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Research Article

MOLECULAR MECHANISM OF ALLIUM SATIVUM (GARLIC) AND THEIR FUNCTIONAL ACTIVE COMPOUNDS: EMERGING TRENDS AND THEIR STATUS IN HEALTH

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A B S T R A C T

Allium sativum (Garlic) is an extremely versatile and delicious vegetable mostly grouped under spices that possesses high nutritional as well as medicinal value underpinnings of their active constituents such as S‑allylcysteine, diallyl disulfide and diallyl trisulfide etc. Its ancient history of medication is near about 3000 year's old and its cultivation documented in several regions of Asia, North Africa and Southern Europe. Nowadays, garlic is more preferable vegetable or spice over other because of its potential medicinal value and multifaceted pharmacological activities. The pharmacological activities includes anti-microbial (anti-fungal, anti-viral, anti-bacterial) anti-cancer, anti-oxidant, anti-diabetic, anti-inflammatory, anti-hypertensive, cardio-protective, neuroprotective and immunomodulatory etc. Moreover, these pharmacological activities are due to the presence of their active constituents, which are having richest amount of phenolic content. Available published data have unconcealed that healthy garlic diet capable to cut down the metastasis statein subjects and also facilitated the aggregated cell dissolution in tissue having malignancy. In this review, the overall objective is to explain briefly about its dosage, nutritional values, related chemistry profile, bio-availability, available phytoconstituents and more specifically its pharmacological or biological activities and its health benefits. Garlic clasp first rank (super spice) in nutrition and healthy vegetables due to presence of the richest amount of phenolic contents as compared to other vegetables or spices.

INTRODUCTION

Garlic clasp first rank (super spice) in nutrition and vegetables due to presence of richest amount of phenolic contents as compared to other vegetables or spices. Natural products of animals, plants and microbial sources are being used by human from ancient time either in crude extracts or in the pure forms. Garlic (Allium sativum), belongs to family Alliaceae, is one of those plants that is exceedingly explored over last decades. In fact, garlic has been used as a spice and also used as a medicine to avert and treat a wide range of conditions and diseases. Garlic is a predominantly rich source of organosulfur compounds, which are thought to be responsible for its flavor and aroma, as well as its potential health benefits. [1]. An enzyme called alliinase is released from the crushed garlic, which catalyzes the formation of allicin from alliin. Further allicin promptly metabolized into a variety of organ sulfur compounds. In in-vitro, allicin breaks down to form a variety of fat-soluble organosulfur compounds, including diallyl trisulfide (DATS), diallyl disulfide (DADS), and diallyl sulfide (DAS), or in the presence of oil or organic solvents, ajoene and vinyldithiins. In in-vivo, allicin can react with glutathione and L-cysteine to produce S-allylmercaptoglutathione (SAMG) and S-allylmercaptocysteine (SAMC), respectively. Usually, it has been used to treat infections, wounds, diarrhoea, rheumatism, heart disease, diabetes and many other disorders [2]. Various research have demonstrated that garlic displays antimicrobial, antihypertensive, cardioprotective, antilipidaemic, anticarcinogenic, immunostimulant and hypoglycaemic properties [3-5].

Recently, aged garlic extract and its ingredients have been found to demonstrate neuroprotective effects in brain diseases [6, 7]. There is increasing interest in understanding the antioxidant and anti-inflammatory properties and the underlying mechanisms of garlic and its active components for its protective effects in heath and disease [8-10]. There is evidence for aged garlic extract to exert its action on distinct signaling pathways associated with oxidative stress and neuroinflammation [6], although the crucial molecular mechanisms remain unclear. Understanding the vital molecular targets of aged garlic extract, particularly in neurodegenerative and neuroinflammatory diseases will help to explore the potential of these compounds as therapeutic agents.

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Garlic has wide-ranged and interesting applications in medicinal world. Thus, based on the documented constructive preliminary results reviewed herein, further research is vital to develop the full potential of allium sativum and its active ingredients into an effective preventative strategy for the disease. Present critical review has focused on the garlic's chemistry and pharmacological effects of its active component against various health issues.

