Agriculture and Food

AIMS Agriculture and Food, 4(2): 386–398.
DOI: 10.3934/agrfood.2019.2.386
Received: 27 December 2018
Accepted: 17 April 2019
Published: 29 April 2019

http://www.aimspress.com/journal/agriculture

Review

Pharmacological effect of Allium sativum on coagulation, blood pressure, diabetic nephropathy, neurological disorders, spermatogenesis, antibacterial effects

Seyyed Abbas Hashemi[1], Sayeh Ghorbanoghli[2,*], Ali Asghar Manouchehri[3] and Mahdi Babaei Hatkehlouei[4]

[1] Department Of Internal Medicine, Faculty Of Medicine, Student Research Committee, Mazandaran University Of Medical Sciences, Sari, Iran
[2] Department Of Traditional Medicine, Faculty Of Medicine, Gorgan University Of Medical Sciences, Gorgan, Iran
[3] Assistant Professor, Forensic Medicine, ShahidBeheshti Hospital, Babol University of Medical Sciences, Babol, Iran
[4] Student Research Committee, Mazandaran University Of Medical Science, Sari, Iran

* **Correspondence:** Email: abbas.hashemi30@gmail.com.

Abstract: For many years, the medicinal plants have been used all over the world for treating and preventing from some diseases. But the effects of some of them have been examined scientifically. The medicinal plants are useful treating methods in both traditional and modern systems. The allium species like garlic and onion are used as food, spices, flavor and local drugs. With the scientific name of Allium sativam, the garlic is from the Liliaceae family and it has attracted a special attention among the modern plants, because it has been spread and is available all over the world. The findings of this study indicate that the garlic consuming can increase infection of some of bacteria. Due to the antioxidant characteristics, the garlic is likely to reduce these hurts significantly through increasing the antioxidant capacity in the kidney. There are several reports on the anticoagulation characteristics of garlic. Also there are some warnings about the simultaneous consumption of the garlic with warfarin and nonsteroidal anti-inflammation drugs. And also, garlic has anti-hypertensive characteristics and its compounds have been investigated in treating infertility, according to the studies done, garlic and the old garlic's extract have anti-stress, anti-aging, memory and learning improving and anti-Alzheimer characteristics. But more studies are needed to be done on the humans in this context.

Keywords: garlic; herbal; medicine; Allium sativum; nephropathy; spermatogenesis; antibacterial

1. Introduction

From long ago and in many different old civilizations, different plants have been used as drugs and in order to treat and prevent from various diseases [1,2]. Garlic (Allium sativum L) is an edible and medicinal plant from Lilliaceae family which was being used in ancient Iranian medicine in treating different diseases [3,4]. In his law book, Avicenna has mentioned garlic as a useful plant in the treatment of joint diseases, dent pains, chronic cough, parasitic infections, snake bites, women's and diseases, infections and headaches, especially one way headaches [5]. Due to the widespread belief of the therapeutic properties of garlic among the people, it has been especially paid attention to in the modern medicine as a medicinal plant, too [3,4]. Also nowadays, widespread researches are done about the compounds existing in the garlic and its therapeutic properties. According to the investigations done, the main and effective material in juice extracted from the garlic or row garlic is called homogenized allicin [6].

2. Diabetic nephropathy

During the recent decades, a huge rise has been occurred for using the medicinal plants and traditional medicine in order to treat diabetes disease and many other diseases. For example, some plants such as onions, ginger and aloe vera can be mentioned. Garlic has medicinal and therapeutic properties such as antibacterial, anticancer, anti-asthma and anti-diabetes properties [7]. Many widespread researches have been done on the anti-diabetic properties of the garlic and it has been cleared that its Sulphuric compounds like allicin act as the hypoglycemic compounds. Also, it has been determined that the 15-day treatment with the garlic oil cause a significant increase in Albumin serum [8]. On the other hand, nephropathy and toxicity created with potassium dichromate cause the oxidative stress in kidney and consuming garlic powder improves the consequences caused by it so that the mice feeding with garlic powder prevents from the significant changes of renal injuries for 2 percent and improves 55 percent of textural injuries caused by potassium dichromate in mice's kidneys [9]. During many studies which have been done in the field of the anti-diabetic properties of garlic and its compounds, most of them have confirmed the garlic's anti-diabetic properties [10].

In 2011, Ryan indicated that the disease of one third of the patients with diabetes disease who regularly consumes garlic along with their medicinal treatment has been improved effectively. Dimirdash [11] found out that the garlic's juice reduces the blood sugar of the groups receiving garlic. Also the garlic's oil and the compounds existing in garlic such as diallyl trisulfide improve the blood sugar levels of diabetic rats [12]. The studies done on the garlic's oil have indicated that the garlic improves the textural changes caused by nephropathy during diabetes disease [6]. Advancing renal damages and high blood pressure are depended upon oxidative and nitro-oxidative stress and consuming the garlic oil and S Allil Cysteine (SAC) reduces the blood pressure and renal damages and it does this work through improving antioxidant system and delaying the renal damages caused by diabetes disease [13].

Also increasing blood sugar during diabetes induces growth factors and cytokines which results in increase of glomeruli growth and expanding the extracellular matrix and creation of sclerosis and

finally fibrosis of the renal texture [14]. The studies have indicated that garlic consumption releases the growth factors and cytokines; therefore, other possible mechanisms of the garlic can be named in reducing the tubular damages and preventing from the release of growth factors and cytokines and also reduction of inflammation factors which result in improvement of hypertrophy of glomerulus and tubules [15].

