Bioactive Compounds and Biological Functions of Garlic (Allium sativum L.)

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Abstract: Garlic (Allium sativum L.) is a widely consumed spice in the world. Garlic contains diverse bioactive compounds, such as allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allyl-cysteine. Substantial studies have shown that garlic and its bioactive constituents exhibit antioxidant, anti-inflammatory, antibacterial, antifungal, immunomodulatory, cardiovascular protective, anticancer, hepatoprotective, digestive system protective, anti-diabetic, anti-obesity, neuroprotective, and renal protective properties. In this review, the main bioactive compounds and important biological functions of garlic are summarized, highlighting and discussing the relevant mechanisms of actions. Overall, garlic is an excellent natural source of bioactive sulfur-containing compounds and has promising applications in the development of functional foods or nutraceuticals for the prevention and management of certain diseases.

Keywords: garlic; phytochemicals; organic sulfides; health benefits; antioxidant; anticancer; cardiovascular protection; antimicrobial

1. Introduction

Garlic (Allium sativum L.) is a common spice with many health benefits, mainly due to its diverse bioactive compounds, such as organic sulfides, saponins, phenolic compounds, and polysaccharides [1–3]. Garlic is commonly consumed and has a long history of being utilized as a traditional medicine in China [4]. 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 [5–11]. Investigations have increasingly focused on black garlic, a processed garlic product with increased polyphenol and flavonoid contents, as well as better antioxidant properties, compared to the fresh garlic [12]. In order to highlight the significance of garlic in human health, we searched high-quality studies from the last five years from the Web of Science Core Collection and reviewed the main bioactive compounds and biological functions of garlic, with special attention paid to the relevant mechanisms of actions. We hope that this review paper will attract more interest in garlic and provide updated scientific evidence for the better utilization of garlic in human health and disease management.
2. Bioactive Compounds of Garlic

Garlic has a variety of bioactive compounds, including organosulfur compounds, saponins, phenolic compounds, and polysaccharides [2,3,13,14]. The major active components of garlic (Figure 1) are its organosulfur compounds, such as diallyl thiosulfonate (allicin), diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), E/Z-ajoene, S-allyl-cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin) [15–18]. In general, organosulfur compounds in raw garlic have higher digestibility than those in cooked garlic [19]. In addition, saponins were found to be more stable in the cooking process [20]. The total amount of saponin in purple garlic was almost 40 times higher than that in white garlic, and several saponin compounds were only found to exist in purple garlic, such as desgalactotigonin-rhamnose, proto-desgalactotigonin, proto-desgalactotigonin-rhamnose, voghieroside D1, sativoside B1-rhamnose, and sativoside R1 [2]. Moreover, garlic contained more than 20 phenolic compounds, with higher contents than many common vegetables [21]. The main phenolic compound was β-resorcylic acid, followed by pyrogallol, gallic acid, rutin, protocatechuic acid, as well as quercetin [22]. Furthermore, garlic polysaccharides were reported to contain 85% fructose, 14% glucose, and 1% galactose [23].

![Chemical structures of main organosulfur compounds in garlic](image)

**Figure 1.** The chemical structures of the main organosulfur compounds in garlic.

The effects of different processing methods on bioactive components of garlic have been also studied. For example, it was found that the 38 components of garlic changed after thermal treatment during the processing of black garlic [24]. In addition, the polysaccharide degraded and the content of reducing sugar increased during the thermal processing of black garlic [25]. Also, increasing temperature and decreasing humidity enhance the contents of polyphenols and the total flavonoids in black garlic [26,27]. In the future, more bioactive compounds produced in the processing of garlic should be separated and identified.

3. Biological functions of Garlic

3.1. Antioxidant Activity

The antioxidant activities of natural products have been widely evaluated, such as fruits, vegetables, mushrooms, cereal, flowers, and wild fruits [28–34]. Accumulating 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 β-carotene bleaching), indicating that the processing could affect the antioxidant property of garlic [35]. In another study, the results of DPPH and oxygen radical absorption capacity (ORAC) assays showed that the ethanolic extract of garlic sprouts exhibited stronger antioxidant activities than the ethanolic extract of raw garlic [36]. In addition, the antioxidant properties of aged garlic were found to be higher than fresh garlic by DPPH, ABTS, FRAP, H2O2 scavenging, and Fe2+ chelating assays [37]. Compared with multi clove garlic extract, single clove garlic extract had a higher amount of phenolic compounds and showed stronger antioxidant activity [38]. Moreover, the antioxidant activity of black garlic increased with thermal treatment, and the highest antioxidant activity was obtained on the 21st day of processing [39,40]. Also, the increased pressure improved the antioxidant activity of garlic paste [41]. However, the antioxidant activity of “Laba” garlic, a traditional Chinese garlic product, decreased during fermentation [42].

The aged garlic extract (AGE) induced the expression of several antioxidant enzymes, such as heme oxygenase-1 (HO-1) and the glutamate-cysteine ligase modifier (GCLM) subunit through the nuclear factor erythroid-2 related factor 2 (Nrf2)-antioxidant response element (ARE) pathway, which protected human endothelial cells against oxidative stress [43]. Garlic saponins were reported to protect mouse-derived C2C12 myoblasts against growth inhibition and DNA damage induced by H2O2, and to scavenge intracellular reactive oxygen species (ROS) [44].

In summary, garlic and its active ingredients (such as phenols and saponins) have certain antioxidant effects. Different processing methods also affected the antioxidant activity of garlic. Usually, raw garlic had a stronger antioxidant activity than cooked garlic, and the antioxidant activity of fermented garlic, such as black garlic, was stronger than that of crude garlic. In addition, the cellular experiment showed that the mechanism of antioxidative action of garlic might be involved with the enhancement of antioxidant enzyme activities and the regulation of the Nrf2-ARE pathway.

3.2. Anti-Inflammatory Activity

Garlic and its bioactive compounds have also been shown to exhibit anti-inflammatory properties. In a study, the ethyl linoleate in garlic reduced the production of nitric oxide (NO) and prostaglandin E-2 by down-regulating the expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX2) in lipopolysaccharide-stimulated RAW 264.7 macrophages [45]. Another study revealed that the garlic 14-kDa protein inhibited the inflammatory mediators including NO, TNF-α, and interleukin (IL)-1β by inhibiting the transcription factor nuclear factor-kappa B (NF-κB) signaling pathway in lipopolysaccharide-stimulated J774A.1 macrophages [46]. In addition, AGE inhibited inflammation in apolipoprotein E-knockout mice. The treatment of AGE reduced the level of tumor necrosis factor-α (TNF-α) and the IL-1 receptor-associated kinase 4 and enhanced the activity of the adenosine monophosphate-activated protein kinase (AMPK) in the liver [47]. Moreover, allicin could be used as a potential complementary treatment against the inflammatory response induced by schistosome infection in BALB/c mice [48]. Furthermore, garlic supplements alleviated osteoarthritis in obese or overweight patients by reducing resistin [49]. Collectively, in both in vitro and in vivo experiments, garlic could inhibit inflammation mainly by inhibiting inflammatory mediators, such as NO, TNF-α, and IL-1. Garlic has great potential to treat inflammatory diseases, such as arthritis, in humans, because of its low or absent toxicity.

