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SYSTEMATIC REVIEW

Herbal Dietary Supplements for Erectile Dysfunction: A Systematic Review and Meta-Analysis

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Abstract

Purpose Erectile dysfunction (ED) is a common condition that significantly affects quality of life and interpersonal relationships.

Objective Our objective was to perform a systematic review and meta-analysis to evaluate the efficacy of herbal dietary supplements in the treatment of ED.

Materials and Methods We searched five databases to identify randomized controlled trials (RCTs) that evaluated the clinical efficacy of herbal medicines in ED. Quality was assessed and risk of bias was estimated using the Jadad score and the Cochrane risk-of-bias tool.

Results In total, 24 RCTs, including 2080 patients with ED, were identified. Among these, 12 evaluated mono-preparations (five ginseng [$n = 399$], three saffron [$n = 397$], two *Tribulus terrestris* [$n = 202$], and one each *Pinus pinaster* [$n = 21$] and *Lepidium meyenii* [$n = 50$]), seven evaluated formulations ($n = 544$), and five investigated dietary supplements in combination with pure compounds ($n = 410$). Ginseng significantly improved erectile function (International Index of Erectile Function [IIEF]-5 score: 140 ginseng, 96 placebo; standardized mean difference [SMD] 0.43; 95% confidence interval [CI] 0.15–0.70; $P < 0.01$; $I^2 = 0$), *P. pinaster* and *L. meyenii* showed very preliminary positive results, and saffron and *T. terrestris* treatment produced mixed results. Several herbal formulations were associated with a decrease of IIEF-5 or IIEF-15, although the results were preliminary. The quality of the included studies varied, with only seven having a prevalent low risk of bias. The median methodological quality Jadad score was three out of a maximum of five. Adverse events were recorded in 19 of 24 trials, with no significant differences between placebo and verum in placebo-controlled studies.

Conclusions Encouraging evidence suggests that ginseng may be an effective herbal treatment for ED. However, further, larger, and high-quality studies are required before firm conclusions can be drawn. Promising (although very preliminary) results have also been generated for some herbal formulations. Overall, more research in the field, adhering to the CONSORT statement extension for reporting trials, is justified before the use of herbal products in ED can be recommended.

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Key Points

Herbal dietary supplements are widely used by men with erectile dysfunction; however, a lack of rigorous regulation means many products reach the market without compelling evidence of efficacy.

The results of this systematic review and meta-analysis suggest that *Panax ginseng* (ginseng) and Prelox® (the combination of pycnogenol and L-arginine aspartate) may be effective in the treatment of erectile dysfunction.

More rigorous clinical trials are needed before the use of herbal dietary supplements can be definitively recommended.

1 Introduction

Erectile dysfunction (ED) has been defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance. Together with premature ejaculation, ED represents the most common among the symptoms of male sexual disorders [1, 2]. The prevalence of ED is difficult to estimate as it varies widely worldwide and depends on many factors, including the adopted ED definition, population selection, and the sampling/tools used for the survey. Nevertheless, prevalence rates of ED are estimated to range from 1 to 10% in adults aged < 40 years to 50–100% for men in their 70 and 80 s [2–5]. Current approaches to ED are primarily based on pharmacotherapy, with phosphodiesterase type 5 (PDE5) inhibitors representing a first-line treatment [6]. The pharmacological action of PDE5 inhibitors may be affected by food intake, and concomitant administration of nitrates or alpha-blockers poses a risk of hypotension, which can be life threatening in the case of nitrates [7].

The use of plant-derived products to enhance male sexual performance has a long—and continuous—history [8]. A number of plants have been used as male sexual performance enhancers in traditional systems of medicine in different countries and different cultures [9]. Nowadays, a variety of herbal extracts are highly publicized by media and widely used by men with ED [10]. Such products have been classified by the Dietary Supplement Health and Education Act as dietary supplements [11], meaning that the rigorous testing adopted for pharmaceutical drugs to reach the market does not apply [11, 12]. With a wide range of products available and little regulation, the health effects of herbal dietary supplements (HDSs) promoted for ED are often confusing for medical practitioners. Although some clinical trials have examined the efficacy of HDSs advocated to treat ED, a comprehensive and objective synthesis of the best available evidence is lacking. Therefore, the aim of this systematic review and meta-analysis is to critically evaluate the evidence from randomized controlled trials (RCTs) about the effectiveness of herbal supplements in patients with ED.

2 Methods

This review was planned and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13], except that the protocol was not registered on any database.

2.1 Literature Search

Two researchers (AAI and FB) independently searched the following electronic databases from their respective inception to June 2017: PubMed/MEDLINE, Google Scholar, Scopus, Web of Science, and Cochrane Library. The search terms were botanicals, phytotherapy, herbal medicine, plant, nutraceutical*, herbal dietary supplement*, or traditional medicine in combination with impotence, erectile dysfunction, and sexual dysfunction. The reference lists of included trials, as well as pertinent reviews and textbooks, were also searched for additional studies. Additionally, manufacturers of the identified medicinal plant were contacted for additional published and unpublished clinical trials. Finally, we searched clinicaltrials.gov for clinical trials that were registered but not yet published.

2.2 Eligibility Criteria

To be eligible for review, studies were required to meet the following conditions:

(1) Study design: RCTs and studies with any form of control (i.e., drug or placebo).
(2) Participants: Studies in patients with ED of any severity (mild, moderate, severe) and etiology (e.g., psychogenic, vascular, drug induced).
(3) Interventions: Studies that investigated herbal preparations (e.g., herbal extracts) as a monopreparation (i.e., preparation derived from one plant only) or a mixture of herbal extracts (herbal formulations, i.e., preparation derived from two or more plants), even in combination with pure compounds; studies evaluating

pure compounds, even if of plant origin (e.g., yohimbine), were excluded.

(4) Outcomes: Studies that assessed at least one of the following outcomes: International Index of Erectile Function (IIEF)-15, IIEF-5, IIEF-EF, or patient satisfaction.

(5) Data accessibility: Studies that were published as full papers and in English, French, German, Spanish, Portuguese, or Italian.

2.3 Data Extraction

Two reviewers (AAI and FB) independently extracted the data. Any disagreement about the eligibility of a study was resolved by discussion with the other authors.

2.4 Quality Assessment and Risk of Bias

Two reviewers (AAI and FB) independently assessed the methodological quality of the trials according to the Jadad scale, a three-item (randomization, blinding, and dropouts/withdrawals), five-point quality scale [14]. Additionally, we evaluated risk of bias for each study using the Cochrane Collaboration's risk-of-bias tool, with reference to the Cochrane handbook [15].

Three reviewers (DD, MI, and CC) independently extracted information on the six domains of bias (selection, performance, detection, attrition, reporting, and other) from seven sources [15].

We attempted to contact all authors where publications did not provide enough information for us to judge risk of bias. Any disagreements on risk of bias were resolved by collective discussion.

2.5 Data Synthesis and Data Analysis

Meta-analyses were performed for IIEF scores and plasma testosterone levels using the Review Manager (RevMan) computer program, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary effect was calculated as standardized mean difference (SMD) for continuous outcomes with different scales of measurement and different versions of IIEF. Statistical heterogeneity among studies was expressed with the χ^2 test and the I^2 index statistic [16]. We used a fixed-effects model for the calculation of the pooled-effect index with values of $P > 0.1$ and $I^2 < 50\%$, which meant homogeneity existed among studies, and applied random-effects models if P values were < 0.01 and $I^2 > 50\%$. However, in this meta-analysis, we applied the random-effects model because of high heterogeneity between studies in areas such as clinical design, dose of plant, and treatment duration. P values < 0.05 and heterogeneity $I^2 < 50\%$ were considered statistically significant. The confidence intervals (CIs) were established at 95%. When available information was insufficient to calculate the standard deviation (SD) for the changes (e.g., a great loss of participants between final measurement and baseline), the SD was calculated using a correlation coefficient value of 0.5 as suggested by the Cochrane Collaboration when available evidence is insufficient to assign a correlation coefficient [17].

3 Results

3.1 Description of the Paper Selection Process and Overview of Reviewed Studies

The literature search (Fig. 1) yielded 2805 papers, with 1200 duplicates. After initial screening, 995 articles were excluded because the title was irrelevant, leaving 205. Following abstract screening, 41 studies were considered potentially eligible and the full text was read. After exclusion of another 17 full-text articles [18–34], 24 articles were included in the systematic review [35–58]. One trial, although originally designated as controlled, was excluded because no patients in the placebo group continued the study [18]. All the included studies were published between 1995 and 2017 and were conducted in Asia (India [n = 2], Thailand [n = 1], Taiwan [n = 1], Japan [n = 1], Korea [n = 4], Iran [n = 3]), Europe (Slovak Republic [n = 1], Bulgaria [n = 3], Serbia [n = 1], Italy [n = 3], Italy/UK [n = 1]), North America (California, USA [n = 1]), and South America (Brazil [n = 2]). Of the selected studies, 12 [35–46] evaluated the effect of herbal monopreparations (five ginseng, three saffron, two *Tribulus terrestris*, and one each *Pinus pinaster* and *Lepidium meyenii*), seven evaluated herbal formulations [47–53], and five evaluated herbal monopreparations/formulations in combination with pure compounds (e.g., L-arginine, para-aminobenzoic acid, glucosamine oligosaccharide, roburin, citrulline, vitamin E) [54–58]. Table 1 shows the composition of the herbal formulations and herbal monopreparations/formulations containing pure compounds.

The study size ranged from 21 to 317 patients (median 60.5) allocated into two (n = 22 RCTs) [36–46, 48–58], three (n = 1 RCT) [35], or four (n = 1 RCT) [47] arms. In total, 20 RCTs were placebo controlled [35–39, 41–49, 52–55, 57, 58], two compared the effects of the HDSs with those of sildenafil [40] or a Kampo preparation [51], one evaluated a formulation (Peironimev-plus®) in combination with verapamil versus verapamil alone in patients with Peyronie's disease [56], and another evaluated the effect of a formulation (IDIProst® Gold)

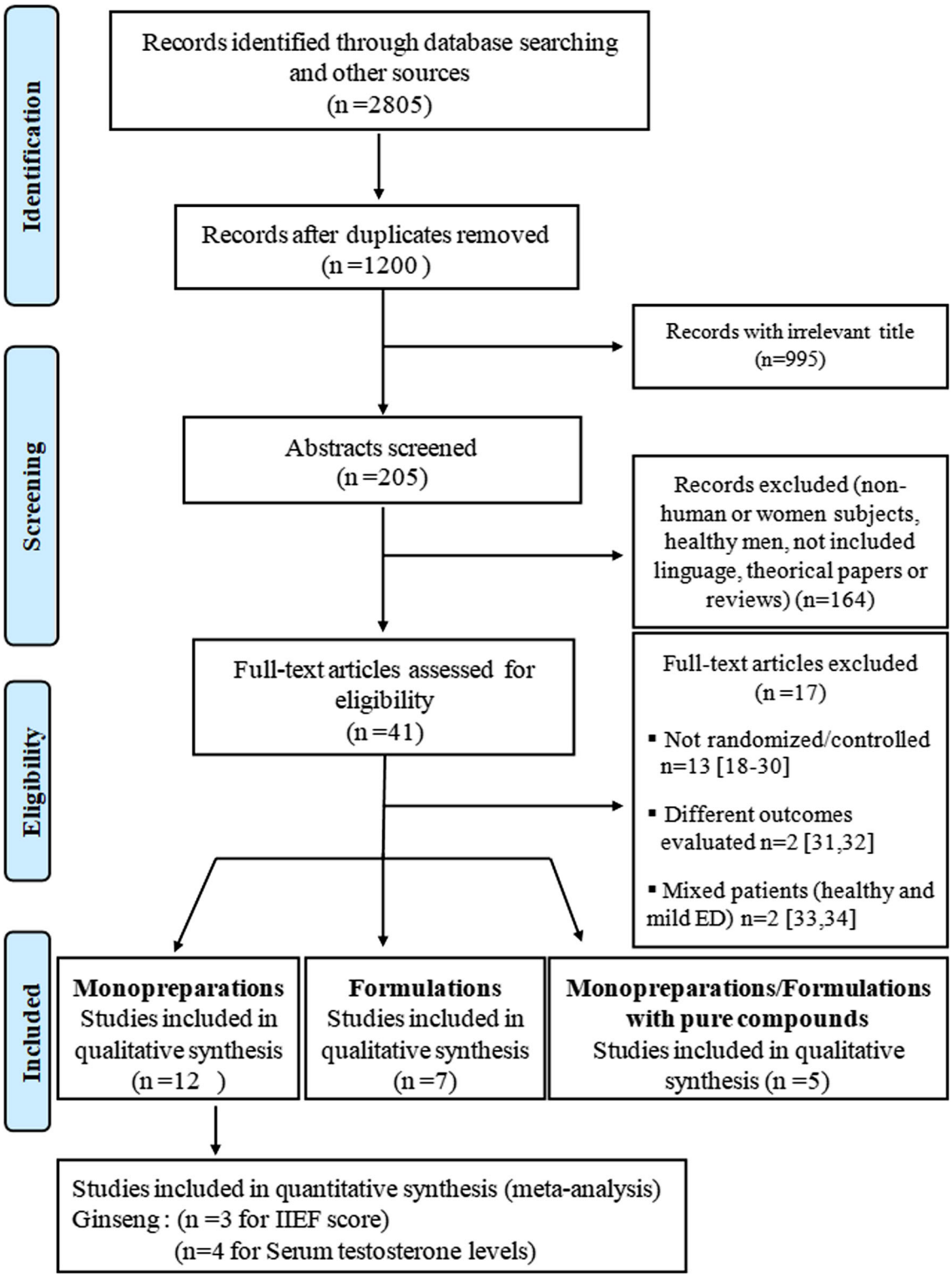

Fig. 1 Flowchart of the systematic research. *ED* erectile dysfunction, *IIEF* International Index of Erectile Function

against one of its components, *Serenoa repens* [50]. Finally, one placebo-controlled study also compared the effects of the HDS to those of trazodone [35]. The concomitant use of drugs known to alter sexual performance was an exclusion criterion in all the selected trials. Only two RCTs did not report the severity of ED [35, 56]. Tables 2, 3, 4, 5 and 6 summarize the baseline characteristics of the selected trials.