The oxidative stress increases significantly during diabetes. Also the induction of oxidative stress in kidney using gentamicin increases producing free radicals in kidney which results in destruction of kidney texture (necrosis of proximal tubules). On the other hand, the researchers have indicated that the garlic and its compounds have strong antioxidant properties due to the sulfur compounds such as (SAC [16] and diallyl trisulfide [12]) and the garlic is likely to reduce the damages caused by diabetic nephropathy through increasing the antioxidant amount in the kidney [17].

Also the studies have indicated that the proportion of kidney weight to the body weight increases in diabetic patients [18]; hence, the results of this study have also indicated that the proportion of kidney weight to the body weight increases during diabetes and consuming garlic oil reduces this proportion in the groups receiving garlic. According to the investigations done by the researchers, it has been cleared that the blood sugar increase in diabetes increases the intercellular protein synthesis and decreases the catabolism of proteins; and this decreases also increases the cells' length and the volume of cellular proteins which result in the hypertrophy of glomerulus and tubules. On the other hand, it has been indicated that in diabetes disease, the activity and production of intracellular proteases like cathepsin [19] significantly decreases due to the increase in production of factors such as TNF- α and Angiotensin ll, and this cause hypertrophy of glomerulus and kidney texture. Since the garlic decreases the production of cytokines [20], so it also prevents from hypertrophy in this way.

Shiju TM, et al. [21] showed that aged garlic extract was able to ameliorate kidney damage an animal model. They revealed that anti-glycation and hypolipidemic activities of aged garlic extract caused renoprotective impacts.

Aged garlic extract has been indicated to have antioxidant [22], anti-thrombotic [23], anti-cancer [24], hypoglycemic [25], hypolipidemic and hypocholesterolemic activities [26]. The renoprotective effect of aged garlic extract on nephrectomised [13,27,28] and nephrotoxic rat models [29–31] has been reported. Ilker Seckiner, et al. [32] indicated that 4% pulverized garlic supplemented diet has preventive role aganist nephrotoxicity induced by gentamicin in rats.

3. Antibacterial effects

In some studies, it has been emphasized on the existence of a relationship between garlic consuming and decrease in helicobacter pylori infection [33–35]. However in some other studies such a relationship has not been observed [36–38].

The recent studies have indicated that due to having allicin, the garlic has antibacterial characteristic on a wide range of positive gram and negative gram bacteria especially on helicobacter pylori so that analyzing or preventing from allicin formation removes the antibacterial activity of the garlic [39,40].

Naturally there is no allicin in the garlic, but also it is produced after hydrolyze and oxidation of a material named allin [41]. In case of cutting or grinding the garlic cloves, the destruction of garlic cells and allinase enzyme changes the allin material into the unstable form of allicin Thiosulfinate

and after that allicin [42]. According to the study, the garlic's effect mechanism is done through preventing from the activity of nuclear factor Kappa (KB) [43].

This factor increases the expression of genes related to inflammation cytokines and it is considered as one of the key molecules in inflammation and cancer. Activation of this nuclear factor is done through signaling the receptors called (Toll-like receptors) TLR 4.TLR 4s are the key receptors in feeling the different microbial productions and stimulating the immune responses [43]. These receptors have several compounds containing cysteine in their cytoplasm and extracellular parts.

The studies have indicated that the allicin existing in garlic contains some compounds called Thiosulfinate which can react to cysteine [43]. As a result, allicin may react to this cysteine existing in the structure of these receptors and prevent from the activity of signaling paths depending upon TLR 4 on the surface of the cellular receptors. Allicin prevents from the activation of nuclear factor of KB through blocking TLR 4 signaling [44].

This prevention is considered as one of the anti-inflammation mechanisms of the garlic. In addition to the mentioned mechanisms, the previous studies have also indicated that the helicobacter pylori produce some antigenic materials such as heat shock proteins, urease and lipopolysaccharide which all of them can be absorbed by the epithelial cells of the gastric and pass the sub-mucosal layer and ultimately make the inflammation factors od CRP and IL-8 and TNF- α synthase [46].

While the Thiosulfinate existing in garlic have the ability to rapidly react with the SH group existing in these compounds and cause the prevention of activation of these compounds and ultimately decrease in colonization of this microbe [47]. Helicobacter pylori increases PH in the gastric and this is followed by the increase of nitrate quickening microbes in the gastric and as a consequence nitrite level which is an important factor of cancer development increases [48]. Allicin may decrease the helicobacter infection and also the cancer development through blocking the nitrous construction and the cleaning role of nitrates and free radicals [48].

In the previous studies it has been indicated that firstly, in the grinding process of the row garlic, the antibiotic properties of allicin existing in it decreases [49]. Secondly, storing garlic powder for a long time also decreases the antibiotic properties of allicin, because allicin is analyzed to the other sulfuric compounds in a long time period and however these compounds have therapeutic properties in their turn, but they cannot induce the potential antibiotic properties of allicin on the bacteria [49].

Developing resistance in different species of helicobacter pylori against the antibiotics is a thousand times easier than developing it against allicin [50]. In addition, the previous studies have indicated that not only the helicobacter pylori do not become resisted against allicin, but also, consuming garlic along with the antibiotics additionally influences the eradication of this bacterium [51–54].

