Herbal Medicines Journal **2018; Vol. 3, No. 4:162-9**
DOI: 10.22087/herb%20med%20j.v3i4.722 **ISSN:** 2538-2144

Review Article

The Phytochemical Basis of the Herbal Remedies Found in Oriental Medicine for Erectile Dysfunction

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Received: 06.03.2019; Accepted: 02.07.2019

Abstract

Background and Aim: Erectile dysfunction (ED) is a common cause of seeking advice from health care professionals. The required advices include information concerning the utility of remedies proposed by traditional medicine. Substantial advertising and the significant business of herbal aphrodisiacs demand the accomplishment of many studies concerning the efficacy and safety of these distinct approaches.
Unfortunately, the majority of potential remedies provided by aphrodisiac plants in Oriental Medicine (OM) have roughly remained unnoticed. Moreover, usually only one pathway regarding the bioactivity of a specific plant is addressed. However, plants contain several bioactive ingredients every one of which engages in various biological systems.
Materials and Methods: In this investigation, the entire plants recommended for ED by OM that were selected from comprehensive pharmacopeia texts, storehouses of medicaments, were identified. Subsequently, their latest scientific names were identified; and finally, the relevant phytochemical and biologic activities of every one of them were extracted from Dr. Duke's Phytochemical and Ethnobotanical Databases.
Results: Out of 210 plants suggested for treating ED in OM, only 76 plants were present in the mentioned database. Meanwhile, 62 (82%) cases of them had phytochemical evidence that might be effective through one or more pathways known to affect the pathophysiology of ED.
Conclusion: This paper primarily provides a multidimensional prospective to herbal remedies for ED, and seeks to suggest more efficient formulations of herbal combinations recommended by OM. The researchers also attempt to propose new ideas for further research in the future.
Keywords: Persian medicine, Greco-Arab medicine, Erectile dysfunction, Phytochemistry, Drug discovery

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Please cite this article as: Al Attar M, Ashrafzade F, Kamalinejad M. The Phytochemical Basis of the Herbal Remedies Found in Oriental Medicine for Erectile Dysfunction. Herb. Med. J. 2018;3(4):162-9.

Introduction

Erectile dysfunction (ED) is a general complaint among men which is defined as the inability to develop or maintain an erection of the penis during sexual activity. Erectile dysfunction (ED) incidence is estimated to entangle about 30% of men younger than the age of 40 and more than 50% of men after this age

(1–4). This problem changes the quality of life, affects the mood, and is a source of interpersonal and social troubles (1, 5).

Since it is a common chronic ailment related to a wide range of clinical conditions like diabetes, hypertension, psychological disorders etc., (6), ED has become one of the most significant subjects of drug advertising the revenues of which exceeded $8 billion just in 2014 (7, 8). However, readily available treatments such as phosphodiesterase 5 inhibitors (PDE5i) have a failure rate of about 50% in some patients, correlated with various side effects in high percentages (9). Due to certain reasons, including, though not limited to, contraindications of intervention, and cultural values, patients generally prefer to use complementary and alternative medicine (CAM) recommendations.

In view of the fact that traditional medicine's knowledge and experiences are generally accepted to be the bases for finding ideas in drug discovery, and also given the fact that some of its remedies are still efficient and safe; historically Oriental Medicine (OM) is the inheritor of ancient medical knowledge in the Middle East collected by famous Greek physicians such as Hippocrates, Pedanius Dioscorides and Galen whose works were translated mainly to Arabic by well-known scientists such as Rhazes and Avicenna. Due to its cultural roots, it is still used by millions of people worldwide (10). The present study sought to focus on current phytochemical evidences in herbal drugs that are suggested for the treatment of erectile dysfunction in Oriental Medicine.

Materials and Methods

A. Selection of OM information source: information concerning herbal medications in OM is available in pharmacopeias and clinical textbooks. The latest and most comprehensive pharmacopeia is Makhzan al-Adviea (the storehouse of medicaments) that was compiled by Aghili Khorasani (18th century). This text contains 1698 monographs structured alphabetically (9, 10). As previous studies have indicated, this book is indeed a comprehensive instance of OM pharmacopeia (11).

