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Review Article

Nutraceutical interventions for erectile dysfunction: a systematic review and network meta-analysis

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Abstract

Background: Although nutraceutical-based treatments are often offered for erectile dysfunction (ED), their efficacy remains doubtful, and the choice of one substance over the other is challenged by the dearth of head-to-head comparative studies.
Aim: We aimed to compare the efficacy of available nutraceutical interventions, alone or in combination with phosphodiesterase type 5 inhibitors (PDE5i), in improving erectile function in men with ED through a network meta-analysis (NMA), which incorporates direct and indirect evidence into one model thus generating a hierarchy of effectiveness.
Methods: PubMed, Scopus, Web of Sciences, and Cochrane Library databases were searched for randomized placebo-controlled trials (RCTs) assessing the effect of any nutraceutical regimen in improving erectile function when compared to each other, placebo, and/or PDE5i in men with ED. Data were included in a random-effects NMA, where efficacy of treatments was ranked by surface under the cumulative ranking curve (SUCRA). Two NMAs were also conducted separately for organic and non-organic ED. Reciprocal comparisons between all treatments were analyzed by league tables.
Outcomes: The main outcome was the standardized mean difference in the score of the International Index of Erectile Function (IIEF)-5 or IIEF-6.
Results: Fifteen RCTs provided information on 1000 men with ED. In the overall NMA, compared to placebo, the combination propionyl L-carnitine (PLC) + acetyl L-carnitine (ALC) + Sildenafil was associated with the highest SUCRA (97%) in improving erectile function score, followed by L-Arginine + Tadalafil (84%), Sildenafil (79%), Tadalafil (72%), and L-Arginine (52%). No other treatment regimen showed efficacy with statistical significance. In patients with organic ED, the efficacy of Sildenafil and Tadalafil was significantly improved by PLC + ALC and L-Arginine, respectively. On the contrary, in non-organic ED, nutraceuticals did not improve the therapeutic performance of daily Tadalafil.
Clinical Implications: This NMA contributes valuable insights into the potential of nutraceutical interventions for ED.
Strengths and Limitations: We employed strict inclusion criteria related to study design and diagnostic tool, ensuring the assumption of transitivity and the consistency of the analysis.
Conclusion: Against a background of general ineffectiveness of most nutraceutical interventions, L-Arginine and the mix PLC + ALC appeared to be of some usefulness in improving erectile function, especially in combination with PDE5i in organic ED.

Keywords: antioxidants; oxidative stress; phosphodiesterase 5 inhibitors; sexual dysfunction; sexuality; dietary supplements.

Introduction

Erectile dysfunction (ED) is reported by more than 50% of community-dwelling men aged 40–70 years with a prevalence strongly related to age, metabolic syndrome, neuropathy, and vascular disease.[1-5] Although phosphodiesterase type 5 inhibitors (PDE5i) are the first-choice drugs,[4,6] interest in the use of nutraceuticals (or dietary supplements) for ED has progressively increased over the past 30 years and remains quite high. Indeed, the use of PDE5i is burdened by a nonnegligible discontinuation rate, which, in a meta-analysis including 22 studies in a total population of 162 936 men, was as high as 50% within 1year, being higher in studies enrolling younger populations and/or with a higher prevalence of associated morbidities such as hypertension and diabetes.[7] Besides comorbidities, the same meta-analysis identified other reasons behind dropout, mainly loss of efficacy, cost, and side effects.[7] Overall, these limitations encourage the search for approaches that could combine more favorable compliance and safety with acceptable efficacy and more affordable treatment. On this basis, global market of sexual enhancement supplements, currently valued at around $215 million, is projected to double in less than 10 years with an annual growth rate of more than 10%.

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Indeed, nutraceuticals combine a good safety profile with mechanisms of action that directly or indirectly can theoretically improve erectile function.[8] Some supplements, including L-Arginine, L-Citrulline, are involved in the molecular pathway of nitric oxide (NO) synthesis,[9,10] some engage more downstream (eg, L-Cysteine), acting in synergy with cyclic guanosine 3',5'-cyclic monophosphate (cGMP) or reducing its catabolism,[11] while for others (eg, *Tribulus terrestris*), the ability to increase the levels of testosterone has been theorized.[12] In addition, most nutraceuticals act as antioxidants counteracting the contribution of free radicals to endothelial dysfunction, which plays a key role in the pathogenesis of ED in many cases.[4-6]

Although some nutraceutical interventions might have a rationale in the treatment of ED in selected patients, in international guidelines, this topic is either not discussed at all[4,13] or is judged not to be supported by sufficient evidence.[6,14] In a meta-analysis by Su et al.,[15] the use of antioxidant compounds was associated with a nearly 3-fold aggregate mean increase in the International Index of Erectile Function (IIEF) score in men with ED. However, the quality of the evidence was greatly downgraded by the large between-studies heterogeneity ($I^2 = 96.5\%$, $P < .0001$), reflecting differences in study populations, severity of ED at baseline, as well as intervention design and protocols, varying in nutraceutical regimens and treatment duration.

Indeed, determining whether nutraceuticals are truly effective in ED and, more importantly, whether some preparations are more effective than others is hardly straightforward for at least 2 reasons: (1) for each type of regimen, the evidence of efficacy comes from one or very few studies, and thus meta-analyses provide an overall class effect, not related to individual substance; (2) head-to-head studies that have directly compared different treatments are rarely available. When direct evidence is lacking, information can be drawn from a network meta-analysis (NMA). Based on the transitivity assumption, if 2 interventions, A and B, have never been directly compared with each other but both have been compared with a third treatment (eg, a placebo), NMA can provide information on the A vs B comparison through the statistical methodology of "indirect comparison."[16,17]

Within this framework, we generated a NMA to compare the effectiveness of available nutraceutical interventions in improving erectile function in men with ED.

