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REVIEW

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Efficacy and putative mechanisms of action of nutraceuticals in the management of erectile dysfunction: a narrative review

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Abstract

Erectile dysfunction (ED) is a common condition in the male population and is influenced by numerous pathophysiological factors. Recently, interest in nutraceuticals and natural remedies as complementary or alternative therapies to traditional pharmacological treatments has increased exponentially. This narrative review aims to analyze the impact of the most studied nutraceuticals in the treatment of ED, analyzing their mechanisms of action, clinical efficacy and safety. Much attention has been paid to compounds such as L-arginine, as well as several medicinal plants including *ginseng*, *maca*, *Tribulus terrestris* and antioxidant substances such as resveratrol and Pycnogenol. These natural products have different mechanisms of action, including modulation of endothelial function, reduction of oxidative stress and balance of sex hormones, thus addressing multiple therapeutical targets for the management of ED. However, despite promising results reported in various preclinical and clinical studies, several limitations to the use of nutraceuticals for ED persist, including variability in study designs, lack of standardized dosages of various compounds and lack of long-term safety evaluations. In fact, although nutraceuticals generally demonstrate a favorable safety profile compared to traditional drugs, they are not completely exempt from possible side effects. Furthermore, issues such as inconsistent patient adherence to treatment and potential interactions with drug therapies require further research and investigation. Therefore, high-quality, adequately sized clinical trials to better evaluate the efficacy and safety of these compounds, alone or in combination with conventional, widely adopted therapeutic regimens are warranted. In conclusion, nutraceuticals present a promising therapeutic option in the management of ED, potentially capable of improving clinical outcomes and patients' quality of life when integrated into an all-inclusive therapeutic strategy.

Keywords

Erectile dysfunction; Nutraceuticals; Herbal medicines; Dietary supplements; Antioxidants

1. Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. ED is a particularly common condition affecting an increasing number of men worldwide, with the prevalence increasing progressively with age: in fact, it is estimated that about 52% of men aged 40–70 years' experience some form of ED, with the prevalence increasing from about 20% at age 40 to 70% in men aged 70 years and older [1]. The prevalence of ED appears to be influenced by several factors including socioeconomic factors, lifestyle and pre-existing comorbidities such as diabetes, hypertension, hepato-gastroenterological disease and cardiovascular disease [2–6]. Indeed, the literature reports that about 20% of men with diabetes mellitus (DM) suffer from ED, a condition that is often difficult to treat because of diabetes-related vascular and nerve damage [7]. Traditionally, the treatment of ED has focused almost entirely on phosphodiesterase type 5 inhibitors (PDE5i) such as sildenafil, tadalafil and vardenafil, and later on, on the use of mechanical devices such as penile prostheses, as well as hormonal modulation [8]. PDE5i by specifically improving peripheral vasodilation through the inhibition of PDE5, represent the most widely used strategy for the treatment of ED, however their use has a number of limitations. In fact, there are many side effects related to the use of this class of drugs among

which the most common ones include headache, dyspepsia, nasal congestion and, in some cases, even severe effects such as loss of vision or hearing [9]. Moreover, not all patients respond adequately to these drugs, particularly those with ED caused by psychological problems or comorbidities such as DM [10]. Additional factors that limit the use of these drugs are their high cost, and the variable adherence to treatment by patients. Hence, the interest in natural and complementary alternatives to traditional drugs [11, 12].

Mounting evidence supports the concept that products isolated or purified from foods can exert biological activity with physiological benefits in numerous chronic diseases; these products when provided in medicinal form are referred to as nutraceuticals (*i.e.*, bioactive products extracted from foods or natural compounds that fit into the gap between nutrition and pharmaceuticals) [13]. Nutraceuticals have proven to be a promising alternative or even, in some cases, a complementary treatment for ED [11, 12, 14]. While conventional therapies target specific pathophysiological mechanisms, nutraceuticals may act on various biological processes, including modulation of endothelial function, reduction of oxidative stress and regulation of sex hormones [14]. The use of nutraceuticals to treat ED is not completely new. In fact, many traditional medicines, such as Chinese medicine, have always used natural remedies to improve male sexual health. Several scientific studies more recently, have begun to more consistently and thoroughly explore the efficacy of these compounds, thus highlighting the need for further research to determine optimal dosages and long-term safety and providing a comprehensive overview of their mechanisms of action and gaps in scientific research [15–18]. This review aims to integrate this knowledge to provide a comprehensive overview on the impact that nutraceuticals may have in the management of ED.

2. Methodology

A review of the literature was performed in order to evaluate the clinical efficacy and mechanism of action of herbal phytochemicals and/or other nutrients used for the management of ED. We searched three databases (Google Scholar, Scopus and PubMed) to identify clinical studies addressing the therapeutic role of herbal medicines in ED as well as preclinical studies evaluating the mechanism of action in the past 20 years. No language restriction was applied. The key terms used for the search were male sexual dysfunction, erectile dysfunction, impotence, phytochemical, botanicals, herbal extract, nutraceutical, dietary supplement and traditional medicine. Review articles (*i.e.*, narrative or systematic review and/or meta-analysis), book chapters and original scientific papers on humans were included in our search. We also included experimental studies in animals which explored the putative mechanism of action of a given compound. Abstracts or Meeting proceedings were excluded.

3. Pathophysiology of ED

ED is a multifactorial condition in which the alteration of various physiological and psychological mechanisms may play a causative role [1]. To understand how nutraceuticals can positively influence ED, it is necessary to first explore the key underlying processes that contribute to its development, thereby investigating all causes and concomitant causes leading to this condition. One of the main factors contributing to the pathogenesis of ED is endothelial dysfunction. The ability to achieve and especially maintain a satisfactory erection is highly dependent on the vascular system and its good health, and, in particular, on the release of nitric oxide (NO) from endothelial cells at the level of the corpora cavernosa of the penis [19]. NO acts as a crucial mediator, stimulating the production of cyclic guanosine monophosphate (cGMP), which relaxes the smooth muscle tissue of the cavernous sinusoids and allows the penile blood vessels to dilate, thereby increasing vascular inflow and thus enabling penile tumescence. This mechanism, however, is often impaired in individuals with ED due to endothelial dysfunction, which results in a major reduction in NO availability that consequently reduces the ability of cavernous sinusoids to dilate [20]. Several nutraceuticals such as L-arginine and *Panax ginseng* have been shown to promote NO production and improve vascular health, thereby mitigating some of the effects of endothelial damage and allowing greater vasodilation at the cavernous level [21, 22]. However, one must keep in mind that these products may represent a serious problem for consumers because of the lack of clear regulations [23].

Another significant factor to consider in the pathophysiology of ED is increased oxidative stress. The accumulation of reactive oxygen species (ROS) can in fact, severely damage endothelial cells, further impairing their ability to produce NO [24]. In addition, oxidative stress also contributes to systemic inflammation, which aggravates vascular remodeling and can also lead to the development of fibrosis in penile tissue, thus reducing its flexibility and function [25]. Several nutraceuticals such as flavonoids, *Ginseng* and *Pycnogenol*, characterized by potent antioxidant properties, have been shown to counteract oxidative damage and help restore normal endothelial activity, thus proving as valuable therapeutical tools in the management of ED [21, 26–29].

Moreover, hormonal imbalance, particularly the reduction in testosterone levels [30], plays a crucial role in the development of ED. This hormone, in fact, is essential for maintaining libido and facilitating the physiological processes of erection [31]. Aging, but also obesity and metabolic syndrome are common causes of low testosterone levels, frequently observed as comorbidities in ED patients [32–34]. Some nutraceuticals, including *Tribulus terrestris* and *Maca*, are well known for their ability to regulate testosterone production and improve libido and hence sexual function, and these properties can be attributed to their ability to increase androgen receptor sensitivity and promote optimal hormone balance [35].

Finally, psychological factors often exacerbate the physical and organic difficulties associated with ED [36]. In fact, conditions such as anxiety, depression and chronic stress are not only common in individuals with ED, but can also create a self-perpetuating cycle that worsens the condition over time by amplifying the sexual dysfunction in these patients [36]. Therefore, addressing psychological aspects is essential for a comprehensive management of ED. Again, several nutraceuticals such as *Ashwagandha* and *Ginseng,* have the potential

of reducing stress and improving overall mental well-being, thus leading to improved erectile function, particularly in cases where psychogenic factors are present [21, 22, 37].

In summary, ED is contributed to by a combination of vascular, hormonal, oxidative, circulatory and psychological factors. The therapeutic potential of nutraceuticals lies in their ability to specifically target these mechanisms, thus offering a complementary approach to traditional treatments (Fig. 1).

4. Nutraceuticals and their role in ED

Nutraceuticals are bioactive substances that come from foods, medicinal plants and natural supplements and are known to offer various therapeutic benefits in a number of chronic pathologic conditions. In addition, these compounds are often safer than traditional drugs, with fewer side effects and a better tolerability profile [38, 39]. In this review, we will examine in detail the main nutraceuticals currently used for ED, thoroughly exploring their mechanisms of action and evaluating the available scientific evidence on their true potential.