B. The effect of herbal extracts on ED as indicated in OM pharmacopeia: the selected pharmacopeia was searched for aphrodisiac (Arabic equivalent: *Mobahi*) and impotence (Arabic equivalent: *zafe bah*). The results were authenticated by a botanical study concerning matching the old medicinal plant names with scientific terminology (12). The latest accepted scientific names were obtained from the plant list database for each item [OM list].

C. Selecting the data source of phytochemical and biologic activities: Dr. Duke's Phytochemical and Ethnobotanical Databases were selected as the data source. The latest accepted scientific names of all plant records were obtained from the plant list. The plants with biologic activities «testosterone-inducer», «testosterogenic», «androgenic», «aphrodisiac» and «PDE-Inhibitor», and plants that contain sulphur compounds recognized by exploration for chemicals with the spelling of «THIOL», «THIONE», «GLUTATHIONE», «CYSTEINE», «MERCAPTAN» were selected.

D. Data combination: based on the latest accepted name in both data collections, the OM list and records were selected from Dr. Duke's database, the data were mixed, and the final table cover the phytochemical evidence of OM climes about efficiency on ED.

Results and Discussion

Based on the selected pharmacopoeia, 279 cases were found eligible to be recommended for ED or claimed to be aphrodisiac, among which 210 cases were plants. We found 113 (54%) plants with accepted scientific names [OM list], but others that were unrecognized were determined as general species name or with unresolved name.

On the other hand, from 2376 plant records of Dr. Duke's Phytochemical and Ethnobotanical Databases, 1730 record were saved as the latest accepted name. We recognized 289 last accepted names. Totally, 2019 plant belonging to the latest accepted names were documented, but we failed to correlate 357 records due to the lack of a specific name.

However; without duplication, 74 (65.4%) plants from OM list matched the records form Dr. Duke's database, which was searched for related activities or sulphur compounds that in turn resulted in 62 (83.8%) items with our phytochemical goal. 8 (12.9%) plants of them acted through one pathway, 12 cases (18.75%) acted through two, 13 (20.3%) through three, 19 plants

(29.6%) acted through four and finally 10 (15.6%)

Table 1: Plants recommended by OM for ED, Phytochemicals involved in pathways relate to ED pathogenesis.

#	Scientific Name	OM Name	Testosterogenic	Androgenic	Aphrodisiac	PDE-Inhibitor	Contain Sulfur	Pathways
1	*Linum usitatissimum L.*	Kattan	ZINC	β-SITOSTEROL	ARGININE	ORIENTIN VITEXIN	CYSTEINE	5
2	*Phaseolus vulgaris L.*	Lubia	ZINC	β-SITOSTEROL BORON	ARGININE ESTRONE	RUTIN	THIOL* GLUTATHIONE	5
3	*Triticum aestivum L.*	Henta	ZINC	BORON	ARGININE	QUERCETIN	CYSTEINE	5
4	*Zingiber officinale Roscoe*	Zanjabeel	ZINC Δ-CADINENE	β-SITOSTEROL BORON	ARGININE MELATONIN	KAEMPFEROL QUERCETIN	CYSTEINE	5
5	*Phoenix dactylifera L.*	Rutab	ZINC	β-SITOSTEROL BORON	ARGININE ESTRONE	QUERCETIN RUTIN	CYSTEINE	5
6	*Brassica oleracea L.*	Karnab	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN	CYSTEINE * THIONE* THIOL*	5
7	*Camellia sinensis (L.) Kuntze*	Chaei Khataee	ZINC Δ-CADINENE	β-SITOSTEROL	ARGININE	(+)-CATECHIN CAFFEINE KAEMPFEROL NARINGENIN QUERCETIN RUTIN THEOBROMINE THEOPHYLLINE VITEXIN	CYSTEINE *	5
8	*Daucus carota L.*	Jazar	ZINC CHRYSIN	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN	CYSTEINE	5
9	*Allium cepa L.*	Basal	ZINC	β-SITOSTEROL BORON	ARGININE MELATONIN	KAEMPFEROL QUERCETIN RUTIN	THIOL CYSTEINE	5
10	*Allium sativum L.*	Thom	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN	CYSTEINE THIONE THIOL GLUTATHIONE	5
11	*Abelmoschus esculentus (L.) Moench*	Bameia	ZINC	β-SITOSTEROL	ARGININE	QUERCETIN		4
12	*Juglans regia L.*	Juz	ZINC	β-SITOSTEROL BORON	ARGININE MELATONIN	KAEMPFEROL QUERCETIN		4
13	*Malus domestica Borkh.*	Tuffah	ZINC	β-SITOSTEROL BORON OCTACOSANOL	ARGININE ESTRONE	(+)-CATECHIN KAEMPFEROL QUERCETIN RUTIN		4
14	*Mangifera indica L.*	Anbaj	ZINC	BORON	ARGININE	KAEMPFEROL QUERCETIN		4
#	Scientific	OM	Testosterogenic	Androgenic	Aphrodisiac	PDE-Inhibitor	Contain Sulfur	Pathways

