

Review

Effectiveness of Ginseng, Rutin and Moringa for the Treatment of Erectile Dysfunction: A Systematic Review

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Abstract: **Introduction,** The aim of this systematic review was to evaluate the current evidence for the effectiveness of ginseng, Rutin and Moringa for treating erectile dysfunction. **Methods,** A broad search of the Scopus, PubMed, Cochrane and Web of Science databases was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The following criteria were required for articles to be included in the review: English language; observational studies (cohort studies, case control/comparative studies, single-arm studies); randomized controlled trials; non-randomized comparative studies; case series; number of participants: ≥ 5 for case series or ≥ 5 patients per group for comparative studies. The Cochrane risk of bias (RoB) assessment tool for RCTs was used to assess the risk of bias of included studies. **Results,** Seven full-text articles were included in this review. All studies were randomized controlled trials. No studies on Rutin and Moringa alone matched the inclusion criteria. The methodological quality of the RCTs was variable. In all studies, the group treated with ginseng reported an improvement of erectile function (EF) compared to the control groups. IIEF and IIEF-5 were used to evaluate erectile function in six studies and in four of them, the improvement of the scores in the group treated with ginseng over the control group reached the statistical significance. **Conclusion,** This review suggests a positive effect of ginseng on EF in men. The association of ginseng along with other nutritional components with potential beneficial effects on ED appears promising and deserves further investigation in large randomized controlled trials.

Keywords: erectile function; ginseng; systematic review; erectile dysfunction

1. Introduction

Erectile dysfunction (ED) is defined as the inability to attain and maintain an erection firm enough to permit a satisfactory sexual intercourse [1]. Epidemiological data shows a high prevalence and incidence worldwide [2]; projections show that ED might affect up to 322 million men by 2025 [3]. The impact of ED on men's quality of life (QoL) and self-esteem increases the incidence of depression and interpersonal relationship problems in affected patients [4]. Moreover, ED is considered as an early manifestation of coronary artery and peripheral vascular disease; therefore, it should not be regarded as a QoL issue only, but also as a potential warning sign of future general health issues [5,6].

Currently available treatment options for ED include oral medication (phosphodiesterase type 5 inhibitors (PDE5is)), the use of alprostadil both as intracavernous injections or urethral suppository, vacuum devices and surgical treatment with penile prosthesis implantation. Despite the wide range of treatment options for ED, patients often are unsatisfied by the proposed therapy [7]. Lack of efficacy, bothersome adverse effects and costs are among the most frequently reported reasons for treatment dissatisfaction and drop-out [8]. For this reason, the use of alternative treatments for ED, including herbal remedies and dietary supplements, is increasing, particularly through over the counter and internet sources [9].

One of the most widely used dietary supplements in sexual medicine is ginseng. Panax ginseng, specifically red ginseng, has been used in traditional Chinese medicine practice [10,11] as an aphrodisiac to improve sexual performance. Indeed, ginseng has turned into a popular global herbal supplement for male sexual performance and ED [12] due to its contribution to smooth muscle relaxation of the corpus cavernosum via the nitric oxide (NO) pathway and its testosterone-like effects [13].

Moringa oleifera has been reported to have antioxidant, hypoglycemic and anti-dyslipidaemia activities [14], while Rutin has shown antioxidant activity and it can inhibit phosphodiesterase type 5, increasing the availability of NO and cGMP. Sulfarol[®] (Bussolengo, Italy) is a food supplement composed of Nutriseox (Panax ginseng root 10%, Moringa oleifera 20% and Rutin) that has been recently investigated in men with ED.

Preliminary data have shown that Sulfarol might improve erectile function (EF) when used in combination with PDE5is in men with ED [15]. However, data on the effect of each component on EF are scarce.

Our hypothesis was that the use of ginseng with Rutin and Moringa may improve the erectile function with or without the use of PDE5 inhibitors. We aimed to evaluate the current literature on the three different treatments.

We performed a systematic review of the current literature to evaluate the current knowledge on the effect of Sulfarol's components on ED.

2. Materials and Methods

2.1. Search Strategy

A broad search of the Scopus, PubMed, Cochrane and Web of Science databases was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16]. The search strategy involved articles reporting on EF and Sulfarol[®] (Bussolengo, Italy) components (ginseng, Moringa and Rutin) up to November 2021. The Medical Subject Headings (MeSH) terms applied for the research were "Erectile Dysfunction"; "Erectile Function"; "Male Sexual Function"; "Ginseng"; "Rutin"; "Moringa". No restrictions in the search of the relevant literature were imposed with respect to the prospective or retrospective design of studies.