Chemistry of Allium Sativum

Garlic comprises at least 17 amino acids, 33 sulphur compounds, several enzymes and minerals such as selenium. Among the all Allium species, garlic contains a higher concentration of sulphur compounds [2]. Garlic's pungent odor and many of its medicinal properties are due to its sulphur compounds. The γ-glutamyl-S-alk(en)yl-L-cysteines are the primary sulfur compounds in the intact garlic, which can be hydrolyzed and oxidized to yield S-alkyl(en) yl-L-cysteine sulfoxide (alliin) [11]. Alliin is the primary odorless, sulfur-containing amino acid, a precursor of allicin, methiin, -S-(trans-1-propenyl)-L-cysteine sulfoxide, and cycloalliin [12-14]. These sulfoxides, except cyloalliin, are transformed into thiosulfinates through enzyme reactions when garlic bulb is crushed or cut [15]. In this metabolic reaction the main enzyme, which play the active role, is alliinase. Among the thiosulfinates allicin is the most biologically active compound in garlic. A study shows that allicin content ranged from 0.16-13.0 mg/g, these finding extracted from the analysis of more than twenty botanical traits of Iranian garlic ecotype [13]. As mention above the thiosulfinates released from crushed garlic are reactive molecules and sustain a number of conversions, depending on the temperature, pH and solvent conditions [16, 17]. Allicin are the least stable among the thiosulfinates. The half-life of allicin (concentration of 0.1-0.4mg/ml) at room temperature is 10 days in 1mM citric acid (pH 3), 4 days in water, 48 h in methanol or chloroform, 24 h in ethanol, 24 h in hexane and 3 h in ether [18].

After a short time of period, allicin is break down to form various volatiles oil-soluble compounds such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), vinyl dithiin and ajoene if conditions are appropriate [19, 20]. Vinyldithiins were first demonstrated to be thermal-degradation products derived from allicin during gas chromatographic analysis of allicin [21]. At the room temperature, Allicin is metabolised into the vinyldithiin within few hours, while during cooking this process happened within minutes. Apitz-Castro *et al*. [22] first isolated ajoene from the ether fraction of garlic extract as a potent antithrombotic agent.

γ-glutamyl -S-alk(en)yl-L-cysteines are also converted to water-soluble organosulfur compounds including S-allyl cysteine (SAC) and S-allyl mercaptocysteine (SAMC) through an enzymatic transformation with g-glutamyltranspeptidase when garlic is extracted with an aqueous solution [23]. SAC, a major transformed product from g-glutamyl-S-allyl-L-cysteine, is a sulfur amino acid detected in the blood, by which the finding shows that SAC is highly biologically active as well as bioavailable [24]. In contrast to the oil-soluble organosulfur compounds, the water-soluble organosulfur compounds are odorless and possess more delicate and less characteristic flavor [23].

Bioavailability of Organosulfur Compounds from Allium Sativum

Specific and inclusive understanding of pharmacokinetic of new chemical components as dynamic ingredients should always be provided to support drug discovery and development. Novel drug delivery systems such as nanoparticles, liposomes and microemulsion have also developed to enhance the constancy, bioavailability and systemic circulation time of relatively stable organosulfur compounds [25]. A study of liver perfusion in rat has been shown that 90% of allicin was decreased just after incubation for 3 minutes while 99% disappeared after 6 minutes [26, 27]. Moreover, study shows pharmacokinetics of vinyldithiins after oral administration of 27 mg 1,3-vinyldithiin and 9 mg of 1,2-vinyldithiin to rats [26]. In serum, kidney, and adipose tissue, both vinyldithiins were detected over a period of 24 hours, whereas in liver only 1,3-vinyldithiin was found. 1,3-vinyldithiin seems to be less lipophilic and was rapidly eliminated from serum, kidney, and adipose tissue, whereas 1,2-vinyldithiin is more lipophilic and showed a tendency to accumulate in fat tissue [28].

The water-soluble organosulfur compounds from garlic comprise of S-allyl cysteine (SAC) and S-allyl mercaptocysteine (SAMC) and it has been reported that their pharmacokinetic properties were quite different from oil-soluble garlic organosulfur compounds [29]. Metabolites of allicin, rather than the agent itself, are responsible for this wide range of beneficial health effects [30, 31]. Several such metabolites are S-allylmercaptocysteine, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allylcysteine [32].

