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Review

Relationship between Male Sexual Dysfunction, Fertility Power and Heart Function: Avicenna's Standpoint

Mehrdad Karimi[1], Laleh Khodaie[2], Samaneh Soleymani[3], Mohammad Reza Mirzaei[4]*, Parinaz Kalejahi[5]

[1]Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Pharmacognosy, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Traditional Pharmacy, School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Traditional Medicine, School of Persian Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Department of Nutrition, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

Infertility and erectile dysfunction (ED) are common health issues and exacerbate as men age. In recent years, it has been realized that cardiovascular disease (CVD) forecasts the incidence of ED; however, there is less evidence of the relationship between fertility with CVD. According to Avicenna, an eminent physician of Persian medicine, there is a connection between CVD, male sexual problems, and fertility. The aim of this study is to discuss the mentioned connection and the role of medicinal plants in mitigating CVD and as a result, male infertility. This library-based study focused on Avicenna's outstanding manuscript "The Canon of Medicine". Scientific databases, such as PubMed, Scopus, and Google Scholar were searched to investigate current pharmacological findings and mechanisms of action of medicinal plants mentioned in "The Canon of Medicine". Avicenna pinpointed that CVD is responsible for insufficient production of the endogenous gaseous substance required for the erection, causing infertility. He mentioned the association between the ability to produce semen of good quality and fertility potential to improve heart function. Medicinal plants mentioned in his manuscript mainly possess antioxidant and anti-inflammatory effects, improve plasma lipid profile, reduce triacylglycerol, and show cardioprotective effects, which consequently boost fertility by improvement of sperm parameters. Expression of the association between cardiac function and male fertility demonstrates Avicenna's significant contribution to improving the sciences of male fertility and cardiology in the medieval era. In addition, the recommended medicinal plants seem to be a valuable source for identifying new remedies for the treatment of male sexual disorders and infertility.

Keywords: Persian medicine; Impotence; Herbal medicine; Spermatogenesis; Molecular mechanism; History of medicine; Avicenna

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*Corresponding Author: Mohammad Reza Mirzaei
Department of Traditional Medicine, School of Persian Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
Email: Dr.mirzaei_m@yahoo.com

Introduction

Normal sexual function has great importance and it is a major and integral part of health and quality of live. Infertility and sexual disorders, such as Erectile Dysfunction (ED) are of partially high prevalence. Approximately 15% of couples suffer from infertility issues. About 40 - 45% of mature women and approximately 20-30% of adult men have various types of sexual dysfunctions [1,2]. ED has been reported in 52% of men aged 40-70 years [3] which is a medical condition and has social aspects. The World Health Organization (WHO) considers infertility as a global challenge with social dimensions [4].

Despite major achievements in the diagnosis and treatment of infertility and ED, different aspects of them are still unknown. For instance, the most prevalent type of infertility which comprises 30- 45% of infertile males is of unknown origin and defined as idiopathic infertility. Most of these patients have idiopathic dysfunctions in their semen characteristics and are labeled as idiopathic oligoasthenoteratozoospermia. Although there are several medications for sexual dysfunctions, they are usually expensive, not easily available, and are along with some side effects [5]. Furthermore, utilizing expensive and invasive Assisted Reproductive Technologies (ART) methods such as *in vitro* fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) were not successful approaches. Additionally, they are not available to most of the infertile couples [6]. Therefore, realizing the novel and effective criteria which affect infertility and ED, and finding helpful therapies for them is of utmost importance.

Recent research has proved that there is a connection between brain activity and testicular function, which includes the process of creating sperms and maintaining normal fertility. The brain is a vital organ in the hypothalamus-pituitary-adrenal (HPA) axis. Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) are the two main interfering hormones in spermatogenesis and fertility. Furthermore, the liver, with its effect on the endocrine glands and metabolism, plays a key role in spermatogenesis and fertility [7]. The heart supplies blood to body organs. Current evidence support the relationship between the heart and sexual function. For instance, some sexual disorders such as ED are associated with cardiovascular disease (CVD) [8]. Studies suggests that ED is primarily a vascular disorder. Endothelial dysfunction appears to be the main cause of ED. Diabetes, hypertension and hyperlipidemia, smoking, and obesity are often found in people with ED [8,9,10].

