medicine	1995	1.12 (2016)	Publishes clinical experiences, scientific research, article and book reviews, integrative medicine in China and abroad, proven remedies, and academic activities.	6
<i>Chinese Journal of Natural Medicines</i>	Elsevier	2003	1.11 (2014)	Resources of traditional Chinese medicines; natural products chemistry; pharmacology methods of natural products	5
<i>Complementary Medicine Research (formerly Research in Complementary medicine)</i>	Karger Publishers	1994	1.05 (2013)	Purpose is to bridge the gap between conventional medicine and CAM on a scientific basis, promoting mutual integration.	1
<i>Complementary Therapies in Clinical Practice</i>	Elsevier	1995	1.70 (2017)	Research, implementation of complementary therapies, legal/ethical concerns, philosophical analysis of emergent trends in complementary therapy, clinical judgment/practice.	3
<i>Complementary Therapies in Medicine</i>	Elsevier	1986	2.08 (2017)	Primary research, reviews, and opinion pieces on complementary therapies	4
<i>European Journal of Integrative Medicine</i>	Elsevier	2005	0.77 (2015)	Research articles and manuscripts for complementary and integrative health care disciplines, with a particular focus on	9

Table 1 (continued)

Title of journal (current)	Publisher (current)	First issue	Approx impact factor	Scope	Papers on sexual health 2005 to current
<i>Evidence-Based Complementary and Alternative Medicine</i>	Hindawi Publishing Corporation	2004	2.06 (2017)	whole systems approaches, public health, self-management, and traditional medical systems	23
<i>Explore: The Journal of Science and Healing</i>	Elsevier	2005	0.99 (2017)	Scientific journal for CAM modalities, especially Asian healing systems, and their health outcomes and biological mechanisms of action	3
<i>Focus on Alternative and Complementary Therapies</i>	Pharmaceutical Press	1996	0.28 (2017)	Interdisciplinary journal which includes scientific principles/applications of evidence-based healing practices, including CAM and cross-cultural medicine, as well as consciousness, healing arts, and environmental factors as they relate to health.	2
<i>Homeopathy</i> (formerly <i>British Homeopathic Journal</i>)	Elsevier	1911	1.52 (2017)	Presents evidence on CAM and features editorials, debates, book reviews, and research summaries accompanied by commentary.	2
<i>JAMA Internal Medicine</i> (formerly <i>Archives of Internal Medicine</i>)	(formerly Nature Publishing Group) American Medical Association	1908	19.99 (2017)	Covers research, reviews, and debates on all aspects of homeopathy.	10
<i>Journal of Alternative and Complementary Medicine</i>	Mary Ann Liebert	1995	1.50 (2017)	Provides innovative and clinically relevant research for practitioners in general internal medicine and internal medicine subspecialties.	4
<i>Journal of Asian Natural Products Research</i>	Taylor & Francis	1998	0.66 (2015)	Scientific research for evaluation and integration of complementary and alternative medicine into mainstream practice. Offers original research. Peer-reviewed	3
<i>Journal of Ethnobiology and Ethnomedicine</i>	Springer	2005	2.18	Chemistry-oriented. Elucidation of natural constituents (including those for non-medical uses), synthesis, and transformation of natural products, pharmacognosy	22
<i>Journal of Evidence-Based Integrative Medicine</i>	SAGE Publications	1995	0.62 (2014)	Research articles, reviews, and commentaries concerning the investigations of the inextricable links between human societies and nature, food, and health	7
				Research articles and reviews, correspondences, editorials, and book reviews on CAM, traditional eastern and western medicine, nutrition supplementation, non-traditional	

Table 1 (continued)