Table 1 Composition of the herbal formulations and herbal monopreparations/formulations containing pure compounds

Study, year	Formulation name (manufacturer)	Composition
Kulkarni 2011 [47]	E-MA-H E-MA-HP (NR)	A capsule of E-MA-H contains *Tribulus terrestris* fruit, *Withania somnifera* roots/rhizomes, *Asparagus adscendens* roots/rhizomes, *Mucuna pruriens* seed, *Asteracantha longifolia* entire plant and *Curculigo orchioides* roots/rhizomes, Asphaltum exudate. E-MA-HP contains two more ingredients: *Anacyclus pyrethrum* root and *Piper longum* fruit
Shah 2012 [48]	VigRX Plus (proprietary blend, Leading Edge Herbals)	A capsule contains: *Panax ginseng* root (100 mg), *Serenoa repens* berry (100 mg), *Crataegus rivularis* berry (100 mg), *Ginkgo biloba* leaf (100 mg), *Turnera diffusa* leaf (100 mg), *T. terrestris* vine (75 mg), *Erythroxylum catuaba* bark (50 mg), *Ptychopetalum olacoides* bark (50 mg), *Cuscuta chinensis* seed (25 mg), *Epimedium sagittatum* leaf (15 mg), Bioperine (extract from *Piper nigrum* fruit [containing 95% of piperine], 5 mg)
Punyawudho 2013 [49]	Cappra® (Zun Seng Heng Medical Factory Ltd., Part, Bangkok, Thailand)	Cervus Nippon Temminck (150 g), *Epimedium brevicornum* Maxim (120 g), *Cynomorium songaricum* Rupr. (844 g), *Carthamus tinctorius* (138 g), *Cistanche deserticola* (150 g)
Cai, 2013 [50]	IDIProst® Gold (IDI-Pharma)	A capsule contains *S. repens* (320 mg), *Pinus massoniana* bark extract (120 mg), and *Crocus sativus* (100 mg)
Nishimatsu 2014 [51]	Leopin Royal (Wakunaga Pharmaceutical Co., Ltd., Osaka, Japan)	A capsule (1 ml) contains concentrate aged garlic extract (0.9 ml), ginseng extract (136.5 mg), oriental bezoar tincture (0.075 ml), velvet antler fluid extract (0.015 ml), cuscuta seed extract (15 mg), epimedium herb extract (2.5 mg)
Udani 2014 [52]	No name reported (Biotropics Malaysia, Berhad, Kuala Lumpur, Malaysia)	*Eurycoma longifolia* 200 mg proprietary product + 100 mg of *Polygonum minus* (not standardized)
Hsieh 2016 [53]	No name reported (AB SCIEX, Framingham, MA, USA)	A capsule contains: *Astragalus membranaceus* (*100 mg), Lepidium meyenii* Walp. (18 mg), *Ophiocordyceps sinensis* (5 mg), *Panax quinquefolium* (100 mg), *Piper nigrum* (100 mg), *Rhodiola rosea* (100 mg), *Serpentes cnidium monnieri* (100 mg). 5 g powder was extracted from 10 kg dried maca root
Stanislavov 2008 [54]	Prelox® (Manhattan Drug Company Inc., New York, NY, USA)	A capsule contains Pycnogenol (20 mg) and L-arginine aspartate (700 mg). L-Arginine aspartate 1 g is equivalent to L-arginine 0.57 g
Ledda 2010 [55]	Prelox® (Manhattan Drug Company Inc., Hillside, NJ, USA	A capsule contains Pycnogenol (20 mg) and L-arginine aspartate (700 mg)
Paulis 2013 [56]	Peironimev-plus® (Farmaceutica Mev)	A tablet contains vitamin E (36 mg), para-aminobenzoic acid (100 mg), propolis (as galangin 100 mg), blueberry anthocyanins (80 mg), soja isoflavones (50 mg), *Muira puama* (25 mg), damiana (25 mg) and *Persea americana* (50 mg).
Sansalone 2014 [57]	Tradamix TX1000 (Tradapharma Sagl, Switzerland)	A tablet contains Alga *Ecklonia bicyclis* (300 mg), *T. terrestris* (450 mg) and glucosamine oligosaccharide (250 mg)
Stanislavov 2015 [58]	Prelox® in combination with roburins and L-citrulline (Laboratoire, GEFA, Chateaugiron, France)	A tablet contains Pycnogenol (20 mg), roburins (10 mg), L-arginine (0.48 g) and L-citrulline (0.3 g)

NR not reported

3.2 Quality Assessment using the Jadad Score

3.2.1 Herbal Monopreparations

The methodological quality of the 12 trials assessing the effect of herbal monopreparations varied, as evaluated with the Jadad score (Table 2), with a median value of 3.5. The Jadad score for trials assessing ginseng score ranged from one to five, with only one study scoring the maximum [39]. Major weaknesses included failing to describe dropouts/withdrawals (three RCTs) [35–37] or the method of generating the sequence of randomization (four RCTs) [35–38]. The *Crocus sativus* RCTs had scores of three (one open-label RCT) [40] and five (two RCTs) [41, 42]. Scores of four (failing to describe dropouts/withdrawals) [43] and five [44] were assigned to the two RCTs concerning *T. terrestris*. Finally, scores of two and three were assigned to RCTs on *P. pinaster* [45] and *L. meyenii* [46], respectively (Table 2).

Table 2 Herbal monopreparations: Characteristics of the included studies

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Panax ginseng										
Choi et al. [35] 1995, Korea	Parallel	30 PL, 30 V, 30 TRA 45.2 ± 9.3 PL, 42.8 ± 7.5 V 43.2 ± 9.3 TRA Psychogenic ED (n = 81) Mild vasculogenic ED (n = 9) 5.8 ± 6.2 years	1.8 g/daily	3 mo	PL, TRA 25 mg at bedtime	AVS-penogram; STL; pt satisfaction	NR	1 (1 + 0 + 0 + 0 + 0)	"Administration of Korean red ginseng has shown to have superior effects compared to the PL or TRA"	TRA was ineffective; comorbidities
Hong et al. [36] 2002, Korea	DB, CO	45 54 ED: 22 severe, 9 moderate, 14 mild NR	Korean red Ginseng (unspecified proprietary product from Korea ginseng and tobacco research institute) 900 mg tid	8 wk	PL	IIEF total IIEF-5 IIEF-EF Rigiscan (3a tip rigidity, 2b tip tumescence) Penile duplex ultrasonography STL	NR (although reported in outcome)	3 (1 + 1 + 0 + 0 + 1)	"Korean red ginseng can be as effective alternative for treating male ED"	Comorbidities
De Andrade et al. [37] 2007, Brazil	DB, parallel	30 PL 30 V 54.3 PL, 52.6 V ED: PL: 15 mild, 15 mild-to-moderate; V: 18 mild, 12 mild-to-moderate NR	Korean red ginseng (information NR) 1 g tid	12 wk	PL	IIEF-5 GAQ Serum hormonal levels	Minor side effects in three pts in ginseng group	3 (1 + 1 + 0 + 0 +1)	"Korean red ginseng can be an effective alternative to the invasive approaches for treating male ED"	Comorbidities
Kim et al. [38] 2009, Korea	DB, parallel	143/86 68/21 PL, 75/65 V 57.5 ± 1.2 PL 60.2 ± 2.0 V Moderate ED ED (IIEF < 51) NR	Tissue-cultured mountain ginseng extract (TMGE, Panax ginseng) 1 g bid	8 wk	PL	IIEF total IIEF-5 IIEF-EF STL	3 pts in ginseng group had headache	4 (1 + 1 + 1 + 0+1)	"[Ginseng] could be utilized for improving erectile function in male pts"	Elevated dropout in PL group (from 68 to 21) (from 75 to 65 in ginseng group); comorbidities
Choi et al. [39] 2012, Korea	DB, parallel	119/118 59 PL, 60/59 V 57.32 ± 8.41 PL 57.49 ± 7.94 V Mild-to-moderate ED Years 4.31 ± 5.12 PL 4.67 ± 5.19 V	Standardized Korean ginseng berry tablets 700 mg bid	8 wk	PL	IIEF-15 IIEF-ED PEDT STL	1 case of mild GI symptoms in PL group; no AEs in the V group; blood chemistry, urinalysis and vital signs: no differences BL and end of tx	5 (1 + 1 + 1 + 1 + 1)	"Oral administration of the [ginseng] extract improved all domains of sexual function. It can be used as an alternative medicine to improve sexual life in men with sexual dysfunction"	ITT analysis; comorbidities

Table 2 continued

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Crocus sativus										
Safarinejad et al. [40] 2010, Iran	OL, CO	346/317 46.6 ± 8.4 ED: Mild 13% Moderate 37.9% Severe 49.05% Moderate or severe (87%) Vasculogenic 72%, neurogenic 3.5%, psychogenic 24.3%. Mo 18.9 ± 6.7 S 18.6 ± 7.1 V	Dried saffron stigma ethanolic (80%) extract 30 mg bid	12 wk	Sildenafil 50 or 100 mg (on demand)	1.IIEF-15, IIEF-EF 2.SEP 3.EDITS 4.GEQ	% of pts reporting AEs: saffron 4.0%, sildenafil 20.8%	3 (1 + 0+ 1 + 1+0)	"Findings do not support a beneficial effect of saffron administration in men with ED"	Power calculation ITT; comorbidities; unclear whether stigma or petals; not standardized extract but reported the extract method of preparation
Modabbernia et al. [41] 2012, Iran	DB, parallel	36/30 (18/15 PL, 18/15 V) 36.6 ± 8.3 V 40.5 ± 9.4 PL Moderate ED: *n* = 4 (1 PL, 3 V) Mild ED: *n*= 26 Fluoxetine-induced ED (minimum 6 wk)	Standardized extract (corresponding to 1.65–1.75 mg crocin) 15 mg bid	4 wk	PL	IIEF-total IIEF-EF	Mild side effects; no differences between the two groups	5 (1 + 1 + 1 + 1 + 1)	"Saffron is a tolerable and efficacious tx for fluoxetine-related ED."	Power calculation; ITT
Mohammadzadeh-Morghadam et al. [42] 2015, Iran	DB, parallel	50/50 (25 PL, 25 V) 58.96 ± 8.71 V 58.44 ± 7.92 PL Moderate ED NR	Topical gel containing 1% saffron (type of preparation NR)	1 mo	PL	IIEF-15, IIEF-EF	No AEs in both groups	5 (1 + 1+ 1 + 1+1)	"This preliminary evidence suggests that saffron can be considered as a tx option for diabetic men with ED"	Comorbidities; diabetic pts
Tribulus terrestris										
Santos et al. [43] 2014, Brazil	DB, parallel	30 (15 PL, 15 V) 60 ± 9.4 V 62.9 ± 7.9 ED: 20% mild 40% mild-to-moderate 30% moderate 10% severe NR	Not standardized extract 400 mg bid	30 days	PL	IIEF-15 STL	NR in paper (but reported in outcome	4 (1 + 1+ 0 + 1+1)	"*T. terrestris* was not more effective than PL in improving symptoms of ED or serum total testosterone."	Comorbidities