There are various modalities of traditional and complementary medicine, such as Ayurveda, Chinese, and Persian Medicine (PM). PM is one of the most ancient forms of traditional medicine that dates back more than 7000 years ago [11]. In PM, there is a holistic viewpoint of the human body based on temperaments (Mizaj). In the medieval ages (5th to 15th century), medical sciences flourished by Persian scientists including Rhazes (865-925 CE), HalyAbbas (949-982 AD), and Avicenna (980-1037 AD) [11]. In PM, proper functionality of the heart, liver, and brain is necessary for appropriate sexual function and normal semen production [12].

Ibn-e-Sīna, known as Avicenna, was a great scientist and man of thought in philosophy, logic, medicine, mathematics, astrology, and other subject areas. He lived in the golden age of science in the ancient Islamic world and authored numerous scientific works in different fields [13]. He wrote about 450 books and was among the scientists who advanced knowledge in different sciences, especially medicine, during the European Middle Ages. His book entitled "the Canon of Medicine" was a masterpiece and a medical and pharmaceutical textbook that was the reference textbook for teaching medicine in western medical schools until the 17th century. Considering the importance of heart, he exclusively wrote on cardiology in two different books titled "*Kitab al-Adviytol Qalbiye*" (the book of Cardiac Medicine) which includes a variety of drugs for the treatment of cardiac diseases [14] and "*Resaley-e-Ragshenasi*" (Treatise on Pulsology) [15,16]. He believed that the heart, along with the brain and liver, are the major organs of the human body and then highlighted the heart for its unique functionality for proper male sexual activity [17].

To the best of our knowledge, the relationship between cardiac function and infertility has not been investigated. Thus, the aim of the present study was to investigate the role of the heart in fertility and sexual function from Avicenna's perspective. Also, the second objective of this study was to investigate the current pharmacological findings and molecular mechanisms of medicinal plants mentioned in *the Canon of Medicine* effective on CVD and infertility.

Methods

In this paper, chapter 3 of *the Canon of Medicine* was studied and considered. The mentioned medicinal plants in this book effective on the heart and male fertility disorders were fully considered and their possible mechanisms of action were described according to the findings of modern medicine. For this purpose, different electronic databases such as PubMed, Scopus, and Google Scholar were searched.

Results and Discussion

The results were tabulated in table 1 which includes herbs studied in three levels *in vitro*, *in vivo,* and human studies.

Relationship between the heart and fertility according to Avicenna and current findings

Avicenna in the manuscript of *Canon of Medicine* distinctly and comprehensively explained the anatomy and diseases of heart and related treatments of CVD. In addition, sexual dysfunctions and poor semen characteristics

were discussed in two separate chapters. "*Nogsan-E-Bah*" (sexual weakness) and "*Ogr o Osr Habl*" (infertility and subfertility). He proposed a direct relationship between the heart with sexual power and normal fertility. Etiologically, he attributed heart failure and other cardiac conditions to be one of the reasons for infertility and impotence. According to his notion, there is a relationship between the cardiac well-being and good-quality semen production as well as the potential of male fertility. He mentioned different criteria to study the functions of the reproductive system and semen quality. One of those determinants was the patient's pulse. According to Avicenna's viewpoint, general body weakness is another reason for infertility and impotence. He ascribed this weakness to a weakened heart that is represented by the patient's pulse [12]. Also, he believed that infertile and impotent patients with general weakness needed to undergo cardiac rehabilitation and treat cardiac disorders [12].

Based on Avicenna's axioms, the brain is the sensual source of sexual arousal, while the heart produces a substance defined as "rih" (probably an indigenous gas or wind) that directly affects normal erection. Similarly, appropriate sexual function, erection, and normal fertility were directly ascribed to a gaseous natural substance originating from the heart [18]. According to a study, endogenous hydrogen sulfide, or H_2S involves in vascular homeostasis and erectile mechanisms. Moreover, the components of smooth muscle were determined as the source of H_2S production. In that manuscript, it was suggested that the pathways of H_2S production are likely to be promising targets for the treatment of ED [19]. Avicenna stated that the heart (directly and indirectly), through other organs such as the liver or kidneys, could affect erectile mechanisms [12]. Therefore, according to Avicenna's theory of erection, when faced with a patient with ED and infertility, a vital task is to assess and treat cardiac disorders. It is yet to enlighten the precise correlation between the endogenous gaseous substance, heart, ED, and fertility.

Some studies have investigated the correlation between erection and cardiac disorders. CVD and ED both have common risk factors including hypertension (HTN), diabetes mellitus (DM), smoking, high cholesterol and body mass index (BMI), and low high-density lipoprotein cholesterol (HDL-C) [20]. Miner et al. demonstrated that incident ED has a greater predictive value for CVD than traditional risk factors such as the family history of myocardial infarction, hyperlipidemia, and smoking. They even signified that ED occurrence in young people can be a prognostic factor for the future occurrence of CVD [21]. Moreover, a meta-analysis of prospective cohort studies showed that ED significantly enhances the risk of CVD and coronary heart diseases [22].

