Therapeutic potential of garlic, aged garlic extract and garlic-derived compounds on pancreatic cancer (Review)

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Abstract. Garlic is a popular ingredient used in cuisines and traditional medicines worldwide. It contains numerous bioactive organosulfur-containing compounds, such as allicin, with reported potential for anticancer and antimicrobial therapy. The biological activity and potential use of garlic and its products have been extensively investigated. Aged garlic extract (AGE) is a product manufactured by aging garlic, and has been shown to have numerous health benefits. It has been previously revealed that several garlic-derived compounds, including AGE, have tumor-suppressive effects in various cancer models. Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive cancers, and carries a dismal prognosis. Recently, numerous tumors, including PDAC, were shown to harbor intracellular bacteria, some of which are oral pathogens. Tumor-associated bacteria have been linked to cancer progression. Garlic may inhibit tumor development, in part, by targeting these bacteria. Although it requires further investigation, pharmacological and antibacterial effects of garlic and its products could offer significant therapeutic benefits for the prevention and treatment of PDAC. In the present review, the therapeutic potential of garlic on PDAC is summarized and discussed.

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1. Introduction

Garlic (*Allium sativum*) is a species of bulbous plant, and has been globally used as a culinary and medicinal herb for centuries. The medicinal properties of garlic have been extensively studied, with a focus on its bioactive sulfur-containing compounds, such as allicin, ajoene, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), dimethyl trisulfide (DMTS), *S*-allyl-cysteine (SAC) and *S*-propargyl-cysteine (SPRC). These compounds are considered to contribute to garlic's various therapeutic effects, including anti-inflammatory, antimicrobial, antioxidant and anticancer activities (1-4). Garlic oil, powder and extract are available as supplements for culinary uses, natural pesticides and medicinal purposes. Aged garlic extract (AGE), a processed form of garlic produced by aging garlic in an ethanol-water mixture for >10 months, has gained attention for its ability to enhance immune function and reduce the risk of chronic diseases (2,3). Furthermore, AGE is rich in beneficial organic sulfur compounds, which provide numerous health advantages. Numerous previous studies have shown that AGE has tumor-suppressive effects on various cancer cells, and its use has shown benefit in patients (5-9). Pancreatic cancer is one of the most aggressive and lethal forms of cancer, characterized by a poor prognosis and high mortality with <10% of patients surviving at five-years (10,11). The development of pancreatic cancer involves complex interactions between genetic and environmental factors, making it a challenging disease to prevent, diagnose and treat. Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer, accounting for >90% of all pancreatic malignancies. Genetics and lifestyle factors such as smoking, alcohol consumption and obesity are known as risk factors of PDAC; however the great majority of PDAC cases develop in individuals without known risk factors (10-12). Of note, increasing evidence points to bacteria as possible contributors to PDAC development (11,12). Recent clinical and experimental investigations have demonstrated the presence of an intratumor microbiome in PDAC and revealed oncological actions of some species of bacteria (11-17). Accumulated

studies have investigated the potential role of garlic, AGE, and their bioactive compounds in the prevention and treatment of PDAC and related conditions, including pancreatitis and periodontitis (1,4,8,18,19). In the present review, it was aimed to summarize and discuss the potential beneficial effects of garlic and its compounds on PDAC, and to highlight the possible role of tumor-associated bacteria in these effects.

2. Effects of garlic, AGE and garlic-derived sulfur compounds on pancreatic cancer

Natural agents derived from plants are intensely studied for the development of supplements, antibiotics and anticancer drugs. Among them, garlic is used for a food source as well as in traditional medicine. Garlic and AGE contain multiple pharmacologically-active sulfur compounds and have great potential to prevent and treat various types of cancers including PDAC (1,5-9). Numerous volatile and non-volatile garlic compounds were previously reported (1,20,21). A case-control study conducted in the San Francisco Bay area has reported that garlic and onion consumption correlated with lower odds of developing pancreatic cancer, suggesting that these vegetables may help in preventing the disease (19). A randomized double-blind clinical trial by Ishikawa *et al* (8) has reported that daily AGE intake with capsules containing 500 mg AGE for 3 months increased both the number and activity of NK cells in patients with advanced liver, pancreatic, or colon cancer. Although not focused on pancreatic cancer, a randomized intervention trial included the use of AGE as part of a blinded and placebo-controlled study. After a follow-up period of over 22 years, the study concluded that this supplementation significantly reduced the risk of death in patients with gastric cancer (9).

