CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

RESEARCH PRIORITY AND CURRENT EVIDENCE OF ERECTILE DYSFUNCTION HERBAL REMEDIES IN PERSIAN MEDICINE

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Abstract:

Erectile dysfunction (ED) is a frequent cause of medical advice from health care professional's especially general practitioners, urologists, and psychologists; however, countless patients care about benefiting from other sources including alternative and traditional medicines, social beliefs or advertisements. The big business of herbal aphrodisiacs besides lack of efficacy and safety information has led to several studies designed to evaluate this claims.

Unfortunately, the majority of studies are planned to assess the effect of a single plant in specific pathway –like PDE5 inhibition- while ED involves complex neuroendocrine pathways, and each plant, having numerous bioactive substances, engages in various biological systems. This challenge of mentioning the importance of periodic evaluation of published evidence and advice research priority; had led to this study design.

In this investigation, all materials recommended for ED by Persian Medicine (PM) in pharmacopoeia texts were identified, each one of 210 resulted plants was counted in PM clinical texts as a proof of description by clinicians (not only pharmacologists), this method decreased the number of recommended plants to 65 items (31%) and achieved quantitative priority for further research.

In addition, all 210 plants were searched in PubMed® database to inspect current scientific data and evidence for ED management, the results were 106 articles in relation to only 22 plants (10%) that are less than sufficient to make clinical decision; however, this end result proves a call for research priority studies.

Key words: *Erectile dysfunction; Persian medicine; Arabic medicine; herbal medicine; drug discovery*

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*Please cite this article in press as Mahmood Khodadoost et al., **Research Priority and Current Evidence of Erectile Dysfunction Herbal Remedies In Persian Medicine**, Indo Am. J. P. Sci, 2017; 4(12).*

INTRODUCTION:

Erectile dysfunction (ED) is a common complaint in clinical practice, the incidence of ED estimated by 52% after the age of 40 and increases with age to 80% in the 8th decade of life [1,2]. This problem has an effect on quality of life, mood changes and causes interpersonal and social problems [3,4].

Impotence or ED is a chronic condition defined as «inability to develop or maintain an erection of the penis during sexual activity», it is related to many common clinical situations in both psychotic disorders or organic diseases like depression, diabetes, hypertension, hormonal imbalance, and drug side effects [5,6].

On hand treatments like Phosphodiesterase 5 inhibitors or PDE5i (Sildenafil, Tadalafil, etc.) are linked to various side effects such as a headache (20%), flushing (18%), and dyspepsia (8%)[7]. Because of the mentioned side effects, treatment failure, contraindications of intervention and other reasons; patients are widely using complementary and alternative medicine (CAM) recommendations.

Persian medicine (PM) is one of the most popular alternative medical schools worldwide [8], Historically it was inheritor of ancient medical knowledge in Middle East region (Egypt, Iraq, Persia, etc) composed by famous Greek physicians like Hippocrates of Kos (c.460-c.370 BC), Pedanius Dioscorides (c.40-c.90 AD), Galen (c.129-c.200 AD), translated and developed mainly in Arabic language by well-known scientists like Rhazes (c. 854-c.932 AD) and Avicenna (c. 980-c.1037 AD) who enriched medicine with clinical observations and experiences. Because of this deeply cultural root, and recommendations regarding lifestyle managements beside conventional medicine limits in some situations; this medical school advices are still used by millions worldwide.

Since traditional medicine experiences are accepted to be a source of finding idea in drug discovery plus the fact that it's effective and safe interventions are suggested to integrate into primary care by WHO and many national health policies, this study is designed to gain current evidence in herbal drugs that are suggested for treatment of Erectile dysfunction in Persian medicine.

MATERIALS AND METHODS:

Information sources:

Information about herbal remedies for erectile dysfunction in Persian and Greco Arab medicine is available in three sources: pharmacopoeia compilations and clinical textbooks as printed or manuscripts; and electronic literature database.

Since there is no comprehensive database for Greco Arab herbal remedies and most of its original compilations are still unstudied and unpublished, most famous texts of pharmacopoeia and clinical practice in both Arabic and Persian language were identified and selected as below.

Pharmacopoeia texts: the largest and most frequently read book in Arabic was Kitab al-jami li mufradat al-adwiya wa al-aghdhiya (Compendium on Simple Medicaments and Foods) which is written by Ibn al-Baytar (1197–1248 AD.), this book referes to 150 previous Arabic and Greek authors and lists more than 1400 heading of drugs and foods with plants, animal and mineral origins[9]. In Persian, the latest and most comprehensive text was Makhzan al-Adviea (The storehouse of medicaments) which is written by Aghili Khorasani (18th century), this book contains 1698 monographs ordered alphabetically[10,11].

