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PRECLINICAL AND PSYCHOPHYSIOLOGY (F GUARRACI AND L MARSON, SECTION EDITORS)

Plant-Derived Supplements for Sexual Health and Problems, Part 2: Further Evidence for Specific Herbal Effects

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Abstract

Purpose of Review In this review, we revisit and evaluate empirical research on six herbal supplements purported to affect sexual and/or reproductive function in men and women.

Recent Findings We summarize and critically review recent evidence—both human and non-human—supporting the role of six commonly cited herbs on men's and women's sexual health, identifying possible mechanisms of action, as well as gaps in the literature.

Summary Burgeoning interest in phytochemical research over the past decade has helped to elucidate potential mechanisms of action through which these plant-derived supplements may exert pro-sexual benefits. More methodologically rigorous, large-scale clinical trials are still needed to determine the extent to which encouraging findings in rodent, cell culture, and *ex vivo* models are generalizable to human populations.

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

Introduction

In this review, we revisit several common herbal supplements promoted for their effect on sexual health, focusing on those that have dominated (or continue to dominate) the scientific literature on sexual effects and reporting on both clinical and experimental research in humans and non-humans. When possible, we present an underlying physiological process that supports the potential pro-sexual effects. Finally, we briefly summarize the current state of this field, noting progress since our 2007 report and commenting on improvements in methodology [1]. We do not attempt to discuss the exhaustive list of purported pro-sexual herbal formulations. Nor do we include natural compounds such as L-arginine and dehydroepiandrosterone (DHEA), as they are not plant-derived and have received significant attention elsewhere [2, 3].

Method

We searched the following databases, using the restrictions of 2005-present and English language: PsycARTICLES, PsycINFO, and MEDLINE/PubMed. Keyword combinations are listed in Table 1. We entered both scientific and common names for the herbs with the Boolean connector "AND" for a variety of keywords related to sexual function.

Results

The 6 plant derivatives included for discussion are listed in Table 1. For each, we mention the general status of the supplement in 2007, provide updates regarding non-human and human studies, address mechanisms of action when possible, mention adverse effects, and provide a brief summary/overview statement.

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Table 1 Keywords used in bibliographic database searches, with all possible combinations used among the three columns

PLANT TERMS	SEXUAL FUNCTION TERMS	OTHER
Epimedium or horny goat weed or icariin or icaritin	sexual health	women
Lepidium meyenii or maca	sexual function or dysfunction	men
Eurycoma longifolia or tongkat ali	sexual desire	non-human
Turnera diffusa or damiana	erection or erectile dysfunction	
Panax ginseng or ginseng	sexual arousal	
Tribulus terrestris or puncture vine	(vaginal) lubrication	
	ejaculation or orgasm	
	sexual pleasure or satisfaction	
	sexual behavior	

Eurycoma longifolia Jack (Tongkat Ali)

Eurycoma longifolia Jack (Simaroubaceae), found primarily in Malaysia and Southeast Asia, is an evergreen shrub commonly used in traditional medicines [4]. Presumably, it helps with a variety of maladies, including fever, hyperglycemia, and certain cancers [5]. *E. longifolia* has also been described as an aphrodisiac that improves sexual vitality, stamina, and libido in men [6]. As discussed previously [1], *E. longifolia* supplementation appears to improve sexual responsivity through androgenic effects, with ongoing research suggesting possible underlying mechanisms of action.

Rodent models of *E. longifolia* treatment have demonstrated elevated sexual arousal and motivation, such as increased pandiculation behaviors (stretching and yawning), decreased ejaculatory latencies, and shorter post-ejaculation intervals [7, 8]. Until recently, these behavioral changes were not definitively linked to enzymatic alterations, but experiments in rodent Leydig cells have indicated that eurycomanone, the predominant quassinoid isolated from *E. longifolia*, can bind to phosphodiesterase 4B, thereby potentiating local cyclic AMP (cAMP) activity [9]. Moreover, both eurycomanone and the aromatase inhibitor, formestane, significantly reduced estrogen production, with the combination treatment conferring greater benefit. Eurycomanone treatment also increased testosterone release in a dose-dependent manner, but was not efficacious during concomitant treatment with aminoglutethimide or ketoconazole, both of which block steroidogenesis by inhibiting cholesterol conversion to steroid hormones such as pregnenolone, testosterone, or cortisol [9]. Thus, eurycomanone may exert androgenic effects by limiting the conversion of testosterone to estrogens and by upregulating expression of the steroidogenic acute regulatory protein (StAR), which is necessary for steroid hormone biosynthesis from cholesterol [10, 11], through cAMP potentiation. In a separate rodent experiment, daily *E. longifolia* extract (25 mg/kg) over 7 weeks elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) compared with controls [12], suggesting that *E. longifolia* may also exert androgenic effects by modulating release of FSH and LH in the hypothalamic-pituitary-gonadal (HPG) axis.