3.3. Antimicrobial Activity

Garlic has a broad spectrum of antibacterial and antifungal properties [50–52]. The antibacterial activities of two special varieties of garlic, “Rosato” and “Caposele”, from the Campania region in Italy were analyzed. It was found that the Caposele variety could significantly suppress the growth of Aspergillus versicolor and Penicillium citrinum, while the Rosato variety had a stronger inhibitory effect on Penicillium expansum [53]. Moreover, AGE was effective in inhibiting Burkholderia cepacia [54]. Garlic
oil also had antibacterial activities and could restrict the growth of *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* [50]. It was found that garlic oil inhibited the fungus *Penicillium funiculosum*, probably by penetrating into cells and organelles, destroying the cell structure, and inducing the leakage of cytoplasm and macromolecules [55]. Additionally, garlic oil was found to disrupt the normal metabolism of *Candida albicans*, which is associated with the induction of key genes involved in oxidative phosphorylation, the cell cycle, and protein processing in the endoplasmic reticulum [56]. Furthermore, in a clinical trial, the treatment of raw garlic inhibited *Helicobacter pylori* in the stomach of patients with *H. pylori* infection [57].

In a word, the antibacterial effects of garlic are related to its varieties and processing methods. Garlic oil was demonstrated to be the main antibacterial ingredient that destroys the structure and the metabolic process of bacterial cells.

### 3.4. Modulating Immune System

Garlic contains many bioactive compounds that are beneficial for the immune system. Garlic polysaccharides have an immunomodulatory effect and regulate the expressions of IL-6, IL-10, TNF-α, and interferon-γ in RAW 264.7 macrophages. Compared with black garlic, polysaccharides in fresh garlic exhibit a more potent activity in immunomodulation. This is probably due to the degradation of fructan constituents during processing [58]. In an in vivo study, the treatment of garlic oil 30 minutes before the administration of diazinon to Wistar rats can normalize several immunological parameters of rats, such as their serum total immunoglobulin concentration and T-cell subtype CD4+ [59]. In addition, the combination of garlic oil and levamisole can significantly balance the T-helper 1 / T-helper 2 response in Wistar rats [60]. Moreover, selenylation modification of garlic polysaccharides significantly improves its immune-enhancing activity, and selenizing garlic polysaccharides promotes lymphocyte proliferation, enhances interferon-γ and IL-2, and increases the serum antibody titer in 14-day-old chickens [61]. Moreover, the consumption of AGE was found to reduce the occurrence and severity of the cold and flu and improve the immune system functions in humans [8]. Overall, polysaccharides appear to be the main immune-modulating components in garlic.

### 3.5. Cardiovascular Protection

Recently, the numbers of deaths from cardiovascular diseases have significantly risen [62]. There has been a growing interest in natural products to protect the cardiovascular system, and garlic is one of the most promising candidates [63–67]. It has been demonstrated that the intake of garlic powder can effectively reduce blood pressure, total cholesterol, low-density lipoprotein cholesterol, and other risk factors related to cardiovascular diseases [68].

#### 3.5.1. Antihypertensive Activity

Garlic can also reduce oxidative stress, increase the production of NO and hydrogen sulfide (H₂S), and inhibit the angiotensin converting enzyme, thereby lowering hypertension [69–74]. A study showed that AGE could stimulate the production of NO, leading to endothelial-dependent vasodilation in the isolated rat aortic rings. Moreover, l-arginine in AGE was crucial in the NOS-mediated NO production [71]. In addition, S-1-propylenecysteine was shown to be the key antihypertensive compound in the AGE. S-1-propylenecysteine was shown to improve peripheral blood circulation and reduce the systolic blood pressure in spontaneous hypertension rats, without affecting the systolic blood pressure of control rats [75]. In another study, the nitrites in the fermented garlic extract (FGE) could be converted into NO in vivo by *Bacillus subtilis*. Further, NO reduced the systolic blood pressure in spontaneous hypertension rats through the soluble guanylyl cyclase (sGC)-cyclic guanosine monophosphate (cGMP)-protein kinases G (PKG) pathway [76]. Also, FGE was shown to alleviate pulmonary hypertension by decreasing the expression of vascular endothelial cell adhesion molecule-1 and matrix metalloproteinase-9 (MMP-9) and increasing the expression of PKG and endothelial nitric oxide synthase (eNOS) in monocrotaline-induced pulmonary hypertension rats [77]. Moreover,
the combination of garlic and its bioactive compound alliin and captopril increased the activity of captopril on inhibiting angiotensin-converting enzyme (ACE) and hypertension in rats [72]. In a placebo-controlled trial, 44 patients with hypertension were given enzymatic browning processed garlic, and their systolic blood pressure and the diastolic blood pressure were significantly reduced [78]. The anti-hypertensive mechanisms of garlic are shown in Figure 2.

![Figure 2. The mechanisms of the antihypertensive properties of garlic extract via increasing the production of nitric oxide (NO) in vascular smooth muscle cells. The l-arginine (L-Arg) in aged garlic extract (AGE) could be transformed into NO and L-citrulline (L-Cit) mediated by nitric oxide synthase (NOS). Moreover, the nitrite in the fermented garlic extract (FGE) could be converted into NO in vivo by Bacillus subtilis. NO and atrial natriuretic peptide (ANP) activated particulate guanylyl cyclase (pGC) and soluble guanylyl cyclase (sGC), thus catalyzing the transform of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The elevated cGMP activated PKG, and PKG decreased intracellular Ca\(^{2+}\) concentration by increasing intracytoplasmic Ca\(^{2+}\) influx. As a result, the vascular smooth muscle relaxed, and the blood vessels dilated.](image)

3.5.2. Anti-hyperlipidemic Activity

Studies demonstrate that garlic can lower blood lipids in animals and people. A study showed that high temperature and high pressure processing could remove the pungency of garlic, and this garlic effectively reduced the levels of total cholesterol, low-density lipoprotein cholesterol, and triglyceride in high-cholesterol diet-fed Sprague–Dawley rats [79]. Another study found that adding 1.5% black garlic extract in high-fat diet for male Sprague-Dawley rats could significantly modulate the metabolism of lipids and cholesterol and decrease the total levels of blood lipids, triglyceride, and cholesterol, which could be due to the reduction of the mRNA expression of sterol regulatory element binding protein-1c (SREBP-1c) [80]. In a cross-sectional study, the intake of garlic (300 mg/day, 8 weeks) was shown to reduce the levels of cholesterol and low-density lipoprotein and elevate the level of high-density lipoprotein, but garlic had no effect on the level of triglycerides in patients with diabetic dyslipidemia [81]. Additionally, a supplement of aged garlic for 13 weeks was found to reduce the activities of myeloperoxidase and lipid hydroperoxide in serum and to decrease the concentrations of F\(_2\)-isoprostanes in plasma and urine in 41 patients with hypercholesterolemia. Moreover, aged garlic had better effects than raw garlic [82].
3.5.3. Heart Protection

Garlic can also protect the heart. Garlic has been shown to increase Na\(^+\)/K\(^+\)-ATPase protein levels and reduce cardiac hypertrophy and remodeling induced by isoproterenol in rats [83]. Another study indicated that garlic extract activated the sirtuin 3-manganese superoxide dismutase pathway by deacetylating manganese superoxide dismutase, thus protecting the heart function in streptomyacin-induced diabetic rats [84]. In addition, adding garlic and fenugreek into the diet improved pathological changes of heart tissues in rats [85]. Garlic extract had protective effects on heart rate variability and improved cardiac, as well as mitochondrial, dysfunction in insulin-resistant obese rats [86]. Moreover, garlic extract treatment ameliorated the heart tissue in a rat model of gentamicin-induced chronic renal failure and induced a reduction in oxidative stress and controlled Na\(^+\)/K\(^+\)-ATPase activity and Ca\(^{2+}\) levels [87]. Furthermore, AGE had a dose-dependent protective effect against isoproterenol-induced cardiotoxicity. SAC combined with atenolol was more effective against isoproterenol-induced myocardial dysfunction in rats [88]. Notably, allicin was easily degraded into organic diallyl polysulfide in the presence of thiols, which was able to effectively provide H\(_2\)S to protect the heart [13].

