Phytochemical compounds and Pharmacological Activities of Garlic (Allium sativum L.): A Review

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SUMMARY

Garlic (Allium sativum L.) is a species of monocotyledonous perennial vegetable plant whose bulbs, with a strong odor and taste, are often used as a condiment in cooking and a traditional remedy for various diseases. Garlic possesses more than 100 biologically useful secondary metabolites, including alliin, alliinase, allicin, S-allyl cysteine (SAC), diallyldisulfide (DADS), diallyltrisulfide (DATS) and methyl allyl trisulfide. The γ-glutamyl-S-alk(en)yl-L-cysteines are the major sulfur compounds present in garlic. Fundamental studies have shown that garlic and its bioactive constituents have antioxidant, anti-diabetic, anti-obesity, neuroprotective, anti-inflammatory, antibacterial, antifungal, immunomodulatory, cardiovascular protective, anticancer, renal protective, digestive system protective, hepatoprotective and wound healing properties.

This review examines the phytochemical composition, and pharmacological activities of A. sativum extracts as well as its main active constituent, allicin to cure many diseases, highlighting and discussing the relevant mechanisms of actions for many of their therapeutic effects.
Introduction

Garlic (*Allium sativum* L.; family: Amaryllidaceae) is a bulbous plant that can grow up to 1.2 m tall. Garlic is easy to grow and can be grown in mild climates. Hardneck garlic and softneck garlic are among the subspecies of garlic. It has long been used as a spice, food and folk medicine and has been extensively researched as a medicinal plant (Ayaz and al., 2007).

Native to Central Asia and northeastern Iran, garlic is one of the oldest and most important herbs in the world, and its consumption and use by humans dates back many years (Newall and al., 1996). The early Egyptians are said to have used garlic to treat diarrhea, and its medicinal power was described on the walls of ancient temples (Block, 2010). Garlic has many health benefits due to its various phytochemicals, such as organic sulfides, phenolic compounds, saponins and polysaccharides (Szychowski and al., 2018). It is known as the second most used *Allium* species along with onion (*Allium cepa* L.), which is used as a remedy to treat several common diseases such as cold, flu, snakebite and hypertension (Barnes and al., 2002).

In recent decades, numerous studies have demonstrated the remarkable biological functions of garlic, including antioxidant, cardiovascular protective, anticancer, anti-inflammatory, immunomodulatory, anti-diabetic, anti-obesity, and antibacterial properties (Yun and al., 2014).

The main constituents responsible for the characteristic odor of garlic are allicin, diallyl disulfide and diallyl trisulfide. It is known that cooking garlic eliminates allicin, which reduces its pungency (Jabar and al., 2007). There are other compounds derived from allicin, such as vinylthiins and ajoene (Newall and al., 1996).

Allicin [S-(2-propenyl)-2-propene-1-sulfinothioate], the most biologically active sulfur-containing compound of garlic, is responsible for its smell and taste (Slusarenko and al., 2008). Alliin (S-allyl-L-cysteine sulfoxide) is the main precursor of allicin, which represents about 70% of total thiosulfinates existing in the crushed cloves (Kaye and al., 2000). Allyl mercaptan is the odorant molecule responsible for the garlic breath and results from the interaction of allicin or diallyl disulfide with cysteine in the presence of S-allyl-mercapto cysteine (Lawson and al., 2005). Allicin is a lipid-soluble sulfur compound, which can be easily damaged by cooking and has the ability to provoke intolerance, allergic reactions, and gastrointestinal disorders (Sobolewska and al., 2015).

Various pharmacological activities have also been reported for the extracts and isolated compounds from garlic. The main aim of this article is to critically review the available scientific information about the, chemical constituents, and pharmacological activities of garlic.

Quercetin, the major flavonoid isolated from garlic, was found to interact with some medications such as vitamin E and C (Al-Jaber and al., 2011), and modify the *in vitro* as well as the *in vivo* transferases and cytochrome P450 isozymes activity, however, the *in vivo* studies revealed that garlic oil and its three allyl sulfide components increase the CYP3A1, 2B1, and 1A1 expression in the hepatic detoxification system (Wanwimolruk and al., 2014).

1.Chemical Compounds:

Garlic contains at least 33 sulfur compounds and minerals like germanium, calcium, copper, iron, potassium, magnesium, selenium and zinc; vitamins A, B1 and C, fibre and water (Sule and al., 2018). (Figure 1)

The volatile oil of *A. sativum* bulbs containing sulfur
compounds (Table 1) such as thiosulfimates (allicin), Ajoene (4,5,9-trithiadodeca-1, 6,11-triene-9-oxide), vinylthiines (2-vinyl-(4H)-1,3-dithiine, 3-vinyl-(4H)-1,2-dithiene), sulfides (diallyl disulfide (DADS), diallyl trisulfide (DATS)) (Al-Snafi and al., 2013).

