Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
https://www.plantsjournal.com
JMPS 2023; 11(4): 34-38

Received: 24-06-2023
Accepted: 18-07-2023

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The effectiveness of *Withania somnifera* supplementation on male sexual health: A systematic review of randomized clinical trials

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Abstract
This review aims to critically evaluate the existing evidence derived from randomized clinical trials to determine the effectiveness of *W. somnifera* (ashwagandha) in enhancing male sexual health outcomes. Extensive searches were conducted in databases including PubMed, Library of Congress, JISC Library, ClinicalTrials.gov, mRCT, Google Scholar, Embase, Web of Science, CINAHL, Medline, and Cochrane. Among the initially identified 8,203 articles with potential relevance, a thorough assessment of full-text articles was performed, resulting in the inclusion of 5 studies that satisfied all predefined inclusion criteria. All included studies were evaluated as having a low risk of bias. Four of the included studies reported significant intergroup differences before and after intervention, thus providing support for the use of W. somnifera as a supplement to enhance male sexual health. However, despite these promising results obtained from clinical trials, the current evidence remains insufficient to firmly endorse the use of W. somnifera for its impact on male sexual health.

Keywords: *Withania somnifera*, ashwagandha, Indian ginseng, winter cherry

1. Introduction
Withania somnifera, commonly referred to as “ashwagandha” or “Indian ginseng,” belongs to the shrub family, *Solanaceae* [1]. The plant is known as Ashwagandha for the distinct wet horse smell of its roots. ‘Ashwa’ meaning horse and ‘gandha’ meaning smell [2]. This perennial herb is endemic to India, Baluchistan, Pakistan, Afghanistan, Sri Lanka, Congo, South Africa, Egypt, Morocco, Australia, and Jordan [1].
For thousands of years, various parts of this plant have been utilized in Ayurvedic and Indigenous medical practices [3]. It was reported as an official drug in Indian Pharmacopoeia in 1985 [4]. Pharmacological studies conducted with *W. somnifera* have demonstrated its anti-inflammatory, anti-stress, and immunomodulatory properties. Studies have also suggested that *W. somnifera* supplementation effects body systems such as the nervous, endocrine, and cardiovascular systems [4]. Studies in rats have demonstrated the ability of *W. somnifera* to treat neurodegenerative diseases [5]. Human clinical trials have demonstrated the effectiveness of *W. somnifera* in treating anxiety, depression, and sleep disorders [6].
Sexual health plays a crucial role in the overall well-being and quality of life of men. Throughout history, various traditional medicines have been used to enhance male sexual function and address sexual health concerns. Ashwagandha is one such herbal remedy that has gained significant attention for its potential benefits in improving male sexual health. Understanding the potential impact of *Withania somnifera* on male sexual health is of great significance, as it may offer a natural and holistic approach to address sexual dysfunction and enhance overall sexual well-being.
The aim of this review is to conduct a thorough critical evaluation of the existing randomized clinical trials that investigate the effects of Ashwagandha on male sexual health. This review will provide a comprehensive evaluation of the potential benefits and limitations of *Withania somnifera* in improving various aspects of male sexual health, including erectile function, libido, fertility, and overall sexual satisfaction. The methodology employed in this systematic review ensures that the findings are based on rigorous scientific evidence and provide a balanced perspective on the effectiveness of *Withania somnifera* supplementation by focusing on methodology, standardization, and quality control. By analyzing and consolidating the results of multiple clinical trials, more reliable conclusions and informed recommendations can be made for both researchers and healthcare practitioners.

This review will emphasize the significance of undertaking meticulously designed, randomized clinical trials to establish both the safety and efficacy of *W. somnifera*.

2. Methods

2.1 Search strategy

In June 2023, a comprehensive search was conducted across various electronic databases, including CINAHL, Medline, Cochrane, ClinicalTrials.gov, mRCT, Google Scholar, Embase, Web of Science, PubMed, Library of Congress, and JISC Library. The search aimed to identify articles with specific terms ('*Withania somnifera*,' 'ashwagandha,' and 'Indian ginseng') in their titles or abstracts. To refine the search, articles with the words 'rats' or 'mice' in their titles were excluded. Additionally, the search parameters required the presence of the phrase 'clinical trial' anywhere in the text.

A manual scoping search was conducted across major electronic databases. Experts in the field of herbal medicine and clinical researchers specializing in dietary supplementation were contacted to uncover any unpublished material that might contribute to the research.

2.2 Inclusion criteria

Randomized clinical trials that evaluated the effectiveness and efficacy of *W. somnifera* supplementation for treating ailments related to male sexual health were included. The trials had to compare *W. somnifera* supplementation against a control group (placebo, active control, or no treatment). Trials utilizing any active ingredient in addition to *W. somnifera* were excluded. After removing duplicates using EndNote 20 software [7] the titles and abstracts of studies were screened. Studies that met the inclusion criteria were reviewed in full by two independent reviewers. A study was included if both reviewers agreed that it fulfilled all the inclusion criteria.