4. Spermatogenesis

Garlic's biological responses include reduction of cardiovascular risk factors, cancer, stimulating immune activity, increased detoxification of foreign compounds, anti-microbial and anti-viral effects, antioxidant activity, protecting from germinal cells in adult male rats that reflect their antioxidant role, protecting from sperm and the cause of ultimate maturation of sperm and its evolution. It has been reported that adding the garlic extract to the drinking water of male rats for a three months period has increased the epididymis's and seminal vesicle weight compared to the normal rats; and also the number of sperms increases significantly [55–58].

Garlic has different compounds such as prostaglandins, pectin, adenosine, vitamins E, C, B6, B2, B1, A, biotin, fatty acids and essential amino acids [49].

Several therapeutic effects and numerous properties have been mentioned for this plant so that it has been considered as the disinfectant of digestive tract, stimulant plant, diuretic and appetizer [59,60].

Mammalians sperm cells have a high amount of unsaturated fatty acids, plasmalogen and Sphingomyelin which are considered as the important substrates in oxidation process [61]. The antioxidant mechanisms are normally present in the reproductive textures and they prevent from the oxidative damages in Gennady and adult spermatozoa cells [62,63]. On the other hand, the intrinsic antioxidant activity of garlic, its extracts and some of its compounds has been widely confirmed in laboratory environments and organisms. It has been cleared that garlic consumption increases the serum level of the total antioxidant potential. The garlic extract increases the superoxide dismutase (SOD), glutathione peroxidase and catalase in the cells [64].

The studies indicate that increase of free radicals negatively influences the reproduction, activity and fertility of sperms. If these radicals' level is not regularly balanced, the normal performance of cells is hindered. According to the studies done, the complex process of spermatogenesis and passing the germinal cells to reach the matureness of the sexual cells depend on being secured from the pathologic and cytotoxic wastages which threaten this phenomena [65].

Antioxidant activity of garlic is due to the sulfur compounds existing in it and they are seen in the garlic extract abundantly. This antioxidant activity eliminates the free radicals and also prevents from the active metabolite of cyclophosphamide active drug (Acroleine) and eliminates them [66,17].

The studies indicate that the garlic extract protects the germinal cells in matured adult rats and this property can be the reflection of its antioxidant role [67].

Glutathione peroxidase enzyme plays an essential role in protecting sperms in testicle and the epididymis texture as an antioxidant; and decrease in this enzyme in the body causes infertility. This enzyme locates in plasma membrane of the sperm, the sperm cell, epididymis liquid and epididymis area and in this way it protects the sperms from the free radicals and this leads to ultimate matureness and development of them [68].

The studies indicate that the antioxidant enzymes, glutathione peroxidase and superoxide dismutase protects the cells through influencing peroxide forms and oxidation reduction. Garlic extract increases the cellular glutathione peroxidase enzyme in all the cells of liver, kidney, breast, testis, etc. [66,67]. Therefore, the garlic extract and especially diallyl disulfide and other sulfur compounds prevent from the destructive influences and DNA break in sperm and sperm-germinal cells through increasing glutathione peroxidase.

In the studies done, the garlic juice protects the germinal cells of male rats and this can be the reflection of its antioxidant role [69].

In 2008, it has been reported that the ethanol extract of rhizome which is called with the scientific name of Curculigo orehioids increases the spermatogenesis in testis of albino rats. This plant has phenol and phenolic glycosides which have antioxidant properties. According to the effects mentioned about phenolic glycosides existing in rhizome, and due to the fact that this compound also exists in the garlic, it can be said that this compound is one of the active and effective components of the garlic in increasing the spermatogenesis [67,70].

Garlic has melatonin which prevents from the degeneration with germinal cells as a strong antioxidant. Melatonin simulates the internal antioxidant system and increases the activity of glutathione S-transferase, superoxide dismutase and the other thiols in blood, liver, testis and kidney [71–73].

The study [74] indicated that the garlic extract influences the increase of releasing the matured sexual cells in addition to influencing the structure of sperm generating ducts and it also improves the spermatogenesis process in experimental groups receiving cyclophosphamide. Cyclophosphamide prevents from reproduction of the germinal cells through influencing DNA molecule and as a consequence, it decreases the number of sperm cells, spermatid, and the primary and secondary spermatocyte. Due to the sulfuric compounds in the garlic, its antioxidant activity eliminates the free radicals and also prevents from the active metabolite of cyclophosphamide (Acroleine) and eliminates it. Probably, inclusion of this plant which is full of useful and effective compounds in the diet of those whose fertility (reproductive activity) has been impaired sue to consumption of chemical drugs can be influential in treating this impairment (inability in reproduction).

5. Neurological disorders

In recent decades' researches, in addition to the stabilization of the garlic's role in treating the diseases especially cardiovascular diseases, its role in treating the central nervous system side effects has been confirmed [75]. According to the study done, garlic has anti-stress, anti-aging properties and it improves memory and learning [76–78]; moreover, old garlic extract have protecting effects on the brain and prevents from oblivion, neuronal apoptosis, Alzheimer and the other neurodegenerative diseases [75,79,80].

Dhingra indicated that the alcohol extract of garlic can have anti-depression properties through inhibition of monoamine oxidases and increase in norepinephrine, dopamine and serotonin level, and decrease in GABA levels in the rat's brain; also the garlic may have mutual function with different brain receptors including α1 adeno-receptors and D2 dopamine receptors, GABAergic and serotonergic receptors [81].