Apoptosis is a form of programmed cell death that plays a vital role in maintaining cellular homeostasis by triggering a series of biochemical events. Decreased expression of anti-apoptosis genes, including B cell lymphoma 2 (Bcl-2), and elevated expression of pro-apoptosis factors such as caspase-3 and Bcl-2 associated X-protein (Bax), are commonly observed phenomena in the apoptotic process. Additionally, other factors such as p21, p53 and cyclins are well-documented contributors to this process. In cancer, survival-related genes are often dysregulated, and the evasion of apoptosis is a hallmark allowing malignant cells to survive and proliferate uncontrollably (21-25). The induction of apoptosis through cell cycle arrest and the regulation of its associated molecules is a critical strategy for controlling cancer progression, as it efficiently promotes the elimination of cancer cells. Various substances found in dietary natural products, including garlic, have been shown to modulate the expression of common genes involved in cancer cell survival, and induce apoptosis and cell cycle regulation in cancer cells (1,26-32). The activity of garlic and its compounds has been evaluated in several *in vitro* studies (Table I).

Garlic oil. Treatment with garlic oil inhibited the proliferation of several PDAC cell lines, including AsPC-1, Panc-1 and MiaPaCa-2, and showed pro-apoptotic effects in a dose-dependent manner. Early stage apoptosis was observed in AsPC-1 cells by transmission electron microscopy. Moreover, flow cytometric analysis revealed that the cell cycle of AsPC-1 cells was arrested at G2/M phase (26).

Allicin. Allicin, which is a naturally occurring product from garlic, is known as one of the major organosulfur compounds present in garlic and is responsible for its pungent smell. Chhabria *et al* (27) conjugated alliinase to a monoclonal antibody against carbohydrate antigen 19-9 (CA19-9), a widely used PDAC biomarker. The conjugate generates allicin *in situ* following the addition of alliin, and thereby reduces PDAC cell viability via induced oxidative stress, cell cycle arrest at the G1 phase, caspase-3 and p21 protein expression, DNA fragmentation and apoptosis. Furthermore, *in situ*-generated allicin increased p21 gene expression at the mRNA level, acetylation of histone H3 lysine 14 and phosphorylation of histone H3 serine 10, and reduced mono-methylation of histone H3 lysine 9 (27). Another study demonstrated the combined effects of allicin and recombinant interleukin-2 (rIL-2) on a murine subcutaneous xenograft model established with BxPC-3 pancreatic cancer cells. While allicin treatment exhihited significant antitumor effects, the combination further inhibited the growth of tumors and improved the survival rate of mice when compared with treatment with allicin or rIL-2 alone. This outcome was attributed to the induction of tumor cell apoptosis, activation of $CD4^+$ T, $CD8^+$ T and NK cells, and increased levels of interferon gamma (28).

DADS. DADS is a bioactive compound present in garlic. A study by Saini *et al* (29) demonstrated the cytotoxicity of DADS and its synthetic derivatives on pancreatic cancer MiaPaCa-2 cells. Among the tested DADS analogs, Bis[3-(3-fluorophenyl) prop-2-ene]disulfide was the most potent compound. In the pancreatic cancer cells, it upregulated Bax and concurrently reduced Bcl-2 protein levels, activated caspase-3, and induced apoptosis by G2/M phase arrest via DNA damage. The apoptotic process was also associated with checkpoint kinase-1 phosphorylation, upregulated levels of inactivated cell division cycle 25C and phosphorylation of Cdc2 (29).

DATS. DATS, a biologically active garlic compound, decreases the viability of PDAC cells and induces the activation of apoptosis through increased cell cycle arrest at the G2/M phase. This polysulfide increases the protein levels of Bax, Fas, p21, p53 and cyclin B1, whereas it decreases Akt, cyclin D1, MDM2 and Bcl-2 expression in pancreatic cancer Capan-2 cells. The DATS treatment was identified to regulate gene transcription in pancreatic cancer cells since the mRNA levels of Bax, Fas and cyclin D1 were upregulated, whereas Akt and Bcl-2 mRNA levels were downregulated by DATS treatment (30). In addition, the pro-apoptotic effects of DATS in various other cancers have been reported (23).

