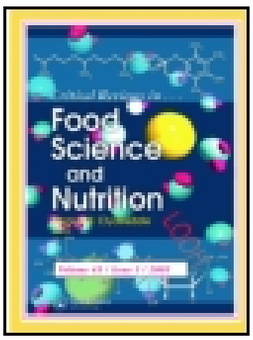

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REVIEW

Improving the bioavailability and bioactivity of garlic bioactive compounds *via* nanotechnology

Xiaoming Lu[a]*, Chaofan Wang[a]*, Meng Zhao[a], Jinxiang Wu[a], Zhonglu Niu[a], Xueli Zhang[a], Jesus Simal-Gandara[b], Ipek Süntar[c], Seid Mahdi Jafari[d], Xuguang Qiao[a], Xiaozhen Tang[a], Zhenlin Han[e], Jianbo Xiao[b,f], and Li Ningyang[a]

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ABSTRACT

This review highlights main bioactive compounds and important biological functions especially anticancer effects of the garlic. In addition, we review current literature on the stability and bioavailability of garlic components. Finally, this review aims to provide a potential strategy for using nanotechnology to increase the stability and solubility of garlic components, providing guidelines for the qualities of garlic products to improve their absorption and prevent their early degradation, and extend their circulation time in the body. The application of nanotechnology to improve the bioavailability and targeting of garlic compounds are expected to provide a theoretical basis for the functional components of garlic to treat human health. We review the improvement of bioavailability and bioactivity of garlic bioactive compounds via nanotechnology, which could promisingly overcome the limitations of conventional garlic products, and would be used to prevent and treat cancer and other diseases in the near future.

KEYWORDS

Nanotechnology; garlic bioactive compounds; bioavailability; bioactivity; applications

1. Introduction

Nanotechnology literally means any nanoscale technology that has real-world applications (Poole and Owens 2003). The prefix "nano" is sourced from the Greek language and it implies "dwarf" (Singh et al. 2017). Nanotechnology is able to create materials for industrial purposes on an atomic, molecular, or supramolecular scale. The National Nanotechnology Initiative (NNI) characterizes it as "the manipulation of matter with at least one dimension sized from 1 to 100 nanometers." But it can be scaled up to 1,000 nm on a wider scale (Bharali et al. 2009). In the recent decades, nanotechnology has attracted wide attention in materials science, food science, agriculture and biomedical engineering. As a new interdisciplinary research field across chemistry, biology, medicine and engineering, nanotechnology is one of the most effective fields in treating cancer (Ferrari 2005). Currently, nanoparticles, nanoliposomes, dendrimers, polymeric nanomicelles, nanocantilever, quantum dots and carbon nanotubes are effective nanodelivery systems for early cancer detection and treatment (Misra, Acharya, and Sahoo 2010). Furthermore, targeted therapies have become increasingly desirable in cancer treatment, because they can specifically kill cancer cells without influencing the normal cells. Thus nanotechnology brings novel methods and directions for targeted cancer therapy (Sanna, Pala, and Sechi 2014). Anticancer drugs can be delivered to tumor tissues using nanoparticles by active or passive targeting. So far, strategies for passive tumor-targeting nanorods have been clinically approved for treating breast cancer (Falagan-Lotsch, Grzincic, and Murphy 2017).

As a species in the genus *Allium*, garlic (*Allium sativum* L.) is native to Northeastern Iran and Central Asia, which is globally utilized to prepare a variety of dishes with a history of several thousand years (Bautista et al. 2005; Singh and Singh 2008). It consists of many bioactive compounds which are primarily sulfur compounds (such as ajoene, allicin, S-allylcysteine (SAC), diallyl sulfide (DAS), diallyl trisulfide (DATS) and diallyl disulfide (DADS)); it is also rich in minerals (such as potassium, iron, zinc, calcium, sulfur,

