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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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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 rem**e**dies 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.

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