Ajoene. Ajoene is an organosulfur compound found in garlic, and it exists as a mixture of two stereoisomers: *Z*-ajoene and *E*-ajoene. *Z*-ajoene reduces PDAC cell viability, induces cell cycle arrest at the G2/M phase, and reduces transcriptional activity and protein level of glioma-associated oncogene (Gli), which is a transcription factor mediating the Hedgehog pathway. In addition, *Z*-ajoene downregulates the protein expressions of Gli1, Gli2, Ptch, and forkhead box protein M1 (FoxM1), a cell cycle regulator of G1/S and G2/M transitions and a known Gli-target protein. By contrast, this sulfur compound does not disrupt Akt protein level. As a consequence, *Z*-ajoene reduces

Table I. Potential therapeutic effects of garlic and its organosulfur compounds on pancreatic cancer.

First author/s, year	Materials tested	Target	Therapeutic effects	(Refs.)
Ishikawa *et al*, 2006	AGE	Advanced cancer patients with liver, pancreatic, or colon cancer	Increase the number and activity of NK cells	(8)
Lan *et al*, 2013	Garlic oil	AsPC-1, MiaPaCa-2, and Panc-1	Inhibit cell proliferation, induce cell cycle arrest and apoptosis	(26)
Chhabria *et al*, 2015	Allicin	MiaPaCa-2	Reduce cell viability, induce cell cycle arrest and apoptosis	(27)
Wang *et al*, 2013	Allicin	BxPC3	Inhibit tumor growth in a mouse xenograft model	(28)
Saini *et al*, 2017	DADS	MiaPaCa-2	Reduced cell viability	(29)
Ma *et al*, 2014	DATS	Capan-2	Reduce cell viability, induce cell cycle arrest and apoptosis	(30)
Lee *et al*, 2019	Ajoene	Panc-1	Reduce cell viability, induce cell cycle arrest	(31)
Wang *et al*, 2015	SPRC	Panc-1	Reduce cell viability, induce cell cycle arrest and apoptosis, inhibit tumor growth in a mouse xenograft model	(32)

AGE, aged garlic extract; DADS, diallyl disulfide; DATS, diallyl trisulfide; SPRC, *S*-propargyl-cysteine; NK, natural killer.

the levels of cell cycle-related proteins including c-myc, cyclin B1 and survivin, all of which are controlled by FoxM1 (31).

SPRC. SPRC, a structural analog of SAC, reduces the viability of PDAC cells, triggers cell cycle arrest during the G2/M phase, and induces apoptosis. Moreover, it inhibits tumor growth in Panc-1 mouse xenograft model by activating the c-Jun N-terminal kinase signaling pathway (32).

Therefore, garlic-derived products can exert direct anticancer effects on PDAC cells through modulating common molecular pathways. In addition, the exploration of survival-associated genes regulated by garlic is important to deepen our understanding of garlic's biological roles in cancer. Such insights can contribute to enhancing the precision of cancer therapies, thereby potentially improving clinical outcomes for patients.

Garlic products may also prevent PDAC by lowering the severity of conditions linked to PDAC development (Table II). Pancreatitis, characterized by inflammation of the pancreas, can increase precancerous lesions that eventually initiate progression to PDAC in the presence of oncogenic mutations (10-12,33). The effects of SPRC, a structural analog of SAC, were studied in a mouse model of acute pancreatitis (AP) induced by cerulein, a factor known to promote PDAC development synergistically with oncogenic Kras (33,34). Treatment of mice with SPRC for 3 h before AP induction significantly reduced inflammation and pro-inflammatory cytokines in the pancreas and lungs, along with increased anti-inflammatory cytokines. The protective effects of SPRC were attributed to its slow release of endogenous hydrogen sulfide (34). The anti-inflammatory actions of DADS were also determined in mice with cerulein-induced AP. Intraperitoneal administration of DADS significantly reduced pancreatic and pulmonary inflammation by decreasing serum amylase levels, myeloperoxidase activity, and histological damage in the pancreas and lungs. Additionally, DADS inhibited cerulein-induced IκB degradation and subsequent nuclear factor-kappa B (NF-κB) translocation (35). The same research group performed further investigation to improve understanding of the molecular mechanisms underlying the effects of DADS on cerulein-induced pancreatitis by focusing on the peroxisome proliferator-activated receptor gamma pathway. It was revealed that DADS attenuated tumor necrosis factor-alpha, cystathionine-gamma-lyase, signal transducer and activator of transcription 3 and NF-κB activation, and increased suppressor of cytokine signaling 3 expression (36). In addition, a recent investigation showed that DMTS, an additional organosulfur compound from garlic, reduced the pancreatic infiltration of leukocytes and cellular damage in mice with AP (37). During AP, DMTS upregulated the level of pancreatic HSP72, a stress-induced protective chaperone whose overexpression attenuates NF-κB activation, enabling accelerated recovery from cerulein-induced tissue injury (37,38). In summary, cumulative evidence supports a potential therapeutic role for garlic and its products in pancreatic cancer.