	Name	Name	nic					ys
15	*Anacardium occidentale L.*	Baladur	ZINC	β-SITOSTEROL BORON	ARGININE	NARINGENIN		4
16	*Phyllanthus emblica L.*	Amolaj	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
17	*Portulaca oleracea L.*	Baghla Hamgha	ZINC	β-SITOSTEROL	ARGININE		GLUTATHIONE	4
18	*Prunus dulcis (Mill.) D.A.Webb*	Luz	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN		4
19	*Prunus persica (L.) Batsch*	Khokh	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL NARINGENIN QUERCETIN		4
20	*Apium graveolens L.*	Karafs	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
21	*Sesamum indicum L.*	Semsem	ZINC	β-SITOSTEROL BORON	ARGININE	PINORESINOL		4
22	*Asparagus officinalis L.*	Helion	ZINC	BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
23	*Urtica dioica L.*	Anjoreh	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
24	*Brassica cretica Lam.*	Karnab	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
25	*Albizia lebbeck (L.) Benth.*	Abreesham		β-SITOSTEROL	ARGININE	KAEMPFEROL QUERCETIN		4
26	*Brassica cretica Lam.*	Karnab	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
27	*Brassica rapa L.*	Shaljam	ZINC	β-SITOSTEROL BORON	ARGININE		CYSTEINE *	4
28	*Coriandrum sativum L.*	Kuzborah	ZINC	β-SITOSTEROL BORON	ARGININE	QUERCETIN RUTIN		4
29	*Ficus carica L.*	Teen	ZINC	β-SITOSTEROL BORON	ARGININE	KAEMPFEROL QUERCETIN RUTIN		4
30	*Myristica fragrans Houtt.*	Juz Boa	ZINC Δ-CADINENE	β-SITOSTEROL BORON		KAEMPFEROL QUERCETIN		3
31	*Acacia nilotica (L.) Delile*	Om Ghilan		OCTACOSANOL		(+)-CATECHIN QUERCETIN		3
32	*Pimpinella anisum L.*	Anison	ZINC	β-SITOSTEROL BORON		QUERCETIN RUTIN		3
33	*Pistacia vera L.*	Fustoq	ZINC	β-SITOSTEROL BORON	ARGININE			3
#	Scientific Name	OM Name	Testosterogenic	Androgenic	Aphrodisiac	PDE-Inhibitor	Contain Sulfur	Pathways

