Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2017, 9 [5]:42-54
[http://scholarsresearchlibrary.com/archive.html]

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

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

Mansoureh Masoudi[1], Rasoul Rahimi[2*]

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

[2]*Rasoul 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 Amaryllidaceous 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 thiosulfinates [such as allicin] through enzyme reactions when raw garlic is cut or crushed [73]. Thus, no thiosulfinates 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 anti0tumor 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, ERK1phosphorylation reduction, and eIF2-α phosphorylation increase. Continuous growth reduction is because of decreased hsp27expression 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-allyl-mercaptocysteine [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 ajoene, 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].

DAS trigger MCF-10A cells viability recovery, DNA strand breaks decrease, and lipid peroxidation reduction [94].

Anti-cancer effect of S-Allyl mercaptocysteine [CySSA] from Allium sativum was assessed. CySSA is known to exhibit anti-cancer effects via decrease in caspases 6/7 activation causing cell apoptosis. This is the first report of an anti-cancer effect of CySSPe [95].

It was shown diallyl trisulfide [DATS] inhibits estrogen receptor-α [ER-α] activity in human breast cancer cells. Administration of DATS caused a decrease in protein levels and overexpression of Pin1. DATS-induced apoptosis was modestly but significantly augmented by overexpression of Pin1. Thus, the result showed for the first-time ER-α as a novel target of DATS in mammary cancer cells [96].

The effect of a protein fraction isolated from fresh Allium sativum on anti-tumor response and intra-tumor lymphocyte infiltration was examined. The results confirm that these fractions enhance CD8 [+] T-cell infiltration into the tumor site, cause tumor growth inhibition. Nonetheless, further investigations are required to prove anticancer effect of the purified polypeptide [97].

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 anticarcinogenic 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-allyl-mercaptocysteine 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 doe 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.

REFERENCES

1. Miraj, S., A review of chemical components and pharmacological effects of Melissa officinalis L, Der Pharmacia Lettre, **2016.** 8 (6): p. 229-237.
2. Miraj, S. and Kiani, S., Study of pharmacological effect of Ocimum basilicum: A review. Der Pharmacia Lettre, **2016.** 8 (9) p. 276-280.
3. Miraj, S., Astragalus membranaceus : A review study of its anti-carcinoma activities, Der Pharmacia Lettre, **2016.** 8 (6):59-65.
4. Miraj, S., Study of pharmacological effect of Avena sativa: A review, Der Pharmacia Lettre, **2016.** 8 (9) p. 137-140.
5. S, MSK., Bioactivity of Sesamum indicum: A review study, Der Pharmacia Lettre, **2016.** 8(6) p.328-334.
6. Masoudi, M., Comparison of the Effects of Myrtus Communis L, Berberis Vulgaris and Metronidazole Vaginal Gel alone for the Treatment of Bacterial Vaginosis. Journal of clinical and diagnostic research: JCDR, **2016.** 10(3):QC04.
7. Miraj, S., Study of pharmacological effect of Thymus vulgaris: A review, Der Pharmacia Lettre, **2016.** 8(6) p.78-82.
8. Miraj, S., Pharmacological effect of Actiumlappa: A review study, Der Pharmacia Lettre, **2016.** 8(6) p.102-106.