The bioavailability of SAC was studied after oral administration to rats, mice and dogs, it was rapidly and easily captivated in the gastrointestinal tract and distributed mainly in the plasma, liver, and kidney [33]. The bioavailability was 98.2, 103.0, and 87.2% in rats, mice, and dogs, respectively [31]. SAC was mainly excreted into urine in the N-acetyl form in rats; however, mice excreted both SAC and the N-acetyl form. The pharmacokinetic observation of SAC in humans was done by oral administration of garlic extract. SAC from garlic consumption was hastily absorbed from the gastrointestinal tract [31]. The half-life of SAC in humans after oral administration was more than 10 h and clearance time was estimated to be more than 30 h [34]. These study results from the evaluation of the safety and efficacy of SAC indicate that SAC seemed to play an important role in the biological effects of garlic [34, 35].

Aged garlic extract is aged for up to 20 months. During the aging process, the odorous, harsh, and irritating compounds of garlic are converted naturally into stable and safe sulfur compounds. Further the safety of aged garlic has been confirmed by various toxicological studies [36].

Pharmacological Activities

Antioxidant Activity

Antioxidantsrichfoods are good for your health and may also assist to lower your infectionsprobability. As multiple studies have been shown that age related disease viz. neurodegenerative, inflammatory, cardiovascular, andcancer are possible because of DNA modification by simple oxidation reaction, proteins and lipids modifications by reactive oxygen species (ROS) generation[37]. Numerous studies revealing garlic extract's anti-oxidative role by showing the presence of

so many phytochemicals, which are water‑soluble and lipid soluble in nature like organosulphur compoundsand flavonoids [15, 36]. Actually, by activating the Nrf2/Keap1 system, garlic derived constituents boost up or regulates the expression of the antioxidant enzymes [38, 39]. Additionally, it has been also found that modulation of nuclear factor ‑kappa B (oxidant‑induced transcription factor) facilitated by garlic extract, which has clinical value in human age related disorders [35, 40].

Antimicrobial Activity

Numerous of studies have suggested that garlic possesses antimicrobial activity. The two great scientists, L. Pasteur and Lehmann devised a protocol and gave a first scientific clue about potential antibacterialand medicinal value of garlic extract [41]. Furthermore various studies have illuminated that garlic extract has antiviral, antibacterial and antifungal activities [42, 43]. Even though, more diluted garlic juice can inhibits the bacterial growth of several types such as cocci (*Streptococcus*,*Staphylococcus*), bacilli (*B. enteritidis, B. typhosus*and*B. dysenteriae*)and Vibrio[44, 45].

Both gram negative and gram positive bacteria shows sensitivity towards the crude extract of garlic [46]. A research paper results expressed that the resistance noted in bacterial cultures against chloramphenicol- a common antibiotic,however, the same bacterial culture shown the sensitivity against garlic [47]. Moreover, garlic extract exerts a static effect on definite proteases and some buccal cavity pathogens, so it may have promising therapeutic potential, especially for periodontitis [48].

Related to anti-fungal activity- extract of garlic showing its activity in more than 40 species of fungi, it delay the proliferation of fungus genera in 8 sample speciesout of 15 tested [49, 50]. A reported activity suggested that the garlic extract possesses the enhanced fungistatic activity when compared to nystatin, amphotericin B and griseofulvin [51, 52, 53]. According to Lemar *et al*., aqueous garlic extract exhibits the inhibition of protein, nucleic acid and lipid syntheses resulted in the diminution in growth of Candida albicans [54,55]. Moreover a study has been reported that the breakdown products of allicin, the main parent antifungal compound in garlic, have a common mode of action against antimicrobial, anticancer and anticholesterol properties [56].

Related to anti-viral activity- garlic extract treated rodents exhibits enhancement in the creation of neutralizing antibody, when inoculated with the influenza vaccine against intranasally-inoculated influenza virus in that rodents [57]. Moreover an in-vitro research study claim a potential activityof garlic extract against elite species of viruses (such as parainfluenza virus type-3, herpes simplex virus(HSV)type-1 and type-2, vesicular stomatitis, Vaccinia, and human rhinovirus (HRV) type-2),revealed that definite constituents of garlic (ajoene,allyl methyl thiosulfinate,allicin and methyl allyl thiosulfinate) are influential virucides[58, 59]. However, a constituent of garlic (diallyl trisulfide)showing antihuman cytomegalovirus (anti-HCMV) activity by suppressing gene transcription within genome of the virus[60].