Materials and methods

This NMA was registered in the PROSPERO (International Prospective Register of Systematic Reviews) with the number CRD42023440278. The results are reported in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for reporting NMAs.[18]

Search strategy

A systematic search was performed in PubMed, Scopus, Web of Science, and Cochrane Library databases, including the following free and vocabulary terms: "erectile dysfunction," erection, "sexual function," acetylcysteine, acetyl L-carnitine (ALC), alpha-tocopherol, alpha-tocotrienol, antioxidant*, arginine, "ascorbic acid," "aspartic acid," astaxanthin, betacarotene, calcitriol, carnitine, carnitine*, carotene, carotenoid*, cholecalciferol, "coenzyme Q10," CoQ10, "dehydroascorbic acid," "eicosapentaenoic acid," EPA, "fatty acids," "fish oil*," flavonoid*, folate, "folic acid," glutathione, isotretinoin, L-Acetylcarnitine, L-Arginine, L-Carnitine, L-citrulline, levoacetylcarnitine, levoarginine, levocarnitine, "lipoic acid," lutein, lycopene, multivitamin*, myoinositol, NAC, N-acetyl cysteine, "nicotinic acid," nutraceutic*, oil, omega, pentoxifylline, "propionyl L-carnitine," PLC, Pentoxifylline, PTX, Pycnogenol, "radical scavenger*," resveratrol, "retinoic acid," riboflavin, selenium, sitosterol, Tribulus, ubidecarenone, ubiquinol, ubiquinone, vitamin*, "vitamin A," "vitamin C," "vitamin D," "vitamin E," yohimbine, zinc, using the Boolean functions AND/OR. Search was restricted to English-language studies enrolling human participants, published up to April 2024. If it was not clear from the abstract whether the study contained relevant data, the full text was retrieved.

The identification of eligible studies was performed by 2 authors independently (D.T. and A.B.), and disagreements resolved by the other investigators. No search software was employed. The reference lists of the identified articles were also scrutinized to find possible additional pertinent studies.

Inclusion and exclusion criteria

The following eligibility criteria were used: (1) randomized controlled trials (RCTs) enrolling men aged 18 years or older with ED of any etiology; (2) interventions including any nutraceutical treatment compared with placebo, PDE5i, and/or other types of nutraceuticals; (3) use of linear scores of IIEF-5 or IIEF-6 for both diagnosis of ED and evaluation of the treatment effect; (4) availability of the mean score ± SD of IIEF before and after treatment(s). To satisfy the assumption of transitivity (evidence of indirect comparison between 2 treatments can be only generated if both were compared with a third treatment, such as a placebo), only RCTs whose design involved a placebo arm were included.

Reviews/meta-analyses, studies other than RCT, lacking placebo arm, lacking to assess nutraceutical preparations, lacking to assess the outcomes of interest, or enrolling not pertinent populations were excluded. To facilitate the rating of efficacy for individual treatments, we excluded studies in which more than 3 different ingredients were used in combination in the same group. Combinations of nutraceutical(s) and PDE5i were also included.

Two independent reviewers (A.B. and D.T.) evaluated the full text of all selected studies for eligibility, and, where disagreement occurred, a third reviewer (G.C.) took a decision after open discussion.

Data extraction

Data were extracted by 2 independent reviewers (A.B. and D.T.) by including the first author, publication year, country/geographic region, sample size, ED etiology, age, intervention type and duration, mean ± SD of the IIEF score before and after treatment(s). When summary statistics were not fully reported, these were calculated, whenever possible.[19]

Risk of bias

Two reviewers (D.T. and F.A.) independently evaluated the quality of each included study using the Cochrane Collaboration Recommendations assessment tools.[20] This tool assesses the following sources of bias: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other bias. Studies were rated as follows: (1) high risk of bias (if ≥1 item was rated

with a high risk); (2) low risk of bias (if ≥3 out of a maximum of 7 items were rated as low risk, and no item was rated with a high risk); and (3) moderate/unclear risk of bias (all other studies).

Data synthesis and analysis

Direct comparisons between different interventions were represented using a network graph where the thickness of the line is proportional to the number of comparisons among the studies included.

We performed a direct pairwise meta-analysis considering treatments that had been compared with placebo in head-to-head RCTs (direct comparison). Data were combined in a random-effects model using the Review Manager of the Cochrane Library (version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration). The random-effects model assumed that the included studies had varying effect sizes, thus providing a conservative estimate of the overall effect. Pooled results were presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs) in pretreatment vs posttreatment IIEF score. In pairwise meta-analysis, the Cochran's Chi square (Cochran's Q) test and the I^2 test were used to analyze heterogeneity between the results of different studies: an $I^2 > 50\%$ and/or $P < .05$ indicated substantial heterogeneity.[21]

A frequentist random-effects NMA was performed to incorporate the estimates of direct and indirect comparisons.[22] In addition to the overall analysis, two NMAs were conducted separately for organic and nonorganic ED. Reciprocal comparisons between all treatments were analyzed by the league table, a square matrix showing all pairwise comparisons in a NMA.[18]

Efficacy of nutraceutical interventions alone and in combination with PDE5i compared to placebo was ranked according to the *P*-score, which is a frequentist equivalent of the surface under the cumulative ranking curve (SUCRA) generated in Bayesian NMA.[23] The SUCRA expresses the percentage of efficacy of each treatment compared with an "ideal" treatment always ranked first without uncertainty. Its values range from 0% to 100%: the higher the SUCRA value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank.[24]

A net-splitting analysis was used to evaluate the presence of statistical inconsistency in the network: this test splits the network estimates for each comparison into the contributions of direct and indirect evidence to assess their agreement degree.[25]

Data were analyzed using the R statistical software (version 3.6.3; R Foundation for Statistical Computing) with the "netmeta" package for NMA.