9. Miraj, S., Astragalus membranaceus : A review study of its anti-carcinoma activities. Der Pharmacia Lettre, **2016.** p. 59-65.
10. Miraj, S., Study of therapeutic effects of Cynara scolymus L.: A review, Der Pharmacia Lettre, **2016.** 8(9) p.168-173
11. Miraj, S., A review study of therapeutic effects of Iranian borage (Echium amoenum Fisch), Der Pharmacia Lettre, **2016.** 8(6) p.102-109
12. Miraj, S., A review study of therapeutic effects of Salvia officinalis L. Der Pharmacia Lettre, **2016.** 8(6) p.299-303.
13. Miraj, S., Lack of Association between ESR1 and CYP1A1 Gene Polymorphisms and Susceptibility to Uterine Leiomyoma in Female Patients of Iranian Descent, Cell journal, **2016.** 16(2):225(9) p.137-140.
14. Seyyedi, F., Comparison of the Effects of Vaginal Royal Jelly and Vaginal Estrogen on Quality of Life, Sexual and Urinary Function in Postmenopausal Women. Journal of clinical and diagnostic research, JCDR, **2016.** 10(5) p.1-5.
15. Miraj, S., Pharmacological activities of Carum carvi L. Der Pharmacia Lettre, **2016.** p. 135-138.
16. Miraj, S., Study of antibacterial, antimycobacterial, antifungal, and antioxidant activities of Foeniculum vulgare: A review, Der Pharmacia Lettre, **2016.** 108-110.
17. Eftekhar, M., et al., The effect of luteal phase gonadotropin-releasing hormone antagonist administration on IVF outcomes in women at risk of OHSS, International journal of reproductive biomedicine (Yazd, Iran), **2016.** 14(8) p. 507-510.
18. Davar, R., Effect of adding human chorionic gonadotropin to frozen thawed embryo transfer cycles with history of thin endometrium, International journal of reproductive biomedicine (Yazd, Iran), **2016.** 14(1)p. 53-56.
19. Taghizade Mortezaee, F., Lack of Association between ESR1 and CYP1A1 Gene Polymorphisms and Susceptibility to Uterine Leiomyoma in Female Patients of Iranian Descent, Cell journal, **2014.** 16(2) p.225-30.
20. Miraj, S., Menstrual diseases as stated in canon fil-Tibb Der Pharmacia Lettre, **2016.** 8(6) p.261-268.
21. Miraj, S., Study of pharmacological effect of Mentha pulegium: A review, Der Pharmacia Lettre, **2016.** 8(9) p.242-245.
22. Jafari, A., the association of serum levels of folic acid and homocysteine in pregnant women with pre-elcampsia Iranian journal of obstetrics,gynecology and infertility, **2014.**
23. Davar, R., Effects of single dose GnRH agonist as luteal support on pregnancy outcome in frozen-thawed embryo transfer cycles: an RCT, Iranian journal of reproductive medicine, **2015.** 13(8) p.483.
24. Miraj, S., review of association between dietotherapy, dystemrament and prevention and treatment of diseases, Der Pharmacia lettre, **2016.**
25. Scott, Z., et al., Native Bee Diversity and Pollen Foraging Specificity in Cultivated Highbush Blueberry (Ericaceae: Vaccinium corymbosum) in Rhode Island. Environmental entomology, **2016.** 45(6) p.1432-1438.
26. Lopez, MD., Effect of climatic conditions and soil type on antioxidant compounds in organic and conventional blueberries (Vaccinium corymbosum L.), Planta medica, **2016.** 81(S 01) p.1-381.
27. Stull, AJ., Blueberries' Impact on Insulin Resistance and Glucose Intolerance. Antioxidants (Basel, Switzerland), **2016.** 5(4).
28. Gao, X., Overexpression of blueberry FLOWERING LOCUS T is associated with changes in the expression of phytohormone-related genes in blueberry plants. Horticulture research, **2016.** 3 p.16053.