Table 2 continued

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Kamenov et al. [44]. 2017, Bulgaria	DB, parallel	180/172 (90/86 PL, 90/86 V) 18–65 Mild-to-moderate ED Moderate ED: *n* = 56 (29 PL, 27 V) Mild ED: *n* = 124 (61 PL, 63 V) Mo 16.37 ± 15.72 PL 13.73 ± 13.46 V	Tribestan (a *T. terrestris* extract standardized to contain no less than 45% of furostanol saponins) 500 mg tid	12 wk	PL	IIEF-5 GEQ STL	1 case of abdominal pain (V) 1 case of gastroesophageal reflux (PL). No difference in AE incidence between groups	5 (1 + 1 + 1 + 1 + 1)	"Significant improvement in sexual function was observed with Tribulus compared with PL"	ED pts with or without HSDD; power calculation; ITT; comorbidities; difference between the groups became significant after 4 wk
Pinus pinaster										
Ďuračková et al. [45]. 2003, Slovak Republic	DB, parallel	21/21 (8 PL, 13 V) 22–69 46.5 ± 12.5 Moderate ED (19% organic, 28.6% psychogenic, 52.4% mixed etiology) NR	Pycnogenol® (extract standardized to contain 70 ± 5% procyanidins) 40 mg tid	3 mo	PL	IIEF-5 Blood parameters of lipid metabolism	NR	2 (1 + 1+ 0 + 0 + 0)	Pycnogenol® seems to have a beneficial effect on tx of ED	A patented extract made from French maritime pine bark (*P. pinaster)*; no BL characteristics
Lepidium meyenii										
Zenico et al. [46] 2008, Italy	DB, parallel	50 (25 PL, 25 V) 36 ± 5 Mild ED (17–21) NR	Not standardized root extract 1.2 g bid	12 wk	PL	IIEF-5 SAT-P STL	No AEs in both groups	3 (1 + 1+ 0 + 0 + 1)	"Small but significant effect of Maca supplementation"	Absence of comorbidities; no BL characteristics

AE adverse event/effect, *AVS-penogram* audiovisual stimulation-penogram, *bid* twice daily, *BL* baseline, *CO* crossover, *DB* double blind, *ED* erectile dysfunction, *EDITS* Erectile Dysfunction Inventory of Treatment Satisfaction, *GAQ* Global Assessment Questionnaire, *GEQ* Global Efficacy Question, *GI* gastrointestinal, *HSDD* Hypoactive Sexual Desire Disorder, *IIEF* International Index of Erectile Function, *IIEF-EF* IIEF Erectile Function domain, *ITT* intention to treat, *mo* month(s), *NR* not reported, *OL* open label, *PL* placebo, *PEDT* Premature Ejaculation Diagnostic Tool, *pt* patient, *S* sildenafil, *SAT-P* Satisfaction Profile, *SEP* Sexual Encounter Profile, *STL* serum testosterone level, *TRA* trazodone, *tid* three times daily, *tx* treatment, *V* verum, *wk* week(s)

[a]Size (number of pts enrolled in the clinical trial/number of pts who finished the trial)

Table 3 Herbal monopreparations: quantitative results of the included studies

Study, year (study design)	Measure	Results	
		Baseline	End of treatment
Panax ginseng			
Choi et al. [35] 1995 (parallel)	AVS-penogram	PG (n = 30) 25/30 type 2 PL (n = 30) 26/30 type 2 TRA (n = 30) 28/30 type 2	13 weeks PG (n = 30) 22/30 type 2 PL (n = 30) 26/30 type 2 TRA (n = 30) 28/30 type 2
	Testosterone (ng/ml)	PG (n = 30) 4.5 ± 1.6 PL (n = 30) 3.9 ± 2.8 TRA (n = 30) 3.8 ± 3.0	13 weeks PG (n = 30) 7.3 ± 4.0 PL (n = 30): no significant variation TRA (n = 30)
	Patient satisfaction		13 weeks PG (n = 30) 43.3 ($P < 0.05$ vs. PL and TRA) PL (n = 30) 13.3 TRA (n = 30) 30.0
Hong et al. [36] 2002 (crossover)	IIEF total (IIEF-15 Korean version)	(n = 45) 28.0 ± 16.70	8 weeks PG (n = 45) 38.13 ± 16.64†† PL (n= 45) 30.92 ± 15.67
	IIEF-5	(n= 45) 8.96 ± 6.14	8 weeks PG (n = 45) 12.70 ± 6.38†† PL (n = 45) 10.33 ± 5.46
	IIEF-EF	(n = 45) 10.60 ± 7.41	8 weeks PG (n = 45) 15.02 ± 8.18* PL (n = 45) 11.24 ± 6.94
	Rigiscan		Tip rigidity (%) 44.5 ± 28.84 vs. 40.42 ± 30.21 ($P < 0.05$) Tip tumescence (cm) 2.33 ± 1.26 vs. 2.33 ± 1.37
	Penile duplex ultrasonography (cm/s)		End diastolic velocity 3.82 ± 3.79 vs. 4.08 ± 3.38 Peak systolic velocity 39.48 ± 22.29 vs. 37.45 ± 20.01
	Serum testosterone levels (ng/ml)	(n = 45) 4.88 ± 2.16	8 weeks PG (n = 45) 4.48 ± 2.02 PL (n = 45) 4.86 ± 3.38
De Andrade et al. [37] 2007 (parallel)	IIEF-5	PG (n = 30) 16.4 ± 2.9 PL (n = 30) 17.0 ± 3.1	12 weeks PG (n = 30) 21.0 ± 6.3 (P = 0.00003 vs. BL; P = 0.0002 vs. PL) PL (n = 30) 17.7 ± 5.6
	GAQ	PG (n = 30) 2.5 ± 0.7 PL (n = 30) 2.8 ± 0.7	12 weeks PG (n = 30) 3.2 ± 1.0 (P = 0.0003) PL (n = 30) 2.9 ± 0.8
	Serum testosterone levels	PG (n = 30) 552.0 ± 120.7 PL (n = 30) 540.3 ± 109.8	Unit of measure NR 12 weeks PG (n = 30) 560.0 ± 112.5 PL (n = 30) 508.8 ± 103.0

Table 3 continued

Study, year (study design)	Measure	Results	
		Baseline	End of treatment
Kim et al. [38] 2009 (parallel)	IIEF total (Korean version)	PG (n = 65) 29.78 ± 13.14 PL (n = 21) 29.71 ± 10.58	8 weeks PG (n = 65) 39.86 ± 15.29‡‡ PL (n = 21) 33.33 ± 10.17
	IIEF-5	PG (n = 65) 11.02 ± 5.08 PL (n = 21) 11.95 ± 4.44	8 weeks PG (n = 65) 15.34 ± 6.13‡‡ PL (n = 21) 13.52 ± 4.46
	IIEF-EF	PG (n = 65) 11.89 ± 5.89 PL (n = 21) 11.38 ± 4.78	8 weeks PG (n = 65) 16.37 ± 7.08‡‡ PL (n = 21) 13.05 ± 4.27
	Testosterone (ng/ml)	PG (n = 49) 4.22 ± 1.17 (49 men) PL (n = 21) 4.02 ± 0.87 (21 men)	8 weeks PG (n = 49) 4.74 ± 1.64 PL (n = 21) 4.21 ± 1.78
Ginseng berry			
Choi et al. [39] 2013 (parallel)	IIEF-15 (Korean version)	GB (n = 59) 40.95 ± 7.05 PL (n = 59) 43.39 ± 7.20	4 weeks GB (n = 59) 44.25 ± 10.74*** (P = 0.011 vs. BL) PL (n = 59) 41.63 ± 11.55 8 weeks GB (n = 59) 46.19 ± 12.69 (P = 0.002 vs. BL) PL (n = 59) 45.61 ± 10.81
	IIEF-EF	GB (n = 59) 17.17 ± 2.57 PL (n = 59) 17.56 ± 2.89	4 weeks GB (n = 59) 17.73 ± 4.72 PL (n = 59) 16.29 ± 5.33 8 weeks GB (n = 59) 18.59 ± 5.99 (P = 0.046 vs. BL) PL 18.00 ± 5.12
	PEDT	GB (nn= 59) 9.14 ± 4.57 PL (n = 59) 10.46 ± 4.79	4 weeks GB (n = 59) 7.97 ± 4.45 (P = 0.004 vs. BL) PL (n = 59) 10.31 ± 4.88 8 weeks GB (n = 59) 7.53 ± 4.26† (P = 0.001 vs. BL) PL (n = 59) 9.66 ± 4.57
	Testosterone (ng/ml)	GB (n = 59) 500.53 ± 189.58 PL (n = 59) 482.05 ± 171.83	4 weeks GB (n = 59) NR PL (n = 59) NR 8 weeks GB (n = 59) 499.32 ± 168.00 PL (n = 59) 469.57 ± 154.02

Table 3 continued

Study, year (study design)	Measure	Results	
		Baseline	End of treatment
Crocus sativus			
Safarinejad et al. [40] 2010 (crossover)	IIEF-15 and SEP[a]	IIEF-EF Saffron (n = 317) 12.2 ± 2.2 Sildenafil (n = 317) 12.1 ± 2.2	IIEF-EF 12 weeks Saffron (n = 317) 13.6 ± 2.6 Sildenafil (n = 317) 22.7 ± 4.2‡‡‡ EDITS Patient Saffron (n = 317) 27.4 ± 4.5‡ Sildenafil (n = 317) 78.6 ± 12.6 Partner Saffron (n = 317) 25.4 ± 3.6‡ Sildenafil (n = 317) 72.4 ± 12.4 GEQ Saffron (n = 317) 4.2%§§§ Sildenafil (n = 317) 91.2%
Modabbernia et al. [41] 2012 (parallel)	IIEF total (IIEF-15)	Saffron (n = 15) 49.3 ± 11.4 PL (n = 15) 43.2 ± 12.9	2 weeks Saffron (n = 15) variation vs. BL 5.5 ± 5.5 PL (n = 15) variation vs. BL –1.1 ± 9.5 4 weeks Saffron (n = 15) difference vs. BL 8.2 ± 3.9§ PL (n = 15) difference vs. BL 0.9 ± 4.5
	IIEF-EF	Saffron (n = 15) 20.7 ± 4.3 PL (n = 15) 21.2 ± 3.1	2 weeks Saffron (n = 15) variation vs. BL 2.2 ± 1.1§ PL (n = 15) variation vs. BL –1.9 ± 3.4 4 weeks Saffron (n = 15) difference vs. BL 4.5 ± 2.5§ PL (n = 15) difference vs. BL –2.5 ± 4.6
Mohammadzadeh-Morghadam et al. [42] 2015 (parallel)	IIEF-15 (Iranian version)	Saffron (n = 25) 34.52 ± 4.07 PL (n = 25) 36.44 ± 3.66	4.5 weeks Saffron (n = 25) 44.32 ± 3.90§ PL (n = 25) 37.56 ± 3.68
	IIEF-EF	Saffron (n = 25) 12.92 ± 1.81 PL (n = 25) 13.56 ± 1.67	4.5 weeks Saffron (n = 25) 17.64§ PL (n = 25) 13.88 ± 1.67
Tribulus terrestris			
Santos et al. [43] 2014 (parallel)	IIEF-5	TT (n = 15) 13.2 (range 5–21) PL (n = 15) 11.6 (range 6–21)	30 days[b] TT (n = 15) 15.3 (range 6–21) §§,c PL (n = 15) 13.7 (range 6–21)§§,c
	Testosterone (ng/dl)	TT (n = 15) 417.1 PL (n = 15) 442.7	30 days[b] TT 4 (n = 15) 09.3 PL (n = 15) 466.3