2.3 Data retrieval and analysis

All relevant articles were managed and organized using EndNote 20 software [7]. The data, including study design, study quality, participant details, intervention methods, outcomes, and adverse events, were extracted and discussed by the reviewers based on predefined criteria.

Each study was independently assessed by two reviewers using the Cochrane risk-of-bias tool for randomized trials [8] the CONSORT statement [9] and the Jadad Scale [10] (Table 2). Key data from each study were summarized in Table 1. Any discrepancies between the two reviewers were resolved by a third reviewer.

3. Results

The database and manual searches conducted in this study yielded a total of 8,203 potentially relevant journal articles. After removing duplicates and conducting initial screenings of titles and abstracts, 7 articles were identified as potentially relevant. The full texts of all 7 articles were retrieved and thoroughly reviewed. Among them, 2 articles were excluded from the analysis due to a lack of randomization [11, 12]. Figure 1 provides a visual representation of the selection process. 5 randomized clinical trials were found to meet the predefined criteria and were included in this review [13-17].

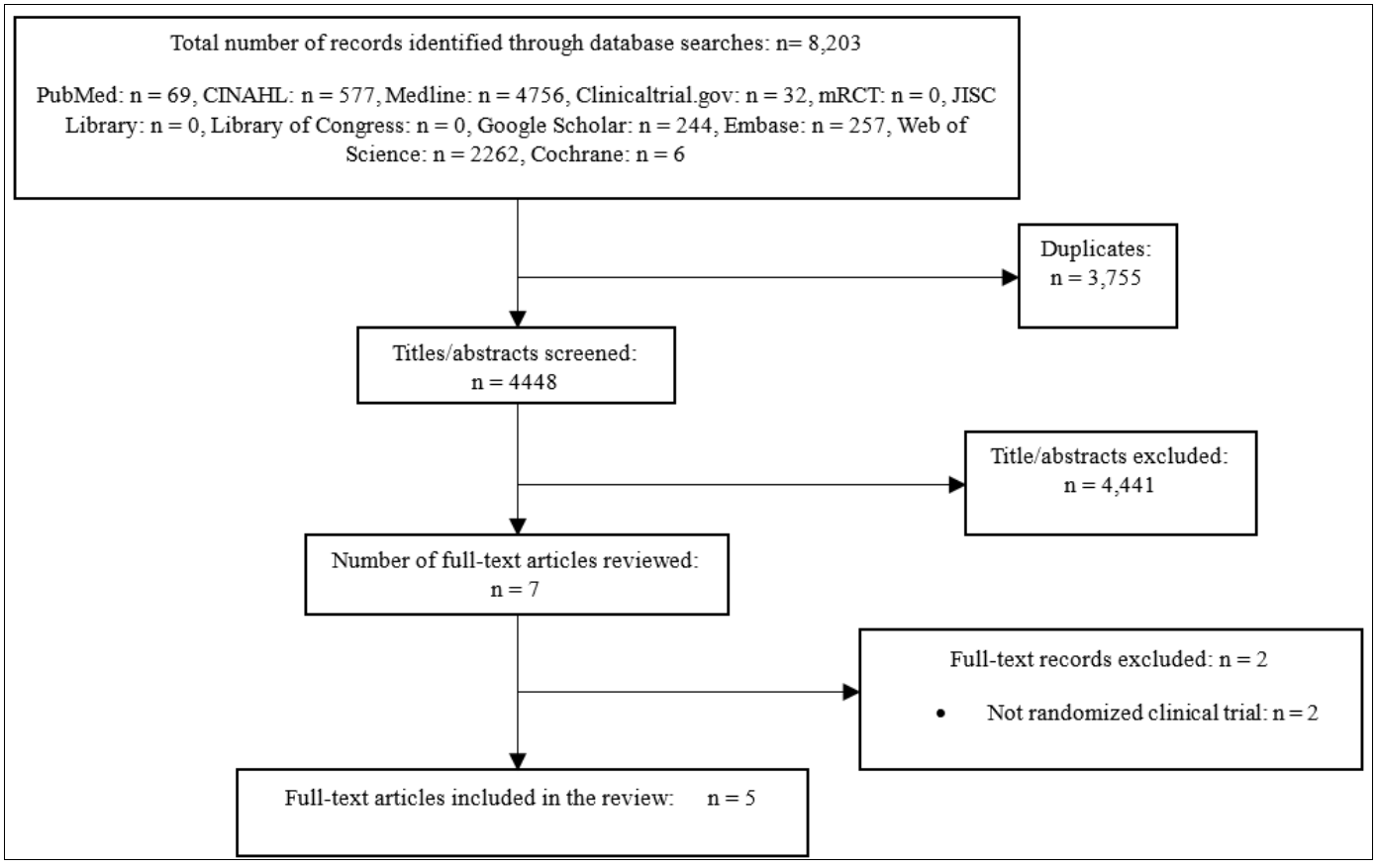

Fig 1: Chart depicting the selection process for inclusion.