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magnesium, manganese and selenium). In addition, it is considered to be one of the abundant sources for phenolic compounds in commonly consumed vegetables (Morales-González et al. 2019; Singh and Singh 2019). Recently, garlic extracts and isolated compounds have been evaluated for a variety of biological activities, including antibacterial, antiviral, antifungal, anthelmintic, antioxidant, anti-inflammatory and anticancer activities. Meanwhile, lots of scientific studies have demonstrated that garlic can be applied to prevent and treat various diseases, such as cancer, myocardial infarction, atherosclerosis, bacterial, fungal and viral infections, as well as digestive and common cold problems. In contrast to antibiotics, garlic can strengthen the immune system rather than weakening it (Bystrická et al. 2018; Sobenin et al. 2019). In the past decades, there has been increasing concern in the anticancer properties of garlic. Epidemiological and laboratory studies have demonstrated that garlic consumption can reduce the incidence of cancers including stomach, colon, breast and cervical cancer. The anticancer activity of garlic mainly reflects its effect on drug metabolizing enzyme, free radical scavenging and antioxidant activities, inhibition and promotion of tumorigenesis, induction of apoptosis and cancer cell cycle, etc. (Rahman 2007).

At present, cancer is the primary reason of human death around the world. Though garlic has a strong medicinal value in preventing and treating cancer, its application in medicine is restricted due to the low stability, high volatility, strong hydrophobicity and other characteristics of the active ingredients extracted from garlic such as allicin and garlic oil (GO) (Fujisawa et al. 2008). Therefore, it is essential to develop new delivery systems to improve the bioavailability of garlic bioactive compounds. As is known, nanoparticles can increase the stability and solubility of phytochemical extracts, improve their absorption and prevent their early degradation, and extend their circulation time in the body. Nanotechnology can deliver active ingredients with sufficient concentrations to the desired action site, prevent them from early exposure to the biological environment during delivery, enhance penetration and retention of affected tissue and improve cellular absorption (Kurmi et al. 2020). Therefore, the application of nanotechnology to improve the bioavailability and targeting of garlic active ingredients is expected to provide a theoretical basis for the functional components of garlic to treat human health. In this context, this review aims at highlighting the main bioactive compounds of garlic, and their important biological functions especially anticancer effects, focusing on the improvement of bioavailability and targeting of garlic compounds by the application of nanotechnology, which could promisingly overcome the limitations of conventional garlic preparation in treating cancer and other diseases in the near future.

2. Bioactive compounds of garlic

Garlic is celebrated for its unique smell and medicinal characteristics. The chemical composition of garlic is various, complex and rich in nutritional value. Garlic bulbs consist of about 28% carbohydrates, 2.3% organic sulfur compounds, 2% protein, 1.5% fiber, 1.2% free amino acids and 65% water. Garlic is also rich in vitamins B_1, B_2, B_6, C and E (Putnik et al. 2019). The minerals in garlic include sodium, potassium, iron, calcium, phosphorus, sulfur, etc., among which phosphorus content is the highest, and organic germanium and selenium content are also relatively rich (De Greef et al. 2020). In addition, garlic contains phenols, flavonoids, steroids, saponins, adenosine, steroid glycosides, lectin, prostaglandins, alkaloids, pectin, niacin, fatty acids, glycolipids, phospholipids, anthocyanins and essential oils components including β-phellandrene, phellandrene, citral, linalool, geranio and other components (Diretto et al. 2017). The chemical structures of garlic bioactive compounds are shown in Figure 1.

2.1. Sulfur-containing compound

The sulfur components in garlic are mainly in the form of γ-glutamyl peptide and L-cysteine sulfoxide, accounting for over 70% of the total sulfur content (Amagase et al. 2001; Suleria et al. 2015). γ-Glutamyl transpeptidase and oxidase can convert γ-glutamyl-S-allyl-L-cysteine (GSAC) into S-allyl-L-cysteine sulfoxide (alliin) during the low temperature storage (Yoo et al. 2010). Alliin is a unique non protein sulfur-containing amino acid in garlic, which is stable, odorless and safe. The content of alliin is the highest in fresh garlic, accounting for 80% of cysteine sulfoxide in garlic. Other flavor precursors are methyl cysteine sulfoxide, propyl cysteine sulfoxide and allyl cysteine sulfoxide (Amagase et al. 2001; Suleria et al. 2015).