Clinical Practice texts: The Canon of Medicine which was written by Avicenna (Ibn Sina) in 1025 AD was the most popular standard medical textbook for centuries in many regions including Europe until 18th century, and it is still used as a source by Unani medicine practitioners in India; Zakhireye Khwarazmshahi which was written by Ismail Gorgani (1040-1136) twice in Arabic and Persian was the equivalent to The Canon of Medicine among Persians.

Search:

Selected Pharmacopoeia texts were searched for aphrodisiac equivalent (Mobahi) and impotence equivalent (zafe Bah), reported entities were categorized by origin (herbal, animal, mineral), authentication of reported medicinal herbs was achieved by previous botanical studies with historical aspect like «matching the old medicinal plant Names with scientific terminology»[12]. In all cases, last accepted scientific names were obtained from «the plant list» database.

In view of the fact that most remedies in clinical textbooks were multiple herbs in a single formula, word count method was used to detect importance of herbs by clinicians in the textbooks; all equal names (Arabic, Persian, etc) were considered in word counting process.

Current evidence of efficacy about reported herbs extracted by electronic literature searches in PubMed® database from its beginning to November 2016; (Erectile dysfunction OR Aphrodisiac) and suggested scientific names for each plant recommended for ED were used as search terms.

RESULTS:

Based on Pharmacopoeia texts 279 entities with aphrodisiac effect or recommended for ED was identified; fifty-nine of them were among animal source, ten were of mineral origin, and 210 remained entities were of plant source.

From 210 plant entities recognized in Pharmacopoeia texts, only 65 (31%) of them were possibly used by clinicians according to their texts; in fact, the range of mean entity count in top and bottom is too wide (19.5:0.5), ultimately, side effects, efficacy, availability, and expenditure observed by the ancient clinicians were the choosing factors, therefore this list provides Quantitative priority for further research. (Table 1).

Table 1: plants used by PM clinician as aphrodisic

#	Suggested scientific name (s)	Traditional Name	N in Canon	N in Zakhire	Mean
1	*Eruca vesicaria (L.) Cav.* *Lepidium sp.*	Jarjeer	20	19	19.5
2	*Cicer arietinum L.*	Hommos	12	24	18
3	*Allium cepa L.*	Basal	14	21	17.5
4	*Daucus carota L.*	Jazar	12	17	14.5
5	*Zingiber officinale Roscoe*	Zanjabeel	8	19	13.5
6	*Vicia faba L.*	Baghella	14	6	10
7	*Corylus avellana L.*	Bondoq	13	6	9.5
8	*Tribulus terrestris L.*	Hasak	9	10	9.5
9	*Prunus dulcis (Mill.) D.A.Webb.*	Lawz	5	13	9
10	*Asparagus officinalis L.*	Zaghbos, Helyon	6	12	9
11	*Polygonatum orientale Desf.*	Shaghaghol	5	13	9
12	*Pinus sp.*	Senobar	13	4	8.5
13	*Ficus carica L.*	Tin	6	9	7.5
14	*Anacyclus pyrethrum (L.) Lag.*	Aagher Gharha	7	6	6.5
15	*Brassica rapa L.*	Shaljam	0	13	6.5
16	*Cinnamomum verum J.Presl.*	Dar Seny	0	11	5.5
17	*Cocos nucifera L.*	Narjeel	11	0	5.5
18	*Phoenix dactylifera L.*	Tamr	5	5	5
19	*Boswellia sacra Flueck.*	Kondor	5	4	4.5
20	*Brassica oleracea L.*	Karnab	8	1	4.5
21	*Cyperus longus L.*	So'ad	6	3	4.5
22	*Linum usitatissimum L.*	Kattan	6	3	4.5
23	*Pistacia vera L.*	Fostoq	5	4	4.5
24	*Portulaca oleracea L.*	Baghlat al-Hamgha	5	3	4
25	*Phaseolus vulgaris L.*	Lobeya	4	4	4
26	*Pistacia terebinthus L.*	Haba al-Khadra	8	0	4
27	*Raphanus sp.*	Fojel	3	5	4
28	*Crocus sativus L.*	Zafaran	7	0	3.5
29	*Mentha × piperita L.*	Nanaa	4	3	3.5
30	*Piper longum L.*	Dar Felfel	6	1	3.5
31	*Thymelaea tartonraira (L.) All.*	Korrath	3	4	3.5
32	*Limonium vulgare Mill.* *Centaurea behen L.*	Bahman	3	4	3.5
33	*Alpinia galanga (L.) Willd.* *Alpinia officinarum Hance*	Kholanjan	3	3	3
34	*Syzygium aromaticum (L.) Merr. & L.M.Perry*	Quronful	4	2	3
35	*Fraxinus excelsior L.*	Lesan al-Asafeer	0	6	3
36	*Narcissus tazetta L.*	Narjes	3	3	3
37	*Matricaria chamomilla L.* *Chamaemelum nobile (L.) All.*	Babonaj	5	0	2.5
38	*Triticum aestivum L.*	Henta	0	5	2.5
39	*Acorus calamus L.*	Waj	0	4	2