29. Chu, W., Composition and morphology of cuticular wax in blueberry (Vaccinium spp.) fruits, Food chemistry, **2017.** 219, p.436-442.
30. Wang, H., Comparison of phytochemical profiles, antioxidant and cellular antioxidant activities of different varieties of blueberry (Vaccinium spp.), Food chemistry, **2017.** 217 p.773-81.
31. Silva, S., et al., Variation of anthocyanins and other major phenolic compounds throughout the ripening of four Portuguese blueberry (Vaccinium corymbosum L) cultivars, Natural product research, **2017.** 31(1) p.93-98.
32. Siddiq, M., Characterization of polyphenol oxidase from blueberry (Vaccinium corymbosum L.). Food chemistry, **2017.** 218 p.216-220.
33. Cheatham, CL., et al., Blueberry Consumption Affects Serum Uric Acid Concentrations in Older Adults in a Sex-Specific Manner. Antioxidants (Basel, Switzerland), **2016.** 5(4).
34. Zhan, W., et al., Effects of blueberries on migration, invasion, proliferation, the cell cycle and apoptosis in hepatocellular carcinoma cells. Biomed Rep. 2016;5(5):579-84.
35. Kanaya, N., et al., Whole blueberry powder inhibits metastasis of triple negative breast cancer in a xenograft mouse model through modulation of inflammatory cytokines, Nutrition and cancer, **2014.** 66(2) p.242-248.
36. Jeyabalan, J., Chemopreventive and therapeutic activity of dietary blueberry against estrogen-mediated breast cancer. Journal of agricultural and food chemistry, **2014.** 62(18) p.3963-3971.
37. Mak, KK. et al. Pterostilbene, a bioactive component of blueberries, suppresses the generation of breast cancer stem cells within tumor microenvironment and metastasis via modulating NF-kappaB/microRNA 448 circuit. Molecular nutrition & food research. **2013.** 57(7) p. 1123-1134.
38. Montales, MT., et al., Repression of mammosphere formation of human breast cancer cells by soy isoflavone genistein and blueberry polyphenolic acids suggests diet-mediated targeting of cancer stem-like/progenitor cells, Carcinogenesis, **2012.** 33(3), p. 652-660.
39. Adams, LS., Whole blueberry powder modulates the growth and metastasis of MDA-MB-231 triple negative breast tumors in nude mice,The Journal of nutrition, **2011.** 141(10) p. 1805-12.
40. Faria, A., et al., Blueberry anthocyanins and pyruvic acid adducts: anticancer properties in breast cancer cell lines, Phytotherapy research: PTR, **2010.** 24(12), p.1862-1869.
41. Adams, LS., Blueberry phytochemicals inhibit growth and metastatic potential of MDA-MB-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway, Cancer research, **2010.** 70(9) p. 3594-3605.
42. Seeram, NP., et al., Blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts inhibit growth and stimulate apoptosis of human cancer cells in vitro, Journal of agricultural and food chemistry, **2006.** 54(25), 9329-9339.
43. McAnulty, LS., et al., Six weeks daily ingestion of whole blueberry powder increases natural killer cell counts and reduces arterial stiffness in sedentary males and females. Nutrition research (New York, NY), **2014.** 34(7) p.577-584.
44. Qi, C., (Blueberry anthocyanins induce G2/M cell cycle arrest and apoptosis of oral cancer KB cells through down-regulation methylation of p53). Yi chuan = Hereditas. **2014.** 36(6) p.566-573.
45. Bunee, A., et al., Anthocyanin determination in blueberry extracts from various cultivars and their antiproliferative and apoptotic properties in B16-F10 metastatic murine melanoma cells. Phytochemistry, **2013.** 95 p. 436-444.
46. Lee, CM., et al., BlueBerry Isolate, Pterostilbene, Functions as a Potential Anticancer Stem Cell Agent in Suppressing Irradiation-Mediated Enrichment of Hepatoma Stem Cells. Evidence-based complementary and alternative medicine : eCAM. **2013.** P. 258-425.

