

Yohimbine as a treatment for erectile dysfunction: A systematic review and meta-analysis

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ABSTRACT

In recent years, several studies have reported promising results of Yohimbine as a natural supplement for erectile dysfunction (ED). However, several studies suggested that the aphrodisiac effects of the extract were only a placebo or due to the increase in peripheral vascular congestion. In contrast, other studies reported that it could provide excellent curative effects on organic impotence. We aimed to review the efficacy of Yohimbine as a pharmacological treatment for ED and performed a comprehensive systematic search of published articles in PubMed and Science Direct databases for eligible randomized controlled trials comparing Yohimbine to placebo or no treatment for ED patients. A total of eight studies out of 543 studies were included in this review. Both Yohimbine alone (odds ratio [OR] = 2.08, 95% CI 1.30-3.32, $P = .002$) and combined (OR = 6.35, 95% CI 3.01-13.41, $P < .001$) showed a significantly greater probability of erectile function improvement compared to the placebo group (OR = 2.87, 95% CI 1.94-4.25, $P < .001$). Yohimbine alone did not show a significant difference in the rate of improved sexual function ($P = .07$); however, the pooled results of both subgroups indicated a higher rate of improved sexual function (OR = 2.65, 95% CI 1.43-4.92, $P = .002$). Sole administration of Yohimbine and its combination with other supplements can improve the erectile function in ED patients. However, it is not able to improve the sexual function if not combined with other treatments.

Keywords: Erectile dysfunction; erectile function; sexual function; Yohimbine.

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for a satisfactory sexual.¹ It is estimated that more than 300 million men will be affected by ED by 2025. The rising global prevalence of ED is high, representing a major burden on the quality of life of men and their spouses.² It is also associated with diabetes, hypertension, and vascular diseases. Proper management of the disease comprising appropriate diagnosis and treatment generates an opportunity to improve the patient's health in various ways.³ The initial management of ED includes educating patients regarding lifestyle changes, such as exercise, weight loss, and quitting smoking.⁴ More severe cases may require additional pharmacological interven-

tion. There are numerous categories of pharmacological medications, including phosphodiesterase type 5 inhibitors (PDE5i), hormonal replacements, and alpha-blockers. Other more invasive alternatives include vacuum devices, intracavernosal injections, and intraurethral suppositories for patients unresponsive to oral pharmacotherapy.⁵ In recent years, several studies have reported promising results of alternative or herbal medicines for ED. One of which is Yohimbine, a natural extract derived from the barks of a species of tree from West Africa. Since ancient times, Yohimbine has been used as an aphrodisiac in Africa.⁶ Researchers believed that the aphrodisiac effects of the extract were only a placebo or due to the increase in peripheral vascular congestion instead of a genuine increase in sexual stimulation at first.

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Many reports published after its discovery suggested that it could provide excellent curative effects on organic impotence.^{7,8} A systematic review by Ernst and Pittler⁹ in 1999 reported its potential as a medication for ED. Since then, many studies were published, adding more evidence to its potential use. Therefore, we aimed to review the efficacy of Yohimbine as a pharmacological treatment for ED.

Methods

This systematic review and meta-analysis were carried out by following the protocol of preferred reporting items for systematic review and meta-analysis (PRISMA).¹⁰ The protocol for this study has been registered on the PROSPERO database (CRD42020207826).

Search Strategy

We conducted a comprehensive systematic search of published articles in PubMed and Science Direct up until April 2021 using the following keywords: (“erectile dysfunction” [Medical Subject Headings {MeSH}]) and “oral supplement” [MeSH]) and (“yohimbine” [MeSH]). Free-text and MeSH search were used as search keywords. Further relevant articles were evaluated by reading the full-text articles using our predefined eligibility criteria.

Eligibility Criteria

All randomized controlled trials (RCTs) compared Yohimbine to placebo or no treatment for patients with ED and reported the following outcomes: improvement rate in erectile and functions, or International Index of Erectile Function (IIEF) domain results were eligible for inclusion in the meta-analysis. We excluded studies with nonrandomized design, no English full text, using PDE5i intervention, and inadequate dosing information.

Main Points

- Several studies have reported promising results of alternative or herbal medicines for erectile dysfunction.
- One of the medicines promoted in recent years is a supplement extracted from the bark of the African tree, Yohimbe.
- Yohimbine is an α 2-adrenergic receptor antagonist, acting at the central serotonergic and adrenergic receptors associated with libido and erection.
- Sole administration of Yohimbine and its combination with other supplements can improve the erectile and sexual functions of ED patients.
- Yohimbine as an adjunctive treatment to other medications could improve sexual function.

