Allicin

Subjects: Oncology

Contributor: Wamidh H. Talib, Media Mohammed Baban, Aya O. Azzam, Jenan J. Issa, Alaa Y. Ali, Alia Kh. AlSuwais, Sana Allala, Lina T. AL Kury

Allicin is one of the main ingredients in garlic (*Allium sativum* L.). It is a bioactive sulfur compound maintained in various plant sections in a precursor state.

Keywords: allicin ; cancer hallmarks ; anticancer ; angiogenesis

1. Introduction

Cancer, the second-leading cause of death worldwide, is one of the biggest public health problems, resulting in the annual mortality of 10 million people [1]. Because of the detrimental effects that cancer and its treatment have on financial resources and the healthcare system, greater focus must be paid to creating novel preventative and therapeutic approaches that are both affordable and efficacious [2]. Natural products are a viable source for the development of new, effective anticancer medications because of their low toxicity, diversity of chemical structures, and capacity to target many cancers [3]. One of these compounds is allicin which is a potent bioactive in garlic [4]. Its antitumor potential is reported in a variety of tumor types [5]. Furthermore, antibacterial [6], cholesterol-lowering [7], anti-inflammatory [8], and antiviral activities of allicin are also described [9]. Several studies have stated that the majority of the lipid-lowering, antioxidant, anti-atherosclerotic, and anticancer effects of whole garlic, as seen in animals and humans, are submitted to allicin, or their spontaneous transformation compounds (allyl polysulfides), or their common metabolite (allyl methyl sulfide, AMS) [10][11]. Interestingly, an increasing amount of research indicates that allicin may target several cancer hallmarks, which are the basic biological functions and characteristics that contribute to the occurrence and progression of cancer [12]. The cancer hallmarks include sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, activation of invasion and metastasis, reprogramming of energy metabolism, and evasion of immune destruction [13]. It has been reported that allicin inhibits cancer cell proliferation, induces cell apoptosis, and enhances the accumulation of reactive oxygen species [14][15][16]. **Figure 1** shows a summary of cancer hallmarks that can be potentially targeted by allicin.

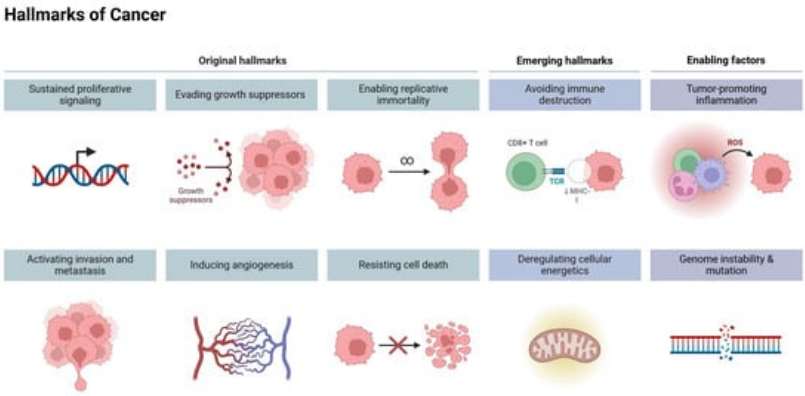

Figure 1. Summary of the potential cancer hallmark targets for allicin.

2. Allicin

2.1. Allicin Chemical Structure and Formation

Garlic (*Allium sativum* L.) contains many well-known organosulfur compounds, including allicin or diallyl thiosulfinate (**Figure 2**). Garlic does not naturally contain allicin; it can only be formed when the cloves are sliced or crushed [17]. Freshly crushed garlic has a distinct odor due to this volatile molecule (allicin), which is weakly miscible in water [18]. When the garlic clove is chopped or cleaved, it activates the alliinase enzyme. Following that, this enzyme transforms the amino

acid alliin (L-(+)-S-Allyl cysteine sulfoxide) into allyl sulfenic acid (2-propene-sulfenic acid), which is unstable and highly reactive at room temperature. Then, two allyl sulfenic acid molecules spontaneously condense to generate allicin [19]. Diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide, allyl methyl trisulfide, dithiins, and ajone vinyldithiines are some of the metabolites of allicin [20].

