

A Systematic Overview of Reviews on the Efficacy of Complementary and Alternative Medicine in Erectile Dysfunction

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ARTICLE INFO	ABSTRACT
<p><i>Article type:</i> Systematic overview article</p>	<p>Background & aim: This systematic overview of reviews on complementary and alternative medicine (CAM) was performed to summarize the clinical efficacy of this approach in the treatment of erectile dysfunction (ED) and assess methodological quality of the included reviews.</p> <p>Methods: A comprehensive search was performed to find the systematic reviews and meta-analyses on CAM interventions (e.g., acupuncture, saffron, yohimbine, and ginseng) for ED treatment, published until October 2017. To this end, we searched the international databases, including PubMed, Scopus, and Cochrane, as well as Iranian databases, such as SID, IranMedex, and Magiran. The assessment of the methodological quality of the included systematic reviews was accomplished using the AMSTAR scale.</p> <p>Results: The searching process led to the inclusion of five systematic reviews examining CAM therapies, including acupuncture, saffron, Yohimbine, and ginseng. The methodological quality of the retrieved reviews was at a favorable level. Positive results were found for the administration of yohimbine, saffron, and ginseng as treatment agents for ED. However, there was insufficient evidence regarding the effect of acupuncture on this health problem. Major methodological defects included the use of a grey literature search, likelihood of publication bias, and conflicts of interests.</p> <p>Conclusion: As the findings indicated, CAM appeared to be an effective treatment for ED. However, it is essential to conduct further studies on the safety and value of CAM for the management of this condition.</p>
<p><i>Article History:</i> Received: 28-Jan-2018 Accepted: 22-Feb-2018</p>	
<p><i>Key words:</i> Acupuncture Erectile dysfunction Ginseng Saffron Sexual dysfunction Systematic reviews</p>	

► Please cite this paper as:

Irani M, Ghafari Sardasht F, Ghazanfarpour M, Mansouri E, Khadivzadeh T. A Systematic Overview of Reviews on the Efficacy of Complementary and Alternative Medicine in Erectile Dysfunction. Journal of Midwifery and Reproductive Health. 2018; 6(4): 1476-1485. DOI: 10.22038/jmrh.2018.29476.1318

Introduction

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One of the most common sexual dysfunctions in men is erectile dysfunction (ED) (1, 2). This health problem is defined as a continuous or frequent failure to keep penile erection for a satisfactory sexual interaction (3, 4). Over 50% of men within the age of 40-70 years will experience ED; accordingly, it concerns more than 150 million men in the earth (5, 6). The global prevalence of this condition is expected to be approximately 322 million men in 2025 (7, 8).

Some of the important risk factors for ED include age, hypertension, smoking, coronary artery disease, life style, obesity, hyperlipidemia, trauma, prostatic hypertrophy, diabetes, and depression (9). Moreover, approximately 20% of the cases have psychological reasons (4). Erectile dysfunction is recognized to impact the psychological, social, and physical health of the families and their quality of life (10-12). In some cases, treatment options for ED include oral medications (e.g., sildenafil, vardenafil, and tadalafil) (11, 12). However, some individuals are not interested in using these medications for several reasons, such as drug interactions, side effects, and cost.

Complementary and alternative medicine (CAM) has been described as a group of products and practices that are not part of conventional medicine. The CAM therapies, such as acupuncture, saffron, yohimbine, and ginseng, have been evaluated in randomized controlled trials (RCTs) for the management of ED. Acupuncture as one of the important CAM techniques is suitable to treat ED (13-16), which is usually used in clinical practice since it is simple, safe, and economic (17). An increasing number of reports discuss the effects of acupuncture, as a common practice, on ED (13, 14, 16).

Crocus sativus (i.e., saffron) is another CAM that is a perennial herb with anti-oxidative prosperities (18-20). This plant is widely produced in Iran. The dried red stigma of saffron is used as a food spice. Saffron has also been usually used in traditional medicine (21, 22). Scientific literature has given a growing interest in using saffron for the treatment of ED (23-26). Yohimbine as an alkaloid is obtained from the African yohimbine tree (27). Several studies have suggested this drug for the

management of ED (28-31).