Figure 1: Flowchart illustrating the selection process for inclusion in the review. A total of 8,203 articles were identified through database searches. After the removal of duplicates and review of titles, abstracts, and full texts, 5 articles were found to meet the criteria

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Table 1: Randomized placebo-controlled trials of *Withania somnifera*

First Author (Year)	Design	Condition	Sample Size (Treatment/ Control), (Age Range)	Treatment	Control	Treatment period	Main Outcome Measures	Between-Group Analysis	Adverse Events/Dropouts
Ambiye, V. (2013) [13]	Double-blind; placebo-controlled; 2 parallel groups	Low sperm count	46, (21/25), (22-40)	225 mg of *W. somnifera*; three times a day	Placebo	12 weeks	(1) Semen parameters (2) Serum hormone levels	There was a substantial significant increase in sperm concentration, semen volume, and sperm motility in the treatment group. There was a significant increase in testosterone and luteinizing hormone in the treatment group.	None; None
Chauhan, S. (2022) [14]	Double-blind; placebo-controlled; 2 parallel groups	Low sexual desire	50, (25/25), (21-45)	300 mg of *W. somnifera*; twice a day	Placebo (maize starch powder)	8 weeks	(1) DISF- M questionnaire (2) Hormonal assessment (3) SF-36 questionnaire	There was a statistically significant improvement in the DISF-M questionnaire and testosterone levels in the treatment group. Improvement in the SF-36 questionnaire in the treatment group were not significant.	7; 0 (3 discontinued treatment but were included in the analysis)
Lopresti, A. (2019) [15]	Double-blind; placebo-controlled; crossover	Overweight (hormone levels and vitality)	57, (29/28), (40-70)	21 mg of *W. somnifera*; once a day	Placebo (roasted rice powder)	8 weeks of treatment (16 total)	(1) Symptomatic changes (2) hormonal changes	8 weeks of supplementation demonstrated an improvement in salivary DHEA-S and testosterone. Supplementation had no significant effect on fatigue, vigour, or sexual or psychological well-being.	None; 14
Mamidi, P. (2011) [16]	Single-blind; placebo-controlled; 2 parallel groups	Erectile dysfunction	95, (46/49), (18-60)	2 g of *W. somnifera*; 3 times a day	Placebo (wheat powder)	60 days	International Index of Erectile Function scores	There was no significant difference between *W. somnifera* and placebo supplementation.	None; 9
Rashidi, M. (2020) [17]	Double-blind; placebo-controlled; 2 parallel groups	Semen disorders (number/motility)	60, (30/30), (18-45)	1 g of *W. somnifera*; 5 times a day	Placebo	12 weeks	Semen performance scores	Supplementation with *W. somnifera* significantly increased semen performance and sperm motility compared to control.	None; None

Table 1: Table 1 presents a comprehensive overview of the crucial data extracted from each study included in the analysis.

Table 2: Methodological quality of trials

First Author (Year)	Was the allocation sequence random?	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Domain 1: Risk-of-bias judgement	Were participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Were there deviations from the intended intervention that arose because of the trial context?	Were these deviations likely to have affected the outcome?	Were these deviations from the intended intervention balanced between groups?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	Domain 2: Risk-of-bias judgement	Items met from the Checklist of Items for Reporting Randomized, Controlled Trials (n=25)	Jadad Scale Rating
Ambiye, V. (2013) [13]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	13	2
Chauhan, S. (2022) [14]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	25	5
Lopresti, A. (2019) [15]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	25	5
Mamidi, P. (2011) [16]	Yes	Yes	No	Low risk	No	Yes	No	N/A	N/A	Yes	N/A	Low risk	18	1
Rashidi, M. (2020) [17]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	17	4

Table 2: Table 2 presents an evaluation of the methodological quality of the clinical trials included in this review. The assessment of methodological quality was conducted using established tools, including the Cochrane risk-of-bias tool,[8] the CONSORT statement,[9] and the Jadad Scale.[10]

Table 1 summaries the main characteristics of all included studies. All the included studies were published in English during the years 2011-2022. There are three countries represented in the selected articles: India, [13, 14, 16] Iran [17] and Australia [15]. The ages of participants ranged from 18-70 with a total of 308 participants [13-17]. Only one study was single-blind [16]. One study did not utilize parallel groups and instead was a cross-over study [15]. Three studies identified the contents of the placebo: wheat powder, roasted rice powder, and maize starch powder [14-16]. The cross-over study had the longest trial period with each treatment being taken for 8 weeks each [15].