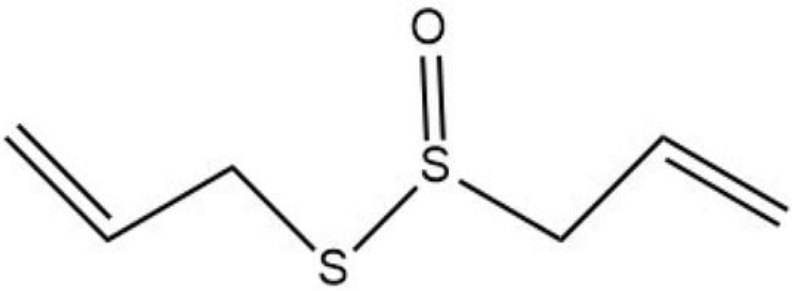

Figure 2. Allicin chemical structure [S-(Prop-2-en-1-yl) prop-2-ene-1-sulfinothioate].

2.2. Allicin Bioavailability

Clinical trial data on garlic's anticancer properties are inconsistent due to variations in the bioavailability of sulfur-containing components between raw garlic and supplement formulations containing allicin as the main pharmacological agent [11]. Studies revealed that garlic extract possesses growth-inhibitory features that are attributed to its water-soluble component, allicin [21]. It is produced by an enzyme alliinase, which reacts to an allin precursor when garlic is cut or chewed [22]. Fortunately, the half-life of allicin has been proven to be less than a minute, which indicates that it is digested quickly [23] due to its quick penetration into several cell compartments. Allicin is highly unstable and thus has strong membrane permeability and significant antioxidant activity [17]. It can be stabilized by monoclonal antibody conjugation and liposome encapsulation; this may also help in reducing its unpleasant aroma. Besides the above-mentioned pharmacological properties, allicin also exhibits high gastrointestinal absorption and good blood–brain barrier permeability [24][25]. Several methods are considered to enhance the bioavailability and anticancer effects of allicin, such as nanoformulations. For instance, a study suggested the use of cyclodextrin-based nanoparticles to improve the cellular delivery of allicin. This approach significantly enhanced the efficacy of allicin in cancer treatment [26]. Recently, researchers utilized this method and encapsulated the compound in solid lipid nanoparticles (SLNs) coated with chitosan-conjugated folic acid and administered it. The results revealed that these nanoparticles have the maximized potential to trigger apoptosis and prevent free radicals in cancer cells by stimulating the intrinsic apoptosis pathways [27]. Remarkably, another study prepared allicin nanoformulations using gelatin nanoparticles (GNPs) surface-conjugated to glycyrrhetinic acid. The application of these particles resulted in increased allicin cytotoxicity towards liver cancer cells (HepG2), suggesting them a successful liver cancer therapy [28]. In addition, an allicin-loaded folic acid and polyethylene glycol (PEG)-modified chitosan/lecithin formulation was also developed to enhance the anti-colon cancer effects of allicin. Their application notably increased allicin toxicity by upsurging caspase 3 and 9 expression and activation of intrinsic apoptotic cascade in treated cancer cells. Additionally, it also confirmed allicin's anti-angiogenic effects [29]. Concludingly, combining allicin with several nano-carriers may not only increase its cellular delivery and bioavailability but also have therapeutic implications.

2.3. Allicin Toxicity

A randomized controlled trial has shown that high doses of allicin in susceptible individuals can result in a range of side effects such as insomnia, vomiting, heartburn, dizziness, diarrhea, tachycardia, sweating, offensive body odor, and flatulence [30]. Chemically, allicin is a lipid soluble so it can cross the cell membrane and enter the cells easily to oxidize cellular thiols and result in structural protein changes [4]. A meta-analysis including eight studies of garlic plants showed that the increased intake of allium vegetables was associated with an increased risk of colon disease in women and using garlic supplements can increase the chances of colorectal cancer (CRC) [31].

2.4. Biological Functions

Allicin and its secondary metabolites have many important biological functions, such as anticancer effects. It not only protects against tumors but also alleviates the adverse effects of anticancer treatment and enhances the chemotherapeutic response [19]. Allicin has an antioxidant, anti-inflammatory, antihypertensive, and cardiovascular protective role in our bodies [32]. As an antioxidant phytochemical, it scavenges reactive oxygen species (ROS) and protects cells from oxidative DNA damage [33]. Alongside this, allicin exhibits telomerase activity inhibition in both dose- and time-dependent manners in gastric cancer cells. Thus, it can serve as a potent anticancer agent [24]. Moving forward,

several studies have indicated that it potentially affects cancer cell growth, proliferation, and metastasis and encourages apoptosis (programmed cell death) [4][34]. Allicin also has an antipathogenic effect against bacteria, viruses, fungi, and parasites. On the other hand, it can increase the gut's normal flora (beneficial bacteria) [4].