Data Extraction and Quality Assessment

Two independent reviewers extracted the data using the piloted data forms, including author, study design, total participant, age of participants, etiology of ED, and treatment protocols. Each reviewer assesses the risk of bias independently using the Cochrane risk of bias tools for randomized trials two by assessing the selection bias, performance bias, detection bias, attrition bias, and reporting bias.^{11,12} Any disagreements were resolved by assessing the full-text article and discussion with the senior authors.

Data Analysis

The overall effect size estimate was pooled as odds ratio (OR) and 95% CI for the primary outcomes reporting the events of erectile and sexual function improvement. We used the I^2 test to assess the heterogeneity of the included trials. Suppose the included trials had small heterogeneity ($I^2 < 50\%$), the fixed-effects Mantel–Haenszel model would be selected for the analysis. If the heterogeneity were significant ($I^2 > 50\%$), the DerSimonian-Laird model would be chosen.^{13,14} We further divided the groups into subgroups of sole Yohimbine and Yohimbine combined with other treatments interventions. Subgroup analysis was assessed for the primary outcomes to explore heterogeneity and find a group or moderator that potentially modifies the effect size.

Results

Systematic Search Results

From the initial searching process in Figure 1, we identified a total of 543 articles. We examined 521 articles after the duplicates were removed. A total of eight trials met the eligibility criteria and were included in the meta-analysis.^{15–22}

Baseline Characteristics

All the included trials were double-blind RCTs with a total of 460 patients with ED. The age of the patients was ranged from 18 to 73 years. The type, etiology, and degree of ED were described in Table 1. The result for risk of bias used was displayed in Figure 2. The overall assessment of the included trials showed a low risk of bias. Three studies do not clearly explain the randomization process.^{15,19,20} Every study presented the blinding process of the participants and research personnel in detail. There is possible selective reporting in three studies.^{15,22,23}

Erectile Function

We included seven trials comparing the erectile function between the Yohimbine group ($n = 246$) and the control group ($n = 258$). The heterogeneity between the trials was low ($I^2 =$