Fung et al., in a prospective study of men aged 30 to 69 years reported that risk factors of heart disease can predict ED occurrence in the next 25 years and improvements in coronary heart disease (CHD) risk factors can reduce the risk of ED [23]. Some researchers assume that sexual function is a reflection of general health in men [24].

An investigation of the correlation between cardiovascular health (CVH) and endothelial function with future ED showed that CVH is independent of endothelial function, but there is a significant correlation with future ED. The prevalence of ED in younger people (45-50 years) with low CVH is similar to that in older people (75-84 years) with high CVH, therefore it was suggested that high CVH in middle and old ages decreases the risk of CVD and also, improves the quality of sexual life among the elderly [25].

There is less evidence on the relationship between fertility with cardiac disorders compared to pieces of evidence with regard to the correlation between ED and CVD. It has been shown that risk factors of CVD such as obesity, HTN, high cholesterol, depression, and stress also affect fertility. Some researchers have even highlighted the importance of cardiac health in urological well-being, especially fertility and sexual health and therefore, urological health is considered equivalent to heart health and, vice versa [26]. Also, normal serum testosterone is an important determinant of normal sexual function and spermatogenesis, and a study conducted by Malkin et al. showed that low serum testosterone is associated with increased mortality among patients with CHD [27].

Herbal remedies for heart and fertility disorders

Herbal preparations have multifaceted properties, typically, they could play bivalent role in the improvement of cardiac disorders and fertility issues by affecting cells and molecules in various ways. Avicenna suggested different medicinal plants to treat the mentioned ailments. Assessment of the phytochemicals and pharmacological effects of these remedies could bring about a better understanding of their mechanisms for treating cardiac infertility. Herbs could function as antioxidant, vasorelaxant, and anti-inflammatory agents verifying their dual action on the mentioned organs. Diverse pharmacological effects, major phytochemicals, and molecular mechanisms of herbs effective on cardiac infertility will be discussed in ensuing sections.

Antioxidant herbs, herbs with anti-inflammatory effects, and herbs increasing nitric oxide production

Reactive Oxygen Species (ROS) take center stage in the functionality of sperm. Excessive amount of ROS triggers lipid peroxidation, DNA damage, a decrease in sperm motility, and embryo miscarriage. Medicinal plants including Red Feathers (*Echium amoenum,* Family: Boraginaceae, chemical components: rosmarinic acid (RA), anthocyanidins, flavonoids, the trace of alkaloids, saponins, unsaturated terpenoids, and sterols),

Quince (Cydonia oblonga, Family: Rosaceae, Chemical components: 3-O-caffeoylquinic, 4-O-caffeoylquinic, 5-O-caffeoylquinic and 3,5-dicaffeoylquinic acids, lucenin-2, vicenin-2, stellarin-2, isoschaftoside, schaftoside, 6-C-pentosyl-8-C-glucosyl chrysoeriol and 6-C-glucosyl-8-C-pentosyl chrysoeriol), Saffron *(Crocus sativus*, Family*:* Iridaceae, Chemical component: Crocin, picrocrocin, Safranal), Common walnut (*Juglans regia*, Family: Juglandaceae, Chemical component: pyrogallol, *p*-hydroxybenzoic acid, ethyl gallate, protocatechuic acid , vanillic acid, gallic acid, and 3,4,8,9,10-pentahydroxydibenzo*),* apple (*Malus domestica*, Family: Rosaceae, Chemical component: catechin, epicatechin, chlorogenic acid, cyanidin-3-galactoside, procyanidin, gallic acid, coumaric acid, phloridzin, quercetin-3 galactoside and quercetin-3-rhamnoside), citron (*Citrus medica*, Family*:* Rutaceae, Chemical component: iso-limonene, citral, limonene, phenolics, flavonones, pectin, vitamin C, decanal, linalool, and nonanal), lemon balm, (*Melissa officinalis*, Family: Lamiaceae, Chemical component: Hydroxycinnamic acid derivatives and flavonoids with caffeic acid, m-coumaric acid, eriodictyol-7-O-glucoside, naringin, hesperidin, rosmarinic acid, naringenin, hesperetin, phenolic content of the extract (gallic acid equivalents), Date palm (*Phoenix dactylifera*, Family: Arecaceae, Chemical component: carotenoids, polyphenols (e.g., phenolic acids, isoflavons, lignans, and flavonoids, tannins, and sterol)[28-34] and all of these plants contain antioxidant ingredients including carotenoids (xanthophyll and carotenes) vitamins (vitamin E and C) and polyphenols (anthocyanins, flavonoids, phenolic acids, lignans, and stilbenes). Nowadays, the role of antioxidants has been recognized in improving fertility due to the improvement of sperm parameters, such as motility and concentration, and the reduction of DNA damage. The herbs listed in table 1 could ameliorate cardiac infertility by preventing lipid peroxidation and ROS production.