Figure 1. Chemical compounds of garlic.

Alliin, the main cysteine sulfoxide is transformed to allicin by allinase enzyme after cutting off the garlic and breaking down the parenchyma (Zeng and al., 2017). S-propylcysteine-sulfoxide (PCSO), allicin and S-methyl cysteine-sulfoxide (MCSO) are the main odoriferous molecules of freshly milled garlic homogenates (Zeng and al., 2017). These active compounds are mainly responsible for protecting the tissue from damage and various disorders (Augusti and al., 1996). Traditionally, garlic and its related compounds have been stated to have several biological activities including anticarcinogenic, antioxidant (Rahman and al., 2006), antidiabetic, renoprotective, antiatherosclerotic, antibacterial, antifungal (Davis and al., 2005), and antihypertensive activities (Badal and al., 2019). Moreover, garlic has been used in traditional medicine to treat indigestion, respiratory and urinary tract infections and cardiac disorders and it showed carminative, antipyretic, sedative, aphrodisiac, and diuretic effects (Souza and al., 2011).

Table 1: Phytochemical Compounds (TesaWye and al., 2015).

<table>
<thead>
<tr>
<th>Plant part</th>
<th>Compounds</th>
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<tbody>
<tr>
<td>Garlic bulb</td>
<td>33 sulfur compounds (alliin, allicin, ajoene, allylprop, diallyl, trisulfide, sallylcysteine, vinylthiines, Sallylmercaptopcystein and others), several enzymes (allinase, peroxidases, myrosinase), minerals (germanium, calcium, copper, iron, phosphorus, potassium, magnesium, selenium and zinc), vitamins A, B1 and C, fiber and water. It also contains 17 amino acids: lysine, histidine, arginine, aspartic acid, threonine, swine, glutamine, proline, glycine, alanine, cysteine, valine, methionine, isoleucine, leucine, tryptophan and phenylalanine. Oligosaccharides, peptides, steroids, terpenoids, flavonoids, and phenols carbohydrates (sucrose and glucose).</td>
</tr>
<tr>
<td>Essential oil</td>
<td>DAS, DADS, diallyl trisulfide, methylallyl disulfide, methylallyl trisulfide, 2-vinyl-4H-1, 3-dithiin, 3- vinyl-4H-1, 2-dithiin, and ajoenes</td>
</tr>
</tbody>
</table>
2. Medicinal and Therapeutic Uses:
Garlic (*Allium sativum*) belongs to the Liliaceae family and is also called "poor man's molasses". Garlic is an Ayurvedic plant that has been widely used as a medicine and flavor enhancer in foods that has therapeutic properties and is probably the most widely used medicinal plant in the traditional system (Butt and al., 2009).

*Allium sativum* is a traditionally cultivated plant that is widely used in culinary foods and used as folk medicine throughout human history (Hunter and al., 2005). Garlic has been used in medicines and foods for nearly three thousand years, as documented in ancient writings from China, Egypt, Greece, and India (Cardelle-Cobas and al., 2009).

3. Pharmacological Activities of Garlic:

3.1. Antidiabetic activity

Diabetes is a metabolic disorder that progressively affects the function of various systems in the body. Unwell controlled blood glucose is believed to be the most important factor in the development of diabetic complications in both type 1 and type 2 diabetes. According to a report by WHO, garlic can be used for helping treatment of hyperglycemia (Ryan and al., 2001). One third of diabetic patients use garlic as an alternative medicine they consider them effective. Garlic and its constituents have been prepared by various means have an antidiabetic action (Ryan and al., 2001)

Oral administration of garlic extract revealed significant decrease in serum glucose, total cholesterol, triglycerides, urea, uric acid, aspartate amino transferase and alanine amino transferase levels, while increased serum insulin in diabetic mice, but not in normal mice (Liu and al., 2006). From a comparison study made between the action of garlic extract and glibenclamide, it was shown that the antidiabetic effect of the garlic was more effective than the glibenclamide (Eidi and al., 2006). It is reported that garlic oil can correct hyperglycemia in diabetic patients. Garlic has been found to be effective in lowering serum glucose levels in STZ-induced as well as alloxan-induced diabetic rabbits, rats and mice. Most of the studies showed that garlic can reduce blood glucose levels in diabetic mice, rats and rabbits. In alloxan-induced diabetic male rabbits, dose of aqueous garlic extract resulted in better utilization of glucose during glucose tolerance tests performed, the hypoglycemic action of garlic could possibly be due to an increase in pancreatic secretion of insulin from β-cells, release of bound insulin or enhancement of insulin sensitivity (Mahesar and al., 2010).

