Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-1 || February 2024 || PP. 147-153

https://doi.org/10.55544/jrasb.3.1.24

Biological Benefits of Diallyl Disulfide, A Garlic-Derived Natural Organic Sulfur Compound

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www.jrasb.com || Vol. 3 No. 1 (2024): February Issue

Received: 05-02-2024	**Revised:** 14-02-2024	**Accepted:** 23-02-2024

ABSTRACT

There is a possibility that diallyl disulfide and diallyl trisulfide can alleviate neuropathic pain in rats that have been subjected to CCI. The mechanisms by which these compounds alleviate pain entail an increase in the levels of H2S, BDNF, and Nrf2 in the sciatic nerve and the dorsal root ganglion (DRG). The use of garlic as a functional food and as a great source of pharmacologically active compounds is widely recognised and generally accepted. One of the most important bioactive components of garlic is called diallyl disulfide (DADS), and it possesses a number of beneficial biological effects. These capabilities include anti-inflammatory, antioxidant, antibacterial, cardiovascular protective, neuroprotective, and anticancer actions. In this review, the biological roles of DADS were reviewed in a systematic manner, and the molecular mechanisms that underlie these functions were explored. We have high hopes that this review will not only offer direction and insight into the existing body of literature, but will also make it possible for future study and the development of DADS for the intervention and treatment of other disorders.

Keywords- DADS, Garlic, Extract, Chemical Compounds.

I. INTRODUCTION

The components that are discovered in plants that are pharmacologically active are of the highest quality. The traditional use of garlic as a medication and functional food has acquired universal support for the treatment and prevention of a variety of disorders, including cancer and infectious diseases [1-4]. Garlic has been used for medicine and functional food for centuries. In accordance with the prevalent idea, the majority of the biological benefits of garlic are attributed to the organic sulphur compounds that it contains [5]. The diallyl disulfide (DADS) chemical is considered to be one of the most significant organosulfur compounds found in garlic. Its molecular formula consists of two sulphur atoms that are connected to two allyl groups (shown in Figure 1) [6, 7]. It has been proven through research that DADS serves a variety of biological goals, some of which include anti-

ISSN: 2583-4053
Volume-3 Issue-1 || February 2024 || PP. 147-153
https://doi.org/10.55544/jrasb.3.1.24

inflammatory, antioxidant, anticancer, and detoxifying properties [4, 7-9]. Previous assessments have brought to light the potential advantages of DADS for a number of diseases, both in terms of disease prevention and disease treatment themselves [6]. In this work, we undertook a complete examination of the biological roles of DADS based on cellular and molecular processes with the intention of giving a more contemporary scientific foundation and insight for future research. Our goal was to provide both knowledge and insight for future research.

Fig: 1 Chemical Structure of DADS

II. METHODOLOGY

We conducted a search for the existing literature on DADS in PubMed, Web of Science, and Green Medical up until February 2024 across these three databases. In addition, we looked for possibly pertinent clinical studies by searching the International Clinical studies Registry Platform as well as ClinicalTrials.gov. For the purpose of creating a supplement, references of the papers and reviews that were included were carefully searched.

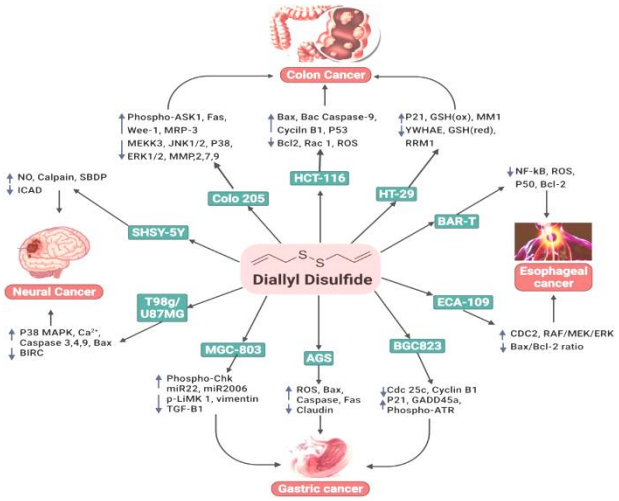

Fig: 2 The anticancer activity of DADS with respect to colon cancer, esophageal cancer, gastric cancer, and neural cancer.