Some of these plants such as *C. Medica, Pistacia vera*, and *M. officinalis* also have anti-inflammatory properties (via reduction of proinflammatory cytokines such as IL-1, IL-6, TNF-α, NF-κB). Also, *Trachyspermum ammi, Curcuma zedoaria*, *C. oblonga*, *Juglans regia*, and *C. medica* improve plasma lipid profile and reduce the levels of TAG, and *P. dactylifera*, *Elettaria cardamomum*, *M. officinalis*, have an anti-apoptotic effect (via enhancing Bcl-2-associated X protein/ B-cell lymphoma-2 andcaspase3) which results in their cardioprotective effects.

It has also been shown that some of these plants, for example, *Cinnamomum verum* and *Cocos nucifera* can increase endogenous nitric oxide production which may exert a positive effect on improving ED. Plants like *Cinnamomum verum* due to eugenol [35] and *Malus domestica* [36] demonstrate positive effects on the HPA axis function. On the other hand, this axis plays a major role in adjusting and controlling sexual function and fertility.

Table 1. Pharmacological effects of some medicinal plants on the heart and fertility and sexual dysfunction recommended by Avicenna

Medicinal plant	Common name/ Phytochemicals	Persian name	Study model	Effect on Heart and sexual organs	Ref
Trachyspermum ammi L.	Ajwain/ Thymol, beta-cymene, gamma-terpinene	Nankhah	A Human study, evaluation of the effect of ajwain essential oil on healthy fertile men	Male contraceptive, spermicidal property and decreasing sperm motility	[39]
			effect of oral seed powder on hyperlipidemia induced in albino rabbits by butter and oral intubation of cholesterol	Cardioprotective by significantly decreasing LPO (antioxidant), antihypertensive, diuretic, antiplatelet-aggregator, and anti-inflammatory	[40]
			An *in vitro* study, evaluation of the effect of essential oil on isolated aortic rings of wistar rats	Cardioprotective by vasorelaxation and antihypertensive activity.	[41]
			In vitro study of essential oil on human blood samples	It indicated anti-aggregatory effect by reduction of formation of thrombaxan B2	[42]

Cinnamomum verum J.Presl	Cinnamon/ Cinamaldehyde, Phenolic compounds	Darchin	Oral administration Cinnamon powder to male rats	↑population, viability and motility of sperms. Total serum testosterone, weights of testis and epididymis	[43]
			Oral administration of cinnamon bark extract to adult male rats	The extract showed amelioration of lipid profile, cardiac enzymes, inflammatory cytokines and oxidative stress markers	[44]
			Oral administration of cinnamon bark essential oil to adult male rats	Surged the weights of testes and epididymides, sperm motility and concentration, ↓testicular LPO, ↑antioxidant enzyme activities in rats. ↓number of abnormal sperms	[45]
			Intravenous administration of methanolic extract of cinnamon to male rats	Antihypertensive by increase in the production of endogenous NO and regulation of dyslipidemia	[46]
			Oral administration of 96% ethanolic extract to male rats	Cardioprotective effects against ischemia-induced arrhythmias and cardiac injury by decrease in infarct size and cardiac injury biomarkers and antioxidant activity.	[47]
Cocos nucifera L.	Coconut/ L-arginine, ascorbic acid, minerals like calcium and magnesium	Nargil	Oral administration coconut oil to male rats	↑Serum testosterone level, antioxidant, ↓testicular MDA levels, no effect on FSH and LH levels	[48]
				↑sperm count ↑ motility and lowered sperm abnormality	[49]
			Oral administration of coconut water to male rats	Improving epididymal spermatogenic cell density, sperm motility, ↑ testosterone level	[50]
			Human study, oral administration of coconut oil to pre-menopausal women	Cardio protective by reduction of the risk of CVD by improvement of lipid profile	[51]
			Human study, oral administration of natural beverage obtained from coconut fruit to hypertensive adult woman	Antioxidant and hypolipidemic activities, It was antihypertensive through affecting NO pathway and calcium channels	[52]