Several human studies have also indicated enhanced fertility from *E. longifolia* [13]. Tambi and Imran [14] provided *E. longifolia* capsules to sub-fertile men (200 mg/day over 9 months), and by 3 months, sperm concentration, percentage motility, and percentage of normal sperm morphology had increased significantly. A similar study compared the efficacy of Physta, a freeze-dried extract of *E. longifolia* (200 mg per tablet) and *Polygonum minus*, an herbal food additive used in Southeast Asia for its antioxidant properties, with placebo (α-lactose/cellulose tablets) in middle-aged men over 12 weeks [15]. Although total testosterone increased significantly following the *E. longifolia* regimen, free (active for binding) testosterone decreased. Despite these somewhat equivocal hormonal findings, participants reported significant improvements in erectile function, sexual satisfaction, and other sexual performance parameters.

Although the majority of *E. longifolia*'s pro-sexual effects have been attributed to its endocrine activity, *E. longifolia* may also preserve sexual function by mitigating inflammation and reactive oxygen species (ROS) accumulation. While some ROS generation is a necessary by-product of cellular metabolism, persistently elevated ROS can damage spermatozoon DNA and may be implicated in smooth muscle cell dysfunction of penile and clitoral tissues [16–18]. Disease states such as metabolic syndrome and type 2 diabetes mellitus are associated with greater ROS production and chronic low-grade inflammation [19–21], which may partly explain lower fertility rates for individuals presenting with such conditions [22]. *E. longifolia* supplementation has demonstrated significant anti-inflammatory effects following inflammation-inducing compounds in mice [23], suggesting that it can reverse inflammatory effects that may impair reproductive functioning.

Interestingly, both the androgenic and anti-inflammatory activities associated with *E. longifolia* can occur in tandem and perhaps function reciprocally to improve sexual function. For example, male rats administered *E. longifolia* extract (200 mg/kg and 800 mg/kg, respectively) for 2 weeks showed a

30% increase (albeit not significant) in serum testosterone [24]. *E. longifolia* also resulted in significantly lower total body weight compared to controls at both doses, with decreases attributed primarily to the omental fat depot at higher doses of supplementation. Since visceral adipose tissue is associated with pro-inflammatory activity and may disrupt T:E_2 ratios [25–27], *E. longifolia*-mediated weight reduction may elevate testosterone levels and reduce inflammatory mediators, thereby conferring pro-sexual benefits. Alternatively, these benefits may be attributed to *E. longifolia*'s ability to lower circulating glucose levels in streptozotocin-induced hyperglycemic rats [28], thereby improving glycemic control. The relationship between unmanaged diabetes and sexual dysfunction has been further supported by recent studies demonstrating decreased androgen receptor (AR) protein content, increased methylation of the AR gene, and lower corpora cavernosal weight in diabetic mice compared with healthy controls [29•].

In females, *E. longifolia* is often promoted on websites for its supposed effects on sexual health; however, our literature search uncovered no empirical studies assessing female sexual response to *E. longifolia* supplementation, either non-human or human. As mentioned previously, although this supplement may impart pro-testosterone (and anti-estrogen activity) along with various anti-anxiolytic effects, such effects have potential to either help or impair sexual function.