When garlic is broken, sulfoxide compounds contact with alliinase to form hyposulfonic acid, and the two hyposulfonic acid molecules spontaneously form thiosulfinates by dehydration condensation. The content of allicin is the highest, accounting for 70%–80% (w/w) of thiosulfinates, which is the cause of typical pungent odor of garlic (Salehi et al. 2019). Thiosulfinates are unstable in the nature (Santhosha, Jamuna, and Prabhavathi 2013), and can be instantly decomposed in vitro to form other compounds, such as DADS, DAS, diallyl tetrasulfide (DATTS), DATS, allyl methyl sulfide (AMS), dipropyl disulfide (DPDS), allyl methyl trisulfide (AMTS), allyl methyl disulfide (AMDS), 2-vinyl-4H-1,3-dithiin, E-ajoene, 3-vinyl-4H-1,2-dithiin and Z-ajoene (Amagase et al. 2001; Salehi et al. 2019). There are a small amount of SAC and S-allylmercaptocysteine (SAMC) in the bulb, which are also produced by the catabolism of GSAC (Amagase et al. 2001; Suleria et al. 2015). As stable and odorless water-soluble compounds, SAC and SAMC also exist in water extract, alcohol extract of fresh garlic and aged garlic, where SAC is the main bioactive components (Santhosha, Jamuna, and Prabhavathi 2013).

2.2. Polysaccharides

The carbohydrates in garlic include monosaccharides, oligosaccharides and polysaccharides. The monosaccharides in garlic are mainly glucose, galactose and fructose with less