			Oral administration of tender coconut water to male rats	Cardioprotective effect by improving activities of mitochondrial enzymes, CPK, SGOT, SGPT and LDH, Reduction of VLDL and LDL-C, and increasing HDL-C	[53]
Corylus avellana L.	Hazelnut/ Monounsaturated fatty acids	Fandogh	Addition of 15% of hazelnut as supplement to the diet of diabetic female rats	↑sex hormones ↑Serum level of FSH and LH	[54]
			The human study, supplementation of hypercholesterolemic men with 40 g/day diet	Cardioprotective effect by improving cardiovascular risk biomarkers and antihyperlipidemic effects	[55]
			Human study, supplementation of hypercholesterolemic men and women with raw hazelnut-enriched diet	Cardioprotective effect by improving the function of endothelium, inhibition of LDL-C oxidation, decreasing lipids and lipoproteins.	[56]
Crocus sativus L.	Saffron/ Crocin and safranal (mainly safranal)	Zafaran	A human study, nonsmoker infertile men supplemented with 150 mg saffron daily	Improving sperm morphology and motility.	[57]
			An animal study, Intraperitoneal administration of saffron aqueous extract and safranal in isoproterenol-induced MI in rats	Cardioprotective via modulation of oxidative stress, ↓Serum LDH and CK-MB, ↓myocardial LPO	[58]
			An animal study, An intravenous administration of aqueous extract of saffron stigma, safranal, and crocin to desoxycorticosterone acetate-induced hypertensive rats.	Hypotensive effect, reduction of mean arterial blood pressure and heart rate	[59]
			An animal study, interventions administration of saffron aqueous extract against ischemia/ reperfusion injured rats	Saffron aqueous extract leads to cardioprotection by limiting myocardial injury by activation of Akt/eNOS/ ERK1/2/GSK3-β and through the Nrf2 pathway and induces antioxidant protection against ischemia	[60]
			In vitro study, 50:50, v/v methanol and water extract of saffron stigma on isolated hearts of male rabbits	↓Infarct size, ↓LPO, ↑increased glutathione peroxidase activity, oxidation of nitro blue tetrazolium by ROS, the induced phosphorylation level of the survival proteins Akt and 4EBP1, and ↓activity of p38	[61]

			In vitro study, 50:50, v/v methanol and water extract of saffron stigma on isolated hearts of male rabbits	↓Oxidative myocardial damage, preserved cardiac troponin T proteins, inhibited the p38 MAPK pathway, activated the AKT/mTOR/4EBP1 pathway in reperfusion- and DOX-treated rabbit hearts	[62]
			An animal study, oral administration of aqueous extract of saffron stigma to the male rats	Significant decrease in susceptibility and incidence of fatal ventricular arrhythmia during the reperfusion period, protective effect is apparently mediated by the decrease of electrical conductivity and prolonging the action potential	[63]
			An animal study, oral administration of 100 mg/mL solution of saffron stigma to the male rats	↓ Intensity of tissue destruction and ↓serum levels of heart troponin I,↑GPx activity protective role of saffron on ischemic hearts by biochemical and histopathological findings, cardioprotective effects on the heart by stability and even amplification of antioxidant system and ↓heart rate and contractility in stressful conditions	[64]
Curcuma zedoaria (Christm.) Roscoe	Zedoary/ Phenolic and flavonoids	Jadvar	Human study, randomized clinical trial, oral administration of herbal tea	Antihypercholesterolemic and antilipidemic, antioxidant, ↓body weight and BMI, ↓TC, ↑HDL-C, ↓serum LDL-C, TAG	[65]
			Animal study, Oral administration of hydroethanolic extract of zedoary to male rats	Anti-hyperlipidemic activities by ↓TAG	[66]
Cydonia oblonga mill.	Quince/ Phenolic acids and flavonoids	Beh (Safarjal)	Animal study, oral administration of quince leaf extract to male rats	↑sperm viability, protection of sperm from oxidative damages due to antioxidant activities.	[67]
			Animal study, oral administration of hydroalcoholic extract of the fruits To male rats	↑ sexual activity, antioxidant	[68]
			Animal study,oral administration of 60% ethanolic extraxt of the leaves of quince to hyperlipidemic rats	Antioxidant and antihyperlipidemic effects. It significantly reduced TC, TAG, LDL-C and MDA, inhibited the activity of ALT, AST and LPS, increased HDL-C content and the activity of SOD, GSH-PX, LPL and HL, and reduced liver steatosis in hyperlipidemic rats.	[69]