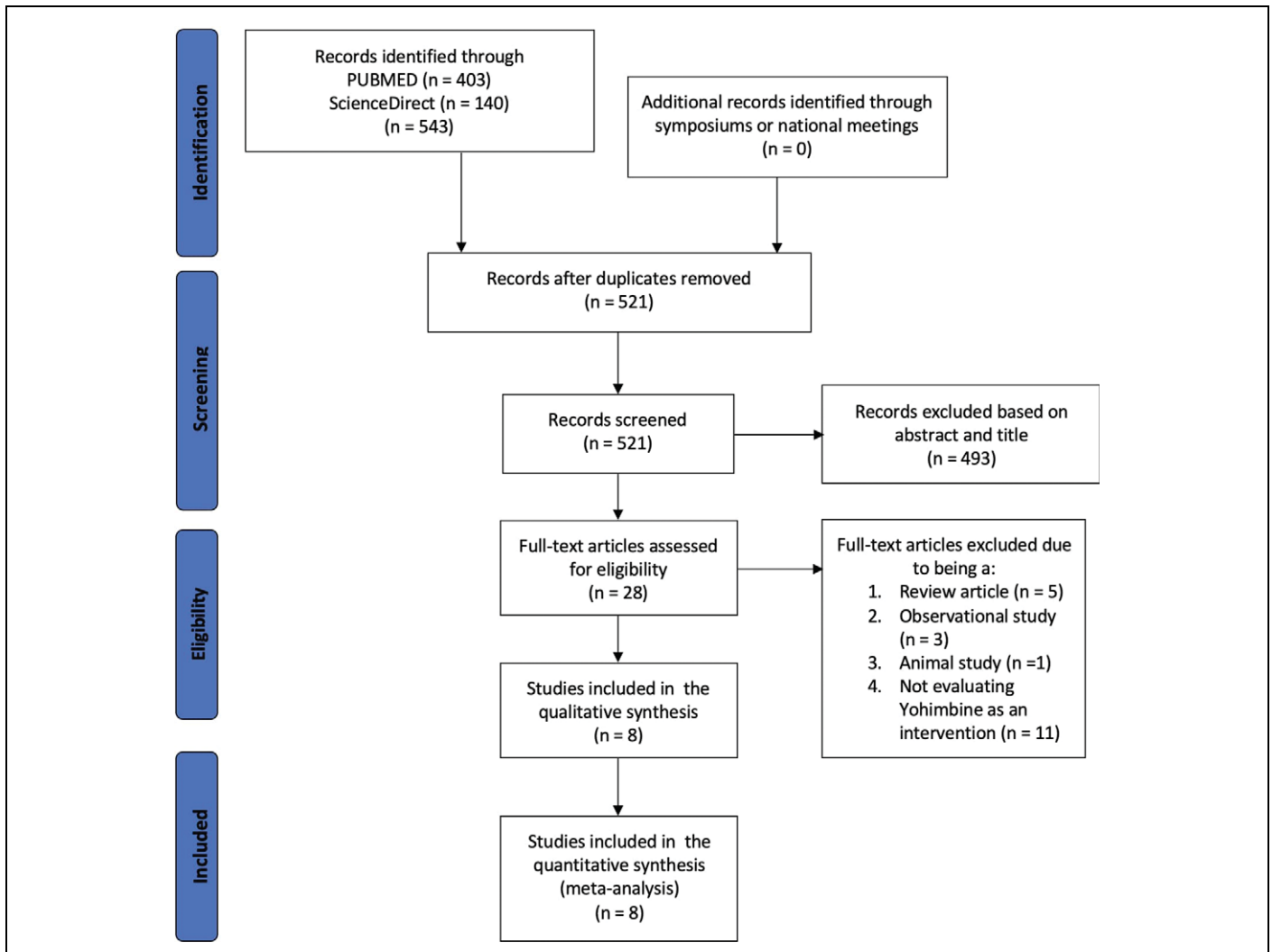


Figure 1. PRISMA flowchart of the systematic search and screening process.

51%, $P = .08$); therefore, a fixed-effects model was chosen. Subgroup analyses were performed based on studies reporting sole Yohimbine administration and Yohimbine combined with other treatments compared to placebo, as shown in Figure 3. Both Yohimbine alone (OR = 2.08, 95% CI 1.30-3.32, $P = .002$) and combined (OR = 6.35, 95% CI 3.01-13.41, $P < .001$) showed a significantly greater probability of erectile function improvement compared to the placebo group (OR = 2.87, 95% CI 1.94-4.25, $P < .001$).

Sexual Function

We managed to include five trials in evaluating sexual function comparing Yohimbine (n = 152) with placebo (n = 166). A fixed effects model was used in the subtotal subgroup and total analyses based on the low heterogeneity ($I^2 < 70\%$, $P > .05$). Figure 4 indicates that Yohimbine alone did not show a signifi-

cant difference in the rate of improved sexual function (OR = 1.93, 95% CI 0.95-3.91, $P = .07$). However, the pooled results of combined Yohimbine alone and in combination indicated a higher rate of improved sexual function (OR = 2.65, 95% CI 1.43-4.92, $P = .002$).

Discussion

Even with the current worldwide increase in ED prevalence, the understanding of the disease's burden and extent remains limited due to under-reporting and underdiagnosis in several areas in the world, especially in developing countries.^{24,25} In Indonesia, one of the tools to assess its severity was only recently validated and published.²⁶ Reports and publications regarding the disease in developing countries have escalated as of late.²⁷⁻²⁹ Several of which focused on the utilization of local