3. Effects of garlic extract and garlic-derived sulfur compounds on cancer chemoresistance

Chemoresistance is a major obstacle in the effective treatment of cancers, and contributes to poor patient prognosis in PDAC (39,40). The mechanisms behind chemoresistance are

Table II. Effects of AGE and garlic compounds on conditions linked to pancreatic ductal adenocarcinoma development.

First author/s, year	Materials tested	Target	Therapeutic effects	(Refs.)
Zini *et al*, 2020	AGE	Adult volunteers with mild to moderate periodontitis	Reduce the level of probing pocket depth	(18)
Sidhapuriwala *et al*, 2012	SPRC	Cerulein-induced AP in male Swiss mouse	Reduce inflammation in the pancreas and lungs	(34)
Mathan Kumar and Tamizhselvi, 2020	DADS	Cerulein-induced AP in male Swiss mouse	Attenuate severity of pancreatic and pulmonary inflammation	(35)
Marimuthu *et al*, 2022	DADS	Cerulein-induced AP in male Swiss mouse	Reduce inflammation in the pancreas and lungs through the pancreatic and pulmonary PPAR-γ activation	(36)
Orján *et al*, 2023	DMTS	Cerulein- or ethanol-palmitoleic acid-induced AP in male FVB/N mouse	Attenuate severity of inflammation	(37)
	DMTS	L-ornithine-HCl-induced AP in male Wister rat	Attenuate severity of inflammation	

AGE, aged garlic extract; SPRC, *S*-propargyl-cysteine; DADS, diallyl disulfide; DMTS, dimethyl trisulfide; AP, acute pancreatitis; PPAR-γ, peroxisome proliferator-activated receptor gamma.

highly complex, often involving alterations in cell survival pathways, efflux pumps and changes in the tumor microenvironment (39-41). Based on accumulated research findings, garlic and its derived bioactive compounds may improve therapeutic efficacy and potentially overcome chemoresistance through modulating multiple cellular pathways and inducing cell death (1,7,21,23). Several studies examined the effects of garlic, and garlic derivatives, on resistance to chemotherapeutic agents including those indicated in PDAC treatment, and the potential benefit of combining garlic or its compounds with these agents (Table III).

Garlic extract. 5-Fluorouracil (5-FU), a widely used pyrimidine nucleoside analogue for managing PDAC, disrupts DNA synthesis by the inhibition of thymidylate synthase activity leading to apoptotic events. A recent study exhibited that white and black garlic extract in combination with 5-FU increases the effects of 5-FU to Caco-2 cells if compared with 5-FU alone (42). Perez-Ortiz *et al* (43) examined combined treatment of garlic extract with either 5-FU or Oxaliplatin, a platinum-based anticancer agent that is utilized in the treatment of PDAC, against colon cancer cells. The results showed that garlic extract enhances the cytotoxicity of each drug (43). A study conducted by Horie *et al* (44) revealed that a standard laboratory diet plus AGE reduces orally administered 5-FU-induced intestinal damage in rats. Gemcitabine is a deoxycytidine analogue extensively used as a first-line chemotherapy for PDAC treatment; however, resistance to gemcitabine is common and significantly limits drug efficacy (39,40). Combining garlic extract with gemcitabine enhanced the chemotherapy cytotoxic effect on breast cancer cells (45), suggesting a potential role for garlic or its bioactive compounds in the management of gemcitabine resistant pancreatic cancer.