47. Tsuda, H., et al., Antioxidant Activities and Anti-Cancer Cell Proliferation Properties of Natsuhaze (Vaccinium oldhamii Miq.), Shashanbo (V. bracteatum Thunb.) and Blueberry Cultivars. Plants (Basel, Switzerland), **2013.** 2(1) p.57-71.
48. Zu XY, Zhang ZY, Zhang XW, Yoshioka M, Yang YN, Li J. Anthocyanins extracted from Chinese blueberry (Vaccinium uliginosum L.) and its anticancer effects on DLD-1 and COLO205 cells. Chinese medical journal. 2010;123(19):2714-9.
49. Simmen, FA., Lack of efficacy of blueberry in nutritional prevention of azoxymethane-initiated cancers of rat small intestine and colon, BMC gastroenterology, **2009.** 9 p.67.
50. Gordillo, G., Oral administration of blueberry inhibits angiogenic tumor growth and enhances survival of mice with endothelial cell neoplasm, Antioxidants & redox signaling, **2009.** 11(1)p.47-58.
51. Suh N, et al. Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. Clinical cancer research : an official journal of the American Association for Cancer Research, **2007.** 13(1) p.350-5.
52. Schmidt, BM., et al., Differential effects of blueberry proanthocyanidins on androgen sensitive and insensitive human prostate cancer cell lines, Cancer letters, **2006.** 231(2) p. 240-246.
53. Matchett, MD., et al., Blueberry flavonoids inhibit matrix metalloproteinase activity in DU145 human prostate cancer cells, Biochemistry and cell biology = Biochimie et biologie cellulaire, **2005.** 83(5) p.637-643.
54. Yi, W., et al., Phenolic compounds from blueberries can inhibit colon cancer cell proliferation and induce apoptosis. Journal of agricultural and food chemistry, **2005.** 53(18) p. 7320-7329.
55. Akter, S., et al., Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population, Japanese journal of clinical oncology, **2016.** 46(8) p. 781-787.
56. Guertin, KA., et al., Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer, The American journal of clinical nutrition, **2015.** 101(5) p.1000-1011.
57. Mahmoud, SS., Hormetic/cytotoxic effects of Nigella sativa seed alcoholic and aqueous extracts on MCF-7 breast cancer cells alone or in combination with doxorubicin, Cell biochemistry and biophysics **2013.** 66: p. 451-60.
58. Hassan, MI., et al., Antineoplastic effects of bee honey and Nigella sativa on hepatocellular carcinoma cells, Integrative cancer therapies **2012.** 11: p. 354-363.
59. Salim, EI., Cancer chemopreventive potential of volatile oil from black cumin seeds, Nigella sativa L, in a rat multi-organ carcinogenesis bioassay, Oncology letters **2010.** 1: p. 913-924.
60. Salomi, MJ., et al., Inhibitory effects of Nigella sativa and saffron (Crocus sativus) on chemical carcinogenesis in mice. Nutrition and cancer **1991.** 16: p. 67-72.
61. Abdel-Aziz, M., et al., Effect of dexamethasone and Nigella sativa on inducible nitric oxide synthase in the lungs of a murine model of allergic Asthma, Iranian journal of allergy, asthma, and immunology, **2014.** 13: p. 324-334.
62. Keyhanmanesh, R., et al., The main relaxant constituents of Nigella sativa methanolic fraction on Guinea pig tracheal chains, Iranian journal of allergy, asthma, and immunology **2013.** 12: p. 136-143.

63. Balaha, MF., et al., Oral Nigella sativa oil ameliorates ovalbumin-induced bronchial asthma in mice, International immunopharmacology, **2012.** 14: p. 224-231.

64. Boskabady, MH., The effect of Nigella sativa alone, and in combination with dexamethasone, on tracheal muscle responsiveness and lung inflammation in sulfur mustard exposed guinea pigs, Journal of ethnopharmacology **2011.** 137: p. 1028-1034.

65. Nikakhlagh, S., Herbal treatment of allergic rhinitis: the use of Nigella sativa, American journal of otolaryngology **2011.** 32: p. 402-407.

66. Boskabady, MH., et al., Antiasthmatic effect of Nigella sativa in airways of asthmatic patients. Phytomedicine: international journal of phytotherapy and phytopharmacology, **2010.** 17: p.707-713.

67. Assayed, ME., Radioprotective effects of black seed (Nigella sativa) oil against hemopoietic damage and immunosuppression in gamma-irradiated rats, Immunopharmacology and immunotoxicology, **2010.** 32: p.284-296.

68. Abbas, AT., Effect of dexamethasone and Nigella sativa on peripheral blood eosinophil count, IgG1 and IgG2a, cytokine profiles and lung inflammation in murine model of allergic asthma, The Egyptian journal of immunology **2005.** 12: p. 95-102.

69. Fallahi, M., et al., Effect of Alpha-Hederin, the active constituent of Nigella sativa, on miRNA-126, IL-13 mRNA levels and inflammation of lungs in ovalbumin-sensitized male rats, Avicenna journal of phytomedicine, **2016.** 6: p. 77-85.