			Animal study, intragastric administration of total flavonoids isolated from leaves of quince to hypertensive rats	Antihypertensive activity	[70]
Elettaria cardamomum (L.) Maton	Cardamom	Hel (Ghagholeh)	Animal study, oral administration of the powder of coffee and cardamom mixture to adult male rats	Protective role on the testis structures and ↑ level of testosterone	[71]
			Animal study, oral administration of aqueous extract to male rats	Cardioprotective effects against ISO-induced myocardial necrosis by free radical scavenging and antioxidant activities, ↑endogenous antioxidants, SOD, CAT, GPx, ↓LPO	[72]
			Animal study, oral administration of aqueous extract of fruits to adult male rats	Cytoprotective agent against DOX cardiotoxicity via ↓oxidative stress, ↓apoptosis & inflammation, ↑tissue regeneration by induction of angiogenesis	[73]
Echium amoenum Fisch. & C.A.Mey.	Borage/ Gamma-linolenic acid	Gav zaban	Animal study, Oral administration of borage oil to male rats	Cardioprotective by amelioration of cardiac remodeling and CHF after induction of MI due to antioxidant and anti-inflammatory effects	[74]
Juglans regia L.	Walnut/ α-linolenic acid (ALA), Docosahexaenoic acid (DHA), Omega 3, 6	Gerdoo	Animal study, oral administration of aqueous extract of walnut leaves to rats	↑ Level of serum testosterone, FSH, LH, sperm count, motility, viability ↓decrease in sperm abnormality. Cardioprotective by decreasing the content of cholesterol	[75]
			Animal study, walnut-enriched diet to mice	Fertility enhancing and improving sperm quality, ↓peroxidative damage	[76]
			Human study, addition of 75 g /day walnut to the diet of healthy young men	Improvement of sperm vitality, motility, and morphology, antioxidant -	[77]
			Human study, oral administration of walnut oil to hyperlipidemic subjects	↓TAG and increase of plasma HDL-C	[78]
			Animal study, oral administration of walnut kernels extract to isoproterenol induced MI in rats	Cardioprotective effects by ↓LPO, ↓oxidative damage, and antilipidemic properties	[79]
Valeriana spp.	Valerian/ Valpoteriates	Sonbol-ol-tib	Human study, oral administration of the combination of *Valeriana officinalis* and *Panax ginseng*.	↑ percentage of active or normokinetic spermatozoids	[80]

			Ex vivo aortic rings test by hexane extract from *V. edulis*	Vasorelaxant effect acts as a calcium channel blocker, through an endothelium-independent pathway	[81]
			Crude extract of *V. wallichii* rhizome studied on rats by intravenous administration,	Hypotensive effects by K+ channel activation	[82]
			Human study, volatile oil of *V. officinalis* on CHD patients with angina pectoris	↓ Attack frequency and shortening the duration of angina, ↓plasma lipids	[83]
Santalum album L.	White sandalwood	Sandal	Animal study, Petroleum ether fraction of sandal wood was administered orally to diabetic rats.	Cardioprotective activity, by anti-hyperlipidemic effect. It significantly decreased TC, LDL-C, TAG, and increased HDL-C levels	[84]
Citrus medica L.	Citron/ antioxidative phenolic content and vitamin C	Otroj	Animal study, Subcutaneous injection of ethanolic extract of fruit peel on Male Wistar albino rats	Cardiotonic and antioxidant drug	[85]
Pistacia vera L.	Pistachio/ Strolls, gallic acid	Fostog	Clinical trial, intake of fruits by male patients	Significant Improves in erectile function parameters, 5-alpha-reductase enzyme inhibitor Cardioprotective by improvement in serum lipid parameters	[86]
			Clinical trial on hyperlipidemic individuals, addition of pistachios to a low fat diet	Cardioprotective (beneficially affects CVD risk factors) by antihyperlipidemic effect	[87]
			Clinical trial on hyperlipidemic individuals addition of pistachios to a moderate-fat diet	Cardioprotective (beneficially affects CVD risk factors) by antihyperlipidemic, ↑beta-sitosterol levels	[88]
			Clinical trial on healthy young men addition of pistachios to their diet	Cardioprotective by significantly deceasing LDL-C	[89]
			In vivo study, methanolic and cyclohexane extracts of the Pistacia vera nut on rabbits received atherogenic diet	significant decrease of aortic surface lesions, it is potentially beneficial in atherosclerosis management.	[90]
Coriandrum sativum L.	Coriander/polyphenol and flavonoids	Geshniz (Kozboreh)	*In vivo* study, oral administration of aqueous and ethanolic extracts of *C. sativum* seeds to male Swiss albino mice exposed to lead nitrate.	Protects against lead-induced oxidative stress	[91]

