





Effect of garlic (*Allium sativum*) on male fertility: a systematic review

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ABSTRACT

Introduction: Fertility in men mainly depends on the number, quality, motility, and morphology of the sperms, and disruption of each of these factors leads to infertility. A large number of couples suffer from infertility problems. Among the various therapies, medicinal herbs are used in many countries to treat male infertility. Current systematic review was conducted to study the effects of garlic on male fertility.

Methods: The information of this systematic review was collected by searching the key words: treatment, fertility, infertility, male, herbal medicine, garlic, *Allium sativum*, medicinal plant, sperm, sex hormones, testis and spermatogenesis in international databases such as: Web of Science (ISI), PubMed, Scopus and Embase until March 2018. This study was conducted in accordance with the PRISMA statement for systematic reviews and meta- analysis. and the SYRCLE risk of bias tool was used for qualitative assessment.

Results: A total of 18 experimental studies were included in the study. Thirteen studies evaluated garlic and 5 studies compared garlic effect with adriamycin, titanium dioxide, furan, vitamin E, N-acetylcysteine and cadmium. All studies were conducted in in vivo condition. The results of the studies indicated the potential effect of garlic on enhancing fertility and spermatogenesis, increasing the level of testosterone and improving the testicular structure.

Conclusion: Garlic can increase fertility probably due to its antioxidant properties. However, more clinical trials are recommended.

Implication for health policy/practice/research/medical education:

This article presented useful information about garlic, especially on fertility and reproduction system which could help pharmacists and scientists in the provision of new drugs.

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Introduction

Failure to have a child is an unpleasant event in the lives of infertile people (1). Inability to become pregnant after one year of regular intercourse, without using contraception, is defined as infertility (2). About 30%-50% of the causes of infertility are related to male problems (3). Each day, the number of medical reports about the extent of infertility in the world increases, according to a systematic review in this regard, about 48.5 million couples around the world affected by this problem (4). The total mean of infertility in Iran is estimated about 11%-19%, which

is more in the age group of 20-39 years (5). Infertility is a multi-parameter phenomenon with a wide range of factors that affects spermatogenesis and sperm quality (6). Spermatogenesis is a process in which male sex cells are produced and the disorder in each of these stages can cause infertility (7). Fertility in men depends largely on the number, quality, motility, and morphology of the sperm, and the disruption of each of these factors leads to infertility in men (3). Infertility, as a psychological crisis, imposes a lot of stress on infertile couples and in different ways threatens their mental health. The most

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emotional and psychological problems of infertile couples are disappointment, frustration, fear and anxiety, and are less associated with anger and aggression. However, the rate of divorce and remarriage among infertile couples has risen. In addition to mental problems, the economical treatment of infertility imposes a relative high cost on infertile couples (8).

Nowadays, various methods are used to treat infertility, including: hormone therapy, surgical procedures, assisted reproductive technology (ART) that include in vitro fertilization (IVF), intra uterine insemination (IUI), zygote intrafallopian transfer (ZIFT), gamete intrafallopian transfer (GIFT), intracytoplasmic sperm injection (ICSI) and third-party fertilization (donation eggs, donation sperm, uterus, and donated embryos) (9).

ART is one of the costly treatments among infertile couples, but many people are not able to do so because financial problems, and surgical procedures have a lot of stress and complications for the family, and in addition they are expensive (8). Hormone therapy is also prohibited in some people, and in many people with impaired hypothalamic-pituitary-gonadal axis function, this treatment is not responsive therefore, due to individual and social problems caused by infertility, couples always try to find low-cost, safe and effective treatments (10). Regarding the problems that have been observed among couples and the high costs of medical interventions, people have turned to complementary medicine (11). Among different therapeutic methods, herbs are used in many countries to treat male infertility (1,12,13). Plants are more affordable and accessible than invasive and chemical treatments (14). Medicinal herbs with high antioxidant properties are used to treat sperm abnormalities, sexual dysfunction, erectile and ejaculatory disorders (1,15). Among the plants that improve male fertility, celery (16), fennel (17), black seed (18), German chamomile (19), saffron (20), *Fumaria parviflora* (21), *Origanum vulgare* (22) and carrot (23) can be mentioned. Some plants change the number and motility of the sperm by changing sex hormones. Other plants with androgenic properties affect the hypothalamus-pituitary axis and increase sex hormones (24). Garlic with its antioxidant properties, have been shown to increase the weight of the epididymis, seminal vesicles and increases the number of sperms (25). Garlic is one of the most potent and most prominent species of plants, which is a part of the onion family (7). Garlic has been known since 5000 years ago. In ancient times, Babylonians, Egyptians, Vikings, Chinese, Greeks, Romans and Hindus used garlic (26). In 3000 BC garlic was used for heart disease, arthritis, uterine disease, pulmonary disease, skin diseases, diarrhea, headache, wound healing and tumor (27,28). It is native to Western Asia, also found in most regions of Iran, especially in the northern regions (29). The perennial plant, has a height of 100-300 cm, has flowers in pink or green (16). It is used