Biological function of DADS

Anti- inflammatory Activity

In this work, the injection of DADS resulted in a reduction and downregulation of TNF-α, IL-1β, NO, iNOS, COX-2, and PGE2, thereby confirming its anti-inflammatory effect against the carrageenan-induced acute inflammatory response in paw tissue. This impact was further proven by increasing the level of IL-10, deactivating NF-κB, and suppressing migration and infiltration of leucocytes and macrophage-derived chemokines. This was demonstrated by the downregulation of MCP-1 level and expression, as well as the suppression of MPO activity. We make the assumption that the decreasing levels of NO could be attributed to the downregulation of iNOS and COX-2, while the lowered levels of proinflammatory mediators might be attributed to the inactivation of NF-κB. It has been claimed that DADS possesses anti-inflammatory properties in a variety of experimental designs. The findings of Chen et al. [7] demonstrated that DADS supplementation has the potential to be utilised as an alternative therapy for the treatment of rheumatoid arthritis. This is accomplished by lowering the volume of the paw and inhibiting the generation of proinflammatory mediators. Following exposure to carbon tetrachloride, it was discovered that DADS is capable of lowering the levels of iNOS mRNA and protein [8]. Furthermore, the injection of DADS was found to protect the stomach mucosa from alcohol-induced acute inflammation by lowering levels of TNF-α and IL-6, in addition to downregulating iNOS [9]. Furthermore, it was observed that DADS exhibited anti-inflammatory properties against cerulein-mediated pancreatic inflammation and the associated pulmonary deficits. This was achieved by inhibiting the production of TNF-α, cystathionine-γ-lyase, preprotachykinin A, neurokinin-1-receptor expression, and hydrogen sulphide. Additionally, it was observed that DADS also inhibited the degradation of I-κB and NF-κB expression and translocation in both the pancreatic and pulmonary tissue [10]. In the same setting, DADS was found to have an anti-inflammatory impact by blocking the NF-κB signalling cascade and quenching reactive oxygen species (ROS) in human Barrett's epithelial cells [11]. It has been shown that DADS has the ability to prevent the formation of colorectal tumours by inhibiting inflammation. This function is mostly accomplished by the regulation of GSK-3β and the inhibition of NF-κB nuclear translocation [12]. In an earlier investigation, it was revealed that the treatment of DADS had a substantial effect on suppressing NO and PGE2 levels, which were related with the downexpression of iNOS and COX-2. Additionally, the administration of DADS decreased the amount and regulation of TNF-α, IL-1β, and MCP-1 in BV2 microglia that were stimulated by lipopolysaccharide (LPS) [13].

The oxidative challenge in the skin tissue was amplified by the injection of carrageenan, as evidenced by an increase in MDA and a decrease in GSH content. According to a number of studies [14], carrageenan has the ability to stimulate the generation of free radicals, such as superoxide anions, hydrogen peroxides, nitric oxide, and its cytotoxic derivative. It has been discovered that the creation of MDA in pathophysiological situations is connected with inflammatory and oxidative responses [15]. This formation is a reflection of the oxidation of membrane lipids that occurs after the production of free radicals. There is a correlation between the consumption of glutathione (GSH) and the development of lipid