4.1 *Ginseng (Panax ginseng)*

Among the most extensively studied nutraceuticals, *Ginseng* occupies a prominent place for the treatment of ED due to its pronounced endothelial vasodilation properties as well as the reduction of oxidative stress produced by ginsenosides, the main bioactive metabolites of *Ginseng* [40]. In fact, ginsenosides, due to the production of NO in the vascular endothelium, improve penile blood flow and modulate neurotransmitter release, further supporting erectile function [21]. In addition, due to their anti-inflammatory and antioxidant effects they protect endothelial cells from oxidative damage [21]. About 20 clinical and preclinical studies have been conducted on mild-to-moderate ED patients treated with ginsenosides, and in these studies, an average improvement of 3–5 points in the International Index of Erectile Function (IIEF) was reported [41]. In particular, a randomized trial of patients with mild-to-moderate ED showed significant benefits with respect to erectile stiffness, duration of erection and libido [42]. Of particular interest, in a systematic review, Lee *et al.* [43] found that *Ginseng* had a trivial effect on ED when compared to a placebo, based on the Erectile Function Domain of the IIEF-15, *i.e.*, (mean difference of about 3 points compared to a placebo) with little or no side effects [43]. Nevertheless, standardization of dosages and confirmation of long-term efficacy require further studies.

4.2 *Tribulus terrestris*

Tribulus terrestris is a compound that has traditionally been used as an aphrodisiac. In fact, this plant modulates hormone levels, specifically increasing testosterone production and androgen receptor sensitivity through its active compound,

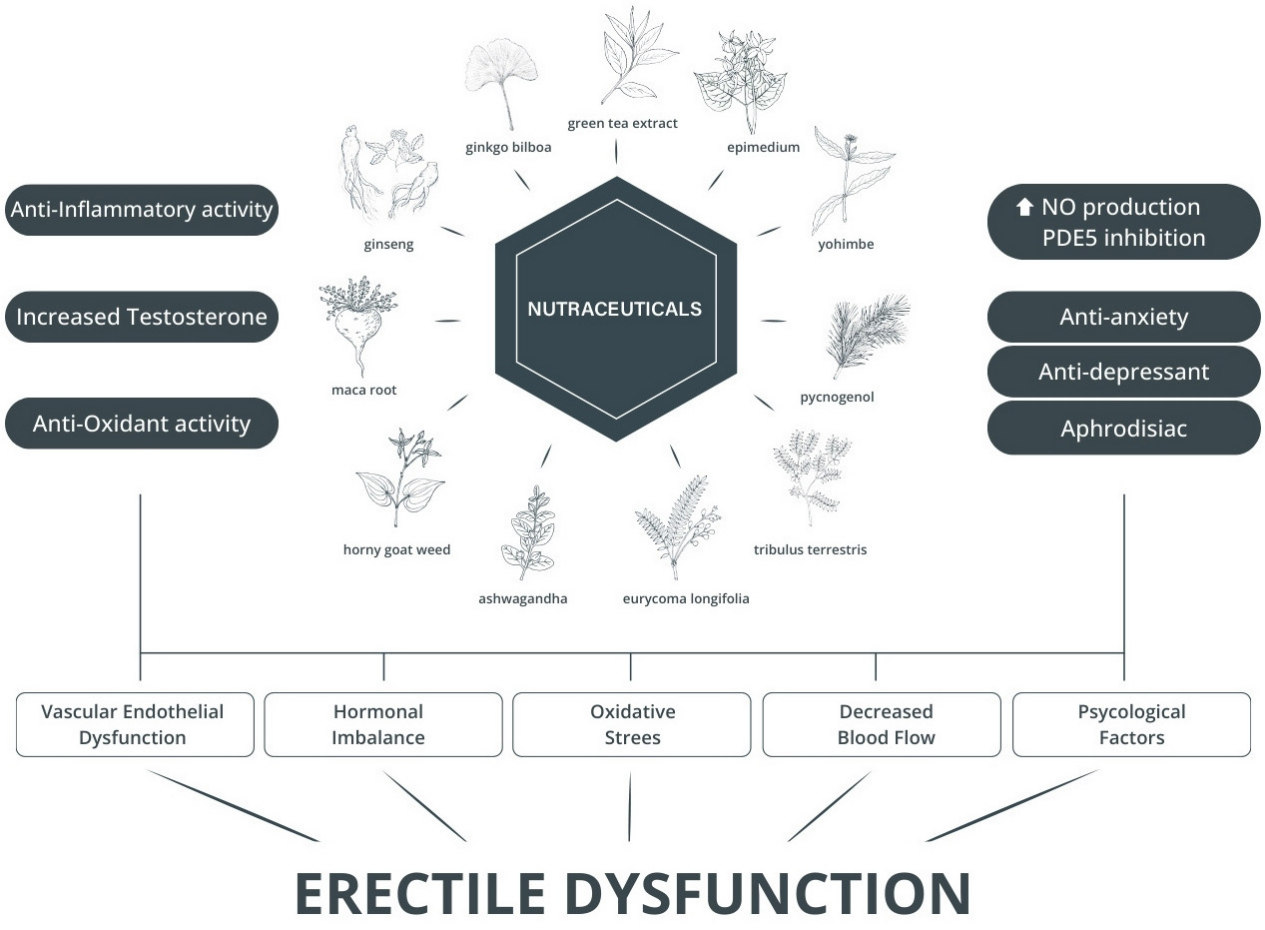

FIGURE 1. Graphical representation of main mechanisms underlying erectile dysfunction and nutraceuticals' targets of intervention. NO: nitric oxide; PDE5: phosphodiesterase type 5.

namely protodioscin [44]. *Tribulus terrestris* has been analyzed in several studies reporting improvements of 2–4 points at IIEF, with effects more pronounced in men with ED related to hormonal imbalances than in those with ED of vascular origin [45]. In particular, Kamenov *et al.* [45] evaluated the efficacy and safety of a standardized extract (Tribestan®, Sopharma AD-coated tablets containing 250 mg of dry extract equivalent to furostanol saponins not less than 112.5 mg) for the treatment of men with mild to moderate ED and with or without hypoactive sexual desire disorder in a prospective, phase IV, randomized, double-blind, placebo controlled clinical trial in parallel groups. The authors showed a significant improvement in erection, libido and orgasmic function in the treated group, in the absence of any difference in the profile of side effects as compared with the placebo [45]. On the other hand, Santos *et al.* [46] in a prospective, randomized, double-blind study of patients with ED found that patients treated with 400 mg of *Tribulus terrestris* extract reported no significant benefit compared to the placebo group [46]. While one case of nephrotoxicity and another of increase in serum bilirubin levels have been described, no clinical trial in which *Tribulus terrestris*-based products were administered, have reported these side effects.

4.3 *Maca (lepidium meyenii)*

Maca is a Peruvian root known for its aphrodisiac properties [47, 48]. Several clinical trials have been performed on healthy men and patients with ED, showing significant improvements in libido and sexual satisfaction in both patient groups [48]. In particular, *Maca* has important potential as an adjuvant therapy to improve overall sexual health [48]. *Maca* has been shown to exert a modest impact on IIEF scores, with improvements of 1–2 points, the more significant effects being on libido and sexual satisfaction [49]. The safety profile is favorable with only mild gastrointestinal disturbances reported by few patients [49]. The properties of *Maca* are mainly due to its bioactive compounds, including alkaloids and flavonoids, which influence hormonal balance and improve mitochondrial energy production [50]. Its efficacy in patients with comorbidities such as obesity or diabetes and its potential for synergistic effects with other interventions are yet to be determined.

4.4 *Epimedium (horny goat weed)*

Epimedium, otherwise known as *Horny Goat Weed*, is a compound particularly well known for its use in ED. Its bioactive components, flavonoids and prenylhydroquinones are potent PDE5i, similar to sildenafil, one of the main drugs used to treat ED [51, 52]. *Epimedium* has been analyzed in several clinical studies showing modest improvements of 2–3 points at IIEF, particularly in combination with antioxidants that synergistically enhance the vasodilating capability of *Horny Goat Weed* [53, 54]. However, further research is needed to address issues such as long-term outcomes and potential anti-inflammatory properties, as well as combination strategies with other nutraceuticals to enhance its efficacy.

4.5 *Yohimbine* (extracted from *pausinystalia yohimbe*)

Pausinystalia yohimbe extract, *Yohimbine*, is an alkaloid that behaves as an antagonist of pre-synaptic alpha-2-adrenergic receptors, thereby promoting blood vessel relaxation and increasing blood flow in the penis. Moreover, *Yohimbine,* is able to enhance sexual arousal through central nervous system (CNS) stimulation thus proving efficacy in the treatment of psychogenic ED [55]. Controlled clinical trials have shown significant 2–3 point improvements in IIEF score in patients treated with *Yohimbine* compared with placebos, although side effects (*e.g.*, hypertension and anxiety) may limit its use [56–58]. Future research directions should be aimed at optimizing dosing regimens to mitigate adverse effects and explore its use in combination with anxiolytics.