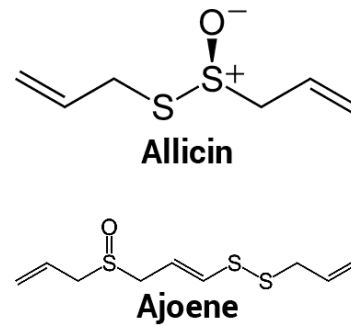


Figure 1: The main compounds of garlic.

commonly as a medicinal herb and food flavor, and it is one of the herbs that have a long history of medical uses (30). Garlic contains many compounds, including vitamins B2, B6, B1, A and C, a lot of antioxidants, flavonoids, sulfur compounds and allicin (7). Allicin (dialkyl thiosulfinate) plays a key role in the garlic medicinal properties, however, this compound is not found in fresh garlic, and made by action of allinase on alliin (*S*-alkyl-L-cysteine sulfoxide). Ajoene is another important compound in garlic (Figure 1) (31). Garlic protects the liver and has anticholesterolemic, antithrombotic, antihypertensive and antimicrobial activity (30), and consumption of garlic acts like insulin receptor and reduces glucose levels in diabetic patients (3). Solving infertility problem is a fundamental issue in every community's health system. Considering the complications and limitations of chemical drugs and surgical procedures, and according to the mentioned therapeutic effects of garlic, this systematic review was conducted to investigate the effects of garlic on male fertility.

Methods

Study protocol

Current systematic review was reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (32). In this study, the search process was done aimed to find studies in English without time limitations.

Search strategy

Data were collected by searching the key words: treatment, fertility, infertility, male, herbal medicine, *garlic*, medicinal plant, sperm, sex hormones and spermatogenesis in international databases such as: Web of Science (ISI), PubMed, Scopus and Embase until March 2018.

Inclusion criteria

- To conduct experimental studies or clinical trials
- Randomization in studies
- Evaluation of fertility, spermatogenesis or male sex hormones
- Mentioning of ethical considerations in articles

Exclusion criteria

- Absence of proper sampling method in studies
- Evaluation of fertility in female, not male, samples
- Not mentioning moral considerations

Selection of studies and data extraction

The articles' information was reviewed independently by two authors based on inclusion and exclusion criteria. Finally, both of authors classified the information and, in cases that the information was inconsistent, the comments of the third author were used. The information obtained from the articles was entered into the checklist considering the quality approval of the articles. The checklist contained: author's name, year of the study, type of study, molecular change, type of sample, type of administration, dosage, part of plant and period of extract administration. SYRCLE risk of bias tool was used for assessment of the quality. This tool is an advanced and improved model of the past quality assessment tools that is specific to animal and pre-clinical studies (33) and solve some of defects of the previous tools that was related to clinical trials.

Results

In the first stage of search, 980 articles were found. After removing duplicates and unrelated articles, 18 experimental studies included in this systematic review (Figure 2).

Thirteen studies evaluated garlic and 5 studies compared

garlic effects with other drugs. A study compared aged garlic extract with adriamycin, a study compared aged garlic extract with titanium dioxide, a study compared garlic oil extract with furan, a study compared garlic blue extract with vitamin E and N-acetyl cysteine and a study compared garlic extract and onion with cadmium.

Qualitative assessment showed that most studies were in high risk for bias. In most of these studies, randomization in animal housing, randomization in sampling, researcher and statistical analyzers blinding were not mentioned clearly (Table 1).