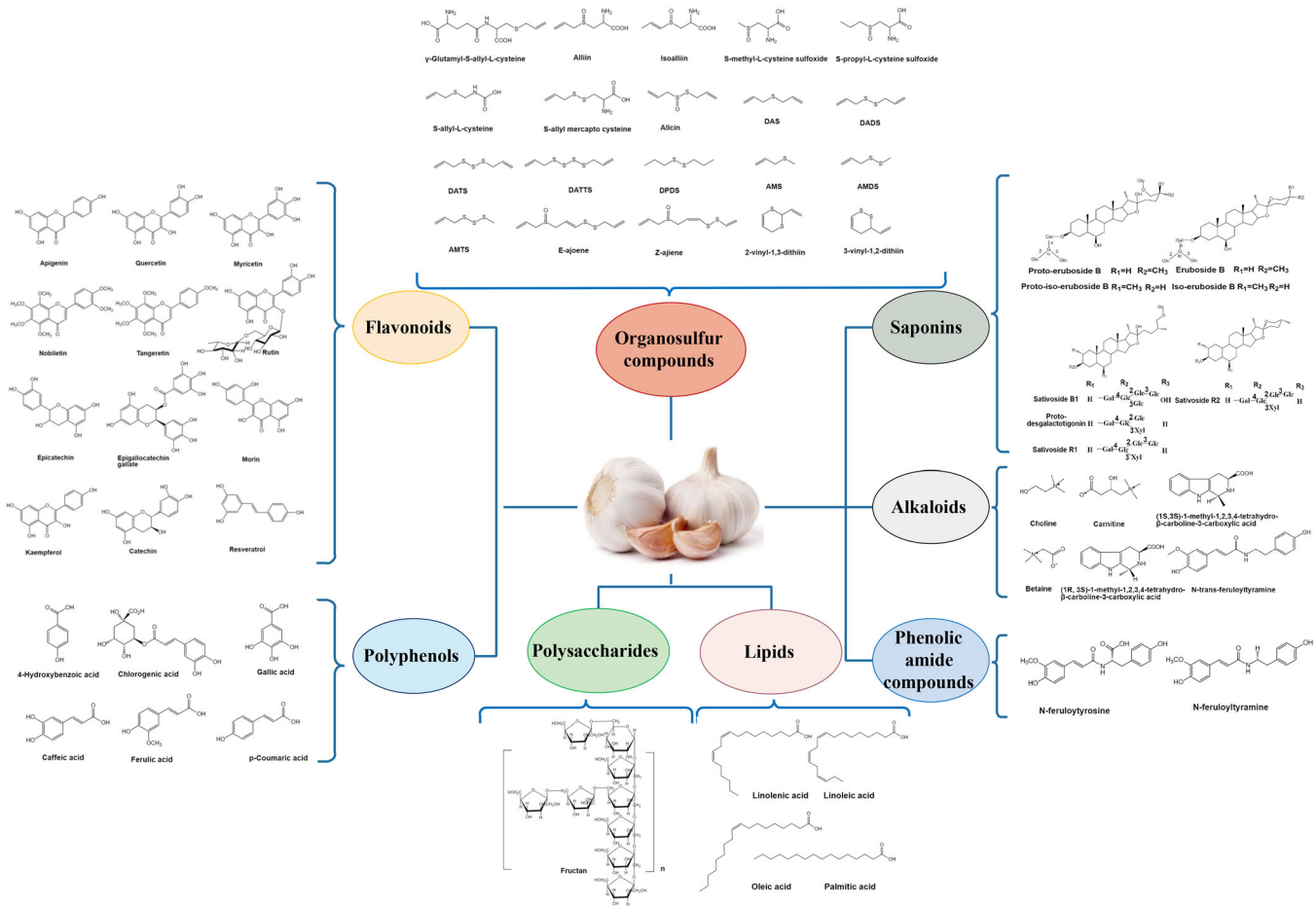

Figure 1. Structures of main functional components in garlic.

content. Oligosaccharides such as fructo-oligosaccharides with different degree of polymerization are found in garlic, which are usually used as prebiotics. Polysaccharides are the main components of garlic carbohydrates, which account for 77% of garlic dry weight. Li et al. (2017) analyzed the monosaccharide components of fresh garlic polysaccharides by high performance thin layer chromatography, and the results showed that garlic polysaccharides were a kind of acidic heteropolysaccharides with molecular weight of about 10 kDa. And fresh garlic polysaccharides principally consisted of galactose, galacturonic acid and fructose at a molar ratio of 25:32:307. Cheng & Huang (2018) obtained pure garlic polysaccharides by extraction, filtration, deproteinization, DEAE cellulose chromatography and freeze-drying. The molecular weight of garlic polysaccharides is 7100 Da, which are composed of glucose, fructose and galactose, and the ratio is 14:1:85. Fructan content is the highest in garlic, and there are some galactan, heterofructan, etc. These polysaccharides are linked together by β-glycoside bonds.

2.3. Phenolic compounds

Bozin et al. (2008) found that the content of total phenol in different garlic extracts varied significantly, ranging from 0.05–0.98 mg of gallic acid equivalents per g of dried extract. The content of total flavonoids changed greatly, which was 4.16 to 6.99 μg quercetin equivalents per g of dried extract. There are over twenty well-known polyphenolic compounds in garlic. The main phenolic compounds in garlic husk and garlic bulbs are pyrogallol, β-resorcylic acid, protocatechuic acid, gallic acid, caffeic acid, 4-hydroxybenzoic acid, p-coumaric acid and ferulic acid (Szychowski et al. 2018). The main flavonoids in garlic are tangeretin, nobiletin, myricetin, rutin, apigenin and quercetin. In garlic, the contents of myricetin, apigenin and quercetin are 639.0 mg/kg, 217.0 mg/kg and 47.0 mg/kg, respectively (Miean and Mohamed 2001). In addition, kaempferol, catechin, epicatechin, epigallocatechin gallate, morin, and resveratrol are also found in some garlic varieties (Cárdenas-Castro et al. 2019).