4.6 *Saffron (crocus sativus)*

The main active compounds in *Saffron*, crocin and safranal, exert neuroprotective and antioxidant effects, improving both psychological and physiological factors involved in ED [59]. *Saffron* seems particularly useful in ED associated with stress or depression, by improving penile rigidity and sexual satisfaction [60]. *Saffron* has been evaluated in several clinical studies and results consistently show an average IIEF improvement of 3 to 4 points after four weeks of treatment [61, 62]. Also, *Saffron* has shown a favorable safety profile without major adverse events [59] Future research should assess its potential therapeutic role in combination therapies for patients with psychological comorbidities.

4.7 L-arginine

L-arginine is an essential amino acid that acts as a precursor of NO, a key mediator of vasodilation and physiologic endothelial function [63]. Supplementation with L-arginine increases the bioavailability of NO, and numerous clinical studies have shown that combining L-arginine with antioxidants (*e.g.*, *Pycnogenol*) consistently improves erectile function in patients with vascular ED, with an improvement in IIEF of about 3–6 points [64, 65]. It should be specified, however, that L-arginine monotherapy produces less consistent results, compared with combination therapy depending on the dose and duration of administration [66–68]. Best results were obtained by administering 6–8 g/day for periods of time ranging from 3 to 6 months [67, 68]. Overall, L-arginine is safe and well-tolerated, suggesting that it might be an alternative treatment in mild-moderate vasculogenic ED patients with adverse effects or contraindications for chronic treatment with PDE5i. It should be used with caution in patients on nitrate therapy.

4.8 *Pycnogenol* (*maritime pine bark* extract)

Pycnogenol, a derivative of *Maritime pine bark*, is a potent antioxidant that improves endothelial function and reduces oxidative stress [69]. It is normally used in synergy with L-arginine, increasing NO production, enhancing vasodilation and consequently promoting erectile activity [64, 65]. Clinical studies involving patients with moderate ED demonstrated that the combination of L-arginine and Pycnogenol significantly

improved the quality of erection within three months of therapy and with no significant side effects, leading to an increase in IIEF scores of 3–6 points [64, 65]. Future research should focus on evaluating its long-term safety profile and efficacy in diverse patient populations.

4.9 *Ashwagandha (withania somnifera)*

Ashwagandha is an adaptogenic compound known for its ability to improve stress response and promote hormonal balance [70]. These effects may have a positive impact on libido and erectile function, particularly in men with psychogenic ED. Furthermore, it has been shown to increase testosterone levels, further supporting libido and erectile function [70, 71]. Several studies have explored the role of *Ashwagandha* in ED, particularly in psychogenic cases [70, 71], whereby showing improvements in IIEF scores of 1–3 points. In particular, in an 8-week randomized, double-blind, placebo-controlled study *Ashwagandha* root extract at a dose of 300 mg twice daily in adult males with psychogenic ED was shown to exert significant improvement of sexual desire without any significant side effect [71]. Furthermore, *Ashwagandha* helps reducing cortisol levels, thereby alleviating stress, a key contributing factor to psychogenic ED, and improves sperm quality, testosterone, levels and libido [72]. However, its specific effects on erectile function require further research. In particular, its long-term clinical impact should be better clarified as well as whether combinations with anxiolytics or PDE5i may offer a more complete solution for patients with complex cases of ED with relevant psychological components [72].

4.10 *Ginkgo biloba*

Ginkgo biloba, a compound known to improve blood circulation due to its vasodilatory effects, acts as a modulator of NO thus ensuring greater blood flow to the corpora cavernosa of the penis [73, 74]. Moreover, the antioxidant properties of *Ginkgo biloba* help reduce oxidative stress, a common factor in ED of vascular origin [74]. *Ginkgo biloba* seems particularly useful in cases of ED caused by circulatory disorders or by the use of antidepressants. In fact, *Gingko biloba* has shown particular efficacy in cases of ED induced by the use of selective serotonin reuptake inhibitors (SSRIs), with patients reporting an improvement in erectile rigidity and overall sexual satisfaction with IIEF improvements ranging from 2 to 4 points [75, 76]. Despite these benefits, more extensive and standardized studies are needed to establish its long-term safety and optimal dosage, and whether it can be integrated with conventional therapies such as PDE5i. In this regard, a recent study has shown that a nutraceutical combination of *Gingko biloba* with alpha lipoic acid and *Vitis vinifera L* given for three months in association with Avanafil significantly increased sexual performance in 123 males with type 2 DM-associated ED, without any significant adverse event [77].

4.11 L-citrulline

L-citrulline is a precursor to NO similar to L-arginine. However, while the latter's efficacy can be limited by rapid metabolism, L-citrulline has better bioavailability and is rapidly converted into L-arginine [78, 79]. Studies show significant improvements in erection rigidity with L-arginine and L-citrulline administration, especially when combined with other compounds like *Pycnogenol* [65, 79], with an increase in IIEF score of 3 to 5 points. In a single-blind study involving patients with mild ED, L-citrulline supplementation significantly increased erection hardness and number of intercourses per month [78]. Because of its superior bioavailability when compared with L-arginine, L-citrulline offers a more effective option for sustained NO production [80].

4.12 Anti-oxidants

Oxidative stress plays a major role in causing vascular endothelial dysfunction which may in turn lead to ED. Therefore, natural compounds with anti-oxidant properties have been regarded to as possible therapeutic agents in this clinical setting. Resveratrol, a nonflavonoid polyphenol, improves endothelial function and reduces oxidative stress [81]. Significant benefits have been observed in cardiovascular health, indirectly linked to ED [81, 82]. It has been shown that resveratrol may provide modest benefits in ED management [82, 83], with IIEF score improvements averaging 2 to 3 points [82, 83]. Resveratrol's cardiovascular benefits also suggest its potential as a preventive strategy for ED linked to metabolic syndrome or other vascular conditions [81]. While resveratrol can be regarded to as a safe agent without major adverse events linked to its use, the optimal dosage, long-term effects, and potential interactions with medications still need to be investigated through well-designed randomized controlled trials (RCTs). Flavonoids, found in abundance in cocoa and green tea, have also demonstrated significant promise in the treatment of ED by improving endothelial function and reducing oxidative stress [84, 85]. The use of these compounds has been associated with moderate increases in IIEF score, typically ranging from 2 to 4 points. By enhancing NO bioavailability and promoting vasodilation, flavonoids offer a natural and potentially preventive approach to managing ED, particularly in vascular-related cases [85, 86].

4.13 Vitamins C and E

Vitamins C and E are antioxidants capable of counteracting ROS, thereby improving vascular health [87]. These compounds have been the subject of numerous studies showing improvements of varying degrees in erectile function [88]. In particular, vitamins C and E have been shown to yeild modest improvements in IIEF scores of approximately 1–2 points. However, although their efficacy as monotherapy is limited, they have demonstrated synergistic effects when combined with other nutraceuticals, such as L-arginine or *Pycnogenol* [89]. Future research for the treatment of ED should focus on optimizing these combinations to increase their therapeutic potential.

4.14 Omega-3 fatty acid

Omega-3 fatty acids reduce systemic inflammation and improve the fluidity of cell membranes, thus enhancing vascular signaling and consequently increasing the endothelial compliance of the cavernous sinusoids [90]. Observational studies indicate a positive association between omega-3 consumption and a reduced incidence of ED [91]. Omega-3 fatty acids, known for their anti-inflammatory and vascular benefits, have been the focus a number of studies which have shown only modest improvements in penile rigidity [92]. They are particularly beneficial in ED cases linked to metabolic syndrome or chronic inflammation [91]. More robust clinical trials are needed to establish their efficacy and explore potential synergies with other nutraceuticals.

4.15 Zinc and other micronutrients

Zinc, a vital micronutrient, has also been explored in ED research [93]. Zinc is essential for testosterone synthesis and testicular function maintenance [93] and its deficiency has been correlated with an increased risk of ED [93]. Other micronutrients, such as magnesium and vitamin D, have been found to be essential in hormonal and vascular regulation [94]. Zinc supplementation has shown slight improvements in IIEF scores (1–2 points), mainly in individuals with underlying zinc deficiencies. Zinc supplementation has also been shown to improve hormonal balance and libido, although its effects on erectile function appear to be more pronounced in combination with other therapies [95]. Future research should be focused on zinc-deficient populations and investigate its interactions with other micronutrients, such as magnesium and vitamin D.

4.16 Probiotics and gut microbiota

Recently, much attention has been paid at the connection between gastrointestinal and genitourinary tracts. In particular conditions which alter the composition of gastrointestinal microbiota may affect the lower urinary tract through the mechanism of the pelvic cross-organ sensitization by which an altered gastrointestinal barrier potentially driven by intestinal dysbiosis may negatively affect adjacent organs through the passage of bacteria or bacterial products [96–99]. While current evidence is preliminary, this area holds great promise for future exploration, particularly in metabolic and vascular-related ED.