Taken together, these studies suggest that *E. longifolia* supplementation may prove beneficial not only by increasing androgen production or availability, but also by protecting against inflammation- and ROS-induced damage to the genital tissues, potentially through the mechanism of glycemic management. However, further study is urgently needed to ensure a higher level of confidence in both its effects and mechanisms of action. To date, the available evidence suggests that healthy individuals can consume *E. longifolia* at manufacturer-specified doses without severe adverse effects [5]. In adult rats of both sexes, daily doses of 100 mg/kg produced no adverse effects throughout the mating period and the entirety of gestation, and lethality in female rats was observed only with single (acute) doses of 2000 mg/kg [30]. Importantly, however, *E. longifolia* does appear to influence immune system parameters in humans. In one such study, neutrophil count was significantly lower in *E. longifolia*-supplemented (50 mg/tablet) participants after 12 weeks, and lymphocyte count was elevated from baseline and compared to placebo [31]. These findings align with prior clinical data, where middle-aged men and women receiving *E. longifolia* (200 mg/day) over 4 weeks [32] showed elevated $CD4^+$ (helper T) cell count compared with both baseline and controls, and higher lymphocyte count compared with placebo. Accordingly, individuals who are immunocompromised or present with autoimmune conditions should consult with their physician or pharmacist before considering an *E. longifolia* regimen.

Epimedium (Horny Goat Weed)

Presumably named by astute shepherds, *Epimedium grandiflorum* is one of more than 50 species of plants belonging to the large Berberidaceae family. While several health benefits have been attributed to the *Epimedium* genus overall, the species *Epimedium grandiflorum* and *Epimedium sagittatum* in particular have been touted as sexual enhancers [33••], with the former (horny goat weed) used in traditional Chinese medicine to overcome sexual problems. The active ingredient of this herb, icariin, has several effects on the endocrine system. Early studies had demonstrated its ability to relax the smooth muscle of isolated rabbit corpora cavernosa, increase testosterone secretion in male rats, and induce nitric oxide (NO) release [1]. Newer research appears to solidify and expand some of these findings.

Men who suffer from diabetes mellitus are three times as likely to experience erectile dysfunction compared with the general public, with more natural, non-drug treatments being valued by some cultures and populations. In an attempt to address a possible mechanism of action for its pro-sexual effects, Liu et al. [34] examined the effects of icariin supplementation (1 mg/kg, 5 mg/kg, and 10 mg/kg, respectively) over 3 months on cavernous smooth muscle in 70 diabetic rats. Following washout, rats were evaluated by cavernous nerve electrical stimulation with intracavernosal pressure (ICP) measurement. Then, postmortem, cavernous and penile tissues were examined for changes, with treated groups showing less collagen accumulation (a measure of pathologic fibrosis) and greater smooth muscle content with higher nitric oxide synthase (NOS) activity—representing increased production of NO, the neurotransmitter associated with penile vasodilation—than sham/control groups [34]. A follow-up study confirmed both effects [35], suggesting that icariin exerts (weak) PDE-5 inhibitor effects, the major action associated with pro-erectile drugs [36].

Epimedium may have effects extending beyond its PDE-5i action that have functional implications. Ding and colleagues [37] observed the effects of 21 days of icariin supplementation at varying doses (50 mg/kg, 100 mg/kg, and 200 mg/kg) on sexual parameters of adult male mice, with treated mice exhibiting shorter ejaculation latencies and more ejaculations than controls, indicating enhanced sexual motivation or capacity. Supporting this effect, icariin-treated groups also had significantly higher blood serum testosterone and NO levels compared with controls—following a dose-dependent pattern—identifying potential underlying physiological processes responsible for the effects. These behavioral and NOS results affirmed the findings of an earlier study suggesting

icariin may expedite recovery from cavernous nerve damage in otherwise healthy rats [38].

Although most studies investigating the pro-sexual effects of *Epimedium*/icariin have targeted male sexual function, interest in women's functioning has also been addressed. Most studies have shown that *Epimedium* has no effect on estrogenic activity, but one recent report suggests that icariin, when metabolized to icaritin, can increase estrogen levels and improve lipid profiles in postmenopausal women [39]. The structure of icaritin is similar to estrogen 8-PN, which easily binds to the estrogen receptor-α (ER-α). However, evidence suggesting an effect on sexual function in either non-human or human females is lacking.

The lack of studies investigating icariin on human sexual response is striking and may result from its adverse effects and potential drug interactions. Beyond typical GI problems, such as nausea or bloating/discomfort, mood changes toward irritability and aggression, thyroid function alteration, racing heart, and feeling hot and sweating have been reported. To date, the dearth of well-designed studies on human populations demonstrating efficacy and safety would, at least for now, caution against the use of this herb for sexual problems.