In 10 studies garlic extract was prescribed as crude plant and powder for animals. The maximum sample size was 62 mice and the lowest sample size was 10 mice that were examined in experimental studies. All studies were conducted in the in vivo condition. The control group received distilled water, normal saline or powder containing starch, and the treatment group received aged garlic extract, adriamycin, titanium dioxide, garlic oil, N-acetylcysteine, vitamin E, cadmium, cooked garlic or garlic juice. The treatment period varied from 7 to 120 days and complications such as impaired spermatogenesis, apoptosis, abnormal sperm, decreased sperm motility, seminal vesicle disorder, increased blood cholesterol, leukocytosis, decreased testicular weight, decreased Leydig cells, increased prostate weight and increased cortisol were mentioned in the studies. All of these complications were reported as chemical substances toxicity. Further information is presented in Table 2.

Discussion

The present study was a systematic review of the effects of garlic on fertility. In general, in this paper, 18 studies were reviewed. Thirteen studies were conducted on the effect of garlic on fertility treatment. Due to the lack of side effects, as well as containing flavonoids, vitamins, fructose and sulfur compounds, garlic can help with neutralizing free radicals (1). Sulfur compounds in garlic, with a direct effect on the metabolism of cytochrome P450 and glutathione *S*-transferase, have a protective effect on spermatogenesis. In addition to sulfur compounds, garlic has antioxidant properties and can increase fertility by reducing lipid peroxidation (32). Given the above mentioned factors, garlic is recommended for the treatment of infertility. In a study by Asadpour et al it was indicated that garlic has antioxidant activity due to presence of vitamin E, which prevents oxygen peroxide (49). Also, the results of the study by Nasr showed that garlic antioxidant properties can reduce the toxicity of harmful drugs on the testes and increase the spermatogenesis and fertility in men (35). In the study by Akabawy and Sherif, it was concluded that garlic inhibited caspase-3 and cytochrome P450 2E1 (CYP2E1) enzymes, which had a toxic effect on the testes and, by decreasing these two enzymes, improved the testicular performance and spermatogenesis (37).

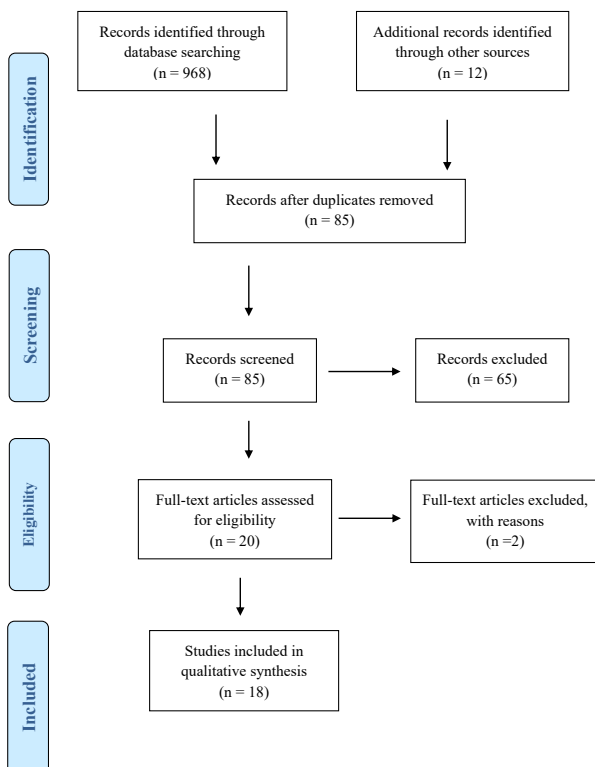


Figure 2. Trend of screening and choosing articles based on PRISMA guidelines.