In Asia, ginseng is one of the valuable trade products, used for the treatment of diseases across 35 countries (32). The therapeutic effects of ginseng are very different. There are several studies investigating the efficacy of this herb in the treatment of several conditions, such as Alzheimer's disease (33), cardiovascular disease (34), hypertension (35), improved quality of life (36, 37), and common cold (38). Some studies support the satisfactory effects of ginseng on ED (39-42). Recently, several systemic reviews and meta-analysis studies have been published on the effects of CAM therapies, such as the implementation of acupuncture or administration of saffron and ginseng, in the treatment of ED erectile dysfunction.

Many patients with ED find pharmacological interventions unattractive and assume that CAM is not supported by sufficient evidence. Therefore, we performed this study to obtain an overview of the systematic reviews investigating the effect of CAM on the treatment of ED with the aim of summarizing the efficacy of this approach and assessing the methodological quality of the included review studies.

Materials and Methods

For the purpose of the study, a systematic search was performed to find the reviews and meta-analyses on the subject of interest published until October 2017 on several international databases, including PubMed, Scopus, and Cochrane, as well as the Iranian databases, such as IranMedex, SID, and Magiran. The reference section of the relevant studies was also examined manually. The searching process was accomplished using the following English keywords: 'Erectile dysfunction', 'Sexual dysfunction', 'Acupuncture', 'Saffron', and 'Yohimbine', 'Ginseng'. Furthermore, the equivalent Persian terms were used for searching the Iranian databases.

Inclusion criteria

The eligibility criteria were as follows:

1) The study must be a systematic review with or without meta-analysis. First, all systematic reviews were chosen. After a

comprehensive overview of the evidence, the reviews clearly claiming to have chosen only selected trials were included.

2) Only the reviews investigating patients with ED based on the International Index of Erectile Function were included (43). No restrictions regarding the type of ED or duration were considered. There were also no limitations regarding the procedures of trials and reviews, and they were all considered eligible.

3) Reviews on the effects of CAM, such as saffron, yohimbine, acupuncture, and ginseng, were included. Reviews were included if they focused on the effectiveness of one or multiple CAM modalities.

4) The full published papers were included if they were published in English or Persian.

On the other hand, abstracts or unpublished studies were excluded. At first, all duplicated studies were eliminated from the references. Then, two reviewers (MI, MGH) independently screened the abstracts of the studies and carried on to obtain the full articles for the included studies. Finally, the review studies were checked in detail to be included in this overview.

We extracted such data as first author, year of publication, number of studies and patients, intervention, comparison, information on meta-analysis, risk of bias assessments, and safety for each review study according to a checklist. The data were independently assessed by two reviewers (MI, MGH), and disparities were resolved by discussion with a third reviewer (TKH). Generally, complete agreement between the two reviewers was obtained.

The quality of the included review studies was assessed by using the Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) scale (44) (Table 2). The AMSTAR scale consists of 11 items, which mainly assess the reviews on RCTs and are answered with four options, namely yes, no, can't answer, and not applicable (44). The scoring of this scale was performed by assigning the score of one to the yes answer and zero to any other response. The maximum and minimum scores of the checklist were 11 and 0, respectively.

The list of criteria for evaluating the quality of the review studies were as follows:

1. Was 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of the studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?" (44, 45)

Results

Out of 5,210 relevant publication reviews, five systematic reviews (46-50) met the eligibility criteria (Figure 1) and included in the study. The characteristics of the included studies are summarized in Table 1.

The reviews were published in 2017 (n=1), 2016 (n=1), 2009 (n=1), 2008 (n=1), and 1998 (n=1). The reviews assessed several therapies, including saffron therapies (n=1), ginseng therapies (n=1), acupuncture (n=2), and yohimbine (n=1). The RCTs and UCTs were investigated in only one review (47), and the other reviews included controlled clinical trials (46, 48-50).