70. Keyhanmanesh, R., The Protective Effect of alpha-Hederin, the Active Constituent of Nigella sativa, on Lung Inflammation and Blood Cytokines in Ovalbumin Sensitized Guinea Pigs. Phytotherapy research: PTR **2015.** 29: p. 1761-1767.

71. Pejman, L., Thymoquinone, the main constituent of Nigella sativa, affects adenosine receptors in asthmatic guinea pigs, Iranian journal of basic medical sciences **2014.** 17: p.1012-1019.

72. Keyhanmanesh, R., et al., The relaxant effect of Nigella sativa on smooth muscles, its possible mechanisms and clinical applications. Iranian journal of basic medical sciences **2014.** 17: p. 939-949.

73. Saadat, S., et al., The protective effect of alpha-hederin, the active constituent of Nigella sativa, on tracheal responsiveness and lung inflammation in ovalbumin-sensitized guinea pigs. The journal of physiological sciences: JPS **2015.** 65: p.285-292.

74. Keyhanmanesh, R., et al., The effect of single dose of thymoquinone, the main constituents of Nigella sativa, in guinea pig model of asthma, BioImpacts: BI **2014.** 4: p.75-81.

75. Boskabady, MH., et al., Effects of aqueous and macerated extracts from Nigella sativa on guinea pig isolated heart activity. Die Pharmazie, **2005.** 60: p. 943-948.

76. Boskabady MH, The possible prophylactic effect of Nigella sativa seed extract in asthmatic patients. Fundamental & clinical pharmacology, **2007.** 21: p. 559-566.

77. Cerella, C., Chemical properties and mechanisms determining the anti-cancer action of garlic-derived organic sulfur compounds, Anticancer Agents Med Chem, **2011.** 11(3): p.267-271.
78. Bagul, M., Crude garlic extract inhibits cell proliferation and induces cell cycle arrest and apoptosis of cancer cells in vitro. *J Med Food,* **2015.** 18(7): p.731-737.
79. Ebrahimi, M., Purified protein fraction of garlic extract modulates cellular immune response against breast transplanted tumors in BALB/c mice model, *Cell J,* **2013.** 15 (1): p. 65-75.
80. Chandra-Kuntal, K., Critical role for reactive oxygen species in apoptosis induction and cell migration inhibition by diallyl trisulfide, a cancer chemopreventive component of garlic, *Breast Cancer Res Treat,* **2013.** 138(1): p. 69-79.
81. Modem, S., Fresh garlic extract induces growth arrest and morphological differentiation of MCF7 breast cancer cells, *Genes Cancer,* **2012.** 3(2): p.177-186.
82. Tsubura, A., Anticancer effects of garlic and garlic-derived compounds for breast cancer control. Anticancer Agents Med Chem, **2011.** 11(3): p. 249-253.
83. Malki, A., Garlic constituent diallyl trisulfide induced apoptosis in MCF7 human breast cancer cells. Cancer Biol Ther. **2009.** 8(22): p. 2174-2184.
84. Milner, JA., Preclinical perspectives on garlic and cancer. *J Nutr,* **2006.** 136(3): p. 827S-31S.
85. Challier, B., Garlic, onion, and cereal fiber as protective factors for breast cancer: a French case–control study, *Eur J Epidemiol,* **1998.** 14(8): p.737-747.
86. Li, G., Anti-proliferative effects of garlic constituents in cultured human breast cancer cells, *Oncol Rep,* **1995.** 2(5): p.787-791.
87. Pourzand, A, et al., Associations between Dietary Allium Vegetables and Risk of Breast Cancer: A Hospital-Based Matched Case-Control Study. *J Breast Cancer,* **2016.** 19(3): p. 292-300.
88. Baraya, YU., The Immunomodulatory Potential of Selected Bioactive Plant-Based Compounds in Breast Cancer: A Review, *Anticancer Agents Med Chem,* **2016.**
89. Shareef, M., Natural cures for breast cancer treatment, *Saudi Pharm J,* **2016.** 24(3): p. 233-240.
90. Liu, Y., et al., Antimetastatic Therapies of the Polysulfide Diallyl Trisulfide against Triple-Negative Breast Cancer (TNBC) via Suppressing MMP2/9 by Blocking NF-kappaB and ERK/MAPK Signaling Pathways. PloS one. **2015.** 10(4): p. e0123781.
91. Huang, J., et al., Diallyl disulfide inhibits growth and metastatic potential of human triple-negative breast cancer cells through inactivation of the beta-catenin signaling pathway. *Mol Nutr Food Res,* **2015.** 59(6): p.1063-1075.
92. Kim, SH., Forkhead Box Q1 Is a Novel Target of Breast Cancer Stem Cell Inhibition by Diallyl Trisulfide, *J Biol Chem,* **2016.** 291(26): p.13495-13508.
93. Xiao, X., et al. Diallyl disulfide suppresses SRC/Ras/ERK signaling-mediated proliferation and metastasis in human breast cancer by up-regulating miR-34a, *PloS one,* **2014.** 9(11): p. e112720.
94. McCaskill, ML., Diallyl sulfide inhibits diethylstilbestrol induced DNA damage in human breast epithelial cells (MCF-10A). Steroids. **2014.** 92: p. 96-100.
95. Zhang W, Apoptosis in MCF-7 breast cancer cells induced by S-alkenylmercaptocysteine (CySSR) species derived from Allium tissues in combination with sodium selenite, *Food Chem Toxicol,* **2014.** 68: p. 1-10.
96. Hahm ER. and Singh SV., Diallyl trisulfide inhibits estrogen receptor-alpha activity in human breast cancer cells. Breast Cancer Res Treat. **2014.** 144(1): p. 47-57.
97. Ebrahimi, M., Purified Protein Fraction of Garlic Extract Modulates Cellular Immune Response against Breast Transplanted Tumors in BALB/c Mice Model, *Cell journal,* **2013.** 15(1): p. 65-75.