Table 1. Risk of bias for animal studies, using the SYRCLE risk of bias tool

Study	1	2	3	4	5	6	7	8	9	10
	Selection bias 1	Selection bias 2	Selection bias 3	Performance bias 1	Performance bias 2	Detection bias 1	Detection bias 2	Attrition bias	Reporting bias	Other potential bias
Hajiuon (34)	x	✓	✓	?	X	?	X	?	✓	✓
Nasr (35)	✓	✓	✓	?	X	X	?	✓	✓	✓
Abu Zeid et al (36)	✓	✓	✓	?	?	?	?	✓	✓	✓
El-Akabawy and El-Sherif (37)	✓	✓	✓	?	?	x	?	✓	✓	✓
Abdelmalik (38)	✓	✓	x	?	X	?	X	?	✓	✓
Ouarda and Abdenmour (39)	?	✓	?	?	?	?	?	?	✓	?
Ghalehkandi (40)	✓	✓	?	?	X	?	?	?	✓	✓
Bahrami et al (7)	✓	✓	✓	?	?	?	?	x	✓	?
Safaei et al (41)	✓	?	✓	?	?	✓	?	?	?	?
Ola-Mudathir et al (42)	✓	✓	✓	✓	?	?	?	?	✓	✓
Omotoso et al (25)	✓	✓	✓	?	?	?	?	?	✓	✓
Nahdi et al (43)	✓	✓	?	?	?	?	?	✓	✓	✓
Hammami et al (44)	✓	✓	?	?	?	✓	?	?	✓	?
Hammami et al (45)	✓	✓	✓	?	?	?	?	?	✓	✓
Oi et al (46)	✓	✓	?	?	✓	?	?	?	✓	✓
Lee et al (47)	✓	✓	x	?	?	?	?	✓	✓	✓
Abdullah et al (48)	✓	✓	✓	?	?	✓	?	?	✓	✓
Asadpour et al (49)	✓	✓	x	?	?	?	?	✓	✓	✓

Hammami and Abdelmalik (38) concluded that garlic contains phytoestrogens, which have a direct effect on estrogen. It is a precursor to testosterone production, so it is possible that garlic stimulates the sexual cells and sex hormones (38,43). The results in the study by Oi et al indicated that garlic supplementation boosts LH from the pituitary gland, and this stimulates testosterone secretion from the testicles (46). Nonetheless, in the study by Bahrami et al (7), it was recommended that the cooked garlic has better therapeutic effects and, while affecting the reproduction of the sexual cells in testes and epididymis, improves spermatogenesis (7).

Due to presence of diallyl disulfide in its biochemical structure, garlic affects the hypothalamic-pituitary axis. Diallyl disulfide stimulates the basophilic cells and secretion of LH sex hormones by affecting the anterior pituitary. LH stimulates Leydig cells in the testes, which in turn is a precursor to secretion and regulation of testosterone (50). Also, diallyl disulfide reduces oxygen free radicals, enhances and strengthens the blood-testis barrier and increases the circulation in the testicles, thus protects the sexual organs (39). By increasing blood flow to the testicles (due to the consumption of garlic), phenol and phenolic glycosides are released which increase the glutathione peroxidase enzyme. The role of this enzyme is to protect sperms in testicular and epididymal tissue (51). The enzyme protects the sperm from the damage of free radicals by placement in the plasma membrane and the nucleus of sperm, epididymal fluid and epididymis,

and leads to ultimate maturation and development of the sperm (52). Also, garlic can repair and protect the DNA of the sperm, in addition to sperm maturation through vitamins C, B, E, which are its potent antioxidants (53). Approximately 45%-50% of infertility has a male cause, but nevertheless, 30-45% is due to idiopathic causes (54). Typically, infertility in men is indicated by oligozoospermia, asthenozoospermia, or teratozoospermia and varicocele (55). Recent studies have shown that, in physiological conditions, reactive oxygen species play a very important role in intracellular messaging processes. On the other hand, during the last decade, reactive oxygen species have been implicated in the development of male infertility, due to excessive production of reactive oxygen species or reduced ability of the antioxidant system of the genital system and sperm. In pathological conditions, reactive oxygen species result in male infertility through disruption of the spermatogenesis process, sperm function and structure, mobility, survival, acrosome reaction, sperm-to-oocyte coupling and even reduced fertilization and implantation (56).

Conclusion

Probably, due to the antioxidant power and the absence of side effects of garlic, it can be useful in enhancing fertility. Due to the limited number of clinical studies, there is no definite overall and reassuring result. In order to ensure the effects of this plant and its compounds, clinical studies with a larger statistical population, as well as an increase