Title of journal (current)	Publisher (current)	First issue	Approx impact factor	Scope	Papers on sexual health 2005 to current
<i>Journal of Herbal Medicine</i>	Elsevier	2011	1.69 (2017)	treatments, preventative medicines, and integrative health and medicine Clinical and professional applications of botanical medicines. With research papers, case studies, research articles and reviews, opinion pieces, book reviews, conference proceedings, etc.	10
<i>Journal of Integrative Medicine</i> (formerly <i>Journal of Chinese Integrative Medicine</i>)	Elsevier and Science Press	2003	1.95 (2017)	Papers on integrative medicine, including traditional Chinese medicine, herbal medicine, homeopathy, nutrition, mind-body medicine, and other forms of CAM	9
<i>Journal of Natural Medicines</i>	Springer Singapore	2006	1.96 (2017)	Original research in naturally occurring medicines, natural products and herbs including chemistry, pharmacology, and biology	1
<i>Journal of Natural Products</i>	ACS Publications	1938	3.89 (2017)	Papers relating to the chemistry and/or biochemistry of naturally occurring compounds	5
<i>Journal of Orthomolecular Medicine</i> (formerly the <i>Journal of Schizophrenia</i> ; formerly <i>Schizophrenia</i>)	Canadian Schizophrenia Foundation	1967	0.77 (2017)	Nutritional research, clinical trials, reviews, letters, and reports describing the orthomolecular approach to health management and treatment of disease	1
<i>Natural Product Communications</i>	SAGE journals	2006	0.77 (2017)	Peer-reviewed journal bringing studies on all aspects of natural products	5
<i>Phytochemical Analysis</i>	John Wiley & Sons	1991	2.50 (2015)	Papers describing analysis of whole plants, plant cells, plant-derived extracts, and plant products	0
<i>Phytomedicine</i>	Elsevier	1994	3.13 (2014)	Studies on efficacy, safety, quality, and mechanisms of action of plant extracts, phytopharmaceuticals, and their isolated constituents. Therapy-focused	5
<i>Planta Medica</i>	Thieme Medical Publishers	2013	2.49 (2017)	Research papers, reviews, and perspectives from researchers on natural products, including fungi, micro-organisms, and medicinal plants	5

placed them on a parabolic path. In a companion paper in this journal, we discuss six supplements that appear to be following a very different path, showing, at least for now, consistently positive and upward development.

***Serenoa repens* (Saw Palmetto)**

Herbal preparations have the potential to improve, impair, or not affect sexual response. In some instances, a supplement may improve sexual function indirectly by improving overall reproductive health. Such was the initial argument underlying the case for *Serenoa repens* (saw palmetto), which has been promoted as a remedy for benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) in men. BPH is a common urological condition affecting aging men [15], and so research efforts to identify natural-based supplements that could mitigate BPH symptoms garnered significant attention. *Serenoa repens*, a palm native to the subtropical USA and particularly abundant in Florida and the Southern United States [16, 17], has long been incorporated in herbal formulations promoted to improve men's reproductive health [6]. Despite its commercial popularity, however, the mechanisms through which saw palmetto could presumably attenuate BPH or LUTS were not particularly clear. One contributing factor was that the bioavailability of phytosterols and fatty acids—many of which possess diverse cell signaling effects—depends upon the form of the supplement (e.g., liquid, capsule, or powder) [18]. The issue was further complicated by paradigm shifts in the etiology and treatment of BPH and LUTS. While early studies demonstrated that elevated androgen levels—particularly dihydrotestosterone (DHT)—could induce prostate cell proliferation [19, 20], more recent approaches have suggested that *low* androgen levels or altered testosterone to estradiol (T:E₂) ratios may actually contribute to disease progression [21, 22]. Finally, although comparisons with finasteride and tamsulosin—the drugs most commonly used to treat BPH [23]—have suggested that saw palmetto does not induce sexual dysfunction [24] as might occur with BPH prescription treatments, evidence supporting improvement in sexual responsivity has been meager or non-existent. While a single report has indicated that intragastrically administered saw palmetto extract can dose-dependently increase inducible nitric oxide synthase (iNOS) mRNA content and decrease phosphodiesterase-5 (PDE-5) activity in mouse and rabbit penile corpus cavernosum (processes related to erectile response [25]), these findings have yet to be independently verified.

Despite the paucity of evidence for sexual benefits, animal research has suggested that long-term saw palmetto administration may be protective against prostatic growth and inflammation. In one such study, male rats were randomized to consume normal or high caloric diets (the latter to induce obesity) over 40 weeks with concomitant supplementation with

lycopene, saw palmetto, or vehicle [26]. Absolute prostate weight in the obese, saw palmetto-supplemented rats was lower than that of normal weight controls, and furthermore, the prostate weight relative to total body weight in supplemented rats was significantly less than both the normal and obese controls, suggesting that saw palmetto might attenuate prostate growth in an animal model of diet-induced obesity. Such findings in rodents gave high hopes both to men suffering from BPH/LUTS and to the herbal supplement enterprise.