ISSN: 2583-4053
Volume-3 Issue-1 || February 2024 || PP. 147-153
https://doi.org/10.55544/jrasb.3.1.24

peroxidation and further oxidative stress. GSH is the first antioxidant defence line against free radicals it is responsible for protecting against. In order to treat or reduce the paw edoema that is caused by carrageenan, it is possible to use antioxidant molecules that have the ability to suppress lipid peroxidation and downregulate Nos2. The administration of DADS was able to successfully ameliorate the redox homeostasis in response to the oxidative damage caused by carrageenan in the skin tissue. This was demonstrated by the increased GSH content and the inhibition of MDA. In agreement with these findings, Liu et al. [16] revealed that DADS decreased the oxidative damage in an emphysema model in rodents by preventing lipid peroxidation and boosting the endogenous antioxidant defence molecules. This was accomplished by blocking lipid peroxidation from occurring. Furthermore, DADS was able to inhibit the progression of oxidative insults in the liver tissue following ethanol intoxication by reducing the activity of free radicals and increasing the activity of Nrf2/HO-1 [17].

III. ANTI-OXIDANT ACTIVITY

Garlic has been shown to have anti-proliferative properties against a variety of cancers, according to a quantity of research that has been accumulated in recent years. [18] There are sulphur compounds in garlic that are both water-soluble and oil-soluble by nature. The effectiveness of oil-soluble chemicals in preventing cancer is superior to that of water-soluble compounds. Examples of oil-soluble compounds include diallyl sulphide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and ajoene. A significant organosulfur molecule that is generated from garlic, known as DADS, has the ability to reduce the number of cancers that are caused by carcinogens in experimental animals and to prevent the proliferation of a variety of cancer cell types.[19] Among its mechanisms of action are the following: the activation of metabolising enzymes that detoxify carcinogens; the suppression of the formation of DNA adducts; the effects of antioxidants; the regulation of cell-cycle arrest; the induction of apoptosis and differentiation; the modification of histones; and the inhibition of angiogenesis and invasion[20].

Anti microbial Activity

Garlic extracts are known to include a chemical called DATS, which is known to occur naturally. The results of this investigation indicated that DATS have antibacterial efficacy against C. jejuni infections. Both the phenotypical and transcriptional levels were utilised in order to investigate the mechanisms underlying the antibacterial effect[21]. We made the observation that DATS had the ability to destroy the bacterial cell membrane and reduce the activity of the transporter system that is found in the bacterial membrane. In addition to this, we found that the number of C. jejuni cells decreased when the DATS therapy was administered in vivo. According to the findings of our study, DATS has the potential to serve as an alternative natural component that can be utilised to combat C. jejuni in beef products. It is necessary to do additional research in order to acquire a better understanding of the entire mechanism behind the antibacterial actions of DATS against infections[22].

Antifungal Activity

Garlic essential oil (EO) was investigated for its toxicity against T. hirsuta and L. sulphureus in the current study. The IC50 value for garlic EO was determined to be 137.3 μg/mL for T. hirsuta and 44.6 μg/mL for L. sulphureus. Xie et al. [23] conducted an evaluation of the antifungal activity of O. vulgare essential oil against T. hirsuta (IC50 = 79.1 μg/mL) and L. sulphureus (IC50 = 36.9 μg/mL). These results are in agreement with the findings of the aforementioned researchers. The inhibitory effect of S. aromaticum essential oil on T. hirsuta was reported by Xie et al. [24], with an IC50 value of 124.9 μg/mL. Both of these findings are similar. Cinnamomum osmophloeum essential oil (EO) shown considerable antifungal activity against L. sulphureus at a concentration of 200 μg/mL, as reported in previous studies [24,25]. Additionally, the results of our study proved that diallyl disulfide and diallyl trisulfide had antifungal efficacy against the fungi that cause wood decay, specifically T. hirsuta and L. sulphureus. An investigation conducted by Cheng et al. [27] shown that α-cadinol exhibited bioactivity against L. sulphureus, with IC50 values of 9.9 μg/mL. In their study, Cheng et al. [28] provided evidence that cinnamaldehyde (IC50 = 35.3 μg/mL) and eugenol (IC50 = 62.9 μg/mL) exhibited bioactivity against L. sulphureus. Additionally, Xie et al. [29] provided evidence that the IC50 value of eugenol against T. hirsuta was determined to be 83.6 μg/mL. Carvacrol was found to possess bioactivity against T. hirsuta (IC50 = 33.6 μg/mL) and L. sulphureus (IC50 = 17.2 μg/mL) in a different research conducted by Xie et al. [30]. Geranial demonstrated antifungal efficacy specifically against T. hirsuta, with an IC50 value of 56.6 μg/mL, and L. sulphureus, with an IC50 value of 33.3 μg/mL [31]. Based on the findings of this investigation, it was determined that the essential oil of garlic possesses effective antifungal properties.

