First International Journal of Andrology
ANDROLOGIA

REVIEW

# Impact of garlic feeding (*Allium sativum*) on male fertility

I. Hammami & M. V. El May

Research Unity 01/UR/08-07, Faculty of Medicine, Department of Histology, Embryology and Cell Biology, Tunis, Tunisia

**Keywords**
Garlic—germ cells—somatic cells—spermatogenesis—testis—testosterone

**Correspondence**
Imen Hammami, 15 Street of Djebel Lakhdar
La Rabta, Tunis 1007, Tunisia.
Tel.: (00 216) 71 563 709;
Fax: (00 216) 71 569 427;
E-mail: hammamiimen@hotmail.fr

Accepted: July 4, 2012

doi: 10.1111/and.12009

## Summary

Many medicinal plants are designed to improve health but their mechanism of action remains not clear. Among these plants, garlic (*Allium sativum*) has attracted particular attention of modern medicine because of its widespread use for the prevention and treatment of some human diseases such as cardiovascular diseases and cancer. However, the impact of garlic on the male reproductive system has not been clearly defined. Some studies have reported that garlic improves male sexual function and has beneficial effect in the recovery of testicular functions. However, other authors have shown that this plant impairs testicular functions (such as inhibition of testosterone production) and has spermicidal effect on spermatozoa. In this review, we attempt to clarify the current ambiguity regarding the effects of garlic and its preparations on the male reproductive system.

## Introduction

Garlic (*Allium sativum*) and its preparations have been investigated extensively for health benefits, resulting in numerous research reports over the last decade alone. It is considered one of the best disease-preventive foods, based on its potent and varied effects. The medicinal use of garlic has a long history. Over the centuries, garlic has acquired a special position in the tradition of many cultures as a formidable prophylactic and therapeutic medicinal agent (Moyers, 1996). Its uses as a remedy for heart disease, tumours, and headaches are documented in the Egyptian Cordex Ebers dating from 1550 BC. Garlic is mentioned in the Bible and Koran, and it has been a traditional treatment in many countries notably the Near East, China, and India (Lawson, 1998; Rivlin, 2001). This plant has attracted particular attention of modern medicine because it helps to maintain good health by prevention and treatment of cardiovascular diseases (Ginter & Simko, 2010; Brankovic *et al.*, 2011). Garlic has been studied extensively *in vitro*, in animal and human clinical trials, and in epidemiological evaluations for its multiple medicinal properties. The medicinal value of garlic and garlic preparations is best known for its lipid-lowering and anti-atherogenic effects in humans and animals (Prasad, 2010). Garlic significantly reduced plasma lipids, especially total cholesterol and low density protein (LDL) cholesterol in humans (Durak *et al.*, 2004; Ashraf *et al.*, 2011), and many authors have shown that supplementation of garlic in the diet depressed the hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, glucose-6-phosphate dehydrogenase and 3 hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase (Prasad, 2010; Padiya *et al.*, 2011). Moreover, it was reported that garlic inhibits antiplatelet aggregation (Hiyasat *et al.*, 2009) and has a fibrinolytic activity (Ginter & Simko, 2010). In recent years, extensive research has focused on the anticarcinogenic potential of garlic and their constituents, for example allylsulphides and flavonoids. Epidemiological studies have shown that higher intake of allium products is associated with reduced risk of several types of cancer (Cerella *et al.*, 2011). But there was no credible evidence to support a relation between garlic intake and a reduced risk of cancer (Kim & Kwon, 2009) or cardiovascular diseases (Banerjee *et al.*, 2003). In this context, some studies shed doubt on garlic benefits especially on fertility. In fact, garlic has been used in oriental medicine, to improve male sexual dysfunction since ancient times, and it has beneficial effect in the recovery of testicular functions (Ola-Mudathir *et al.*, 2008). But other authors reported the spermicidal effect of garlic (Qian *et al.*, 1986; Chakrabarti *et al.*, 2003). Following these contradictory studies, we asked whether the consumption of garlic is beneficial or not on male fertility. So in this review, we attempted to clarify the current ambiguity regarding the effects of garlic and its preparations on testicular functions.