Panax ginseng (Ginseng)

Panax ginseng has been used in Asian countries by herbal medicine practitioners for centuries to address a variety of health concerns. Both the roots and berries of the plant have medicinal properties implicated in the maintenance of erectile function [40]. In our 2007 review, research suggested a pro-erectile effect for ginseng [1], with evidence indicating that ginseng might help alleviate erectile dysfunction (ED). Initially, ginseng was thought to exert its effects by elevating testosterone and/or LH, but analysis by Murphy and Lee [41], in a pre-post design, measured no change in hormone levels following consumption of ginseng berry extract (10, 50, or 100 mg/kg for 4 weeks). At that time, the underlying mechanisms of action, as well as potential for positive effects on women's sexual health, were poorly delineated.

Since then, a systematic review and meta-analysis examining 28 studies has been carried out, evaluating ginseng supplementation in the treatment of ED arising from both vasculogenic and psychogenic sources [42]. This analysis indicated that ginseng might improve erectile impairment, but conclusions bearing confidence were limited by the studies themselves: randomized clinical trials numbered only 7, sample sizes were relatively small, and gold standard assessment/methodological techniques were lacking. A recent systematic review and meta-analysis on several herbal supplements, including ginseng, concluded that ginseng monotherapy might alleviate symptoms of ED, but that low methodological quality necessitated more rigorous testing to validate these clinical findings [40]. Earlier studies may have addressed some concerns by evaluating the effect of ginseng extract on the entire sexual response in men with mild-to-moderate ED, including through ejaculation. Men reported broad-based improvements in sexual function, encompassing/including erectile function, intercourse satisfaction, orgasmic function, libido, and overall sexual satisfaction [43, 44].

The active ingredients in ginseng are presumably ginsenosides, which can induce activation of large-conductance calcium-activated potassium channels (K^+ [Ca^{2+}]) in smooth muscle tissue, presumably via NO activity. Smooth muscle relaxation allows the corpora cavernosa to fill with blood during sexual arousal, facilitating erection. Thus, ginseng's pro-erectile activity may occur through ginsenosidal effects on smooth muscle sensitivity to NO, as well as on NO-mediated relaxation of the vascular smooth muscle, thereby facilitating penile blood flow [41, 44]. Some of these ginsenosides also appear to have inhibitory action on PDE enzymes, thereby prolonging cyclic GMP (cGMP) or cAMP activity in the urogenital tissues [45]. Ginseng may also improve semen quality, as ginseng-treated (100, 500, or 1000 mg/kg/day for 5 weeks) males demonstrated elevated mRNA and protein content of the cation channels of sperm (CatSper) in testicular tissue, required for sperm hyperactivation, relative to vehicle-treated counterparts [46].

Less understood is the potential for ginseng to improve sexual functioning in women. One recent report suggested that ginseng (50 and 100 mg/kg/day over 1 month) might exert relaxing effects on clitoral cavernosal and vaginal smooth muscle in female rats [47]—with similar outcomes demonstrated in female rabbits [48, 49]. The investigators surmised that this mechanism might help women with arousal difficulty. When ginseng effects were examined in 28 menopausal women (3 g/day), sexual arousal was reportedly enhanced [50]; however, a subsequent placebo-controlled study on 32 premenopausal women (3 g/day for 8 weeks) failed to confirm these effects [51]. As for a potential mechanism, evidence that ginseng or its derivative ginsenosides promote estrogenic activity is equivocal, with some reports suggesting direct binding affinity to the estrogen receptors [52], others proposing a primarily indirect estrogen-like effect [53], and still others indicating negligible activity [54].

Ginseng is generally well tolerated, with the typical GI adverse effects (nausea, diarrhea, discomfort, etc.) and sometimes insomnia [55]. A potential to exacerbate inflammatory responses and/or to affect cardiovascular function (heart rate, blood pressure) is more concerning [56, 57], but serious reactions from normal doses (e.g., 0.2–3 g/day) tend to be unusual and do not consistently appear in either animal or human studies [58, 59]. Many of the severe adverse effects are reported for combination products that contain a variety of herbal derivatives, as opposed to ginseng monotherapy [55]. Certain isolated ginsenosides have exhibited teratogenic effects in murine embryo cultures [60], suggesting that pregnant women

should, at least until further data are obtained, avoid ginseng supplementation. Overall, *P. ginseng* is a relatively safe herbal supplement that may potentially enhance sexual functioning in men and women; ongoing research efforts will likely help to contextualize the circumstances under which ginseng is likely to be efficacious.