Insecticidal Activity

Garlic extracts gave so many hard-hitting pesticides to the market and there are so many field trails projects, which are based on breeding of mosquitoes, depicted that garlic oil is very efficacious and potential eradication method against several species of mosquitoes [61]. Furthermore, researchers also figure out the toxic visual aspect of garlic oil and unprocessed methanolic extract against larvae (especially 3rd stage) of *Culex tarsalis*, *C.peus*, *Aedessirensis*,*A. aegypti*, *A. trisoriatus*, and also larvae (especially 3rdand 4thstage) of extremely insecticide resistant variety of *A. nigromaculis*[62] and than they have to comes on a conclusion that partly refined oil fraction was shown better toxicity than the unrefined extract. However, later on the larvicidal value of garlic oil was found to be due topresence of some important constituents such as diallyl disulfide and diallyl trisulfide [63]. Also, an another active constituent of garlic allicin carry a potential to stamp down infections caused by mosquitoes strains (especially malaria)via a mechanism in which garlic active constituent allicin inhibit cysteine proteases of that particular parasite[64].

Leishmanicidal Activity

Potent leishmanicidal activity also delineated by another bioactive compound of garlic named ajoene in *in-vitro*studies against *Leishmaniadonovani*and *L. mexicana* and this activity of ajoene is due to the alteration in morphology of biomembrane of mitochondria and neuclear membrane and also due to some large autophagic vacuoles formation[65]. A scientist, Leon *et al.*reported about mild protective effect of garlic extract against *L. donovani* that might be exerted by enhanced secretion of interferon-gamma[66].

The cidal activity of allicin againstmolluscs (especially snail) exhibited due to pronounced declination of enzymes such as alkaline phosphatase, lactic dehydrogenase and acetylcholinesterase within the neural structure tissue of aquatic snail (freshwater snail- Lymnaea acuminate) [67, 68,69].

Antidiabetic Activity

A common endocrine disorder which we called diabetes mellitus defined by high blood sugar level or hyperglycemia, which leads to chronic complications mainly affects the eyes, blood vessels, renal, neurons and skin. Moreover, the pathogenesis Increased glycation of proteins and accumulation of advanced glycation end‑products have been associated with the pathogenesis of diabetic complications leading to formation of free radicals via autoxidation of glucose and glycated proteins [70]. Recent studies suggest that aged garlic extract suppresses the production of advanced glycation end‑products in vitro and formation of glycation‑derived free radicals [71]. S‑Allylcysteine, a key component of aged garlic, is a potent antioxidant and can inhibit advanced glycation end‑products formation [72, 73]. Compounds with combination of antiglycation and antioxidant properties may offer therapeutic potential against hyperglycemia [74].

Cardioprotective Effect

Cardiovascular disease is associated with multiple elevated factors including serum total cholesterol, low density lipoprotein (LDL), LDL oxidation, platelet aggregation,

hypertension, diabetes [75]. There are a lot of studies that have confirmed the ability of garlic to reduce these parameters [76, 77]. Thus, garlic has been shown to inhibit enzymes involved in lipid synthesis, decrease platelet aggregation, prevent lipid peroxidation of oxidized erythrocytes and LDL, increase antioxidant status, control diabetes, besides inhibiting ACE [78, 79]. Many of these findings have also been evaluated in clinical trials. These studies point to the fact that garlic reduces cholesterol, inhibits platelet aggregation, reduces blood pressure and increases antioxidant status [4]. Since 1993, 44% of clinical trials have indicated a reduction in total cholesterol, and the most profound effect has been observed in garlic's ability to reduce the ability of platelets to aggregate [80].

Diverse finding have been obtained in the area of blood pressure and oxidative stress reduction. The adverse results obtained in some clinical trials may also have resulted from usage of different garlic preparations, unknown active constituents and their bioavailability [81, 82]. Additional reasons could include inadequate randomization, selection of inappropriate subjects and short duration of trials. Moreover, garlic consumption and progression of cardiovascular disease is inversely correlated as per epidemiologic studies. Thus, analyses of these in vitro and in vivo studies published since 1993 suggests that although garlic appears to hold promise in reducing parameters associated with cardiovascular disease, more in-depth appropriate studies are required [33].