The retrieved reviews included 4-7 trials with a total sample size of 126-419 cases. Out of the five reviews, only 80% (n=4) of the articles conducted meta-analyses. All reviews assessed the risk of bias using the Cochrane risk of bias assessment (n=3) (46), Jadad score (n=1) (47-49), and Oxford rating scale (n=1) (50). The quality assessment of the included studies revealed a good level of quality; accordingly, most of the reviewed articles received 8 of 11 possible points (Table 2).

While all reviews accomplished a systematic literature search, some of the them did not include grey literature (47, 50). Research question, inclusion criteria, independent data

extractors, achievement of a consensus, characteristics of studies, comprehensive

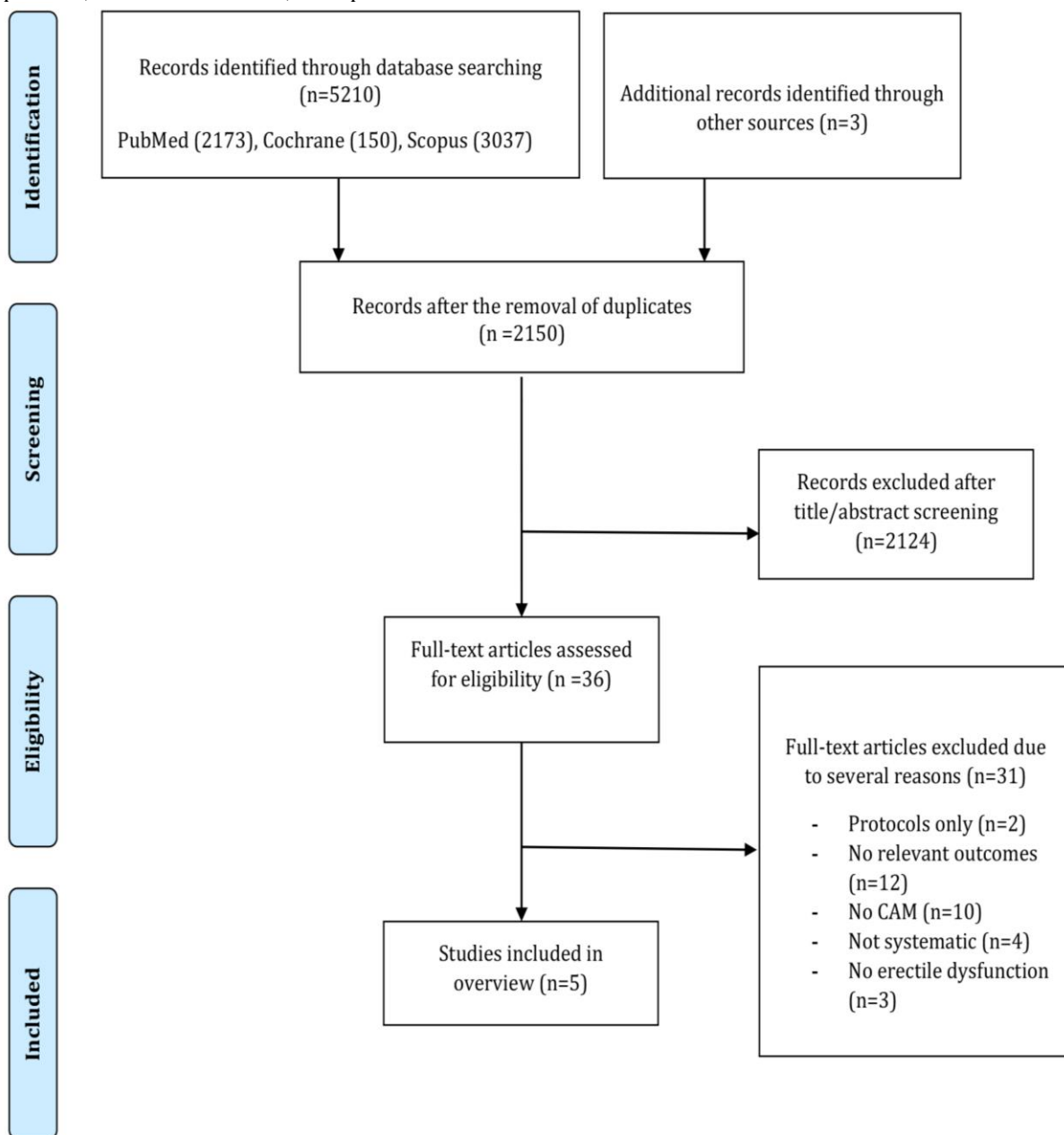


Figure 1. PRISMA flowchart of the study selection process

literature search, risk of bias assessment, and appropriate scientific quality of the included studies used in formulating conclusions were included in all reviews.