34	*Syzygium aromaticum (L.) Merr. & L.M.Perry*	Qaranful	ZINC Δ-CADINENE	β-SITOSTEROL BORON		KAEMPFEROL QUERCETIN BIFLORIN		3
35	*Tribulus terrestris L.*	Hasak		β-SITOSTEROL	HARMINE	KAEMPFEROL QUERCETIN RUTIN		3
36	*Withania somnifera (L.) Dunal*	Eskande		β-SITOSTEROL		QUERCETIN RUTIN	CYSTEINE	3
37	*Tanacetum parthenium (L.) Sch.Bip.*	Oqhowan	ZINC Δ-CADINENE	β-SITOSTEROL ELEUTHEROSIDE-B-1	MELATONIN			3
38	*Achillea millefolium L.*	Hazanbal	ZINC Δ-CADINENE	β-SITOSTEROL		QUERCETIN RUTIN		3
39	*Brassica oleracea L.*	Karnab	ZINC		ARGININE	KAEMPFEROL QUERCETIN		3
40	*Cannabis sativa L.*	Qunnab	Δ-CADINENE		ARGININE	ORIENTIN		3
41	*Cocos nucifera L.*	Narjeel	ZINC	β-SITOSTEROL BORON	ARGININE			3
42	*Corylus avellana L.*	Jellouz, Bondoq	ZINC	β-SITOSTEROL BORON		KAEMPFEROL QUERCETIN		3
43	*Alpinia officinarum Hance*	Kholanjan	Δ-CADINENE			KAEMPFEROL QUERCETIN		2
44	*Matricaria chamomilla L.*	Babonaj		β-SITOSTEROL		KAEMPFEROL QUERCETIN RUTIN		2
45	*Nerium oleander L.*	Defli		β-SITOSTEROL		QUERCETIN RUTIN		2
46	*Calendula officinalis L.*	Azarion		β-SITOSTEROL		KAEMPFEROL QUERCETIN RUTIN		2
47	*Capparis spinosa L.*	Kabar		β-SITOSTEROL		QUERCETIN RUTIN		2
48	*Cyanus segetum Hill*	Juz Jandom		β-SITOSTEROL		KAEMPFEROL QUERCETIN		2
49	*Chamaemelum nobile (L.) All.*	Babonaj	ZINC			RUTIN		2
50	*Cicer arietinum L.*	Hommus	ZINC		ARGININE			2
51	*Cinnamomum verum J.Presl*	Dar Seini	ZINC	β-SITOSTEROL BORON				2
52	*Citrus × aurantium L.*	Naranj	ZINC Δ-CADINENE			NARINGENIN		2
53	*Crocus sativus L.*	Zafarzan			ARGININE	KAEMPFEROL QUERCETIN		2
#	Scientific Name	OM Name	Testosterogenic	Androgenic	Aphrodisiac	PDE-Inhibitor	Contain Sulfur	Pathways
5	*Elaeagnus*	Qubayra			HARMINE	KAEMPFERO		2

4	*angustifolia L.*					L QUERCETIN	
55	*Alpinia galanga (L.) Willd.*	Kholanjan			ARGININE		1
56	*Lawsonia inermis L.*	Hanna		β-SITOSTEROL			1
57	*Smilax china L.*	Chob Chini				RUTIN	1
58	*Trachyspermum ammi (L.) Sprague*	Nankhah	ZINC				1
59	*Boswellia sacra Flueck.*	Kundor	Δ-CADINENE				1
60	*Acorus calamus L.*	Waj	ZINC Δ-CADINENE				1
61	*Senna tora (L.) Roxb.*	QulQul	ZINC				1
62	*Abrus precatorius L.*	Aein al-Deek		β-SITOSTEROL			1

plants acted through all the five pathways [Table 1]. Eventually, 28 phytochemicals in plants recommended in OM related to ED were identified. Table 2 indicates these phytochemicals that have been classified based on their roles.

The twelve remained items without the related phytochemical were listed as scientific name [OM name] mentioned as follows: *Narcissus tazetta L.* [Narjes], *Zataria multiflora Boiss.* [Saatar], *Saccharum officinarum L.* [Sokkar], *Calicotome spinosa (L.) Link* [Dar Shisheaan], *Colchicum autumnale L.* [Soranjan], *Commiphora mukul (Hook. ex Stocks) Engl.* [Muql], Thymbra *capitata (L.) Cav.* [Hasha], Curcuma *zedoaria (Christm.) Roscoe* [Jadwar], *Syzygium cumini (L.) Skeels* [Jamon*], Ferula assa-foetida L.* [Anjedan], *Jasminum officinale L.* [Yasamin], *Tulipa gesneriana L.* [Khesi al-thalab].

Since erectile dysfunction (ED) is a common problem among men, they seek cures from various sources including herbal and traditional medicine remedies. Likewise, the studies that are conducted to examine the efficacy and safety of various approaches are of high significance for professional health care providers. Unfortunately, roughly all remedies of aphrodisiac plants in Oriental Medicine (OM) have remained unexamined. This study provides phytochemical evidence for claims raised in OM on ED management for the first time. Furthermore, this investigation confirms the findings of a number of previous studies, and puts forward new ideas for further research.