3.5.4. Other Cardiovascular Protective effects

Garlic also has other cardiovascular protective effects. Garlic was reported to inhibit platelet aggregation, which might be related to the antioxidant activity of garlic and its antioxidant compounds [13,89]. The polyphenols in aged black garlic extract had a relaxing effect on coronary arteries before and after ischemia-reperfusion (I/R) in rat hearts and improved myocardial contractility [90]. Moreover, AGE treatment inhibited inflammatory response to prevent atherosclerosis by reducing the serum level of C-reactive protein and thromboxane B-2, the protein level of TNF-\(\alpha\) and IL-1 receptor-associated kinase 4, and increasing AMPK activity in the liver of apolipoprotein E-knockout mice [47]. Furthermore, AGE inhibited the vascular inflammation and lipid deposition in progress of atherosclerosis at an early stage in the apolipoprotein E-knockout mice, and AGE also inhibited the development of coronary artery calcification in humans [91].

In short, numerous studies have found that garlic exhibits protective cardiovascular effects and can alleviate hypertension, hyperlipidemia, and heart disease. Garlic’s mechanisms of action could be mainly related to the reduction of oxidative stress, suppression of angiotensin converting enzymes, a reduction of lipid peroxidation, and an increase of NO and H\(_2\)S production.

3.6. Anticancer Activity

Cancer is acknowledged to be a primary cause of death in the world, and various natural products like berries, cruciferous vegetables, tomatoes, and ginger have been demonstrated to possess anticancer properties [92–100]. Recent studies have also shown that garlic and its active constituents can protect against diverse cancers, such as colorectal, lung, gastric, and bladder cancers [101–106].

3.6.1. Regulating Metabolism of Carcinogenic Substances

People are exposed to various carcinogens in their daily lives [107]. A study revealed that garlic and its sulfur compounds can diminish the activation of carcinogens, thus reducing the risk of cancer [108]. In addition, garlic and its organic allyl sulfides can inhibit the generation of nitrosamines, a kind of carcinogen produced during cooking and storage [109,110]. Moreover, garlic allyl sulfides can block DNA alkylation, which is an early step in nitrosamine carcinogenesis [108].

3.6.2. Suppressing Cell Growth and Proliferation

Cancer cells have the characteristic of infinite proliferation [111]. It was reported that crude garlic extract exhibited an anti-proliferative effect on human cancer cell lines, including liver (HepG2), colon (Caco2), prostate (PC-3), and breast (MCF-7) cancer cells [112]. Garlic extract induced G\(_2\)/M-phase cell
cycle arrest in EJ bladder cancer cells by activating ataxia-telangiectasia mutated and checkpoint kinase 2, and then inhibiting the phosphorylation of Cdc25C (Ser216) and Cdc2 (Thr14/Tyr15), down-regulating the expression of Cyclin B1, and up-regulating p21WAF1 [113]. The bioactive compounds of garlic, DATS, can suppress the proliferation of SGC-7901 gastric cancer cells and block the cell cycle in the G2/M-phase [114]. Moreover, SAC can induce G1/S-phase cell cycle arrest in A2780 human epithelial ovarian cancer cells [115]. S-propargyl-L-cysteine (SPRC), an analogue of SAC, reduced the proliferation of human pancreatic ductal adenocarcinoma cells and induced cell cycle arrest in the G2/M-phase [116]. The garlic derived S-allylmercaptocysteine (SAMC) suppressed the proliferation of hepatocellular carcinoma cells and negatively affected the cell cycle. It decreased the percentage of the S phase and increased the percentage of the G0/G1 phase [117]. Another study showed that SAMC could inhibit the proliferation of human colorectal carcinoma SW620 cells [118]. Moreover, allicin was found to inhibit the proliferation of gastric adenocarcinoma cells. It induced cell cycle arrest in the S-phase, without affecting normal intestinal cells (INT-407) [18]. Furthermore, ajoene was shown to restrain the growth of glioblastoma multiforme cancer stem cells and human breast cancer cells [119,120].

In addition, AGE had anti-tumor effects on 1,2-dimethylhydrazine (DMH)-induced colon cancer in rats and could delay cell cycle progression during the G2/M-phase by inactivating the NF-κB signaling pathway and down-regulating the expression of Cyclin B1 and Cyclin-dependent kinase 1 [121]. Another study found that ethanol-based garlic extract suppressed the growth of multiple myeloma and prostate cancer cells in vitro. The growth of mammary tumor cells was also suppressed in vivo by ethanol-based garlic extract by increasing stress on the endoplasmic reticulum [122]. Figure 3 shows the mechanisms of cell cycle inhibition by garlic.

![Figure 3. The mechanisms of garlic and its active compounds on the inhibition of the cell cycle in cancer cells. Garlic extract activated ataxia-telangiectasia mutated (ATM) and checkpoint kinase 2 (CHK2), and inhibited the phosphorylation of Cdc25C and Cdc2, which down-regulated cyclin B1 and up-regulating p21WAF1, thereby inhibiting the cell cycle in the G2/M-phase. Aged garlic extract can down-regulate Cyclin B1 and Cyclin-dependent kinase 1 (CDK1) and block the cell cycle in the G2/M-phase. Diallyl trisulfide and S-propargyl-L-cysteine can also block the cell cycle in the G2/M-phase. Moreover, S-allyl-cysteine induced cell cycle arrest in the G1/S-phase, and allicin induced cell cycle arrest during the S-phase.](image-url)
3.6.3. Inducing Apoptosis

The intake of raw and crushed garlic was found to upregulate apoptotic-related genes, such as aryl hydrocarbon receptor, hypoxia-inducible factor 1α, and proto-oncogene c-Jun, which influenced the expression of genes related to immunity and cancer in the blood of human beings [123]. DATS induced apoptosis via the accumulation of B cell lymphoma-2 (Bcl-2) associated X (Bax), p53 and cytochrome C, and the decrease of Bcl-2 expression in SGC-7901 gastric cancer cells. DATS also significantly induced tumor apoptosis in a mouse model with SGC-7901 gastric cancer cells [114]. In addition, SAC could induce the apoptosis of A2780 human epithelial ovarian cancer cells, decrease pro-caspase-3, poly(ADP-ribose) polymerase-1 (PARP-1) and Bcl-2, and increase the expression of active caspase-3 and Bax protein [115]. SAC induced apoptosis via the Jun N-terminal kinase (JNK) and p38 mitogen activated protein kinase (p38 MAPK) pathways in SW620 human colorectal carcinoma cells [118]. Moreover, alliin was shown to induce the apoptosis of gastric adenocarcinoma cells by producing ROS and could decrease the membrane potential of mitochondria through down-upregulating the protein level of Bax/Bcl-2 and up-regulating cytochrome C [18]. Furthermore, S-propargyl-l-cysteine led to apoptosis in human pancreatic ductal adenocarcinoma cells and limited tumor growth in the Panc-1 xenograft model in vivo by activating the JNK pathway [116].

3.6.4. Suppressing Angiogenesis

It was reported that AGE inhibited cell motility, proliferation, and tube formation of ECV304 endothelial cells and the transformed rat lung endothelial cells [124]. Further, DATS effectively inhibit the angiogenesis in MDA-MB-231 human breast cancer cells [125]. Furthermore, the combination of garlic and lemon aqueous extracts had an inhibitory effect on EMT6/P breast cancer cells in BALB/c mice by inhibiting the expression of vascular endothelial growth factor (VEGF) and, finally, angiogenesis [126].