Results

Study selection and characteristics

The electronic search yielded a total of 4216 articles, and 12 additional papers were obtained after manual search. After removal of duplicates, 1954 articles were obtained, of which 1903 were excluded, because they were deemed not relevant based on title and/or abstract reading. Thus, as shown in Figure 1, a total of 51 articles were identified, of which 15 randomized placebo-controlled trials, involving 1000 men (mean age: 45 years) with ED, met the inclusion criteria.[26-40]

The included 15 RCTs investigated 14 different intervention regimens: details are presented in Table 1.

Assessment of risk of bias

The assessment of risk of bias is shown in Figure 2. With respect to the individual risk of bias, 10 trials illustrated the specific methods of random sequence generation. Six trials stated allocation concealment, whereas others did not. Thirteen trials had a low risk in the performance bias, whereas 6 trials had a low risk in the detection bias. Only one trial had a high risk in the attrition. Finally, an unclear risk of bias was assigned to 7 trials in the reporting and 10 trials in the "other bias" item. Overall, among the 15 RCTs included, 11 were classified as having a low risk of bias, 2 a high risk, and 2 a moderate/unclear risk of bias.

Synthesis of results: Pairwise and network meta-analyses

The network graph of direct comparisons among the 15 RCTs included is shown in Figure 3. All treatments had been compared at least once with placebo. Few preparations had been directly compared head-to-head with each other; these included: Yohimbine, which was directly compared with both placebo and the combination L-Arginine + Yohimbine; the mix PLC + ALC + Sildenafil, which was directly compared with both placebo and Sildenafil; L-Arginine, which was directly compared with placebo, Tadalafil, and the combination of L-Arginine + Tadalafil. Treatments most often compared with placebo were L-Arginine and Tadalafil, alone or in combination, as well as the mix Pycnogenol + L-Arginine aspartate and Vitamin E + Ginseng.

At the pairwise meta-analysis (Figure S1), various treatments resulted in a significant increase in IIEF score compared with placebo, including L-Arginine alone or in combination with Yohimbine, Tadalafil (5-10 mg daily), or Adenosine; Vitamin E + Ginseng; Sildenafil (100 mg on demand) alone or in combination with PLC + ALC; Tadalafil (5-10 mg daily). Overall, the pooled SMD estimated by the random-effects model was 2.00 (95% CI, 1.36–2.64; $P < .00001$), with evidence of large heterogeneity between the studies ($I^2 = 94.5\%$, $P < .00001$).

When compared with placebo within the overall NMA (Figure 4), among nutraceuticals, only L-Arginine (alone but especially in combination with Tadalafil) and the mix PLC + ALC (in combination with Sildenafil) induced significant increases in IIEF score. PLC + ALC + Sildenafil was the intervention reaching the highest SUCRA score (97%), followed by L-Arginine + Tadalafil (84%), Sildenafil (79%), Tadalafil (72%), and L-Arginine (52%).

Subgroup analyses and league tables

To check therapeutic effects of nutritional interventions according to different etiologies of ED, we carried out 2 subgroup NMAs and league tables separately including studies on organic[27,30,31,33,36-38] (Figure 5) and nonorganic DE[26,28,29,32,34,35,39,40] (Figure 6) respectively.

Among the studies on organic ED, the treatments most frequently compared with placebo were L-Arginine and Tadalafil alone, and their combination (Figure 5A). At the subgroup NMA (Figure 5B), among nutraceuticals, only L-Arginine (alone but especially in combination with Tadalafil) and the mix PLC + ALC (in combination with Sildenafil)

Table 1. Characteristics of the studies included.

Study	Country	*N*	Organic etiology (type)	Tool	Age: mean values or range (years)	Intervention (daily dose)	Follow-up (weeks)	Side effects
Abu El-Hamd et al.[26]	Egypt	90	No	IIEF-5	>60	L-Arginine (5 g) vs. L-Arginine (5 g) + Tadalafil (5 mg) vs. Tadalafil (5 mg)	6	NA
Agostini et al.[27]	Italy	176	Yes (diabetes)	IIEF-5	50-70	Myo-inositol (4 g) + Folic acid (400 mcg)	12	NA
Akhondzadeh et al.[28]	Iran	40	No	IIEF-6	38.3	Yohimbine (NA) + L-Arginine (NA)	4	Itching: 3 (15%); Hypertension: 1 (5%); Headache: 5 (25%); Insomnia: 3 (15%)[a]
Aoki et al.[29]	Japan, UK	23	No	IIEF-5	51.0	Pycnogenol (60 mg) + L-Arginine aspartate (690 mg)	8	None
Cavallini et al.[30]	Italy	61	Yes (prostatectomy)	IIEF-6	61.4	PLC (2 g) + ALC (2 g) + Sildenafil (100 mg on demand) vs. Sildenafil (100 mg on demand)	16	Events in PLC/ALC/Sildenafil arm ($n = 32$) included: headache: 8 (25.0%); flushing: 7 (21.8%); dizziness: 3 (9.4%); nausea: 2 (6.2%); nasal congestion: 2 (6.2%); euphoria: 2 (6.2%)[b]
El Taieb et al.[31]	Egypt	81	Yes (diabetes)	IIEF-5	43.7	L-Arginine (5 g) vs. L-Arginine (5 g) + Tadalafil (10 mg) vs. Tadalafil (10 mg)	8	NA
El-Sisi et al.[32]	Egypt	40	No	IIEF-5	40-60	Vitamin E (400 IU)	6	NA
La Vignera et al.[33]	Italy	75	Yes (vasculogenic)	IIEF-5	56.0	L-Arginine (2.5 g) + PLC (250 mg) + Nicotinic acid (20 mg)	Up to 24	NA
Lebret et al.[34]	France	45	No	IIEF-6	56.7	Yohimbine (6 mg) and Yohimbine (6 mg) + L-Arginine (6 g)	6	Occasional headache and moderate insomnia (4 cases in the Yohimbine arm and 2 in Yohimbine/L-Arginine arm).
Ledda et al.[35]	Italy, UK	111	No	IIEF-6	44.2	Pycnogenol (80 mg) + L-Arginine aspartate (2800 mg)	Up to 24	NA
Menafra et al.[36]	Italy	95	Yes (vasculogenic)	IIEF-6	51.4	L-Arginine (6 g)	12	Not clinically relevant events in 5.88% of patients, including gastric pyrosis, urticarial reaction, and scrotal itching.
Morano et al.[37]	Italy	16	Yes (diabetes)	IIEF-5	55.8	PLC (2 g)	12	NA
Mozaffari-Khosravi et al.[38]	Iran	69	Yes (diabetes)	IIEF-6	51.4	L-Arginine (5 g)	4	NA
Neuzillet et al.[39]	France	26	No	IIEF-6	56.4	L-Arginine (8 g) + Adenosine (200 mg)	NA	Mild gastrointestinal complaints in 2 patients.
Tadayon Najafabadi et al.[40]	Iran	52	No	IIEF-6	41.2	Vitamin E (100 IU) + Ginseng (107 mg)	6	Headache: 1 (3.85%); dry mouth: 2 (7.69%); nausea: 2 (7.69%); vomiting: 3 (11.54%); itching: 1 (3.85%); constipation: 2 (7.69%); dizziness: 2 (7.69%)[a]