Out of the reviews performing meta-analyses, two cases did not state the methods for combining the studies. A random effects model ought to be used if heterogeneity exists

(44). The likelihood of publication bias (which must include a combination of graphical aids like funnel plot) was not assessed in all of the reviews, and two articles did not entail the **Table 1**. Characteristics of the included reviews

conflict of interests (48, 49).
Conclusions and side effects of the relevant

First Author	Year of publication	Country	Meta-analysis	Intervention	Comparison group	Type of included studies	Number of studies; Number of participants	Bias assessment risk	Safety (AE/SAE)
Lee	2009	South Korea	Yes	Auricular acupuncture or needle acupuncture, with or without electrical stimulation	Sham-acupuncture and non-acupuncture	UCTS, RCT	4;126	Jadad score	50 %, nr (-), AE 50% No SAE
Cui	2016	China	NO	Manual acupuncture Or electro-acupuncture	Psychological therapy, placebo, and sham-acupuncture	RCT	3;183	Cochrane risk of bias assessment	Not assessed; not reported
Ernst	1998	UK	Yes	Yohimbine	Placebo	RCT	7;419	Jadad score	10%-30% AE No SAE
Maleki	2017	Iran	Yes	Saffron (<i>Crocus sativus</i>)	Placebo	RCT	4;215	Oxford Center for Evidence-Based Medicine checklist	Not assessed; not reported
Jang	2008	South Korea	Yes	Ginseng	Placebo	RCT	7;363	Jadad scale	No SAE

RCT: randomized clinical trial, UCTs: Uncontrolled clinical trials, SAE: serious adverse event, AE: adverse event, NR: not reported, (-): not mentioned in text

interventions are summarized in Table 3.

Acupuncture Interventions

Two review studies, with and without meta-analyses, evaluated the effects of acupuncture. The first review (47) had insufficient evidence to advise acupuncture as a helpful intervention to treat ED. Likewise, seven years later, the second review (46) with meta-analysis found inadequate evidence. On the other hand, the RCTs studies of acupuncture for ED were reasonable; however, they were rare with weak

methodology (e.g. inadequate study design, small sample size, and inadequate reporting of results).

Ginseng Intervention

One review evaluated the effects of ginseng on ED (48). The results showed the positive effect of ginseng on the treatment of this health problem. Nonetheless, the number of RCTs and the total sample size included in the mentioned study were small. Moreover, the methodological quality of the included primary studies was poor. These drawbacks prevented making more absolute decision

about the efficacy of ginseng. However, this review enjoyed good quality.

The results of seven RCTs showed that yohimbine played a greater role in ED

Yohimbine Intervention

Table 2. Assessment of the quality of included systematic reviews by AMSTAR tool

First author	Year of publication	Country	Research question and inclusion criteria?	Two independent data extractors and a consensus procedure?	Comprehensive literature search?	Statement on inclusion of grey literature? Language?	List of included and excluded studies?	Characteristics of reviewed studies, for example, tables?	Quality of risk of bias assessment?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate? Test on heterogeneity	Likelihood of publication bias assessed?	Conflict of interests stated?	Sum
Lee	2009	South Korea	Yes	Yes	Yes	Cannot answer	No	Yes	Yes	Yes	Cannot answer	No	Yes	8
Cui	2016	China	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	No	Yes	9
Ernst	1998	UK	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Cannot answer	No	No	8
Maleki	2017	Iran	Yes	Yes	Yes	Cannot answer	No	Yes	Yes	Yes	Yes	No	Yes	8
Jang	2008	South Korea	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8