3.6.5. Inhibiting Invasion and Migration

Both invasion and migration are malignant behaviors of tumor cells [111]. Garlic extract inhibited the expression of MMP-9, reduced the binding activity of the transcription factor activator protein 1 (AP-1) (specificity the protein-1 and NF-κB motifs), and increased the expression of heat shock protein A6, which blocked the migration and invasion of bladder cancer EJ cells [113]. AGE decreased the invasive capacity of SW480 and SW620 colorectal cancer cells by inhibiting cell motility and cell proliferation [124]. In addition, SAC reduced the migration of A2780 epithelial ovarian cancer cells by significantly reducing the expression of wingless-type MMTV integration site family member 5A (Wnt5a), phosphor-protein kinase B, and c-Jun proteins [115]. In another study, DATS inhibited SGC-7901 gastric tumor cell migration and invasion by regulating the protein expressions of MMP-9 and E-cadherin in BALB/c-nude mice [114].

3.6.6. Alleviating the Adverse Effects of Anticancer Therapies

Garlic has been indicated to mitigate the adverse effects of several anticancer therapies [127]. In one study, AGE improved the renal histological, ultrastructural, and biochemical changes induced by cisplatin therapy, such as hemorrhaging, glomerular atrophy, tubular necrosis, and degeneration in adult male rats [128]. Furthermore, allicin enhanced the anticancer effect of tamoxifen in mice and reduce the liver injury caused by tamoxifen treatment. Allicin improved the tamoxifen-induced changes in the levels of superoxide dismutase, glutathione, aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase [129]. Additionally, garlic had a protective effect against febrile neutropenia in patients who received chemotherapy for hematological malignancies in the lower-risk febrile neutropenia subgroup [130].
3.6.7. Other Anti-Cancer Actions

AGE was shown to enhance the in vitro production of interferon-γ in splenocytes and increase the ratio of CD4+/CD8+ on implanted fibrosarcoma tumors in BALB/c mice, which improved the immune responses of mice to fibrosarcoma and inhibited tumor growth [131]. Additionally, the garlic and lemon aqueous extract were demonstrated to activate the immune system against implanted breast cancer in mice by increasing interferon-γ, IL-2, and IL-4 levels [126]. Moreover, DADS prevented colorectal tumorigenesis induced by azoxymethane and dextran sulfate in FVB/N mice. The treatment of DADS reduced inflammation by suppressing glycogen-synthase kinase-3β and the nuclear localization of NF-κB [132].

In summary, garlic and its active components can prevent and manage different cancers (Table 1). These anticancer mechanisms include the regulation of carcinogen metabolism, inhibition of cell growth and proliferation, induction of apoptosis, suppression of angiogenesis, and inhibition of invasion and migration. Garlic can also diminish the negative effects of anticancer therapies.

3.7. Hepatoprotective Activity

Accumulating studies have revealed that several natural products, including garlic, had hepatoprotective effects [133–135]. In an in vitro study, the black garlic extract reduced the damage of tert-butyl hydroperoxide in rat clone-9 hepatocytes by inhibiting apoptosis, lipid peroxidation, oxidative stress, and inflammation [136]. In another study, garlic attenuated liver damage induced by alloxan in rats and improved the biochemical plasma factors of hepatic functions, such as urea, creatinine, aspartate transaminase, and alanine transaminase [137]. In addition, the combination of garlic and ascorbic acid protected against the liver toxicity induced by Cd in albino mice [138]. Moreover, single clove garlic had a stronger protective effect than multi-clove garlic on CCl4-induced acute liver injury in male rabbits [38].

Moreover, garlic oil was shown to enhance the activities of hepatic antioxidant enzymes, block metabolic activation of 1,3-dichloro-2-propanol, and reduce apoptosis in the liver, indicating a protective effect against liver injury in rats [139]. Also, it was reported that the active compounds of garlic, such as DAS, DADS, and S-methyl-l-cysteine, could prevent and treat liver damage, such as acute and chronic ethanol-induced liver damage [140]. DADS in garlic essential oil was found to attenuate nonalcoholic fatty liver disease, which was induced by a high-fat diet in rats. DADS significantly reduced the release of pro-inflammatory cytokines in the liver and increased antioxidant activity by inhibiting the expression of cytochrome P450 2E1 [141].

Compared with unfermented garlic extract, the fermented garlic extract by Lactobacillus plantarum BL2 (LAFGE) was able to more effectively reduce liver lipid levels and ameliorate hepatic steatosis in mice [142]. Another study revealed that LAFGE inhibited liver cell apoptosis partly by suppressing MAPK phosphorylation and down-regulating p53, which protected the liver from acetaminophen-induced injury in rats [143]. Furthermore, LAFGE was considered as a potential treatment for mild hepatic dysfunction. In a double-blind, randomized, placebo-controlled study, 36 adults with mildly high level of serum gamamyl glutamyl transpeptiase (GGT) received LAFGE, and the levels of GGT and alanine aminotransferase were improved without adverse effects [144]. However, an animal study showed that an overdose of garlic has negative morphological effects on the liver. After 30 days of injecting fresh garlic extract at 500 mg and 1000 mg/kg via a gastric tube in Wistar albinism rats, bleeding and nodular swelling appeared on the external surfaces of the liver, and the weight of the liver increased [145].

Generally speaking, garlic can effectively alleviate acute or chronic liver injury, but the side effects of excessive consumption of garlic also need to be considered. It is necessary to evaluate the safe dose and duration of garlic usage in humans.
3.8. Digestive System Protection

Garlic has been reported to have therapeutic efficacy against gastric tissue injury. A study showed that black garlic extract can stimulate gastrointestinal peristalsis, promote gastrointestinal emptying, and facilitate defecation. The water fraction of black garlic had a better effect on improving gastrointestinal functions compared with the n-butanol fraction and ethyl acetate fraction in the small intestine in vitro [146]. Additionally, the treatment by garlic and cabbage extract reduced the length of gastric ulcers, total gastric acid, gastric juice volume, total bacteria count, and changes in histopathology. This treatment also improved the pH value of gastric juice in rats [147]. Furthermore, the oral administration of AGE was shown to heal gastric mucosal injury induced by indomethacin in male rats and reduce the total microbial amount in the stomach [148]. AGE was effective in preventing indomethacin-induced ulcers in rats via the reduction in oxidative stress and the elevation of prostaglandin E-2, glutathione, and NO in gastric tissue [149].

The bioactive compounds in garlic were also crucial in the protection of the digestive system. Allicin was demonstrated to inhibit the activation of the AP-1/NF-κB/signal transducer and activator of transcription-1 (STAT-1) by inhibiting the phosphorylation of p38, JNK, and the extracellular signal-regulated kinase 1/2 (ERK1/2)-regulated peroxisome proliferator-activated receptor (PPAR)-γ, which alleviated ulcerative colitis in mice [150]. DADS reduced interferon-inducible protein-10, IL-6, and DAS inhibited NO, as well as the expression of STAT-1 in interferon-γ-stimulated intestinal cells. Further, DAS and DADS improved the colitis induced by dinitrobenzenesulfonic acid in mice [70]. In addition, intake of raw garlic was shown to decrease bacterial urease activity and reduce Helicobacter pylori in the stomach of 15 patients [57].

In general, garlic and its bioactive compounds can improve gastrointestinal functions and alleviate colitis, gastric ulcers, and other gastrointestinal diseases by reducing oxidative stress, inhibiting inflammation, and decreasing Helicobacter pylori.

3.9. Anti-Diabetic Activity

Garlic has been shown to reduce pancreatic cell injury, oxidative stress, and pathological changes in streptomyacin-induced type 1 diabetic rats [151]. In addition, garlic had a protective effect on diabetic retinopathy in diabetic rats. The weight, blood glucose, and morphological changes of retinal tissue in the group treated with garlic improved after 7 weeks of gastric gavage of raw garlic extract in rats [152]. Moreover, AGE had a dose-dependent anti-diabetic effect on streptomyacin-induced diabetic rats [153]. Furthermore, a meta-analysis was performed on 768 patients with type 2 diabetes mellitus in nine randomized controlled trials, and the result showed that garlic supplements significantly reduced fructosamine and glycosylated hemoglobin. This study demonstrated that garlic supplements were effective in the management of type 2 diabetes mellitus [154]. Thus, garlic and its bioactive components might be effective agents to help treat diabetes and diabetic complications.