Emerging evidence suggests that a "healthy" gut microbiota strongly contributes to normal sexual functioning [100, 101]. In the context of ED, dysbiosis (*i.e.*, an imbalance within gut microbiota community), may lead to systemic inflammation, endothelial dysfunction and hormonal imbalances, all key factors in ED pathogenesis. A decrease in short chain fatty acids production, such as butyrate, may alter gut barrier integrity, and impair endothelial function by promoting inflammation and reducing NO availability [101]. Moreover, the modulation of bile acid metabolism by gut microbiota influences energy balance and immune homeostasis through the interaction with bile acid receptors [101]. Finally, dysbiosis can lead to alterations in neurotransmitter production, immune activation and hypothalamic–pituitary–adrenal axis regulation, potentially affecting mood and stress levels, which are known to influence erectile function. All of these processes are critical in the maintenance of vascular health and in the regulation of sex hormones, both essential for erectile function. Therefore, intestinal dysbiosis may contribute to ED by the alteration of hormone levels, by dysruption of the gut-brain axis leading to stress/anxiety-mediated (*i.e.*, psychogenic) ED, or by influencing the development of altered metabolic conditions such as obesity and diabetes mellitus or hypertension [102]. Therefore, it has been suggested that improving gut health might positively influence endothelial function and reduce systemic inflammation, indirectly benefiting erectile performance [102]. Moreover, it has been demonstrated that in ED there is a decrease in beneficial bacteria such as *Alistipes* and *Bifidobacterium* and an increase in harmful bacteria such as *Actinomyces* and *Bacteroides* [101]. Based on this, treatment strategies for ED through the modulation of gut microbiota by using specifically designed probiotic/symbiotic formulations or even fecal microbiota transplantation (FMT) represent a promising area of research [101]. It would therefore be crucial to identify specific bacterial strains or microbial metabolites that exert a beneficial effect on erectile function. In this regard, it has been suggested that taxa like *Ruminococcaceae* and *Lactobacillus,* as well as metabolites like butyrate may reduce systemic inflammation and improve vascular health, thus positively affecting male sexual function [101]. However, the association between specific gut microbial taxa and ED is derived from cross-sectional studies which do not account for potential confounders such as nutritional status, the use of medication such as antibiotics or gastric acid secretion inhibitors, and comorbidities like obesity, diabetes and hypertension, all of which can affect the gut microbiota composition. Moreover, only a limited number of observational and pilot studies have explored gut microbiota-targeted strategies in ED, and, therefore, well-designed randomized clinical trials are warranted to assess the real efficacy of gut microbiota manipulation in specific types of ED.

4.17 *Muira puama*

Muira puama (*i.e.*, *Ptychopetalum olacoides*) is a plant native to the Amazonian regions of Brazil, particularly in rainforest areas. It is traditionally used by Brazilian indigenous populations, and is known for its aphrodisiac and stimulating properties [103]. The name "*Muira puama*" originates from the local language, with "muira" meaning "strength" or "energy" and "puama" referring to the plant itself [104]. The bark and roots are the parts of the plant primarily used for medicinal purposes, containing a range of bioactive compounds, such as alkaloids, sterols and flavonoids, believed to be responsible for the stimulating effects on sexual function [103, 104]. *Muira puama* has shown positive effects on libido and quality of erections [105], particularly in cases of psychogenic ED [105]. A few studies have shown improvements in IIEF score of approximately 3–4 points after 8 weeks of treatment with *Muira puama*, with a significant increase in erectile rigidity and sexual satisfaction [105, 106]. *Muira puama* primarily acts as a central nervous system stimulant, enhancing sensitivity and sexual response [103]. Its effects are linked to hormonal

modulation, which can reduce psychological stress, a key factor in ED [104].

4.18 *Cocoa* polyphenols

Cocoa polyphenols, especially flavonoids, are known for their positive effects on cardiovascular health and consequently on erectile function, thanks to their ability to increase the bioavailability of NO [107]. There are numerous studies suggesting that the consumption of flavonoid-rich *cocoa* can improve blood flow and erectile function in patients with ED associated with endothelial dysfunction [108]. In particular, patients with mild ED have been reported to achieve significant improvements in penile rigidity after 4 weeks of treatment with high-flavonoid cocoa [108, 109].

4.19 *Reishi (ganoderma lucidum)*

Reishi, otherwise known as *Ganoderma lucidum*, is a medicinal mushroom known for its adaptogenic and antioxidant properties, with beneficial effects on vascular health and consequently on erectile function [110]. Although research on its efficacy in ED is still limited, some clinical studies suggest that *Reishi* may improve erectile function, especially in cases of vascular or stress-related dysfunction. In fact, the use of *Reishi* for 12 weeks has been shown to lead to improvements in penile rigidity [111]. The mushroom acts on various fronts in the treatment of ED: on the one hand, by regulating fibrosis and the Nitric Oxide Synthase/Extracellular signal-Regulated Kinase/Janus Kinase (NOS/ERK/JNK) pathway [111], on the other hand, by reducting oxidative stress, thus preserving endothelial health of the penile corpora cavernosa [112].

4.20 *Cordyceps sinensis*

Cordyceps sinensis is another medicinal mushroom that has positive effects on sexual function due to its ability to improve cellular energy and blood circulation. In particular, its benefits are due to the stimulation of Adenosine Triphosphate (ATP) production, which increases the energy efficiency of cells and promotes vasodilation to improve penile blood flow, and increased synthesis of NO [113]. In different clinical studies conducted on patients with ED of vascular origin, supplementation with *Cordyceps* for 8 weeks led to a significant improvement in penile rigidity. Also, in patients with chronic fatigue, *Cordyceps* increased erectile rigidity, sexual desire and the overall sensation of a firm and sustained erection leading to improvement in sexual performance and confidence [114, 115]. When taken in high doses, *Cordyceps sinensis* may have a few side effects such as epigastric pain and diarrhea. Therefore, it is important to choose the safe dose and duration of treatment prior to considering it as a possible ergogenic aid in ED patients.

4.21 *Capsicum frutescens*

Capsicum frutescens is a bioactive compound found in hot chili peppers, known for its stimulating effects on metabolism and blood flow [116]. Specifically, *Capsicum frutescens* acts as a vasodilator, through a positive effect on the release of NO [116, 117]. Several clinical studies suggest that *Capsicum frutescens* may be beneficial in the treatment of ED, particularly in cases of mild to moderate ED [116]. *Capsicum frutescens* supplementation has been demonstrated to lead to a significant improvement in penile hardness, possibly mediated by boosted production of NO in endothelial cells of the corpora cavernosa [117]. Because of its capacity of improving circulation and reducing oxidative stress, *Capsicum frutescens* might be useful in patients with heart failure-related ED [118].

4.22 *Quercetin*

Quercetin is a flavonoid found in foods such as apples, onions, red grapes and citrus fruits, known for its potent antioxidant and anti-inflammatory properties [119]. *Quercetin* has been considered as a potential treatment for ED due to its ability to reduce oxidative stress [119]. Specifically, *Quercetin* can improve vascular health and promote vasodilation, thereby enhancing blood flow to the penis and improving erectile function [120]. In different studies conducted in patients with mild ED, *Quercetin* supplementation for 12 weeks showed significant improvements in IIEF scores, with an average increase of 3–4 points [121]. The benefits were primarily attributed to *Quercetin*-induced reduction in ROS-related alteration of endothelial function [121]. Moreover, *Quercetin* has been shown to modulate NO production [120].

4.23 *Schisandra (schisandra chinensis)*

Schisandra is an adaptogenic plant also known for its ability to reduce stress, improve physical resistance and stimulate vital energy, especially used in Chinese medicine for its tonic effects and its ability to balance vital energy, known as “Qi” [122]. *Schisandra* is mainly used as a tonic, but its therapeutic applications also include the promotion of cardiovascular and sexual health. In addition, this plant seems to have positive effects on blood circulation and production of NO, and is especially appreciated for its antioxidant properties [122–124]. In different studies conducted in men suffering from stress- or fatigue-related mild ED, *Schisandra* led to an improvement in erectile rigidity, sexual desire and the overall sensation of a firm and sustained erection leading to improved sexual performance and confidence.

4.24 *Astragalus (astragalus membranaceus)*

Astragalus is a plant that has been used for thousands of years in traditional Chinese medicine, where it is mainly recognized for its tonic properties and its ability to strengthen the immune system. This plant is used in the treatment of many conditions, but numerous studies underline its beneficial effects on blood circulation and cardiovascular health [125]. *Astragalus* shows important antioxidant properties, being capable of reducing oxidative stress and protecting the endothelial cells that line the blood vessels, thus preserving the good functioning of the cardiovascular system. *Astragalus* appears to improve blood flow to the penis by increasing intracellular levels of cyclic adenosine 3′-5′-monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are both signaling molecules involved in penile erection. Moreover, this plant has has been shown to have anti-inflammatory properties that can be

useful in cases of ED caused by vascular inflammation or damage to the vessels [126]. In a clinical study involving 122 patients with ED, Hongjing I granules, a herbal Chinese medicine containing *Astragalus*, was significantly superior to a placebo after 8 weeks of treatment, and this was particularly evident in patients with ED related to chronic stress or vascular inflammation [127]. *Astragalus* might be regarded as a useful supportive treatment for ED, especially for patients with comorbidities such as diabetes or hypertension, in which inflammation and poor blood circulation are predominant factors. Furthermore, its ability to tone the body and improve circulation could contribute to the general improvement of sexual health [128]. *Astragalus* use is associated to a limited number of side effects such as skin eruption, headache and diarrhea, whose occurrence is however very rare.