Tribulus terrestris (Puncture Vine)

Tribulus terrestris (Zygophyllaceae) is a perennial plant native to Southern Europe and both tropical and temperate climates across Africa and Asia [61, 62]. The herb has been used in Indian and Chinese medicine for centuries and has recently garnered the attention of European and North American markets [1]. Herbal medicine practitioners have recommended *T. terrestris* for alleged anti-inflammatory benefits, urinary tract infection resolution, and aphrodisiac properties. [63]. While *T. terrestris* contains several bioactive phytochemicals, the most widely studied component is a steroidal saponin known as protodioscin [64].

A collection of studies have suggested promising pro-sexual effects of *T. terrestris*, incorporating both *in vivo* and *in vitro* components. Castrated male rats receiving daily *T. terrestris* (5 mg/kg/day for 8 weeks) showed less prostate gland shrinkage than castrated controls [65], suggesting protective effects against decreasing androgen levels. Additionally, *T. terrestris* has been associated with greater mounting and intromission frequencies, as well as shorter mounting, intromission, and ejaculation latencies, all indices of increased sexual activation. Penile intracavernous pressure (ICP) also increased in *T. terrestris*-supplemented rats compared with castrated controls, indicating partial restoration of erectile function following the herbal regimen. In intact males, varying doses of *T. terrestris* (2.5, 5, and 10 mg/kg/day for 8 weeks) resulted in significantly shorter mounting latencies compared with controls, although mounting and intromission frequencies were elevated only at the higher doses [64]. Moreover, ICP was significantly elevated at higher doses of *T. terrestris*, suggesting a modest pro-erectile effect distinct from androgenic effects.

To more thoroughly discern the underlying mechanisms of *T. terrestris* supplementation, Do and colleagues examined the effect of *T. terrestris* extract on corpora cavernosa isolated from rabbits following pretreatment with the contractile agent phenylephrine [61]. *T. terrestris* increased corpora cavernosa relaxation in a dose-dependent fashion. In a follow-up study, *T. terrestris*-mediated relaxation was significantly attenuated upon concomitant treatment with L-arginine methyl ester (L-NAME), a potent inhibitor of NO synthesis. Elevated levels of cAMP in the corpora cavernosa were also seen at all doses of *T. terrestris* administration. Since NO activity is a critical mediator of penile erection and is often disrupted or compromised in metabolic dysfunction [66•, 67], *T. terrestris* supplementation may exert pro-sexual effects by maintaining NO signaling pathways and its constituent mediators, such as cAMP [68].

While initially hypothesized that *T. terrestris* improves sexual function by increasing androgen levels—particularly testosterone (T), dihydrotestosterone (DHT), and/or DHEA—not all studies have substantiated these claims. For example, Martino-Andrade and colleagues [69] supplemented intact male and ovariectomized female rats with low (11 mg/kg/day), moderate (42 mg/kg/day), and high (110 mg/kg/day) doses of *T. terrestris* over 4 weeks. In males, neither serum T nor fecal androgenic metabolites differed from controls; in ovariectomized females, neither the uterine nor vaginal luminal epithelium differed from controls. Taken together, these studies suggest that the pro-sexual effects attributed to *T. terrestris* may occur through an androgen-*independent* mechanism.

Studies on humans have generally supported this line of investigation. Neychev and Mitev [70] observed that *T. terrestris* supplementation (10 mg/kg/day or 20 mg/kg/day, respectively) did not significantly increase serum testosterone, androstenedione, or LH concentrations in young men over 4 weeks, although the validity of the findings were compromised by the study's limitations: the small sample size, inadequate description of the criteria for healthy subjects, and the lack of anthropometric data such as body composition measures. Regarding this last issue, participants at the higher end of reported body weight—nearly 275 lb—may actually present as overweight or obese. Since white adipose tissue contains aromatase enzymes, excess body fat may actually disrupt T:E_2 ratios [71, 72], overwhelming any potential androgenic effect derived from *T. terrestris* supplementation.