Table 3 continued

Study, year (study design)	Measure	Results	
		Baseline	End of treatment
Kamenov et al. [44] 2017 (parallel)	IIEF-15	TT (n = 90) 18.01 ± 3.21	12 weeks
		PL (n = 90) 18.22 ± 3.44	TT (n = 86) 22.76 ± 5.11[¶]
			PL (n = 86) 20.19 ± 4.73
	GEQ		12 weeks
			TT (n = 86) 68 ± 79.07
			PL (86) 39 ± 45.35
	Testosterone (nmol/l)	TT (n = 90) 15.42 ± 6.04	12 weeks
		PL (n = 90) 16.01 ± 5.48	TT (n = 85) 13.93 ± 5.86
			PL (n = 85) 13.91 ± 5.20
Pinus pinaster			
Ďuračková et al. [45] 2003 (parallel)	IIEF-5 (mean ± SEM)	PP (n = 13) 12.6 ± 1.1	3 months
		PL (n = 8) 11.3 ± 1.3	PP (n = 13) 16.8 ± 0.8[**]
			PL (n = 8) 8.9 ± 1.2[†††]
Lepidium meyenii			
Zenico et al. [46] 2008 (parallel)	IIEF-5	NR	12 weeks
			Increase from BL: LM (n = 25) 1.6 ± 1.1[¶]
			PL (n = 25) 0.5 ± 0.6
	Total testosterone (ng/ml)	LM (n = 25) 5.9 ± 0.8	12 weeks
		PL (n = 25) 6.2 ± 0.7	LM (n = 25) 6.1 ± 0.9
			PL (n = 25) 6.0 ± 0.9
	Free testosterone (pg/ml)	LM (n = 25) 12.4 ± 1.2	12 weeks
		PL (n = 25) 12.1 ± 1.1	LM (n = 25) 12.5 ± 1.0
			PL (n = 25) 11.8 ± 0.9

Data are presented as mean ± standard deviation unless otherwise indicated

AVS-penogram audiovisual stimulation-penogram, *BL* baseline, *ED* erectile dysfunction, *EDITS* Erectile Dysfunction Inventory of Treatment Satisfaction, *GAQ* Global Assessment Questionnaire, *GB* ginseng berry, *GEQ* Global Efficacy Question, *IIEF* International Index of Erectile Function, *IIEF-EF* IIEF Erectile Function domain, *LM Lepidium meyenii*, *NR* not reported, *PEDT* Premature Ejaculation Diagnostic Tool, *PG Panax ginseng*, *PL* placebo, *PP Pinus pinaster*, *SEM* standard error of the mean, *SEP* Sexual Encounter Profile, *TRA* trazodone, *TT Tribulus terrestris*

[*]$P < 0.05$ vs. PL, [**]$P < 0.05$ vs. BL, [***]$P = 0.04$ vs. PL, [†]$P = 0.017$ vs. PL, [††]$P < 0.01$ vs. PL, [†††]$P < 0.01$ vs. BL (worsening of ED), [‡]$P = 0.001$ vs. sildenafil, [‡‡]$P < 0.001$ vs. BL, [‡‡‡]$P < 0.001$ vs. BL and saffron, [§]$P < 0.001$ vs. PL, [§§]$P = 0.0004$ vs. BL, [§§§]$P = 0.0001$ vs. sildenafil, [¶]$P < 0.0001$ vs. PL

[a]The Authors reported the single values of each item

[b]No standard errors or deviations are reported

[c]No differences between TT and PL

3.2.2 Herbal Formulations

The Jadad score for the seven trials of herbal formulations [47–53] ranged from one to five (median three), with three studies scoring the maximum [48, 49, 52] (Table 4). The sequence of randomization (randomization method) was clear and appropriate in three RCTs [48, 49, 52]. Three RCTs were double blind [48, 49, 52], one was triple blind [47], two were open label [50, 51], and one did not address this outcome [53].

Five RCTs [47, 48, 50–52] used a parallel-group design and two [49, 53] used a crossover design. All studies bar one RCT [53] reported information on dropouts and/or withdrawal.

3.2.3 Herbal Monopreparations/Formulations in Combination with Pure Compounds

Five RCTs were retrieved, with a median Jadad score of three (range 2–5) (Table 6). Two studies scored the maximum of five [55, 58]. Three RCTs were double blind [54, 55, 58], one single blind [57], and one unblinded [56]. A parallel-group design was adopted in three RCTs

Table 4 Herbal formulations: Characteristics of the included studies

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention[b]	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Kulkarni et al. [47] 2011, India	TB, parallel	148/140 (32 PL, 36 V1, 36 V2, 36 V3)[c] 40.1 ± 1.49 PL 39.7 ± 1.09 V1 40.2 ± 1.51 V2 39.6 ± 1.21 V3 Mild-to-moderate ED IIEF-EF = 11–21 NR	E-MA-H (V1 and V2, two doses); E-MA-HP (V3)	60 days	PL	IIEF-EF, IPE, EDITS, STL	80 mild to moderate AEs (no significant differences among groups)	3 (1 + 1 + 1 + 0 + 0)	"Tx with E-MA-H and E-MA-HP is well tolerated and more effective than PL"	ITT analysis; pt number different for some outcomes
Shah et al. [48] 2012, India	DB, parallel	78/75 (39/36 PL; 39/39 V*) 35.23 ± 6.62 V 34.33 ± 5.89 PL Mild-to-Moderate: 44 (21 V, 23 PL) Moderate: 34 (18 V, 16 PL) Years 2.27 ± 1.80 V 2.01 ± 1.35 PL	VigRX Plus; two capsules bid (each capsule contained 360 mg extract or 720 mg[d])	12 wk	PL	IIEF-15, IIEF-EF, EDITS, STL	Similar incidence in PL and verum groups	5 (1 + 1 + 1 + 1 + 1)	"VigRX Plus was well tolerated and more effective than PL in improving sexual function in men"	ITT analysis only for safety
Punyawudho et al. [49] 2013, Thailand	DB, CO	63/61 45 ± 7.14 V 44 ± 6.7 PL (first tx period) Mild and mild-to-moderate NR	Cappra®; three capsules in 2 wks (1 tablet 1 h before planned sexual activity)	2 wk	PL	IIEF-5, IIEF-EF	Mild side effects. Most common AEs: dizziness (13.3% Cappra®, 9.6% PL), face numbness (1.6% Cappra®, 0% PL), and tachycardia (1.6% Cappra®, 0% PL)	5 (1 + 1 + 1 + 1 + 1)	"Cappra® is effective and well-tolerated and can be used as alternative therapy for mild and mild to moderate ED"	Power calculation; ITT analysis; comorbidities

Table 4 continued

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention[b]	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Cai et al. [50] 2013, Italy	Not blind, parallel	132/129 85/83 IDIProst 47/46 *Serenoa repens* 58.9 ± 3.56 IDIProst 59.1 ± 3.68 *S. repens* Mild ED (IIEF-5 < 21) NR	IDIProst® Gold. One capsule daily (950 or 540 mg)	3 mo	*S. repens* 320 mg, q24 h	IIEF-5	Few AEs in each group	2 (1 + 0 + 1 + 0 + 0)	IDIProst® Gold significantly improves sexual function	Pts with LUTS due to BPH and ED; power calculation; unclear amount of extracts in a capsule
Nishimatsu et al. [51] 2014, Japan	OL, parallel	49/46 (24/21 LER, 25/25 Kampo) LER 61.9 ± 11.4 Kampo 63.7 ± 12.5 ED Mild (n = 2) Mild-to-moderate (n = 4) Moderate (n = 8) Severe (nn = 32) NR	LER; one capsule bid	6 mo	Kampo preparations	IIEF-5, ADAM, STL, free testosterone	Two AEs (epigastric discomfort and skin rash) in LER group	2 (1 + 0 + 1 + 0 + 0)	"[the formulation] is possibly superior to [a Kampo formulation] on the rate of improvement of symptoms of aging, including ED"	
Udani et al. [52] 2014, California	DB, parallel	30/26 15/12 V, 15/14 PL 40–65 y Mild ED IIEF 17–25 NR	*Eurycoma longifolia* 200 mg proprietary product + 100 mg *Polygonum minus* (not standardized). A tablet per day	12 wk	PL	IIEF-5, EDITS, STL	No AEs attributed to test product; no serious AEs reported	5 (1 + 1 + 1 + 1 + 1)	"Supplementation for 12 weeks… was well tolerated and more effective than PL in enhancing sexual performance in healthy volunteers"	No BL characteristics

Table 4 continued

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention[b]	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Hsieh et al. [53] 2016, Taiwan	CO	67 45.6 ± 5.8 V 46.5 ± 5.9 PL IIEF-5 13.9 ± 3.3 V 14.5 ± 3.6 PL NR	Herb formula comprising seven plant extracts (dosage NR)	1 mo	PL	IIEF-5	In the herb group, one pt complained of visual disturbance, two pts reported facial flushing, three pts experienced temporary mild stomach burning sensation	1 (1 + 0 + 0 + 0 + 0)	"Combination of oral herbs and PVS tx provides an enhanced outcome to impotent pts refractory to medicine and unsatisfied with PVS monotherapy alone"	Pt with PVS and nonresponders to PDE-5 inhibitors; CO only for PL group (control group was previous PL tx group); BL characteristics (only age)

ADAM androgen deficiency in the aging male, *AE* adverse events, *bid* twice daily, *BL* baseline, *BPH* benign prostatic hyperplasia, *CO* crossover, *DB* double blind, *ED* erectile dysfunction, *EDITS* Erectile Dysfunction Inventory of Treatment Satisfaction, *HHD* high-dose E-MA-H, *HLD* low-dose E-MA-H, *HP* E-MA-H, *IIEF* International Index of Erectile Function, *IIEF-EF* IIEF Erectile Function domain, *IPE* Index of Premature Ejaculation, *ITT* intention to treat, *LER Leopin Royal*, *LUTS* lower urinary tract symptoms, *mo* month(s), *NR* not reported, *OL* open label, *PDE5* phosphodiesterase type 5, *PL* placebo, *pt(s)* patient(s), *PVS* penile venous stripping, *q24 h* every 24 h, *STL* serum testosterone level, *TB* triple blind, *tx* treatment, *V* verum, *wk* week(s)

*No dropouts were reported but the discussion stated that one pt withdrew because of malaria; unclear amount of extracts in a capsule

[a]Number of patients enrolled in the clinical trial/number of patients that finished the trial

[b]See Table 1 for composition of herbal formulations

[c]V1 = E-MA-H 2 capsules at night (HLD); V2 = two capsules bid for 30 days followed by two capsules at night for 30 days (HHD); V3 = E-MA-HP = two capsules bid for 60 days

[d]It is not clear if the capsule contains 360 mg or 720 mg

Table 5 Herbal formulations: Quantitative results of the included studies

Study, year (study design)	Treatment[a]	Measure	Results	
			Baseline	End of treatment
Kulkarni et al. [47] (2011) (parallel)	E-MA-H E-MA-HP	IIEF-EF (mean ± SEM)	HLD (n = 38) 18.15 ± 0.83 HHD (n = 37) 19.45 ± 0.60 HP (n = 36) 17.61 ± 0.74 PL (n = 36) 17.69 ± 0.54	Day 60 HLD (n = 38) 24.86 ± 0.81* HHD (n = 37) 25.45 ± 0.62* HP (n = 36) 25.25 ± 0.71* PL (n = 36) 20.75 ± 0.82
		IPE	HLD (n = 38) 27.18 ± 0.93 HHD (n = 37) 27.40 ± 0.82 HP (n = 36) 26.88 ± 0.98 PL (n = 36) 26.47 ± 1.03	Day 60 HLD (n = 38) 36.86 ± 1.17* HHD (n = 37) 37.67 ± 0.91* HP (n = 36) 38.25 ± 0.96* PL (n = 36) 30.25 ± 1.33
		Testosterone (ng/dl)	HLD (n = 38) 553.13 ± 34.45 HHD (n = 37) 579.10 ± 28.61 HP (n = 37) 513.84 ± 24.99 PL (n = 36) 538.23 ± 34.06	Day 60 HLD (n = 38) 507.37 ± 30.67 HHD (n = 37) 477.11 ± 28.49 HP (n = 37) 480.07 ± 32.31 PL (n = 36) 529.75 ± 34.19
		EDITS	No possibility to score	Day 60 HLD (n = 36) 78.55 ± 3.04†† HHD (n = 36) 75.83 ± 2.56†† HP (n = 36) 73.16 ± 3.51†† PL (n = 34) 54.00 ± 4.25
Shah et al. [48] (2012) (parallel)	VigRX Plus	IIEF-15	VigRX (n = 39) 42.56 ± 3.09 PL (n = 36) 42.54 ± 5.10	12 weeks VigRX (n = 39) 63.13 ± 10.06†† PL (n = 36) 43.86 ± 8.45
		IIEF-EF	VigRX (n = 39) 16.08 ± 2.87 PL (n = 36) 15.86 ± 3.24	12 weeks VigRX (n = 39) 25.08 ± 4.56†† PL (n = 36) 16.47 ± 4.25
		Testosterone (ng/dl)	VigRX Plus (n = 37) 544.46 ± 207.64 PL (n = 25) 518.10 ± 197.51	12 weeks VigRX (n = 37) 527.66 ± 155.47 PL (n = 25) 471.75 ± 160.38
		EDITS	No possibility to score	12 weeks Patient *VigRX* (n = 39) 82.31 ± 20.23‡ PL (n = 36) 36.78 ± 22.53 Partner VigRX (n = 12) 88.75 ± 9.80‡ PL (n = 10) 18.50 ± 9.44
Punyawudho et al. [49] (2013) (crossover)	Cappra	IIEF-EF		Mean change from BL to end of tx V (n = 61) 4.87** PL (n = 61) 3.44
Cai et al. [50] (2013) (parallel)	IDIProst® Gold	IIEF-5	IDIProst® Gold (n = 83) 14.9 ± 3.5 *Serenoa repens* (n = 46) 15.1 ± 3.7	3 months IDIProst® Gold (n = 83) 19.3 ± 1.0 *S. repens* (n = 46) 16.1 ± 1.2