But in contrast to the observed benefits of saw palmetto supplementation in non-human species, human clinical work has largely failed to demonstrate any reasonable treatment effect. For example, Bent and colleagues [27] randomly assigned 225 men with BPH symptoms to receive either saw palmetto extract (2 capsules of 160 mg each) or placebo over 12 months, and found no differences in BPH symptoms, as assessed by the American Urological Association Symptom Index (AUASI) or urinary flow values. This lack of effect was confirmed in more recent studies on LUTS/BPH, where multiple doses and a variety of assessment procedures had been used [28, 29]. And finally, a meta-analysis published in 2012 concluded that saw palmetto was no better than placebo in reducing LUTS, based on a wide range of symptoms [30]. Thus, repeating the plight of other touted herbal supplements, while once seen as a means to promote urinary health in men, when investigated rigorously from a scientific approach, saw palmetto seems to offer no discernible benefit on urinary or prostate health.

While *Serenoa repens* may not be effective in reducing LUTS on its own, one recent study suggested that, in combination with other natural substances, it may serve as an enhancer. Urinary and ejaculatory parameters were assessed in men who received either tamsulosin monotherapy; a mixture of saw palmetto, selenium, and lycopene, or a combination of both treatments over a 12-month period [31]. Those receiving the combination therapy experienced greater decreases in International Prostate Symptom Score (IPSS) values and better urinary flow (Q_{max}) relative to either monotherapy condition. Unfortunately, this study provided no means to parse out the effects of saw palmetto from lycopene and selenium, so the study offered no definitive conclusion.

Despite the lack of evidence of efficacy in men, saw palmetto continues to be promoted as a supplement for sexual health. Fortunately, for those who do take it, saw palmetto appears to be relatively innocuous for healthy individuals at least in the short term, with the most frequent adverse events being headache, fatigue, and gastrointestinal (GI) discomfort [32•]. Moreover, saw palmetto supplementation has no apparent effect on liver P450 enzymes [33], indicating that its potential to interact with other medications is limited. Nevertheless, saw palmetto appears to offer little or no documented benefit on sexual health, so men currently have little/no rationale for its use for this purpose.

***Pausinystalia johimbe* (Yohimbe/Yohimbine)**

Pausinystalia johimbe, known as the yohimbe tree, grows abundantly in Central and West African countries [34]. While crude extracts of yohimbe bark, typically consumed as a beverage or tonic, have often been used by traditional medicine practitioners, the majority of animal studies and human clinical trials have relied upon the alkaloid yohimbine isolated from the plant [35].

The story of the scientific investigation of yohimbine dates back 3 to 4 decades, and we have included this supplement because it appears to provide a classic example of the fate of a purported plant-derived supplement for sexual response. Yohimbine is classified as an alpha-2 (α_2) adrenergic receptor antagonist [5•] and may thus promote erectile function in men by reducing inhibitory (i.e., detumescence) activity attributed to the α -adrenergic receptors [36, 37]. Moreover, yohimbine activity can increase nitric oxide (NO) release [38], and NO-mediated pathways are known to maintain erectile response [39–41]. Yohimbine use has been associated with adverse effects such as high-blood pressure, tachycardia, and GI upset [42], and cases of very high doses of yohimbine—reported predominantly in bodybuilders pursuing an unsubstantiated anabolic steroid effect—have resulted in seizures, vomiting, and cardiac dysfunction [43, 44]. Under certain circumstances, yohimbine can also exacerbate psychological conditions, such as anxiety, potentially by binding to α -adrenergic receptors in the locus coeruleus and other subcortical regions [45]. Despite these potentially serious side effects, yohimbine has proven mildly efficacious in improving erectile response.

Yohimbine stimulated a wave of studies in the last decades of the twentieth century, culminating in a surge of research on humans around the turn of the twenty-first century, including several that used a double-blind, placebo controlled design [9, 46–49]. Most such studies yielded mild effects, typically restricted to subsets of men who were not readily characterized (that is, it was not clear why some men responded and others did not). Furthermore, the magnitude and gravity of adverse effects tended to restrict further interest in yohimbine, with few men, for example, electing to continue the yohimbine regimen at the end of the trial.

