Allium Sativum: A Review of Ethnopharmacology, Phytochemistry, and anti-breast cancer activity

Mansoureh Masoudi¹, Rasoul Rahimi²*

¹Mansoureh Masoudi, MD in gynecology, Valiasr Eghlid hospital, Shiraz University of medical sciences, Shiraz, Iran

²Rasoul Rahimi, MD, assistant professor of surgery, shahrekord university of medical sciences, shahrekord, Iran

Corresponding author: Rasoul Rahimi, MD, assistant professor of surgery, shahrekord university of medical sciences, shahrekord, Iran

ABSTRACT

Introduction: Allium Sativum, commonly known as garlic, a member of the family Liliaceae, is a species in the onion genus. Allium sativum is a bulbous plant with hermaphrodite flowers growing up to 1.2 m in height. The aim of this article was to review ethnopharmacology, Phytochemistry, and anti-breast cancer activities of Allium sativum.

Methods: This review article was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases from 1995 to 2016. Totally, of 108 found articles, 47 articles were included. The search terms were “Allium sativum”, “Ethnopharmacology”, “anti-breast cancer”, “complementary medicine”.

Result: It was shown that anti-breast activity of Allium sativum have been attributed to its oil-soluble sulfur ingredients, especially diallyl sulfide [DAS], diallyl disulfide [DADS], and diallyl trisulfide [DATS]. These compounds are not only inhibiting the growth of cancerous cells but also inhibits the proliferation of MCF-7 cells as well as cause MCF-7 cells death.

Conclusion: Allium sativum was shown to hold anti-breast cancer activity due to both its phytochemical compound and mechanism of action. Selenium-enriched Allium sativum or organ selenium compounds protect better against
breast cancer and inhibit both growth, proliferation of breast cancer cells. Besides, they cause breast cancerous cell apoptosis. Thus, Allium sativum and Allium sativum-derived compounds are shown to be good candidate for breast cancer control.

**Keywords**: Allium sativum, Ethnopharmacology, anti-breast carcinogenesis, complementary medicine

**INTRODUCTION**

The role of herbal medicine in the treatment of many diseases was proven [1-24]. Allium sativum, commonly known as garlic is a member of the family Liliaceae [25]. Allium sativum is a bulbous plant with hermaphrodite flowers [26,27]. It is native to Central Asia and northeastern Iran. It is grown in temperate and tropical regions all over the world [28]. It contains an abundance of chemical compounds that have been shown to possess beneficial effects to protect against several diseases, including antidiabetic activity [29], aphrodisiac [30], pain relief [31], anti-bacterial [32,33], anti-fungal [34,35], insecticidal [34], antioxidant activities[36], anti-cardiovascular [37],anti-hypertension activity[38], hypolipidemic[39], antiplatelet[40], and procirculatory effects [41]. It prevents cold and flu symptoms through immune enhancement [42]. AGE also has hepatoprotective, neuroprotective, and antioxidative activities, whereas other preparations may stimulate oxidation [3]. The most important of all is its anti-cancer activity [43-45]. Allium sativum consumption is associated with a lower risk of stomach cancer in the Korean population [46]. Another study suggests an association between higher Allium sativum consumption and a lower risk of prostate cancer [47]. It has anti-colorectal [48], anti-gastric cancer [49] anti-lung cancer [50] property as well.

The anti-cancer effects of this plant are associated to the presence of organosulfur compounds, predominantly allyl derivatives. Organosulfur compounds modulate the activity of several metabolizing enzymes that activate or detoxify carcinogens and inhibit the formation of DNA adducts in several target tissues [51].

**TAXONOMY**

Allium sativum L., also known as garlic, is a bulbous plant.it is a member of Amaryllidaceae family, and it belongs to Allium L. genus including onion, wild onion, onion. It is indigenous to Central Asia and northeastern Iran. It is grown in temperate and tropical regions all over the world [28]. The taxonomical classification of this plant is as follow: kingdom: Plantae; division: Tracheophyta; Cultivation

Garlic is easy to grow and produces numerous bulbs after a long growing season [52]. It is frost tolerant [53]. Beyond its intense flavor and culinary uses, “the stinking rose” is good in the garden as an insectifuge [54].

**Traditional uses**

Medicinal plants are widely utilized in traditional medicine [55]. Garlic is among the most important of these plants [56]. For this purpose, garlic has been extensively used worldwide for centuries, especially in the Far East. Garlic is reported to be a wonderful medicinal plant owing to its preventive characteristics in cardiovascular diseases [57], regulating blood pressure, lowering blood sugar and cholesterol levels, effective against bacterial, viral, fungal, and parasitic infections [58], enhancing the immune system and having antitumoral and antioxidant features [59].
Chemical compound

It contains sulfur compounds [allicin, alliin and a gene][60], volatile oils[61], enzymes [allinase, peroxidase and miracynase] [62], carbohydrates [sucrose and glucose][63], minerals [selenium][64], amino acids such as cysteine, glutamine, isoleucine and methionine which help to protect cells from the harms of free radical s[65], bioflavonoids such as quercetin and cyanidin, allistatin I and allistatin II[66], and vitamins C, E and A which help to protect us from oxidation agents [67] and free radicals[68], and other vitamins such as niacin, B1 and B2 and beta-carotene[69].