Abbreviations: ALC, acetyl L-carnitine; IIEF, international index of erectile function; NA, not available; PLC, propionyl L-carnitine. [a]Not significantly different from placebo arm. [b]Not significantly different from Sildenafil arm.

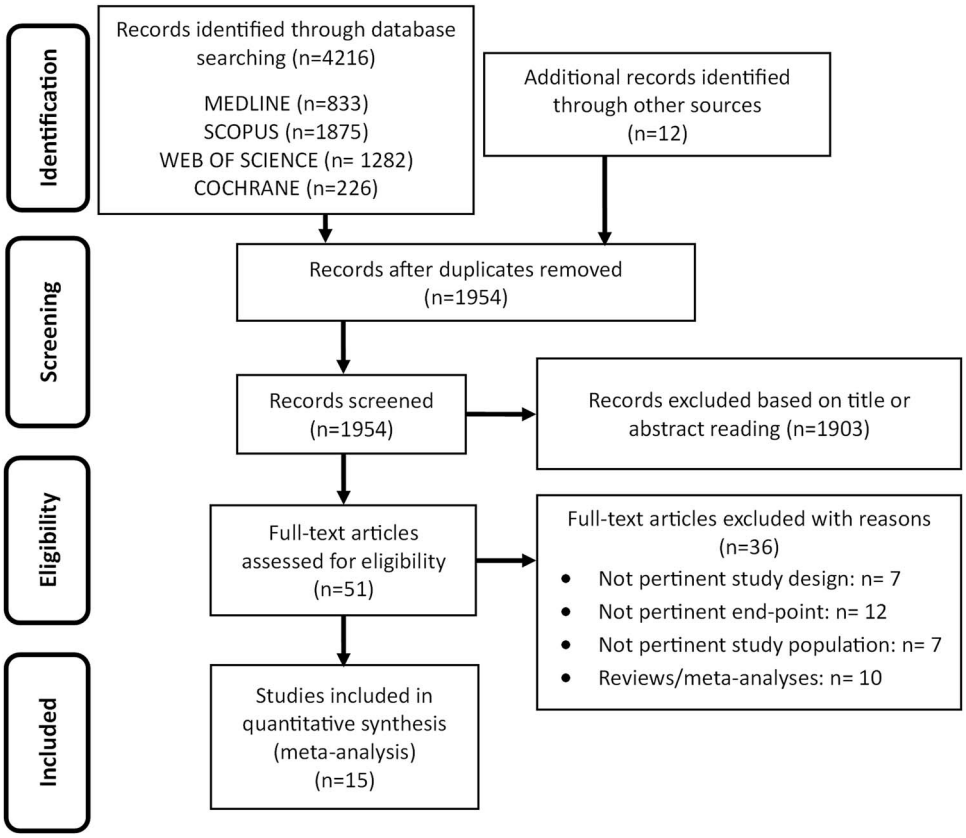


Figure 1. Flow diagram showing an overview of the study selection process.

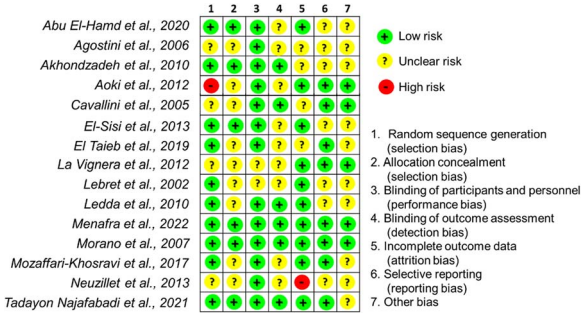


Figure 2. Assessment of risk of bias of the included randomized controlled trials.