Table 1. Baseline Characteristics of the Included Studies

Author	Design	Year of Publication	n	Age (Years)	Instrument of Evaluation	Etiology and Severity of ED	Treatment Protocol
Akhondzade et al. ²²	RCT	2010	40	25-50	IIEF-15	Mild-moderate ED	Yohimbine + L-arginine (Nature's Gift SX) 2,800 mg oral 1×/day vs placebo oral 1×/day for 4 weeks
Lebret et al. ²¹	RCT	2002	44	>18	IIEF-15	Mild-moderate ED	Yohimbine 6 mg + L-arginine 6,000 mg oral 1×/day vs placebo oral 1×/day (22) for 2 weeks
Telöken et al. ²⁰	RCT	1998	22	28-69	Self-made questionnaire	Organic ED	Yohimbine 100 mg oral 1×/day (11) vs placebo oral 1×/day (11) for 30 days
Susset et al. ¹⁹	RCT	1989	82	40-73	Self-made questionnaire	All etiologies of ED	Yohimbine 5.4 mg oral 4×/day (41) vs placebo oral 4×/day (41) for 30 days
Riley et al. ¹⁸	RCT	1989	61	18-70	Self-made questionnaire	All etiologies of ED	Yohimbine 5.4 mg oral 3×/day (30) vs placebo oral 3×/day (31) for 56 days
Reid et al. ²³	RCT	1987	48	18-70	Self-made questionnaire	Psychogenic ED	Yohimbine 6 mg oral 3×/day (28) vs placebo oral 3×/day (19) for 70 days
Morales et al. ²³	RCT	1987	100	18-70	Self-made questionnaire	Organic ED	Yohimbine 5.4 mg oral 3×/day (50) vs placebo oral 3×/day (50) for 70 days
Montorsi et al. ¹⁵	RCT	1994	63	23-50	Self-made questionnaire	Psychogenic ED	Yohimbine 5 mg oral 3×/day + trazodone 50 mg oral 1×/day vs for 8 weeks

RCT: randomized controlled trial; ED: erectile dysfunction

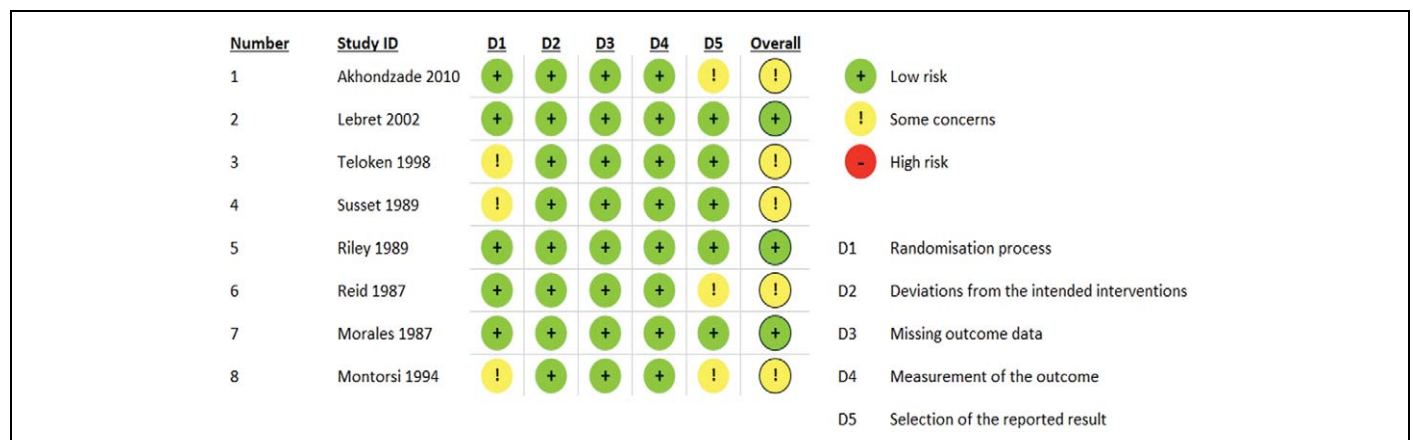


Figure 2. Risk of bias of the included trials evaluated using the Cochrane RoB tool 2.