The major sulfur-containing compounds in intact garlic are γ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxides [alliin] [70]. Both are abundant as sulfur compounds, and alliin is the primary odorless, sulfur-containing amino acid, a precursor of allicin [71], methiin, [+]-S-[trans-1-propenyl]-L-cysteine sulfoxide, and cycloalliin [72]. These sulfoxides, except cyloalliin, are converted into thiosulfimates [such as allicin] through enzyme reactions when raw garlic is cut or crushed [73]. Thus, no thiosulfimates are found in intact garlic.

Processed garlic contains a wider variety of organosulfur volatiles than the intact garlic clove. Typical volatiles that have been identified in crushed garlic and garlic essential oil include DAS, DADS, diallyl trisulfide, methylallyl disulfide, methylallyl trisulfide, 2-vinyl-4H-1, 3-dithiin, 3-vinyl-4H-1, 2-dithiin, and [E, Z]-ajoenes [74].

Mechanism of action

Studies have shown strong evidence that garlic OSCs may affect cancer cells by promoting early mitotic arrest followed by apoptotic cell death without affecting healthy cells [75]. The ability of OSCs to hinder cancer cell proliferation and viability tightly correlates with the length of the sulfur chain [76]. Current data support a mechanism of mitotic arrest of cancer cells due to the alteration of the microtubule network, possibly as a consequence of the high reactivity of sulfur atoms against the thiol groups of different cellular macromolecules controlling crucial regulatory functions [77].

RESULTS

Anti-Breast cancer effect

In an animal study, the effects of crude extract of Allium sativum on the proliferation of human breast cancer cell lines was investigated. This extract showed to induce cell cycle arrest as well as to self-destruct in PC-3 cells in a dose-dependent manner. The result suggested that the lipid bioactive compounds are reliable candidate as anti-breast cancer agents [78].

The effect of fresh Allium sativum on anti-tumor response and intra-tumor lymphocyte infiltration was examined. The result confirms that protein fractions purified from fresh Allium sativum bulbs augment CD8[+] T-cell infiltration into the tumor site, inhibiting tumor growth more efficiently than Allium sativum extract. The result suggested that more research are needed to prove anti-tumor and anti-breast cancer activity of purified polypeptide [79].

In a human study, the mechanisms of action of anti-breast cancer activity of Allium sativum was assessed. The results showed that Allium sativum induce heme oxygenase-1 via DATS that was partially lessened by overexpression of Mn-SOD. Thus, it was found for the first time that anticancer effects of DATS is mainly due to its reactive oxygen species [80].
Fresh extracts of Allium sativum showed that reduce the growth MCF7 breast cancer cells and changed its morphology via early down-regulation of cyclin D1, ERK1 phosphorylation reduction, and eIF2-α phosphorylation increase. Continuous growth reduction is because of decreased hsp27 expression and Rb and p21 increased levels [81].

In an animal study, mammary cancer effect of Allium sativum was investigated. Oil-soluble compounds derived from Allium sativum, such as diallyl disulfide are shown to be more useful in suppressing breast cancer than water-soluble compounds. Diallyl disulfide combine the effect of eicosapentaenoic acid and irritate the effect of linoleic acid. Thus, Allium sativum and Allium sativum-derived compounds are strong anti-breast cancer agents [82].

The effect of diallyl trisulfide [DATS] on growth of two cell lines i.e. MCF-7 and MCF-12a was examined. The result showed that the apoptosis via DATS is due to pro-apoptotic Bax protein induction and upregulation of p53 protein expression of MCF-7 cells. Thus, it was shown that DATS is a good candidate for human breast cancer treatment [83].

The anticancer properties of fresh Allium sativum extracts, aged Allium sativum, Allium sativum oil, and a number of specific organosulfur compounds was assessed. The result showed that the anti-cancer activity of Allium sativum was due to dose- and temporal-related changes involved in the cancer process. Allyl sulfur compounds showed to cause shift in sulfhydryl groups, alterations in glutathione, and subsequent changes in cellular redox status [84].

In a study, it was shown that consumption of unsaturated fat in Allium sativum decrease the risk of breast cancer in post-menopausal women [p= 0.03] [85].

