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ORGANO-SULFUR COMPOUNDS OF GARLIC OIL: PROMISING THERAPEUTIC POTENTIAL

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ABSTRACT

Garlic (*Allium sativum*) is a plant of the family *Allium* and it has been using as a potential medicinal herb for prevention and treatment of inflammation, gastro-intestinal disorders, microbial infections, hypertension and many other health disorders. This review is aimed to highlight the therapeutic effects of different organosulfur compounds (OSCs) derived from *Allium sativum*. OSCs of garlic oil are allicin and its derivatives like allyl sulfide, diallyl disulfide, diallyl trisulfide, E-ajoene, Z-ajoene, etc. The phyto-chemicals derived from *Allium sativum* possess therapeutic health benefits such as, anti-diabetic, anti-inflammatory, anti-bacterial, anti-fungal, anti-viral, protective role against cardiovascular diseases, hypotensive, hypo-cholesterolemic even anti-tumor, anticancer, and antimetastatic without contributing any harmful side effect.

KEYWORDS: Garlic, Organo-sulfur compounds, Phyto-medicine, Therapeutic uses.

INTRODUCTION

Modern science has found phyto-medicines from nature that can detoxify environmental toxicants and they treat, prevent, and retard diseases; most importantly avoid potential adverse effects of conventional medicines. Garlic (*Allium sativum*) has a significant therapeutic history of 5000 years. The use of garlic is multiple. It is used differently in different cultures, such as in intact form, natural extracts, powder with its unique flavour, the aroma in our food, and also as an effective medicinal herb (Ariga and Seki, 2006; O'Gara et al., 2000; Simon,2020). Garlic contains about 0.1 percent of essential oil. Major active phyto-chemicals of garlic oil are organo-sulfur compounds (OSCs). These organo-sulfur compounds (OSCs) with beneficial medicinal values have a high consideration worldwide (Simon, 2020; Daka, 2011; Bhandari, 2012; Encyclopaedia Britannica, 1998) and have currently drawn the attention of investigators as competent therapeutic agents in the different diseases. Among the leading global human health problems, diabetes mellitus, hypertension, cardiovascular diseases, cancer and different microbial infections are important. Constituents of garlic extract have always been seriously investigated for their disease preventive capabilities (Chidinma et al., 2019).

Bioactive compounds of garlic

Diverse bioactive compounds are present in garlic and these are organosulfur compounds, phenolic compounds, saponins, and polysaccharides (Shang et al., 2019). The organosulfur compounds (OSCs) of garlic oil are major active components of garlic (Figure 1) and these are diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), diallyl-thiosulfonate (allicin), S-allyl-cysteine (SAC), S-allyl-cysteine sulfoxide (alliin) and E/Z-ajoene (Yoo et al., 2014; Kodera et al., 2017; Yoo et al., 2014; Mansingh et al., 2018). OSCs in cooked garlic have lower digestibility than those in raw garlic (Torres-Palazzolo et al., 2018).