**Figure 2.** The chemical structures of the main organosulfur compounds in garlic.
The beneficial effect of garlic on diabetes mellitus is mainly due to the presence of volatile sulfur compounds, such as alliin, allicin, diallyl disulfide, diallyl trisulfide, diallyl sulfide, S-allyl cysteine, ajoene and allyl mercaptan. Several studies like Padiya and Banerjee, 2013 showed that garlic extracts were effective in reducing insulin resistance. In addition, allyl propyl disulfide, allicin, cysteine sulfoxide and S-allyl cysteine sulfoxide decreased blood glucose levels by preventing liver-induced insulin activation, enhancing insulin secretion by pancreatic beta cells, isolating insulin from bound forms and increasing cell sensitivity to insulin (Faroughi and al., 2018).

In the same context Zhai (2018) reported that the activity of alliin in reducing diabetes mellitus in rats was similar to that demonstrated by glibenclamide and insulin. Indeed, alliin cysteine a bioactive component derived from garlic, restored erectile function in diabetic rats by preventing the formation of reactive oxygen species through modulation of NADPH oxidase subunit expression (Goncharov and al., 2021). Another mechanism proposed by researchers indicates that the antioxidant effect of S-allyl cysteine sulfoxide, a product isolated from garlic, may support its beneficial effect on diabetes. Another study shows that treatment with metformin and garlic in diabetic patients for 12 weeks reduced fasting blood glucose (FBG), but the percentage change in FBG was greater with metformin supplemented with garlic than with metformin alone (Kumar and al., 2013).

In brief, research claims that garlic can act as an antidiabetic agent by either increasing pancreatic insulin secretion from β-cells or bound insulin release (Adinortey and al., 2019).

3.2. Antioxidant activity

Collecting studies have found that garlic has strong antioxidant properties. A study evaluated the antioxidant capacities of both raw and cooked garlic and found that the raw garlic exhibited stronger antioxidant activity (by 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay, 2,2’-Azino-bis (3-ethyl benzothiazoline-6-sulfonic acid) (ABTS) radical scavenging assay, and ferric ion reducing antioxidant power (FRAP) assay). Stir-fried garlic was also shown to have stronger antioxidant capacities (by -carotene bleaching), indicating that the processing can affect the antioxidant property of garlic (Locatelli and al., 2017).

In addition, it was detected that two lipophilic organosulfur compounds, (DAS) and (DADS) and two hydrophilic organosulfur compounds, s-ethyl cysteine (SEC) and n-acetyl cysteine (NAC), nearing extinction against lipid-related oxidations by activating associated antioxidant enzymes. In vivo the antioxidant properties of these four organosulfur compounds against lipid-associated oxidations were due to the activation and modification of some enzymes such as 3-hydroxy-3-methylglutaryl-CoA reductase, glutathione-transferase and catalase (Miri and al., 2018). In the fructose-induced metabolic syndrome, aqueous garlic extract reduces oxidative stress and prevents vascular remodelling by suppressing NAD (P) Hoxidase (Pérez-Torres and al., 2016). The aged extracts gotten from the leaves showed the best antioxidant activity as comparison to flowers and bulbs. Garlic is rich in antioxidants which help abolish free radical particles that can damage cell membranes and DNA and may back to the aging process (Singh and al., 2019).
3.3. Antihypertensive Potential

Hypertension (systolic blood pressure (SBP) ≥ 140 mm Hg; diastolic blood pressure (DBP) ≥ 90 mm Hg) is a known risk factor for cardiovascular morbidity and mortality, which is of concern to approximately 1 billion individuals worldwide. Garlic preparations have been generally used to inhibit and alleviate cardiovascular disorders such as hypertension, arrhythmia, thrombosis, hyperlipidemia and atherosclerosis (Varshney and al., 2016). Several experimental and human studies have rendered the antihypertensive effect of garlic extracts to its derived bioactive compounds (Drobiova and al., 2011). For example, Sobenin et al, showed the plasma fibrinolytic activity of garlic extracts and found that it increased fibrinolytic activity in healthy participants and those with acute myocardial infarction. The blood pressure lowering properties of garlic have been linked to its production of hydrogen sulfide and its content of allicin - released from alliin and the enzyme allinase which has angiotensin II inhibitory and vasodilatory effects, as shown in animal and human cell studies. For example, consumption of 2% wild garlic leaf powder for 8 weeks decreased blood pressure in normotensive rats (Sobenin and al., 2012).

Garlic is used as a medicinal herb to control blood pressure worldwide via the following mechanism: garlic contains many active sulfur-containing molecules, which have been shown to stimulate endothelial contraction and relaxation factors, resulting in a decrease in blood pressure. Garlic has also been shown to stimulate the production of nitric oxide (NO) and hydrogen sulfide (H2S), ultimately leading to vasodilation (Ried and al., 2014).