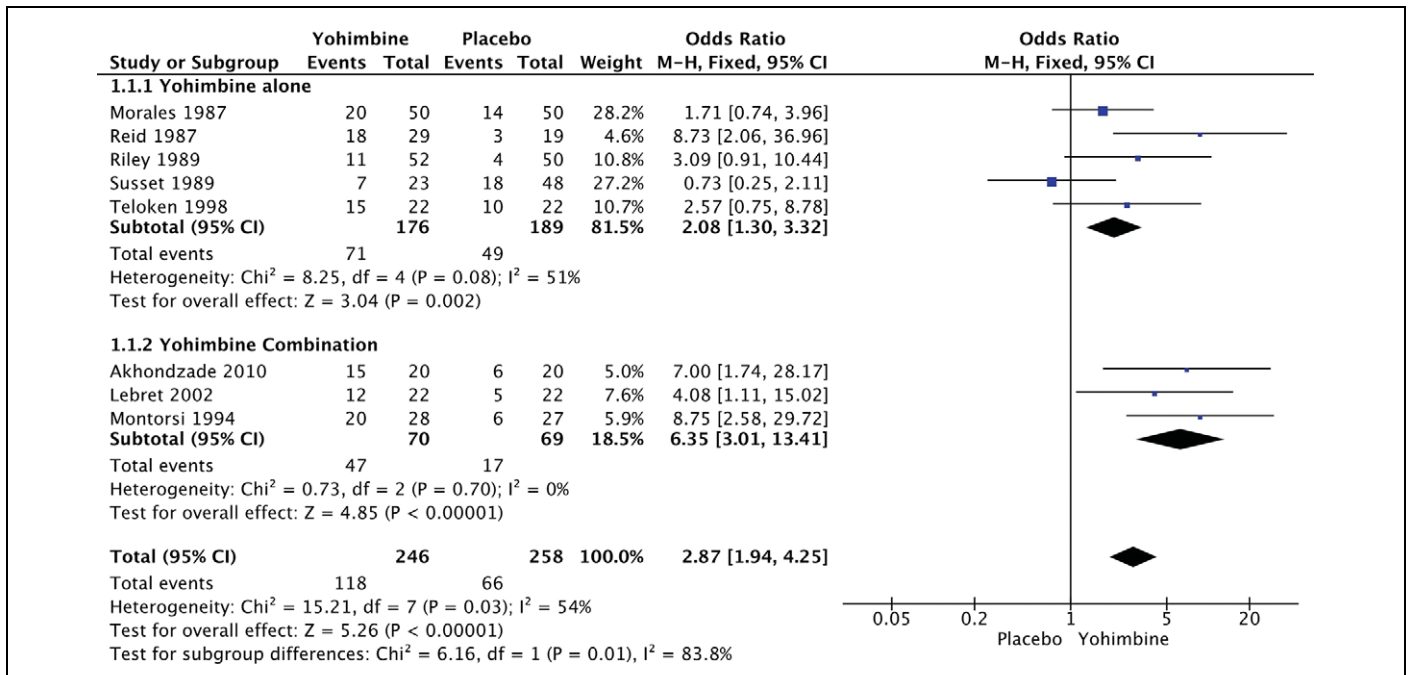


Figure 3. Forest plot showing the higher probability of erectile function improvement in both the “Yohimbine alone” and “Yohimbine combination” subgroups and overall pooled result.