The findings of our study indicated that diallyl trisulfide exhibited a more potent antifungal activity against T. hirsuta (IC50 = 56.1 μg/mL) and L. sulphureus (IC50 = 31.6 μg/mL) than diallyl disulfide did against T. hirsuta (IC50 = 116.2 μg/mL) and L. sulphureus (IC50 = 73.2 μg/mL). On the other hand, garlic essential oil (EO) exhibited IC50 values of 137.3 and 44.6 μg/mL for T. hirsuta and L. sulphureus, respectively. In addition, Huang et al. [33] and Zhao et al. [32] demonstrated that diallyl trisulfide is the fumigant component in garlic essential oil that poses the greatest threat. Based on these findings, it was determined that diallyl trisulfide could be responsible for the fumigant toxicity of garlic essential oil. In a previous study, Gándara-Ledezma and colleagues [34] shown that diallyl trisulfide exhibited inhibitory

ISSN: 2583-4053
Volume-3 Issue-1 || February 2024 || PP. 147-153
https://doi.org/10.55544/jrasb.3.1.24

action against B. cinerea that was significantly higher than that of diallyl disulfide. Furthermore, it has been extensively documented that diallyl trisulfide exhibits a high level of contact/fumigant toxicity against S. oryzae (LD50 = 6.2 μg/mg; LC50 = 8.4 mg/L), S. zeamais (LD50 = 5.54 μg/mg; LC50 = 6.32 mg/L), and T. castaneum (LD50 = 1.02 μg/mg; LC50 = 0.83 mg/L) [35]. Similar to the previous example, it has been demonstrated that diallyl trisulfide, which has a mortality rate of 100% when exposed to 0.125 μL/L for a period of 48 hours, is more hazardous to R. speratus than diallyl disulfide, which has a mortality rate of 33% when exposed to 0.125 μL/L for 48 hours [36]. The contact toxicity of diallyl trisulfide against Bursaphelenchus xylophilus was found to be significantly higher (LC50 of 2.79 μL/L) compared to diallyl disulfide (LC50 of 37.06 μL/L) throughout the study [37]. In accordance with the literatures that have been described, it has been found that diallyl trisulfide is more effective against C. chinensis than diallyl disulfide. Furthermore, the LD50 values of diallyl trisulfide and diallyl disulfide are 0.64 and 11.04 μg/adult, respectively [38]. The findings presented above suggest that the primary components of garlic essential oil, in particular diallyl trisulfide, have the potential to be effective in the management of pests [39].