Table 5 continued

Study, year (study design)	Treatment[a]	Measure	Results	
			Baseline	End of treatment
Nishimatsu et al. [51] 2014 (parallel)	LER	IIEF-5	LER (n = 21) 5.6 ± 3.3 Kampo (n = 25) 6.5 ± 5.1	3 months LER (n = 21) 8.4 ± 6.1* Kampo (n = 25) 6.7 ± 4.6 6 months LER (n = 21)7.5 ± 5.7* Kampo (n = 25)6.4 ± 5.0
		Testosterone (ng/ml)	LER (n = 18) 3.28 ± 2.03 Kampo (n = 14) 3.60 ± 0.82	6 months LER 3.44 ± 2.08 Kampo (n = 14) 3.80 ± 0.75
		Free testosterone (pg/ml)	LER (n = 18) 7.89 ± 3.73 Kampo (n = 11) 7.67 ± 3.28	6 months LER (n = 18) 9.32 ± 6.08 Kampo (n = 11) 6.99 ± 3.38
Udani et al. [52] (2014) (parallel)	*Eurycoma longifolia* proprietary product + *Polygonum minus*	IIEF-5 (mean ± SEM)	No values reported	No values reported. Authors stated: "no significant differences between groups"
		EDITS	No possibility to score	6 weeks V (n = 12) 52.56 ± 6.8 PL (n = 14) 68.59 ± 8.03 12 weeks V (n = 12) 74.68 ± 8.98*** PL (n = 14) 78.53 ± 9.89
		STL (ng/dl)	V (n = 12) 359.23 ± 27.09 PL (n = 14) 308.43 ± 23.70	6 weeks V (n = 12) 396.57 ± 36.41† PL (n = 14) 334.33 ± 27.86† 12 weeks V (n = 12) 396.46 ± 47.26† PL (n = 14) 321.67 ± 27.51†
Hsieh et al. [53] (2016) (crossover)	Herbal formula comprising seven plant extracts	IIEF-5[b]	Formulation (n = 35) 13.9 ± 3.3 PL (n = 32) 14.5 ± 3.6	1 month Formulation (n = 35) 19.6 ± 3.4†† PL (n = 32) 15.1 ± 3.5 1 month (PL cross study n = 32) Formulation 19.9 ± 3.2†††

Data are presented as mean ± standard deviation unless otherwise indicated

BL baseline, *EDITS* Erectile Dysfunction Inventory of Treatment Satisfaction, *HHD* high-dose E-MA-H, *HLD* low-dose E-MA-H, *HP* E-MA-H, *IIEF* International Index of Erectile Function, *IIEF-ED IIEF* Erectile Function domain, *IPE* Index of Premature Ejaculation, *LER Leopin Royal*, *NR* not reported, *PL* placebo, *SD* standard deviation, *SE* standard error, *SEM* standard error of the mean, *STL* serum testosterone level, *tx* treatment, *V* verum

*$P < 0.05$ vs. BL, **$P < 0.032$ vs. PL, ***$P = 0.027$ vs. 6 weeks, †$P < 0.005$ vs. BL, ††$P < 0.001$ vs. PL, †††$P < 0.001$ vs. control group (i.e., PL after 1 month), ‡$P < 0.0001$ vs. PL

[a]See Table 1 for the composition of herbal formulations

[b]No indication was provided as to whether data were ± SD or SE

[55–57], whereas two trials adopted a crossover design [54, 58]. All studies reported information on patient dropouts and/or withdrawals.

3.3 Cochrane's Risk-of-Bias Assessment

3.3.1 Herbal Monopreparations

Figures 2 and 3 summarize the risk-of-bias assessment for the 12 RCTs (Fig. 2a–e, risk-of-bias item for each included study; Fig. 3a–e, risk-of-bias item presented as percentages across all included studies).

The risk of bias was predominantly unclear in four [35–38] of the five ginseng trials (Figs. 2a and 3a). Specifically, two studies [35, 37] had an unclear risk of bias in six of seven domains, and another two trials had unclear risk of bias in four [36] or five [38] domains. The remaining trial [39] was predominantly at low risk of bias (six of seven domains).

Collectively, the ginseng trials were considered to have (1) an unclear risk of bias, mainly for sequence generation, allocation concealment, blinding of outcome assessors (all 80% of unclear risk), blinding of participants and personnel, incomplete outcome data, and selective outcome reporting (all 60% of unclear risk) and (2) a high risk of bias, mainly for other sources of bias (80%). Low risk of bias was not prevalent in all domains of the ginseng trials (Figs. 2a and 3a).

By contrast, a low risk of bias was prevalent in the three *C. sativus* trials (Figs. 2b and 3b). Specifically, sequence generation was completely at low risk of bias, and blinding of participants and personnel, blinding of outcome assessor, and selective outcome reporting were all predominantly at low risk of bias (67%). However, the domain other sources of bias was completely at unclear risk of bias (100%).

Concerning the two *T. terrestris* trials (Figs. 2c and 3c), a low risk of bias was observed for sequence generation and blinding of participants and personnel (both at 100%), allocation concealment, blinding of outcome assessors, and incomplete outcome data (all at 50%, with the remaining 50% being at unclear risk of bias). A high risk of bias was assigned for selective outcome reporting and other sources of bias (both at 50%).

Finally, the risk of bias was predominantly unclear for both *P. pinaster* (Figs. 2 and 3d) and *Leipdium meyenii* (Figs. 2e and 3e).

3.3.2 Herbal Formulations

All the selected studies (n = 7) [47–53] had at least one domain rated as high risk of bias, including those with a Jadad score of five (Fig. 4a, b). Only two trials [48, 52] had a predominantly low risk of bias (four of seven domains). One study [49] had a high risk of bias (five of seven domains). Collectively, a low risk of bias was reported only for the selective outcome reporting domain (57%); unclear risk of bias was predominant for allocation concealment (71%), sequence generation (57%), and blinding of outcome assessors (57%). High risk of bias was reported for other sources of bias (100%).

3.3.3 Herbal Monopreparations/Formulations in Combination with Pure Compounds

Figure 5a, b summarize the risk-of-bias assessment in the five RCTs evaluating the effect of herbal monopreparations/formulations in combination with pure compounds. At least three domains were rated as at high risk of bias in all [54, 55, 57, 58] except one [56] study. A low risk of bias was reported for blinding of outcome assessors (80%), sequence generation (60%), and blinding of participants and personnel (60%); an unclear risk of bias was reported for allocation concealment (60%); and a high risk of bias was reported for other sources of bias (100%), selective outcome reporting (80%), and incomplete outcome data (60%).

3.4 Efficacy

3.4.1 Herbal Monopreparations

Panax ginseng (ginseng) Five (four from Korea and one from Brazil) ginseng RCTs [35–39] were included in the systematic review, for a total of 399 men with ED (age range 42.8–60.2 years). All the included studies were placebo controlled, with three adopting a two-arm parallel-group design [37–39], one a three-arm parallel-group design (placebo, ginseng, and trazodone) [35], and the remaining one [36] a crossover design. All except one [35] were double blind using an identical matching placebo. The duration of treatment ranged from 2 to 3 months. One study was performed in patients with psychogenic (81 patients) or mild vasculogenic (nine patients) ED but the severity of the ED was not reported [35]. The ED etiology was not reported in the remaining four studies, although all scored the severity according to IIEF score (IIEF-5, IIEF-15, and/or IIEF-EF). All four of these [36–39] reported a significant difference in favor of ginseng versus placebo and/or baseline values. The remaining RCT [35] showed superiority (60 vs. 30%) of ginseng compared with placebo, as evaluated by monthly questioning of patients.

Three of five studies (n = 191 patients) [36–38] that assessed efficacy with the IIEF-5 score were included in the meta-analysis (Fig. 6). Two studies were not included in the meta-analysis because IIEF score was lacking [35] or ginseng berries were used instead of roots [39]. Meta-analysis showed that ginseng had a positive effect on IIEF-5 as compared with the placebo groups (n = 140 for ginseng; n = 96 for placebo; SMD 0.43; 95% CI 0.15–0.70; $P < 0.01$; $I^2 = 0$) (Fig. 6).

A detailed analysis of each response for the five single domains of the IIEF-15 questionnaire revealed a positive effect of red ginseng on the following domains: improving erectile function (SMD 0.34; 95% CI 0.07–0.61; $P = 0.01$; $I^2 = 0$), sex desire (SMD 0.36; 95% CI 0.09–0.63; $P < 0.01$; $I^2 = 0$), maintaining erection (SMD 0.37; 95% CI 0.10–0.64; $P < 0.01$; $I^2 = 0$), and ameliorating overall satisfaction (SMD 0.35 points; 95% CI 0.08–0.62; $P = 0.01$; $I^2 = 0$) (Fig. 7). However, ginseng did not significantly improve responses in the orgasmic function domain (SMD 0.26; 95% CI −0.01–0.53; $P = 0.06$; $I^2 = 0\%$).

All five ginseng studies [35–39] investigated changes in serum testosterone levels. Four [35–38] of these (n = 281

Table 6 Herbal monopreparations or herbal formulations in combination with pure compounds: Characteristics of the included studies

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention[b]	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Stanislavov et al. [54] 2008, Bulgaria	DB, CO	50/50 37 Moderate ED NR	Prelox® two capsules bid	1 mo	PL	IIEF-EF; STL	No unwanted effects reported in both groups	3 (1 + 1 + 1 + 0 + 1 − 1 + 0)	"Prelox is a promising alternative to treat mild to moderate ED"	
Ledda et al. [55] 2010, Italy/UK	DB, parallel	124/111 (62/57 PL, 62/54 V) 44.5 ± 4 V; 44.0 ± 4 PL Mild-to-moderate ED NR	Prelox® two capsules bid	6 mo	PL	IIEF-EF; STL, sexual well-being	NR	5 (1 + 1 + 1 + 1 + 1)	"Prelox is effective for improving erectile function"	Some evidence exists that erectile function continues to improve the longer the therapy is used. Excluded all drugs
Paulis et al. [56] 2013, Italy	Not blind, parallel	22 (11 V; 11 VER) NR NR NR	PP one tablet daily	6 mo	VER injection (peri-lesional) 10 mg/every 2 wk + VER iontophoresis/ 5 mg/three times a wk	IIEF-EF	No side effects	2 (1 + 0 + 1 + 0 + 0)	PP associated with VER is effective in treating ED in pts with PD	Pts with ED due to PD; pts treated with PP were also treated with VER (both doses); 22 pts were a subgroup of 64 pts with PD, therefore no characteristics referring to the 22 pts were reported
Sansalone et al. [57] 2014, Serbia	SB, parallel	200/177 (100/90 PL, 100/87 V) 63.92 ± 9.3 V; 65.37 ± 8.81 PL Mild-to-moderate ED NR	Tradamix TX1000, one tablet bid	3 mo	PL	IIEF-15; IIEF-EF; testosterone levels	All subjects included in the study protocol tolerated tx; no reported AEs	3 (1 + 0 + 1 + 1 + 0)	"Tradamix improves erectile and ejaculation function and sexual QOL in pts with mild-moderate ED and particularly for those with moderate arterial dysfunction"	Power calculation; comorbidities

Table 6 continued

Study, year, country	Design	Participant characteristics: size[a], age, condition, duration of onset	Intervention[b]	Duration	Control group	Main outcomes	AEs	Jadad score	Authors' conclusions	Comments
Stanislavov et al. [58] 2015, Bulgaria	DB, CO	50/50 37.28 ± 6.09 V; 37.32 ± 5.55 PL Moderate ED; IIEF = 11–17 NR	Prelox® plus roburins and L-citrulline; two tablets bid	4 wk	PL	IIEF-15; IIEF-EF; QOL, plasma testosterone levels	No unwanted effects reported	5 (1 + 1+ + + 1)	"The combination offers an option for tx of ED without unwanted effects"	Prelox containing L-arginine 0.48 g instead of 0.399 g

AE adverse event, *bid* twice a day, *CO* crossover, *DB* double blind, *ED* erectile dysfunction, *IIEF* International Index of Erectile Function, *IIEF-EF* IIEF Erectile Function domain, *mo* month(s), *NR* not reported, *PD* Peyronie's disease, *PL* placebo, *PP* Peironimev-plus®, *pt(s)* patient(s), *QOL* quality of life, *SB* single blind, *STL* serum testosterone level, *tx* treatment, *V* verum, *VER* verapamil, *wk* week(s)

[a]Number of patients enrolled in the clinical trial/number of patients who finished the trial

[b]See Table 1 for the composition of herbal formulations

patients) were included in the meta-analysis (the study using berries [39] was excluded) (Fig. 8). The analysis of change in serum testosterone levels from baseline showed a non-significant difference for ginseng versus placebo (SMD 0.26 points; 95% CI −0.10–0.61; $P = 0.15$; $I^2 = 53\%$).