Administration of garlic at a dose of 100 mg/kg for 5 days resulted in complete prevention of acute hypoxic pulmonary vasoconstriction caused by endothelin-1 in isolated rat pulmonary arteries, and they demonstrated that garlic acts by reducing the production of endothelin-1 and angiotensin II (Varshney and al., 2016). Garlic has played an important role in inhibiting thrombosis as well as platelet adhesion or aggregation in humans. Aged garlic extract (AGE) has been reported to suppress both binding of ADP-activated platelets to immobilized fibrinogen and platelet aggregation by inhibiting the GPIIb/IIIa receptor and increasing cAMP (Rahman and al., 2016). In addition, garlic has been reported to reduce the risk of plasma viscosity, unstable angina, and peripheral arterial occlusive disorders and to increase blood vessel elasticity and capillary perfusion (Bayan and al., 2014). Gamma-glutamylcysteine isolated from garlic is thought to decrease blood pressure by inhibiting angiotensin converting enzyme (ACE). Dubey et al, revealed that allicin shows remarkable activity in reversing dexamethasone-induced systolic blood pressure and improves body weight and food intake in dexamethasone-induced hypertension in rats (Sobenin and al., 2012).

3.4. Anticancer Activity

Recent studies have also shown that garlic and its active constituents can protect against diverse cancers, such as colorectal, lung, gastric, and bladder cancers (Shang and al., 2019).

This study revealed that garlic and its sulfur compounds can decrease the activation of carcinogens thus reducing the risk of cancer (Shang and al., 2019). In addition, garlic and its organic allyl sulfides can inhibit the generation of nitrosamines, a kind of carcinogen produced during cooking and storage (Singh and al., 2008). Moreover, garlic allyl sulfides can block DNA alkylation, which is an early step in nitrosamine carcinogenesis (Nicastro and al.,
This study revealed that garlic and its sulfur compounds can decrease the activation of carcinogens thus reducing the risk of cancer (Shang and al., 2019). In addition, garlic and its organic allyl sulfides can inhibit the generation of nitrosamines, a kind of carcinogen produced during cooking and storage (Singh and al., 2008). Moreover, garlic allyl sulfides can block DNA alkylation, which is an early step in nitrosamine carcinogenesis (Nicastro and al., 2015).

In addition, crude garlic extract has been reported to exhibit an anti-proliferative effect on human cancer cell lines, including liver (HepG2), colon (Caco2), prostate (PC-3) and breast (MCF-7) cancer cells (Yi and al., 2019).

Another study showed that S-allylmercaptocysteine (SAMC) could inhibit the proliferation of SW620 human colorectal carcinoma cells (Zhang and al., 2014). In addition, allicin inhibited the proliferation of gastric adenocarcinoma cells. It induced cell cycle arrest in S-phase, without affecting normal cells.

The bioactive compounds of garlic, DATS, can inhibit the proliferation of SGC-7901 gastric cancer cells and block the cell cycle in the G2/M phase (Luo and al., 2016). In addition, DATS can induce cell cycle arrest in the G1/S phase in human ovarian epithelial cancer cells A2780 (Upadhyay and al., 2017). S-propargyl-L-cysteine (SPRC), an analogue of SAC, reduces the proliferation of human pancreatic ductal adenocarcinoma cells and induces G2/M phase cell cycle arrest (Mondal and al., 2021). S-allylmercaptocysteine (SAMC), derived from garlic, suppressed the proliferation of hepatocellular carcinoma cells and negatively affected the cell cycle, decreasing the percentage of S phase and increasing the percentage of G0/G1 phase (Xu and al., 2014).

In another study they showed that SAMC suppressed the proliferation of human colorectal carcinoma SW620 cells (Zhang and al., 2014). Ajoene, a garlic compound, decreased the growth of glioblastoma multiforme cancer stem cells and human breast cancer cells (Jung and al., 2014).

In addition, AGE had antitumour effects on 1,2-dimethylhydrazine (DMH)-induced colon cancer in rats and were able to delay cell cycle progression during the G2/M phase by inactivating the NF-κB signalling pathway and down-regulating cyclin B1 and cyclin-dependent kinase 1 expression (Rodgers and al., 2013).

Another study showed that ethanol-based garlic extract suppressed the growth of multiple myeloma and prostate cancer cells in vitro. The growth of mammary tumour cells was also suppressed in vivo by ethanol-based garlic extract by increasing stress on the endoplasmic reticulum (Shang and al., 2019). Figure 3 shows the mechanisms of cell cycle inhibition by garlic.

Garlic extract activated mutated ataxia-telangiectasia (ATM) and checkpoint kinase 2 (CHK2), and inhibited the phosphorylation of Cdc25C and Cdc2, resulting in down-regulation of cyclin B1 and up-regulation of p21WAF1, thereby inhibiting the cell cycle in the G2/M phase.

Aged garlic extract can downregulate cyclin B1 and cyclin-dependent kinase 1 (CDK1) and block the cell cycle in the G2/M phase.

Diallyl trisulphide and S-propargyl-L-cysteine can also block the cell cycle in the G2/M phase.