References

1. Mattiuzzi, C.; Lippi, G. Cancer statistics: A comparison between world health organization (WHO) and global burden of disease (GBD). Eur. J. Public Health 2020, 30, 1026–1027.
2. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249.
3. Choudhari, A.S.; Mandave, P.C.; Deshpande, M.; Ranjekar, P.; Prakash, O. Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Front. Pharmacol. 2020, 10, 1614.
4. Catanzaro, E.; Canistro, D.; Pellicioni, V.; Vivarelli, F.; Fimognari, C. Anticancer potential of allicin: A review. Pharmacol. Res. 2022, 177, 106118.
5. Oommen, S.; Anto, R.J.; Srinivas, G.; Karunagaran, D. Allicin (from garlic) induces caspase-mediated apoptosis in cancer cells. Eur. J. Pharmacol. 2004, 485, 97–103.
6. Leontiev, R.; Hohaus, N.; Jacob, C.; Gruhlke, M.C.H.; Slusarenko, A.J. A comparison of the antibacterial and antifungal activities of thiosulfinate analogues of allicin. Sci. Rep. 2018, 8, 6763.
7. Sharifi-Rad, J.; Cristina Cirone Silva, N.; Jantwal, A.; Bhatt, D.I.; Sharopov, F.; Cho, C.W.; Taheri, Y.; Martins, N. Therapeutic potential of allicin-rich garlic preparations: Emphasis on clinical evidence toward upcoming drugs formulation. Appl. Sci. 2019, 9, 5555.
8. Metwally, D.M.; Al-Olayan, E.M.; Alanazi, M.; Alzahrany, S.B.; Semlali, A. Antischistosomal and anti-inflammatory activity of garlic and allicin compared with that of praziquantel in vivo. BMC Complement. Altern. Med. 2018, 18, 135.
9. Ma, T.; Chen, D.; Tu, Y.; Zhang, N.; Si, B.; Deng, K.; Diao, Q. Effect of supplementation of allicin on methanogenesis and ruminal microbial flora in Dorper crossbred ewes. J. Anim. Sci. Biotechnol. 2016, 7, 1.
10. Cavallito, C.J.; Bailey, J.H. Allicin, the antibacterial principle of Allium sativum. I. Isolation, physical properties and antibacterial action. J. Am. Chem. Soc. 1944, 66, 1950–1951.
11. Lawson, L.D.; Hunsaker, S.M. Allicin Bioavailability and Bioequivalence from Garlic Supplements and Garlic Foods. Nutrients 2018, 10, 812.
12. Talib, W.H.; Daoud, S.; Mahmod, A.I.; Hamed, R.A.; Awajan, D.; Abuarab, S.F.; Odeh, L.H.; Khater, S.; Al Kury, L.T. Plants as a source of anticancer agents: From bench to bedside. Molecules 2022, 27, 4818.
13. Fouad, Y.A.; Aanei, C. Revisiting the hallmarks of cancer. Am. J. Cancer Res. 2017, 7, 1016–1036.
14. Tu, G.; Zhang, Y.F.; Wei, W.; Li, L.; Zhang, Y.; Yang, J.; Xing, Y. Allicin attenuates H2O2-induced cytotoxicity in retinal pigmented epithelial cells by regulating the levels of reactive oxygen species. Mol. Med. Rep. 2016, 13, 2320–2326.
15. Wang, S.; Ren, D. Allicin protects traumatic spinal cord injury through regulating the HSP70/Akt/iNOS pathway in mice. Mol. Med. Rep. 2016, 14, 3086–3092.
16. Wang, W.; Du, Z.; Nimiya, Y.; Sukamtoh, E.; Kim, D.; Zhang, G. Allicin inhibits lymphangiogenesis through suppressing activation of vascular endothelial growth factor (VEGF) receptor. J. Nutr. Biochem. 2016, 29, 83–89.
17. Omar, S.H.; Al-Wabel, N.A. Organosulfur compounds and possible mechanism of garlic in cancer. Saudi Pharm. J. 2010, 18, 51–58.
18. Marchese, A.; Barbieri, R.; Sanches-Silva, A.; Daglia, M.; Nabavi, S.F.; Jafari, N.J.; Izadi, M.; Ajami, M.; Nabavi, S.M. Antifungal and antibacterial activities of allicin: A review. Trends Food Sci. Technol. 2016, 52, 49–56.
19. Borlinghaus, J.; Albrecht, F.; Gruhlke, M.C.H.; Nwachukwu, I.D.; Slusarenko, A.J. Allicin: Chemistry and biological properties. Molecules 2014, 19, 12591–12618.
20. Ariyanta, H.A.; Ivandini, T.A.; Yulizar, Y. A novel way of the synthesis of three-dimensional (3D) MoS2 cauliflowers using allicin. Chem. Phys. Lett. 2021, 767, 138345.
21. Modem, S.; DiCarlo, S.E.; Reddy, T.R. Fresh garlic extract induces growth arrest and morphological differentiation of MCF7 breast cancer cells. Genes Cancer 2012, 3, 177–186.