At first hand, about 85% of OM recommended plants act on more than one pathway involved in ED, while our results present a multi-target paradigm in the explanation of herbal effects. Moreover, in many cases, there are two or more bioactive compounds that might synergize each other. This finding challenges the data reductionism approach used in the majority of previous articles. Furthermore, OM scholars noted that CNS pathway plays a significant role in sexual function. Hence, they prescribed odorant plants like *Jasminum officinale L.* and *Narcissus tazetta L.*, both of which are without chemicals related to ED in this investigation. However, a number of recently conducted studies have proposed that olfactory stimulation could activate brain areas of sexual arousal (11).

On the other hand, our restricted knowledge in matching ancient botanical names with scientific ones necessitates greater attention to ancient botanical knowledge as well as applications like drug discovery. Previous studies had reorganized only 24% of scientific names from 2962 entities (12). Moreover, well designed, fine documented, updated and comprehensive botanical, Phytochemical and ethnobotanical databases for OM are missing. For Instance, thiol is another name for Mercaptan, which has been mentioned in separate records. This sulfur compound includes L-Cysteine that drew attentions

Table 2: Frequency of Phytochemicals related to ED in OM herbal remedies.

activity	Count	Chemicals	Frequency
Testosterone-Inducer Testosterogenic	3	ZINC	47
		Δ-CADINENE	12
		CHRYSIN	1
Androgenic	4	β-SITOSTEROL	45
		BORON	32
		OCTACOSANOL	2
		ELEUTHEROSIDE-B-1	1
Aphrodisiac	4	ARGININ	41
		MELATONIN	5
		ESTRONE	3
		HARMINE	2
PDE-Inhibitor	12	QUERCETIN	42
		KAEMPFEROL	31
		RUTIN	26
		NARINGENIN	4
		(+)-CATECHIN	3
		ORIENTIN	2
		VITEXIN	2
		BIFLORIN	1
		CAFFEINE	1
		THEOBROMINE	1
		THEOPHYLLINE	1
		PINORESINOL	1
Sulfur Compound	5	CYSTEINE	11
		THIOL	6
		GLUTATHIONE	3
		MERCAPTAN→ CYSTEINE	2
		THIONE	2

following the recognition of hydrogen sulfide (H_2S) gasotransmitter on erectile function (13,14), and many of them might be influential in hydrogen sulfide pathway. This phenomenon highlights the need for having a hierarchy tree for chemical compounds.

Moreover, with the medical community desperately calling for the development of new pharmacologic treatments for ED in coming years for many reasons, particularly the absence of innovative options (15), herbal remedies of ancient medical schools could still play their typical role in drug discovery. This alternative becomes more significant when an examination of the results of previous studies indicate that only eight percent of OM remedies for ED have been scientifically investigated (in vivo and in vitro) the efficacy of all of which has been confirmed. However, no more than four plants have been enrolled in human clinical trials (16).

Finally, OM scholars have usually prescribed herbal combination formulas because they believed in the synergic effect of plants. They have undertaken multi-target strategies to multiply the efficacy and at once decrease the dosage of single plants in order to reduce side effects. However, understanding the principles, analyzing this formulas, and prioritizing them for clinical research are still complex.

Conclusion

This investigation provides a new approach to the understanding of the phytochemical basis of OM remedies in ED management. More than 82 percent of the recommended plants have chemical evidence. However, only 8 percent of them have been scientifically investigated. Hence, the recognition of this shortage might be helpful in identifying research priorities concerning the herbal management of ED or in drug discovery. Furthermore, it might be used to clarify the role of every section used by OM clinicians in poly herbal formulation.

Acknowledgment

The authors would like to thank Dr. Ardalan Memar and Mr. Ahmad Al Eid for their valuable suggestions, proofreading, and language editing.

Conflict of Interest

The authors declare that they have no conflict of interest. This research did not receive any specific grant from funding agencies in public, commercial, or not-for-profit sectors.

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