**Table 1** General composition of garlic

| Component | Amount (Fresh garlic; %) |
|---|---|
| Water | 62–68 |
| Carbohydrates (mainly fructans) | 26–30 |
| Protein | 1.5–2.1 |
| Amino acids: common | 1–1.5 |
| Amino acids: cysteine sulphoxides | 0.6–1.9 |
| y-Glutamylcysteines | 0.5–1.6 |
| Lipids | 0.1–0.2 |
| Fibre | 1.5 |
| Total sulphur compounds | 1.1–3.5 |
| Total lipid-soluble compounds | 0.15 |
| Total water-soluble compounds | 97 |

## Composition of garlic and its preparations

The majority of garlic is water, and the bulk of the dry weight is composed of fructose containing carbohydrates, sulphur compounds, protein, fibre and free amino acids. Garlic also contains high levels of saponins, phosphorus, potassium, sulphur, zinc, moderate levels of selenium and vitamins A and C, and low levels of calcium, magnesium, sodium, iron, manganese and B-complex vitamins (Block, 1985) (Table 1).

Garlic represents the most dietary supplement among 91 supplements, used by American people (Amagase *et al.*, 2001). The most used and studied garlic preparations are raw garlic homogenate, garlic powder, aged garlic extract and garlic oil. Although no dose of garlic extract can be defined, the World Health Organisation (WHO) recommended a daily intake of 2–5 g raw garlic or 10–15 g boiled garlic. These doses are necessary to enjoy the benefits of garlic and to prevent cancer development (WHO, 2002). Raw garlic homogenate has been the major preparation of garlic subjected to intensive scientific study, because it is the most common method of garlic consumption. Raw garlic homogenate is essentially the same as the aqueous garlic extract that has been used in various scientific studies. Allicin (allyl 2-propene thiosulphinate or diallyl thiosulphinate) was long thought to be the principal bioactive compound present in aqueous extract or raw garlic homogenate (Augusti & Mathew, 1975). When garlic is chopped or crushed, allinase enzyme, present in garlic, is activated and acts on alliin (present in whole garlic) to produce allicin (Fenwick & Hanley, 1985). Other important sulphur-containing compounds present in garlic homogenate are allyl methyl thiosulphonate, 1-propenyl allyl thiosulphonate and L-glutamyl-S-alkyl-L-cysteine (Block, 1985; Moyers, 1996). The enzyme allinase responsible for converting alliin (S-allyl cysteine sulfoxide) to allicin is inactivated by heat. Thus, the water extract of heat-treated garlic contains primarily alliin. Although thiosulphinates such as allicin have long been thought to be active compounds due to their characteristic odour, it is not necessary for garlic preparations to contain odorous compounds to be effective. They decompose and disappear during any processing (Harunobu, 2006). The composition of each garlic preparation is presented in Table 2.

### Raw garlic homogenate

Raw garlic homogenate is prepared from peeled raw garlic cloves that are crushed in blender with a volume of distilled water. The mixture was then allowed to stand for 30 min at 25 °C. After filtration through cheesecloth, the raw garlic homogenate sample was obtained (Kasuga *et al.*, 2001).

### Garlic powder

To obtain this preparation, garlic cloves are cut, crushed, dehydrated and pulverised into powder. This form of garlic is one of the preparations used as material for food supplements. The main sulphur compound in both raw garlic and garlic powder is alliin. A complete dehydration (with the minimum of loss) allows obtaining 2–2.5 mg alliin $g^{-1}$ of garlic powder (Iberl *et al.*, 1990).

### Aged garlic extract

Sliced raw garlic stored in 15–20% ethanol for 20 months, at room temperature, is referred to as aged garlic extract. This whole process is supposed to cause

**Table 2** Principal sulphur compounds of garlic preparations

| Raw garlic juice | Garlic powder | Aged garlic extract | Garlic oil |
|---|---|---|---|
| Allicin | Aliin | S-allyl cysteine | Diallyl sulphide |
| Méthyl allyl thiosulphinate | | S-allyl mercapto-cysteine | Diallyl disulphide |
| 1-Propenyl allyl thiosulphinate | | | Diallyl trisulphide |
| L-Glutamyl-S-alkyl-L-cysteine | | | Allyl methyl disulphide |
| | | | Allyl methyl trisulphide |
| | | | Allyl methyl tetrasulphide |
| | | | Dimethyl trisulphide |
| | | | Vinyl-dithiin |
| | | | Ajoene |

considerable loss of allicin and increased activity of certain new water-soluble compounds such as S-allylcystéine and S-allylmercaptocysteine (Kasuga *et al.*, 2001).