2.4. Other ingredients

2.4.1. Protein

There are about 20 kinds of amino acids found in garlic, and the contents of arginine (1768.5 mg/100 g dw) and lysine (320.8 mg/100 g dw) are relatively higher: the contents of aspartic acid, asparagine, glutamic acid and glutamine are over 100 mg/100 g dw, but the content of cysteine (0.1 mg/100 g dw) is relatively lower (Liu et al. 2020). Peptides in garlic are mainly formed by amino acids and γ-L-glutamine, and the most abundant polypeptides are water-soluble γ-L-glutamyl-S-(*trans*-1-propenyl)-L-cystine and GSAC (Chen et al. 2015). Garlic cloves also contain two mannose-specific lectins, garlic lectins I and garlic lectins II which are also

bulk proteins found in garlic. Mannose-specific garlic lectins I can stabilize glyproteinase-alliinase by close interaction with mannose-residues on the protein surface (Shin et al. 2018). Alliinase is particularly abundant in garlic, accounting for 10–12% of soluble protein in garlic cloves. In addition to alliinase, garlic also contains superoxide dismutase, catalase, trypsin and other enzymes.

2.4.2. Lipids

The lipids in fresh garlic are mainly neutral lipids, glycolipids and phospholipids. The main component of neutral lipid is triglyceride. Glycolipids are mainly etherified and nonetherified sterol glucosides, and lecithin is the main component of phospholipids. Presently, over 70 kinds of fatty acids have been determined in garlic, among which palmitic acid, linoleic acid, α-linolenic acid and oleic acid are the most abundant, which account for 80% of the total lipids (Tsiaganis, Laskari, and Melissari 2006).

2.4.3. Saponins

Saponins are water-soluble compounds, which are more stable during garlic processing and cooking (Lanzotti, Bonanomi, and Scala 2013). According to the molecular structure of aglycones, saponins are usually characterized into two categories, namely steroidal saponins and triterpenoid saponins. Steroidal saponins can be further divided into three categories, namely spirostanol, furostanol and cholestanoside (Sobolewska et al. 2016). Currently, eruboside B, proto-eruboside B, iso-eruboside-B, proto-iso-eruboside B, proto-desgalactotigonin and sativoside B1 have been successively detected in garlic; and satiposide R1 and satiposide R2 have also been detected in roots, which are the chief saponins identified in garlic (Lanzotti 2006; Lanzotti, Scala, and Bonanomi 2014). Gianfranco and colleagues characterized 17 saponins in garlic, and 12 saponins were detected in white garlic and purple garlic, including β-chlorogenin, gapanthagenin, diosgenin, desgalactotigonin, eruboside-B-rhamnose, eruboside B, proto-eruboside B, sativoside B1-rhamnose, gitogenin, sativoside R2-rhamnose, sativoside R2, and voghieroside E1. The other saponins, including proto-desgalactotigonin, desgalactotigonin-rhamnose, voghieroside D1, proto-desgalactotigonin- rhamnose, sativoside R1 and sativoside B1-rhamnose, are unique in purple garlic, which are mainly located in the outer part of capsule and clove. The saponins in purple garlic are 40 times of those in white garlic (Diretto et al. 2017).

2.4.4. Alkaloids

Huzaifa et al. (2014) quantitatively analyzed the bioactive components of garlic bulb aqueous solution, and determined that garlic contained 0.12 g/100g alkaloids. Fresh garlic contains choline, betaine and carnitine (Molina-Calle et al. 2017). Aged garlic also contains tetrahydro-β-carbolines, which are structurally similar to flavonoids (Hosono et al. 2005). Lu et al. (2017) detected two kinds of β-carboline alkaloids in black garlic, namely (1 R, 3S)−1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid and (1S, 3S) − 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid. Gao et al. (2019) isolated an amide alkaloid–N-trans-feruloyltyramine from the blue pigment of Laba garlic. Additionally, two kinds of N-feruloyl amides including N-feruloyl tyramine and N-feruloy tyrosine were found in the roots of garlic (Manchanda and Garg 2011).