Crocus sativus (saffron) Three RCTs [40–42], all performed in Iran and all using both IIEF-EF and IIEF-15 as the main outcome measures, were included in the systematic review. A fourth study was not included because it was not controlled [20]. One of these studies [40] adopted a crossover design and compared the efficacy of saffron (60 mg/daily for 12 weeks) with that of sildenafil in 317 patients with moderate or severe vasculogenic, neurogenic, or psychogenic ED. In contrast to sildenafil, saffron was ineffective in men with ED [40] (Tables 2 and 3). Two other RCTs, for a total of 80 patients aged 36.6–58.9 years, adopted a placebo-controlled (identical-appearing treatment), two-arm (40 placebo, 40 saffron), parallel-group design [41, 42]. Modabbernia et al. [41] used an oral preparation (30 mg daily for 4 weeks) in antidepressant-induced ED (four patients with moderate ED and 26 with mild ED) [41]; the other trial [42] used a topical gel for 1 month in a selected cohort of patients with diabetes and moderate ED. A meta-analysis of the two placebo-controlled studies was not possible because of the different administration routes (oral vs. topical).

Tribulus terrestris Two double-blind, placebo-controlled RCTs, including 202 men with ED, were retrieved [43, 44]. Both trials used an identical matching placebo. Kamenov et al. [44] found that the herbal preparation was superior to placebo in patients with ED with or without hypoactive sexual desire disorders ($n = 172$ men, trial duration 12 weeks). Conversely, another small study found no difference between placebo and *T. terrestris* groups in IIEF-5 and serum testosterone levels ($n = 30$, trial duration 30 days) [43]. Meta-analysis was not possible because one trial [43] lacked SDs.

Pinus pinaster A small double-blind RCT ($n = 21$) showed that 3 months of treatment with a patented extract made from *P. pinaster* (French maritime pine) bark (Pycnogenol®, manufactured by Horphag Research, Geneva, Switzerland) was superior to placebo in patients with moderate ED [45]. Although the authors stated the trial was double blind, no information on the use of an identical matching placebo was reported [45].

Lepidium meyenii A small placebo-controlled, double-blind (an identical matching placebo was used) RCT ($n = 50$) found that a 12-week treatment with a standardized extract from *L. meyenii* was effective in patients with mild ED [46].

A

	Risk of bias	Choi 1995	Hong 2002	de Andrade 2007	Kim 2009	Choi 2012
1	Sequence generation	?	?	?	?	+
2	Allocation Concealment	?	?	?	?	+
3	Blinding of participants and personnel	?	+	?	?	+
4	Blinding of outcome assessors	?	?	?	?	+
5	Incomplete outcome data	?	?	?	+	+
6	Selective outcome reporting	?	-	?	?	+
7	Other sources of bias	-	-	-	-	?

B

	Risk of bias	Safarinejad 2010	Modabbernia 2012	Mohammadzadeh -Morghadam 2015
1	Sequence generation	+	+	+
2	Allocation Concealment	?	+	?
3	Blinding of participants and personnel	-	+	+
4	Blinding of outcome assessors	-	+	+
5	Incomplete outcome data	-	+	+
6	Selective outcome reporting	+	+	?
7	Other sources of bias	?	?	?

C

	Risk of bias	Santos 2014	Kamenov 2017
1	Sequence generation	+	+
2	Allocation Concealment	?	+
3	Blinding of participants and personnel	+	+
4	Blinding of outcome assessors	?	+
5	Incomplete outcome data	?	+
6	Selective outcome reporting	-	+
7	Other sources of bias	-	?

D

	Risk of bias	Durackova 2003
1	Sequence generation	?
2	Allocation Concealment	?
3	Blinding of participants and personnel	?
4	Blinding of outcome assessors	?
5	Incomplete outcome data	+
6	Selective outcome reporting	?
7	Other sources of bias	-

E

	Risk of bias	Zenico 2009
1	Sequence generation	?
2	Allocation Concealment	?
3	Blinding of participants and personnel	?
4	Blinding of outcome assessors	?
5	Incomplete outcome data	?
6	Selective outcome reporting	+
7	Other sources of bias	-

Fig. 2 Herbal monopreparations: risk of bias item for each included randomized controlled trial. **a** Ginseng, **b** saffron, **c** *Tribulus terrestris*, **d** *Pinus pinaster*, **e** *Lepidium meyenii*

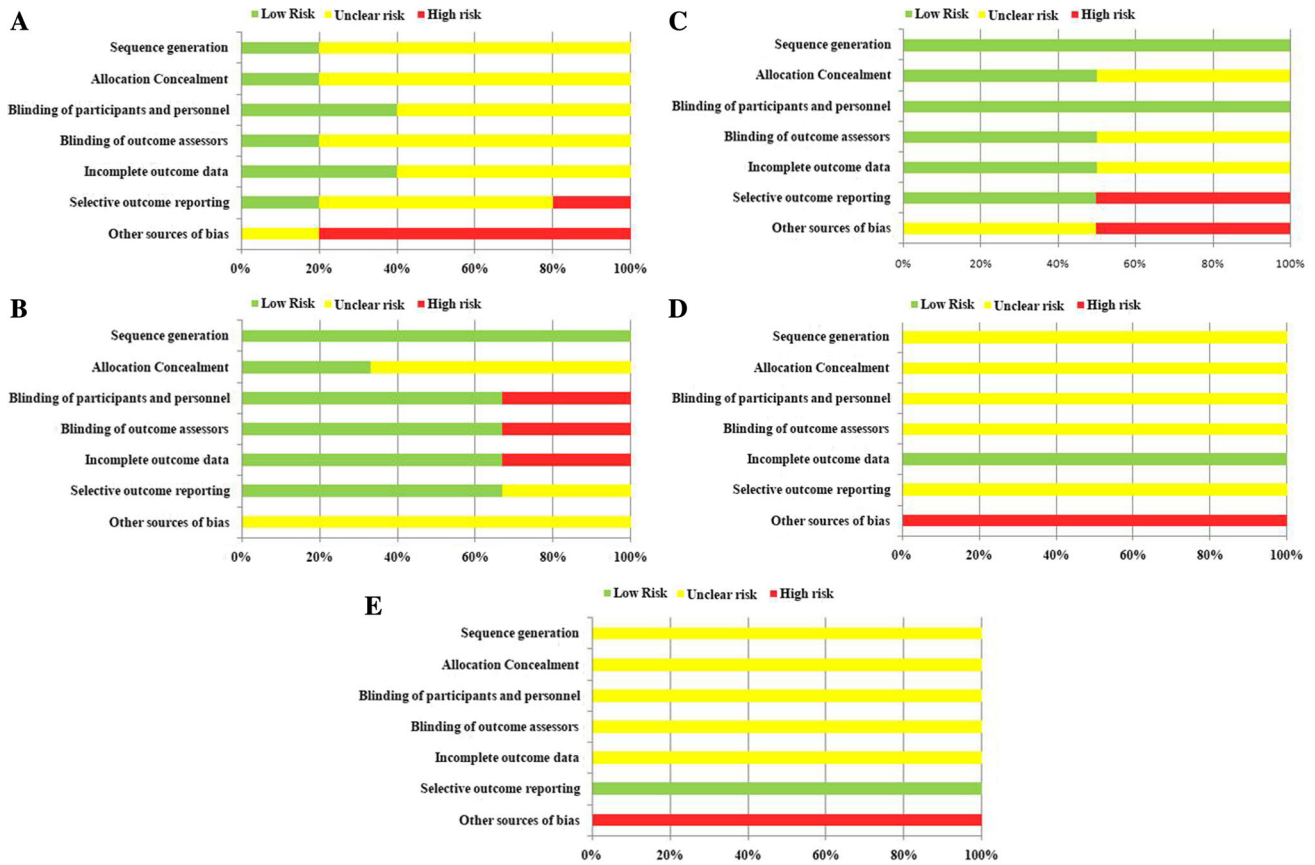

Fig. 3 Herbal monopreparations: Risk-of-bias item presented as percentages across all included randomized controlled trials **a** ginseng, **b** saffron, **c** *Tribulus terrestris*, **d** *Pinus pinaster*, **e** *Lepidium meyenii*

3.4.2 Herbal Formulations

Seven RCTs evaluating the effect of seven different herbal formulations (see composition in Table 1), for a total of 544 men, were included in the systematic review (Table 6) [47–53]. Although four trials were reported to be double (or triple) blind [47–49, 52], only three adopted identical-appearing treatments [48, 49, 52]. Five of the included studies were placebo controlled (n = 369), and all reported superiority of the formulation over the placebo [47–49, 52, 53] (see details in Tables 4 and 5). Two other studies showed superiority of the formulation IDIProst® Gold over *S. repens* (which was one of the components of the formulation; n = 129 patients with lower urinary tract symptoms [LUTS]) [50] and superiority of the formulation Leopin Royal over a *Kampo* preparation (n = 46 patients with mild to severe ED) [51].

3.4.3 Herbal Monopreparations/Formulations in Combination with Pure Compounds

Key results are summarized in Table 7. Four placebo-controlled RCTs (n = 388 men) [54, 55, 57, 58] plus a small trial with verapamil as control (n = 22 men) [56] were retrieved. Two of the four placebo-controlled trials, which investigated a commercial preparation named Prelox®, were double blind (identical matching placebo) and reported effectiveness of the formulation in patients with moderate (n = 50) or mild-to-moderate (n = 111) ED [54, 55]. A further double-blind (identical matching placebo) RCT evaluated the efficacy of Prelox® plus roburins and L-citrulline in 50 patients with moderate ED and yielded similar results [58]. Moreover, a placebo-controlled single-blind study showed superiority of the formulation Tradamix TX1000 over control in 177 patients with mild-to moderate ED [57]. Finally, an open-label, parallel study showed that the formulation Peironimev-plus® in combination with verapamil was more effective than verapamil alone in improving erectile function in 22 patients with Peyronie's disease (severity of ED not reported) [56]. A meta-analysis of the two studies evaluating Prelox efficacy [54, 55] was considered but proved infeasible because the total SD (i.e., the SD that included the first and the second treatment) was lacking from the study that used a cross-over design [55].

A

	Risk of bias	Kulkarni 2011	Shah 2012	Punyawudho 2013	Cai 2013	Nishimatsu 2014	Udani 2014	Hsieh 2016
1	Sequence generation	?	+	+	?	?	+	?
2	Allocation Concealment	+	?	-	?	?	?	?
3	Blinding of participants and personnel	?	+	+	?	-	+	?
4	Blinding of outcome assessors	?	+	-	?	?	+	?
5	Incomplete outcome data	+	-	-	-	?	?	?
6	Selective outcome reporting	+	+	-	-	+	+	?
7	Other sources of bias	-	-	-	-	-	-	-

B

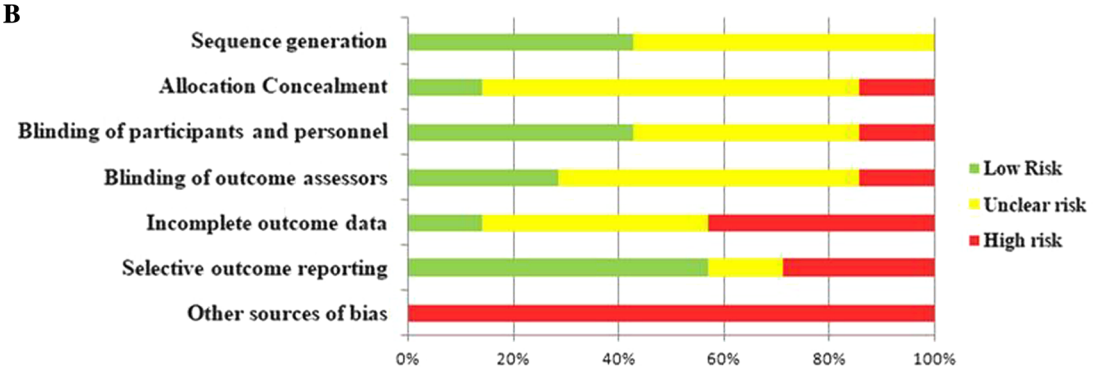

Fig. 4 Herbal formulations: assessment of bias

3.5 Adverse Events

Adverse events were recorded in 19 of 24 studies. Specifically, adverse events were not reported in two ginseng RCTs [35, 36], in one of the two *T. terrestris* RCTs [43], in the *P. pinaster* trial [45], or in one RCT investigating the herbal formulation Prelox® [55]. Two such studies [36, 43] stated that they recorded adverse events, but none were reported within the original manuscript. Adverse effects were mild and included headache, skin, and gastrointestinal symptoms. In placebo-controlled studies, adverse events were similar between the placebo and the verum groups.