More recently, two randomized, double-blinded clinical trials have evaluated the potential pro-sexual benefits of *T. terrestris*. Using a pre-post design, the first study examined *T. terrestris* (3 capsules totaling 750 mg/day) in premenopausal women with hypoactive sexual desire disorder (HSDD), a dysfunction characterized by distress over one's persistent lack of sexual desire/interest [73••]. While overall Female Sexual Function Index (FSFI) scores did not differ at baseline, overall sexual satisfaction scores were significantly greater in the treated group. These women also showed improvement on all FSFI subdomains, whereas control women were unchanged on lubrication and pain subdomains. Scores on the QS-F questionnaire showed similar overall patterns. The second study conducted on men with mild-to-moderate ED with or without concomitant HSDD found that those in the *T. terrestris* group (500 mg thrice daily) reported greater erectile functioning than placebo after 4 weeks, with higher overall and subdomain scores on the International Index of Erectile Function (IIEF) [74]. Improved sexual functioning and satisfaction were not related to changes in androgen levels.

Adverse effects in *T. terrestris* are not well documented, partly because side effects are not prominent when the herb is given in small dosages. Most effects are GI related, including stomach pain, diarrhea, and nausea. Behavioral effects have included agitation and insomnia; more concerning are rare reports of kidney damage and effects on blood sugar levels [75–77]. A few sporadic cases of priapism requiring medical intervention also occurred [78]. Until more is known about this herb, use by pregnant or lactating women is strongly discouraged, particularly as the long-term safety/effects of *Tribulus* are unknown. In contrast to earlier reports proposing an androgenic effect of *T. terrestris* supplementation, the current body of evidence supports androgen-independent mechanisms such as NO-cAMP/cGMP pathways and increased blood flow to the genital tissues. Additional data are needed to further elucidate potential mechanisms of action as well as adverse effects or drug interactions.

Maca Andina (*Lepidium meyenii* Walp)

Maca root has long been used among Andean populations to increase fertility and induce sexual desire in both men and women [1]. Research on both males and females suggests beneficial effects on sexual and reproductive health. In a summary article, Gonzales [79] reports that maca root increases sexual behavior and sperm count and reduces prostate size in male rats; it also improves embryo quality in pregnant female mice.

Human studies have tended to yield positive effects too, but are relatively sparse. For example, in a randomized, placebo-controlled study, Gonzales-Arimborgo et al. [80] examined differences between red and black maca supplementation (3 g/day over 12 weeks) on sexual desire in men and women at both low and high altitudes. Both types of maca increased self-reported sexual desire, but red maca appeared to be more potent in low altitude regions [80]. Maca (1.75 g/day for 12 weeks) may also affect sperm parameters in men, with one recent study indicating increased total sperm count by 20%, along with rises in sperm concentration, motile sperm count, semen volume, and normal-morphology sperm [81]. Surprisingly, men in the placebo group also showed a 20% increase in sperm count, but other semen parameters were either unaffected or decreased.

Studies of maca in women have also been sparse though offer some preliminary promise. A recent maca supplementation trial in women with anti-depressant-induced sexual dysfunction (AISD) suggests that maca might attenuate sexual side effects of anti-depressant medication [82]. In one study, 45 women experiencing AISD were randomized to receive either placebo or maca root (3 g/day) over 12 weeks [83]. Sexual arousal, orgasm, and satisfaction were assessed bi-weekly using standardized instruments, with remission of sexual dysfunction defined *a priori* by specific threshold levels on sexual function questionnaires. Overall, remission rates of sexual dysfunction were higher in maca-supplemented women, and adjustment for menopausal status revealed that postmenopausal women benefitted most from maca. Postmenopausal women experienced greater improvements related to orgasm, while premenopausal women showed greater improvement in the arousal domain. Changes in serum testosterone were also observed, suggesting that maca may affect androgens in women.

Maca may also alleviate menopausal symptoms including hot flashes and sleep issues. While at small doses maca is generally considered safe, it reportedly may affect mood and sleep, and because it might impart steroidal hormonal effects, its long-term use could have significant ramifications. Despite the somewhat positive impact of maca supplements on men's and women's sexual and reproductive function, the number of studies is very limited and possible mechanisms of action for altering sexual desire and/or behavior, or affecting reproductive parameters such as sperm viability or menopausal symptoms, remain unknown [33••].