Anti-carcinogenic effect of aged Allium sativum extract and some of its constituents i.e. S-allylcysteine [SAC], and S-allylmercaptocysteine [SAMC] was investigated. V-H-ras Transfection cause aggressive subset of MCF-7 cells that is estrogen independent it was found an anti-cancer activity of SAC and SAMC was because of both anchorage dependent as well as glutathione level change [86].

The anti-antiproliferative effect of Allium sativum has been described. Findings suggested that high consumption of Allium sativum is likely to decrease the risk of breast cancer, while high intake of cooked onion may be associated with an increased risk of breast cancer [87].

Allium sativum, Arctium lappa and Curcuma longa were reported to possess strong anti-breast cancer activity. The bioactive immunomodulatory activity of these plant is responsible for as their anticancer effects these major chemical compounds include ajone, arctigenin, β-carotene, curcumin, epigallocatechin-3-gallate, ginsan, glabridin and quinic acid [88].

Over-expression of several prognostic biomarkers trigger breast cancer by blockage of these biomarkers can inhibit breast cancer but a plant with no adverse side effects should be selected. The result showed twelve compounds to be active against the targets [44].

Biochemical properties of Allium sativum, Echinacea, Curcuma longa, Arctium lappa, Camellia sinensis, Panax ginseng and Flax seed was reviewed. The volatile oils and extracts of these herbs and plants inhibit mevalonate synthesis lessening the tumor growth and cholesterol synthesis [89].
The effects of diallyl trisulfide on migration and invasion in three breast cancer cells was investigated. The result showed that diallyl trisulfide have inhibitory activity against MMP2/9 activity and TNBC cells metastasis. The anti-cancer activity of this organosulfur compound is associated to down-regulation of signaling pathways [90].

The antitumor activity of DADS in triple-negative breast cancer [TNBC] cell lines based in vitro and in vivo models was evaluated. Results show that the antitumor effect of DADS on TNBC cells is mediated by the β-catenin pathway, suggesting that DADS could be used as a potential therapeutic agent for treating or preventing breast cancer [91].

In an in vivo study, Diallyl trisulfide [DATS] was shown to targets breast cancer stem cells via decrease in the protein level of FoxQ1 and ALDH1 activity inhibition in SUM159 xenografts. There was a reverse relationship between FoxQ1 and DACH1 gene expression in breast cancer cell lines and tumors. These results indicate that FoxQ1 is a novel target of bCSC inhibition by DATS [92].

In an in vivo study, it was demonstrated that DADS could be a rich anticancer agent for breast cancer through up-regulation of miR-34a expression. MiR-34a not only cause to breast cancer growth inhibition but trigger the improvement of antitumor effect of DADS as well. The results suggest that. MiR-34a may also demonstrate a potential gene therapy agent that could enhance the antitumor effects of DADS [93].

DADS induce apoptosis in the MCF-7 breast-cancer cell line through interfering with cell-cycle growth phases as well as decreasing the removal of an acetyl group from an acetylated substrate and induces histone-4 [H4] hyper-acetylation. The result showed that breast cancer cells apoptosis of DADS is due to its HDACi properties [98].

Anti-breast cancer effect of fresh extracts of Allium sativum was investigated. It was shown that the extract cause to inhibit the growth of MCF7 breast cancer cells via deregulation of levels of E-cadherin, cytokeratin8/18, and β-catenin involved in apoptosis [99].

Allium sativum extract showed to reduce the side effects induced by anti-cancer agents. Thus, Allium sativum and Allium sativum-derived compounds are reliable candidates for breast cancer treatment [100].

The prevalence of multivitamins, folic acid and herbal supplement usage in African American breast cancer survivors was determined and the effect of Allium sativum was confirmed [101, 102].
It was found that DATS showed a strong anti-proliferative effects in human breast cancer MCF-7 cells. The results suggest that DATS-induced apoptosis is through ROS activity and subsequent activation of JNK and AP-1[103].

The effect of diallyl disulfide [DADS] on apoptosis in human mammary cancer cell line [MCF-7] and its mechanisms was investigated. The results suggest that DADS both inhibits the proliferation of MCF-7 cells and induces apoptosis of MCF-7 cells. The mechanisms may include the inhibition of ERK and the activation of the SAPK/JNK and p38 pathways [104]. The effect of DAS on DES-induced reactive oxygen species was investigated. DAS was found to cause anti-breast cancer activity via ROS inhibition triggering DES bioactivation inhibition [105].

**DISCUSSION**

Consumption of diets rich in fruits and vegetables is often associated with a reduced risk of developing cancer, particularly breast cancer. Considering that 1 in 8 women in the United States will develop breast cancer in the course of her lifetime, dietary manipulation could have a major impact on the incidence of breast cancer. Identification of agents that are nontoxic but can delay onset and/or progression of breast cancer, which is the main leading cause of cancer-related deaths among women, is highly desirable. The anti-carcinogenesis property of Allium sativum was associated to different factors: 1] Chemical compound in Allium sativum including: Chemopreventive effects of Allium sativum have been attributed to its oil-soluble sulfur ingredients, such as diallyl sulfide [DAS], diallyl disulfide [DADS], and diallyl trisulfide [DATS] [103].