4 Discussion

Dietary supplements include vitamins, amino acids, proteins, minerals, and plant extracts (i.e., mixtures of phytochemicals of which the pharmacologically active compound(s) often constitutes only a small part) [59]. To the best of our knowledge, the present article represents the first systematic review and meta-analysis of RCTs examining the evidence for and against the efficacy of HDSs (both monopreparations and herbal formulations) in the management of ED. The most frequently assessed outcome in the retrieved RCTs was IIEF-5 or IIEF-ED score. Overall, results suggest that some HDSs, namely *Panax ginseng* (ginseng), and some herbal formulations (e.g., Prelox®), may be effective, although a number of limitations, including low trial numbers, total sample sizes, methodological quality of primary trials, and imprecise identification/standardization of extracts used may reduce enthusiasm for possible utility in everyday clinical practice.

Preparations from the roots of *P. ginseng* are claimed to exert antioxidant, antidiabetic, immunomodulating, and aphrodisiac properties [60]. Evidence showed that ginseng was effective in treating ED in all the retrieved studies. Four of five trials used roots as the starting material, and efficacy was observed for doses ranging from 1.8 to 3.0 g extract/day. Pooled analysis of three studies, applying IIEF-5 scores to evaluate erectile function, showed positive effects of ginseng compared with placebo. In addition, ginseng treatment was effective in four of the five IIEF-15 domains. We did not perform a test for funnel-plot asymmetry because only three studies were included in the meta-analysis. This small number of studies rendered the power of the tests too low to distinguish change from real asymmetry. A previous systematic review of RCTs [61] that specifically evaluated the evidence for the effectiveness of ginseng in ED yielded similar conclusions, although it did not include the two more recent RCTs published in 2009 and 2012 [38, 39]. A further systematic

A

	Risk of bias	Stanislavov 2008	Ledda 2010	Paulis 2013	Sansalone 2014	Stanislavov 2015
1	Sequence generation	-	+	?	+	+
2	Allocation Concealment	-	?	?	?	+
3	Blinding of participants and personnel	+	+	?	-	+
4	Blinding of outcome assessors	+	+	?	+	+
5	Incomplete outcome data	?	-	+	-	-
6	Selective outcome reporting	+	-	-	-	-
7	Other sources of bias	-	-	-	-	-

B

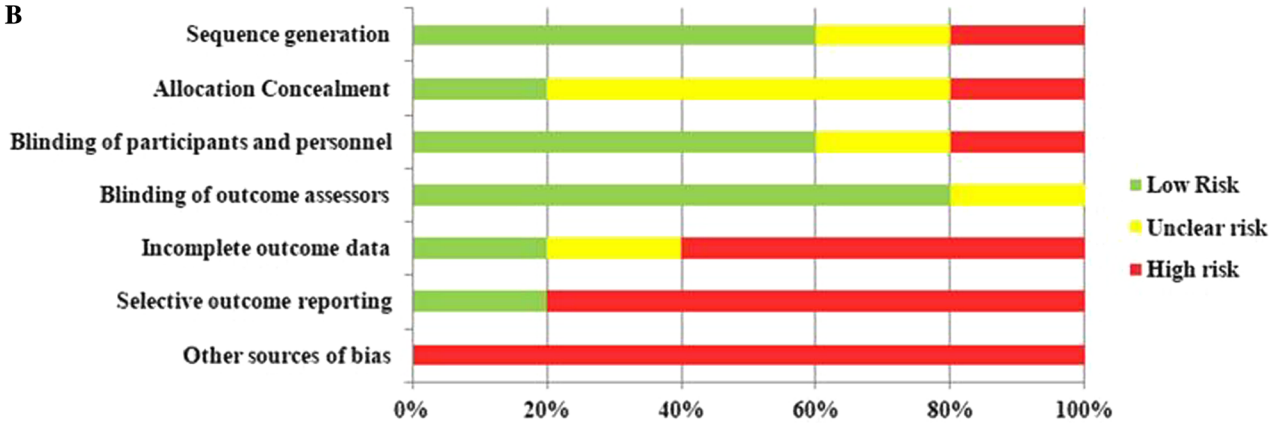

Fig. 5 Herbal monopreparations and herbal formulations in combination with pure compounds: assessment of bias

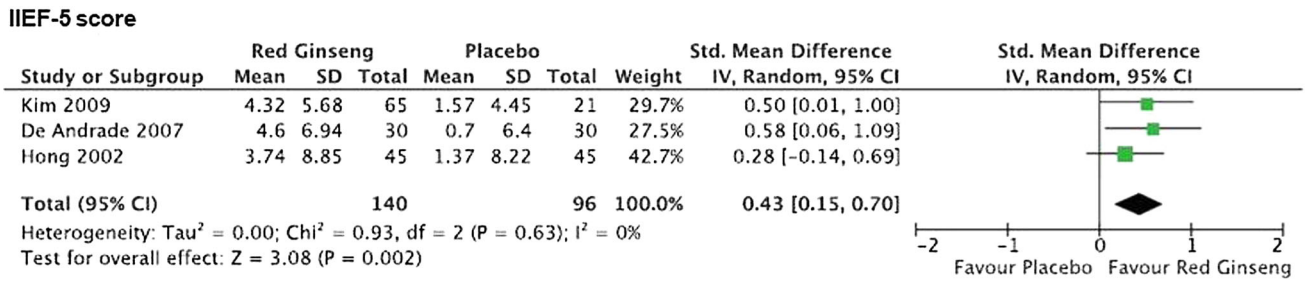

Fig. 6 Forest plot showing changes in International Index of Erectile Function-5 (IIEF-5) from baseline to endpoint in patients with erectile dysfunction using ginseng versus placebo. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

review of RCTs, assessing the effect of ginseng for any indication, concluded that "the most promising evidence supports its [ginseng] use in moderating glucose metabolism and the immune response" [62].

The methodological quality of the retrieved RCTs was not optimal, with only one RCT having the maximum Jadad score of 5 [39]. The major weakness identified was failing to describe the method of generating the sequence of randomization. Furthermore, the risk of bias was unclear or high in many studies, limiting the weight of the evidence. Other weaknesses included a lack of information on the preparation type used [35–38], elevated number of dropouts in one study [38], failure to report adverse effects [36], and the use of trazodone [35], the effectiveness of which in ED is questionable, as a positive control [63].

Experimentally, ginseng preparations have been shown to relax corporal smooth muscle and improve erectile function in rodents [64, 65] with a mechanism likely involving the nitric oxide (NO) signaling pathways [66]. Hormonal mechanisms, such as changes in testosterone levels, seem to be clinically unlikely since our pooled analysis showed no changes in serum testosterone levels.

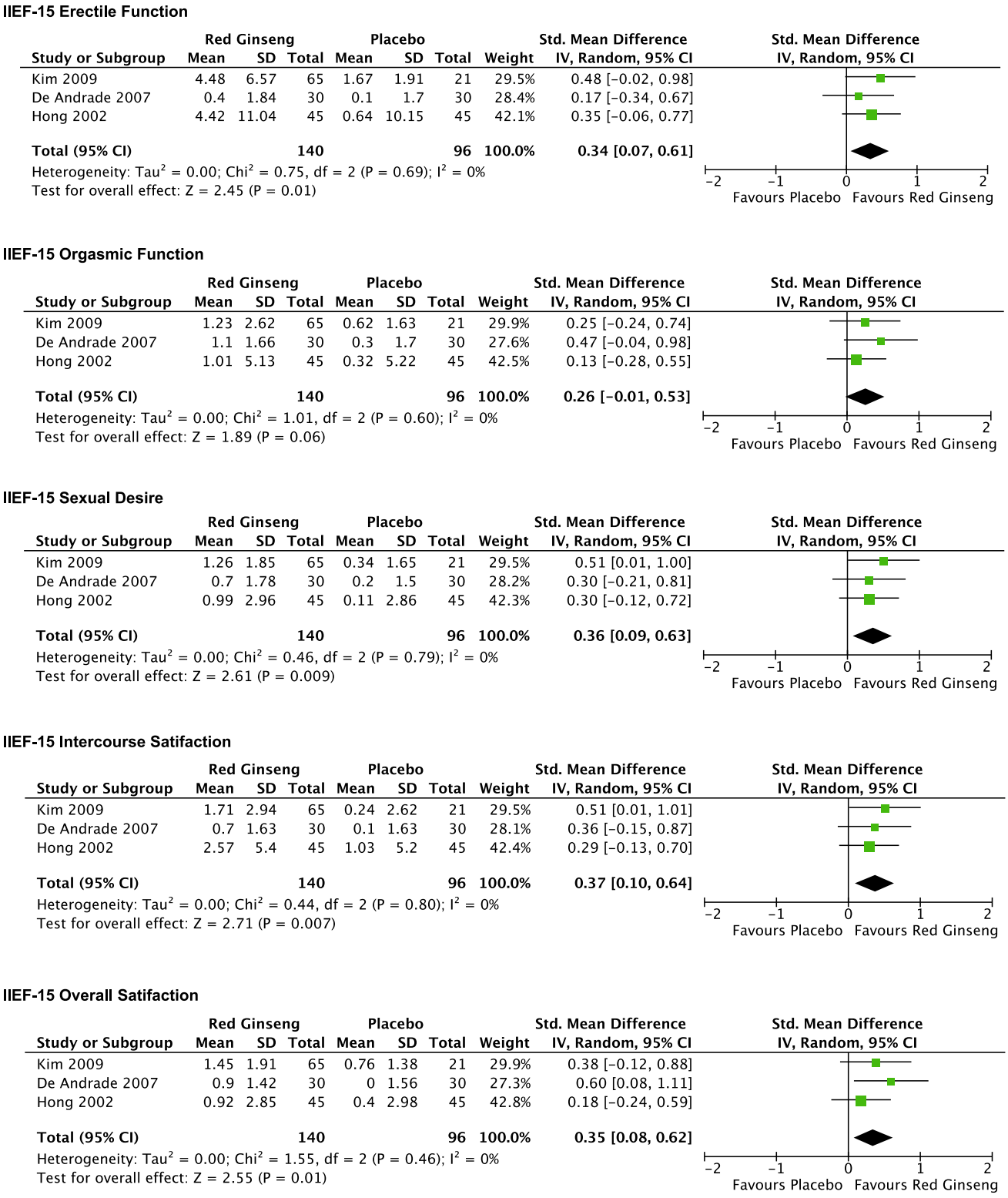

Fig. 7 Forest plot showing changes in the single five domains of the International Index of Erectile Function Score-15 (IIEF-15) from baseline to endpoint in patients with erectile dysfunction using ginseng versus placebo. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

The RCTs evaluating the effect of *C. sativus* (saffron) generated mixed results. Two double-blind RCTs that were small but of good methodological quality revealed superiority of saffron versus placebo [41, 42]. However, the findings of an open-label trial, in which saffron effect was compared with that of sildenafil, did not support a

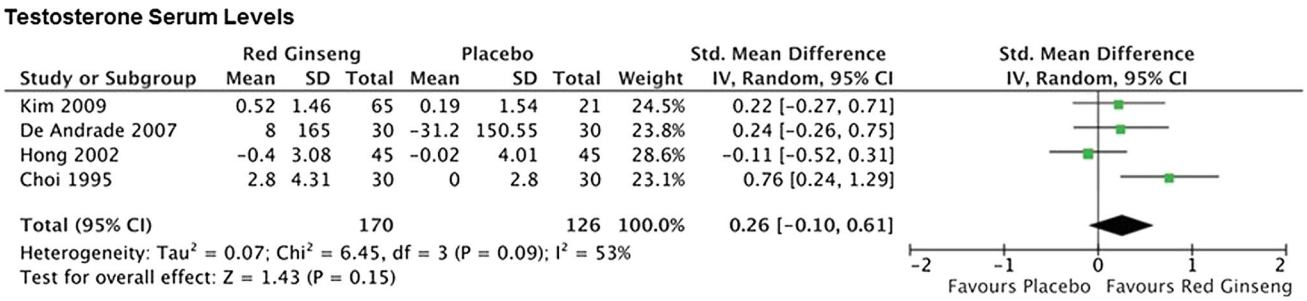

Fig. 8 Forest plot showing changes in testosterone serum levels from baseline to endpoint in patients with erectile dysfunction using ginseng versus placebo. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

beneficial effect of saffron [40]. Incidentally, saffron is one of the components of the formulation IDIProst® Gold, which has been shown to improve sexual function in patients affected by LUTS due to benign prostatic hyperplasia and ED (see formulations) [50]. The possible mechanism of action of saffron is unknown. No studies in the literature have examined the effects of saffron preparations on the isolated corpus cavernosum.