Table 3. Overview of the conclusions and side effects of the assessed complementary and alternative medicines of the included systematic reviews

Intervention	Definition	Conclusion	Side effects	Contraindications
Acupuncture (46, 47)	Insertion of needles into specified sites of the body for therapeutic reasons	There was insufficient evidence for supporting acupuncture as a successful therapy for ED. Further well-designed RCTs were suggested to assess the benefits of acupuncture in ED treatment	Mild side effects, such as pain or bleeding; serious side effects, such as infections, pneumothorax, and cardiac tamponed	Serious bleeding condition
Yohimbine (49)	Alpha-2 blocker that is the most important active component of yohimbine bark	The benefits of Yohimbine intervention for the treatment of ED were more important than its risks. So, it was a good therapeutic choice for ED.	Anxiety, hallucinations, agitation, dizziness, seizures, headache, hypertension, panic attacks, nervous excitation,	Pregnancy, lactation, psychological disease, kidney, liver, and heart disorder

Continuous of Table 1.					
Saffron (50)	perennial herb with anti-oxidative riches	There was evidence revealing the effectiveness of Saffron in men with ED. But, there was methodological flaws and huge heterogeneity among the included studies.	sleeplessness, tachycardia, bronchospasm, renal failure	Mild to moderate side effects, such as headache, flushing, nausea, dyspepsia, diarrhea, as well as decreased and increased appetite	Not reported
Ginseng (48)	Permanent herb, the chief ingredients of which include panaxosides and ginsenosides	There was evidence for the effectiveness of ginseng intervention in the treatment of ED. But, the qualities of most of the included RCTs were poor to draw final conclusions.	Insomnia, headache, gastric upset, constipation	Pregnancy, lactation	

RCT: randomized control trail, ED: erectile dysfunction

treatment, compared to placebo (49). The review on yohimbine had a good quality, and its conclusion was that “the benefit of yohimbine medication for ED seems to outweigh its risks.” The side effects of yohimbine are indicated in Table 2. However, in the RCTs, the side effects were reversible and scarce.

Saffron Intervention

Saffron intervention was utilized in one review (50), revealing the positive effects of saffron interventions on men with ED. Despite the good quality of the mentioned review study, there was a large heterogeneity among the included RCTs. Therefore, the methodological flaws of the reviewed RCTs limited the interpretation of the results.

Side effects

Side effects were assessed in all reviews. Most of the side effects were mild to moderate; however, many trials did not sufficiently report the side effects.

Discussion

Overall, five systematic reviews (46-50) evaluated the effects of CAM therapies, including acupuncture, saffron, yohimbine, and ginseng, on ED. All of the reviews included RCTs and UCTS. Four reviews conducted a met-analysis (47-50). The risk of bias

assessment of the included trials was presented in all studies. The reviews had a good level of methodological quality (46-50). This study depicted some evidence to demonstrate the use of ginseng, saffron, and yohimbine in the treatment of ED.

However, there was no good evidence supporting the effectiveness of acupuncture on this health condition. We applied AMSTAR scale (44) for evaluating the methodological quality of the included systemic reviews. Though the primary studies included in the systemic reviews were not sufficiently accurate. All included systemic reviews stated the side effects of the applied CAM therapy (46-50).

Furthermore, they all reported a low frequency rate regarding the side effects of CAM therapy. In this regard, in a systemic review conducted by Maleki et al. (50), the total number of side effects after saffron was low. In another review performed by Jang et al. (48), the total number of side effects after ginseng was also minor. However, the serious side effects of yohimbine were documented in a study carried out by Ernst (49).

The therapeutic index of this compound is not great, and there is probably an interaction. Therefore, it is uncertain whether the benefits of yohimbine are more important than its risks. Furthermore, it is important to emphasize that

the mild side effects of acupuncture are repeated (46, 47).

The potential mechanisms of saffron action may include those of the opioid systems and nitric oxide that play an important function in the erectile function (51-53). The potential mechanisms of yohimbine action might involve the activation of cholinergic and dopaminergic receptors, as well as enhancement of noradrenaline release (49).