S-allyl-cysteine induced cell cycle arrest in the G1/S phase, and allicin induced cell cycle arrest in the S phase.
3.5. Anti-Alzheimer’s Disease Activity

Alzheimer’s disease (AD) is the leading cause of aberration in elderly people with neurodegenerative and cerebrovascular disorders (Ray and al., 2011). Garlic bulb oil nullifies the activity of acetylcholinesterase (AChE), which is the main enzyme that converts acetylcholine (ACh) in the nervous system into acetate and choline (Takim and al., 2021). Depletion of ACh in the central nervous system has been compromised in the pathophysiology observed in AD, which explains why donepezil (an AChE inhibitor) has been effective in preventing AD (El-Saber Batiha and al., 2020). In vivo consumption of A. sativum extracts has been shown to improve memory by scavenging free radicals that cause oxidative damage and by inhibiting the enzyme AChE (El-Dorrigiv and al., 2020). In a recent study, they found that allicin inhibited the enzymes AChE and butyrylcholinesterase (BuChE) (enzymes that break down the neurotransmitter choline), which increased the concentration of ACh in the brain. As a result, cognitive decline and dementia were delayed (El-Saber Batiha and al., 2020).

According to the amyloid hypothesis, the accumulation of _amyloid (A_) aggregates in the brain is the pathological factor behind AD. The study of Haider et al showed that prolonged intake of garlic is related to the promotion of memory function by affecting levels of the neurotransmitter, serotonin. (El-Saber Batiha and al., 2020). In the same context, borek evaluated the neuroprotective effect of AGE using an animal model and showed that these extracts protected the brain against neurodegenerative diseases by preventing brain damage after ischaemia, preserving neurons from apoptosis and inhibiting oxidative death caused by amyloid(A_)(Silva and al., 2020). In addition, Mbyirukira and Gwebu reported that AGE or SAC inhibits degeneration of the frontal lobe of the brain, promotes memory and learning retention, and prolongs lifespan (Mbyirukira and al., 2003).

Garlic is also being studied for its immunomodulatory effects, as the combination of allicin with cholinesterase inhibitors (CHIs), including rivastigmine, galantamine and donepezil, is now the most commonly used treatment for Alzheimer’s disease, as it corrects the cholinergic deficiency observed in this disease. (CHOUGLE and al., 2021). For example, Millard et al reported that AChE incubated with allicin produced rapid inactivation that was concentration and time dependent, therefore, the search for new derivatives extracted from the natural product with dual function and lesser side effects could be useful for AD patients. (Ahmed and al., 2021).

Table 2. The pharmacological activity of garlic (Allium sativum) and its related compounds.