T. terrestris preparations were found to be effective in a relatively large (n = 172 patients) RCT of good methodological quality [44], but not in a small (n = 30) low-quality trial [43]. *T. terrestris* preparations are most often used for infertility and loss of libido. Experimental evidence suggests possible endothelium and NO-dependent mechanisms underlying its pro-erectile actions [67].

Pycnogenol® and maca (*L. meyenii*) are two HDSs that, based on the retrieved RCTs, have been shown to be effective in ED. However, the small sample sizes and failure to report patients' baseline characteristics, dropouts, and randomization method make the value of these results questionable. Pycnogenol® (an extract standardized to contain 70% procyanidin from *P. pinaster* bark) is believed to have a powerful antioxidant activity and has been clinically evaluated in a number of chronic disorders, such as asthma, attention-deficit/hyperactivity disorder, chronic venous insufficiency, diabetes mellitus, hypertension, and osteoarthritis [68]. The mode of action of *P. pinaster* in ED is unknown and, to date, no studies have evaluated the effects of *P. pinaster* preparations on the isolated corpus cavernosum. Maca preparations are obtained from the Andine plant *L. meyenii*. There is no evidence for an androgen-mediated action of maca, and its site of action (central or peripheral) has not yet been identified [69]. Maca preparations have been clinically evaluated for improving the quality of semen [70] and for the treatment of menopausal symptoms [71].

We also retrieved a number of herbal formulations (i.e., mixture of multiple HDSs) or herbal monopreparations/formulations combined with pure phytochemicals, that appeared to be effective in patients with ED, although in a very preliminary fashion. The methodological quality of the retrieved RCTs was good in 5 of 12 studies, having the maximum Jadad score of 5 [48, 49, 52, 55, 58]. The risk of bias was unclear for several domains. Main shortcomings included failure to report the randomization method [47, 50, 51, 53, 54, 56], power calculation [47, 48, 51–56, 58], and intention-to-treat analysis [50–53, 55, 57] and the absence of a double-blind design [50, 51, 53, 56, 57]. We retrieved one RCT for each formulation, except for Prelox®, which two RCTs investigated [54, 55] and reported positive results. A third good-quality study, which used Prelox® in combination with L-citrulline and the polyphenolic compound roburins, found this combination to be effective in 50 patients with ED [58]. A previous systematic review of controlled clinical trials, in which the search was extended to Chinese databases, concluded that the Chinese herb formulae cannot be recommended for ED [72].

The vast majority (19) of retrieved RCTs recorded adverse effects and that they were mild. The most commonly reported adverse effects included gastrointestinal and dermatological symptoms. No difference between HSD treatment and placebo was reported in placebo-controlled RCTs. A search of the literature for safety data on the retrieved HDSs indicated that the present data are in line with other analyses of ginseng safety [73].

In this systematic review, only the efficacy of herbal monopreparations and formulations (alone or in combination with pure compounds) for ED was considered. Information on the potential of pure plant-derived molecules in ED can be found elsewhere [74]. For example, plants and extracts containing polyphenols—especially a class of compounds called kraussianones—appear to be promising in ED [74]. Additionally, an early clinical review on yohimbine, an alkaloid isolated from the bark of the *Pausinystalia yohimbe*, yielded inconclusive results [75].

4.1 Study Limitations

A number of limitations are worthy of mention. First, although our search strategy was comprehensive and meticulous, we cannot exclude the possibility that we

Table 7 Herbal monopreparations or herbal formulations in combination with pure compounds: quantitative results of included studies

Study, year (study design)	Treatment[a]	Measure	Results	
			Baseline	End of treatment
Stanislavov et al. [54] (2008)(crossover)	Prelox®	IIEF-EF[b]	First treatment Prelox (n = 25) 13.4 ± 1.4 PL (n = 25) 13.8 ± 1.3 Second treatment Prelox (n = 25) 17.6 ± 2.5 PL (n = 25) 14.9 ± 1.3	4 weeks (first treatment) Prelox (n = 25) 27.0 ± 0.4† PL (n = 25) 15.1 ± 0.4 4 weeks (second treatment) Prelox (n = 25) 28.1 ± 1.2† PL (n = 25) 15.4 ± 0.5
		STL[b]	First treatment Prelox ((n = 25) 18.13 ± 2.4 PL (n(n= 25) 17.51 ± 3.7	4 weeks (first treatment) Prelox (n = 25) 21.97 ± 2.63†† PL (n = 25) 18.29 ± 3.06*** 4 weeks (second treatment) Prelox (n = 25) 19.33 ± 2.07††† PL (n = 25) 22.24 ± 2.85†††
Ledda et al. [55] (2010) (parallel)	Prelox®	IIEF-EF	Prelox (n = 54) 15.2 ± 6.6 PL (n = 57) 15.1 ± 7.0	13 weeks Prelox (n = 54) 25.2 ± 2.1* PL (n = 57) 19.1 ± 3.0 26 weeks Prelox (n = 54) 27.1 ± 2.1* PL (n = 57) 19.0 ± 3.1
		STL (nmol/L)	Prelox (n = 54) 15.9 ± 2.3 PL (n = 57) 16.9 ± 2.4	26 weeks Prelox (n = 54) 18.9 ± 2.6* PL (n = 57) 17.3 ± 2.3
Paulis et al. [56] (2013) (parallel)	Peironimev-plus®	IIEF-EF	NR	Verum (n = 11) +4.9 ± 1.97 increase vs. BL (effective improvement of ED) Verapamil (n = 11) +3.0 ± 1.53 Verum vs. verapamil: P = 0.02
Sansalone et al. [57] (2014) (parallel)	Tradamix TX1000	IIRF-15 IIEF-15	NR	Mean change from BL to end of treatment Tradimix (n = 87) 11.54 ± 2.47*,** PL (n = 90) 1.32 ± 2.67
		IIEF-EF		Mean change from BL to end of treatment Tradimix (n = 87) 0.35 ± 1.42 PL (n = 90) 0.04 ± 1.0
		Testosterone (nmol/l)	Tradimix (N = 87) 14.69 ± 1.25 PL (N = 90) 13.26 ± 1.02	12.5 weeks Tradimix (n = 87) 14.26 ± 2.05 PL (n = 90) 13.31 ± 1.32

Table 7 continued

Study, year (study design)	Treatment[a]	Measure	Results	
			Baseline	End of treatment
Stanislavov et al. [58] (2015) (crossover)	Prelox plus roburins and L-citrulline	IIEF-15	First treatment Verum (n = 25) 36.8 ± 2.8 PL (n = 25) 36.6 ± 2.9	4 weeks (first treatment) Verum (n = 25) 66.8 ± 3.1‡ PL (n = 25) 37.7 ± 3.4
		IIEF-15	Second treatment Verum (n = 25) 35.8 ± 2.3 PL (n = 25) 38.2 ± 2.2	4 weeks (second treatment) Verum (n = 25) 67.6 ± 2.4‡ PL (n = 25) 39.5 ± 2.0
		IIEF-EF	First treatment Verum (n = 25) 16.4 ± 1.8 PL (n = 25) 17.2 ± 1.2	4 weeks (first treatment) Verum (n = 25) 28.2 ± 1.5‡ PL (n = 25) 17.8 ± 0.6
		IIEF-EF	Second treatment Verum (n = 25) 16.6 ± 1.0 PL (n = 25) 17.5 ± 1.0	4 weeks (second treatment) Verum (n = 25) 29.5 ± 0.6‡ PL (n = 25) 17.9 ± 0.4

Data are presented as mean ± standard deviation

BL baseline, *ED* erectile dysfunction, *IIEF* International Index of Erectile Function, *IIEF-EF* IIEF erectile function domain, *NR* not reported, *PL* placebo, *STL* serum testosterone levels

*$P < 0.05$ vs. baseline, **$P < 0.05$ vs. PL, ***$P < 0.02$ vs. baseline, †$P < 0.001$ vs. baseline, ††$P < 0.00005$ vs. baseline, †††$P < 0.000005$ vs. end of first treatment, ‡Significant vs. baseline

[a]See Table 1 for the composition of herbal formulations

[b]Data provided by the authors

missed relevant published reports; we also ignored pertinent unpublished trials. It is plausible that negative RCTs have remained unpublished, thus altering the global conclusions. To this point, it should be noted that a strong publication bias in favor of positive results has been demonstrated for alternative therapies [76]. Second, our search strategy was limited to the main Western European languages, thus excluding a number of Korean and Chinese trials identified by our search strategy. Studies published in Chinese and Korean languages can be found in recently published systematic reviews [72, 77]. Third, the degree of thoroughness with which the studies were conducted is uncertain, with the risk of bias of most included studies being rated as unclear, mainly because of inadequate reporting. The unclear risk of bias of most included studies suggests that more rigorous trials, possibly adhering to the elaborated CONSORT statement on the reporting of RCT, are warranted. Fourth, we did not include every intervention in a meta-analysis because only single studies were reported for some remedies. When multiple studies for a specific preparation were available, our ability to use statistical techniques to combine their results were precluded by data heterogeneity, different scoring systems (not all studies used the IIEF-5), different administration routes (oral [41, 42] vs. topical [43] in the saffron RCTs), and different parts of the plant used (ginseng berries rather than roots in one study) [39]. Fifth, the included trials had a median duration of 3 months, with seven studies lasting $\leq$ 1 month [41–43, 49, 53, 54, 58] and no study lasting $>$ 6 months. Moreover, follow-up periods were not reported in primary trials. Thus, there is a lack of clinical evidence regarding the long-term safety and efficacy of herbal products for ED. Sixth, the vast majority of the studies (79%) did not report a power calculation, and sample sizes were very small in some RCTs, with five having $\leq$ 30 participants [41, 43, 45, 52, 56]. Only seven RCTs performed an intention-to-treat analysis [39–41, 44, 47–49], although four other RCTs specifically reported the absence of withdrawals/dropouts [42, 54, 56, 58]. Finally, and importantly, descriptions of chemistry, standardization, fingerprint, amount of active ingredients, solvent extraction, or drug extract ratio was

inadequate or not reported in most cases, thus raising the possibility that results could lack reproducibility. This was despite attempts to contact study authors for further information. Collectively, these drawbacks limit the conclusions of the present systematic review.

5 Conclusions

Encouraging evidence suggests that some HDSs may be effective for ED, as revealed by IIEF-5, IIEF-15, or IIEF-EF values. However, many of the included RCTs were of uncertain methodological quality, with an unclear risk of bias. Hence, more rigorous research in the field is required before HDSs can be definitively recommended for the treatment of ED. Similarly, the long-term safety of these products needs to be established, as does the impact on patient outcomes of extraction and preparation methods and administration route. Despite the uncertain evidence on the efficacy and safety, these products are commonly used, often without medical guidance. Thus, a degree of familiarity with the efficacy and safety of HDSs used in ED can help medical practitioners properly to inform and counsel their patients.

Author Contributions All authors collectively planned the study. FB and AAI drafted the systematic review manuscript. FB and AAI assessed the eligibility of included articles and extracted data. DD, MI, and CC assessed the quality of the studies. All authors served as adjudicators for disagreements. CC performed the meta-analysis. All authors reviewed the manuscript for intellectual content and approved the final version.

Compliance with Ethical Standards

Conflict of interest Francesca Borrelli, Cristiano Colalto, Domenico V. Delfino, Marcello Iriti, and Angelo A. Izzo have no conflicts of interest that are directly relevant to the content of this manuscript.

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