98. Altonsy, MO., Diallyl disulfide-induced apoptosis in a breast-cancer cell line (MCF-7) may be caused by inhibition of histone deacetylation, *Nutr Cancer*, **2012.** 64(8): p. 1251-1260.
99. Modem, S., Fresh Garlic Extract Induces Growth Arrest, and Morphological Differentiation of MCF7 Breast Cancer Cells, *Genes Cancer*, 2012. 3(2): p. 177-186.
100. Tsubura, A., Anticancer effects of garlic and garlic-derived compounds for breast cancer control, *Anticancer Agents Med Chem*, **2011.** 11(3): p. 249-253.
101. Bright-Gbebry M., et al., Use of multivitamins, folic acid, and herbal supplements among breast cancer survivors: the black women's health study. BMC Complement Altern Med. **2011.** 11: p. 30.
102. McLay, JS., Complementary and alternative medicines use by Scottish women with breast cancer. What, why and the potential for drug interactions? *Eur J Clin Pharmacol*, **2012.** 68(5): p. 811-819.
103. Na, HK., Diallyl trisulfide induces apoptosis in human breast cancer cells through ROS-mediated activation of JNK and AP-1, *Biochem Pharmacol*, **2012.** 84(10): p. 1241-1250.
104. Lei, XY., et al. Apoptosis induced by diallyl disulfide in human breast cancer cell line MCF-7. Acta Pharmacol Sin. **2008.** 29(10): p. 1233-1239.
105. Gued, LR., Diallyl sulfide inhibits diethylstilbestrol-induced lipid peroxidation in breast tissue of female ACI rats: implications in breast cancer prevention, *Oncol Rep*, **2003.** 10(3): p. 739-743.
106. Kim, SH., Forkhead Box Q1 Is a Novel Target of Breast Cancer Stem Cell Inhibition by Diallyl Trisulfide. *J Biol Chem, jbc*, **2016.**
107. Gued, LR., Diallyl sulfide inhibits diethylstilbestrol-induced lipid peroxidation in breast tissue of female ACI rats: implications in breast cancer prevention, *Oncol Rep*, **2003.** 10(3): p. 739-744.
108. Fukushima, S., Cancer prevention by organosulfur compounds from garlic and onion. *J Cell Biochem Suppl*, **1997.** 67(S27): p.100-105.