Turnera diffusa (Damiana)

Turnera diffusa (Turneraceae), a shrub native to Latin America, has been long been associated with anxiolytic, anti-inflammatory, and pro-sexual effects by herbal medicine practitioners [84, 85]. Moreover, *T. diffusa* treatment in MDA-MB-231 breast cancer cells has suggested cytotoxic benefits [86]. Various phytochemicals have been identified within *T. diffusa* leaves, including flavonoids, phytosterols, and glycosides [87, 88]. Essential oils such as α-pinene and limonene have also been extracted from harvested *T. diffusa* samples [89]. Damiana has traditionally been prepared as a beverage [1, 90], but tinctures/isolated extracts are increasingly common. While the effects of *T. diffusa* remain understudied, new findings have emerged suggesting that *T. diffusa* might improve sexual function in both men and women.

Interestingly, one way that *T. diffusa* might improve sexual responsivity is through anxiety mitigation. Although the relationship between anxiety and sexual dysfunction is not always straightforward [91], elevated anxiety or cognitive distraction typically limits the individual's ability to attend to erotic stimuli and thus reduces physiological arousal [92•, 93]. Over a decade ago, Kumar and Sharma evaluated the anxiolytic effects of *T. diffusa* (single dose of 50, 75, 100, 125, or 150 mg/kg) in mice following an 18 h fast [88]. In elevated plus-maze testing, mice receiving oral *T. diffusa* exhibited more entries into, and time within, the open arms, indicating diminished overall fear. However, effects were modest in comparison with oral diazepam-treated mice, and further, they were not dose-consistent, suggesting problems with the homeopathic preparations. In a follow-up study, mice injected with

Table 2 Overview of plant-derived supplements discussed in this review

Herbal supplement	Quality and preponderance of evidence[1]	Effect on sexual response or reproductive functioning[2]			Side effects and adverse events[3]
			Human	Non-human	
Eurycoma longifolia (tongkat ali)	2	Male	↑↑	↑↑	Elevated lymphocyte count, hypoglycemia
		Female	↑	↑	
Epimedium (horny goat weed)	2	Male	↑	↑↑	GI upset, changes in mood (irritation/aggression), heat insensitivity, thyroid function alteration, racing heart
		Female	↔	↑	
Panax ginseng (ginseng)	3	Male	↑↑	↑	GI upset, insomnia, *exacerbation of some pro-inflammatory conditions*, *racing heart*
		Female	↔	↑	
Tribulus terrestris (puncture vine)	2	Male	↑	↑↑	GI upset, insomnia, changes in mood (agitation), diarrhea, vomiting, hypoglycemia, *kidney dysfunction*, *priapism*
		Female	↑	↔	
Lepidium meyenii (maca)	2	Male	↑	↑	Mood changes (irritability/agitation), insomnia
		Female	↑↑	↔	
Turnera diffusa (damiana)	1	Male	↔	↑↑	GI upset, insomnia, *hypoglycemia*
		Female	↑↑	↔	

[1] Assessed on an ordinal scale, with 0, very poor quality/insufficient evidence; 1, lower quality/caliber; 2, intermediate quality; 3, higher quality. Lower quality evidence is characterized by a lack of trials in humans or trials that use a combination supplement rather than the isolated herb/compound. Intermediate-quality evidence includes both non-human and human trials, but the human trials may include only one sex (men or women) or the number of available trials is small. Mechanisms of action are proposed for herbs in this category, but they may be speculative. Higher quality evidence indicates that the number of studies on the herb is quite extensive, incorporating both non-human and human intervention trials. Moreover, potential mechanisms of action are clearly specified for these herbs

[2] Assessed on an ordinal scale, with ↔, no benefit/insufficient data; ↑, mild potential benefit; ↑↑, moderate benefit; ↑↑↑, strong/consistently-supported benefit

[3] Adverse events in *italics* represent outcomes that are relatively uncommon, as opposed to the more frequently documented side effects of these supplements

apigenin, a flavonoid from *T. diffusa*, exhibited diminished fear during murine anxiety assays (e.g., time spent in the lit component of a chamber) [85]. Despite these favorable outcomes, several methodological issues may have compromised the conclusions drawn from this study.