2.2. Study Selection

Four reviewers (PC, LB, CM and GR) screened the results of the literature search. Duplicates were deleted using titles and abstracts. The references and full texts of hypothetically appropriate literature were examined for further screening as recommended in the PRISMA guidelines [16].

2.3. Inclusion and Exclusion Criteria

The following criteria were required to be included in the review: English language; observational studies (cohort studies, case control/comparative studies, single-arm studies); randomized controlled trials; non-randomized comparative studies; case series; number of participants: ≥ 5 for case series or ≥ 5 patients per group for comparative studies. We excluded reviews, editor letters, single case report, non-English language publications, and papers on animal models.

2.4. Data Extraction

Four review authors (PC, MR, LB, CM) autonomously extracted data from the text of included papers using a predefined data collection form developed according to the study outcomes. Any disagreement was resolved by discussion.

The primary outcome of interest was to evaluate the effects of each component of Sulfarol[®] (Bussolengo, Italy) on the EF as assessed with either validated questionnaires or single questions. As a secondary outcome, treatment-related adverse events were considered.

2.5. Assessment of the Risk of Bias

Three independent reviewers (LB, CM, MR) assessed the risk of bias using the Cochrane risk of bias (RoB) assessment tool for RCTs [17].

3. Results

An initial selection of 146 articles was considered. After the exclusion of review articles, duplicates, conference abstracts, and non-English abstracts, 67 abstracts were selected for further evaluation. After a comprehensive screening process, 12 full text articles were eligible. Five studies were excluded (non-English full text) and seven full-text articles were finally included in this review, according to the aforementioned inclusion criteria. Figure 1 represents the PRISMA flowchart.

3.1. Risk of Bias and Methodological Quality

A summary of the risk of bias assessment is reported in Table 1. Six studies presented random sequence generation and blinding of both participants and personnel. Regarding the primary outcome, all studies were at low risk of bias. Overall, the methodological quality of the included RCTs was variable. The method of randomization was described just in one trial, as was the method of double blinding. Three trials described details of dropout rates and withdrawals. Dropout rates extended from 0% to 25%. Only Farnia et al. [18] reported details on allocation concealment.

Table 1. RoB Assessment.

| Author | Year | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Incomplete Outcome Data | Selective Reporting | Other Bias |
|------------|------|----------------------------|------------------------|--|-------------------------|---------------------|--------------------|
| Kim | 2009 | No | No | Yes | No | No | No |
| Choi | 2012 | Yes | Unclear | Yes | No | No | No |
| de Andrade | 2007 | Yes | Unclear | Yes | No | No | No |
| Hong | 2002 | Yes | Unclear | Yes | No | No | No |
| Farnia | 2019 | Yes | Yes | Yes | No | No | No |
| Choi | 1995 | Yes | Unclear | NR | No | No | IIEF not evaluated |
| Mirone | 2021 | Yes | Unclear | Yes | No | No | No |