The previous human and animal studies have indicated the anti-pain effects of the garlic so that it decreases dental pain, colic gastrointestinal pains, the pains caused by inflammation of the middle ear, chest pains and the intermittent claudication pain which is due to peripheral vascular obstruction [82–85]. Although, no conclusive reason has been mentioned for this anti-pain property of the garlic in these studies, the previous animal studies have shown that the old garlic extract can prevent from the memory and learning disorders which are caused by aging [76,85]. Also, in these studies it has been determined that the garlic is able to prevent from the frontal brain shrinkage of the old rats' brains, atrophy and reduction of brain size [76].

In his review study, Borek has emphasized on the fact that the garlic can prevent from the brain's side effects caused by aging including Dementia, oblivion and Alzheimer; however, he considers the anti-oblivion property of the garlic the reason of prevention of these factors due to the shared risk factors among the cardiovascular diseases and oblivion and Alzheimer such as blood pressure, increase in blood cholesterol and homocysteine levels and inflammation and the fact that the garlic prevents from the cardiovascular diseases; also, regarded to the role of free radicals in these diseases and its antioxidant properties, they can be the reason.

At the end of the study, the author considers the treatment with old garlic extract useful in preventing from degeneration of brain's frontal lobe, memory loss and learning and increase in lifetime [75]. In the other studies, the anti-stress effects of garlic have been confirmed [77]. A study indicated that in the presence of old garlic extract, the cultured hippocampus neurons grow more and the number of their branches increases; this characteristic can be the indicator of the reason of

garlic's effect on increasing learning and cognitive functions [76]. S-Allil Cysteine (SAC) can prevent from the formation of Beta Amyloid caused by stress oxidative in hippocampus of rats and decrease the learning deficits; the authors consider these effects caused by antioxidant effects [86].

6. Coagulation

Acting against the microorganisms, and anti-cancer, anti-intoxication, anti-inflammation activities are from the numerous and useful properties of garlic which reduces the blood pressure and sugar, simulates immune system and it is anti-allergy and anti-goiter [87–94] and also it has anti-coagulation properties and in this regard, it improves the activity of warfarin and nonsteroidal anti-inflammation drugs' influence [95–105].

In his study, lee Moffitt considers the existence of adenosine de-amines and cAMP phosphodiesterase in garlic as one of the important reasons of anti-coagulation and vascular dilator properties of this plant [100]. Also, the compound of Ajoene existing in garlic is a strong anti-platelet agent which inhibits the platelet aggression reversibly and in the form of Invitro and anyway it influences the BT process. Ahmad-Ni-Lavrik et al. have also emphasized on the adverse effect of garlic on the platelet activity; however, many researchers including Jabbari and Hagdan emphasize that in order to determine the clear effect of garlic on blood pressure–inhibition of platelet and fat aggression, etc. it is required to consume it for three months [98,99]. One of the most important issues which has been referred in different references [95,97,100,101] is the simultaneous consumption of garlic with anti-coagulation drugs like warfarin or nonsteroidal anti-inflammation drugs like aspirin, the garlic can intensify their effect and lead to bleeding.

Anesthesiologists and some researchers emphasize on not consuming garlic before surgeries because of the increased bleeding risk [95,97,100].

Fakhar and Hashemi [104] revealed that garlic as a supplementary treatment can decrease platelet aggregation.

7. Blood pressure

There has been reported that garlic has anti-hypertensive effect through mechanism of intracellular nitric oxide and hydrogen sulfide production besides reducing the production of angiotensin-II [105–112].

8. Conclusions

Regarded to the antioxidant properties of the garlic which has been previously confirmed, it is likely to reduce these damages significantly through increasing antioxidant capacity in the kidney. Due to the mentioned results, we indicated that the garlic is able to prevent from the diabetic side effects of kidney. The results findings indicate that advising to consume garlic along with antibiotic can help reduce and eradicate helicobacter pylori and the other bacteria. Finally, it must be mentioned that however the garlic has been posed as a factor for reducing infection, but there are still many ambiguities in this regard.

There are numerous reports about the anti-coagulation properties of the garlic. Also there have been some warnings about its simultaneous consumption with warfarin and nonsteroidal

anti-inflammation drugs. In this research, it has been tried to investigate the influence of garlic on the coagulation tests in order to guide the patients especially the ones with coagulation problems better about how to consume garlic in case of the proved adverse effects on the coagulation process. Anesthesiologists and some researchers emphasize on not consuming garlic before surgeries because of the increased bleeding risk. Also garlic has the anti-blood pressure properties and its compounds have been studied for treating infertility.

According to the study done, garlic has anti-stress, anti-aging properties and it improves memory and learning; moreover, old garlic extract have protecting effects on the brain and prevents from oblivion, neuronal apoptosis, Alzheimer and the other neurodegenerative diseases.

Conflict of interest

The authors declare no conflict of interest.