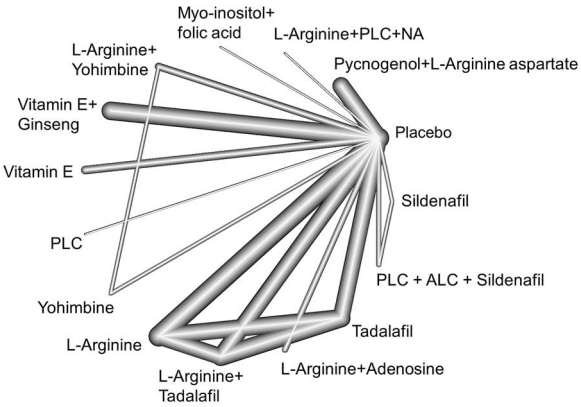


Figure 3. Network graph of direct comparisons assessed in the randomized controlled trials included. Abbreviations: ALC, acetyl L-carnitine; PLC, propionyl L-carnitine.

induced significant increases in IIEF score when compared with placebo. PLC + ALC + Sildenafil was the intervention reaching the highest SUCRA score (99%), followed by Sildenafil (76%), L-Arginine + Tadalafil (73%), Tadalafil (47%), and L-Arginine (27%). The league table revealed that the mix PLC + ALC + Sildenafil was significantly more effective than Sildenafil alone (SMD: 5.60, 95% CI, 1.62–9.58), and the mix L-Arginine + Tadalafil was significantly more effective than Tadalafil alone (SMD: 3.45, 95% CI, 0.49–6.41) (Figure 5C).

Among the studies on nonorganic ED, the treatments most frequently compared with placebo were the combination of Vitamin E + Ginseng and Pycnogenol + L-Arginine aspartate, followed by L-Arginine and Tadalafil, both alone and in combination (Figure 6A). At the subgroup NMA (Figure 6B), only Tadalafil alone or in combination with L-Arginine induced significant increases in IIEF score when compared with placebo. Although the combination Tadalafil + L-Arginine reached a higher SUCRA score (88%) than Tadalafil (83%), the league table (Figure 6C) revealed that the addition of L-Arginine did not significantly increase the efficacy of Tadalafil (SMD: -1.38, 95% CI, -11.86–9.10).

Inconsistency analysis

To check the consistency assumption, we carried a net-splitting analysis of the results produced by the overall NMA. As shown in Figure S2, in each comparison for which direct evidence was available, the direct and indirect components

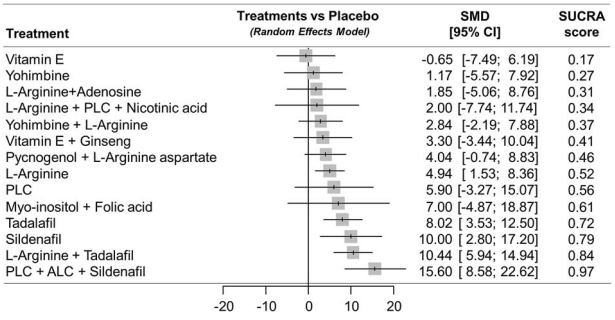


Figure 4. Forest plot depicting the estimation of standardized mean differences (SMD) in IIEF score between treatments and placebo in men with erectile dysfunction. Abbreviations: ALC, acetyl L-carnitine; IIEF, international index of erectile function; PLC, propionyl L-carnitine; SUCRA, surface under the cumulative ranking curve.

of the overall (network) estimate did not differ significantly: the high degree of agreement between direct and indirect estimates supported the overall consistency of the overall model.