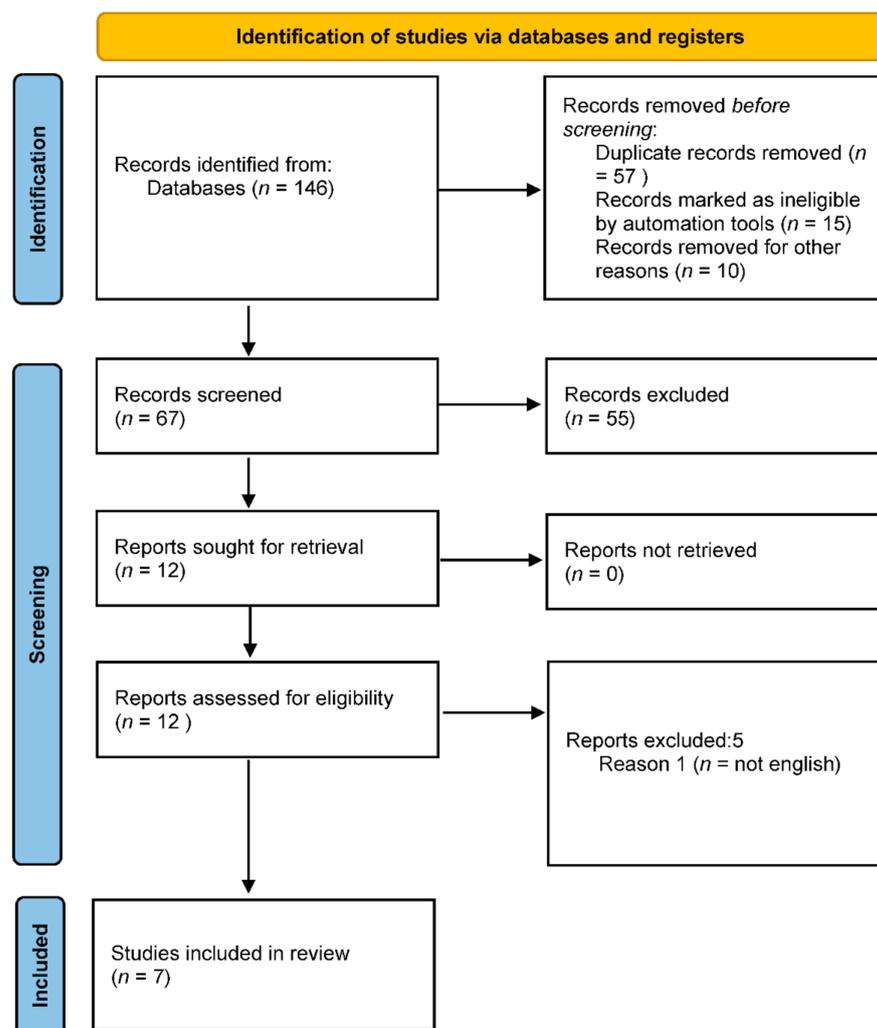


Figure 1. PRISMA checklist.

3.2. Study Characteristics

The search identified seven prospective clinical trials and key data from included papers are summarized in Table 2. No studies on Rutin and Moringa alone matched the inclusion criteria; all included studies focused on ginseng and one [15] examined the combination of nutritional supplements composed by ginseng, Moringa, and Rutin and Tadalafil 5 mg.

Two studies were multicenter and five were single center studies. Overall, 596 men aged 26 to 70 years old were evaluated in the selected studies. Treatment duration ranged from 4 to 12 weeks, while the dose of ginseng varied from 1000 to 3000 mg per day mostly divided in three oral administrations. Most trials were not specific on the etiology of ED, but excluded patients with organic ED due to previous pelvic surgery and spinal cord injuries. The individual outcome measures were the International Index of Erectile Function (IIEF) for all studies except for Choi et al. (1995) [19], where no index was scored and the author made structural interview questionnaires related to EF (without testing reliability). All baseline IIEF-EF domain scores classified ED as mild or moderate in most cases. Hong et al. [20] used Duplex sonography and RigiScan in addition to IIEF to evaluate the EF.

Table 2. a: main study characteristics; b: main study outcomes. Legend: NR = Not Reported.