<table>
<thead>
<tr>
<th>Pharmacological Activities</th>
<th>Compounds</th>
<th>Main Effects and Possible Mechanisms of Action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic</td>
<td>Allyl propyl disulfide, allicin, cysteine sulfoxide, and S-allyl cysteine sulfoxide, alliin</td>
<td>Decreasing the insulin secretion from pancreatic cells, increasing liver metabolism, and thus enhancing the short-acting insulin production</td>
<td>(Zhai and al., 2018 ;Al-brakati and al.,2016). (Wang and al., 2017; Kaur and al., 2016).</td>
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<td></td>
<td></td>
<td>Protecting against diabetic retinopathy Improving weight, blood glucose, and morphological changes of retinal tissue Reducing fructosamine and glycosylated hemoglobin</td>
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<tr>
<td>Category</td>
<td>Substance</td>
<td>Effect</td>
<td>Reference(s)</td>
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<tr>
<td>Antihypertensive</td>
<td>Gamma-glutamylcysteine</td>
<td>Inhibiting the angiotensin-converting enzyme</td>
<td>(Bayan and al., 2014).</td>
</tr>
<tr>
<td>Hypolipidemic, hypocholesterolaemic</td>
<td>Different garlic preparations</td>
<td>Decreasing serum TC, TG, and LDL levels and moderately elevating HDL cholesterol</td>
<td>(Qidwai and al., 2013).</td>
</tr>
<tr>
<td>AntiAtherosclerotic, antithrombotic</td>
<td>Different garlic preparations S-allyl cysteine (SAC), alliin, and diallyl thiosulfonate (allicin)</td>
<td>Preventing ADP-activated platelets binding to immobilized fibrinogen and platelet aggregation, inhibiting GPIIb/IIIa receptor and increasing cAMP</td>
<td>(Drobiova and al., 2011; Slusarenko and al., 2008). (Arreola and al., 2015; Kaye and al., 2000). (Bayan and al., 2014; Shang and al., 2019; Ayaz and al., 2007).</td>
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<td></td>
<td></td>
<td>SMFM (sucrose methyl 3-formyl4-methylpentanoate) a natural compound isolated from garlic significantly inhibited thrombotic lesions</td>
<td></td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Allicin, Alliin, DAS, DADS, and DATS S-allyl cysteine (SAC), alliin, and diallyl thiosulfonate (allicin) Saponins</td>
<td>Controlling ROS generation and preventing mitogen-activated protein kinase (MAPK) Suppressing the enzymatic activity of cytochrome P450-2E1, reducing the generation of reactive oxygen and nitrogen species. Protecting cells against oxidative stress: Inducing the expression of several antioxidant enzymes, HO-1 and GCLM subunit, through Nrf2-ARE pathway Protecting cells against the growth inhibition and DNA damage induced by H2O2: Scavenging intracellular reactive oxygen species</td>
<td>(Chen and al., 2016). (Abdel-Daim and al., 2018; Arreola and al., 2015). (Bayan and al., 2014; Shang and al., 2019). (Liu and al., 2018; Kang and al., 2016).</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>Allicin SMFM (sucrose methyl 3-formyl4-methylpentanoate) Garlic oil</td>
<td>Chemical interaction with enzymes containing thiol significantly inhibited bacterial infection Inhibiting the growth of bacteria Disrupting the normal metabolism of bacteria: Penetrating into cells and organelles Destroying the cell structure Leading to the leakage of cytoplasm and macromolecules Inducing key genes involved in oxidative phosphorylation, the cell cycle, and protein processing in the endoplasmic reticulum</td>
<td>(Fufa, 2019). (Fratiani and al., 2016). (Wallock-Richards and al., 2014). (Guo, 2014). (Li and al., 2014). (Zardast and al., 2016; Ryu and al., 2017).</td>
</tr>
<tr>
<td>Antifungal</td>
<td>DADS, DATS</td>
<td>Irreversible ultrastructural changes in the fungal cells, loss of structural integrity and affected the germination ability</td>
<td>(Pârvu, 2019; Li, 2016).</td>
</tr>
<tr>
<td>Category</td>
<td>Substances</td>
<td>Effects</td>
<td>References</td>
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<tr>
<td>Antiviral</td>
<td>Allicin, DATS S-allyl cysteine (SAC), alliin, and diallyl thiosulfonate (allicin)</td>
<td>Chemical interaction with enzymes containing thiol Enhancing Natural killer-cell (NK-cell) activity that destroys virus-infected cells. In a clinical study on humans, dietary consumption of 2 g of garlic every 2–3 days, boosted the basal plasma IFN-α levels which are known to be protective against viral infections and prevent viral replication. Importantly, these pre-clinical studies highlight the efficacy of garlic in mitigating pulmonary fibrosis, lung injury, and sepsis-associated organ failure, all of which are symptoms observed in patients with advanced COVID-19 infection.</td>
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<td></td>
<td>Prevention of the parasite's RNA, DNA and protein synthesis. Inhibiting the human glutathione reductase and T. cruzi trypanothione reductase.</td>
<td>(Zhen and al., 2006). (Arreola and al., 2015). (Bayan and al., 2014; Shang and al., 2019). (Bhattacharyya and al., 2007; Deng and al., 2019).</td>
</tr>
<tr>
<td>Antiprotozoal</td>
<td>Allicin, DATS, Ajoene</td>
<td>Preventing the parasite's RNA, DNA and protein synthesis. Inhibiting the human glutathione reductase and T. cruzi trypanothione reductase.</td>
<td>(Hazaa and al., 2016).</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Allicin, DAS, Thiacremone S-allyl cysteine (SAC), alliin, and diallyl thiosulfonate (allicin)</td>
<td>Enhancing the immune cell activity f, inhibiting the SDF1_chemokine and Transendothelial migration of neutrophils Diminishing the expression of the inflammatory cytokines (e.g., NF- <em>B, IL-1</em>, and TNF-_), and ROS generation by suppressing CYP-2E1 hepatic enzyme Blocking the NF-B activity significantly reduced the fibrotic lesions, alveolar wall thickening, and collagen deposition. SAC also reduced inflammatory cells in the alveolar spaces and attenuated lung injury by reducing the expression of inflammatory genes namely iNOS, TNF-α, and matrix metalloproteinase-9 (MMP-9), and reducing levels of oxidative stress markers like inducible NO synthase (iNOS) in lungs, total nitrites and nitrates (NOx), ROS, and lung lipid peroxides. Inhibited the inflammatory response by inhibiting NF-κB and peroxisome proliferator-activated receptor γ (PPARγ) in lipopolysaccharides induced acute lung injury rat mode. SMFM (sucrose methyl 3-formyl4-methylpentanoate) a natural compound isolated from garlic significantly inhibited alveolar damage. SMFM also inhibited proinflammatory cytokines TNF-α, IL-6, and IL-1β in the peritoneal fluid which are known to cause vital organ damage.</td>
<td>(Abdel-Hafeez and al., 2015). (Abd-Elkader and al., 2020). (Arreola and al., 2015; Bayan and al., 2014; Shang and al., 2019) (Nie and al., 2021; Mizuguchi and al., 2006; Tsukioka and al., 2017; Wang and al., 2017) (Arreola and al., 2015; Bayan and al., 2014; Shang and al., 2019)</td>
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<tr>
<td>Anti-cancer</td>
<td>Allicin, alliin, DADS, DAS Z-Ajoene</td>
<td>Enhancing p38 expression and cleaved caspase 3. Stimulating apoptosis in human leukemic cells, promoting the peroxide production, caspase-3-like, and caspase-8 activities.</td>
<td>(Zhang and al., 2015). (Bayan and al., 2014).</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Allicin, DATS, S-allyl cysteine (SAC),</td>
<td>Suppressing BuChE and AChE.</td>
<td>(Liu and al., 2015).</td>
</tr>
<tr>
<td>Alliin, and diallyl thiosulfonate (allicin)</td>
<td>Garlic is a potent immunomodulator</td>
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<tr>
<td>Polysaccharides/Fructan</td>
<td>Exerting immunomodulatory effect</td>
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<tr>
<td>Garlic oil</td>
<td>Normalizing several immunological parameters of rats, such as the serum total immunoglobulin concentration and T-cell subtype CD4+</td>
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<tr>
<td>Selenizing garlic</td>
<td>Combination of garlic oil and levamisole could balance the T-helper 1/T-helper 2 response</td>
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<tr>
<td>Polysaccharides</td>
<td>Proliferation Enhancing interferon- and IL-2 increase the serum antibody titer</td>
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<td>Reducing the occurrence and severity of cold and flu Improving the immune system functions</td>
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| Anti-obesity | Ajoene | Decreasing the fat accumulation in 3T3-L1 adipocytes and dramatically decreases the body weight gain Decreasing the C/EBP_, PPAR2, and LPL expression and the PPAR effect in human adipocytes |