2.4.5. Ingredients in processed garlic products

Garlic powder contains a small amount of oil-soluble sulfur compounds and alliin. GO impregnating agent contains residual alliin and oil soluble sulfur compounds including ajoene, disulfide and other components. The major volatiles identified from garlic essential oil are DATS, DADS, DAS, disulfide and ajoene. Aged garlic extract (AGE) mainly contains water-soluble compounds, including SAMC and SAC. Additionally, black garlic contains high amount of polyphenols and flavonoids in black garlic is high (Kimura et al. 2017).

3. Anticancer properties of garlic

In the 1950s, garlic was used as an anticancer agent. It could prevent esophagus, stomach, lung, colon, breast, cervical, skin cancer, prostate cancer, and many other human cancers. Recently, it is found that garlic contains various anticancer compounds, including allicin, diallyl sulfoxide, DAS, DADS, diallyl sulfone, DATS andSAC, SAMC, methionine, etc. (Saud et al. 2016). Its anticancer mechanism includes the following types: changing mitochondrial permeability, inhibiting angiogenesis and invasion, scavenging free radicals and antioxidant and activation of carcinogen detoxification metabolism enzyme, inhibiting the formation of DNA adduct and regulating cell proliferation, apoptosis, blocking the cell cycle, chromosome stability and immune response, histone modifications, carcinogenic activation, and changing the proteasome dependence protein degradation (Saud et al. 2016). The detailed anticancer effects and mechanisms of garlic are summarized in Table 1.

3.1. Colon cancer

Colon cancer is a common malignancy that begins in the large intestine (colon). Allicin has a cytotoxic effect on human colon cancer cells. Li et al. (2019) studied the antiproliferative potential of allicin on azoxymethane/dextran sodium sulfate (AOM/DSS) colorectal cancer in vivo, demonstrating the apoptosis and inhibiting proliferation of cancer cells via STAT3 signaling pathway in vitro and in vivo and decreased of the expression of Mcl-1, Bcl-2 and Bcl-xL. The sulfur-containing compounds found in garlic, such as DAS, DADS and DATS can induce colon cell cycle arrest and apoptosis (Bottone et al. 2002; Hosono et al. 2005; Saud et al. 2016). The activation of nuclear factor κB (NF-κβ) could be inhibited by DADS, resulting in lower levels of cyclooxygenase (COX)-2 and reduction of overall inflammation. DADS can induce cell apoptosis, promote cell cycle

Table 1. Effects and potential action mechanisms of garlic in exerting biological activities.