| a: Main Study Characteristics | | | | | | | | | | | | | |
|-------------------------------|------|--|--|--|--|-----------------------------|---|---|-------------------------------------|--------------------------------|---------|-----------------------|---|
| Author | Year | Number of Centers | Type of Center | Country | Study Design | Time Point for Outcome | Tool Use to Assess Erectile Function | N of Patients (Total Cohort) | Mean/Median Age of Patients (Range) | | | | |
| Kim | 2009 | Single | University Hospital | Korea | Prospective | 8 weeks | IIEF-5 | 143 | 58.1 (33–79) | | | | |
| Choi | 2012 | Multicenter | University Hospital | Korea | Prospective | 4/8 weeks | IIEF-5 | 118 | 57.5 (7.9) | | | | |
| de Andrade | 2007 | Single | University Hospital | Brazil | Prospective | 12 weeks | IIEF-5 | 60 | 52.6 (26–70) | | | | |
| Hong | 2002 | Single | University Hospital | Korea | Prospective | 8 weeks | IIEF-duplex sonography-RigiScan | 45 | 54 | | | | |
| Farnia | 2019 | Single | University Hospital | Iran | Prospective | 4 weeks | IIEF-BSFI | 54 | 38.25 | | | | |
| Choi | 1995 | Single | University Hospital | Korea | Prospective | 12 weeks | NR | 90 | 45 (26–70) | | | | |
| Mirone | 2021 | Multicenter | University Hospital | Italy | Prospective | 12 weeks | IIEF-5 | 86 | 59.98 (38–69) | | | | |
| b: Main Study Outcomes. | | | | | | | | | | | | | |
| Author | Year | Baseline IIEF-EF Mean (Range)-INTERVENTION | Baseline IIEF-EF Mean (Range)-COMPARATOR | IIEF-EF Mean (Range)-INTERVENTION | IIEF-EF Mean (Range)-COMPARATOR | p-Value | Baseline IIEF-5 Mean (Range)-INTERVENTION | Baseline IIEF-5 Mean (Range)-COMPARATOR | IIEF-5 Mean (Range)-INTERVENTION | IIEF-5 Mean (Range)-COMPARATOR | p-Value | Adverse Events | Limitations |
| Kim | 2009 | 11.0 | 11.9 | 16.4 (±7.1) | 13 (±4.2) | 0.01 | 11.0 (±5.1) | 11.9 (±4.4) | 15.3 (±6.1) | 13.5 (±4.4) | 0.06 | 3 (minor headaches) | No random sequence generation and no allocation concealment |
| Choi | 2012 | 14.3 | 14.6 | 4 weeks: 17.7 (4.7); 8 weeks: 18.6 (5.9) | 4 weeks: 16.3 (5.3); 8 weeks: 18.0 (5.1) | 4 weeks: 0.06; 8 weeks: 0.5 | 14.3 (±1.8) | 14.6 (±1.8) | NR | NR | NR | 0 | Unclear allocation concealment |
| de Andrade | 2007 | 16.4 (±2.9) | 17.0 (±3.1) | NR | NR | NR | 16.4 (±2.9) | 17.0 (±3.1) | 21.0 (±3.3) | 17.7 (±5.6) | <0.01 | 3 (headache-insomnia) | Unclear allocation concealment |
| Hong | 2002 | 8.93 (±6.14) | 8.93 ± 6.14 | 38.13 (±16.64) | 30.92 (±15.67) | 0.01 | 8.93 (±6.14) | 8.93 (±6.14) | 12.70 (± 6.38) | 10.33 (5.46) | <0.01 | 0 | Unclear allocation concealment and crossover studio |

Table 2. Cont.

| b: Main Study Outcomes. | | | | | | | | | | | | | |
|-------------------------|------|--|--|-----------------------------------|---------------------------------|-----------------|---|---|----------------------------------|--------------------------------|-----------------|-----------------------------|---------------------------------|
| Author | Year | Baseline IIEF-EF Mean (Range)-INTERVENTION | Baseline IIEF-EF Mean (Range)-COMPARATOR | IIEF-EF Mean (Range)-INTERVENTION | IIEF-EF Mean (Range)-COMPARATOR | <i>p</i> -Value | Baseline IIEF-5 Mean (Range)-INTERVENTION | Baseline IIEF-5 Mean (Range)-COMPARATOR | IIEF-5 Mean (Range)-INTERVENTION | IIEF-5 Mean (Range)-COMPARATOR | <i>p</i> -Value | Adverse Events | Limitations |
| Farnia | 2019 | NR | NR | 15.14 (±3.99) | 12.04 (±2.46) | NR | NR | NR | NR | NR | NR | 4 (sleeplessness agitation) | No statistical results |
| Choi | 1995 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | No standardized outcome measure |
| Mirone | 2021 | 13.18 (±7) | 14.15 (±6.4) | NR | NR | NR | 13.18 (±3.75) | 14.15 (±5) | 20.48 (±2.24) | 14.15 (±4.4) | <0.01 | 20 (headache flushing) | Unclear allocation concealment |

3.3. Erectile Function Outcomes

Therapeutic efficacy (i.e., EF improvement) was reported in all studies comparing ginseng with placebo and all favored ginseng (see Table 2). Improvement of IIEF ranged from 2 to 7 points, obtaining statistical significance in four trials [13,15,20,21]. Choi et al., using a self-produced questionnaire, also reported improvement of EF after administration of ginseng. Overall, adverse effects were mild and were reported in six studies (Table 2).

4. Discussion

The results of this review suggest that ginseng is better than placebo in handling ED. Moreover, the combination of ginseng along with other supplements such as moringa and Rutin appears promising. Nevertheless, the number of reports and the sample size are low; therefore, definitive conclusions cannot be drawn.