References

1. Rivlin RS (2001) Historical perspective on the use of garlic. *J Nutr* 131: 951–954.
2. Jiang Y, David B, Tu P, et al. (2010) Recent analytical approaches in quality control of traditional Chinese medicines—a review. *Anal Chim Acta* 657: 9–18.
3. Nagourney RA (1998) Garlic: Medicinal food or nutritious medicine? *J Med Food* 1: 13–28.
4. Tattelman E (2005) Health effects of garlic. *Am Fam Physician* 72: 103–106.
5. Avecina A (1991) Ghanoon in Medicine: 458–465.
6. Koch HP, Lawson LD (1995) *Garlic: The Science and Therapeutic Application of Allium Sativum L. and Related Species.* Baltimore: Williams & Wilkins, 34–108.
7. Mathew BC, Daniel RS, Augusti KT (1996) Hypolipidemic effect of garlic protein substituted for casein in diet of rats compared to those of garlic oil. *Indian J Exp Biol* 34: 337–340.
8. Anwar MM, Meki AR (2003) Oxidative stress in streptozotocin-induced diabetic rats: Effects of garlic oil and melatonin. *Comp Biochem Physiol A Mol Integr Physiol* 135: 539–547.
9. Pedraza-Chaverri J, Yam-Canul P, Chirino YI, et al. (2008) Protective effects of garlic powder against potassium dichromateinduced oxidative stress and nephrotoxicity. *Food Chem Toxicol* 46: 619–627.
10. Liu CT, Sheen LY, Lii CK (2007) Does garlic have a role as an antidiabetic agent? *Mol Nutr Food Res* 51: 1353–1364.
11. El-Demerdash FM, Yousef MI, El-Naga NI (2005) Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. *Food Chem Toxicol* 43: 57–63.
12. Liu CT, Hse H, Lii CK, et al. (2005) Effects of garlic oil and diallyl trisulfide on glycemic control in diabetic rats. *Eur J Pharmacol* 516: 165–173.
13. Cruz C, Correa-Rotter R, Sánchez-González DJ, et al. (2007) Renoprotective and antihypertensive effects of S-allylcysteine in 5/6 nephrectomized rats. *Am J Physiol Renal Physiol* 293: F1691–F1698.
14. Mensah-Brown EP, Obineche EN, Galadari S, et al. (2005) Streptozotocin-induced diabetic nephropathy in rats: The role of inflammatory cytokines. *Cytokine* 31: 180–190.
15. Yin MC, Hsu CC, Chiang PF, et al. (2007) Antiinflammatory and antifibrogenic effects of s-ethyl cysteine and s-methyl cysteine in the kidney of diabetic mice. *Mol Nutr Food Res* 51: 572–579.

16. Maldonado PD, Barrera D, Rivero I, et al. (2003) Antioxidant S-allylcysteine prevents gentamicin-induced oxidative stress and renal damage. *Free Radic Biol Med* 35: 317–324.
17. Moreno FJ, Corzo-Martı´nez M, del Castillo MD, et al. (2006) Changes in antioxidant activity of dehydrated onion and garlic during storage. *Food Res Int* 39: 891–897.
18. Hamada Y, Fukagawa M (2007) A possible role of thioredoxin interacting protein in the pathogenesis of streptozotocin-induced diabetic nephropathy. *Kobe J Med Sci* 53: 53–61.
19. O'Bryan GT, Hostetter TH (1997) The renal hemodynamic basis of diabetic nephropathy. *Semin Nephrol* 17: 93–100.
20. Kalantarinia K, Awad AS, Siragy HM (2003) Urinary and renal interstitial concentrations of TNF-alpha increase prior to the rise in albuminuria in diabetic rats. *Kidney Int* 64: 1208–1213.
21. Shiju TM, Rajesh NG, Viswanathan P (2013) Renoprotective effect of aged garlic extract in streptozotocin-induced diabetic rats. *Indian J Pharmacol* 45: 18–23.
22. Moriguchi T, Takasugi N, Itakura Y (2001) The effects of aged garlic extract on lipid peroxidation and the deformability of erythrocytes. *J Nutr* 131: 1016S–1019S.
23. Fukao H, Yoshida H, Tazawa Y, et al. (2007) Antithrombotic effects of odorless garlic powder both *in vitro* and *in vivo*. *Biosci Biotechnol Biochem* 71: 84–90.
24. Yeh YY, Liu L (2001) Cholesterol lowering effect of garlic extracts and organosulphur compounds: Human and animal studies. *J Nutr* 131: 989S–993S.
25. Saravanan G, Ponmurugan P, Kumar GPS, et al. (2009) Anti-diabetic properties of S-allylcysteine, a garlic component on streptozotocin induced diabetes in rats. *J App Biomed* 7: 151–159.
26. Wang X, Jiao F, Wang QW, et al. (2012) Aged black garlic extract induces inhibition of gastric cancer cell growth *in vitro* and *in vivo*. *Mol Med Rep* 5: 66–72.
27. Bautista-Garcia P, Sanchez-Lozada LG, Cristobal-Garcia M, et al. (2006) Chronic inhibition of NOS-2 ameliorates renal inhury, as well as COX-2 and TGF-beta 1 overexpression in 5/6 nephrectomized rats. *Nephrol Dial Transplant* 21: 3074–3081.
28. Fujihara CK, Antunes GR, Mattar AL, et al. (2007) Chronic inhibition of nuclear factor-kappa B attenuates renal injury in the 5/6 renal ablation model. *Am J Physiol Ren Physiol* 292: F92–99.
29. Maldonado PD, Barrera D, Medina-Campos ON, et al. (2003) Aged garlic extract attenuates gentamicin induced renal damage and oxidative stress in rats. *Lif Sci* 73: 2543–2556.
30. Wongmekiat O, Thamprasert K (2005) Investigating the protective effects of aged garlic extract on cyclosporine induced nephrotoxicity in rats. *Fundam Clin Pharmacol* 19: 555–562.
31. Kabasakal L, Sehiril O, Cetinel S, et al. (2005) Protective effect of aqueous garlic extract against renal ischemia/reperfusion injury in rats. *J Med Food* 8: 319–326.
32. Seckiner I, Bayrak O, Can M, et al. (2014) Garlic supplemented diet attenuates gentamicin nephrotoxicity ın rats. *Int Braz J Urol* 40: 562–567.
33. Mahady GB, Matsuura H, Pendland SL (2004) Allixin, a phytoalexin from garlic, inhibits the growth of Helicobacter pylori in vitro. *Am J Gastroenterol* 96: 3454–3455.
34. O'Gara E, Hill D, Maslin D (2000) Activities of garlic oil, garlic powder, and their diallyl constituents against helicobacter pylori. *Appl Environl Microbiol* 66: 2269–2273.
35. Cañizares P, Gracia I, Gómez LA, et al. (2004) Thermal degradation of allicin in garlic extracts and its implication on the inhibition of the in-vitro growth of helicobacter pylori. *Biotechnol Prog* 20: 32–37.
36. Gail MH, You WC (2006) A factorial trial including garlic supplements assesses effect in reducing precancerous gastric lesions. *J Nutr* 136: 813S–815S.