Cancer Chemopreventive

To explore the use of phytochemical supplements as chemoprevention or adjuvant drugs in cancer treatment, it is necessary to validate their biological effects and correlative mechanisms. Considerable evidences demonstrated the anticarcinogenic potential of garlic with their constituents, viz., allylsulfides and flavonoids [83]. Epidemiological studies are well correlated with research findings depict that high dose of allium satium is able to reduce risk of several type of cancer [34]. Its active constituents can alter several enzymes activity which is involved in the development of cancer. Their ability to suppress experimentally-induced tumors in a various sites including skin, mammary and colon, suggests a general mechanism of action [84]. Certain allyl Sulphur compounds can effectively slow tumor proliferation and induce apoptosis [85]. Anti-tumorigenic properties of garlic may also be attributed to changes in cellular thiol and phosphorylation stains [86].

A study was performed to evaluate the dose-dependent effect of diallyl disulfide (DADS) on an androgen-dependent prostate cancer cell line [87]. DADS acts as a good antiproliferative agent, also induced apoptosis and nuclear segmentation in the higher doses [87]. Another study shows that SAC, S-allylcysteine, a potent compound present in garlic, suppressed the proliferation of PC-3 cells and led to cell cycle arrest at the G0/G1 phases, resulting cell undergoes to apoptosis [88]. This was accompanied by the decreased expression of Bcl-2 and increased expression of Bax and caspase-8 [88, 89]. Garlic extract also helpful to reduce oral cancer via downregulate the osteopontin plasma level, which is play a critical role in progression of oral cancer [90].

Diallyl trisulfide (DATS), a sulfane sulphur-containing compound of garlic has the potential to suppress the development of cancer in HepG2 cells [91]. This compound increased the H2O2 formation, lowered the thiol level, and shows the strongest inhibition of cell proliferation [91]. Moreover, DATS plays a role as like protagonist in the induction of caspase 3 activity in HepG2 cells [92]. DATS did not alter the activity of sulphur transferases and reduced sulfane sulphur level in HepG2 cells. It appears that sulfane sulphur containing DATS can be bioreduced in cancer cells to hydroperthiol that leads to H2O2 generation, thereby influencing transmission of signals regulating cell proliferation and apoptosis [92, 93].

Ajoene, another chemical constituent of garlic, was given the inhibiting results against proliferation and encourage the apoptosis in several human leukaemia CD34-negative cells [94]. The anti-proliferation activity of ajoene is associated with a block in the G2/M phase of cell cycle in human myeloid leukaemia cells [95]. Additionally, ajoene with the combination of two chemotherapeutic drugs viz. cytarabine and fludarabine has shown the more effective anti-apoptotic properties in human CD34-positive resistant myeloid leukaemia cells through enhancing their bcl-2 inhibitory and caspase-3 activation activities [94].

Neuroprotective

Elevated levels of cholesterol, inflammation and hypertension are the crucial factor behind the cardiovascular disease, besides also play a decisive role to enhance probability of dementia, mainly in Alzheimer's disease (AD) [96, 97]. A number of studies have explained that high cholesterol is increase the formation beta-amyloid (Abeta) plaque, the hallmark of AD [97]. Aging along with oxidative damage is a major aspect in both cardiovascular disease and dementia [98, 99].

The antioxidant property of garlic extract scavenges oxidants, increases anti-oxidant levels, besides suppressing lipid peroxidation and inflammatory prostaglandins [100]. Inhibition of HMG-CoA reductase by garlic extract reduces cholesterol synthesis. These effects retard arterial plaque formation [101, 102]. Aged garlic extract decreases blood pressure and increases microcirculation, which is important not only in diabetes management but also reduces dementia risks [103, 104]. AGE also may help prevent cognitive decline by protecting neurons from Abeta neurotoxicity and apoptosis [104]. This prevents ischemia or reperfusion-related neuronal death, thus improves learning and memory retention. Evidence supports the beneficial health effects attributed to aged garlic extract add to prevent cardiovascular, cerebrovascular diseases, lowering the risk of dementia and AD [105, 106].