Allicin. It was reported that allicin can enhance the anticancer effects of 5-FU across different types of cancer cells (46-48). Moreover, allicin has been recently found to reverse resistance to the anticancer drug Paclitaxel in non-small cell lung cancer cells by inhibiting Cathepsin B activity and P-glycoprotein, a transmembrane transporter that functions as a drug efflux pump (49).

DADS. It was recently reported that DADS enhances the cytotoxic effects of 5-FU on gastric cancer cells (50). Other studies reported that DADS and DATS also contribute to chemosensitivity across multiple drugs (23,51).

Ajoene. Ajoene was reported to augment the therapeutic effects of cytarabine and fludarabine in resistant myeloid leukemia cells, by enhancing caspase-3 activation and Bcl-2 inhibition (52).

In addition to their therapeutic potential, garlic and its components may mitigate the side effects of anticancer drugs by alleviating tissue damage, modulating immunocytes, and potentially allowing for lower dosage of the agents (44,53,54). Taken together, these studies lay the foundation for using garlic or its derivatives as adjunctive treatments to overcome chemoresistance and improve the clinical management of patients with PDAC.

4. Pancreatic cancer cells harbor intracellular bacteria

Several previous studies have revealed the presence of a diverse microbiome within human PDAC tissues (13,14,55-57). Geller *et al* (55) found the presence of *Gammaproteobacteria* in PDAC tissue specimens obtained from patients who exhibit resistance to gemcitabine treatment. Similarly, Riquelme *et al* (56) conducted an analysis of the PDAC microbiome, and found

Table III. Effects of garlic, and garlic derivatives, on resistance to chemotherapeutic agents including those indicated in pancreatic ductal adenocarcinoma treatment, and the potential benefit of combining garlic or its compounds with these agents.

First author/s, year	Materials tested	Chemotherapeutic agent	Therapeutic effects	(Refs.)
Perez-Ortiz *et al*, 2020	Garlic extract	5-FU and Oxaliplatin	Enhance cytotoxic effects	(43)
Horie *et al*, 2001	AGE	5-FU	Prevent intestinal damage caused by 5-FU	(44)
Petrovic *et al*, 2018	Garlic extract	Gemcitabine	Enhance cytotoxic effects	(45)
Zou *et al*, 2016	Allicin	5-FU	Enhance cytotoxic effects, induce apoptosis, increase intracellular ROS production, reduce mitochondrial membrane potential, activate caspase-3 and PARP, downregulate Bcl-2	(46)
Khakbaz *et al*, 2021	Allicin	5-FU	Enhance cytotoxic effects, induce apoptosis, decrease P-gp and CD44 protein level	(47)
Tigu *et al*, 2020	Allicin	5-FU	Enhance cytotoxic effects	(48)
Gao *et al*, 2024	Allicin	Paclitaxel (Taxol)	Enhance cytotoxic effects, inhibit CTSB and P-gp activity, inhibit growth of tumor nodules in an orthotopic A549/Taxol nude mice model	(49)
Su *et al*, 2024	DADS	5-FU	Enhance cytotoxic effects	(50)
Hassan, 2004	Ajoene	Cytarabine and Fludarabine	Enhance cytotoxic effects, activate caspase-3, inhibit Bcl-2	(52)

AGE, aged garlic extract; DADS, diallyl disulfide; 5-FU, 5-fluorouracil; ROS, reactive oxygen species; PARP, poly ADP-ribose polymerase; Bcl-2, B cell lymphoma 2; CD44, cluster of differentiation 44; CTSB, cathepsin B; P-gp, P-glycoprotein.