40	*Costus sp.*	Qust	3	1	2
41	*Cyperus esculentus L.*	Hab al-Zelem	1	3	2
42	*Juglans regia L.*	Jouz	4	0	2
43	*Urtica pilulifera L.* *Urtica dioica L.* *Urtica urens L.*	Anjareh	0	4	2
44	*Lepidium sativum L.* *Nasturtium officinale R.Br.*	Harf	2	2	2
45	*Sinapis alba L.* *Sinapis arvensis L.* *Brassica nigra (L.) K.Koch*	Khardal	1	3	2
46	*Alhagi maurorum Medik.*	Taranjabin	3	0	1.5
47	*Apium graveolens L.*	Karafs	2	1	1.5
48	*Senna tora (L.) Roxb.*	Felfel	3	0	1.5
49	*Glossostemon bruguieri Desf.*	Mughath	2	1	1.5
50	*Sesamum indicum L.*	Semsem	1	2	1.5
51	*Allium sativum L.*	Thum	0	2	1
52	*Amomum granum-paradisi L. (unresolved)*	Joz al-Sherk	1	0	0.5
53	*Cannabis sativa L.*	Qunab	1	0	0.5
54	*Colchicum autumnale L.*	Soranjan	1	0	0.5
55	*Cotoneaster nummularia*	Sheer Kheshet	1	0	0.5
56	*Myristica fragrans Houtt.*	Basbasa	0	1	0.5
57	*Inula helenium L.*	Rasan	1	0	0.5
58	*Jasminum officinale L.*	Yasmin	1	0	0.5
59	*Nigella sativa L.*	Shoneez	1	0	0.5
60	*Malus domestica Borkh.*	Tufah	0	1	0.5
61	*Quercus ilex L.*	Ballot	1	0	0.5
62	*Zataria multiflora Boiss.*	Sattar	0	1	0.5
63	*Zingiber zerumbet (L.) Roscoe ex Sm.*	Zoronbad	1	0	0.5
64	*Carthamus tinctorius L.*	Qurtum	1	0	0.5
65	*Luffa cylindrica (L.) M.Roem.*	Luf	1	0	0.5

All findings were categorized by research type and key result. 25 items were mentioned as in papyro - use in other medical systems like Indian traditional medicine, Chinese traditional medicine-, etc (for 14 entities); 11 items were using entities in society (In soci) as aphrodisiac (for 8 entities); 8 items were In vitro studies (for 5 entity), and finally 45 items were in vivo studies (for 12 entity).(Table 2)

All 210 plant entities were searched for their Current efficacy evidence in the electronic literature which resulted in 106 items for only 22 (10%) plants, which decreased to 18 (8%) entities after excluding unrelated items. 192 (92%) plants are so far not studied for their aphrodisiac potential.

Table 2: current studies about aphrodisiac plants in described in PM

n	scientific name	Traditional Name	#	Type of Study	Key Result
1	*Allium cepa L.*	Basal	4	In vivo [13] In vitro [13] In papyro [14]	Clinically improved sexual potential [13]; PDE5 Inhibitor [13]; Contain sulphur-compound [14].
2	*Allium sativum L.*	Thum	5	In papyro [17,18] In vivo[19–21]	Effective in RCT[20]; Contain sulphur-compound [17,18]; Androgenic activity [19,22]; Antioxidant[21]
3	*Anacyclus pyrethrum (L.) Lag.*	Aagher-gharha	2	In vivo[23,24] In papyro[24]	Androgenic activity[24]; Improved sexual potential[24]
4	*Brassica rapa L.*	Shaljam	1	In papyro[25]; In vivo[25]; In soci[25]	Androgenic activity[25]

