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Anti-Cancer Effects of Organosulfur Compounds in Garlic

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ABSTRACT: Garlic (*Allium sativum*), a member of the family Liliaceae, contains an abundance of chemical compounds that have been shown to possess beneficial effects to protect against several diseases, including cancer. Evidence supports the protective effects of garlic in stomach, colorectal, breast cancer in humans. The protective effects appear to be related to the presence of organosulfur compounds, predominantly allyl derivatives, which also have been shown to inhibit carcinogenesis in forestomach, esophagus, colon, mammary gland and lung of experimental animals. The exact mechanisms of the cancer-preventive effects are not clear, although several hypotheses have been proposed. Organosulfur compounds modulate the activity of several metabolizing enzymes that activate (cytochrome P450s) or detoxify (glutathione *S*-transferases) carcinogens and inhibit the formation of DNA adducts in several target tissues. Antiproliferative activity has been described in several tumor cell lines, which is possibly mediated by induction of apoptosis and alterations of the cell cycle. Organosulfur compounds in garlic are thus possible cancer-preventive agents.

KEYWORDS-garlic,anti-cancer,preventive,apoptosis,organosulfur,enzymes

I. INTRODUCTION

Garlic (*Allium sativum* L.) possesses numerous pharmacological potential, including antibacterial, antiarthritic, antithrombotic, anticancer, hypoglycemic, and hypolipidemic effects. The anti-cancer action of garlic is likely the best researched of the many advantageous pharmacological effects, and its use offers significant protection against the risk of developing cancer. A few active metabolites of garlic have been reported to be essential in the destruction of malignant cells due to their multi-targeted activities and lack of significant toxicity. [1,2,3]The bioactive compounds in garlic having anticancer properties include diallyl trisulfide, allicin, allyl mercaptan diallyl disulfide, and diallyl sulphide. Different garlic-derived constituents and their nanoformulations have been tested for their effects against various cancers including skin, ovarian, prostate, gastric, breast, and lung, colorectal, liver, oral, and pancreatic cancer. The objective of this review is to summarize the antitumor activity and associated mechanisms of the organosulfur compounds of garlic in breast carcinoma. Breast cancer continues to have a significant impact on the total number of cancer deaths worldwide. Global measures are required to reduce its growing burden, particularly in developing nations where incidence is increasing quickly and fatality rates are still high. It has been demonstrated that garlic extract, its bioactive compounds, and their use in nanoformulations can prevent breast cancer in all of its stages, including initiation, promotion, and progression. Additionally, these bioactive compounds affect cell signaling for cell cycle arrest and survival along with lipid peroxidation, nitric oxide synthase activity, epidermal growth factor receptor, nuclear factor kappa B (NF-κB), and protein kinase C in breast carcinoma.[5,7,8]

Despite strong anticancer activity of various garlic derived plant therapeutics, these compounds suffer from oral bioavailability and off target toxicity. Therefore, several nanoformulations have been tried to improve the bioavailability of these compounds. Garlic extracts contain anticancer chemicals can combine to generate nano-conjugates that can help stop the spread of cancer cells. When administered at a concentration of 100 g/mL, garlic clove extract-mediated silver nanoparticles (G-AgNPs) displayed cytotoxic action against the MCF-7 cell line. Additionally, it affected the nucleus morphology of MCF-7 cells, causing cell clumping and membrane instability (Menon et al., 2012). G-AgNPs did not cause any toxicity or mortality in neonates of *Corylus cornuta*. In a different study, garlic extract-mediated silver nanoparticles (Ag-S2) caused cytotoxicity in the MCF-7 cancer cell line by reducing cell viability in a concentration-dependent manner (Ahamed et al., 2021). Nevertheless, MCF-7 cells were not toxicated by

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the gold nanoparticles (G-AuNPs) produced by garlic extract. Superparamagnetic hematite nanoparticles made from garlic extract were synthesized, and their cytotoxicity against the breast cancer MCF-7 cell line was examined. The findings imply that at an IC_{50} of 346.25 mg/mL, the cell proliferation was inhibited in a dose responsive manner (Talluri et al., 2017). Even ZnO-reduced graphene oxide nanocomposites (ZnO-RGO NCs) made from the extract of garlic cloves showed increased cytotoxicity against MCF-7 cells (Kim et al., 2020).[9,10,11] DADS nanoparticles (solid lipid) demonstrated higher cytotoxicity than DADS alone against MCF-7 carcinoma cells by inducing apoptosis (*via* intrinsic signaling pathway) associated with elevated expression levels of Bax, Bad, caspase-3, and caspase-9, and decreased protein expression level of Bcl-2 (Lee et al., 2015). Figure 1 presents a proposed pathway for garlic induced apoptosis in breast cancer.