Table 2. Effect of garlic on reproductive system and fertility

Effect of garlic	Type of extract	Duration of treatment	Dose	Administration	Sample study	Part used	Result	Ref.
Effects on sexual hormones	Hydro alcoholic extract	30 days	200 and 400 mg/kg	Orally	Rats	Leaves	↓Testosterone levels, ↓Estrogen, ↑Progesterone	(34)
	Aged garlic extract	7-14 days	250 mg/kg	Orally	Rats	Seeds	↑Testosterone levels, ↓MDA concentration, ↑GSH level, ↑GSH-Px, ↑CAT, and SOD activity	(35)
	Aged garlic extract	65 days	2 mL/kg	Orally	Rats	Leaves	↑Androgen levels	(36)
	Garlic oil	NM	4 mg/kg	Orally	Rats	NM	↓Testosterone levels, ↓Caspase-3, ↓Cytochrome P450 2E1	(37)
	NM	120 days	30 g	Orally	Rats	NM	↓Testosterone levels	(38)
Effects on spermatogenesis and testicular structure and other results	NM	14 days	50 g	Orally	Rabbits	Seeds	↑Sperm motility and viability, ↑Sperm speed, ↑White blood counts	(39)
	Garlic juice	30 days	60 and 120 mg/kg	Gavage	Rats	Seeds	↓Semen MDA activity, ↓TAS activity	(40)
	NM	30 days	5% and 15% of raw garlic and cooked garlic	Orally	Rats	Seeds	In cooked garlic, ↓Weight Loss, ↑Number of spermatocyte cells, ↑Number of spermatozoa, ↑Number of sperm cells, ↑Number of Sertoli cells, ↑Testicle weight, ↑External diameter of the epididymide, ↑The inner diameter of epididymide, ↑Sperm volume	(7)
	Alcoholic extract	30 days	0.05%, 0.1% and 0.2%	Orally	Rooster	Leaves	Garlic alcoholic extract 0.2%: ↑Semen volume, ↑Testicle weight, ↑Sperm counts, ↑Percentage of mobility and sperm biocompatibility, ↑Laydic cell count	(41)
	NM	Between 7-21 days	0.5 mL/100 g. BW	Gavage	Rats	Leaves	↑LOP, ↑Glutathione S-transferase, ↑GSH, ↑SOD, ↑CAT, ↑Epididymal sperm concentration, ↑Sperm progress motility, ↓Lipid peroxidation	(42)
	Aqueous Extract	28 days	500 and 100 mg/kg	Feeding tube	Rats	Leaves	↓Spermatozoa count, ↓SOD activity in the blood	(25)
	NM	NM	5%, 10% and 15%	Orally	Rats	Leaves	↑Number of tubules deprived of spermatozoa, ↓Apoptosis of testicular germ cells, ↓Testosterone levels	(43)
	NM	30 days	5%, 10% and 15% of 30 g	Orally	Rats	Seeds	↑CASP3 levels, ↑Caspase inhibitors BIRC3 and BIRC2, ↑IAP inhibitor DIABLO, ↓AMH, RHOX5 and CDKN1B, ↑GATA4	(44)
	NM	30 days	5%, 10%, 15% and 30% of 9 g	Orally	Rats	Seeds	↓Prostate weight, ↓Seminal vesicle weight, ↓Testosterone levels, ↑LH levels, ↑Phosphatase acid activity	(45)
	NM	28 days	8 g	Intraperitoneal injection	Rats	-	↑LH levels, ↑Testicular testosterone, ↓Plasma corticosterone	(46)
	Ethanol extract	37 days	5, 10, 20 and 40 mg/kg/bw	Perorally	Rats	Leaves	↓Weight loss, ↓Testicular weight, ↑Spermatogenesis	(47)
	NM	90 days	100 mg/kg/d	Intraperitoneal injection	Mice	Leaves	↑Weight of seminal vesicles and epididymides, ↑Sperm count, ↑Weight loss, ↑WBC, ↓RBC	(48)
NM	35 days	400 mg/kg	Gavage	Rats	Leaves	↑Sperm motility and viability, ↑MDA level, ↑SOD activities	(49)	

NM: not mentioned, MDA: malondialdehyde, GSH: glutathione, GSH-px: glutathione peroxidase, SOD: superoxide dismutase, CAT: catalase, TAS: total antioxidant status, BIRC3: baculoviral IAP repeat-containing protein 3, BIRC2: baculoviral IAP repeat-containing protein2, AMH: anti-Mullerian hormone, CDKN1B: cyclin-dependent kinase inhibitor 1B, LH: luteinizing hormone

in the duration of its administration, comparison with safe drugs and the determination of the exact molecular mechanism are recommended.

Authors' contributions

All authors contributed equally in planning and carrying out this work. All authors read the manuscript and confirmed the publication for final version.

Conflict of interests

None.

Ethical considerations

Not applicable.

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