n	scientific name	Traditional Name	#	Type of Study	Key Result
5	*Cinnamomum verum J.Presl.*	Dar-Seeni	2	In papyro[26]; In vitro[26,27];	Arginase inhibitor[26]; Improved sexual potential[26]; PDE5 Inhibitor[27] Rho-kinase 2 inhibitor[28]
6	*Cocos nucifera L.*	Narjeel	1	In soci [29]	
7	*Crocus sativus L.*	Zaafaran	13	In vivo[30–35]; In papyro[36–38]	Effective in RCT[30,32–35,42], Ineffective in RCT[31]
8	*Ferula assa-foetida L.*	Anjedan	2	In vivo[43]; In papyro[43,44]	Androgenic activity[43]; improved sexual potential[43]
9	*Myristica fragrans Houtt.*	Jouz-Boua/ Basbaseh	2	In vivo[45,46]	improved sexual potential[45,46]
10	*Phoenix dactylifera L.*	Rutab, Tamr	2	In soci[47]	improved sexual potential[48]; Androgenic activity[48]
11	*Pimpinella anisum L.*	Anison	2	In papyro[49]	
12	*Pistacia terebinthus L.*	Haba-Khdraa	2	In papyro[50]; Excluded[51];	
13	*Prunus dulcis (Mill.) D.A.Webb*	Lawz	1	In soci [25]; In vivo[25]; In papyro[25];	Androgenic activity[25]
14	*Tribulus terrestris L.*	Hasak	37	In vivo[52–70] In vitro[63,65,71] In papyro[72–78] In soci[15,79]	Effective in RCT[52,66] Ineffective in RCT[70] Improved sexual potential [53,54,57,60,67]; Androgenic activity [53–55,57,58,61,67,69]; Androgenic ineffective[56,68] Antioxidant [55,57,65] Relaxation of the corpus cavernosum [59,63,71] Increased intracavernous pressure [59,63,67] PDE5 Inhibitor[27] Rho-kinase 2 inhibitor[28] caused Priapism [64] Testicular protective[65]
15	*Withania somnifera (L.) Dunal*	Eskande	8	In vivo[57,84–87] In vitro[87] In soci [15] In papyro[77,84]	Ineffective in RCT[89] Androgenic activity[57,84] Antioxidant[57,86] Improved sexual potential[57,85] up regulation in GnRH release[87] Rho-kinase 2 inhibitor[28]
16	*Zingiber officinale Roscoe*	Zanjabeel	11	In soci [25,29,90]; In vivo[25,91]; In papyro[25];	Androgenic activity[25] Antioxidant[91] PDE5 Inhibitor[91]
17	*Carthamus tinctorius L.*	Qurtom	1	In soci[29]	
18	*Brassica nigra (L.) K.Koch*	Khardal	2	Excluded	
19	*Syzygium aromaticum (L.) Merr. & L.M.Perry*	Quronful	4	In papyro[28] In vivo[28,95–97] In vitro[28]	Rho-kinase 2 inhibitor[28] Androgenic activity[95] Improved sexual potential[96,97]

Experimental studies (in vivo, in vitro) were designed to detect Androgenic activity in 11 entities (21 items), Antioxidant activity in 4 entities (7 items), Arginase inhibition in one entity (1 item), PDE5 Inhibition in 4 entities (4 items), Rho-kinase 2 Inhibition in 4 entities, evaluation of sexual potential in 8 entities (15 items), effect on corpus cavernosum in two entities (6 items), testicular protection and regulation of GnRH release in one entity (one item) for each. Human Randomized clinical trials (RCT) were done for only 4 entities (12 items), and finally, accidental observation was

obtained for two entities (improved sexual potential, caused Priapism).

DISCUSSION:

According to our investigation, most published articles targeted one plant at a time, while most PM remedies in clinical textbooks are polyherbal formulations which were designed to treat a specific type of ED, and each part of the formulation had its role like possessing synergic activity or being a multi-target drug. Therefore current studies can't prove PM claims or reject the efficacy of its remedies.

In addition, each plant has tens of bioactive chemicals that affect complex networks in multi-dimensional fashion, while current studies at the best are very poor to illustrate a clear view of plant activities in ED pathways. In fact, there are no complete in vitro models to qualify herbal activity on ED mechanisms.

Furthermore, existing experimental studies for each plant are various in duration, dosage, supplementation, measured outcome, rendering the analysis impossible.

On the other hand, all PM remedies investigated gained one or more evidence to be effective in ED management, which brings new hope to drug discovery.

CONCLUSION:

Erectile dysfunction (ED) is a chronic and common complaint, while limitations in clinical practice lead patients to use traditional medicine schools remedies. While traditional medicine observations and experiments are widely accepted to be a starting place for new idea development and base for drug discovery; available studies in this topic lack high-quality design and are devoid of safety declaration, in addition, their numbers are limited. For this reason, methodology and priority investigates are a keystone for future advances. Our study provided first literature-based priority suggestions from both traditional textbooks and current pieces of evidence.

ACKNOWLEDGMENT:

It is a part of PhD thesis, Number 164, Presented in School of Traditional Medicine, Shahid Beheshti University of Medical Sciences.

REFERENCES:

1. Wespes E, Eardley I, Giuliano F, Hatzichristou D, Hatzimouratidis H, Moncada I, et al. Guidelines on Male Sexual Dysfunction. European Association of Urology; 2013.
2. Prins J, Blanker MH, Bohnen AM, Thomas S, Bosch JLHR. Prevalence of erectile dysfunction: a systematic review of population-based studies. Int J Impot Res. 2002 Dec;14(6):422–32.
3.Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the united states: Prevalence and predictors. JAMA. 1999 Feb 10;281(6):537–44.
4.foroutan sayed kazem, jadid milani maryam. The Prevalence of Sexual Dysfunction among Divorce Requested. Daneshvar. 2009 Jan 1;16(78):39–44.
5.Foroutan SK, Rajabi M. Erectile dysfunction in men with angiographically documented coronary artery disease. Urol J. 2007 Winter;4(1):28–32.
6.Ernst E, Posadzki P, Lee MS. Complementary and alternative medicine (CAM) for sexual dysfunction and erectile dysfunction in older men and women: An overview of systematic reviews. Maturitas. 2011 Sep;70(1):37–41.
7.Stuckey BGA, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F, et al. Sildenafil Citrate for Treatment of Erectile Dysfunction in Men With Type 1 Diabetes Results of a randomized controlled trial. Diabetes Care. 2003 Feb 1;26(2):279–84.
8.World Health Organization, editor. WHO traditional medicine strategy. 2014-2023. Geneva: World Health Organization; 2013. 76 p.
9. (ed.) RR. Encyclopedia of the History of Arabic Science [Internet]. Vol. 3. Routledge; 1996 [cited 2016 Oct 14]. Available from: http://gen.lib.rus.ec/book/index.php?md5=95f40f2e4a5b5d52a9054971ed23f230
10.MODABBERI M. AGHILI ALAVI KHORASANI AND MAKHZAN AL-ADVIYEH. J Fac Lett Humanit KERMAN. 2002 WINTER - SPRING;8–9:102–17.
11. Zarshenas MM, Zargaran A, Müller J, Mohagheghzadeh A. Nasal Drug Delivery in Traditional Persian Medicine. Jundishapur J Nat Pharm Prod. 2013;8(3):144–148.
12. Ghahreman A, Okhovvat AR. matching the old medicinal plant Names with scientific terminology. 1st ed. Tehran: Unversity of Tehran; 2004.
13. Lines TC, Ono M. FRS 1000, an extract of red onion peel, strongly inhibits phosphodiesterase 5A (PDE 5A). Phytomedicine Int J Phytother Phytopharm. 2006 Mar;13(4):236–9.
14. Valle G, Carmignani M, Stanislao M, Michelini S, Volpe AR. Traditional medicine, corpus cavernosum and hydrogen sulphide. J Sex Med. 2011 Feb;8(2):631–2.
15. Majewski M. Allium sativum: facts and myths regarding human health. Rocz Panstw Zakl Hig. 2014;65(1):1–8.
16. Bełtowski J. Hydrogen sulfide in pharmacology and medicine--An update. Pharmacol Rep PR. 2015 Jun;67(3):647–58.
17. al-Bekairi AM, Shah AH, Qureshi S. Effect of Allium sativum on epididymal spermatozoa, estradiol-treated mice and general toxicity. J Ethnopharmacol. 1990 May;29(2):117–25.