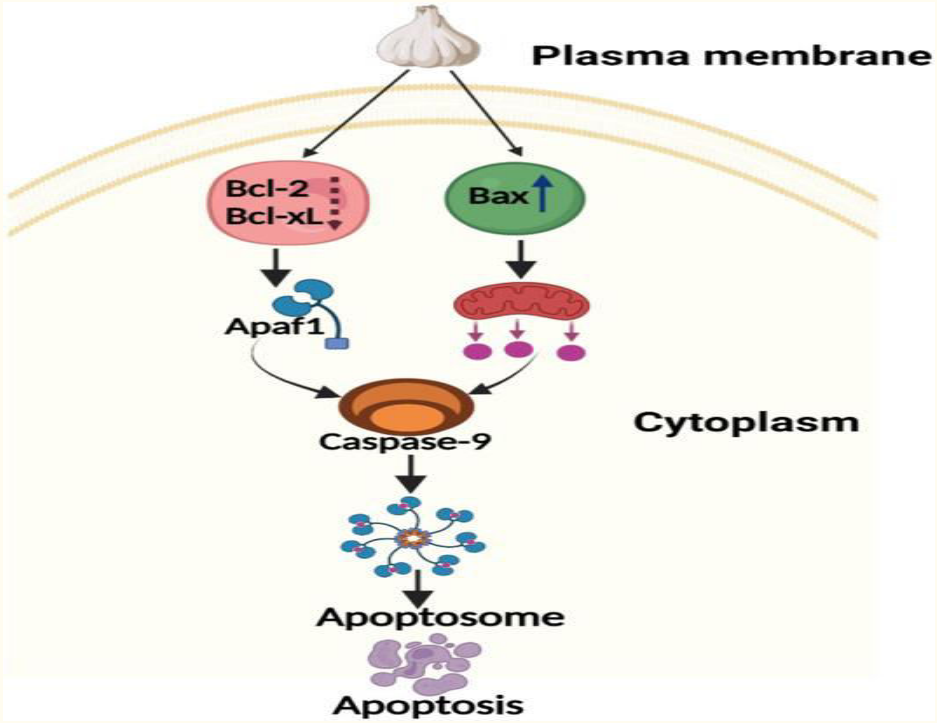

FIGURE 1
Proposed pathway for garlic induced apoptosis in breast cancer.

II. DISCUSSION

Garlic (*Allium sativum*), a member of the family Liliaceae, contains an abundance of chemical compounds that have been shown to possess beneficial effects to protect against several diseases, including cancer. Evidence supports the protective effects of garlic in stomach, colorectal, breast cancer in humans. The protective effects appear to be related to the presence of organosulfur compounds, predominantly allyl derivatives, which also have been shown to inhibit carcinogenesis in forestomach, esophagus, colon, mammary gland and lung of experimental animals. The exact mechanisms of the cancer-preventive effects are not clear, although several hypotheses have been proposed. Organosulfur compounds modulate the activity of several metabolizing enzymes that activate (cytochrome P450s) or detoxify (glutathione S-transferases) carcinogens and inhibit the formation of DNA adducts in several target tissues. [12,13,15]

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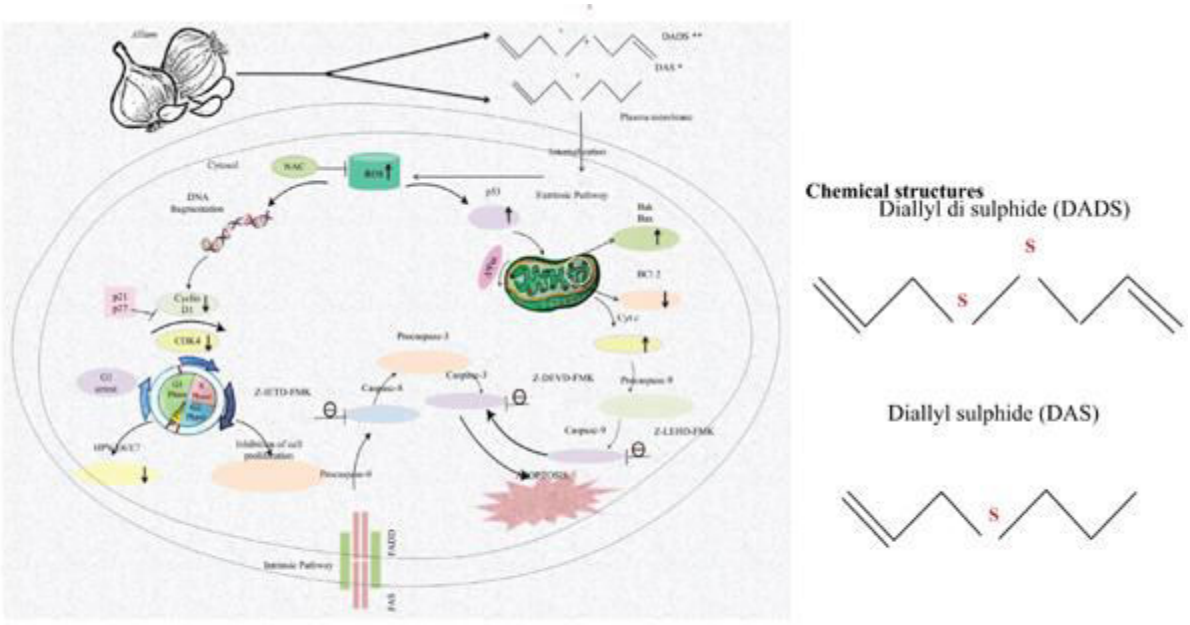