Immunomodulatory

Numbers of studies were performed to investigate the effects of garlic extract on immune functions. Specifically aged garlic extract markedly decreased the antigen-specific ear swelling [107, 108]. Additionally, it also down regulated the growth of allogenic (Sarcoma-180) and LL/2 lung carcinoma cells transplanted into the mice. Simultaneously, there was an increase in natural killer cells activities of spleen cells in Sarcoma-180-bearing mice [109, 110]. These studies strongly advocate that aged garlic extract could be a promising approach as an immune modulator, which maintains the homeostasis of immune functions [50]. As compared with

Bacillus Calmette‐Guerin (BCG), the approved immunotherapy for human bladder cancer, garlic is effective when added to the diet [111]. On revealing the mechanism of this anti-tumor effect, it was found that garlic detoxifies carcinogens by stimulation of cytochrome P (450) enzymes, antioxidant activity or sulphur compound binding [112]. Evidence suggests a direct toxic effect of garlic to sarcoma, gastric, colon, bladder and prostate cancer cells in tissue culture. However, in in-vivo studies, it cannot give the satisfactory results against the inhibition of growth of tumors [113]. The most likely explanation of this effect is immune stimulation. Garlic and BCG, both stimulate proliferation of lymphocytes and macrophage phagocytosis [111]. They stimulate the infiltration of macrophages and lymphocytes in transplanted tumors. Both produce splenic hypertrophy; induce release of interleukin‐2, tumor necrosis factor‐alpha and interferon‐gamma [114]. These findings represent effective stimulation of the immune response. Studies advocate that garlic may be useful in preventing the suppression of immune response that is associated with increased risk of malignancy [107].

Dosage

Although various studies have been carried out on garlic's efficacy against various disease in-vitro as well as in in-vivo, still the effective dose of garlic has not been resolute. Usually dosage recommended in the literature for adults are 4 g of raw garlic per day [115], one 300‐mg dried garlic powder tablet (including approximately 1.3% alliin or 0.6% allicin yield) thrice in a day, or 7.2 g of AGE once in a day [116].

Safety and toxicity

The effectiveness of garlic may be prevention rather than therapy, thus it may need long-term supplementation. Although garlic has been used safely in cooking as a popular condiment or flavoring and used traditionally for medicinal purposes [117]. Apart from the valuable medicinal properties garlic may also act toxically when overdosed. Long term uses of garlic ingestion produces toxic effects [118]. The most apparent problem with using garlic in human medicine is its strong odor. A problem of clinical importance is that some people are allergic to sulfur based compounds [119]. Other adverse effects associated with garlic are: stomach disorders and diarrhea decrease of serum protein and calcium, anemia, bronchial asthma contact dermatitis, inhibition of supermatogenesis and damage of intestinal lining and the stomach [120, 121]. Nakagawa *et al*. [122] reported that raw garlic juice at a dose 5 ml/kg body weight caused death of rats due to stomach injury. Consumption of garlic enhances the pharmacological effects of anticoagulants (Warfarin, fluindione) and reduces the efficacy of antiAIDS drug Saquinavir [121]. Moreover, it has already documented that allicin is one of the major irritants in raw garlic, oil soluble sulfur compounds are more toxic than water soluble compounds; and when garlic is extracted in water for a certain period, its toxicity is greatly reduced [123]. Toxicological and clinical studies of aged garlic have been showed no adverse effects. The safety of aged garlic has been across the following parameters: acute and substance toxicity tests, chronic toxicity test, mutagenicity tests, general toxicity tests, teratogenicity tests, conducted by the FDA, and clinical studies conducted on more than 1000 volunteers [124].

CONCLUSION

Multifaceted garlic is considered as a super natural remedies for most of ailments because of remarkable nutritional as well as medicinal potential. Nowadays, garlic is more preferred vegetable or spice over other because of its pronounced mitigating effects against several disease or disorders and having so many reported pharmacological activities. The present review emphasizes the realism that the garlic's originated constituents available in market have astonishing effects. Moreover so many scientific reports orliterature's studies from all over world disclosed their credence for the potential of garlic against microbial (fungal, viral, bacterial) cancer, oxidation, diabetes, inflammatory, hypertension, and cardio-vascular diseases.However, some researchers claims thatthe garlic shows an efficacy toward neuroprotection but still there is some constraint for which we requires more investigation or to gather more information to know exact molecular mechanism of actions of its components, to improve its bioavailability and to make possible active biochemical combinations with other drugs towards high effectiveness.

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