Nevertheless, research into yohimbine's effect continued, though more typically on rodents, in order to demonstrate its potential on overall erectile functioning. For example, Senbel and Mostafa [50] attempted to demonstrate potential enhancing effects for yohimbine on rats injected with either placebo, sildenafil, yohimbine, or both yohimbine and sildenafil. Yohimbine alone had no potentiating effect on erection, but when combined with sildenafil, it prolonged the erectile response. Furthermore, sildenafil appeared to amplify the effect of yohimbine on male

copulatory performance though not on sexual motivation. Later, Saad and colleagues carried out a related study, demonstrating that yohimbine could induce direct relaxant activity on corpus cavernosal tissue [51]. Importantly, these benefits were apparently not associated with increases in androgen or gonadotropin levels, as testicular cholesterol concentration was unchanged. Other experiments have suggested that yohimbine may also act upon central nervous system (CNS) α -adrenergic receptors in rodents, thereby stimulating the spinal generator for ejaculation [52, 53]. With the relatively recent discovery of an analogous structure in men [54], this pathway may represent another mechanism through which yohimbine exerts prosexual effects.

Yohimbine has also been evaluated in women with desire and arousal disorders, albeit with limited utility. In the late 1990s, Piletz and colleagues [55] examined the effect of yohimbine supplementation (5.4 mg, thrice daily) in women presenting with hypoactive sexual desire disorder (HSDD), hypothesizing that lower desire was related to decreased CNS noradrenergic activity. To assess this possibility, the investigators measured 3-methoxy-4-hydroxyphenylglycol (MHPG), the predominant norepinephrine metabolite, at the follicular, ovulatory, and mid-luteal phases of the menstrual cycle. While yohimbine treatment significantly increased MHPG concentration relative to baseline, sexual desire was not different from placebo treatment. A second study evaluated the effect of yohimbine on female sexual arousal disorder (FSAD), operationally defined as the inability to maintain sufficient lubrication during sexual encounters with concomitant distress [56]. Participants received either yohimbine hydrochloride (6 mg), yohimbine hydrochloride plus L-arginine glutamate (dissolved in water), or placebo, 27 min prior to evaluation. The combination treatment (yohimbine and L-arginine) elicited significantly greater vaginal response relative to the placebo-treated counterparts, but yohimbine alone was not effective. More importantly, neither experimental condition significantly increased subjective measures of sexual arousal, indicating that the physiological changes in vaginal tissue were disconnected from the psychological perception of arousal, or that methods of arousal assessment were insufficient to detect changes. Yohimbine has also been evaluated as a potential regimen to ameliorate symptoms of fluoxetine-induced sexual dysfunction in women [57], but to no avail.

Taken together, the current body of evidence suggests that yohimbine supplementation may yield mild improvement in erectile function in men, with underlying mechanisms possibly identified. But its use is contraindicated for several health conditions, particularly diseases affecting the cardiovascular system, and the relatively high prevalence and gravity of adverse effects restricts the desirability and long-term use of this herb to mitigate ED symptoms. In women, yohimbine may have limited potential to improve biogenic aspects of vaginal response (e.g., lubrication), but it appears to have negligible effects on psychophysiological constructs—such as desire or arousal—that constitute the subjective sexual experience.

Table 2 A sampling of herbs appearing with relative frequency in journals on complementary and alternative medicine, 2006–2019