### Garlic oil

Medicinally used garlic oil is prepared by steam distillation process. Whole garlic cloves ground in water are distilled by heat or extracted by an organic solvent (e.g. hexane) to obtain fractionated oil. The oily fraction of garlic cloves represents 0.2–0.5% of crude garlic (Amagase *et al.*, 2001). This fraction does not contain water-soluble compound, in particular allicin, but mainly contains a variety of sulphides [such diallyl dissulfide (DADS) and diallyl trisulfide (DATS)] and thiosulphinates (such as vinyldithiins and ajoene) (Banerjee *et al.*, 2003). A typical commercial preparation of oil of *Allium sativum* contains 26% DADS, 19% DATS, 15% allyl methyltrisulphide, 13% methyl disulphide, 8% diallyl tetrasulphide, 6% allyl methyltetrasulphide, 3% dimethyl trisulphide, 4% pentasulphide and 1% hexasulphide (Banerjee & Maulik, 2002).

## Effects of garlic preparations on fertility

The male reproductive system is extremely sensitive to various environmental factors such drugs and pollution that can induce structural and functional alterations (Saradha & Mathur, 2006). Carlsen *et al.* (1992) first reported a decline in sperm density of human semen during the past 50 years. Similarly, Pajarinen *et al.* (1997) showed that the incidence of normal spermatogenesis decreased among middle-aged Finnish men between 1981 and 1991. They also reported the incidence of disorders of spermatogenesis and pathological alterations in testis. Marked decrease in sperm density is related to male sterility, which is diagnosed as male sexual dysfunction. In urology, male sexual dysfunction includes both hypospermatogenesis and impotence. In oriental medicine, several herbs, including garlic, have been used to improve male sexual dysfunction since ancient times.

## Effects on testicular morphology

There are two opposite findings about the effect of garlic on histology of testis. Three studies showed morphological alterations after garlic feeding evidenced by the increase in the number of empty seminiferous tubules and spermatogenesis arrest (Dixit & Joshi, 1982; Hammami *et al.*, 2008; Abdelmalik, 2011) Indeed, Dixit & Joshi (1982) reported that chronic administration of garlic powder at 50 mg dose, over 70 days, induced histological alterations in somatic cells. In our laboratory, we showed that the use of different doses (10%, 15% and 30%) of crude garlic, for 1 month, induced an impairment of Leydig and Sertoli cell ultrastructure on male adult rats. Sertoli cells showed numerous and voluminous lipid droplets and reduction in nucleus volume and presence of more condensed chromatin. Leydig cells showed a normal structure except the abundance of lipid droplets. Spermatocytes and spermatid cells showed vacuolisation in the nucleus and interruption of the nuclear envelope (Hammami *et al.*, 2008). An apoptotic effect was described in these germ cells. A recent study of Abdelmalik (2011) confirmed histological and ultrastructural changes in testicular cells of adult rat, using crude garlic at 20% dose; but compared with the previous study, the apoptotic effect of crude garlic consumption also targeted Sertoli cells, germ cells, interstitial Leydig cells and myoid cells.

In other studies, garlic or its metabolites have been studied as a protective adjuvant to different types of toxins (Unsal *et al.*, 2004; Murugavel & Pari, 2007; Khalil *et al.*, 2008; Sadik, 2008). Indeed, induction of testicular hypogonadism by heat is prevented in part by different types of garlic preparations (garlic juice, heated garlic juice, garlic powder or the more potent aged garlic extract) (Kasuga *et al.*, 2001). Garlic aqueous extract (Ola-Mudathir *et al.*, 2008) or its metabolites diallyl sulphide (Sadik, 2008) and diallyl tetrasulphide (Murugavel & Pari, 2007) offer protection against cadmium-induced testicular damages on adult rat. Crude garlic, at 5 mg $kg^{-1}$ dose, is also effective in restoring the testicular histology altered by EDTA on rat (Khalil *et al.*, 2008). The antioxidant activities of garlic extract, at 5 mg $kg^{-1}$ dose during 5 days, were shown to decrease the toxic effects of free radicals induced by testicular torsion and detorsion on rat (Unsal *et al.*, 2004).