3.10. Anti-Obesity Activity

Garlic oil has anti-obesity properties and has been shown to counteract the influence of a high-fat diet on the weight of body and adipose tissue in hyperlipidemia rats [155]. In addition, the oral administration of LAFGE reduced the weight of high-fat diet male C57BL/6J mice. LAFGE also reduced their epididymal, retroperitoneal, and mesenteric adipose tissue mass. The possible mechanism of action was that LAFGE inhibited lipogenesis by down-regulating the mRNA and protein expression of PPAR-γ, C/EBPα, and lipogenic proteins [9]. Moreover, the methanolic extract of black garlic was found to reduce the weight of rats fed with a high-fat diet. This treatment regulated lipid metabolism by up-regulating the expression of AMPK, forkhead box protein O1, perilipin, and adiponectin in the adipose tissue of the rats and down-regulating the cluster of differentiation 36 (CD36), plasminogen activator inhibitor 1, resistin, and TNF-α [156].
Collectively, the studies demonstrate that fermented garlic products have certain positive effects on obesity by inhibiting lipogenesis and regulating lipid metabolism.

3.11. Neuroprotection

A study revealed that AGE and its carbohydrate derivative N-α-(1-deoxy-D-fructos-1-yl)-l-arginine alleviated neuroinflammation by inhibiting the production of NO and regulating the expression of multiple protein targets related to oxidative stress in lipopolysaccharide-activated murine BV-2 microglial cells [157]. In another study, the anti-neuritis activity of garlic was related to the organosulfur compounds in lipopolysaccharide-stimulated BV2 microglia cells [158]. The treatment of garlic during pregnancy and lactation was shown to decrease the concentration of Pb in the blood and brain and partially prevent the Pb-induced apoptosis of neurons during the hippocampal development in rats [159]. The Basso, Beattie, and Bresnahan (BBB) scoring system was used to conduct a neurological evaluation on the influence of AGE on a spinal cord I/R model of rats. Compared with the I/R group, the BBB score of the AGE group was markedly higher, thus demonstrating that AGE had a significant neuroprotective effect [160]. Additionally, AGE attenuated the loss of cholinergic neurons and enhanced the level of vesicular glutamate transporter 1 and glutamate decarboxylase in the hippocampal area of rats, which attenuated the damage of working memory [161]. Moreover, the ethanol extract of garlic was shown to improve memory. Garlic activated Na⁺/K⁺ ATPase, Ca²⁺ ATPase, and glutamine synthetase in the hippocampus of diabetic Wistar rats [162]. Furthermore, the ethanol extract of fermented garlic effectively prevented working memory via the damage induced by monosodium glutamate [163]. Z-ajoene was able to prevent I/R-induced delayed neuronal death and gliosis and reduce the lipid peroxidation in the CA1 region of the hippocampus [15]. Moreover, SAC ameliorated cognitive impairment in rats by reducing oxidative stress, neuroinflammation, astrogliosis, and acetylcholinesterase activity [164].

In conclusion, both in vivo and in vitro experiments showed that garlic has significant neuroprotective properties and mainly acts on the hippocampus. Organic sulfur compounds were shown to play a major role in neuroprotection.
Table 1. The biological activities of garlic and its active components.

| Product                        | Compounds         | Study Type     | Subjects/Cell Lines | Main Effects                                                                 | Possible Mechanisms                                                                 | Ref.  |
|--------------------------------|-------------------|----------------|--------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------|
|                                |                   |                |                    |                                                                              | Inducing the expression of several antioxidant enzymes, HO-1 and GCLM subunit, through Nrf2- ARE pathway |       |
| Aged garlic extract            |                   | In vitro       | Human endothelial cells | Protecting cells against oxidative stress                                   | Protecting cells against the growth inhibition and DNA damage induced by H$_2$O$_2$ | [43]  |
|                                | Saponins          | In vitro       | Mouse-derived C2C12 myoblasts | Scavenging intracellular reactive oxygen species |                                                                              | [44]  |
|                                | Ethyl linoleate   | In vitro       | Lipopolysaccharide-stimulated RAW 264.7 macrophages | Reducing the production of NO and prostaglandin E-2 Inhibiting the inflammatory mediators such as NO, TNF-α, and IL-1β | Down regulating the expression of iNOS and COX2 Inhibiting the transcription factor NF-κB signaling pathway Reducing the level of TNF-α and interleukin IL-1 receptor-associated kinase 4 Increasing the activity of AMPK in the liver | [45]  |
|                                | Garlic 14-kDa protein | In vitro       | Lipopolysaccharide-stimulated J774A.1 macrophages | Inhibiting the inflammatory mediators such as NO, TNF-α, and IL-1β | Inhibiting the transcription factor NF-κB signaling pathway Reducing the level of TNF-α and interleukin IL-1 receptor-associated kinase 4 Increasing the activity of AMPK in the liver | [46]  |
| Aged garlic extract            |                   | In vivo        | Apolipoprotein E-knockout mice | Inhibiting inflammation | Protecting against the inflammatory response induced by schistosome infection | [47]  |
|                                | Allicin           | In vivo        | BALB/c mice         |                                                                              |                                                                                     | [48]  |
| Garlic tablets (equal to 2.5 g fresh garlic daily) | Clinical trial | 40 post-menopausal obese or overweight patients | Alleviating osteoarthritis | Reducing resistin |                                                                                        | [49]  |
|                                | Garlic “Rosato” and “Caposele” | In vitro       | Aspergillus versicolor, Penicillium citrinum and Penicillium expansum | Inhibiting the growth of bacteria |                                                                                    | [53]  |
|                                | Aged garlic extract | Allicin        | Burkholderia cepacia | Inhibiting the growth of bacteria |                                                                                     | [54]  |
| Product            | Compounds         | Study Type | Subjects/Cell Lines                                      | Main Effects                                      | Possible Mechanisms                                                                 | Ref.    |
|--------------------|-------------------|------------|--------------------------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------------------|---------|
| Garlic oil         | In vitro          | *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* | Inhibiting the growth of bacteria                  | Penetrating into cells and organelles              | [50]                                             |         |
|                    | In vitro          | *Penicillium funiculosum* | Inhibiting the growth of bacteria                    | Destroying the cell structure                      | [55]                                             |         |
|                    | In vitro          | *Candida albicans*     | Disrupting the normal metabolism of bacteria         | Inducing key genes involved in oxidative phosphorylation, the cell cycle, and protein processing in the endoplasmic reticulum | [56]                                             |         |
| Raw garlic         | Clinical trial    | 15 patients with *H. pylori* infection | Inhibiting *Helicobacter pylori* in the stomach      |                                                   | [57]                                             |         |

**Modulating Immune System**

| Fresh garlic       | Polysaccharides/ Fructan | In vitro | RAW 264.7 macrophages | Exerting immunomodulatory effect                  | Regulating the expressions of IL-6, IL-10, TNF-α, and interferon-γ | [58] |
|--------------------|--------------------------|----------|----------------------|--------------------------------------------------|-------------------------------------------------------------------|---------|
|                    |                          |          |                      | Normalizing several immunological parameters of rats, such as the serum total immunoglobulin concentration and T-cell subtype CD4⁺ |                                                                   |         |
|                    | Garlic oil               | In vivo  | Wistar rats           | Combination of garlic oil and levamisole could balance the T-helper 1/ T-helper 2 response Promoting lymphocyte proliferation |                                                                   | [59,60]|
|                    | Selenizing garlic polysaccharides | In vivo | 14-day-old chickens  | Enhancing interferon-γ and IL-2 Increase the serum antibody titer Reducing the occurrence and severity of cold and flu |                                                                   | [61]   |
| Aged garlic extract| Clinical trial           | 56 healthy human participants | Improving the immune system functions              |                                                   |                                                                   | [8]     |
Table 1. Cont.