18. Nishimatsu H, Kitamura T, Yamada D, Nomiya A, Niimi A, Suzuki M, et al. Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines - comparison with traditional herbal medicines (Kampo). Aging Male Off J Int Soc Study Aging Male. 2014 Jun;17(2):112–6.
19. Yang J, Wang T, Yang J, Rao K, Zhan Y, Chen R-B, et al. S-allyl cysteine restores erectile function through inhibition of reactive oxygen species generation in diabetic rats. Andrology. 2013 May;1(3):487–94.
20.Kasuga S, Uda N, Kyo E, Ushijima M, Morihara N, Itakura Y. Pharmacologic activities of aged garlic extract in comparison with other garlic preparations. J Nutr. 2001 Mar;131(3s):1080S–4S.
21. Sharma V, Boonen J, Spiegeleer BD, Dixit VK. Androgenic and spermatogenic activity of alkylamide-rich ethanol solution extract of Anacyclus pyrethrum DC. Phytother Res PTR. 2013 Jan;27(1):99–106.
22. Sharma V, Thakur M, Chauhan NS, Dixit VK. Effects of petroleum ether extract of Anacyclus pyrethrum DC. on sexual behavior in male rats. Zhong Xi Yi Jie He Xue Bao. 2010 Aug;8(8):767–73.
23.Qureshi S, Shah AH, Tariq M, Ageel AM. Studies on herbal aphrodisiacs used in Arab system of medicine. Am J Chin Med. 1989;17(1–2):57–63.
24.Goswami SK, Inamdar MN, Jamwal R, Dethe S. Effect of Cinnamomum cassia methanol extract and sildenafil on arginase and sexual function of young male Wistar rats. J Sex Med. 2014 Jun;11(6):1475–83.
25.Dell'Agli M, Galli GV, Dal Cero E, Belluti F, Matera R, Zironi E, et al. Potent inhibition of human phosphodiesterase-5 by icariin derivatives. J Nat Prod. 2008 Sep;71(9):1513–7.
26. Goswami SK, Pandre MK, Jamwal R, Dethe S, Agarwal A, Inamdar MN. Screening for Rho-kinase 2 inhibitory potential of Indian medicinal plants used in management of erectile dysfunction. J Ethnopharmacol. 2012 Dec 18;144(3):483–9.
27. Abudayyak M, Özdemir Nath E, Özhan G. Toxic potentials of ten herbs commonly used for aphrodisiac effect in Turkey. Turk J Med Sci. 2015;45(3):496–506.
28. Cai T, Morgia G, Carrieri G, Terrone C, Imbimbo C, Verze P, et al. An improvement in sexual function is related to better quality of life, regardless of urinary function improvement: results from the IDIProst® Gold Study. Arch Ital Urol Androl Organo Uff Soc Ital Ecogr Urol E Nefrol. 2013 Dec 31;85(4):184–9.
29. 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. Int J Impot Res. 2010 Aug;22(4):240–50.
30. 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. J Evid-Based Complement Altern Med. 2015 Oct;20(4):283–6.
31.Quarto G, Cola A, Perdonà S. Efficacy of IDIProst® Gold, a formulation containing Serenoa repens, Crocus sativus and PMBE, in men with concomitant LUTS and ED. Minerva Urol E Nefrol Ital J Urol Nephrol. 2016 Sep 1;
32. Shamsa A, Hosseinzadeh H, Molaei M, Shakeri MT, Rajabi O. Evaluation of Crocus sativus L. (saffron) on male erectile dysfunction: a pilot study. Phytomedicine Int J Phytother Phytopharm. 2009 Aug;16(8):690–3.
33.Hosseinzadeh H, Ziaee T, Sadeghi A. The effect of saffron, Crocus sativus stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats. Phytomedicine Int J Phytother Phytopharm. 2008 Jun;15(6–7):491–5.
34. Hosseinzadeh H, Nassiri-Asl M. Avicenna's (Ibn Sina) the Canon of Medicine and saffron (Crocus sativus): a review. Phytother Res PTR. 2013 Apr;27(4):475–83.
35. Alavizadeh SH, Hosseinzadeh H. Bioactivity assessment and toxicity of crocin: a comprehensive review. Food Chem Toxicol Int J Publ Br Ind Biol Res Assoc. 2014 Feb;64:65–80.
36. Srivastava R, Ahmed H, Dixit RK, Dharamveer null, Saraf SA. Crocus sativus L.: A comprehensive review. Pharmacogn Rev. 2010 Jul;4(8):200–8.
37. Modabbernia A, Sohrabi H, Nasehi A-A, 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 (Berl). 2012 Oct;223(4):381–8.
38.Bagheri SM, Yadegari M, Porentezari M, Mirjalili A, Hasanpor A, Dashti RMH, et al. Effect of Ferula assa-foetida oleo gum resin on spermatic parameters and testicular histopathology in male wistar rats. J Ayurveda Integr Med. 2015 Sep;6(3):175–80.
39.Bafghi AF, Bagheri SM, Hejazian SH. Antileishmanial activity of Ferula assa-foetida oleo gum resin against Leishmania major: An in vitro study. J Ayurveda Integr Med. 2014 Dec;5(4):223–6.
40. Tajuddin null, Ahmad S, Latif A, Qasmi IA, Amin KMY. An experimental study of sexual function improving effect of Myristica fragrans Houtt. (nutmeg). BMC Complement Altern Med. 2005 Jul 20;5:16.
41. Tajuddin null, Ahmad S, Latif A, Qasmi IA. Aphrodisiac activity of 50% ethanolic extracts of Myristica fragrans Houtt. (nutmeg) and Syzygium