a distinct intra-tumoral microbiome signature in long-term survivors, comprising *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora* and *Bacillus clausii*. Additionally, a multinational research group investigated the oral and gut microbiomes of patients with PDAC, and found 4 enriched species (*Streptococcus anginosus*, *Streptococcus oralis*, *Veillonella parvula* and *Veillonella atypica*) and a depleted *Faecalibacterium prausnitzii* in the gut signatures of patients with PDAC across 3 countries, Japan, Spain and Germany. Notably, these 4 microbial species are known to reside in the oral cavity (58). These emerging findings suggest the potential impact of the microbiome on cancer biology, including its effects on cell phenotype, immune responses, tumor progression and treatment outcomes. However, of note, several bacterial species known to colonize the oral cavity have been identified in PDAC tissues (59). These include species associated with periodontitis, a condition reported to increase PDAC risk (11,12). Periodontitis is a prevalent inflammatory disease that affects the gingival tissue and alveolar bone, and is generally initiated by a range of pro-inflammatory factors produced by the host in response to a dysbiotic microbiome (4,60,61). Epidemiological studies have shown that oral pathogens, such as *Porphyromonas gingivalis* (*P. gingivalis*), *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and *Fusobacterium* species are linked to increased risk of pancreatic cancer (60,62-64). *P. gingivalis* is an anaerobe closely associated with the progression of periodontitis, and it has been recently demonstrated that *P. gingivalis* translocates to the pancreas from the oral cavity in mice, where it induces acinar-to-ductal metaplasia, a precursor lesion to neoplasia (14,15). Moreover, repetitive administration of *P. gingivalis* to mice expressing oncogenic Kras in the pancreas accelerated pancreatic intraepithelial neoplasia progression to PDAC (15). *P. gingivalis* was also shown to promote the growth of pancreatic cancer *in vivo* in xenograft models (14,65). In addition, a study reported the detection rate for *Fusobacterium* species in pancreatic cancer tissue to be 8.8%, and found higher mortality in the *Fusobacterium*-positive group (64). A study by Udayasuryan *et al* (16) found that *Fusobacterium nucleatum* (*F. nucleatum*) infection elicited normal pancreatic and PDAC cells to secrete cytokines including granulocyte macrophage colony stimulating factor and C-X-C motif chemokine ligand 1 (CXCL1). Conditioned medium from infected cells promoted non-infected cell proliferation, and motility of non-infected and infected PDAC cells (16). Moreover, an independent study has reported that intracellular *F. nucleatum* promoted PDAC progression via the CXCL1 and C-X-C motif chemokine receptor 2 axis, and *F. nucleatum* positive patients with PDAC had larger tumor size and worse survival rate (17). Collectively, PDAC harbors a microbiome including oral pathogens, and emerging evidence indicates that these bacteria may contribute to the initiation and progression of PDAC. Although the effects

Table IV. Potential antimicrobial effects of garlic, its extract, and their organosulfur compounds on microorganisms related to pancreatic ductal adenocarcinoma.

First author/s, year	Materials tested	Target	Antimicrobial effects	(Refs.)
Shams-Ghahfarokhi *et al*, 2006	Aqueous extracts of garlic	*Malassezia furfur* and other *Malassezia* species	Inhibit fungal growth	(66)
Ohta *et al*, 1999	Ajoenes (isolated from oil-macerated garlic extract), Allicin	*H. pylori*	Inhibit bacterial growth	(68)
Cellini *et al*, 1996	Aqueous garlic extract	*H. pylori*	Inhibit bacterial growth	(69)
O'Gara *et al*, 2000	Garlic oil, garlic powder, Allicin, and their diallyl sulfur components	*H. pylori*	Inhibit bacterial growth	(70)
Iimuro *et al*, 2002	AGE	*H. pylori*-induced gastritis in male Mongolian gerbils	Alleviate gastric inflammation	(71)
Bachrach *et al*, 2011	Allicin	*A. actinomycetemcomitans* and *F. nucleatum*	Inhibit bacterial growth	(75)
	Allicin	*P. gingivalis*	Reduce protease activity of *P. gingivalis*	
Bakri and Douglas, 2005	Aqueous extract of garlic	*A. actinomycetemcomitans*, *F. nucleatum* and *P. gingivalis*	Inhibit bacterial growth, reduce protease activity of *P. gingivalis*	(76)
Shetty *et al*, 2013	Ethanolic and aqueous extracts of garlic	*P. gingivalis* and *A. actinomycetemcomitans*	Inhibit bacterial growth, reduce protease activity of *P. gingivalis*	(77)
Velliyagounder *et al*, 2012	Garlic extract and Allicin	*A. actinomycetemcomitans*	Inhibit bacterial growth	(78)
	DAS	*A. actinomycetemcomitans*	Inhibit bacterial growth and biofilm formation	

AGE, aged garlic extract; DAS, diallyl sulfide; *H. pylori*, *Helicobacter pylori*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *F. nucleatum*, *Fusobacterium nucleatum*; *P. gingivalis*, *Porphyromonas gingivalis*.

of garlic or its compounds on the PDAC microbiome are as yet unknown, these findings suggest that targeting tumor bacteria is an attractive potential therapeutic strategy in PDAC prevention and treatment.