4.25 *Damiana (turnera diffusa)*

Damiana (*Turnera diffusa*), a plant native to Central and South America, has traditionally been used to increase libido and improve sexual function. This plant is known primarily for its aphrodisiac properties, but its application also extends to the treatment of digestive and respiratory disorders [129]. As for ED, *Damiana* is often used as a tonic to increase energy and promote sexual well-being by stimulating the central nervous system and hormonal production [130]. *Damiana* has also been shown to increase the production of dopamine, a neurotransmitter essential in sexual stimulation and desire [129]. Furthermore, *Damiana* appears to have positive effects on blood circulation by improving blood flow to the penis, which explains its potential use in the treatment of mild to moderate ED [130]. While not a primary treatment for ED, *Damiana*, due to its aphrodisiac and sexual tonic effects, may be considered a natural option to be used in combination with other treatments, especially in patients with psychogenic or aging-related ED experiencing loss of libido or sexual fatigue [129, 131, 132]. Although research on *Damiana* for ED is limited, some studies have found significant improvements in IIEF scores. In particular, in one study conducted in men with mild to moderate ED, the use of this herb for six weeks showed an average increase of 2 points in IIEF, with significant benefits regarding erectile strength and sexual satisfaction [132].

4.26 *Catuaba (erythroxylum catuaba)*

Catuaba (*Erythroxylum catuaba*) is an aphrodisiac plant native to Brazil that indigenous populations of the Amazon used to increase sexual desire and sexual performance [133]. Although there is currently no impressive clinical evidence in this regard, the plant is used and appreciated for its positive effects on blood circulation and for its stimulating action on the central nervous system (CNS). *Catuaba* is believed to act as a tonic for the body, also improving resistance and sexual vitality. These properties are due to the alkaloids contained in the plant such as flavonoids and tannins that have an aphrodisiac action [134]. *Catuaba* is also known for its neuroprotective properties and the ability to increase the production of dopamine, a key neurotransmitter linked to sexual desire and pleasure [134]. Also, it may act as a PDE5i [134]. Although research on *Catuaba* for ED is limited, some studies indicate that this plant may improve erection quality and stimulate sexual desire in the presence of factors such as stress and fatigue [135]. In fact, in a study conducted in men with mild ED, the supplementation of this compound for eight weeks showed a significant improvement of about 2–3 points in IIEF scores. In addition, treated patients also reported improvements in erection rigidity, duration and sexual satisfaction [136].

4.27 *Bacopa monnieri (Brahmi)*

Bacopa monnieri, also known as *Brahmi,* is an adaptogenic herb widely used in Ayurvedic medicine to improve memory, concentration and reduce stress that has recently attracted attention for its potential positive effects on male sexual function. In particular, this herb acts as a tonic for the CNS, helping reduce anxiety and improve the body's response to stress, which is often responsible of sexual problems [137]. Although research is still limited, there is some evidence that *Bacopa monnieri* may improve erectile function, particularly in men with psychogenic or stress-induced ED. Furthermore, it has been shown that one of the main mechanisms through which *Bacopa monnieri* exerts its effects on erectile dysfunction is through the stimulation of NO production [138]. In a study conducted on men with mild ED, administering *Bacopa* for six weeks led to an average increase of 2 points in IIEF scores, showing improvements in erection and sexual satisfaction [139]. Although the efficacy of *Bacopa Monnieri* is not yet well established, its positive effects on stress reduction, increased blood circulation and NO production could make it useful in combination with other therapies for ED, especially for those patients suffering from psychogenic ED.

4.28 *Suma (pfaffia paniculata)*

Suma, also known as "Brazilian ginseng", is a plant that primarily grows in the Amazon and is traditionally used to boost energy, vitality and improves sexual health [140]. Although scientific research on *Suma* is still in the preliminary stages, there is evidence to suggest that this plant may have an important action on sexual activation especially for those who suffer from ED due to fatigue or stress. *Suma* has been shown to increase the production of testosterone, thus counteracting the decrease in libido associated with low hormone levels typically found in a number of patients with ED [141]. Although studies on *Suma* and ED are limited, some suggest that this herb helps significantly in counteracting poor sexual stamina and low energy levels [142].

4.29 *Paeonia lactiflora (Peony)*

Paeonia lactiflora or *Peony*, is a plant used in traditional Chinese medicine to treat various disorders, including those related to sexuality. This plant is known for its anti-inflammatory and antioxidant properties, which can help improve cardiovascular health and blood circulation, therefore it may have a role in the treatment of ED, often linked to circulatory problems [143, 144]. Furthermore, *Peony* is known for its calming effects, which may help reduce performance anxiety, a common psychological factor that may sometimes play a particularly impactful role in psychogenic ED [144, 145]. It

should be noted that although the data at our disposal are still scarce, some small clinical studies have shown that the use of *Paeonia* supplements leads to improvements in erectile rigidity, sexual desire and the overall sensation of a firm and sustained erection, leading to improved sexual performance and confidence [144, 145]. Furthermore, it has been noted that its anti-inflammatory action may reduce oxidative damage to endothelial cells, improving vascular function and, consequently, supporting erectile function.

4.30 *Longjack (eurycoma longifolia)*

Longjack or *Eurycoma longifolia*, is a plant from Southeast Asia that has been used for centuries as a natural aphrodisiac. This plant, also known as Tongkat Ali, is known for its ability to stimulate the production of testosterone, a hormone of vital importance for male sexual health [146]. *Longjack* has been studied extensively for its positive effects on libido, fertility and sexual function and has also been used to treat hypogonadism, a condition characterized by low testosterone production that is one of the most common causes of ED [147]. The effectiveness of this herb has been analyzed in several clinical studies. In particular, in a study involving 109 men with ED and low testosterone levels, taking *Longjack* for 12 weeks showed significant improvements in IIEF scores, with an average increase of 3–4 points. In addition, the study participants reported significant improvements from a qualitative point of view in terms of erection hardness, erection duration and sexual satisfaction [148, 149]. The herb seems to act mainly by stimulating testosterone production, but it also improves blood circulation, thereby increasing the supply of oxygen and nutrients to the penile corpora cavernosa. This might be particularly useful for men with vascular-based ED [149]. *Longjack* has also been shown to have positive effects on fertility, as it appears to improve sperm quality and quantity, making it a very interesting therapeutic option not only for men seeking to improve erectile function, but also for those who have difficulty conceiving [149]. While *Longjack* is very promising as a natural therapeutic agent for altered sexual function, it is important to note that its effectiveness may vary between individuals and that further research is certainly needed to determine its long-term benefits and the optimal dose for therapy. In summary, *Longjack* represents a very promising treatment for patients with ED associated with low testosterone levels and may be particularly useful as a complement to hormonal therapies to help improve male sexual health.

4.31 *Hypoxis hemerocallidea (African potato)*

Hypoxis hemerocallidea, also known as *African potato*, is a plant from southern Africa traditionally used to treat a variety of disorders, first of all, ED. In fact, the extracts of *Hypoxis* are rich in phytosterols, saponins and flavonoids, known for their antioxidant and anti-inflammatory properties [150]. Also, the plant acts by increasing testosterone levels and improving blood circulation, two fundamental factors to ensure the sexual health of men [150]. Several clinical studies have shown that *Hypoxis* extracts lead to an improvement in sexual function, mainly in patients with ED associated with low testosterone levels or vascular problems. In particular, daily intake of *Hypoxis* extracts resulted in an increase of approximately 2–3 points in IIEF scores, with clear and significant improvements in erection quality and libido [151, 152]. In addition, positive effects have been shown on prostate health, which also is a crucial factor for sexual function [152].

4.32 *Sclerocarya birrea (Marula)*

Sclerocarya birrea, commonly known as *Marula*, is a plant native to sub-Saharan Africa, whose fruits and seeds are rich in unsaturated fatty acids, vitamins and antioxidants, which contribute to the improvement of cardiovascular health and, consequently, of erectile function [153]. Traditionally, *Marula* infusions have been used as a tonic to increase libido and sexual stamina. The plant, in fact, improves blood flow, thus reducing the likelihood of ED related to circulatory problems. Furthermore, *Marula* is also known for its anti-inflammatory and antioxidant properties, which can help counteract oxidative cell injury and damage to blood vessels [154, 155]. Although evidence-based efficacy of *Marula* on ED is still limited, because of its beneficial effects on vascular health one may hypothesize that this plant may serve as a therapeutic alternative to treat ED of vascular origin.

4.33 *Cissus quadrangularis (veldt grape)*

Cissus quadrangularis, commonly known as *Veldt grape*, is a climbing plant native to Africa, which has traditionally been used to treat a variety of conditions, including ED. *Cissus* extracts contain antioxidants, flavonoids and phenolic compounds that improve blood circulation and vascular function, especially at the penile cavernous level [156]. The plant is also known for its anti-inflammatory properties and for supporting bone and muscle health, but it is its positive effects on vascular health that make it promising for the treatment of ED [157]. Clinical studies on men with mild ED have shown improvements in IIEF scores, with increases of 2–3 points [158]. Although further research is needed to confirm these results, the plant seems to have a very important potential for the treatment of ED of vascular origin both alone or in combination.