Diallyl trisulfide [DATS], a metabolic byproduct of Allium sativum, is known to inhibit the growth of breast cancer cells in vitro and in vivo. It was shown that DATS targets breast cancer stem cells [bCSC] [106]. Allium sativum organosulfide diallyl trisulfide [DATS] inhibits estrogen receptor-α [ER-α] activity in human breast cancer cells. DATS treatment caused a decrease in protein levels of peptidyl-prolyl cis-trans isomerase [Pin1], and overexpression of Pin1 partially attenuated ER-α downregulation by DATS [96]. DATS-induced apoptosis is mediated through ROS generation and subsequent activation of JNK and AP-1[103]. The results found for the first time that ROS [107] reactive oxygen species has a critical role for anticancer effects of DATS [80].

Organosulfur compounds, especially allyl derivatives from Allium sativum effectively inhibit growth of transplanted as well as spontaneous cancers in preclinical animal models without any adverse side effects [108]. Oil-soluble compounds derived from Allium sativum, such as diallyl disulfide [DADS], are more effective than water-soluble compounds in suppressing breast cancer. Diallyl disulfide [DADS] both inhibits the proliferation of MCF-7 cells and induces apoptosis of MCF-7 cells. The mechanisms may include the inhibition of ERK and the activation of the SAPK/JNK and p38 pathways [104]. DADS synergizes the effect of eicosapentaenoic acid, a breast cancer suppressor, and antagonizes the effect of linoleic acid, a breast cancer enhancer [82]. Antitumor effect of DADS on TNBC cells is mediated by the β-catenin pathway, suggesting that DADS could be used as a potential therapeutic agent for treating or preventing breast cancer [91]. DADS showed to be a promising anticancer agent for breast cancer. MiR-34a may also demonstrate a potential gene therapy agent that could enhance the antitumor effects of DADS [93].

Diallyl sulfide [DAS] is an Allium sativum organosulfide that has been shown to inhibit both the initiation and promotion phases of cancer in vivo and in vitro, as well as reduce the risk of cancer in epidemiological studies. DAS inhibits the production of ROS which suggests that DAS effectively inhibits DES bioactivation in female ACI rats which may have implications for chemopreventive intervention strategies [105]. The chemopreventive effects of DAS are attributed to modulation of enzymes to alter the bioactivation of xenobiotics. Diethylstilbestrol [DES] is a synthetic estrogen that causes breast cancer in female ACI rats subsequent to metabolism with concurrent free radical production [94].
lipid bioactive compounds in CGE have the potential as promising anticancer agents [78] protein fractions purified from fresh Allium sativum bulbs [purified polypeptide] augment CD8\([+\)] T-cell infiltration into the tumor site, inhibiting tumor growth more efficiently than Allium sativum extract [79] [97]. Saturated fat intake and breast cancer risk are associated in post-menopausal women [p value for trend = 0.03]. Conversely, it suggests that unsaturated fat intake could lower the risk in the same subgroup [85]. S-Allylmercaptocysteine [CySSA] from Allium sativum is known to exhibit anti-cancer effects [95]. These antitumor and antitumorigenic characteristics appear to arise through both dose- and temporal-related changes in a number of cellular events involved with the cancer process [84] anti-proliferative response to S-allylcysteine [SAC], and S-allylmercaptocysteine SAMC was observed on both anchorage dependent and independent conditions and an alteration in glutathione level [86].

Diethylstilbestrol [DES] is a synthetic estrogen causing cancer in animals and humans. Diallyl sulfide [DAS] is an Allium sativum organosulfide that has been shown to inhibit both the initiation and promotion phases of cancer in vivo and in vitro, as well as reduce the risk of cancer in epidemiological studies. MCF-10A cells, regarded as a normal breast epithelial cell line, were treated with varying concentrations of DES, DAS or various dose combinations of DES and DAS concomitantly, and assessed for cell viability, DNA strand breaks, and lipid peroxidation. The results of this research suggest that DAS is effective in recovering cell viability, attenuating DNA strand breaks, and decreasing lipid peroxidation in MCF-10A cells [94].

CONCLUSION

Allium sativum was shown to hold anti-carcinogenic activity due to both its phytochemical compound and mechanism of action. Selenium-enriched Allium sativum or organoselenium compounds provide more potent protection against mammary carcinogenesis in rats and greater inhibition of breast cancer cells in culture than natural Allium sativum or the respective organosulfur analogues. Allium sativum and Allium sativum-derived compounds are shown to be good candidates for breast cancer control.

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