Cardiovascular activity

Among the leading causes of death among diabetic patients, cardiovascular disease is one of the most crucial factors. There is a growing body of research that demonstrates that garlic possesses a wide range of biological actions, which may be attributed to its antioxidant potential. In this work, we evaluated the effects of garlic oil (GO) and its two principal components, diallyl disulfide (DADS) and diallyl trisulfide (DATS), on diabetic cardiomyopathy in rats. Specifically, we looked at how these components prevented the progression of the condition. The echocardiography technique was utilised in order to acquire physiological heart parameters.[40] Both TUNEL and DAPI labelling were utilised in order to inspect the apoptotic cells. The methodology of Western blotting was utilised in order to ascertain the amounts of protein expression. In diabetic rat hearts, our findings indicated that there was a significant decrease in the fractional shortening percentage, an increase in the levels of nitrotyrosine, an increase in the number of TUNEL-positive cells, an increase in the levels of caspase 3 expression, and a decrease in the activities of the PI3K-Akt signalling pathway[42]. Furthermore, all of these modifications were reversed after administration of both GO and DATS (or DADS). This was accomplished by raising the activity of the PI3K-Akt signalling pathway and decreasing both the death receptor-dependent and the mitochondria-dependent apoptotic pathways. Based on the findings of this study, it can be concluded that DATS and DADS, with DATS being more effective than DADS, had the potential to be used as therapeutic interventions for the treatment of diabetic cardiomyopathy. On top of that, the therapeutic effects of GO on diabetic cardiomyopathy ought to mostly originate from DATS and DADS[43].

Neuropathic Pain

Rats that were treated with diallyl disulfide and diallyl trisulfide did not experience any alteration of their H2S levels when a BDNF blocker was present. This finding lends credence to the notion that BDNF is the downstream mediator of H2S[44].To put it another way, diallyl disulfide and diallyl trisulfide have the potential to raise the levels of hydrogen sulphide, which might ultimately lead to an increase in the expression of BDNF, which would then be followed by an increase in Nrf2, which would decrease neuropathic pain relief. This claim is backed by reports of research that have been published in the past and suggest that an increase in H2S levels may contribute to an increase in the expression of BDNF, which in turn has protective effects [45]. Therefore, it is possible to postulate that diallyl disulfide and diallyl trisulfide may cause an increase in the production of hydrogen sulphide, which would then be followed by an increase in the expression of BDNF and Nrf2 in the sciatic nerve and the dorsal root ganglion (DRG) in order to alleviate neuropathic pain in rats that have been subjected to chronic constriction. To demonstrate the direct connection between H2S, BDNF, and Nrf2 in a signalling cascade that involves diallyl disulfide and diallyl trisulfide, on the other hand, additional tests are necessary to demonstrate the pain-reducing effects of these two compounds. It has also been shown that diallyl disulfide can activate the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) [46]. The activation of this receptor is believed to reduce the neuropathic pain that is caused by chemotherapy [47]. In light of this, it is feasible that future research will investigate the potential role of PGC-1α in the pain-reducing effects of organosulfur compounds in nerve-injury-induced neuropathic pain cases. There is a possibility that diallyl disulfide and diallyl trisulfide can alleviate neuropathic pain in rats that have been subjected to CCI. The mechanisms by which these compounds alleviate pain entail an increase in the levels of H2S, BDNF, and Nrf2 in the sciatic nerve and the dorsal root ganglion (DRG)[49,50]

IV. CONCLUSION

Garlic (*Allium sativum*) has been used as a raw material in medicine and pharmacy for several centuries. This raw material contains many biologically active substances that have a wide range of pharmacological effects and are confirmed by various methods of analysis. This review presents numerous phytochemical and pharmacological studies, and various methods for obtaining garlic extract, the following biologically active substances have been identified in these extracts: alliin, allicin, allyl sulfide, DAS, DADS, DATS, 1,2-vinyldithiin, ajeons, etc. These biologically active

ISSN: 2583-4053

Volume-3 Issue-1 || February 2024 || PP. 147-153

https://doi.org/10.55544/jrasb.3.1.24

substances have the following pharmacological effects: antioxidant, anticancer, antimicrobial, antiviral, cardiovascular protection, antidiabetic, antibacterial, and immunomodulatory effects.

As a result of research and review of literature data, it was revealed that the chemical composition and pharmacological effects of local garlic have not been studied in Kazakhstan. This raw material can become a good raw material base for the production of medicines. A large number of analyses were studied to determine the chemical composition, bioactive substances, and conditions affecting the phytochemical profile of garlic to fully illustrate the content of plant raw materials and to identify prospects for further research.

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