| Product                          | Compounds                        | Study Type | Subjects/Cell Lines | Main Effects                                           | Possible Mechanisms                                                                 | Ref.     |
|----------------------------------|----------------------------------|------------|---------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------|----------|
| Aged garlic extract              |                                  | In vitro   | Isolated rat aortic rings | Leading to endothelial-dependent vasodilation         | Stimulating the production of NO                                                   | [71]     |
|                                  |                                  |            |                      | Relaxing coronary arteries before and after ischemia-reperfusion in rat |                                                                                     |          |
| Aged black garlic extract        | Polyphenols                      | In vivo    | Isolated hearts of male Sprague–Dawley rats | Preventing the decrease of myocardial contractility |                                                                                     | [90]     |
|                                  |                                  |            |                      | Improving peripheral blood circulation                |                                                                                     |          |
| Aged garlic extract              | S-1-propylenecysteine            | In vivo    | Spontaneous hypertension rats | Reducing the systolic blood pressure                   |                                                                                     | [75]     |
| Fermented garlic extract by Bacillus subtilis |                                  | In vivo    | Spontaneous hypertension rats | Reducing the systolic blood pressure                   | Modulating the sGC-cGMP-PKG pathway                                               | [76]     |
|                                  |                                  |            |                      |                                                        | Decreasing the expression of vascular endothelial cell adhesion molecule-1 and MMP-9 |          |
|                                  |                                  |            |                      |                                                        | Increasing the expression of PKG and eNOS                                         |          |
| Garlic                           | Alliin                           | In vivo    | Female Wistar albino rats | Increasing the activity of captopril on inhibiting ACE and hypertension | Modulating the metabolism of lipid and cholesterol                                  | [72]     |
| 1.5% black garlic extract        |                                  | In vivo    | High-fat diet-fed male Sprague–Dawley rats | Decreasing the levels of blood total lipids, triglyceride, and cholesterol | Reducing the mRNA expression of sterol regulatory element binding protein-1c | [80]     |
| Raw garlic                       | Allyl methyl sulfide/Allyl methyl sulfoxide | In vivo | Male Sprague–Dawley rats | Reduce cardiac hypertrophy remodeling induced by isoproterenol | Increasing Na⁺/K⁺-ATPase protein level                                             | [83]     |
| Raw garlic                       |                                  | In vivo    | Streptomycin-induced diabetic rats | Protecting the heart function Activating sirtuin 3-manganese superoxide dismutase pathway | Deacetylating manganese superoxide dismutase                                     | [84]     |
| Product                          | Compounds                        | Study Type | Subjects/Cell Lines                        | Main Effects                                                                 |
|---------------------------------|----------------------------------|------------|-------------------------------------------|-------------------------------------------------------------------------------|
| Garlic extract                  | In vivo                          | Rat model of gentamicin-induced chronic renal failure | Protecting the heart tissue                                                  | Reducing oxidative stress, controlling Na⁺/K⁺-ATPase activity and Ca²⁺ levels  |
| Aged garlic extract             | SAC                              | In vivo    | Rats with myocardial dysfunction induced by isoproterenol | Protecting against cardiotoxicity                                             | Reducing serum level of C-reactive protein and thromboxane B-2, protein level of TNF-α and IL-1 receptor-associated kinase 4 |
| High temperature and high pressure-processed garlic | In vivo                          | High-cholesterol diet-fed Sprague–Dawley rats | Inhibiting the vascular inflammation and lipid deposition in the early stage of atherosclerosis development | Decreasing the level of cholesterol and low-density lipoprotein cholesterol and triglyceride |
| Garlic                          | Cohort study                     | 30 patients with diabetic dyslipidemia | Decreasing the level of cholesterol and low-density lipoprotein               | Increasing the level of high-density lipoprotein                             |
| Aged garlic                     | Clinical trial                   | 41 patients with hypercholesterolemia | Reducing the activity of myeloperoxidase and lipid hydroperoxide in serum | Decreasing the concentration of F2-isoprostanes in plasma and urine           |
| Enzymatic browning processed garlic | Clinical trial | 44 patients with hypertension | Reducing systolic blood pressure and diastolic blood pressure                |                                                                               |
| Product          | Compounds                  | Study Type | Subjects/Cell Lines                                                                 | Main Effects                                                                                     | Possible Mechanisms                                                                 | Ref.  |
|------------------|----------------------------|------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------|
| **Anticancer Activity** |                            |            |                                                                                     |                                                                                                |                                                                                                                                          |       |
| Garlic extract   | In vitro                   |            | Bladder cancer EJ cells                                                             | Inducing G2/M-phase cell cycle arrest                                                           | Activating the ATM pathway and CHK2; Inhibiting the expression of MMP-9               | [113] |
|                  |                            |            |                                                                                     | Inhibiting cell growth                                                                          | Reducing the binding activity of transcription factors AP-1, specificity protein-1 and NF-κB motifs |       |
|                  |                            |            |                                                                                     | Inhibiting cell migration and invasion                                                           | Increasing the expression of heat shock protein A6                                     |       |
|                  |                            |            | Colorectal cancer cell lines (SW480 and SW620)                                       | Decreasing invasive activity                                                                    | Inhibiting cell motility                                                              | [124] |
|                  |                            |            | ECV304 cells and the transformed rat lung endothelial cells                         | Inhibiting cell proliferation                                                                  | Down regulating the expression of cyclin B1 and CDK1                                |       |
|                  |                            | In vitro   | DLD-1 human colon cancer cells (ATCC CCL-221)                                       | Inhibiting cell proliferation                                                                  | Inhibiting of activation of NF-κB                                                      | [121] |
| Aged garlic extract |                            |            |                                                                                     |                                                                                                |                                                                                                                                          |       |
| Crude garlic extract | Lipid bioactive compounds  | In vitro   | Human liver cancer (Hep-G2)                                                          | Inhibiting the growth rate of Hep-G2, PC-3, MCF-7, and TIB-71 cells by 80%–90% at 72 h (P < 0.05). | Inhibiting cell proliferation                                                                                                         | [112] |
|                  |                            |            | Colon cancer (Caco-2)                                                                |                                                                                                |                                                                                                                                          |       |
|                  |                            |            | Prostate cancer (PC-3)                                                              |                                                                                                |                                                                                                                                          |       |
|                  |                            |            | Breast cancer (MCF-7)                                                               |                                                                                                |                                                                                                                                          |       |
|                  |                            |            | Mouse macrophage cell (TIB-71) lines                                                |                                                                                                |                                                                                                                                          |       |
| Allicin          | In vitro                   |            | Human gastric adenocarcinoma cell line                                               | Inhibiting cell proliferation                                                                  | Inducing cell cycle arrest at S-phase                                               | [18]  |
| DATS             | In vitro                   |            | Human gastric carcinoma cell line (SGC-7901)                                        | Inhibiting cell proliferation                                                                  | Accumulating Bax, p53, and cytochrome C and decreasing the expression of Bcl-2     | [114] |
|                  |                            |            | Human breast cancer cell line (MDA-MB-231)                                          | Blocking cell cycle                                                                             | Increasing apoptotic cell death                                                       |       |
|                  |                            |            | Glioblastoma multiforme cells                                                        | Inhibiting angiogenesis                                                                         |                                                                                                                                   |       |
|                  |                            |            |                                                                                     | Inhibiting the growth of the cancer stem cells population                                       |                                                                                                                                   |       |