			In vivo study, methanolic extract of seeds administered intraperitoneally to isoproterenol induced cardiotoxicity model in male Wistar rats	Cardioprotective by preventing myocardial infarction by inhibiting myofibrillar damage, prevent myocardial infarction by inhibiting myofibrillar damage, preventing oxidative damage by ↓ROS	[92]
			In vivo study, aqueous extract of coriander seeds were administered orally to rats	↓TC, LDL-C and TAG, and atherosclerosis.	[93]
			In vivo study, Coriandrum sativum seeds aqueous extract orally administered to isoproterenol-induced to rats	Cardioprotective, protection from heart failure, improve left ventricular functions and baroreflex sensitivity, ↓LPO, hypolipidemic effects, modulate the expression of endothelin receptors,	[94]
Cicer arietinum L.	Pea /quercetin-3-O-glucoside and quercetin-3-O-glucuronic acid	Hemmas	In vivo study,5% concentration of chicken pea diet to gibrillic acid (GA3)-induced infertility in male rats.	Protective effect of sex organs and spermatogenesis, antioxidant and hormonal effect	[95]
			Clinical trial, received chickpea diet administered to free-living adults	↓ TC and LDL-C	[96]
			In vitro study, human umbilical vein endothelial cell (HUVEC) model	Antihypertensive by inhibition of the angiotensin-converting enzyme, antioxidant	[97]
			In vitro study, Dietary apple polyphenol (AP) from unripe apple administered orally to rats	Hypocholesterolemic and antiatherogenic effects through the promotion of cholesterol catabolism and inhibition of intestinal absorption of cholesterol.	[98]
			In vivo study, Supplementation of rats with 20% of three Portuguese apple cultivars	↓serum levels of triglycerides, total and LDL-C concentrations.	[99]
Melissa officinalis L.	Lemon balm/ flavonoids and phenols compounds, Polyphenols and terpenes	Badranjbouyeh	*In vivo* study, Ethanolic extract of arial parts was administered orally to adult rats exposed to lead.	Protective effects on sperm parameters and spermatogenesis (↑epididymis weight, testis weight, sperm motility (and viable sperm), antioxidant	[100]
			In vivo study, aqueous extract of *M. officinalis* administered intraperitoneally to male rats	Cardioprotective by antiarrhythmic effect, ↓Cardiac rate, the extract has a mild protective effect against reperfusion-induced lethal ventricular arrhythmias in rats.	[101]

			In vivo study, Wistar rat heart with/without cardiac injury	Cardioprotective by ↑heart resistance to myocardial injury by improving the balance of the system and reducing the heart rate, Improving the balance of the redox system by ↓the heart rate, ↑heart resistance to injury	[102]
			In vivo study, male albino rats	Induced oxidative stress by ↓LPO, protein oxidation, and total oxidant capacity depletion and by ↑antioxidant capacity, inhibited inflammatory responses by ↓the expressions of NF-κB, TNF-α, and COX-2 and the activity of myeloperoxidase, induced apoptotic tissue damage	[103]
			In vivo study, rats	Improvement of sperm and DNA quality, antioxidant and hormonal effects	[104]
			In vivo study, male rats	Sex enhancer (↑mount, ejaculation, intromission frequencies, and ejaculation latency), antioxidant and hormonal effects,	[105]
Phoenix dactylifera L.			*In vivo* study, ethanolic extract of date palm pollen on isoproterenol-induced myocardial infarction (MI) in rats	Cardiopreventive effect by antioxidant and inhibition of angiotensin-converting enzyme activity and inhibition of the generation of ROS	[106]
			In vivo study, oral administration of an aqueous ethanolic extract of the heart of the *Phoenix dactylifera* tree to male Sprague Dawley rats	↓Cardiotoxicity and nephrotoxicity serum markers, apoptotic percentage, caspase-3, and COX-2 level, improvement antioxidant enzymes	[107]
			In vivo study, oral administration of ethanolic extract of dates fruit on isoproterenol model on male Westar rats	Mobilize endogenous circulating progenitor cells, promote tissue repair following ischemic injury	[108]
			Ex vivo study on cardiomyoblast cells, in vivo study of oral administration of aqueous extract of dates fruit on isoproterenol-induced cardiomyopathy.	↓expressions of proinflammatory cytokines and apoptotic markers and upregulating the anti-apoptotic protein, ↓myonecrosis, edema, and infiltration of inflammatory cells and restored the cardiomyocytes architecture	[109]
Rosa damascena Mill	Damask rose/ Flavonoids: isoquercitrin , afzelin, quercetin,	GoleSorkh (Vard-e-ahmar)	Human study, ingestion of *Rosa damascena* oil by male patients with opium use disorder under methadone maintenance therapy	Improving sexual and erectile dysfunction and increased testosterone levels.	[110]