In contrast to damiana's purported anxiolytic benefits [94], which could potentially improve sexual functioning through indirect mechanisms, the herb may also have direct effects on sexual behavior. For example, Arletti and colleagues [87] administered oral extracts of *T. diffusa* (0.25, 0.5, or 1 mL/kg) to both sexually experienced and sexually sluggish male rats, 1 h before sexual behavior testing. While *T. diffusa* did not alter mounting, intromission, or ejaculation latencies in the sexually experienced rats, these parameters improved significantly among the sexually sluggish rats relative to impotent controls, this latter group defined by the failure to ejaculate in pre-experimental tests. A similar study in sexually exhausted male rats showed that high doses (80 mg/kg) of *T. diffusa* significantly increased the percentage of males displaying mounting, intromission, and ejaculation behaviors in the presence of a novel, sexually receptive female, after males had mated for 4 h with a single female to produce exhaustion [84]. Damiana treatment also significantly lowered post-ejaculatory intervals of sluggish mice.

Several mechanisms have been proposed to account for the pro-sexual benefits of damiana. First, it may exert effects through NO-cGMP-mediated pathways, as concomitant treatment with L-NAME in male rats increased intromission latency and attenuated the decrease in ejaculatory latency observed with *T. diffusa* alone [95]. *T. diffusa* leaves also contain caffeine [84, 96], a known PDEi able to potentiate cGMP activity [97] and to affect sexual behavior in animal models [e.g., 98]. Second, Zhao and colleagues [90] have isolated several phytochemicals from *T. diffusa* that appear to modestly inhibit aromatase enzymes that allow conversion of testosterone to estrogen, but further work is needed to elucidate this possibility [94]. Finally, experiments with apigenin supplementation in cultured murine Leydig cells illustrated greater gene expression of StAR and elevated testosterone production, suggesting that *T. diffusa* may act in conjunction with other mediators, such as cAMP, to alter steroid hormone biosynthesis [98].

While *T. diffusa* treatment has not been extensively tested in humans, two studies in women illustrate a possible pro-sexual effect. Ito and colleagues assessed the effects of ArginMax—a supplement containing *T. diffusa*, *P. ginseng*, *Ginkgo biloba*, and L-arginine—on FSFI parameters in women seeking to increase their sexual function [99]. After 4 weeks, women in the ArginMax condition reported greater improvement in the domains of sexual desire, overall sexual satisfaction, frequency of intercourse, and sexual relationship with their partner compared with placebo controls. A similar study evaluated ArginMax

supplementation in relation to menopausal status [100], with some improvements occurring in all women and others dependent upon menopausal status. Unfortunately, the inability to parse out the effects of damiana from the other ingredients of this preparation limits the conclusions that can be drawn.

Other than mild GI upset or insomnia, known adverse effects of *T. diffusa* are fairly limited: neither human clinical study described here reported any severe adverse effects, such as blood pressure changes [99, 100]. Due to the relative paucity of studies, however, damiana could yet have unidentified consequences. For example, damiana contains glucose-lowering compounds [101, 102], and so care should be taken by individuals prone to hypoglycemia. In summary, at this juncture, it is too early to evaluate damiana as a pro-sexual supplement for humans, not only are more clinical data needed, but also purported mechanisms of action, continued clinical investigation, and replication of prior studies.

Conclusion

This update attests to the greater attention given to the potential benefits of plant-derived supplements on sexual functioning. As might be expected, much of the work emanates from regions of the world where herbal medicines have had long-standing traditions and value. Furthermore, many of the studies over the past decade have provided more rigorous testing of hypothetical effects, using both larger sample size and improved methodologies and, in the process, generated both encouraging and discouraging outcomes. Based on our review of six popular plant derivatives, all have received at least some support for beneficial effects on sexual function (Table 2). Most effects, however, have been demonstrated in men, with either little or no effect observed in women, or alternatively, a lack of testing in women. Such bias may partly reflect the cultural context in which some studies are carried out, where women's sexuality tends to be strongly curtailed by social scripts [103]. Alternatively, this pattern may reflect a true lack of results in women where psychosocial variables tend to play a more pronounced role in sexual responsivity. Nevertheless, concerns about effect sizes (typically not included in studies), long-term side effects, the inability to reasonably quantify the benefit/cost ratio, and publication bias (issues discussed in the companion paper) limit confidence in the use of any of these supplements.

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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- •• Of major importance

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