22. Revtovich, S.; Lyfenko, A.; Tkachev, Y.; Kulikova, V.; Koval, V.; Puchkov, V.; Anufrieva, N.; Solyev, P.; Morozova, E. Anticandidal Activity of In Situ Methionine γ-Lyase-Based Thiosulfinate Generation System vs. Synthetic Thiosulfinates. Pharmaceuticals 2023, 16, 1695.
23. Zhang, Y.; Liu, X.; Ruan, J.; Zhuang, X.; Zhang, X.; Li, Z. Phytochemicals of garlic: Promising candidates for cancer therapy. Biomed. Pharmacother. 2020, 123, 109730.
24. Sarvizadeh, M.; Hasanpour, O.; Naderi Ghale-Noie, Z.; Mollazadeh, S.; Rezaei, M.; Pourghadamyari, H.; Masoud Khooy, M.; Aschner, M.; Khan, H.; Rezaei, N. Allicin and digestive system cancers: From chemical structure to its therapeutic opportunities. Front. Oncol. 2021, 11, 650256.
25. Pandey, P.; Khan, F.; Alshammari, N.; Saeed, A.; Aqil, F.; Saeed, M. Updates on the anticancer potential of garlic organosulfur compounds and their nanoformulations: Plant therapeutics in cancer management. Front. Pharmacol. 2023, 14, 1154034.
26. Chen, X.; Li, H.; Xu, W.; Huang, K.; Zhai, B.; He, X. Self-assembling cyclodextrin-based nanoparticles enhance the cellular delivery of hydrophobic allicin. J. Agric. Food Chem. 2020, 68, 11144–11150.
27. Alyasiri, F.J.; Ghobeh, M.; Tabrizi, M.H. Preparation and Characterization of Allicin-Loaded Solid Lipid Nanoparticles Surface-Functionalized with Folic Acid-Bonded Chitosan: In Vitro Anticancer and Antioxidant Activities. FBL 2023, 28, 135.
28. Ossama, M.; Hathout, R.M.; Attia, D.A.; Mortada, N.D. Enhanced Allicin Cytotoxicity on HEPG-2 Cells Using Glycyrrhetinic Acid Surface-Decorated Gelatin Nanoparticles. ACS Omega 2019, 4, 11293–11300.
29. Hashemy, S.I.; Amiri, H.; Hosseini, H.; Sadeghzadeh, F.; Jaseem, M.M.M.; Tabrizi, M.H. PEGylated lecithin–chitosan–folic acid nanoparticles as nanocarriers of allicin for in vitro controlled release and anticancer effects. Appl. Biochem. Biotechnol. 2023, 195, 4036–4052.
30. Alare, K.; Alare, T. Review of toxicity of allicin from garlic. Open Access J. Toxicol. 2020, 3.
31. Zhu, B.; Zou, L.; Qi, L.; Zhong, R.; Miao, X. Allium vegetables and garlic supplements do not reduce risk of colorectal cancer, based on meta-analysis of prospective studies. Clin. Gastroenterol. Hepatol. 2014, 12, 1991–2001.
32. Bhattacharya, S.; Das, S.; Banik, S. Fabrication and physicochemical investigation of pH-responsive alginate/pectin hybrid network hydrogel for improved stability and controlled release of diallyl thiosulfinate. Mater. Today Commun. 2024, 38, 108235.
33. Talib, W.H.; Atawneh, S.; Shakhatreh, A.N.; Hamed, R.A.; Al-Yasari, I.H. Anticancer potential of garlic bioactive constituents: Allicin, Z-ajoene, and organosulfur compounds. Pharmacia 2024, 71, 1–23.
34. Țigu, A.B.; Moldovan, C.S.; Toma, V.-A.; Farcaș, A.D.; Moț, A.C.; Jurj, A.; Fischer-Fodor, E.; Mircea, C.; Pârvu, M. Phytochemical analysis and in vitro effects of Allium fistulosum L. and Allium sativum L. extracts on human normal and tumor cell lines: A comparative study. Molecules 2021, 26, 574.