**Table 1. Cont.**
| Product                        | Study Type | Subjects/Cell Lines                           | Main Effects                          | Possible Mechanisms                                                                 | Ref.  |
|-------------------------------|------------|-----------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------------|-------|
| In vitro Human breast cancer cells (MDA-MB-231) | In vitro  | Inhibiting cell growth                        | Targeting the folding of proteins in the endoplasmic reticulum of cancer cells Decreasing the expression of pro-caspase-3, Parp-1 Bcl-2 and increasing active caspase-3 and Bax | [120] |
| SAC                           | In vitro  | Inducing cell apoptosis                       | Reducing the expression of Wnt5a, phosphorylation protein kinase B and c-Jun proteins | [115] |
| SPRC                          | In vitro  | Inhibiting cell proliferation                 | Inducing G1/S-phase cell cycle arrest  | Regulating the level of JNK protein factor | [116] |
| SAMC                          | In vitro  | Inducing apoptosis                            | Inducing G2/M-phase cell cycle arrest  | Regulating JNK and p38 MAPK pathways | [118] |
| Alliin                        | In vitro  | Regulating cell apoptosis                     | Generating reactive oxygen species     | Decreasing mitochondrial membrane potential by Bax/Bcl-2 | [117] |
| Aged garlic extract           | In vivo    | Improving the renal histological, ultrastructural and biochemical changes, such as hemorrhage, glomerular atrophy, tubular necrosis and degeneration | Increasing the ratio of CD11b⁺/CD3⁺⁺⁺ Producing interferon-γ in splenocytes Inhibiting the expression of vascular endothelial growth factor Increasing interferon-γ, IL-2, and IL-4 levels | [128] [131] [126] |
| Garlic and lemon aqueous extract | In vivo    | Improving the immune responses of mice to fibrosarcoma Reducing tumor size | Activating the immune system | [126] |
| Product                  | Compounds       | Study Type | Subjects/Cell Lines | Main Effects                                                                 | Possible Mechanisms                                                                 | Ref.  |
|-------------------------|-----------------|------------|--------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------|
| Allicin                 | In vivo         | Female Swiss albino mice | Alleviating liver injury induced by tamoxifen | Preventing colorectal tumorigenesis induced by azoxymethane and dextran sulfate | Regulating the expressions of MMP-9 and E-cadherin protein                          | [129] |
| DADS                    | In vivo         | FVB/N mice |                     | Inhibiting tumor growth                                                      | Reducing the nuclear localization of NF-κB                                           | [132] |
| DATS                    | In vivo         | Female BALB/c-nude mouse xenograft model of human gastric carcinoma SGC-7901 cells | Promoting tumor apoptosis | Regulating the level of JNK protein                                           | Interacting with the Wnt-pathway co-receptor LRP6 on the cell membrane              | [114] |
| SPRC                    | In vivo         | Mouse xenograft model of hepatoma HuH-7 cells | Inhibiting tumor growth       | Inhibiting tumor growth                                                      | Regulating the level of JNK protein                                           | [116] |
| SAMC                    | In vivo         | Mouse xenograft model of hepatoma HuH-7 cells | Up-regulating seven genes including AHR, ARNT, HIF1α, JUN, NFAM1, OSM and REL | Up-regulating seven genes including AHR, ARNT, HIF1α, JUN, NFAM1, OSM and REL        | Protecting effect on febrile neutropenia in lower-risk subgroup                   | [117] |
| Raw, crushed garlic     | Cohort study    | 17 volunteers from Beltsville, Maryland |                    | Up-regulating seven genes including AHR, ARNT, HIF1α, JUN, NFAM1, OSM and REL | Protecting effect on febrile neutropenia in lower-risk subgroup                   | [123] |
| Garlic extract          | Cohort study    | Patients who received chemotherapy for hematological malignancies | Protective effect on febrile neutropenia in lower-risk subgroup | Inhibiting apoptosis, lipid peroxidation, oxidative stress, and inflammation | Attenuating the liver damage induced by alloxan                              | [130] |
| Hepatoprotective Activity |                |            |                    | Inhibiting apoptosis, lipid peroxidation, oxidative stress, and inflammation | Attenuating the liver damage induced by alloxan                              | [136] |
| Black garlic extract    | In vitro        | Rat clone-9 hepatocytes |                    | Inhibiting apoptosis, lipid peroxidation, oxidative stress, and inflammation | Attenuating the liver damage induced by alloxan                              | [137] |
| Garlic extract          | In vivo         | Wistar rats |                    | Inhibiting apoptosis, lipid peroxidation, oxidative stress, and inflammation | Attenuating the liver damage induced by alloxan                              | [138] |
| Single clove garlic extract | In vivo        | Male rabbits | Protecting against CCl4-induced acute liver injury | Protecting against CCl4-induced acute liver injury | Protecting against CCl4-induced acute liver injury | [38]  |
| Product | Compounds | Study Type | Subjects/Cell Lines | Main Effects | Possible Mechanisms | Ref. |
|---------|-----------|------------|---------------------|--------------|---------------------|-----|
| LAFGE   | In vivo   | C57/BL6 J mice | Reducing the liver lipid level | Suppressing MAPK phosphorylation | [142] |
|         | In vivo   | rats       | Inhibiting liver cell apoptosis | Down regulating p53 | Enhancing the activities of hepatic antioxidant enzymes | [143] |
| Garlic oil | In vivo   | 1,3-Dichloro-2-propanol-treated rats | Protecting liver | Blocking metabolic activation of 1, 3-dichloro-2-propanol | [139] |
| DADS    | In vivo   | Wistar rats | Protecting mice from nonalcoholic fatty liver disease induced by long-term high-fat diet. | Increasing antioxidant activity by inhibiting the expression of cytochrome P450 2E1 | [141] |
| LAFGE   | Clinical trial | 36 adults with mildly high level of serum gamma-aminotransferase | Improving the levels of gamma-aminotransferase and alanine aminotransferase without adverse effects | | [144] |

**Digestive System Protection**

| Product | Study Type | Subjects | Main Effects | Ref. |
|---------|------------|----------|--------------|-----|
| Black garlic extract | In vitro | Small intestine | Stimulating gastrointestinal peristalsis | [146] |
| DADS DAS | In vitro | Interferon-γ-stimulated intestinal cells | Promoting gastrointestinal emptying and facilitates defecation. | [70] |
|         | In vivo   | Male ICR mice | Reducing interferon-inducible protein-10, IL-6 | Improving the colitis induced by dinitrobenzenesulfonic acid | [70] |
Table 1. Cont.

| Product                  | Compounds             | Study Type     | Subjects/Cell Lines | Main Effects                                                                 | Possible Mechanisms                                                                 | Ref.  |
|-------------------------|-----------------------|----------------|--------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------|
| Garlic and cabbage      | In vivo Sprague–Dawley rats | Reducing the length of gastric ulcer, the total gastric acid, gastric juice volume, total bacteria count, and histopathological changes caused by aspirin | Improving the pH value of gastric juice                                         | Healing the gastric mucosal injury induced by indomethacin                            | [147] |
| extract                 | In vivo Male albino rats | Reducing the total microbial amount in stomach             |                                                                  | Releasing the oxidative stress                                                                                       | [148] |
| Aged garlic extract     | In vivo Male Wistar rats | Preventing the indomethacin-induced ulcer                  |                                                                  | Elevating the level of prostaglandin E-2, glutathione, and NO in gastric tissue                                    | [149] |
|                         | In vivo Dextran sulfate sodium-induced colitis mice | Alleviating the ulcerative colitis induced by dextran sulfate sodium |                                                                  | Inhibiting the phosphorylation of p38, JNK, and extracellular signal-regulated kinase 1/2- regulated PPAR-γ | [150] |
| Allicin                 | In vivo Dextran sulfate sodium-induced colitis mice | Reducing the bacterial urease activity Reducing the residing of Helicobacter pylori in the stomach |                                                                  | Inhibiting the activation of AP-1/NF-κB/signal transducer and activator of transcription-1 | \[150\] |
| Raw garlic              | Clinical trial 15 patients with H. pylori infection | Decreasing the bacterial urease activity Reducing the residing of Helicobacter pylori in the stomach |                                                                  |                                                                                                                                    | [57]  |