5. Antimicrobial activity of garlic, AGE and organosulfur compounds

Garlic and its derived products have antimicrobial properties on a wide spectrum of bacteria and fungi, suggesting that treatment with garlic products may impact PDAC indirectly through effects on the microbes associated with this cancer (Table IV) (4,66-78). Three cases will be considered to illustrate this point. First, in both human and mouse models of PDAC, a unique fungal community inhabits the pancreas (79-83). *Malassezia* species, including *Malassezia globosa*, were enriched in PDAC samples and associated with a poorer survival rate (79,80). Garlic extracts strongly inhibit the growth of *Malassezia* species in a dose dependent manner and with activity comparative to a known antifungal compound, ketoconazole (66). Second, garlic products were shown to be active against *Helicobacter pylori* (*H. pylori*), a spiral shaped bacterium that resides in the stomach lining and is a well-established risk factor for chronic gastritis, duodenal and gastric ulcers, and gastric cancer (84). The presence of *H. pylori* was also determined in the oral cavity and pancreas, and its prevalence was reported to have positive association with pancreatitis and periodontitis (84-88). Moreover, *H. pylori* infection is considered to increase risk of PDAC although the evidence remains debated (89-92). Garlic and garlic extract are bactericidal against *H. pylori* (68-70). In addition, ajoenes isolated from oil-macerated garlic extract and allicin inhibited *H. pylori* proliferation (68). *In vivo*, AGE alleviated *H. pylori*-induced gastritis, indicating that garlic extract could serve as an effective agent in preventing an inflammatory disorder caused by *H. pylori* infection (71). Thus, garlic activity against this pathogen may impact PDAC risk. Finally, evidence that garlic products are active against oral anaerobic bacterial species associated with periodontal disease may also link garlic's antimicrobial activity to inhibition of the