Ginseng potential mechanisms could involve the nitric oxide pathways relaxing the smooth muscles of the corpus cavernosum (54). Modern medicine recognizes the Yin-Yang balance in a healthy body as the balance of the autonomic nervous system (ANS), such as that of the sympathetic and parasympathetic activities. Based on the ANS, acupuncture may have a positive influence on the treatment of ED (55).

Regardless of all prior findings and conclusions, there are some limitations that could restrain the results of this overview. The first limitation concerns the systematic reviews included in this overview. Despite the application of a wide search strategy in the present study, there is no definite guarantee that all relevant systematic reviews have been obtained. Another limitation of this study concerns the validity of any overview of systematic reviews that has its own drawbacks. All systematic reviews are at the risk of publication bias; therefore, their results and conclusions may be misinterpreted.

This study revealed that there is a limited number of high-quality CAM studies in ED. Despite the significant methodological flaws that CAM studies are facing, the precise investigation of this area is clearly feasible. Future trials and systematic reviews of CAM ought to be accompanied by increased methodological quality, if those trials and reviews aim to influence the treatment guidelines and decision makers. In summary, there is a positive evidence supporting the efficacy of yohimbine, saffron, and ginseng in treating ED. However, further research is needed to confirm the current findings.

Conclusion

As the findings indicated, CAM was an

effective treatment for ED. However, it is essential to conduct more studies on the safety and value of CAM in the treatment of ED.

Acknowledgements

The authors thank the Deputy of Research of Mashhad University of Medical Sciences, Mashhad, Iran, for funding this study.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira Jr ED, et al. Definitions/epidemiology/risk factors for sexual dysfunction. *The Journal of Sexual Medicine*. 2010; 7(4 Pt 2):1598-1607.
- Shamloul R, Ghanem H. Erectile dysfunction. *The Lancet*. 2013; 381(9861):153-165.
- Heidelbaugh JJ. Management of erectile dysfunction. *American Family Physician*. 2010; 81(3):305-312.
- Khera M, Goldstein I. Erectile dysfunction. *BMJ Clinical Evidence*. 2011; 2011:1803.
- Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *The Journal of Urology*. 2000; 163(2):460-463.
- Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. *Urology*. 2003; 62(1):121-125.
- Aytac I, McKinlay J, Krane R. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU International*. 1999; 84:50-56.
- Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Annals of Internal Medicine*. 2003; 139(3):161-168.
- Köhler TS, McVary KT. Contemporary treatment of erectile dysfunction: a clinical guide. New York: Springer; 2016.
- Hatzimouratidis K, Amer E, Eardley I, Giuliano F, Hatzichristou D, Moncada I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *European Urology*. 2010; 57(5):804-814.
- Mayo Clinic Staff. Erectile dysfunction. Available at: URL: www.mayoclinic.org/diseases-conditions/erectiledysfunction/basics/definition/con-20034244; 2015.