37. Ernst E (1999) Is garlic an effective treatment for Helicobacter pylori infection? *Arch Intern Med* 159: 2484–2485.
38. Aydin A, Ersoz G, Tekesin O, et al. (2000) Garlic oil and Helicobacter pylori infection. *Am J Gastroenterol* 95: 563–564.
39. Prasad K, Laxdal VA, Yu M, et al. (1996) Evaluation of hydroxyl radical-scavenging property of garlic. *Mol Cell Biochem* 154: 55–63.
40. Lai PK, Roy J (2004) Antimicrobial and chemopreventive properties of herbs and spices. *Curr Med Chem* 11: 1451–1460.
41. Bakri IM, Douglas CWI (2005) Inhibitary effect of garlic extract on oral bacteria. *Arch Oral Biol* 50: 645–650.
42. Ferary S, Auger J (1996) What is the true odour of cut allium? Complementarity of various hyphenated methods: Gas chromatography-mass spectrometry and high-performance liquid chromatography-mass spectrometry with particle beam and atmospheric pressure ionization interfaces in sulphenic acids rearrangement components discrimination. *J Chromatogr* 750: 63–74.
43. Qiutang L, Inder MV (2002) NF-KB regulation in the immune system. *Immunology* 2: 725–734.
44. Yamaoka Y, Kikuchi S, El–Zimaity HMT, et al. (2002) Importance of helicobacter pylori oipA in clinical presentation, gastric inflammation and mucosal interleukin 8 production. *Gastroenterology* 123: 414–424.
45. Crabtree JE (1996) Gastric mucosal inflammatory responses to Helicobacter pylori. *Aliment Pharmacol Ther* 10 Suppl 1: 29–37.
46. Reuter HD, Koch HP, Lawson LD (1996) Therapeutic effects and applications of garlic and its preparations. In: *Garlic: The Science and Therapeutic Application of Allium Sativum and Related Species*. 2 Eds., Baltimore: William & Wilkins,162–172.
47. Rhodes MJC (1996) Physiologically-active compounds in plant foods: An overview. *Proc Nutr Soc* 55: 371–384.
48. Correa P (1992) Human gastric carcinogenesis: A multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 52: 6735–6740.
49. McNulty CAM, Wilson P, Havinga W, et al. (2008) A pilot study to determine the effectiveness of garlic oil capsules in the treatment of dyspeptic patients with helicobacter pylori. *Helicobacter* 6: 249–253.
50. Chowdhury AK, Ahsan M, Islam SN, et al. (1991) Efficacy of aqueous extract of garlic and allicin in experimental shigellosis in rabbits. *J Med Res* 93: 33–36.
51. You WC, Zhang L, Gail MH, et al. (1998) Helicobacter pylori infection, garlic intake and precancerous lesions in a Chinese population at low risk of gastric cancer. *Int J Epidemiol* 27: 941–944.
52. Keiss HP, Dirsch VM, Hartung T (2003) Garlic (Allium sativum L.) modulates cytokine expression in lipopolysaccharide-activated human blood thereby inhibiting NF-kappaB activity. *J Nutr* 133: 2171–2175.
53. Salih BA, Abasiyanik FM (2003) Does regular garlic intake affect the prevalence of Helicobacter pylori in asymptomatic subjects? *Saudi Med J* 10: 1152.
54. Cellini L, Di Campli E, Masulli M, et al. (1996) Inhibition of Helicobacter pylori by garlic extract (Allium sativum). *FEMS Immunol Med Microbiol* 13: 273–277.