| Cardiovascular Protection | Polyphenols | Leading to endothelial-dependent vasodilation by Stimulating the production of NO |
| | S-1-propylenecysteine | Relaxing coronary arteries before and after ischemia-reperfusion in rat |
| | Alliin | Preventing the decrease of myocardial contractility Improving peripheral blood circulation |
| | Allyl methyl sulfide/Allyl methyl Sulfoxide | Reducing the systolic blood pressure by Modulating the sGC-cGMP-PKG pathway and Decreasing the expression of vascular endothelial cell. |
| | SAC | Alleviating pulmonary hypertension by adhesion molecule-1 and MMP-9 |
| | | Increasing the expression of PKG and eNOS. |
| | | Increasing the activity of captopril on inhibiting ACE and hypertension |
| | | Modulating the metabolism of lipid and cholesterol |
| | | Decreasing the levels of blood total lipids, triglyceride, and cholesterol by reducing the mRNA expression of sterol regulatory element binding protein-1c |
| | | Reduce cardiac hypertrophy remodeling induced by isoproterenol by increasing Na+/K+-ATPase protein level |
| | | Protecting the heart function Activating sirtuin 3-manganese superoxide dismutase pathway by Deacetylation manganese superoxide dismutase |
| | | Protecting heart rate variability, cardiac dysfunction, and mitochondrial dysfunction |
| | | Protecting the heart tissue Reducing oxidative stress Controlling Na+/K+-ATPase activity and Ca2+ levels |
| | | Protecting against cardiotoxicity |

(Arreola and al., 2015; Bayan and al., 2014; Shang and al., 2019) (Li and al., 2017) (Hassouna and al., 2015) (Mohamed and al., 2015) (Qiu and al., 2015) (Percival and al., 2016) (Han and al., 2011) (Keophiphath and al., 2009) (Weiss and al., 2006) (Garcia-Villalón and al., 2016) (Zhang and al., 2019) (Gheibi and al., 2018) (Zhang and al., 2019) (Asdaq and al., 2010) (Al-Numair and al., 2009; Ha and al., 2015) (Khatua and al., 2017) (Supakul and al., 2014; Khatua and al., 2017; Alkreathy and al., 2010).
Figure 3. The mechanisms of garlic and its active compounds on cell cycle inhibition in cancer cells

4. Recommended Dose, Combination Therapy with Other Drugs and Adverse Effects and Toxicity Toxic Side Effects of Garlic

4.1. Recommended Dose and Combination Therapy with Other Drugs

Recommended doses for daily garlic intake in the elderly are generally 4 g raw garlic or 7.2 g EFA or one dried garlic powder tablet two to three times a day (Tattelman, 2005). Many studies have shown that garlic toxicity is dose-dependent, for example Rana et al. Found that oral or intraperitoneal administration of 50 mg/kg of garlic to rats did not report any effect on liver and lung tissue (Rana and al., 2011).