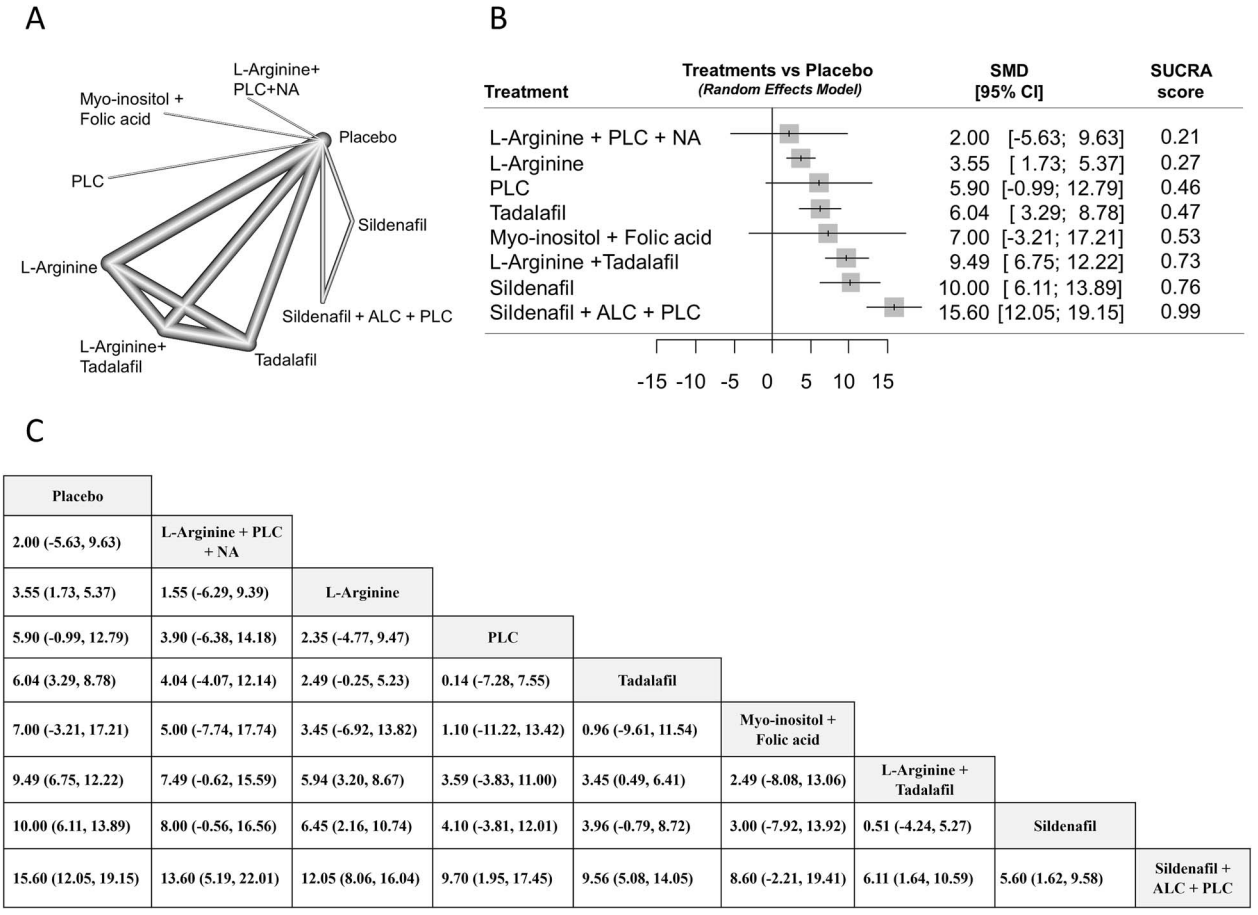
Discussion

In this study, which to our knowledge represents the first NMA on the topic, among the nutraceuticals investigated in available RCTs, only L-Arginine and the mix PLC + ALC, especially in combination with a PDE5i, were effective in significantly improving erectile function score in patients with ED. Although the pairwise traditional meta-analyses showed that many nutraceutical interventions exhibited superiority over placebo with a significant aggregate effect, within the network of comparisons, the efficacy of most of them was lost, and only L-Arginine (alone but especially in combination with Tadalafil) and the mix PLC + ALC (in combination with Sildenafil) were confirmed to be of potential utility.

Our model is an example of how NMA provides information that cannot be inferred from pairwise meta-analyses. Indeed, when there are no head-to-head comparison studies and each nutraceutical molecule has been tested against placebo in only one or a few studies, the traditional meta-analytic approach provides insight into the aggregate class effect without clarifying whether and to what extent one molecule is more effective than the others. According to the results of our pairwise meta-analysis, in the study by Su et al.,[15] antioxidant compounds overall induced a significant improvement in erectile function. However, the aggregate result was burdened with a large and significant heterogeneity ($I^2 = 96.5\%$ in the study by Su et al. and 96.0% in our analysis), largely due to the variable efficacy of individual interventions, as suggested by the aggregate estimates at the subgroup analyses. However, pairwise meta-analysis does not definitively establish which is the most effective intervention. This limitation is overcome by the NMA, where the overall estimates are derived from the statistical processing of direct and indirect evidence incorporated into a single model. This approach can result in different order of magnitudes of effect sizes compared with pairwise meta-analysis and allows many treatments to be discarded, thus selecting a small pool of substances with significant efficacy grading for further investigation in targeted prospective studies. In our analysis, the selection was restricted to 3 treatment regimens, L-Arginine alone or in combination with Tadalafil, and the mix PLC + ALC in combination with Sildenafil.

Additional information of clinical relevance arose from subgroup analyses and league tables by ED etiology. Although in the nonorganic ED, L-Arginine did not significantly improve the performance of daily Tadalafil, in the organic ED (post-prostatectomy, vasculogenic, diabetes-related ED), the addition of PLC + ALC appeared to produce a slight, albeit significant, increase in Sildenafil efficacy, as did the addition of L-Arginine that of Tadalafil. Our findings are in line with those of a meta-analysis by Mykoniatis et al.,[41] which showed that the addition of antioxidants can significantly increase the efficacy of PDE5i. Indeed, overcoming the limitations of the pairwise meta-analyses, our model provides key additional and novel information on which molecules to use and in which type of patient.

The specific mechanisms through which the selected molecules could improve erectile response deserve a better discussion. L-Arginine is used by NOS synthase (NOS) as a NO precursor[42] in mediating smooth muscle release.[43-45] In a recent study by Petre et al.,[8] who used an analytical scoring system approach completely different from the NMA, L-Arginine was found to be among the few nutraceuticals of potential utility. However, the authors pointed out that in most available commercial products, L-Arginine is present at an incorrect dosage. Carnitines would mainly exert antioxidant activities related to their shuttle activity at the mitochondrial level to produce energy from β-oxidation of long-chain fatty acids.[46] This process could facilitate the disposal of peroxidized lipids at the cell membrane level by blocking the oxidative chain within the phospholipid bilayer.[47,48] In addition to L-carnitine, the endogenous carnitine pool includes the short-chain carnitine esters, ALC and PLC, which, when administered exogenously, exhibit greater bioavailability than L-carnitine. Notably, PLC readily crosses cell and mitochondrial membranes, is rapidly converted to L-carnitine and propionyl-coenzyme A, and exerts superoxide anion scavenger activities.[49] Such antioxidant activities could enhance erectile response considering the pathogenetic role that reactive oxygen species play in ED.[50] Superoxide anion radical, generated either in endothelial cells as a result of univalent oxygen reduction during mitochondrial electron transport or by activated phagocytic cells by nicotinamide adenine dinucleotide phosphate hydrogenase oxidase, reduces the bioavailability of NO, as it interacts with the latter generating peroxynitrite.[51] This process, which is a key factor in the pathogenesis of ED in many cases,[52] is also involved in the genesis of atherosclerosis[53] and triggers a vicious cycle: peroxynitrite reacts with the tyrosyl residue of proteins, thus inactivating superoxide dismutase, the enzyme responsible for catabolism of superoxide anion.[54] Oxidative stress mediated by superoxide anion and peroxynitrite also represents a powerful trigger of the mitochondrial pathway of apoptosis.[55] Apoptosis leads to denudation of the endothelium with further decrease in NO bioavailability.[53] These events are further aggravated by the vasoconstrictive effect of superoxide anion that can oxidize a cysteine residue in the active site of RhoA resulting in calcium sensitization.[56] Finally, NO, in addition to directly mediating