			In vitro study	Improving the cardiovascular system by inhibiting HMG-CoA reductase Cyanidin-3-O-beta-glucoside significantly suppressed angiotensin I-converting enzyme	[111]
			In vivo study, Intra peritoneal injection of hydro-alcoholic extract of R. damascena to male Wistar rats	Beneficial effect on the cardiovascular system, hypotensive effect by probably because of antispasmodic and relaxant effects	[112]
			Ex vivo study, aqueous-ethanolic extract from *R. damascena* were examined on isolated guinea-pig hearts	The chronotropic, inotropic effect due to the stimulatory effect of this plant on beta-adrenoceptors	[113]
			In vivo study, 70% ethanolic extract of *Rosa damascena* on Male Wistar rats	The extract reduces myocardial damage and attenuates isoproterenol-induced lysosomal membrane destabilization by preventing the leakage of its enzyme. By increasing the antioxidant enzyme levels and membrane bound Na+/K+ ATPases integrity	[114]
Zingiber zerumbet L.	Bitter ginger/ Zerumbone and kaempferol	Zoronbad	*In vivo* study, ethanolic extract of *Zingiber zerumbet* was administered orally to the male rats	Antihyperlipidemic effects by ↑lipid metabolism through the up-regulation of hepatic PPARα expression,	[115]
			In vivo study, Oral administration of zerumbone (cyclic sesquiterpene) to Syrian golden hamsters	Zerumbone is effective to improve dyslipidemia by modulating the genes expression involving in the lipolytic and lipogenic pathways of lipids metabolism.	[116]

ACE, Angiotensin converting enzyme; Akt, protein kinase B; ATP, Adenosine Tri Phosphate; Bax, B24EBP1, 4E-binding protein1; BCL2-associated X Protein; Bcl2, B cell lymphoma 2; cAMP, Cyclic adenosine monophosphate; Catalase, CAT ; COX-2, Cyclooxygenase-2; ; CHD, coronary heart disease; CK-MB, Creatine Kinase MB; CPK, Creatinine Phosphokinase; CRP, C-reactive protein; CVD, cardiovascular disease; DOX, Doxorubicin; ERK, extracellular signal-regulated kinases; eNOS, endothelial nitric oxide synthase; GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamate Pyruvate Transaminase; GPx, Glutathione Peroxidase; GSH, Glutathione; GSK3-β, glycogen synthase kinase 3 beta; HDL-C, High density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; ; IL-6, Interleukin 6; ISO, isoproterenol; LDH, Lactate dehydrogenase; LDL-C, Low Density Lipoprotein cholesterol; LPO, lipid peroxidation; LVdp, Left ventricular diastolic pressure; LVdP/dtmax/P, Left ventricular systolic pressure; LVEDP, Left ventricular end-diastolic pressure; MAPK, Mitogen-activated protein kinase; MDA, Malondialdehyde; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kappa B;NO, Nitrous oxide; Nrf2, Nuclear factor E2-related factor 2; ; p38, mitogen-activated protein kinases; ROS, Reactive oxygen species; SOD, Superoxide Dismutase; TC; Total cholesterol; TCA, Tricarboxylic acid; TAG, Triacylglycerol; TNF-α, Tumor necrosis factor alpha; TxB2, Thromboxane; sVCAM-1, soluble vascular cell adhesion molecule-1; VPB, ventricular premature beats; VT, ventricular tachycardia

Conclusion

Despite many advances in understanding the physiopathology of infertility and sexual problems, many aspects of infertility and sexual problems, including erectile dysfunction, still remain unknown and unclear. Still, in many cases, the causes of infertility are considered idiopathic and unexplained. Maybe finding the relationship of some vital organs such as heart with sexual function and fertility will be useful in finding new methods to treat these patients [37,38].

Conflict of Interests
None.

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