Organosulphur compounds (DADS and DAS) induce ROS-mediated apoptosis and cell cycle arrest in cervical cancer cells *via* downregulating the expression of HPV E6/E7 oncoproteins (DADS represents more pronounced effect as compared to DAS*).**

III. RESULTS

According to the results of the present study, on the one hand, some OSCs from garlic (mainly γ-glutamyl-S-alk(en)ylcysteines and, to a lesser extent S-alk(en)ylcysteine sulfoxides and ajoenes) have antihyperlipidemic activities through different mechanisms, especially inhibition of pancreatic lipase and NPC1L1. On the other hand, GI absorption of γ-glutamylS-alk(en)ylcysteines is relatively low. Then, it can be inferred that a significant part of antihyperlipidemic activities of garlic products may be locally exerted in the intestinal lumen. [15,17,18]Also, it seems that the products containing fresh whole garlic, thermal dehydrated garlic, and freeze-dried garlic products may possess more antihyperlipidemic activities due to the higher levels of γ-glutamyl-S-alk(en)ylcysteines and, to some extent, S-alk(en)ylcysteine sulfoxides considering the chemical structure of sulfur compounds in different garlic products. OSCs present in different garlic products was virtually studied for antihyperlipidemic activities against various therapeutic targets of hyperlipidemia, including pancreatic lipase, HMG-CoA reductase, PPAR-α, and NPC1L1. Initially, 25 OSCs were studied based on their binding affinity for the 4 above-mentioned targets. Then, they were tested for their pharmacokinetic properties. Among the screened OSCs, γ-glutamyl-Salk(en)ylcysteines displayed the highest binding affinity for all targets, especially pancreatic lipase and NPC1L1. On the contrary, their GI absorption was low, suggesting that, firstly, a substantial part of antihyperlipidemic activities of garlic products are probably exerted directly in the intestinal lumen, and secondly, fresh whole garlic, thermal dehydrated garlic, and freeze- dried garlic products may have more antihyperlipidemic activities due to their higher levels of γ-glutamyl-S-alk(en)ylcysteines[19,20,21]

IV. CONCLUSIONS

For over several thousand years, garlic has been consumed by humans not only as a kind of flavoring food but also as a medicinal food or a topical agent. As a medicinal food, raw or cooked garlic has been used to treat infections[1,2,3,4,5,6,7], to lower cholesterols[8,9,10,11] and to inhibit the formation of blood clots, etc.[12,13,14]. The antibacterial properties of garlic were first described by Pasteur as early as in 1858. The topical applications of the raw garlic pastes were widely used as anti-infection agents in the WWI and WWII by the soldiers[15,16]. In the recent decades, the anticancer properties of garlic have also been extensively studied in cell cultures, in animals, and in humans.[22,23,25]

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Most anticancer studies in humans were the retrospective survey to determine whether there were possible connections between the consumption of the cooked garlic and cancer incidents or slower progression17,18,19,20,21. Some studies were the intervention studies by feeding the human subjects with garlic. But direct evidence supporting an anticancer contention of garlic was weak22,23. The compounds extracted from the garlic, especially the sulfuric compounds, have also been shown to mildly reduce the incident rates and severity of the tumor formation induced by the administrated *N*-nitroso compounds in animal models24. The reductionist view also led to many studies of the individual compounds isolated from garlic for their anticancer properties. In most animal studies, when garlic or the purified garlic compounds were given via ingestion, the direct anticancer effects were weak at best[25,27,28]

There are also many studies suggesting that garlic may have direct anticancer properties in cell culture. For an example, in a large study of 34 different vegetable juices against eight different human cancer cell lines, raw garlic extract (RGE) when added directly to the cultured cancer cells stood out as the most-effective anticancer agent in comparison with all other 33 raw vegetable extracts26. Furthermore, this cytotoxic effect was highly specific against cancer cells but not the non-cancerous cells27,28. This highly selective anticancer cytotoxicity without harming normal cells was also in agreement with the commonly known fact that garlic is a food and can be consumed safely in large quantities without significant adverse side-effect. Similar anticancer properties of garlic in cell culture were also reported by other studies using different cancer cells29,30. Despite the efforts in the last several decades, the anticancer effects of garlic still lack a piece of convincing evidence: a decisively curative result against aggressive cancer in the animal models or in humans.[29,30,31]

There is also an apparent difference in anticancer effects when garlic is cooked or not and exposed to cancer cells directly or going through gastrointestinal (GI) tract first. [32,33]

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