12. Muneer A, Kalsi J, Nazareth I, Arya M. Erectile dysfunction. *BMJ Clinical Evidence*. 2014; 348:g129.
13. Aydin S, Ercan M, Çaşkurlu T, Taşçı AI, Karaman İ, Odabaş Ö, et al. Acupuncture and hypnotic suggestions in the treatment of non-organic male sexual dysfunction. *Scandinavian Journal of Urology and Nephrology*. 1997; 31(3):271-274.
14. Engelhardt PF, Daha LK, Zils T, Simak R, König K, Pflüger H. Acupuncture in the treatment of psychogenic erectile dysfunction: first results of a prospective randomized placebo-controlled study. *International Journal of Impotence Research*. 2003; 15(5):343-346.
15. Kho HG, Sweep CG, Chen X, Rabsztyń PR, Meuleman EJ. The use of acupuncture in the treatment of erectile dysfunction. *International Journal of Impotence Research*. 1999; 11(1):41-46.
16. Jiang XP, Liu XY, Li Q. Clinical observation on effect of acupuncture combined with psychological therapy. *The Chinese and Foreign Health Abstract*. 2012; 9:401-402.
17. Kaptchuk T. *The web that has no weaver: understanding Chinese medicine*. New York: BookBaby; 2014.
18. Pham TQ, Cormier F, Farnworth E, Tong VH, Van Calsteren MR. Antioxidant properties of crocin from *Gardenia jasminoides* Ellis and study of the reactions of crocin with linoleic acid and crocin with oxygen. *Journal of Agricultural and Food Chemistry*. 2000; 48(5):1455-1461.
19. Botsoglou N, Florou-Paneri P, Nikolakakis I, Giannenas I, Dotas V, Botsoglou E, et al. Effect of dietary saffron (*Crocus sativus* L.) on the oxidative stability of egg yolk. *British Poultry Science*. 2005; 46(6):701-707.
20. Kanakis CD, Tarantilis PA, Tajmir-Riahi HA, Polissiou MG. Crocetin, dimethylcrocetin, and safranal bind human serum albumin: stability and antioxidative properties. *Journal of Agricultural and Food Chemistry*. 2007; 55(3):970-977.
21. Basker D, Negbi M. Uses of saffron. *Economic Botany*. 1983; 37(2):228-236.
22. Rios JL, Recio MC, Giner RM, Manez S. An update review of saffron and its active constituents. *Phytotherapy Research*. 1996; 10(3):189-193.
23. Shamsa A, Hosseinzadeh H, Molaei M, Shakeri MT, Rajabi O. Evaluation of *Crocus sativus* L.(saffron) on male erectile dysfunction: a pilot study. *Phytomedicine*. 2009; 16(8):690-693.
24. Safarinejad MR, Shafiei N, Safarinejad S. An open label, randomized, fixed-dose, crossover study comparing efficacy and safety of sildenafil citrate and saffron (*Crocus sativus* Linn.) for treating erectile dysfunction in men naïve to treatment. *International Journal of Impotence Research*. 2010; 22(4):240-250.
25. Mohammadzadeh-Moghadam H, Nazari SM, Shamsa A, Kamalinejad M, Esmaeeli H, Asadpour AA, et al. Effects of a topical saffron (*Crocus sativus* L) gel on erectile dysfunction in diabetics: A randomized, parallel-group, double-blind, placebo-controlled trial. *Journal of Evidence-Based Complementary & Alternative Medicine*. 2015; 20(4):283-286.
26. Modabbernia A, Sohrabi H, Nasehi AA, Raisi F, Saroukhani S, Jamshidi A, et al. Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial. *Psychopharmacology*. 2012; 223(4):381-388.
27. De Smet PA. Yohimbe Alkaloids—general discussion. *Adverse effects of herbal drugs*. Berlin, Heidelberg: Springer; 1997. P. 181-205.
28. Riley AJ, Goodman RE, Kellett JM, Orr R. Double blind trial of yohimbine hydrochloride in the treatment of erection inadequacy. *Sexual and Marital Therapy*. 1989; 4(1):17-26.
29. Susset JG, Tessier CD, Wincze J, Bansal S, Malhotra C, Schwacha MG. Effect of yohimbine hydrochloride on erectile impotence: a double-blind study. *The Journal of Urology*. 1989; 141(6):1360-1363.
30. Mann K, Klingler T, Noe S, Röschke J, Müller S, Benkert O. Effects of yohimbine on sexual experiences and nocturnal penile tumescence and rigidity in erectile dysfunction. *Archives of Sexual Behavior*. 1996; 25(1):1-16.
31. Vogt HJ, Brandl P, Kockott G, Schmitz JR, Wiegand MH, Schadrack J, et al. Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction. *International Journal of Impotence Research*. 1997; 9(3):155.
32. Baeg IH, So SH. The world ginseng market and the ginseng (Korea). *Journal of Ginseng Research*. 2013; 37(1):1.
33. Lee MS, Yang EJ, Kim JI, Ernst E. Ginseng for cognitive function in Alzheimer's disease: a systematic review. *Journal of Alzheimer's Disease*. 2009; 18(2):339-344.
34. Buettner C, Yeh GY, Phillips RS, Mittleman MA, Kaptchuk TJ. Systematic review of the effects of ginseng on cardiovascular risk factors. *Annals of Pharmacotherapy*. 2006; 40(1):83-95.
35. Hur MH, Lee MS, Yang HJ, Kim C, Bae IL, Ernst E. Ginseng for reducing the blood pressure in patients with hypertension: a systematic review and meta-analysis. *Journal of Ginseng Research*. 2010; 34(4):342-347.
36. Bahrke MS, Morgan WP, Stegner A. Is ginseng an ergogenic aid? *International Journal of Sport Nutrition and Exercise Metabolism*. 2009; 19(3):298-322.
37. Coleman CI, Hebert JH, Reddy P. The effects of