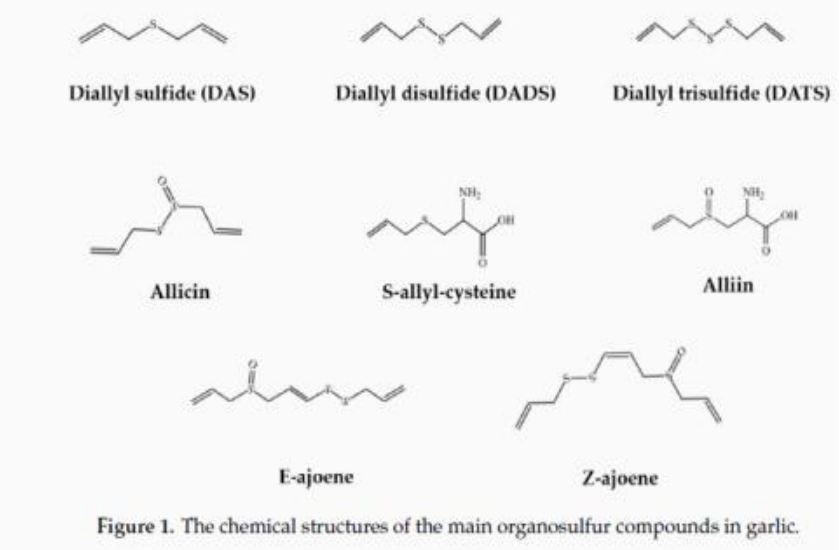

Figure 1. The chemical structures of the main organosulfur compounds in garlic.

Source: Shang A et al., Foods 2019, 8, 246; doi: 10.3390/foods8070246

Table 1: Organo-sulfur compounds (OSCs) found in Garlic oil and their solubility

Organo-sulfur Compound	Solvent
Alliin (S-allyl-cysteine sulphoxide)	Water
Allicin (Diallyl thiosulphate)	Water, mostly organic
Ajoene	Edible oils
Allyl-propyl disulphide	Diethyl ether/ chloroform
Allyl-methyl trisulphide	Alcohol
Diallyl sulphide (DAS)	Organic solvents
Diallyl disulphide (DADS)	Organic solvents
Diallyl trisulphide (DATS)	Acetone, ethanol, DMSO, DMF
Dithiins	DMSO
S-allyl marcaptocysteine	Water

Updates on the therapeutic uses of garlic oil organo-sulfur compounds

Extracts from garlic include many OSCs (mentioned in Figure 1), polyphenols, and carotenoids that possess protective properties against many disorders and diseases like oxidative stress, cancer, inflammation, immune-modulation, microbial, hypo-glycemic, and cardiovascular (Viswanathan et al., 2014).

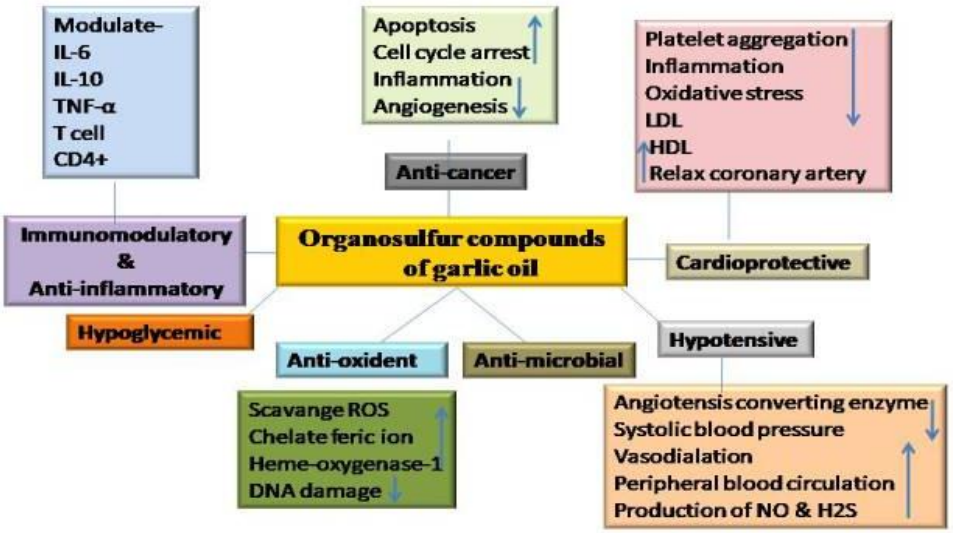

Figure 2: Therapeutic effects of OSCs of garlic oil.