55. Bozin B, Mimica-Dukic N, Samojlik I, et al. (2008) Phenolics as antioxidants in garlic (Allium Sativum L. Alliacea). *Food Chem* 111: 925–929.
56. Song K, Milner JA (2001) The influence of heating on the anticancer properties of garlic. *J Nutr* 131: 10545–10575.
57. Santos J, Almajano MP, Carbo R (2010) Antimicrobial and antioxidant activity of crude onion (Alliam cepa L.) extracts. *Int J food Sci Technol*: 403–409.
58. Dmotoso Go, Oyewopo AO, Kadir RE, et al. (2010) Effects of aqueous extracts of Allium Sativum (Garlic) on semen Parameters in Wistar rats. *Int J urology* 7: 35–42.
59. Corzo-Martinez M, Corzo N, Villamiel M. (2007) Biological properties of onions and garlic. *Trends Food Sci Technol* 18: 609–625.
60. Jakubowski H (2003) On the health benefits of Allium sp. *Nutrition* 19: 167–168.
61. Aitken RJ, Clar Kson JS, Fishel S (1989) Generation of reactive oxygen species lipid per oxidation and human sperm function. *Biol Reprod* 41: 183–197.
62. Chen CS, Chao HT, Pan RL, et al. (1997) Hydroxyl radicalinduesed decline in Motility and increase in lipid per oxidation and DNA modification in human sperm. *Biochem Mol Biol Int* 43: 291–303.
63. Kaemmerer H, Mitzkat HJ (1985) Ion-exchange chromatography of amino acids in ejaculates of diabeties. *Andrologia* 17: 485–487.
64. Ali BH (2003) Agents ameliorating or augmenting experimental gentamicin nephrotoxicity: Some recent research. *Food Chem Toxicol* 41: 1447–1452.
65. Agarwal A, Nallella KP, Allamaneni SS, et al. (2004) Role of antioxidants in treatment of male in fertility: An overview of the literature. *Reprod Biomed Online* 8: 616–627.
66. Pal R, Vaiphei K, Arbab S, et al. (2006) The effect of garlic on isoniazid and rifam picin-induced hepatic in Jury in rats. *World J Gastroenterol* 28: 636–639.
67. Pdraza-chaverri J, Maldonado PD, Medine-Campos ON, et al. (2000) Garlic ameliorates gentamicin nephrotoxicity: Relation to antioxidant enzymes. *Free Radic Biol Med* 29: 602–611.
68. SU D, Novoselov SV, Sun QA, et al. (2005) Mammalian selenoprotein thioredoxin-glutathione reductase roles in disulfide bond formation and sperm maturation. *J Biol Chem* 280: 26491–26498.
69. Anwar MM, Meki AR (2003) Oxidative stress in streptozotocin-induced diabetic rats, effects of garlic oil and melatonin comp. *Biochem physiol* 135: 539–547.
70. Chauhan NS, Raoch V, Dixit VK (2008) Effect of curculigo orchioides rhizomes on sexual behavior of made rats. *Int J Appl Res Nat Products* 1: 26–31.
71. Lanzotti V (2006) The analysis of onion and garlic. *J Chramatogr A* 1112: 3–22.
72. Guneli E, Tugyan K, Ozturk H, et al. (2008) Effect of melatonin on testicular damage in streptozotocin-induced diabetes rats. *Eur Surg Res* 40: 354–360.
73. Martiez-Cruz F, Guerrero IM, Osuna C (2002) Melatonin prevents the formation of pyrrolized proteins in human plasma induced by hydrogen peroxide. *Neurosci Lett* 326: 147–150.
74. Mirfard M, Johari H, Mokhtari M, et al. (2011) The effect of Hydro-Alcoholic garlic extract on testis weight and spermatogenesis in mature male rats under chemotherapy with cyclophosphamide. *J Fasa Univ Med Sci* 3: 123–130.
75. Borek C (2006) Garlic reduces dementia and heartdisease risk. *J Nutr* 136: 810–812.
76. Moriguchi T, Saito H, Nishiyama N (1997) Anti-ageing effect of aged garlic extract in the inbred brain atrophy mouse model. *Clin Exp Pharmacol Physiol* 24: 235–342.