4.34 *Kigelia africana (sausage tree)*

Kigelia africana, commonly known as the *Sausage tree*, is a plant native to sub-Saharan Africa that is traditionally used to treat various disorders, including ED [159]. *Kigelia* extract is rich in flavonoids and phenolic compounds, which have antioxidant and anti-inflammatory properties which are beneficial to sexual health. Also, this plant has been shown to be able to improve blood circulation and stimulate libido [160]. Although data on the effects of *Kigelia africana* in ED are still limited, some preliminary studies have suggested that *Kigelia* extracts may have positive effects on erectile quality, with several studies showing that IIEF scores increased by approximately 2–3 points, especially in combination with other aphrodisiac remedies [161]. However, further research is needed to confirm the effectiveness of the plant, and additional clinical studies will certainly be needed to confirm its specific improvements in sexual function.

4.35 *Mondia whitei (whitei)*

Mondia whitei is a climbing plant from Central and West Africa that is traditionally used as an aphrodisiac, with its extract being used to stimulate testosterone production and help improve blood circulation, two essential factors for proper erectile function [162]. In addition, this plant is also used to treat digestive disorders and to improve physical endurance [163]. A number of preliminary studies have been performed, suggesting that *Mondia whitei* could also be useful in the treatment of ED, with improvements in erectile rigidity, sexual desire and the overall sensation of a firm and sustained erection, leading to improved sexual performance [164].

4.36 *Astragali complanati* semen

Semens of *Astragali complanati* are dried ripe seeds of *Flatstem Milkvetch*, which is mainly used in traditional Chinese medicine for the treatment of reproductive system diseases such as ED [165]. Among its components complanatoside, astragalin, complanatoside B, and kaempferol have recently been found to be responsible for its anti-ED effect [166]. *Astragali complanati* semen due to its content of flavonoids also positively affects oxidative stress and lipid metabolism, thus lowering serum lipids. Despite its traditional use for male health, efficacy in ED has never been tested in a systematic manner in clinical trials.

4.37 *Detarium senegalense*

Detarium senegalense J.F.Gmel. is a medicinal plant native to the west African region and is commonly known as the African star apple or tallow tree, rich in flavonoids, tannins, saponins, alkaloids and phenolic compounds [167]. A recent computational investigation on the therapeutic effects of *Detarium senegalense* has shown that among its flavonoid components, catechin, epicatechin and gallic acid have the capability of targeting six enzymes which are relevant to erectile function showing a significant binding affinity to PDE5, comparable to that exhibited by sildenafil [168]. Catechin in particular shows superior binding energies, favourable pharmacokinetic profile, and good binding conformation/interaction at the receptor site and might therefore be regarded as a multitarget inhibitor of key enzymes involved in the pathogenesis of ED. Therefore, the flavonoid-rich fraction of *Detarium senegalense* could lead to improved sexual performance and sustained erection for satisfactory sexual intercourse. Moreover, catechin could serve as a potential lead compound for development of a drug for the management of ED, due to its satisfactory pharmacokinetic profile, good binding affinity and good interaction at the receptor sites of the enzymes. Also, the flavonoid components of *Detarium senegalense* have shown high gastrointestinal absorption, good bioavailability and drug likeness [168]. Overall, this study supports the potential of *Detarium senegalense* phytochemicals as promising candidates for developing new, safer and more effective therapies for ED, offering an alternative to current treatments with fewer side effects. However, further research is needed to exactly quantify these compounds in *Detarium senegalense* and evaluate their efficacy in animal experimental models and, subsequently in clinical trials.

4.38 *Fadogia agrestis*

Fadogia agrestis, *Schweinf. Ex Hiern*, locally referred to by the Hausas of Northern Nigeria as *gai gai* and in English as Black aphrodisiac is a plant belonging to the *Rubiaceae* family. In ethnomedicine, it has been used to improve athletic performance, to increase sex drive and to treat ED. A recent study conducted in male Wistar rats has shown that aqueous extracts of *Fadogia agrestis* are capable of restoring the NO/cGMP pathway and ED-associated key enzymes in the penile and testicular tissues, which is attributed to its antioxidant activity [169]. This suggests that aqueous extracts of this medicinal plant should be tested in clinical trials to evaluate whether they may prove useful in the treatment of ED.

4.39 *Kaempferia parviflora*

Kaempferia parviflora Wall. ex Baker (KP), known in Thailand as Black Ginger or Krachai Dam, belongs to the family of the *Zingiberaceae* family and is widely distributed in Southeast Asia. It has traditionally been employed to ameliorate physical capacities. Ethnopharmacological evidence indicates that a rhizome of *Kaempferia parviflora* is able to increase libido and sexual function [170].

5. Clinical usefulness of the most evidence-based nutraceuticals

Leisegang and Finelli [21] and Petre *et al.* [72] in a systematic review and meta-analysis of recent studies on alternative medicine for ED, have thoroughly evaluated the evidence on the clinical efficacy of the most used phytochemicals and/or nutraceutical formulations in patients with ED (*i.e.*, *Panax ginseng,* L-arginine, *Pycnogenol* and *Tribulus terrestris*).

Panax ginseng efficacy in ED has been investigated in four double-blind RCTs as a single herbal extract having, as an outcome, IIEF improvement. In three of them *Panax ginseng* was effective at a dose varying from 2000 mg/day for 8 weeks to 3000 mg/day for 8–12 weeks, whereas, in another study, at the dose of 1400 mg/day it showed to be effective at 4 weeks but not at 8 weeks of treatment. The efficacy of *Panax ginseng* has been confirmed in a metanalysis of 5 studies including 216 ED patients and 153 controls [72]. No significant side effects were reported [21, 72]. Efficacy of *Pycnogenol* (120 mg/day for 4 months) was tested in two studies as a sole herbal intervention for ED, with both studies reporting improvement in erectile function. Moreover, a nutraceutical formulation of *Pycnogenol*, L-arginine, L-citrulline and roburins, as a combination therapy, was assessed in four studies all reporting beneficial effects on erectile function and other domains of the IIEF [21]. Also, in an uncontrolled trial, L-arginine caused a non-significant improvement in erectile function over 1 month. Introduction of *Pycnogenol* together with L-arginine in the same cohort caused a significant improvement of erectile function over the next month; in the third month, doubling the dose of *Pycnogenol* further improved IIEF in the same cohort of patients, without any adverse events [64]. Petre *et al.* [72], however, found that L-arginine, in a meta-analysis

of four RCTs with 246 patients (intervention group N = 133 patients; control group N = 113 patients), led to a significant improvement in erectile performance as assessed by IIEF. L-arginine has been suggested to be more effective in patients with ED with low NO, where patients with low urinary nitrites and nitrates appear to have greater benefits [21]. This dietary supplement has been reported as a well tolerated natural dietary supplement with good absorption and bioavailability, thus might be considered for long lasting treatment for ED [21]. *Tribulus terrestris* at a dose ranging from 750 mg to 1560 mg/day for 3 months was investigated as a single herb in two of the studies included in the meta-analysis, both using standardized extractions for saponins, and was reported having a positive effect on the IIEF [21]. However, Santos *et al.* [46] in a prospective, randomized, double-blind study with *Tribulus terrestris* extract at a dose of 400 mg/day reported no significant benefit compared to the placebo group. No side effects have been reported in clinical trials in which *Tribulus terrestris*-based products were administered.

Dosing strategy is relevant and inconsistent outcomes in clinical trials often stem from under-dosing or short treatment duration. For example, L-arginine appears effective only at doses $\geq$6 g/day sustained over several months [68], whereas earlier trials using $\leq$3 g/day showed no significant benefit [67]. Similarly, positive results with *Tribulus terrestris* involved standardized high-saponin extracts at 750 mg/day [45], while negative trials used lower or unstandardized doses [46]. We therefore recommend adhering to dosages validated in literature and maintaining therapy for at least 4–12 weeks to assess efficacy.

6. Discussion

Nutraceuticals offer a viable therapeutic option for ED, thanks to their ability to specifically target many of the pathophysiological mechanisms responsible for ED, coupled with a favorable safety profile (Table 1, Ref. [40–170]). In detail, due to their anti-inflammatory and anti-oxidant activity, they may counteract vascular dysfunction. Moreover, due to stimulatory effects on sex hormones they may be useful in ED related to hormonal imbalance. Finally, because of their ability to stimulate NO production or to inhibit PDE5, they may increase blood supply to the penile corpora cavernosa, thus, exerting a potential beneficial effect in ED related to circulatory problems. In addition, some nutraceuticals with anxiolytic and neuroprotective effects, could help by supporting mental well-being and improving erectile response in patients with ED of psychogenic origin, where anxiety, stress or depression play a significant role.