Herb/plant derivative	Number of citations	Phytochemical description	Reported effects on sexual behavior
<i>Mondia whitei</i> /ginger	17	Components: reducing sugars, triterpenes, phenolic compounds, flavonoids. Increases NOS activity with corresponding increased NO; generates cGMP, cross-activation PKA and generates cAMP	Aphrodisiac, improves libido Male: improves erection, increases testosterone levels
<i>Ginkgo biloba</i>	15	EGb761 and 304U-1. Components: flavonoid glycosides, kaempferol, quercetin glucorhamnoside esters, terpene lactone, and terpenes of ginkgolides and bilobalides. Circulation enhancer; inhibits MAO and uptake of certain neuro-transmitters (NA and 5-HT) in CNS; induces NO in endothelial cells; relaxing effect on corpus cavernosum tissue and vascular smooth muscle	Both sexes: increases blood flow to genitals, resolves SSRI-induced sexual dysfunction Female: increases sexual desire Male: facilitates erectile dysfunction recovery Rats: enhances erection, increases number of ejaculations. Recovery of erectile dysfunction
<i>Crocus sativus</i> /saffron	15	Contents: crocin, safranal, carotenoids, monoterpene aldehydes. Stimulates beta-2 adrenoceptors	Male: increased erectile effect freq. and duration in ED patients Female: improved fluoxetine-induced problems of arousal, lubrication, and sexual pain Rats: increased mounting freq., intromission freq., erection freq.; decreased erection latency, intromission latency, ejaculation latency
<i>Withania somnifera</i> /Ashwagandha	15	Components: steroid alkaloids (withanine), steroidal lactones (anolides), flavonoids. Down regulation of nNOS; decreases audiogenic stress-induced increase of NO _x levels in cortex, hypothalamus, hippocampus	Aphrodisiac, remedy for premature ejaculation, anxiety-related or stress-related sexual dysfunction
<i>Mucana pruriens</i> /velvet bean	9	L-3, 4-Dihydroxyphenyl alanine (L-DOPA), glutathione, lecithin, serotonin; increases protein level in testis and epididymis, increases epididymal alkaline phosphatase activity	Males: remedy for erectile dysfunction, increases testicular testosterone level Both sexes: arouses sexual desire
<i>Asparagus racemosus</i>	8	Steroidal saponins, flavonoids-glycosides, isoflavones, oligospirostanoside, polysaccharides, alkaloid-aspargamine	Rats (male): delays time of ejaculation, enhances penile erection, reduces hesitation toward females, assists sexual weakness, increases mounting freq., decreases mount latency, decreases ejaculation latency, decreases post-ejaculatory latency, decreases in intromission latency Rats (female): aphrodisiac, arouses sexual desire, enhances sexual appetite
<i>Chlorophytum borivilianum</i> /Safed Musli/white gold	6	Components: saponin, polysaccharide, Rho-kinase 2 inhibition	Male: improves penile erection. Remedy for premature ejaculation, remedy for erectile dysfunction Rats: aphrodisiac, increased mounting freq., increased intromission freq., increased ejaculation freq.

Therefore, the initial hope and optimism that had characterized early research on yohimbine has since faded, and given the limited benefit/cost ratio (mild or no effect relative to unpleasant side effects), interest and research have waned, largely disappearing altogether over the past decade with the exception of several residual rodent studies. Yohimbine is yet available in major retail stores and continues to carry a legacy as a prosexual supplement

on the web. Yet, one can only wonder why, when other proven pharmaceuticals are available for men with erectile problems, yohimbine, at least in its current preparation, would ever serve as the treatment of choice by the typical male with an erectile problem. The story of yohimbine may serve as a harbinger for other plant-derived supplements for sexual function—showing a meteoric rise and fall over the span of less than four decades.

Discussion

Unlike more promising herbal supplements currently under investigation (see the companion paper in this issue), a role for saw palmetto in alleviating BPH/LUTS symptoms has, upon rigorous testing, not been supported. In addition, clinical studies on yohimbine, after an initial crescendo, have decreased in recent years, suggesting waning interest and potential, likely due to its adverse/unpleasant side effects and the availability of more effective alternatives [9].

These two case studies demonstrate that the individual cost/benefit ratio of any herbal supplement will play heavily into decisions regarding its recommendation and use. While natural substances to improve sexual health may hold appeal for many men and women, the lack of control/confidence in product purity, together with uncertain efficacy and undocumented effects of long-term use, essentially renders objective evaluation of these supplements impossible. Not only might the long-term use of some supplements incur risk, but they may also interact negatively with over-the-counter and prescription medications [58–60]. The problem is that, unlike with pharmaceuticals that have undergone clinical trials and obtained regulatory agency approval, neither the manufacturer/distributor nor the user is able to assess the true benefit/cost ratio of herbal supplements, as the *magnitudes* of neither parts of this ratio have been documented.

As mentioned previously, clinical trials for regulatory agencies require documentation of efficacy as well as documentation of the occurrence, magnitude, and frequency of adverse effects. Furthermore, for drugs where little or no effect can be documented or where adverse effects are serious or substantial, pharmaceutical houses are not likely to pursue regulatory (e.g., FDA) approval. In contrast, no similar vetting process occurs for plant-derived supplements. Indeed, no efficacy standards exist, as the products themselves cannot claim to treat or cure disease, but may claim only to support “a structure and function of the body.” As for safety, whereas for pharmaceuticals, the manufacturer must prove them safe; for supplements, the burden lies on the FDA to prove them *unsafe*. Such a regulatory environment does little to encourage manufacturers of plant-derived supplements to demonstrate efficacy, ensure safety or purity, or even include the presumed active ingredient of the herbal compound. Given this “non-regulatory” climate for herbal supplements, it is not surprising that, even when studies appear to support their use for sexual health, the evidence may not be trustworthy.