77. Ushijima M, Sumioka I, Kakimoto M, et al. (1997) Effect of garlic and garlic preparations on physiological and psychological stress in mice. *Phytother Res* 11: 226–230.
78. Chauhan NB, Sandoval J (2007) Amelioration of early cognitive deficits by aged garlic extract in Alzheimer's transgenic mice. *Phytother Res* 21: 629–640.
79. Chauhan NB (2006) Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576. *J Ethn Opharmacol* 108: 385–394.
80. Yao M, Nguyen TV, Pike CJ (2005) Beta-amyloid-induced neuronal apoptosis involves c-Jun N-terminal kinasedependent downregulation of Bclw. *J Neurosci* 25: 1149–1158.
81. Dhingra D, Kumar V (2008) Evidences for the involvement of monoaminergic and GABAergic systems in antidepressantlike activity of garlic extract in mice. *Indian J Pharmacol* 40: 175–179.
82. Diaz MR, Sembrano JM (1985) A comparative study of the efficacy of garlic and eugenol as palliative agents against dental pain of pulpal origin. *J Philipp Dent Assoc* 35: 3–10.
83. Kumar GR, Reddy KP (1999) Reduced nociceptive responses in mice with alloxan induced hyperglycemia after garlic (Allium sativum Linn.) treatment. *Indian J Exp Biol* 37: 662–666.
84. Nagourney RA (1998) Garlic: Medicinal food or nutritious medicine? *J Med Food* 1: 13–28.
85. Nishiyama N, Moriguchi T, Morihara N, et al. (2001) Ameliorative effect of S-allylcysteine, a major thioallyl constituent in aged garlic extract, on learning deficits in senescenceaccelerated mice. *J Nutr* 131: 1093–1095.
86. Pérez-Severiano F, Salvatierra-Sánchez R, Rodríguez-Pérez M, et al. (2004) SAllylcysteine prevents amyloid-beta peptide-induced oxidative stress in rat hippocampus and ameliorates learning deficits. *Eur J Pharmacol* 489: 197–202.
87. Kalantari H, Salehi M (2001) The protective effect of garlic oil on hepatototoxicity induced by acetaminophen in mice and comparison with N-acetylcysteine. *Saudi Med J* 22: 1080–1084.
88. Tirranem LS, Borodina EV, Ushakova SA, et al. (2001) Effect of volatile metabolites of dill, radish and garlic on growth of bacteria. *Acta Astronaut* 49: 105–108.
89. Senapati SK, Dey S, Dwivedi SK, et al. (2001) Effect of garlic (Allium sativum L.) extract on tissue lead level in rats. *J Ethnopharmacol* 76: 229–332.
90. Kannar D, Wattanapenpaiboon N, Savage GS, et al. (2001) Hypocholestrolemic effect of an enteric-coated garlic supplement. *J Am Coll Nut* 20: 225–231.
91. McNulty CA, Wilson MP, Havinga W, et al. (2001) A Pilot study to determine the effectiveness of garlic oil Capsules in the treatment of dyspeptic patients with Helicobacter Pylori. *Helicobacter* 6: 249–253.
92. Cicero AF, Derosa G, Gaddi A (2004) What do herbalists suggest to diabetic patients in order to improve glycemic control? Evaluation of scientific evidence and potential risks. *Acta Diabetol* 41: 91–98.
93. Josling P (2001) Preventing the common cold with a garlic supplement: Adouble-blind, placebo-comtrolled survey. *Adv Ther* 18: 189–193.
94. Williamson EM (2005) Interactions between herbal and conventional medicines. *Expert Opin Drag Sas* 4: 355–378.
95. Warren Grant Magnuson clinical center, National Institutes of Health Drug-Nutrient interaction Task force (2003) Maryland USA, Important information to know when you are taking: Coumadin and vitamin k. *Acta Diabetol* 41: 91–98.
96. IZZO AA, Di-carlo G, Borrelli F, et al. (2005) Cardiovascular pharmacotherapy and herbal medicines: The risk of drug interaction. *Int J Cardiol* 98: 1–14.

97. Tattelman E (2005) Health effects of Garlic. *Am Fam Physician* 72: 103–106.
98. Jabbari A, Argani H, Ghorbanihaghgo A, et al. (2005) Comparision between swallowing and chewing of garlic on levels of serum lipids, cyclosporine, creatinine and lipid peroxidation in renal tnansplant recipient. *Lipids Health Dis*: 72–77.
99. Hagdon Jane (2005) Garlic and organosulfur compounds. *Plant Bioact Res Institute*, orem, utah, USA, 1–8.
100. Lee Moffitt (2005) Herbal supplements that modulate coagulation in cancer patients. C*ancer Control Res Institute* 12: 149–157.
101. Ramsay NA, Kenny MW, Davies G, et al. (2005) Complimentary and alternative medicine use among patients starting warfarin. *Br J Haematol* 130: 777–780.
102. Blumenthal M, Goldberg A, Brinckman J (2004) Herbal medicine: Expanded commission E Monographs. *American Botanical Council*. Newton: Integrative medicine Communication, 1029 Chestnut street, 139–148.
103. Lawson LD (2004) A review of its medicinal effect and indicated active compounds. In: Lawson, LD., Bauer, R., Eds. *Phytomedicines of Europe*: *Chemistry and Biological Activity*. Washington, Dc: *American Chemical Society Symposium Series* 691, 176–209.
104. Fakhar H, Hashemi Tayer A (2012) Effect of the garlic pill in comparison with Plavix on platelet aggregation and bleeding Time. *Iran J Ped Hematol Oncol* 2: 146–152.
105. Al-Qattan KK, Thomson M, Al-Mutawa'a S, et al. (2006) Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. *J Nutr* 136: 774S–776S.
106. Sharifi AM, Darabi R, Akbarloo N (2003) Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rat. *J Ethnopharmacol* 86: 219–224.
107. Morihara N, Sumioka I, Moriguchi T, et al. (2002) Aged garlic extract enhances production of nitric oxide. *Life Sci* 71: 509–517.
108. Benavides GA, Squadrito GL, Mills RW, et al. (2007) Hydrogen sulfide mediates the vasoactivity of garlic. *Proc Natl Acad Sci USA* 104: 17977–17982.
109. Chuah SC, Moore PK, Zhu YZ (2007) S-allylcysteine mediates cardioprotection in an acute myocardial infarction rat model via a hydrogen sulfide-mediated pathway. *Am J Physiol Heart Circ Physiol* 293: H2693–H2701.
110. Shouk R, Abdou A, Shetty K, et al. (2014) Mechanisms underlying the antihypertensive effects of garlic bioactives. *Nutr Res* 34: 106–115.
111. Karin Rie, Peter Fakler (2014) Potential of garlic (Allium sativum) in lowering high blood pressure: Mechanisms of action and clinical relevance. *Integr Blood Press Control* 7: 71–82.
112. Ried K (2014) Effect of garlic on blood pressure, serum cholesterol and immunity: Updated meta-analyses and review. *J Nutr* 71–82.

AIMS Press