## Effect of garlic on spermatogenesis

Several studies, *in vivo* and *in vitro*, have reported the impairment of spermatogenesis after treatment with garlic and its metabolites. Dixit & Joshi (1982) reported that chronic administration of 50 mg of garlic powder to adult rat over 70 days induced a spermatogenetic arrest at the primary spermatocyte stage. Moreover, aqueous garlic extract (Chakrabarti *et al.*, 2003) and the metabolite diallyl trisulphide (Qian *et al.*, 1986) have spermicidal effects on adult rats. In contrast, Al-Bekairi *et al.* (1990) reported an increase in epididymal spermatozoa after feeding mice with 100 mg $kg^{-1}$ aqueous garlic extract over 3 months. Another study did not show any change in epididymis sperm density after 1 month of treatment of adult rat with 10%, 15% and 30% crude garlic (Hammami *et al.*, 2008). This discrepancy in the studies could be linked to differences in the garlic preparation and the period length of treatment.

Kasuga *et al.* (2001) compared garlic products for improving health. They investigated the pharmacological activities of four garlic preparations, raw garlic juice, garlic powder, heated garlic juice and aged garlic extract, on testicular hypogonadism (hypospermatogenesis and impotence) induced by warm water treatment. The results showed that aged garlic extract at 4 ml $kg^{-1}$ dose for 13 days significantly enhanced spermatogenesis and improved impotence after warm water treatment of mice. In contrast, the other preparations were only slightly effective. This study reported that different garlic preparations have different pharmacological properties, and aged garlic juice is the most consistent in recovery of spermatogenesis (Kasuga *et al.*, 2001)

Phyto-oestrogens are plant constituents with oestrogenic effect (Dixon, 2004). Garlic has been reported to contain two phyto-oestrogens, lignin (Hernandez *et al.*, 2004) and quercetin (Sengupta *et al.*, 2003). Phyto-oestrogens have been used in botanical medicine for a wide variety of female complaints including menopausal symptoms (Sengupta *et al.*, 2003). Some studies reported that oestrogen-like substances induce direct disruption of cells in testes (Sharp & Korach, 1998; Raychoudhury *et al.*, 1999; Hughes *et al.*, 2000; Fitzpatrick, 2003; Abdelmalik, 2011). For example, isoflavonoids and lignans inhibit 5α-reductase activity, thereby reducing the conversion of testosterone to the active form dihydrotestosterone (DHT) (Evans *et al.*, 1995). A number of phyto-oestrogens, including lignans, isoflavonoids daidzein and equol, enterolactone and genistein, were found to induce sex hormone binding globulin (SHBG) production in the liver (Adlercreutz *et al.*, 1992; Mousavi & Adlercreutz, 1993). Furthermore, phyto-oestrogens like endocrine disrupters were showed to have a negative effect on male fertility and/or semen quality (Giwercman, 2011).

## Effect of garlic on testicular cells

In terms of Sertoli cells, for the first time, in previously study, we evaluated several Sertoli cell markers, and we showed that crude garlic at 10% and 15% doses induced modifications in the expression of these markers (Hammami *et al.*, 2009). These modifications were associated with decrease in testosterone (Hammami *et al.*, 2008; Abdelmalik, 2011) and folliculo stimuling hormone (FSH) levels (Hammami *et al.*, 2008), hormones that regulate Sertoli cell functions.

Concerning germ cells, the results of studies developed in our laboratory revealed that the consumption of crude garlic over 1 month induces apoptosis of spermatocytes (pachytenes stage) and spermatids by the activation of caspase-3 and the increase in Smac (pro-apoptotic protein) and IAPs (anti-apoptotic protein) (Hammami *et al.*, 2009). The apoptosis of germ cells was confirmed by the study of Abdelmalik (2011), who described morphological aspects suggesting apoptosis of somatic and myoid cells of adult rat after treatment with 20% of crude garlic during 4 months.