aromaticum (L) Merr. & Perry. (clove) in male mice: a comparative study. BMC Complement Altern Med. 2003 Oct 20;3:6.
42. Hasan M, Mohieldein A. In Vivo Evaluation of Anti Diabetic, Hypolipidemic, Antioxidative Activities of Saudi Date Seed Extract on Streptozotocin Induced Diabetic Rats. J Clin Diagn Res JCDR. 2016 Mar;10(3):FF06-12.
43. Tahvilzadeh M, Hajimahmoodi M, Rahimi R. The Role of Date Palm (Phoenix dactylifera L) Pollen in Fertility: A Comprehensive Review of Current Evidence. J Evid-Based Complement Altern Med. 2016 Oct;21(4):320–4.
44. Albert-Puleo M. Fennel and anise as estrogenic agents. J Ethnopharmacol. 1980 Dec;2(4):337–44.
45.Bozorgi M, Memariani Z, Mobli M, Salehi Surmaghi MH, Shams-Ardekani MR, Rahimi R. Five Pistacia species (P. vera, P. atlantica, P. terebinthus, P. khinjuk, and P. lentiscus): a review of their traditional uses, phytochemistry, and pharmacology. ScientificWorldJournal. 2013;2013:219815.
46.Sawidis T, Yurukova L, Askitis T. Chios mastic, a natural supplement for zinc to enhance male sexuality and prostate function. Pharm Biol. 2010 Jan;48(1):48–54.
47. Sansalone S, Leonardi R, Antonini G, Vitarelli A, Vespasiani G, Basic D, et al. Alga Ecklonia bicyclis, Tribulus terrestris, and glucosamine oligosaccharide improve erectile function, sexual quality of life, and ejaculation function in patients with moderate mild-moderate erectile dysfunction: a prospective, randomized, placebo-controlled, single-blinded study. BioMed Res Int. 2014;2014:121396.
48. Sahoo HB, Nandy S, Senapati AK, Sarangi SP, Sahoo SK. Aphrodisiac activity of polyherbal formulation in experimental models on male rats. Pharmacogn Res. 2014 Apr;6(2):120–6.
49.Gauthaman K, Adaikan PG, Prasad RNV. Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats. Life Sci. 2002 Aug 9;71(12):1385–96.
50. Shalaby MA, Hammouda AAE-K. Assessment of protective and anti-oxidant properties of Tribulus terrestris fruits against testicular toxicity in rats. J Intercult Ethnopharmacol. 2014 Sep;3(3):113–8.
51. Sellandi TM, Thakar AB, Baghel MS. Clinical study of Tribulus terrestris Linn. in Oligozoospermia: A double blind study. Ayu. 2012 Jul;33(3):356–64.
52. Sahin K, Orhan C, Akdemir F, Tuzcu M, Gencoglu H, Sahin N, et al. Comparative evaluation of the sexual functions and NF-κB and Nrf2 pathways of some aphrodisiac herbal extracts in male rats. BMC Complement Altern Med. 2016 Aug 26;16(1):318.
53. Gauthaman K, Adaikan PG. Effect of Tribulus terrestris on nicotinamide adenine dinucleotide phosphate-diaphorase activity and androgen receptors in rat brain. J Ethnopharmacol. 2005 Jan 4;96(1–2):127–32.
54.Do J, Choi S, Choi J, Hyun JS. Effects and Mechanism of Action of a Tribulus terrestris Extract on Penile Erection. Korean J Urol. 2013 Mar;54(3):183–8.
55. Singh S, Nair V, Gupta YK. Evaluation of the aphrodisiac activity of Tribulus terrestris Linn. in sexually sluggish male albino rats. J Pharmacol Pharmacother. 2012 Jan;3(1):43–7.
56. El-Tantawy WH, Temraz A, El-Gindi OD. Free serum testosterone level in male rats treated with Tribulus alatus extracts. Int Braz J Urol Off J Braz Soc Urol. 2007 Aug;33(4):554-558; discussion 558-559.
57.Kavitha P, Ramesh R, Subramanian P. Histopathological changes in Poecilia latipinna male gonad due to Tribulus terrestris administration. In Vitro Cell Dev Biol Anim. 2012 May;48(5):306–12.
58. Kam SC, Do JM, Choi JH, Jeon BT, Roh GS, Hyun JS. In vivo and in vitro animal investigation of the effect of a mixture of herbal extracts from Tribulus terrestris and Cornus officinalis on penile erection. J Sex Med. 2012 Oct;9(10):2544–51.
59. Campanelli M, De Thomasis R, Tenaglia RL. Priapism caused by "Tribulus terrestris." Int J Impot Res. 2016 Feb;28(1):39–40.
60. Rajendar B, Bharavi K, Rao GS, Kishore PVS, Kumar PR, Kumar CSVS, et al. Protective effect of an aphrodisiac herb Tribulus terrestris Linn on cadmium-induced testicular damage. Indian J Pharmacol. 2011 Sep;43(5):568–73.
61.Iacono F, Prezioso D, Illiano E, Romeo G, Ruffo A, Amato B. Sexual asthenia: Tradamixina versus Tadalafil 5 mg daily. BMC Surg. 2012;12 Suppl 1:S23.
62.Gauthaman K, Ganesan AP, Prasad RNV. Sexual effects of puncturevine (Tribulus terrestris) extract (protodioscin): an evaluation using a rat model. J Altern Complement Med N Y N. 2003 Apr;9(2):257–65.
63. Neychev VK, Mitev VI. The aphrodisiac herb Tribulus terrestris does not influence the androgen production in young men. J Ethnopharmacol. 2005 Oct 3;101(1–3):319–23.
64. Gauthaman K, Ganesan AP. The hormonal effects of Tribulus terrestris and its role in the management of male erectile dysfunction--an evaluation using primates, rabbit and rat. Phytomedicine Int J Phytother Phytopharm. 2008 Jan;15(1–2):44–54.
65. Akhtari E, Raisi F, Keshavarz M, Hosseini H, Sohrabvand F, Bioos S, et al. Tribulus terrestris for treatment of sexual dysfunction in women: randomized double-blind placebo - controlled study. Daru J Fac Pharm Tehran Univ Med Sci. 2014 Apr 28;22:40.
66. Adaikan PG, Gauthaman K, Prasad RN, Ng SC. Proerectile pharmacological effects of Tribulus