Whereas garlic at 250, 500 and 1000 mg/kg per day caused acute deformities of liver and lung tissue in rats, Garlic intake at 500 and 1000 mg/kg/day decreased auto-antioxidants without altering the level of lipid peroxidation, while 1000 mg/kg daily caused morphological deformations in the liver by light microscopy and ultrastructural examination, histological examination revealed focal non-specific lesions of hepatocytes. Also, Mikaili et al showed that ingestion of garlic bulb extracts to male and female rats at 300 and 600 mg for 21 days, exerted a growth retardation and affected biological and histological parameters (Mikaili and al., 2013).

Recent research has shown that combination therapy of fresh garlic extracts and antibiotics has resulted in high antibacterial activity. such as those of Ismail et al who reported that combined aqueous garlic extract-ampicillin treatment gave a potent synergistic effect against K. pneumoniae, S. typhi, E. coli and P. aeruginosa. (El-Saber Batiha and al., 2020). Mikaili et al, revealed the combined effect of allicin and polymyxin B against various yeasts and filamentous fungi and this combination therapy was found to increase plasma membrane permeability in S.cerevisiae (Mikaili and al., 2020). In addition, combination treatments of garlic with captopril showed a higher synergistic effect regarding ACE inhibition (Corzo-
Martínez and al., 2020). The combination therapy of 250 mg/kg garlic with hydrochlorothiazide shows synergistic antihypertensive and cardioprotective activities against fructose and isoproterenol toxicity. Asdaq and Inamdar. (Asdaq and al., 2011). Also, the combination of 250 mg/kg garlic with propranolol revealed a remarkable increase in antioxidant enzyme activities throughout the ischemic injury (Asdaq and al., 2011).

Notably, the combined treatment of AGE with methotrexate showed better activity against the significant increase in liver function enzymes, pro-inflammatory cytokines and antioxidants (Jalil Ali and al., 2016). In addition, Vathsala and Murthy revealed the potent immunomodulatory and anti-plasmodial effect of the combined garlic-artemether treatment (El-Saber Batiha and al., 2020). They reported that this combination therapy could play a potential role in reducing organ damage and protecting against Plasmodium species by affecting NO production, suggesting new treatment options for malaria (El-Saber Batiha and al., 2020).

4.2. Adverse Effects and Toxicity

The US Food and Drug Administration (FDA) considers garlic to be safe for humans, it may cause gastric distress, especially if ingested in large doses by sensitive individuals.

Randomised controlled trials have been conducted to assess the safety of garlic, the results of which show that garlic has side effects such as insomnia, vomiting, heartburn, dizziness, diarrhoea, tachycardia, nausea, bloating, flushing, headache, mild orthostatic hypotension, sweating, unpleasant body odour and flatulence (El-Saber Batiha and al., 2020). These are caused by ingestion of high doses of raw garlic on an empty stomach which induces changes in the intestinal flora, flatulence and gastrointestinal disturbances (El-Saber Batiha and al., 2020).

Recent studies in healthy participants show conflicting results regarding the effect of garlic on the pharmacokinetics of protease inhibitors, as well as anticoagulants due to its antithrombotic properties (Borrelli and al., 2007). Many surgeons have recommended stopping high-dose garlic administration up to 7-10 days before surgery because of its effect on prolonging bleeding time, which was observed in a patient with a spontaneous epidural haematoma (Borrelli and al., 2007).

Chen et al, showed that dehydrated raw garlic powder, when administered orally, induced acute damage to the gastric mucosa (Rana and al., 2011).

While Yuncu et al reported that AGE, the sulphur-free compound, protected the intestinal mucosa of experimental animals (Seetapong and al., 2016).

In conclusion, Allicin is a membrane-permeable compound that can readily enter cells and interact with cellular thiols such as glutathione or cysteine residues in proteins (C Borlinghaus and al., 2021), as well as with enzymes containing reactive cysteine, which could explain the toxicity of allicin (El-Saber Batiha and al., 2020).

Conclusions

Garlic is a widely consumed spice with a characteristic smell. It contains many bioactive components, such as organic sulfides, saponins, phenolic compounds and polysaccharides.

This review has focused on Organic sulfides such as allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl, trisulfide, ajoene and S-allyl-cysteine, which are the main
bioactive components of garlic. These have many biological functions, such as antioxidant, anti-inflammatory, immunomodulatory, cardiovascular protective, anticancer, hepatoprotective, digestive system protective, antidiabetic, anti-obesity, neuroprotective, renal protective, antibacterial and antifungal activities.

Allicin, the active substance in garlic, can induce gastric agitation, especially when administered in high doses. In addition, A. sativum has been reported to affect the pharmacokinetics of antiretroviral drugs, as well as anticoagulants.

In the future, more biological functions of garlic should be studied, and the relative compounds of garlic should be separated and identified. In addition, the effects of processing should be studied in more detail as they may have an impact on the biological functions and safety of garlic. On the other hand, more clinical trials should be conducted to confirm the human health benefits of garlic, and special attention should be paid to side effects.

Conflicts of Interest

There is no conflict of interest.

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