Anti-oxidant properties

OSCs of garlic oil possess some important and beneficial health effects. They act as an exogenous antioxidant and help to neutralize free radicals by inhibiting Reactive Oxygen Species (ROS). Thus, they prevent oxidative stress-associated disorders (Gonzalez et al., 2012). Polyphenolic compounds of garlic oil also directly correlate with antioxidant activity *in vitro* (Nenciniet al., 2010). DADS and DATS, present in garlic oil are associated with increased antioxidant activity. They can donate hydrogen atoms to neutralize 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and break the free radical chain. Allylsulfide, a phenolic compound present in oil extracted from garlic is extremely effective in scavenging and reducing the harmful free radicals (Bae et al., 2014). Extracts of aged garlic induce several antioxidant enzymes (heme oxygenase-1, glutamate-cysteine ligase modifier subunit via nuclear factor erythroid-2 related factor 2-antioxidant response element pathway) expressions, which prevent oxidative stress and protect human endothelial cells (Liu et al., 2018). Saponin contents of garlic oil were also reported to scavenge intracellular ROS and efficiently inhibit hydrogen peroxide (H_2O_2)-induced DNA damage (Kang et al., 2016).

Hypo-glycemic properties

It is proven, that garlic extracts have hypo-glycemic influences. Components of garlic extract can significantly decrease fasting blood glucose in fructose-induced insulin resistance rats (Jalal et al., 2007). A model of streptozotocin (STZ)-induced diabetic rats *(*in *vivo* and *ex vivo*), observed by Liu et al., has shown that garlic oil treatment improved oral glucose and insulin tolerance in rats. Insulin-stimulated glucose utilization also improved in synthesizing skeletal muscle glycogen (Liu et al., 2005). Later, in another study with STZ-induced diabetic rats, they demonstrated the mechanism where they reported that garlic oil can elevate the expression of glucose transporter (GLUT4), and thus improve glucose tolerance, and insulin sensitivity. During this treatment, the antioxidant defence system was improved, and nitric oxide (NO) production was simultaneously reduced. Thus, the study results provide a scientific explanation for using garlic oil to improve insulin sensitivity in diabetes (Liu et al., 2012). Each garlic preparation, including garlic oil, has an acute hypo-glycemic effect. It may directly act upon stimulating insulin secretion from the pancreas or releasing it from the bound state (Jain, and Vyas, 1975). El-Demerdash et al. in 2005 also reported that garlic juice reduces blood glucose levels in alloxan-induced diabetic rats (El-Demerdash et al., 2005).

Immunomodulatory properties

The immune functions of living bodies are regulated by different intrinsic and extrinsic factors and diet also plays a key role in its proper functioning (Lin and Karin, 2007). OSCs of garlic are reported to inhibit the activity of nuclear factor κB (NF-κB), and the production of TNF-α, interleukin (IL)-1beta (IL-1β), and NO in different cell types (Aggarwal and Shishodia, 2004). These OSCs also show their affectivity (concentration-dependent) on the proliferation of (IL)-2 and interferon (INF)-γ gene expression of stimulated lymphocytes and that is (Hanieh, 2012). In an additive manner, components of garlic oil have direct and/or indirect stimulations on nitric oxide production in macrophages (Keisset al., 2003). OSCs like DATS, DADS, DAS and many others (mentioned in figure 1) can inhibit the master regulatory transcription factor NF-*κ*B, inhibiting the transcription of several cytokine genes (TNF-α, IL-1β, IL-6, IL-12, p70), and MCP-1) responsible for pro-inflammatory responses (Arreola et al., 2015). Regular dietary garlic consumption enhances T-cell proliferation which might have a direct/indirect effect on enhanced B-cell proliferation, and differentiation (Hanieh, 2010).