Despite the successful advent of PDE5is for treating ED, their long-term use is affected by a significant dropout rate [22] due to either adverse events or treatment costs and many patients with mild ED are unenthusiastic to use PDE5is and would rather choose phytotherapy over medication or more invasive treatments. Alternative treatments that can improve sexual function research have focused on ginseng, which has been widely used in Asian countries to promote several health aspects [23]. To date, ginseng is one of the most appealing choices for ED in the field of complementary and alternative medicine, rarely presenting side effects [23]. However, the optimum therapeutic dose of ginseng is still unknown and the availability and quantity of the many constituents in the preparation is unclear. In our review, included studies were heterogeneous in terms of dosage and modality of administration of ginseng. Moreover, except for Choi et al. [19], no one reported details on the method of component extraction. Nevertheless, results seem encouraging since significant improvement of EF after administration of ginseng was reported by six of over seven included studies, irrespective of dosage and timing of outcome measurement. Only Farnia et al. [18] did not report EF improvement; of note, their study was designed to evaluate overall sexual function, which was improved without a specific evaluation of EF. Kim et al. [21] evaluated 143 patients after 8 weeks of ginseng administration against placebo and reported significantly higher scores in all the five domains of the IIEF in the treated group, while no significant improvement was detected in the placebo group. De Andrade et al. [13] reported similar findings with an important improvement in total score (IIEF-5 score), particularly for questions 3 and 5 within the treated group. Additionally, Choi et al. [24] reported significant improvement with an increase of the IIEF-EF domain from 17.17 ± 2.57 to 18.59 ± 5.99 in the treatment group by the 8th week. Among other variables, Hong et al. [20] reported significant improvement of penile tip rigidity on RigiScan for ginseng versus placebo. Probable mechanisms of action of ginseng include hormonal testosterone-like effects; however, three studies [13,15,20] assessed levels of serum prolactin cholesterol and testosterone after treatment without noting statistically significant differences between the groups ($p > 0.05$), leaving this aspect open to further research.

Moringa oleifera has been used extensively in traditional medicine. Two studies [14,25] have reported its antioxidant, hypoglycemic, anti-dyslipidemia, analgesic, antihypertensive and immunomodulatory activities. Rutin has antioxidant activity and it has been shown that, in vitro, Rutin is able to inhibit PDE5 and arginase, increasing the availability of NO and cGMP [26,27]. Unfortunately, there is a lack of clinical studies investigating the effects of Rutin and Moringa on ED men. In the study by Mirone et al. [15], the use of Sulfarol in combination with PDE5i against PDE5i alone was investigated, reporting a statistically significant improvement of IIEF-5 for the combination group ($p < 0.005$). From a biological standpoint, this effect on EF might be related to nutritional supplement properties that enhance endothelial NO and cGMP production. Overall, six studies [13,15,18,20,21,24] reported mild adverse effects in the treatment arm: 26 cases of headache or insomnia and four cases of agitation. On the other hand, 20 cases of adverse effects occurred in the placebo group, but it is necessary to underline that 18 of them were related to the administration of tadalafil in one study [15].

4.1. Limitations

This review has several limitations; the most relevant is that we cannot be certain that our research was able to locate all relevant randomized clinical trials in the literature since there are several non-English language papers. Moreover, it is plausible that various negative RCTs have stayed unpublished since some studies were funded by manufacturers or did not specify the funding source, which may have presented a degree of bias. Even though all trials used placebo controls, none described the success of blinding. Moreover, only one trial reported the concealment of treatment allocation. Inadequate blinding and inadequate allocation concealment may lead to selection bias and are likely to show overstated results. Certain studies inadequately described the outcome in their articles without providing statistical significance.

4.2. Recommendations

In the evaluation and treatment of erectile dysfunction, the use of phytotherapy is reliable and may improve the outcome without being burdened by heavy side effects. Indeed, ginseng appears to be safe and effective in the initial management of mild ED, being a useful tool in the hands of the clinician especially for patients that are reluctant to start a proper pharmacologic therapy.

5. Conclusions

This review suggests a positive effect of ginseng on EF in men. The association of ginseng along with other nutritional components with potential beneficial effects on ED appears promising and deserves further investigation in large randomized controlled trials.

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