Indeed, due to publication bias favoring studies showing significant effects, many well-designed studies on various herbal supplements likely go unpublished, due to a lack of significant effects beyond placebo. Given such bias, we underscore the need for journals to actively solicit and

publish high-quality research—establishing *a priori* criteria including effect sizes—that demonstrates *little or no effect* and/or *significant* adverse effects for sex-related herbal remedies. Alternatively, professional organizations that sponsor or affiliate with specific journals might serve as repositories for abstracts describing well-designed research that has yielded no significant effects on sexual health. For example, the NIH National Center for Complementary and Integrative Health (USA), the Royal Pharmaceutical Society (UK: sponsor of *Focus on Alternative and Complementary Therapies*), the European Scientific Cooperative on Phytotherapy (a collaboration of a dozen European nations and publisher of *Phytotherapy*), and the Chinese Academy of Chinese Medical Sciences (China: affiliated with the *American Journal of Chinese Medicine*) might represent viable and willing hosts for such an endeavor. Alternatively, given the need for specificity within, and understanding of, the field of sexual medicine, the International Society of Sexual Medicine (ISSM: publisher of *Journal of Sexual Medicine*; *Sexual Medicine Reviews*; and *Sexual Medicine*) might serve as a clearinghouse for studies specifically relating herbal supplements to sexual health.

We anticipate an *increasing* need for such documentation in the forthcoming years as new supplements are identified. The potential for isolated compounds from various plants to improve health in general, and sexual health specifically, has had a substantial and rich history (consider, for example, of the first-ever major tranquilizer reserpine, derived from the Indian Snake plant (*rauwolfia*); or of papaverine, an opium alkaloid for intracavernosal injection). In fact, as we searched journals for recent studies on the six supplements reviewed in the companion paper, we tracked other (emerging) herbal supplements claiming to benefit sexual health. These supplements, listed and described in Table 2, may well warrant expanded coverage in future critical reviews on the topic. To further illustrate the enormous potential of this field, an extensive review by Bussmann et al. [61] catalogs 409 medicinally marketed plant species available for purchase in one South American city (Bogota, Columbia), 92 of which purportedly have effects on sexual health, none of which are among the list of six in the companion study, and none of which appeared in our list of emerging supplements (Table 2)¹.

Fortunately, barriers to the in-depth investigation of plant-derived supplements may be gradually disappearing. Mainstream, government-funded health research will

¹ One of us (DLR) has made it a point during travels to African nations, China, Central Asia, the Asian subcontinent, and Southeast Asia to inquire about local traditional remedies for sexual performance. While many plant-derived concoctions and remedies were named, the English name equivalents and/or species names were typically unknown and the plants themselves were often very specific to the region.

likely continue to focus on life-threatening contagious diseases and chronic conditions such as cancer, cardiovascular disease, and metabolic syndrome; sexual health is low on the agenda [5•]. But, over the past several decades, pharmaceutical houses have seen economic opportunity in pursuing a quality-of-life research agenda, as exemplified in testosterone patches for aging men, dopamine agonists for restless leg syndrome, drugs that treat sexual problems, treatment of alopecia in men, and postmenopausal women, and so on [62]. Furthermore, with interest in and expertise with specific herbal remedies often situated in specific geo-cultural niches, an international agenda regarding herbal supplements for the treatment of sexual problems appears to be emerging. Such an approach to health and healing often integrates well with (and provides critically needed assessment of) long-standing traditional notions and remedies [63]. Asian nations—which have come to increasingly embrace the Western idea of academia as a research and knowledge enterprise—may be well-positioned to take the lead on the funding, rigorous testing, and product development of potential supplements.

Conclusions

Consumers and health care professionals alike must make decisions about the use of plant-derived supplements for sexual health without the advantage of reliable information to evaluate their benefit/cost ratio, often having to depend on web pages, marketing, and bottle labels. At the individual level, such supplements may, in some instances, be used by health-compromised populations already on various medications or, in many regions of the world, by those having limited access to modern healthcare systems. Furthermore, the risks involved in using an herbal supplement must be balanced against the documented benefits bestowed by current medications available for treating various sexual problems. At the societal/global level, demonstrating the efficacy of specific herbs and isolating the effective ingredients in order to reduce adverse effects continue to be major challenges. However, the future may be characterized by a changing economic and medical climate that values and chronicles well-designed investigation into such remedies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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