Anti-inflammatory properties

Extracts of garlic contain several biochemical OSCs that possess anti-inflammatory properties (Ban et al., 2012). During chronic inflammation, these OSCs contribute to the attenuation of the immunosuppressive environment. The downstream consequences are to assist the host in escaping tumor-mediated immune suppression followed by eliciting an anti-tumor immune response (Schäfer and Kaschula 2014). Treatment results with the application of garlic OSCs, found in garlic oil confirmed that they can remarkably slow down inflammation along with all the other infection-induced parameters such as nitric oxide syntheses (NOs), the cytokines IFN-γ, and IL-6; plasma levels of alanine, and aspartate amino transferases, alkaline phosphatase, γ-glutamyl transferase, total bilirubin, even the production of nitric oxide derived products (nitrite/nitrate), malon di-aldehyde, glutathione levels, activities of catalase, and superoxide dismutase. Data indicate that garlic can counteract the loss of glutathione, and the activities of catalase, and superoxide dismutase (Dkhil et al., 2011). Alliin is an OSC usually present in unprocessed garlic cloves is catalyzed to allicin by alliinase, and other OSCs during processing. This breakdown products present in garlic, and their byproducts like garlic oil, garlic powder, show anti-proliferative effects (Siegers et al., 1999). Allicin and its leading derivatives are shown to be effective for the development of anti-inflammatory drugs with lesser side effects (Krishna and Yadav, 2012). The significant anti-oxidative effects of garlic OSCs can either be due to the prevention of intracellular glutathione depletion, and the removal of peroxides or inhibition of NF-β activation (Ide and Lau, 2001). DAS, an active OSC present in garlic oil was shown to inhibit both pro-and anti-inflammatory cytokines (TNF, IL1, IL6, IL10) which were associated with the suppression of NO and prostaglandin E2 (PGE2) production in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages. DADS, another active OSC present in garlic oil in the same study enhanced IL-1 and IL-6; suppressed IL-10 and TNF, while Allyl methyl sulfide (AMS), an oil-soluble component of garlic oil decreased

NO production and TNF but enhanced IL-10 (Chang et al., 2005).

Anti-microbial properties

Garlic OSCs have anti-microbial (anti-bacterial, anti-fungal, and anti-viral) properties. In a study done by Fufa, extracts of garlic in different solutions (aqueous, ethanol, and chloroform) effectively inhibited the growth of the pathogenic bacteria (Fufa, 2019).

Ajoene, an active OSC of garlic oil is very effective as a topical antifungal agent. Studies proved that garlic OSCs are able to inhibit fungal growth with the similar potentiality of some anti-fungal drugs available in markets like ketoconazole. It was effective against the fungi *Malassezia furfur, Aspergillus, Trichosporon, Rhodotorula, Trichophyton, Cryptococcus, Candida albicans, Candida Torulopsis*, and other *Candida* species. They can decrease the oxygen uptake, and reduce the growth of the microorganism also, able to inhibit the synthesis of macromolecules like lipids, proteins, and nucleic acids and damage the cell membranes (Chidinma et al., 2019, Bayan et al., 2014).

Studies reported that garlic oil derived OSCs are highly effective against specific groups of bacteria including, gram-positive, gram-negative, and acid-fast. These are species of *Staphylococcus, Micrococcus, Streptococcus, Escherichia, Enterobacter, Lactobacillus, Klebsiella, Shigella, Pseudomonas, Proteus, Salmonella, and Helicobacter pylori* (Tsao and Yin, 2001).

Allicin produced by the enzymatic breakdown of alliin by the enzyme alliinase is considered to be the most effective antibacterial component present in garlic oil. It can be unstable and break down within 16 h at 23°C (Hahn, 1996).

OSCs present in garlic oil including allicin and ajoene has effective anti-protozoan activity (Bayan et al., 2014). In treating giardiasis, garlic is recommended as uses of synthetic pharmaceuticals cause unpleasant side effects and increase resistance. The anti-protozoan activity of garlic OSCs against *Giardia sp.* was observed with crude extract at 25 mg/mL, and the established lethal dosage at approximately 50 mg/ mL (Soffar and Mokhtar, 1991). Several studies reported on the usefulness of effective OSCs present in oil extracted from garlic in preventing the hosts of protozoa such as, *Opalinaranarum sp., Candida albicans, Entamoeba histolytica,* Balanitis diumentozoon, *Leishmania, Trypanosomes, Crithidia, and Leptomonas sp.* (Reuter et al., 1966; Lemar et al., 2002).