An effort should be made in identifying which ED patients are the most suitable for this therapeutical approach. We hypothesize that patients with mild to moderate ED might be among the ideal candidates for the use of nutraceuticals. We however emphasize that nutraceuticals should always be considered as adjuncts to, rather than replacements for, established medical or behavioral interventions, especially lifestyle improvements. Interventions such as weight reduction, physical activity, dietary improvements, and smoking cessation can significantly enhance erectile function, and nutraceuticals may complement these measures. Another group that could benefit from this therapeutical approach are patients who prefer non-pharmacologic options or those who do not respond adequately to PDE5i or who have contraindications to their use, such as those who are on nitrate therapy or have severe cardiovascular disease. Finally, patients with cardiovascular risk factors or metabolic syndrome may also benefit from nutraceuticals, particularly those with vasodilator and antioxidant properties, which may help improve vascular health and, consequently, erectile function.

Further research is needed to standardize dosages, and supplement formulations, to identify the most effective combinations, to assess long-term safety for agents like *Cordyceps sinensis*, and possible interactions with other nutraceuticals or drugs. Also, studies aimed at dissecting out, at the molecular level, the mechanisms by which nutraceuticals exert their beneficial effects in ED are warranted. Also computational analysis of nutraceuticals may lead to the identification of their most biologically active components, which may serve as a template for developing new, safer and more effective therapies for erectile dysfunction, thereby offering an alternative to current treatments with fewer side effects. Moreover, mounting evidence suggests that alteration of gut microbiota may play a pathogenic role in ED due to the interconnection between microbiome and systemic inflammation, metabolism and vascular health. Identifying the gut microbiota profile which plays a role in the normal sexual functioning or the one which is linked to ED would, therefore, be crucial in planning interventional studies. In this context, Zhang *et al.* [171] in a two-sample Mendelian randomization study evaluated the causal link between intestinal microbiota and ED by analyzing genetic variants of gut microbiota obtained from MiBioGen consortium containing 18,340 individuals. They found that genetically proxied *Lachnospiraceae*, *Lach-*

TABLE 1. Summary of nutraceuticals' effect on ED as assessed by improvement in IIEF score and underlying mechanism of action.

Compound/(Plant Family)	Active Component and Part Used	Mode of Action	Average IIEF Increase	Reference
Panax Ginseng/(Araliaceae)	Ginsenoside Rg1, Rb1, Rg3 extracted from root	Increases NO production, vasodilation, anti-oxidant and anti-inflammatory effect	3–5 points	[40–43]
Tribulus Terrestris/(Zygophillaceae)	Protodioscin extracted from fruits (sometimes leaves)	Modulates hormone levels by increasing testosterone production and androgen receptor sensitivity	2–4 points	[44–46]

TABLE 1. Continued.

Compound/(Plant Family)	Active Component and Part Used	Mode of Action	Average IIEF Increase	Reference
Maca (*Lepidium meyenii*)/(*Brassicaceae*)	Macamidi and macaeni extracted from root	Modulates sexual hormones, increases mitochondrial energy production	1–2 points	[47–50]
Epimedium (*Horny Goat Weed*)/(*Berberidaceae*)	Icariin, flavonoids, prenylhydroquinones extracted from leaves	PDE5 inhibition, promotes muscle relaxation and increases blood flow	2–3 points	[51–54]
Pausinystalia johimbe/(*Rubiaceae*)	Yohimbine extracted from bark	Alpha-2 adrenergic receptor antagonist, increases blood flow, stimulates nervous system	2–3 points	[55–58]
Saffron (*Crocus sativus*)/(*Iridaceae*)	Crocin, picrocrocin, safranal extracted from stigmas (red part of the flowers)	Antioxidant and neuroprotective, improves penile rigidity, reduces stress	3–4 points	[59–62]
L-Arginine	L-arginine (isolated amino acid typically from fermentation)	Precursor of NO, improves endothelial function and blood flow	3–6 points (with *Pycnogenol*)	[63–66]
Pycnogenol/(*Pinaceae*)	Oligomeric procianidine in bark extract from maritime pine (*pinus pinaster*)	Antioxidant, increases NO production and improves endothelial function	3–6points (with L-Arginine)	[67–69]
Ashwagandha/(*Solanaceae*)	Withanolides extracted from root or leaves	Adaptogen, reduces cortisol, balances hormones	1–3 points	[70–72]
Ginkgo Biloba/(*Ginkgoaceae*)	Ginkgolids, bilobalide extracted from leaves	Improves circulation and endothelial function through vasodilation	2–4 points	[73–77]
L-Citrulline	L-citrulline (isolated aminoacid also found in watermelon)	NO precursor with better bioavailability than L-Arginine	3–5 points (with P*ycnogenol*)	[78–80]
Anti-Oxidants	Poliphenol and nonpolyphenol flavonoids typically in red wine, fruits	Improve endothelial function, reduces oxidative stress	2–4 points	[81–86]
Vitamin C and E	Ascorbic acid and tocotrienols in isolated nutrients (fruit, vegetables, oils)	Antioxidants, improve vascular health	1–2 points (with other nutraceuti-cals)	[87–89]
Omega-3 Fatty Acids	EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid) in fish or algae oil	Reduce systemic inflammation and improve vascular signaling	Not determined	[90–92]
Zinc and other Micronutri-ents	Elemental zinc (Zn^{2+}) mineral from plant or animal sources	Essential for testosterone synthesis and hormonal balance	1–2 points (especially in case of deficiency)	[93–95]
Probiotics and Gut Micro-biota	Beneficial bacterial strains from food or fermentation	Improve gut health, endothelial function and reduce systemic inflammation	Not determined	[96–102]
Muira Puama/(*Olacaceae*)	Coumarins extracted from root and bark	Stimulates central nervous system, improves erectile rigidity and sexual desire	3–4 points	[103–106]
Cocoa Polyphenols/(*Malvaceae*)	Epicatechin extracted from seeds (cocoa beans)	Increases NO bioavailability, improves blood flow, reduces oxidative stress	Not determined	[107–109]

TABLE 1. Continued.

Compound/(Plant Family)	Active Component and Part Used	Mode of Action	Average IIEF Increase	Reference
Reishi (*Ganoderma lucidum*)/(*Ganodermataceae*)	Triterpenes, ganoderic acids extracted from fruiting body (mushroom)	Reduces oxidative stress, stimulates NO production, improves vascular health	Not determined	[110–112]
Cordyceps Sinensis/(Cordycipitaceae)	Cordycepin, adenosine extracted from fruiting body and mycelium	Stimulates ATP and NO production, improves blood flow and cellular energy	Not determined	[113–115]
Capsicum Frutescens/(Solanaceae)	Capsaicin in fruit of chili peppers (*Capsicum spp.*)	Stimulates NO production, improves blood flow, reduces oxidative stress	Not determined	[116–118]
Quercetin/(common in *Fagaceae, Rosaceae, Fabaceae*)	Quercetin extracted from onions, apples, berries, green tea	Antioxidant and anti-inflammatory, improves endothelial function and vasodilation	3–4 points	[119–121]
Schisandra (*Schisandra chinensis*)/(*Schisandraceae*)	Schisandrin A, B, C extracted from berries	Adaptogen, improves circulation, reduces oxidative stress	Not determined	[122–124]
Astragalus (*Astragalus membranaceus*)/(*Fabaceae*)	Astragalosides extracted from root	Antioxidant and anti-inflammatory, improves blood flow and vascular function	Not determined	[125–128]
Damiana (*Turnera diffusa*)/(*Passifloraceae*)	Arbutin, damianin extracted from leaves	Stimulates the central nervous system, improves circulation and sexual desire	2 points	[129–132]
Catuaba (*Erythroxylum catuaba*)/(*Erythroxylaceae*)	Catuabine, tannins extracted from bark	Stimulates central nervous system, improves circulation and libido	2–3 points	[133–136]
Bacopa Monnieri (*Brahmi*)/(*Plantaginaceae*)	Bacosides extracted from aerial parts (leaves and stems)	Reduces stress, improves NO production and vasodilation	2 points	[137–139]
Suma (*Pfaffia paniculata*)/(*Amaranthaceae*)	Ecdysteroids, saponins extracted from root	Stimulates testosterone production	Not determined	[140–142]
Paeonia (Peony)/(*Paeoniaceae*)	Paeoniflorin extracted from root	Antioxidant and anti-inflammatory, improves circulation, reduces performance anxiety	Not determined	[143–145]
Longjack (*Eurycoma longifolia*)/(*Simaroubaceae*)	Eurycomanone, quassinoids extracted from root	Stimulates testosterone production, improves blood circulation	3–4 points	[146–149]
Hypoxis Hemerocallidea (*African Potato*)/(*Hypoxidaceae*)	Hypoxoside, rooperol extracted from root and rhizome	Increases testosterone levels and improves circulation	2–3 points	[150–152]
Sclerocarya Birrea (*Marula*)/(*Anacardiaceae*)	Flavonoids and phenolic acids extracted from bark and seeds	Antioxidant and anti-inflammatory, improves cardiovascular health	Not determined	[153–155]
Cissus Quadrangularis (*Veldt Grape*)/(*Vitaceae*)	Quadrangularin A, phytosterols, vitamin C extracted from stems	Antioxidant and anti-inflammatory, improves blood flow	2–3 points	[156–158]
Kigelia Africana (*Sausage Tree*)/(*Bignoniaceae*)	Iridoids, kigelinone extracted from fruit and bark	Improves circulation and stimulates libido	2–3 points	[159–161]
Mondia Whitei/(*Apocynaceae*)	Saponins, alkaloids, coumarins extracted from root	Stimulates testosterone production, improves circulation	Not determined	[162–164]
Astragali Complanati (Fabaceae)	Astragalosides saponins, flavonoids, extracted from root	Improves blood circulation, reduces oxidative stress and influences neurotransmission	Not determined	[165, 166]

TABLE 1. Continued.