3.1 Semen performance
Two studies yielded results pertaining to the performance of patients' semen [13, 17]. One study found a substantial increase in sperm concentration, semen volume, and sperm motility in the treatment group. All these increases were highly significant ($p< 0.0001$) [13]. The other study also found that there was a significant increase in semen performance (Number and motility) [17].

3.2 Hormone levels
Three of the studies assessed the effect of *W. somnifera* on hormone levels. [13-15] One study found a significant increase in luteinizing hormones in the treatment group [13]. All three studies found a significant increase in the levels of testosterone in the treatment group compared to the control. [13-15] One study found supplementation demonstrated an improvement in salivary DHEA-S [15].

3.3 Erectile function
Two studies examined the ability of *W. somnifera* supplementation to treat erectile function [14, 16]. One study used the International Index of Erectile Function scores [16] and the other used a DISF- M questionnaire [14] to determine erectile function. One study found statistically significant improvements in scores [14] while the other found no significant difference between groups [16].

3.4 Sexual desire and overall well-being
Two studies measured the effect of *W. somnifera* supplementation on overall well-being, including sexual desires [14, 15]. Both studies utilized self-report questionnaires, SF-36[14] and POMS-SF [15]. One study found significant improvements in the SF-36 questionnaire [14] while the study utilizing the POMS-SF found no significant difference [15].

3.5 Adverse events
Only two studies reported dropouts that were not included in the statistical analysis.[15,16] There was a total of 7 adverse events between all included studies.[14] All adverse events were observed within the same study.[14] 3 out of the 7 adverse events found in this study discontinued treatment but were still included in the analysis.[14] Four of the adverse events were reported in subjects assigned to the *W. somnifera* treatment: two subjects experienced sleepiness, one developed mild abdominal pain, and one subject developed joint pain.[14]

4. Discussion
A total of 5 randomized clinical trials of *W. somnifera* met the inclusion criteria of this review [13-17]. By PRISMA [18] the Cochrane risk-of-bias tool [8] was applied to all included studies. All trials [13-17] were determined to have a low risk of bias [8]. Trials are considered to be of good methodological quality if they receive 3 or more points on the Jadad scale [10]. Only three studies [14, 15, 17] met this threshold while two of those received the maximum score of 5 [14, 15]. Two studies [14, 15] met all of the items in the CONSORT statement [9]. Three studies met less than 20 items, [13, 16, 17] with the lowest being 13 [13].

The results of this review demonstrate that *W. somnifera* supplementation may have a positive impact on sexual function and enhance overall sexual well-being [13-15, 17]. However, results are not consistent across all studies as there was one study that reported no significant differences between the treatment and control groups [16]. With the majority of the studies reporting profound positive results, *W. somnifera* supplementation must be evaluated much further. The effect of *W. somnifera* on male testosterone is promising with three trials reporting significant improvements [13-15]. There is potential for *W. somnifera* to treat low testosterone related ailments, and this must be studied further.

W. somnifera is regarded as a stress reducing agent in forms of Indigenous medicines [4] and is advertised as a key ingredient in relaxation supplements. Only one study examined the effect of supplementation on stress related erectile dysfunction and there were no significant improvements [16]. There is evidence to support the existence of a positive correlation between erectile dysfunction and stress levels [19]. Men that are able to reduce or manage their daily stress levels have been able to improve their erectile function [20]. If *W. somnifera* is effective in reducing stress levels, there is a potential for it to help alleviate stress related erectile dysfunction. This relationship should be investigated further with larger sample sizes.

There are multiple limitations of this review. Although considerable efforts were made to identify relevant studies, it is impossible to guarantee complete success in retrieving all of them. An additional concern in this study is the potential presence of publication bias, as the data utilized solely originated from scientific journals. This bias arises from the tendency of journals to preferentially publish studies with positive or significant results, possibly leading to an incomplete representation of the overall body of evidence. It is important to note that his study only focused on clinical trials regarding male subjects. There are, however, several studies that have investigated the effect of *W. somnifera* on female sexual health [21-23]. These studies should be examined to further deepen the understanding of the effect of *W. somnifera* on sexual health.

5. Conclusion
W. somnifera may have therapeutic effects on male sexual health, specifically testosterone production and semen performance. However, there is a lack of quality studies assessing this claim. Additional research is necessary on this promising herbal supplement.

6. Registration and protocol
The current review was not registered, and the protocol is not accessible or available for reference.

7. Declaration of conflicting interests
The authors affirm that they have no conflicts of interest regarding the authorship and publication of this article.

8. Funding
The authors did not receive any financial support for the research or authorship of this article.

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