Hypo-tensive properties

Garlic OSCs, present in garlic oil are effective in reducing blood pressure. This hypo-tensive property is related to its ability to produce hydrogen sulfide and the content of allicin, produced from the breakdown of alliin, and the enzyme alliinase (catalyzing the breakdown). This enzyme has an effect on inhibiting angiotensin II and elevating vaso-dilation. Though there are very limited studies concerning the effect of garlic consumption on blood pressure in both animals and humans inconsistent results of the effect of garlic on blood pressure are abounding (Londhe et al., 2011). Besides allicin, γ-glutamyl-S-allyl cysteine may also contribute to the hypo-tensive effects by inhibiting angiotensin-converting enzymes and inducing endothelium-dependent and -independent relaxation (Matsutomo, 2019). On a daily basis, 600 to 900 mg of garlic supplementation may exert potent hypo-tensive effects in individuals with high blood pressure (Sobenin et al., 2010).

Cardio protective properties

To date, cardiovascular diseases (CVDs) are among the biggest causes of death and disability. According to the report of the WHO, in 2011, approximately 17.3 million people died due to CVD 2008. Over 80 % of these incidents occurred in low- and middle-income countries. WHO estimates that if it continues like this then almost 23.6 million people will die due to CVD by the year 2030 (Mendis et al., 2011).

Hyper-lipidemia is considered a major etiological factor for atherosclerosis which is a most common form of CVDs, and garlic as an herbal plant is well recognized for its effect in reducing plasma lipid level and anti-atherogenic effect (Banerjee and Maulik, 2002). Several cultural studies conducted in rat hepatocytes and human HepG2 cells reported that constituents of garlic are able to inhibit the key enzymes involved in cholesterol and fatty acid synthesis (Rahman and Lowe, 2006). It has also been shown that the water-soluble compounds like S-allyl cysteine present in garlic oil (found more in aged garlic extract (AGE)) are more efficient in inhibiting cholesterol biosynthesis than the lipid-soluble OSCs such as DAS. Also, they are less toxic (Yeh and Liu, 2001). AGE can reduce fatty streak development, vessel wall cholesterol accumulation, and the development of fibro-fatty plaques, and exhibit protective effects against the initiation of atherosclerosis in neo-intimal cholesterol-fed rabbits. In a cell culture study, allicin, and ajoene considerably reserved the Anti-proliferative activity of smooth muscle cells from atherosclerotic aortic plaques. In the study with hyper-cholesterolemic rabbits, the aortic lesions and lipid content of existing fatty plaques were significantly reduced by garlic supplements (Omar, 2013).

High blood pressure is one of the predisposing factors of CVDs. In a review done by Stabler et al. after screening 72 publications and including 2 trials in their study, they concluded that with treatment with garlic preparations the systolic blood pressure was decreased by 10–12 mm Hg, and diastolic blood pressure was decreased by 6–9 mm Hg (Stabler et al., 2012).

Anti-cancer properties

The World Health Organization estimated that approxim ately 10 million deaths in 2020 were caused by cancer, a nd that number is likely to rise to 28.4 million new cases by 2040 (Sung et al., 2021). Chemotherapy, radiation, and surgery are the three basic cancer treatments among others. However, a number of undesirable side effects including system toxicity are associated with clinical applications of these therapies. The effectiveness of phytochemicals as 'anticancer agents' has been supported by their favourable pharmacokinetics, drug int eractions, appropriated doses, long-term safety, and low level of side effects (Sofi et al., 2018). Numerous epidemiological studies have indicated that garlic is crucial in lowering the incidences of cancer.