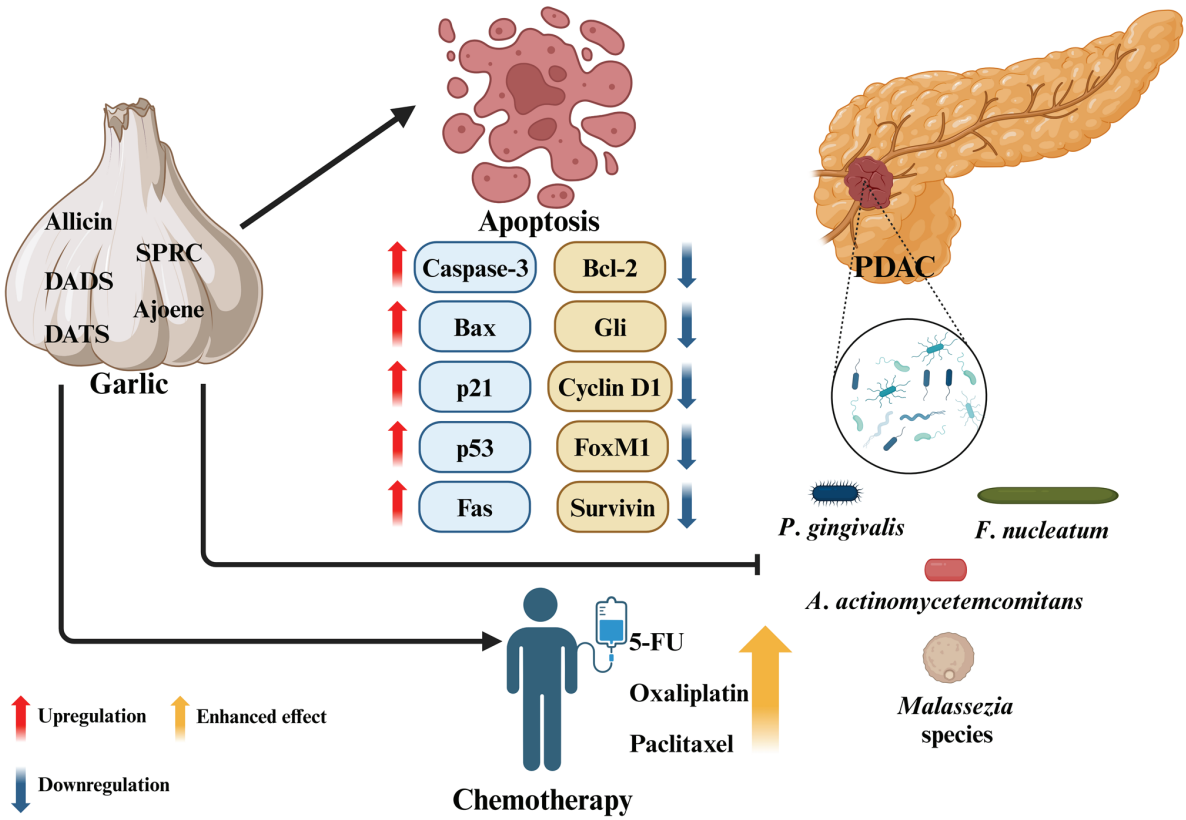

Figure 1. Schematic diagram of the potential therapeutic effects of garlic and its organosulfur compounds on PDAC. Garlic components inhibit PDAC cell proliferation by modulating survival-related molecules and inducing apoptosis. They also enhance the efficacy of chemotherapeutic agents, such as 5-FU, Oxaliplatin and Paclitaxel. PDAC tissue harbors microorganisms, including oral bacteria and fungi such as *Malassezia* species. The antimicrobial activity of garlic products has significant potential to prevent and treat pancreatic malignancies. The figure was created using BioRender.com. DADS, diallyl disulfide; DATS, diallyl trisulfide; SPRC, *S*-propargyl-cysteine; Bax, Bcl-2 associated X-protein; Bcl-2, B cell lymphoma 2; Gli, glioma-associated oncogene; FoxM1, forkhead box protein M1; 5-FU, 5-fluorouracil; PDAC, pancreatic ductal adenocarcinoma; *P. gingivalis*, *Porphyromonas gingivalis*; *F. nucleatum*, *Fusobacterium nucleatum*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*.

progression of PDAC (75-78). Bachrach *et al* (75) reported inhibitory effects of allicin on the periopathogenic species *A. actinomycetemcomitans*, *F. nucleatum* and *P. gingivalis*. It was also demonstrated that allicin can reduce the activity of *P. gingivalis* proteases, known as major virulence factors of this bacterium (75). In addition, pharmacological studies have shown that the aqueous extract of garlic inhibited the proliferation of *P. gingivalis*, *F. nucleatum* and *A. actinomycetemcomitans*, and blocked the proteolytic activity of *P. gingivalis* proteases (76,77). The garlic compound DAS also inhibits the proliferation and biofilm formation of *A. actinomycetemcomitans* (78). Finally, a randomized controlled double-blind study has reported that daily intake of an AGE product containing 300 mg of AGE powder for 18 months reduced the level of probing pocket depth, indicating that AGE can prevent and improve the progression of periodontitis (18). Taken together, garlic products such as AGE have great potential to modulate microbial and inflammatory contributors to PDAC, and thereby reduce the risk of PDAC development.

6. Conclusion and future perspectives

PDAC remains among the most difficult of cancers and there is an urgent need for improvements in early diagnosis and effective therapy. Garlic, along with its derived compounds and products, holds great potential to contribute to the prevention and treatment of PDAC by exerting direct effects on tumor growth and indirect effects on tumor-associated microbes (summarized in Fig. 1). However, to explore the full potential of garlic in managing PDAC, further mechanistic studies, and pharmacological experiments aimed at optimizing the delivery of bioactive compounds to the pancreas, are necessary. The antimicrobial potential of garlic against intratumor microbes, and in particular intracellular bacteria, is an exciting area for exploration, along with garlic's contribution to the balance of reactive oxygen species in PDAC, and to the tumor immune microenvironment. These studies will determine how to integrate garlic products in the future treatment toolbox for PDAC.

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HK was a major contributor in writing the manuscript. GN revised and provided comments during all stages of writing the manuscript. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Patient consent for publication

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