## Effect on testosterone biosynthesis

Testosterone is essential for spermatogenesis completion because it stimulates the conversion of round spermatids into elongated spermatids between stage VII and stage VIII of the spermatogenetic cycle (Dixon, 2004). A limited number of studies investigated the effect of garlic on testosterone. For example, our study reported that the consumption of crude garlic at 5%, 10%, 15% and 30%, by adult rats, reduces testosterone secretion and alters spermatogenesis (Hammami *et al.*, 2008). The reduction in circulating and intratesticular testosterone levels was associated with elevated luteinizing hormone (LH) levels suggesting a diminished responsiveness of Leydig cells to LH and/or a direct inhibition of testicular steroidogenesis and as such a testicular alteration in the gonadotrophin–testosterone axis. In contrast, Oi *et al.* (2001) indicated that increased testicular testosterone concentrations after treatment with 8 g of garlic powder are associated with an increase in LH plasma levels. This discrepancy could be attributed to the different types of garlic preparations that do not contain the same active compounds. Biosynthesis of serum cholesterol, the vital testosterone precursor, was not changed in the study by Hammami *et al.* (2008), while Dixit & Joshi (1982) demonstrated an inhibition of cholesterol biosynthesis in rat serum and liver.

In this context, the different steps of testosterone biosynthesis were evaluated. Conversion of cholesterol to biologically active testosterone is a multi-step enzymatic process, including *Star* that controls the transport of cholesterol from the outer to the inner mitochondrial membrane, *Cyp11a1, Hsd17b3* and *Hsd3b5* (Stocco, 2000). Testosterone can be metabolised by *Srd5a2* or *Cyp19a1*. Garlic was shown to alter testosterone production, as *Star*, *Cyp11a1*, *Hsd17b3* and *Hsd3b5*, mRNA levels were decreased in a dose-dependent manner. Given that testosterone protects germ cells, especially spermatocytes and spermatids, against apoptosis (Woolveridge *et al.*, 1999; Stocco, 2000; Bakalska *et al.*, 2004), its decrease induced by garlic consumption might be an explanation for the death of spermatocyte and spermatid cells via an apoptotic process, while interestingly, garlic extract is known to reduce serum cholesterol levels (in humans and animals) and inhibit cholesterol biosynthesis (Campbell *et al.*, 2001). Alteration in testosterone production was not related to cholesterol metabolism but to steroidogenic enzyme modification (Hughes *et al.*, 2000). Table 3

**Table 3** Comparative study about garlic effects on male reproductive system

| Garlic preparation | Animal model | Mode of administration | Dose and duration | Observed effects | References |
|---|---|---|---|---|---|
| Detrimental effects | | | | | |
| Garlic powder | Rat | Gavage | 50 mg $kg^{-1}$ $day^{-1}$; 45–75 days | Histological alterations in somatic cells<br>Arrest of spermatogenesis at the primary spermatocyte stageReduction in serum concentrations of total protein and sialic acid, cholesterol, triglycerides, phospholipids and transaminase enzyme activity | Dixit & Joshi, 1982; |
| Diallyl trisulphide | Rat and Hamster | *In vitro* | 7.5 mg $ml^{-1}$ | Inhibition of spermatozoa motility | Qian *et al.*, 1986; |
| Raw garlic juice | Rat | Oral | 600 mg $kg^{-1}$ $day^{-1}$; 21 days | Toxic effects affecting weight growth, biological parameters and histological structures | Fehri *et al.*, 1991; |
| Raw garlic juice | Ram and Human | *In vitro* | 0.25 and 0.5 g $ml^{-1}$ | Spermatozoa immobilization | Chakrabarti *et al.*, 2003; |
| Crude garlic | Rat | Oral | 30 g/100 g of diet; 30 days | Diminution of testosterone<br>Alteration in prostate and seminal vesicles<br>Increase in the percentage of empty seminiferous tubules<br>Histological alterations in somatic and germinal cells | Hammami *et al.*, 2008; |
| Crude garlic | Rat | Oral | 15 g/100 g of diet; 30 days | Apoptosis of spermatocytes pachytenes and spermatids (caspase-dependent); Reduction in expression of steroidogenic enzymes with testosterone decrease and LH elevation | Hammami *et al.*, 2009; |
| Crude garlic | Rat | Oral | 20 g/100 g of diet; 4 months | Apoptosis of germ cells, somatic cells and myoid cells; Decreased testosterone and LH elevation | Abdelmalik, 2011; |
| Beneficial effects | | | | | |
| Raw garlic juice | Mice | Oral (drinking water) | 100 mg $kg^{-1}$ $day^{-1}$; 3 months | Increase in seminal vesicles and epididymis weight<br>Increase in epididymal spermatozoa count | Al-Bekairi *et al.*, 1990; |
| Garlic powder | Rat | Oral | 0.8 g/100 g of diet; 28 days | Increased testosterone secretion | Oi *et al.*, 2001; |
| Diallyl disulfide | Rat | Injection into femoral vein | 30 mM (4.28 mg); 30 min | Increased LH concentration | Oi *et al.*, 2001 |

summarises the different studies that evaluated the impact of *Allium sativum* on spermatogenesis.