Based on their chemical compositions, different OSCs in garlic oil such as, water-soluble *S*-allylmercaptocysteine (SAMC), S-allylcysteine (SAC); and oil-soluble diallyl disulfide (DADS), diallyl sulfide (DAS) are categorized and their mode of action in cancer are identified (Omar & Al-Wabel, 2010). Furthermore, application of garlic oil in N-nitrosodiethylamine (NDEA)-induced hepatocarcinoma in rat significantly reduce the numbers and sizes of the tumor nodules, recover the histopathological damages. The mRNA and protein levels of Bcl-2, Bcl-xl, and β-arrestin-2 were decreased whereas Bax and caspase-3 were significantly increased in hepatocellular carcinoma (Zhang et al., 2012). In addition, S-allylmercaptocysteine inhibited the progression at G2-M stage in cell cycle, where S-allylcysteine caused inhibition of cell cycle progression from G1 to S in SW-480 and HT-29 cells. SAMC induced rise in jun kinase activity and a marked increase in endogenous levels of reduced glutathione (Shirin et al., 2001). In another experiment, diallyl trisulfide (DATS) induced apoptosis in PC-3 cells by phosphorylation of apoptosis related protein Bcl-2, reduced Bcl-2 : Bax interaction, and cleavage of procaspase-9 and -3 as well as activation of extracellular-signal-regulated kinase 1/2 (ERK1/2) and c-jun N-terminal kinase 1 (JNK1) (Xiao et al.,2014). In HCT-15, A549 and SK MEL-2 cell lines, DADS caused apoptosis characterized by morphological changes and DNA fragmentation caused by increase intracellular free calcium levels (Sundaram and Milner, 1996). SAC caused G_1/S phase arrest and induced apoptosis, as well as decreased the expression of pro-caspase-3, Parp-1 and Bcl-2, and increased expression of active caspase-3 and Bax in ovarian cancer cells (A2780 cells) in time & dose dependent manners. SAC also decreased the protein expression of Wnt5a, p-AKT and c-Jun in A2780 cells (Xu et al., 2014). Diallyl trisulfide (DATS) inhibited hypoxia-induced hematogenous metastasis of MDA-MB-231 cell by dose-dependent manner by inhibiting HIF-1α transcriptional activity through inhibiting Trx-1 protein (Wei et al., 2017). Diallyl trisulfide significantly inhibited tumor growth and promoted tumor apoptosis in a xenograft model of gastric cancer cell SGC-7901 by inhibiting tumor migration and invasion by modifying MMP9 and E-cadherin protein expressions as well as DATS increased the TNF-α, IFN-γ and IL-12 cytokine release (Jiang et al.,2017). Additionally, SAMC increases the expression of the tumour protein p53 and activates Bax in human colorectal cancer (SW620 cells) cells via inducing apoptosis through the JNK and p38 signalling pathways (Zhang et al., 2014).

CONCLUSION

Till date BC is in the list of leading global health concerns. So, there is a serious urge for advanced therapy with minimal side effects for this treatment.

From ancient times garlic, a medicinal herb, has many prospective uses in the fields of nutrition, pharmacology, medicine, and as well as in the world trade of business too. Evidences showed that although having anti-cancer, hypo-glycemic, cardio-protective, anti-hypertensive, anti-inflammatory, anti-microbial, and hypo-cholesterolemic effects, garlic OSCs like allicin, DAS, DADS, DATS, E-, and Z-ajoene possess potential anti-cancer properties too. Garlic OSCs can reduce ROS generation, oxidative stress, and inflammation, and reduce the progression and metastasis of cancer by inducing apoptosis and cell cycle arrest. In some cases, where both innate and adaptive drug resistance is observed with synthetic drugs, even chemotherapy becomes resistant; there a number of studies have confirmed the affectivity of garlic OSCs.

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Nil.

Declaration of interests

The authors declare no conflicts of interest.

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