Compound/(Plant Family)	Active Component and Part Used	Mode of Action	Average IIEF Increase	Reference
Detarium senegalense/(*Fabaceae*)	Flavonoids, tannins, triterpenes extracted from bark and seeds	Improves NO production and inhibits PDE5	Not determined	[167, 168]
Fadogia agrestis/(*Rubiaceae*)	Steroidal saponins extracted from stems and root	Antioxidant, restores the NO/cGMP pathway in the penile tissue	Not determined	[169]
Kaempferia parviflora/(Zingiberaceae)	5,7dimethoxyflavone, kaempferol, extracted from rhizome	Increases libido and sexual function	Not determined	[170]

IIEF: International Index of Erectile Function; PDE5: phosphodiesterase type 5; NO: nitric oxide; cGMP: cyclic guanosine monophosphate; ATP: adenosine triphosphate.

nospiraceae NC2004 group, *Oscillibacter*, *Senegalimassilia* and *Tyzzerella-3* increased the risk of ED, whereas *Ruminococcaceae UCG013* were protective against ED [171]. Similar results were obtained by Zhu *et al.* [172] who confirmed that the 6 bacterial taxa above mentioned possibly have a causal relationship with ED. These studies therefore seem to have been able to identify important bacterial taxa which may serve as candidates for microbiome intervention in future ED clinical trials. Therefore, a promising avenue to pursue is the modulation of gut microbiota in patients with ED through the use of probiotics, prebiotics, symbiotics, dietary interventions, or FMT in order to restore microbial balance and improve erectile function. However, to date, only a small number of observational and pilot studies have explored gut microbiota-targeted strategies in ED, particularly in patients with comorbid metabolic syndrome or obesity. Randomized controlled trials with pre/pro/symbiotic formulations or FMT are necessary in order to clarify whether targeted manipulation of gut microbiota might be an appropriate therapeutic strategy, alone or in association with conventional therapies, in specific types of ED or in ED patients with a peculiar gut microbioma profile.

Because different nutraceuticals may target different aspects of ED, one may envision the use of a given nutraceutical, alone or in combination with conventional therapies and/or life-style modifications, in specific types of ED. In hormone-related ED, nutraceuticals like *Tribulus terrestris* and *Eurycoma longifolia* (Tongkat Ali) have demonstrated testosterone-boosting effects in small clinical trials [45, 173]. These agents may support libido and arousal in hypogonadal men, but are not substitutes for testosterone replacement in clinically deficient patients. In psychogenic, anxiety-related ED, agents acting on central arousal pathways, such as *Yohimbine*, *Ashwagandha* and *Muira puama*, may serve as appropriate therapeutic agent [57, 70, 105]. Their use could be particularly relevant when pharmacological therapy has failed in the absence of organic causes. In the case of vasculogenic ED, men with endothelial dysfunction, obesity, type 2 DM or cardiovascular risk factors may benefit from nutraceuticals enhancing NO bioavailability or reducing oxidative stress. In this respect, L-arginine, L-citrulline, *Panax ginseng* and *Pycnogenol* have all shown promise in this therapeutic context [41, 63, 64].

Finally, one must keep in mind that nutraceuticals consist of bioactive compounds which, even though of natural origin, are not necessarily safe, thus, exerting a biological activity which may lead to adverse events. Also, they may interact with other conventional therapeutical agents or with other food components. Nutraceuticals used for ED are generally considered safe, with the majority of clinical trials reporting only mild and transient adverse effects, such as headache or gastrointestinal discomfort [45]. Nonetheless, we acknowledge that rare but clinically relevant adverse events have been documented. For example, *Yohimbine* may cause hypertension, tachycardia, anxiety, and increased frequency of urination which are consistent with its sympathomimetic action, particularly in sensitive individuals [57]. Also, mild gastrointestinal symptoms have been reported by patients treated with *Maca* [49]. Finally, *Astragalus* use may cause a limited number of side effects such as skin eruption, headache and diarrhoea. Moreover, although herb-drug interactions remain relatively uncommon, they are not negligible. *Ginkgo biloba*, for instance, has been associated with increased bleeding risk when combined with anticoagulants such as warfarin, with some studies reporting a bleeding hazard ratio of 1.3–1.5 [174]. Also, *Epimedium sagittatum* extracts, and in particular its component icariin, in an experimental study in rats have been demonstrated to alter the pharmacokinetics of sildenafil by decreasing its bioavailability. Therefore, this suggests that co-administration of *Epimedium sagittatum* extract and sildenafil in clinical practice should be avoided due to potential herb-drug interaction that may impact on the efficacy of sildenafil [175]. *Yohimbine* may negatively interact with anxyolitic agents due to its stimulating activity of the central 5-hydroxytryptaminergic system, and with anti-hypertensive drugs due to its inhibition of presynaptic alpha-2-adrenergic receptors. However, due to its sympathomimetic effects, it has been demonstrated to be able to counteract clonidine-induced toxic states such as depression of the CNS and hypotension [176]. Finally, a theoretical risk of hypotension should be considered when L-arginine is used alongside PDE5i or nitrates. Infact, L-arginine, PDE5i and nitrates increase NO signalling via different mechanisms and therefore may exert a synergistic effect on blood pressure, causing hypotension. Therefore, although severe interactions are rare, clinicians should remain vigilant, especially in pa-

tients on multiple therapies.

An additional issue that should be taken into account when using nutraceuticals in general and in the context of ED in particular is the lack of regulatory oversight and standardization which represents a fundamental weakness in their clinical use. The standardization of herbal preparations is crucial for ensuring the reliability and efficacy of medications. Therefore, determining the concentration of their active ingredients and conforming to physical, chemical and physiochemical standards, as well as *in vitro* and *in vivo* parameters is of great relevance in order to ensure the efficacy of each nutraceutical product. Unlike pharmaceuticals, dietary supplements are not subjected to pre-market approval by regulatory agencies such as the Food and Drug Administration (FDA), as established by the Dietary Supplement Health and Education Act. Oversight typically occurs only after adverse events are reported [177]. This regulatory gap together with a well established variability in the standardization of plant extracts [178] allows for substantial variability between and even within products. A "ginseng" capsule from one manufacturer may contain different concentrations or purity levels than another, and even batches of the same product may vary in active compound content due to inconsistent sourcing and production processes [179]. This may lead to inconsistency in clinical results, making it difficult to understand the real efficacy or to define the exact dosing of a given herbal product. Also, herbal-herbal or herbal-drug interactions may be difficult to assess if the composition of a product is not well standardized.

Moreover, the global market is invaded by counterfeit and adulterated nutraceuticals claimed to be of natural origin sold with a therapeutic claim. The variability in definition of these products across countries together with differences in the registration procedures may facilitate their manipulation, leading to the diffusion of adulterated and counterfeit products without appropriate control. In fact, many of the nutraceuticals advertised for ED have been found to be adulterated with active pharmaceutical ingredients (*i.e.*, PDE5i) and mislabeled as being natural, thus posing a major health hazard for consumers [23]. Additionally, issues such as contamination with heavy metals and pesticides further highlight the inconsistency and safety concerns linked to poorly regulated products [180]. Adulteration of herbal products may have a severe impact on consumers' well being, with a possibility of serious adverse effects such as acute liver injury, kidney failure, pulmonary embolism, stroke or even death.

A limitation of this review is that we did not systematically evaluate quality or bias of included studies, even though this is strictly required for systematic reviews and/or meta-analyses and not for a narrative review [181]. However, this review represents a focused summary of the current knowledge and understanding on the topic of nutraceutical use in ED treatment, and provides implications for future research.

7. Conclusions

Nutraceuticals present a valuable therapeutic resource for different profiles of patients with ED, being able to target a number of pathophysiological mechanisms, and with a generally favorable safety profile. However, an individualized approach is essential to optimize their potential therapeutical benefits. Integrating nutraceuticals with conventional existing therapies, including lifestyle interventions, such as healthy diet and exercise, and pharmacological therapy, could significantly improve clinical outcomes and quality of life of patients suffering from this clinical problem which carries such a high negative impact on their relationship life.

AVAILABILITY OF DATA AND MATERIALS

There are no datasets included in the study to share.

AUTHOR CONTRIBUTIONS

LR and MM—designed the study and wrote the manuscript. CI, CS, FC, MDS—conceptually reviewed the manuscript. LN, LS, CM, DA, BB, UA and AT—provided help in the literature search. FF, PPP and AC—helped writing the manuscript and collecting data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Lorenzo Romano is serving as one of the Editorial Board members of this journal. We declare that Lorenzo Romano had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to BB.

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