## Conclusions

Garlic has played an important dietary and medicinal role throughout the history of mankind. In some Western countries, the sale of garlic preparations ranks with those of leading prescription drugs. The therapeutic efficacy of garlic encompasses a wide variety of ailments, including cardiovascular, cancer and hepatic diseases and microbial infections. However, the elucidation of the mechanism for its therapeutic actions has proved to be more elusive and a unifying theory, which could account for its reported multifarious activities, especially on male reproduction. In traditional oriental medicine, garlic has been used to improve male sexual dysfunction and to recover testicular functions. But in the literature, there are very few studies about the potential effects of garlic on spermatogenesis (about ten studies), and their results are contradictory. These discrepancies could be related to three main factors (i) the type of preparations, (ii) the way of administration and (iii) the dose. Moreover, the concentration of bioactive components of garlic is highly variable from one preparation to another. Furthermore, garlic consumption to reduce cardiovascular risk and as antihyperlipidaemic agent represents long-term consumption, which could have another potential negative effect with regard to spermatogenesis. Also, we must note the potential interference that may exist between drugs and garlic consumption. In this context, people must be advised to pay attention to garlic consumption, particularly men who consume garlic every day for therapeutic purposes. Other point is the possibility of interferences between consumption of garlic (at normal doses) with other alimentary endocrine disruptors enhancing its influence on spermatogenesis. For these reasons, this review may be a good reference on relations between garlic and male sexual function and evidences the need for new experiments targeting interferences between garlic and drugs or alimentary endocrine disruptors leading to adversary effects on spermatogenesis.

## Acknowledgement

The authors acknowledge the receipt of financial support from the Tunisian Ministry of Superior Education and Scientific Research.

## References

Abdelmalik SW (2011) Histological and ultrastructural changes in the adult male albino rat testes following chronic crude garlic consumption. *Ann Anat* 193:134–141.

Adlercreutz H, Mousavi Y, Clark J, Höckerstedt K, Hämäläinen E, Wähälä K, Mäkelä T, Hase T (1992) Dietary phytoestrogens and cancer: *in vitro* and *in vivo* studies. *J Steroid Biochem Mol Biol* 41:331–337.

Al-Bekairi AM, Shah AH, Qureshi S (1990) Effect of *Allium sativum* on epididymal spermatozoa, estradiol-treated mice and general toxicity. *J Ethnopharmacol* 29:117–125.

Amagase H, Petesch BL, Matsuura H, Kasuga S, Itakura Y (2001) Intake of garlic and its bioactive components. *J Nutr* 131:955–962.

Ashraf R, Khan RA, Ashraf I (2011) Garlic (*Allium sativum*) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. *Pak J Pharm Sci* 24:565–570.

Augusti KT, Mathew PT (1975) Effect of allicin on certain enzymes of liver after a short term feeding to normal rats. *Experentia* 31:148–149.

Bakalska M, Atanassova N, Koeva Y, Nikolov B, Davidoff M (2004) Induction of male germ cell apoptosis by testosterone withdrawal after ethane dimethanesulfonate treatment in adult rats. *Endocr Regul* 38:103–110.

Banerjee SK, Maulik SK (2002) Effect of garlic on cardiovascular disorders: a review. *J Nutr* 19:1–4.

Banerjee SK, Mukherjee PK, Maulik SK (2003) Garlic as an antioxidant: the good, the bad and the ugly. *Phytother Res* 17:97–106.

Block E (1985) The chemistry of garlic and onions. *Sci Am* 252:114–119.

Brankovic S, Radenkovic M, Kitic D, Veljkovic S, Ivetic V, Pavlovic D, Miladinovic B (2011) Comparison of the hypotensive and bradycardic activity of ginkgo, garlic, and onion extracts. *Clin Exp Hypertens* 33:95–99.