- Panax ginseng on quality of life. *Journal of Clinical Pharmacy and Therapeutics*. 2003; 28(1):5-15.
38. Seida JK, Durec T, Kuhle S. North American (Panax quinquefolius) and Asian Ginseng (Panax ginseng) preparations for prevention of the common cold in healthy adults: a systematic review. *Evidence-Based Complementary and Alternative Medicine*. 2011; 2011:282151.
 39. Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. *International Journal of Impotence Research*. 1995; 7(3):181-186.
 40. Choi HK, Choi YJ. Evaluation of clinical efficacy of Korea red ginseng for erectile dysfunction by international index of erectile function. *Journal of Ginseng Research*. 2001; 25:112-117.
 41. Kim SW, Paick JS. Clinical efficacy of Korea red ginseng on vasculogenic impotent patients. *Korean Journal of Andrology*. 1999; 17(1):23-28.
 42. De Andrade E, De Mesquita AA, de Almeida Claro J, De Andrade PM, Ortiz V, Paranhos M, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. *Asian Journal of Andrology*. 2007; 9(2):241-244.
 43. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997; 49(6):822-830.
 44. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*. 2007; 7(1):10.
 45. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *Journal of Clinical Epidemiology*. 2009; 62(10):1013-1020.
 46. Cui X, Zhou J, Qin Z, Liu Z. Acupuncture for erectile dysfunction: a systematic review. *BioMed Research International*. 2016; 2016:2171923.
 47. Lee MS, Shin BC, Ernst E. Acupuncture for treating erectile dysfunction: a systematic review. *BJU International*. 2009; 104(3):366-370.
 48. Jang DJ, Lee MS, Shin BC, Lee YC, Ernst E. Red ginseng for treating erectile dysfunction: a systematic review. *British Journal of Clinical Pharmacology*. 2008; 66(4):444-450.
 49. Ernst E, Pittler M. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. *The Journal of Urology*. 1998; 159(2):433-436.
 50. Maleki-saghooni N, Mirzaii K, Hosseinzadeh H, Sadeghi R, Irani M. A systematic review and meta-analysis of clinical trials on saffron (*Crocus sativus*) effectiveness and safety on erectile dysfunction and semen parameters. *Avicenna Journal of Phytomedicine*. 2017; 13:1-11.
 51. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacological Reviews*. 2011; 63(4):811-859.
 52. Khorri V, Alizadeh AM, Yazdi H, Rakhshan E, Mirabbasi A, Changizi S, et al. Frequency-dependent electrophysiological remodeling of the AV Node by Hydroalcohol Extract of *Crocus sativus* L.(Saffron) during experimental atrial fibrillation: the role of endogenous nitric oxide. *Phytotherapy Research*. 2012; 26(6):826-832.
 53. Hosseinzadeh H, Jahanian Z. Effect of *Crocus sativus* L.(saffron) stigma and its constituents, crocin and safranal, on morphine withdrawal syndrome in mice. *Phytotherapy Research*. 2010; 24(5):726-730.
 54. O'Hara M, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. *Archives of Family Medicine*. 1998; 7(6):523.
 55. Yaman LS, Kiliç S, Sarica K, Bayar M, Saygin B. The place of acupuncture in the management of psychogenic impotence. *European Urology*. 1994; 26:52-55.