C

Placebo								
2.00 (-5.63, 9.63)	L-Arginine + PLC + NA							
3.55 (1.73, 5.37)	1.55 (-6.29, 9.39)	L-Arginine						
5.90 (-0.99, 12.79)	3.90 (-6.38, 14.18)	2.35 (-4.77, 9.47)	PLC					
6.04 (3.29, 8.78)	4.04 (-4.07, 12.14)	2.49 (-0.25, 5.23)	0.14 (-7.28, 7.55)	Tadalafil				
7.00 (-3.21, 17.21)	5.00 (-7.74, 17.74)	3.45 (-6.92, 13.82)	1.10 (-11.22, 13.42)	0.96 (-9.61, 11.54)	Myo-inositol + Folic acid			
9.49 (6.75, 12.22)	7.49 (-0.62, 15.59)	5.94 (3.20, 8.67)	3.59 (-3.83, 11.00)	3.45 (0.49, 6.41)	2.49 (-8.08, 13.06)	L-Arginine + Tadalafil		
10.00 (6.11, 13.89)	8.00 (-0.56, 16.56)	6.45 (2.16, 10.74)	4.10 (-3.81, 12.01)	3.96 (-0.79, 8.72)	3.00 (-7.92, 13.92)	0.51 (-4.24, 5.27)	Sildenafil	
15.60 (12.05, 19.15)	13.60 (5.19, 22.01)	12.05 (8.06, 16.04)	9.70 (1.95, 17.45)	9.56 (5.08, 14.05)	8.60 (-2.21, 19.41)	6.11 (1.64, 10.59)	5.60 (1.62, 9.58)	Sildenafil + ALC + PLC

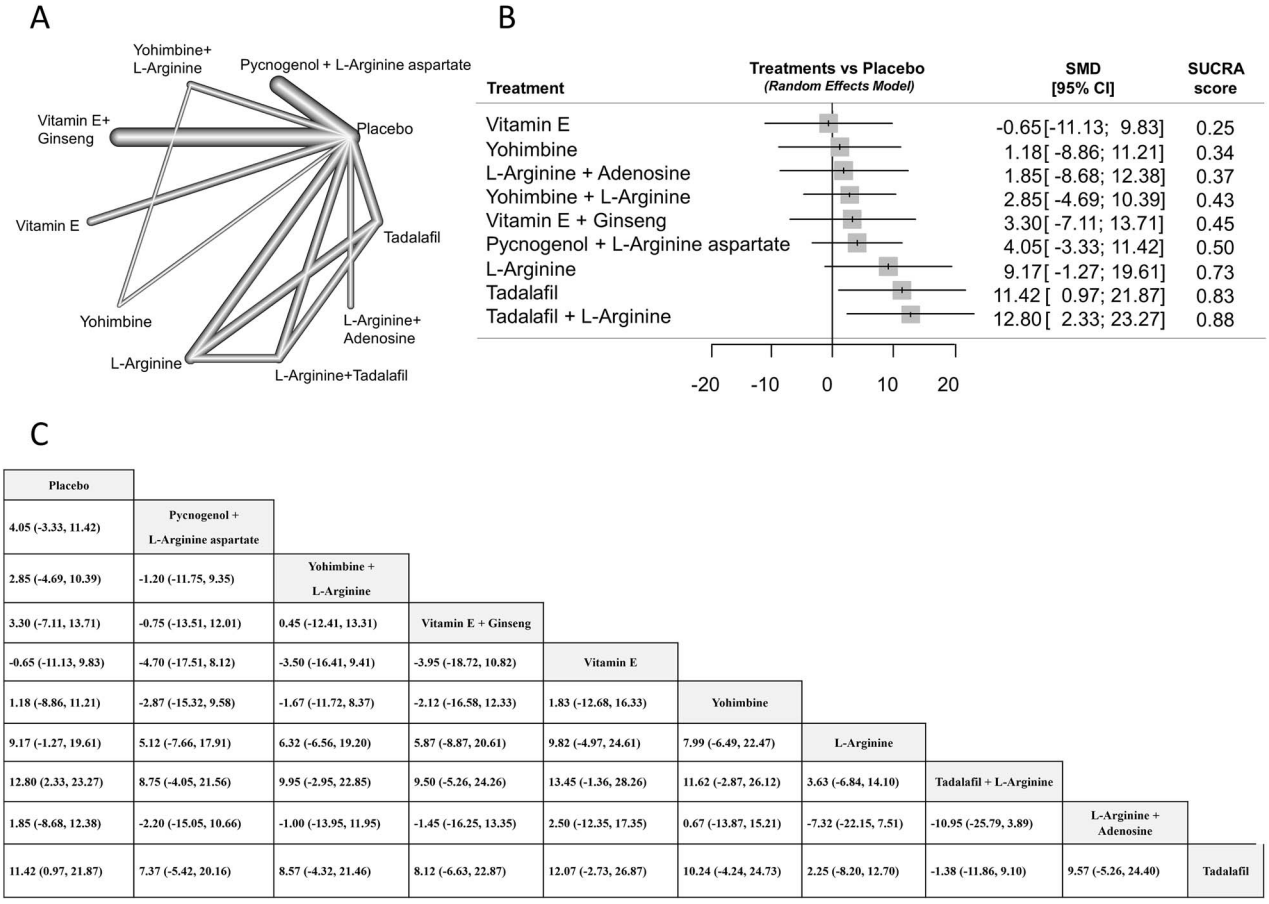
Figure 5. Subgroup analysis including studies on organic erectile dysfunction. The figure shows the network graph of direct comparisons assessed in the randomized controlled trials (A), the forest plot of standardized mean differences (SMD) in IIEF score between treatments and placebo (B), and the league table including all pairwise comparisons (C). Abbreviations: ALC, acetyl L-carnitine; IIEF, international index of erectile function; NA, nicotinic acid; PLC, propionyl L-carnitine; SUCRA, surface under the cumulative ranking curve.