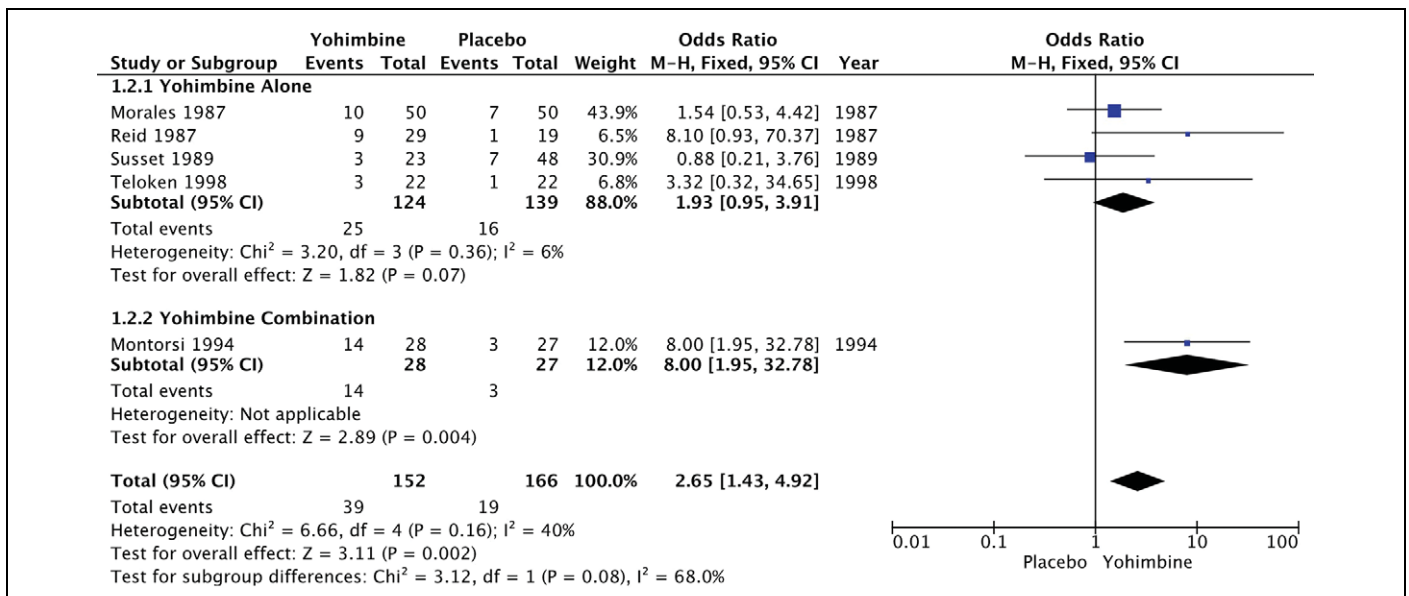


Figure 4. Forest plot showing the higher probability of sexual function improvement in the pooled result of “Yohimbine alone” and “combination subgroups” but not the “Yohimbine alone” group.

herbal or traditional medicines. One of the most popular herbal medicines used is Yohimbine. In the United States, Yohimbine chloride is approved by the Food and Drug Administration under 49 different brands.³⁰ In this review, we discovered that

Yohimbine administration positively impacts ED based on the findings of five clinical trials evaluating the efficacy of sole Yohimbine administration and three clinical trials evaluating its combination with other supplements. Telöken et al.²⁰ evaluated

20 patients with organic ED who were given a single dose of 100 mg Yohimbine per day for 30 days. However, they discovered that the difference between the treated and placebo groups was not significant. Out of the 22 patients receiving placebo, only one patient showed improvement in complete erection, nine patients showed partial response, and 11 patients showed no response. In the treatment group, three patients showed complete response, 12 patients showed partial response, four were unresponsive, and three showed a worsening function. Their trial was the only one that reported a worsening erectile function in patients receiving the treatment. However, their study showed that all patients could tolerate a high dose of Yohimbine administration for 30 days without significant side effects.²⁰ Other trials evaluated patients who were given Yohimbine three times a day with positive results.^{15,16,18,19,23}

The patients with varying degrees of ED showed mild side effects; however, Susset et al.¹⁹ and Montorsi et al.¹⁵ each reported eight patients who dropped out of the trial due to intolerable side effects. Kunelius et al.³¹ reported a patient who dropped out due to hypertensive crisis and palpitation. One patient suffered from agranulocytosis in a trial reported by Siddiqui et al.³² However, the patient had a history of cerebrovascular attack, and the link between the complication and Yohimbine was unclear. In this review, we discovered that Yohimbine administration showed a significant improvement of erectile function (OR = 2.87, 95% CI 1.94-4.25, $P < .001$). Both administrations of sole Yohimbine (OR = 2.08, 95% CI 1.30-3.32, $P = .002$) and its combination with other supplements (OR = 6.35, 95% CI 3.01-13.41, $P < .001$) showed a significant erectile function improvement. The sexual function of patients given Yohimbine was also superior to the placebo group (OR = 2.65, 95% CI 1.43-4.92, $P = .002$). The administration of Yohimbine combined with other supplements showed an improvement in sexual function (OR = 2.65, 95% CI 1.43-4.92, $P = .002$). However, sole Yohimbine administration generated similar results to the control group (OR = 1.93, 95% CI 0.95-3.91, $P = .07$). The previous meta-analysis published in 1998 concluded that Yohimbine has a potential for ED; however, they also stated that its sole administration as a monotherapy would not be effective.⁹ Another study suggested combining Yohimbine with arginine.²¹ This is due to the theory that arginine has to be available in the patient's system before Yohimbine can produce nitrous oxide.³³ Other combinations in this review included PDE5 inhibitors. Current studies evaluating this combination only examined animal models.³⁴

This systematic review has several limitations. The dose and duration of administration between studies are slightly varied, leading to a possible bias due to heterogeneity among the

included studies. Older studies did not use a standard questionnaire, as the IIEF questionnaire was published in 1997. More studies evaluating subjects with the same questionnaire would allow quantitative analyses using continuous data from the score results. The patients of the included studies had varying degrees of ED. Future reviews should evaluate each patient group based on different severity to determine the ideal dose and duration of administration for each classification.

Conclusion

Sole administration of Yohimbine and its combination with other supplements can improve the erectile and sexual functions of ED patients. However, sole Yohimbine administration did not significantly improve sexual function. To improve sexual function, it must be given as an adjunct to other treatments.

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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