**Anti-Diabetic Activity**

| Garlic                  | In vivo Diabetic rats | Protecting against diabetic retinopathy Improving weight, blood glucose, and morphological changes of retinal tissue |                                                                                      |                                                                                                                                    | [152] |
|                        | Clinical trial 768 patients with type 2 diabetes mellitus | Reducing fructosamine and glycosylated hemoglobin |                                                                                                                                    |                                                                                                                                    | [154] |
Table 1. Cont.

| Product                     | Compounds       | Study Type  | Subjects/Cell Lines                  | Main Effects                                                                 | Possible Mechanisms                                                                 | Ref. |
|-----------------------------|-----------------|-------------|--------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------|
| *Anti-Obesity Activity*     |                 |             |                                      |                                                                               |                                                                                    |      |
| LAFGE                       | In vivo         | High-fat diet-fed male C57BL/6J mice | Reducing the weight               | Reducing the epididymal, retroperitoneal, and mesenteric adipose tissue mass   | Inhibiting the lipogenesis by down-regulating the mRNA and protein expression of PPAR-γ, C/EBPα, and lipogenic proteins | [9]  |
| Methanolic extract of black garlic | In vivo       | High-fat diet-fed male Wistar rats | Reducing the weight               | Regulating lipid metabolism                                                  | Upregulating the expression of AMPK, forkhead box protein O1, perilipin, and adiponectin in the adipose tissue | [156]|
| Garlic oil                  | In vivo         | High-fat diet-fed male Sprague–Dawley rats | Counteracting the influence of high-fat diet on the body weight and adipose tissue weight |                                                                             | Down-regulating cluster of differentiation 36, plasminogen activator inhibitor 1, resistin, and TNF-α |      |
| *Neuroprotection*           |                 |             |                                      |                                                                               |                                                                                    |      |
| Aged garlic extract         | FruArg          | In vitro    | Lipopolysaccharide-activated murine BV-2 microglial cells | Alleviating neuroinflammation                                                | Inhibiting the production of NO                                                  | [157]|
| Garlic extract              | In vivo         | Female Wistar rats | Preventing the Pb-induced apoptosis of neurons |                                                                               | Regulating the expression of multiple protein targets related to oxidative stress |      |
| Aged garlic extract         | In vivo         | Adult male Wistar rats | Attenuating the damage of working memory |                                                                               | Improving the loss of cholinergic neurons                                           | [161]|
| Ethanol extract of garlic   | In vivo         | Diabetic Wistar rats | Improving memory                     |                                                                               | Increasing the activity of Na⁺/K⁺ ATPase, Ca²⁺ ATPase, and glutamine synthetase in the hippocampus | [162]|
|                            |                 |             |                                      |                                                                               |                                                                                    |      |
| Product | Compounds | Study Type | Subjects/Cell Lines | Main Effects | Possible Mechanisms | Ref. |
|---------|-----------|------------|---------------------|--------------|---------------------|-----|
| Z-ajoene | In vivo | Male gerbils | Preventing I/R-induced delayed neuronal death and gliosis region of the hippocampus | Reducing lipid peroxidation in the CA1 | [15] |
| SAC | In vivo | Male albino Wistar rats | Ameliorating the cognitive impairment | Reducing oxidative stress, neuroinflammation, astrogliosis, and acetylcholinesterase activity | [164] |
| **Renal Protection** | | | | | |
| Aqueous extract of garlic | In vivo | Type 1 diabetic rats | Reducing the oxidative stress in the kidneys | | [165] |
| | In vivo | Wistar rats | Improving the renal plasma biochemical factors induced by alloxan | | [137] |
| DATS | In vivo | Male albino rats | Protecting the kidney from oxidative stress injury induced by As | Activating the Nrf2-ARE pathway | [166] |

Abbreviations: ACE, angiotensin-converting enzyme; AHR, aryl hydrocarbon receptor; allicin, diallyl thiosulfonate; alliin, S-allyl-cysteine sulfoxide; AMPK, adenosine monophosphate-activated protein kinase; AP-1, activator protein 1; ARE, antioxidant response element; ARNT, aryl hydrocarbon receptor nuclear translocator; ATM, ataxia-telangiectasia mutated; Bax, Bcl-2 associated X; Bcl-2, B cell lymphoma-2; CDK1, cyclin-dependent kinase 1; cGMP, cyclic guanosine monophosphate; CHK2, checkpoint kinase 2; COX2, cyclooxygenase-2; DADS, diallyl disulfide; DAS, diallyl sulfide; DATS, diallyl trisulfide; eNOS, endothelial nitric oxide synthase; FruArg, N-α-(1-deoxy-D-fructos-1-yl)-l-arginine; GCLM, glutamate-cysteine ligase modifier; HIF1A, hypoxia-inducible factor 1α; HO-1, heme oxygenase-1; IL, interleukin; iNOS, inducible NO synthase; JNK, Jun N-terminal kinase; JUN, proto-oncogene c-Jun; LAFGE, fermented garlic extract by Lactobacillus plantarum BL2; MMP-9, matrix metalloproteinase-9; NFAM1, nuclear factor of activated T cells (NFAT) activating protein with immunoreceptor tyrosine-based activation motif 1; NOS, nitric oxide; Nrf2, nuclear factor erythroid-2-related factor 2; ASTM, oncostatin M; PARP-1, poly-(ADP-ribose)polymerase-1; PKG, protein kinases G; PPAR-γ, peroxisome proliferator-activated receptor-γ; p38 MAPK, p38 mitogen activated protein kinase; REL, V-relavian reticuloendotheliosis viral oncogene homolog; SAC, S-allyl-cysteine; sGC, soluble guanylyl cyclase; SAMC, S-allylmercaptocysteine; SPRC, S-propargyl-l-cysteine; STAT-1, signal transducer and activator of transcription-1; TNF-α, tumor necrosis factor-α; Wnt5a, wingless-type MMTV integration site family member 5A.
3.12. Renal Protection

Garlic was shown to effectively alleviate nephrotoxicity [10]. The aqueous extract of garlic was shown to reduce the oxidative stress in the kidneys of diabetic rats [165]. In addition, the aqueous extract of garlic improved the renal plasma biochemical factors induced by alloxan in Wistar rats [137]. Moreover, DATS was reported to activate the Nrf2-ARE pathway, protecting the kidney from oxidative stress injury induced by arsenic in rats [166].

4. Conclusions

Garlic is a widely consumed spice with a characteristic odor. It contains many bioactive components, such as organic sulfides, saponins, phenolic compounds, and polysaccharides. The organic sulfides, such as allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allyl-cysteine, are major bioactive components in garlic. Garlic and its bioactive components show many biological functions, such as antioxidant, anti-inflammatory, immunomodulatory, cardiovascular protective, anticancer, hepatoprotective, digestive system protective, anti-diabetic, anti-obesity, neuroprotective, renal protective, antibacterial, and antifungal activities. Generally, garlic is non-toxic or has low toxicity. Therefore, garlic and its bioactive compounds are promising as functional foods or nutraceuticals for the prevention and treatment of different diseases. In the future, more biological functions of garlic should be evaluated, and the relative compounds of garlic need to be separated and identified. More investigations should be conducted to deeply illustrate garlic’s mechanisms of action. In addition, the effects of the processing, such as fermentation and heat, on garlic should be further studied because they could impact the biological functions and safety of garlic. Furthermore, more clinic trials should be carried out to confirm the health benefits of garlic on humans, and special attention should be paid to the side effects/safety of garlic.

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