Campbell JH, Efendy JL, Smith NJ, Campbell GR (2001) Molecular basis by which garlic suppresses atherosclerosis. *J Nutr* 131:1006–1009.

Carlsen E, Giwercman A, Keiding N, Skakkebaek NE (1992) Evidence for decreasing quality of semen during past 50 years. *BMJ* 305:609–613.

Cerella C, Dicato M, Jacob C, Diederich M (2011) Chemical properties and mechanisms determining the anti-cancer action of garlic-derived organic sulfur compounds. *Anticancer Agents Med Chem* 11:267–271.

Chakrabarti K, Pal S, Bhattacharyya AK (2003) Sperm immobilization activity of *Allium sativum* L. and other plant extracts. *Asian J Androl* 5:131–135.

Dixit VP, Joshi S (1982) Effects of chronic administration of garlic (*Allium sativum* Linn) on testicular function. *Indian J Exp Biol* 20:534–536.

Dixon RA (2004) Phytoestrogens. *Annu Rev Plant Biol* 55:225–261.

Durak I, Kavutcu M, Aytac B, Avci A, Devrim E, Ozbek H, Ozturk HS (2004) Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. *J Nutr Biochem* 15:373–377.

Evans BA, Griffiths K, Morton MS (1995) Inhibition of 5 alpha-reductase in genital skin fibroblasts and prostate tissue by dietary lignans andisoflavonoids. *J Endocrinol* 147:295–302.

Fehri B, Aiache JM, Korbi S, Monkni M, Ben Said M, Memmi A, Hizaoui B, Boukef K (1991) Toxic effects induced by the repeat administration of *Allium sativum* L. *J Pharm Belg* 46:363–374.

Fenwick GR, Hanley AB (1985) The genus Allium. Part 2. *Crit Rev Food Sci Nutr* 22:273–377.

Fitzpatrick LA (2003) Alternatives to estrogen. *Med Clin North Am* 87:1091–1113.

Ginter E, Simko V (2010) Garlic (*Allium sativum* L.) and cardiovascular diseases. *Bratisl Lek Listy* 111:452–456.

Giwercman A (2011) Estrogens and phytoestrogens in male infertility. *Curr Opin Urol* 21:519–526.

Hammami I, Nahdi A, Mauduit C, Benahmed M, Amri M, Ben Amar A, Zekri S, El May A, El May MV (2008) The inhibitory effects on adult male reproductive functions of crude garlic (*Allium sativum*) feeding. *Asian J Androl* 10:593–601.

Hammami I, Amara S, Benahmed M, El May MV, Mauduit C (2009) Chronic crude garlic-feeding modified adult male rat testicular markers: mechanisms of action. *Reprod Biol Endocrinol* 24:57–65.

Harunobu A (2006) Clarifying the real bioactive constituents of garlic. *J Nutr* 136:716–725.

Hernandez BY, McDuffie K, Franke AA, Killeen J, Goodman MT (2004) Reports: plasma and dietary phytoestrogens and risk of premalignant lesions of the cervix. *Nutr Cancer* 49:109–124.

Hiyasat B, Sabha D, Grotzinger K, Kempfert J, Rauwald JW, Mohr FW, Dhein S (2009) Antiplatelet activity of *Allium ursinum* and *Allium sativum*. *Pharmacology* 83:197–204.

Hughes PJ, McLellan H, Lowes DA, Kahn SZ, Bilmen JG, Tovey SC, Godfrey RE, Michell RH, Kirk CJ, Michelangeli F (2000) Estrogenic alkylphenols induce cell death by inhibiting testis endoplasmic reticulum Ca (2+) pumps. *Biochem Biophys Res Commun* 277:568–574.

Iberl B, Winkler G, Muller B, Knobloch K (1990) Quantitative determination of allicin and alliin from garlic by HPLC. *Planta Med* 56:320–326.

Kasuga S, Uda N, Kyo E, Ushijima M, Morihara N, Itakura Y (2001) Pharmacologic activities of aged garlic extract in comparison with other garlic preparations. *J Nutr* 131:1080–1084.

Khalil WK, Ahmed KA, Park MH, Kim YT, Park HH, Abdel-Wahhab MA (2008) The inhibitory effects of garlic and Panax ginseng extract standardized with ginsenoside Rg3 on the genotoxicity, biochemical, and histological changes induced by ethylenediaminetetraacetic acid in male rats. *Arch Toxicol* 82:183–195.