the molecular pathway of the erectile response, also reduces the adhesion of platelets and leukocytes to endothelial cells. Therefore, when NO bioavailability is reduced, the activity of platelet- and leukocyte-derived vasoconstrictive agents, such as thromboxane A2 and leukotrienes, increases, which further worsens ED.[50]

On this basis, by different mechanisms, L-Arginine and carnitines may increase the bioavailability of NO, and thus cGMP generation, enhancing the therapeutic effect of PDE5i, especially in organic ED. Intriguingly, it has been reported that serum L-carnitine levels can be significantly lower in patients with ED nonresponders to PDE5i when compared with controls without ED.[57]

This study has some limitations. First, the included RCTs are quite heterogeneous in ED etiology (organic in 47% of studies), mean age of patients (38.3 to 61.4 years), and duration of treatment/follow-up (4 to 24 weeks). This variability could contribute to the high heterogeneity of the overall estimate in pairwise meta-analysis and does not allow to definitively provide indications regarding both the best candidate patient and duration of this kind of intervention. Another limitation is the variable dosage at which treatments were used in different studies. Subgroup analyses allowed us to downsize at least some of the limitations of this heterogeneity by suggesting which molecules may be most useful (PLC + ALC and L-Arginine) in which patients (organic ED). Furthermore, the strict inclusion criteria related to study design (only RCTs including a placebo arm) and diagnostic tool (IIEF-5 or -6 only) ensured that the assumption of transitivity was met, and the consistency of the analysis model was high. Unfortunately, the available studies cannot be categorized by ED severity because they enrolled populations with varying degrees of ED. Therefore, it is not possible to determine whether the findings of this NMA are applicable regardless of the ED degree. Finally, the risk of bias across included studies, with some RCTs categorized as having a high or unclear risk, emphasizes the need to interpret these results with caution.

In conclusion, our NMA contributes valuable insights into the potential of nutraceutical interventions for ED. L-Arginine and the mix PLC + ALC appeared to be of some usefulness in improving erectile function, especially in combination with PDE5i in organic ED. On the contrary, in nonorganic forms of ED, nutraceuticals did not improve the therapeutic performance of daily Tadalafil. Although doses and duration of treatments remain to be defined, considering the ineffectiveness of most nutraceutical preparations investigated in the available RCTs, these results may help select the few molecules worthy of further investigation in future prospective studies.



Placebo									
4.05 (-3.33, 11.42)	Pycnogenol + L-Arginine aspartate								
2.85 (-4.69, 10.39)	-1.20 (-11.75, 9.35)	Yohimbine + L-Arginine							
3.30 (-7.11, 13.71)	-0.75 (-13.51, 12.01)	0.45 (-12.41, 13.31)	Vitamin E + Ginseng						
-0.65 (-11.13, 9.83)	-4.70 (-17.51, 8.12)	-3.50 (-16.41, 9.41)	-3.95 (-18.72, 10.82)	Vitamin E					
1.18 (-8.86, 11.21)	-2.87 (-15.32, 9.58)	-1.67 (-11.72, 8.37)	-2.12 (-16.58, 12.33)	1.83 (-12.68, 16.33)	Yohimbine				
9.17 (-1.27, 19.61)	5.12 (-7.66, 17.91)	6.32 (-6.56, 19.20)	5.87 (-8.87, 20.61)	9.82 (-4.97, 24.61)	7.99 (-6.49, 22.47)	L-Arginine			
12.80 (2.33, 23.27)	8.75 (-4.05, 21.56)	9.95 (-2.95, 22.85)	9.50 (-5.26, 24.26)	13.45 (-1.36, 28.26)	11.62 (-2.87, 26.12)	3.63 (-6.84, 14.10)	Tadalafil + L-Arginine		
1.85 (-8.68, 12.38)	-2.20 (-15.05, 10.66)	-1.00 (-13.95, 11.95)	-1.45 (-16.25, 13.35)	2.50 (-12.35, 17.35)	0.67 (-13.87, 15.21)	-7.32 (-22.15, 7.51)	-10.95 (-25.79, 3.89)	L-Arginine + Adenosine	
11.42 (0.97, 21.87)	7.37 (-5.42, 20.16)	8.57 (-4.32, 21.46)	8.12 (-6.63, 22.87)	12.07 (-2.73, 26.87)	10.24 (-4.24, 24.73)	2.25 (-8.20, 12.70)	-1.38 (-11.86, 9.10)	9.57 (-5.26, 24.40)	Tadalafil

Figure 6. Subgroup analysis including studies on nonorganic erectile dysfunction. The figure shows the network graph of direct comparisons assessed in the randomized controlled trials (A), the forest plot of standardized mean differences (SMD) in IIEF score between treatments and placebo (B), and the league table including all pairwise comparisons (C). Abbreviations: IIEF, international index of erectile function; SUCRA, surface under the cumulative ranking curve.

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Author contributions

A.B.: Conceptualization-Lead, Data curation-Equal, Formal analysis-Lead, Investigation-Equal, Methodology-Lead, Project administration-Equal, Validation-Lead, Visualization-Equal, Writing–original draft-Lead, Writing–review & editing-Equal. D.T.: Conceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Methodology-Equal, Project administration-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal. F.A.: Data curation-Equal, Methodology-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal. L.S.: Data curation-Equal, Methodology-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal. F.C.: Data curation-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal. A.B.D.P.: Data curation-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal. M.M.: Data curation-Equal, Methodology-Equal, Project administration-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal. G.C.: Conceptualization-Equal, Data curation-Equal, Methodology-Equal, Project administration-Equal, Validation-Equal, Visualization-Equal, Writing–review & editing-Equal.

Supplementary material

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Conflicts of interest

None declared.

Data availability

The authors confirm that data supporting the findings of this study are available within the article and its supplementary materials.

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