terrestris extract on the rabbit corpus cavernosum. Ann Acad Med Singapore. 2000 Jan;29(1):22–6.
67. Sahoo HB, Nandy S, Senapati AK, Sarangi SP, Sahoo SK. Aphrodisiac activity of polyherbal formulation in experimental models on male rats. Pharmacogn Res. 2014 Apr;6(2):120–6.
68. Gauthaman K, Adaikan PG, Prasad RNV. Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats. Life Sci. 2002 Aug 9;71(12):1385–96.
69. Neychev V, Mitev V. Pro-sexual and androgen enhancing effects of Tribulus terrestris L.: Fact or Fiction. J Ethnopharmacol. 2016 Feb 17;179:345–55.
70.Qureshi A, Naughton DP, Petroczi A. A systematic review on the herbal extract Tribulus terrestris and the roots of its putative aphrodisiac and performance enhancing effect. J Diet Suppl. 2014 Mar;11(1):64–79.
71. Stasiak M, Żarłok K, Tomaszewski W. [Erectile dysfunction - treatment with substances of natural origin]. Wiadomosci Lek Wars Pol 1960. 2016;69(3 pt 2):576–81.
72. Malviya N, Jain S, Gupta VB, Vyas S. Recent studies on aphrodisiac herbs for the management of male sexual dysfunction--a review. Acta Pol Pharm. 2011 Feb;68(1):3–8.
73. Ho CCK, Tan HM. Rise of herbal and traditional medicine in erectile dysfunction management. Curr Urol Rep. 2011 Dec;12(6):470–8.
74.Qureshi A, Naughton DP, Petroczi A. A systematic review on the herbal extract Tribulus terrestris and the roots of its putative aphrodisiac and performance enhancing effect. J Diet Suppl. 2014 Mar;11(1):64–79.
75.Mutheeswaran S, Pandikumar P, Chellappandian M, Ignacimuthu S. Documentation and quantitative analysis of the local knowledge on medicinal plants among traditional Siddha healers in Virudhunagar district of Tamil Nadu, India. J Ethnopharmacol. 2011 Sep 1;137(1):523–33.
76. Sökeland J, Albrecht J. [Combination of Sabal and Urtica extract vs. finasteride in benign prostatic hyperplasia (Aiken stages I to II). Comparison of therapeutic effectiveness in a one year double-blind study]. Urol Ausg A. 1997 Jul;36(4):327–33.
77. Ambiye VR, Langade D, Dongre S, Aptikar P, Kulkarni M, Dongre A. Clinical Evaluation of the Spermatogenic Activity of the Root Extract of Ashwagandha (Withania somnifera) in Oligospermic Males: A Pilot Study. Evid-Based Complement Altern Med ECAM. 2013;2013:571420.
78. Ilayperuma I, Ratnasooriya WD, Weerasooriya TR. Effect of Withania somnifera root extract on the sexual behaviour of male rats. Asian J Androl. 2002 Dec;4(4):295–8.
79. Walvekar M, Shaikh N, Sarvalkar P. Effects of glycowithanolides on lipid peroxidation and lipofuscinogenesis in male reproductive organs of mice. Iran J Reprod Med. 2013 Sep;11(9):711–6.
80. Kataria H, Gupta M, Lakhman S, Kaur G. Withania somnifera aqueous extract facilitates the expression and release of GnRH: In vitro and in vivo study. Neurochem Int. 2015 Oct;89:111–9.
81.Mamidi P, Thakar AB. Efficacy of Ashwagandha (Withania somnifera Dunal. Linn.) in the management of psychogenic erectile dysfunction. Ayu. 2011 Jul;32(3):322–8.
82.Oliveira CH, Moraes MEA, Moraes MO, Bezerra FAF, Abib E, De Nucci G. Clinical toxicology study of an herbal medicinal extract of Paullinia cupana, Trichilia catigua, Ptychopetalum olacoides and Zingiber officinale (Catuama) in healthy volunteers. Phytother Res PTR. 2005 Jan;19(1):54–7.
83.Ferrini MG, Hlaing SM, Chan A, Artaza JN. Treatment with a combination of ginger, L-citrulline, muira puama and Paullinia cupana can reverse the progression of corporal smooth muscle loss, fibrosis and veno-occlusive dysfunction in the aging rat. Androl Open Access. 2015 Jun;4(1).
84.Mishra RK, Singh SK. Safety assessment of Syzygium aromaticum flower bud (clove) extract with respect to testicular function in mice. Food Chem Toxicol Int J Publ Br Ind Biol Res Assoc. 2008 Oct;46(10):3333–8.
85.Tajuddin null, Ahmad S, Latif A, Qasmi IA. Effect of 50% ethanolic extract of Syzygium aromaticum (L.) Merr. & Perry. (clove) on sexual behaviour of normal male rats. BMC Complement Altern Med. 2004 Nov 5;4:17.
86.Tajuddin null, Ahmad S, Latif A, Qasmi IA. Aphrodisiac activity of 50% ethanolic extracts of Myristica fragrans Houtt. (nutmeg) and Syzygium aromaticum (L) Merr. & Perry. (clove) in male mice: a comparative study. BMC Complement Altern Med. 2003 Oct 20;3:6.