Kim JY, Kwon O (2009) Garlic intake and cancer risk: an analysis using the Food and Drug Administration's evidence-based review system for the scientific evaluation of health claims. *Am J Clin Nutr* 89:257–264.

Lawson LD (1998) Garlic: a review of its medicinal effects and indicated active compounds. In: Phytomedicines of Europe. Lawson LD, Bauer R (eds). American Chemical Society, Washington, DC, pp 176–209.

Mousavi Y, Adlercreutz H (1993) Genistein is an effective stimulator of sex hormone-binding globulin production in hepatocarcinoma human liver cancer cells and suppresses proliferation of these cells in culture. *Steroids* 58:301–304.

Moyers S (1996) History of garlic. In: Garlic in Health, History and World Cuisine. Moyers S (ed.). Suncoast Press, St Petersburg, FL, pp 1–36.

Murugavel P, Pari L (2007) Diallyl tetrasulfide modulates the cadmium-induced impairment of membrane bound enzymes in rats. *J Basic Clin Physiol Pharmacol* 18:37–48.

Oi Y, Imafuku M, Shishido C, Kominato Y, Nishimura S, Iwai K (2001) Garlic supplementation increases testicular testosterone and decreases plasma corticosterone in rats fed a high protein diet. *J Nutr* 131:2150–2156.

Ola-Mudathir KF, Suru SM, Fafunso MA, Obioha UE, Faremi TY (2008) Protective roles of onion and garlic extracts on cadmium-induced changes in sperm characteristics and testicular oxidative damage in rats. *Food Chem Toxicol* 46:3604–3611.

Padiya R, Khatua TN, Bagul PK, Kuncha M, Banerjee SK (2011) Garlic improves insulin sensitivity and associated metabolic syndromes in fructose fed rats. *Nutr Metab (Lond)* 27:53–58.

Pajarinen J, Laippala P, Penttila A, Karhunen PJ (1997) Incidence of disorders of spermatogenesis in middle aged Finnish men, 1981-91: two necropsy series. *BMJ* 314:8–13.

Prasad K (2010) Natural products in regression and slowing of progression of atherosclerosis. *Curr Pharm Biotechnol* 11:794–800.

Qian YX, Shen PJ, Xu RY, Liu GM, Yang HQ, Lu YS, Sun P, Zhang RW, Qi LM, Lu QH (1986) Spermicidal effect *in vitro* by the active principle of garlic. *Contraception* 34: 295–302.

Raychoudhury SS, Blake CA, Millette CF (1999) Toxic effects of octylphenol on cultured rat spermatogenic cells and Sertoli cells. *Toxicol Appl Pharmacol* 157:192–202.

Rivlin RS (2001) Historical perspective on the use of garlic. *J Nutr* 131:951–954.

Sadik NA (2008) Effects of diallyl sulfide and zinc on testicular steroidogenesis in cadmium-treated male rats. *J Biochem Mol Toxicol* 22:345–353.

Saradha B, Mathur PP (2006) Effect of environmental contaminants on male reproduction. *Environ Toxicol Pharmacol* 21:34–41.

Sengupta A, Ghosh S, Das S (2003) Tomato and garlic can modulate azoxymethane-induced colon carcinogenesis in rats. *Eur J Cancer Prev* 12:195–200.

Sharp RM (1998) Toxicity of spermatogenesis and its detection. In: Reproductive and Developmental Toxicology. Korach KS (ed.). Marcel Dekker, New York, NY, pp 625–663.

Stocco DM (2000) Intramitochondrial cholesterol transfer. *Biochim Biophys Acta* 1486:184–197.

Unsal A, Eroglu M, Avci A, Cimentepe E, Guven C, Derya Balbay M, Durak I (2004) Protective role of natural antioxidant supplementation on testicular tissue after testicular torsion and detorsion. *Scand J Urol Nephrol* 40:17–22.

WHO (2002) Traditional Medicine Strategy 2002–2005. WHO, Geneva.

Woolveridge I, de Boer-Brouwer M, Taylor MF, Teerds KJ, Wu FC, Morris ID (1999) Apoptosis in the rat spermatogenic epithelium following androgen withdrawal: changes in apoptosis-related genes. *Biol Reprod* 60:461–470.