Cancer type		Models	Components of garlic	Effects	Anticancer mechanisms	References
Colon cancer	*Vitro*	HCT 116	Combination use of SAMC and rapamycin	Induced colon cancer cell apoptosis and suppresses tumor growth	Induced apoptosis; activation of Autophagy; downregulation of p62; Reversed the oxidative stress	Li et al. (2017)
		HCT-116; HCT-15	DADS	Inhibited cell proliferation	Induced apoptosis; increased NAG-1 protein expression and p53	Saud et al. (2016)
		SW480	DADS	Inhibited proliferation of cancer cells	Inhibited NFκB nuclear translocation; inhibited GSK-3β activity; reduced COX-2 expression; blocked nuclear translocation of P65	Bottone et al. (2002)
		HCT-15; DLD-1	DATS	Inhibition of cell growth	Induced apoptosis; increased caspase-3 activity; inhibited tubulin polymerization	Hosono et al. (2005)
	Vivo	(DMH)-induced carcinogenesis in F344 rats	AGE	Suppressed cell proliferation	Delay of the cell cycle at the G2/M phase was caused a decrease in the population of cells in the S phase	Jikihara et al. (2015)
		DMH-induced colon carcinogenesis in C57BL/6J mice	DAS	Reduced the frequency of colorectal adenocarcinoma		Wargovich (1987)
		AOM/DSS mice	Allicin	Decreased in number and size of tumors; inhibited the proliferation and promoted the apoptosis of multiple colorectal cancer	Expression of Mcl-1, Bcl-2 and Bcl-xL was all down-regulated; suppressed the activation of STAT3 signaling pathway	Li et al. (2019)
		Colo 205 xenograft mice	DAS, DADS, DATS	Reduced the weight of the tumor	Promoted Mdr1, MRP1, MRP3, MRP4 and MRP6 gene expression	Lai et al. (2012) 54
Hematological cancers	*Vitro*	K562	DADS	Induced apoptosis of cancer cells	Induced of apoptosis, transient G2/M and p21 expression	Dasgupta and Sengupta (2013)
		KG1 (human CD34+ resistant myeloid leukemia)	Ajoene	Induced apoptosis in human leukemic cells	Induced apoptosis in human leukemic cells via stimulation of peroxide production and activation of nuclear factor kB	Dirsch, Gerbes, and Vollmar (1998)
		K562/A02	DATS	Enhanced adriamycin cytotoxicity	Inhibited the function and expression of P-gp; increased expression of caspase-3; decreased expression of NF-κB/p65	Xia et al. (2012)
		K562 leukemic cells	DAS	DAS sensitized K562/R cells to the cytotoxicity of vinblastine	P-gp were reduced to normal levels with the administration of DAS and vinblastine; accumulation of DXR	Arora, Seth, and Shukla (2004)
		U937	DATS	Inhibited leukemia cell growth	Down-regulation of Bcl-2, XIAP, and cIAP-1 protein levels, cleavage of Bid proteins, activation of caspases and collapse of mitochondrial membrane potential	Choi and Park (2012)
		U937	N-benzylN-methyldecan-1-amine (NBNMA)	Inhibited the growth and apoptosis	Induced cell cycle arrest at the G2/M phase and apoptotic cell death;	Jeong et al. (2014)
	Vivo	WEHI-3 in male BALB/c mice	NAC	prevented death from WEHI-3 leukemia cell-induced AML		Shih et al. (2018)
Bladder cancer	*Vitro*	T24	DATS	Inhibitory cancer cell growth	Induced G2/M phase cell cycle arrest; increased expression of Apaf-1, and activated caspase-9, caspase-3, and PARP; decreased the expression of Bcl-2 and Bcl-xl; upregulated the levels of Bax	Wang, Hsieh, et al. (2012)
		T24	DADS	Induced cell cycle arrest and apoptosis	Promoted caspase-3 activity; increased cyclin E and decreased CDK2 gene expression which may lead to the G2/M arrest of T24 cells	Lu et al. (2004)
			SAC	Inhibited cell proliferation and colony formation	Reduced phosphorylation of AKT; decreased the expression of Bcl-2; increased the expression	Ho et al. (2018)

(*continued*)

Table 1. Continued.

Cancer type		Models	Components of garlic	Effects	Anticancer mechanisms	References
		HTB5, HTB9, JON, UMUC14, T24, cisplatin resistant-T24R2			of Bax; change in the expression of PARP and caspases, in favor of apoptosis	
		T24	DATS	Inhibited T24 cell proliferation	Reduced the expression of anti-apoptotic Bcl-2 and Bcl-xL, and inhibitor of apoptosis protein family proteins; activated caspase-8 and -9, the respective initiator caspases of the extrinsic and the intrinsic apoptotic pathways; increase in mitochondrial membrane depolarization was correlated with activation of effector caspase-3 and cleavage of poly-ADP-ribose polymerase, a vital substrate of activated caspase-3; blockage of caspase activation through treatment with a pan-caspase inhibitor consistently inhibited apoptosis and abrogated growth inhibition	Shin et al. (2014)
Ovarian cancer	*Vitro*	A2780	SAC	Inhibited the proliferation of A2780 cells and the colony formation of A2780 cells	Resulted in G1/S phase arrest and induced apoptosis, accompanied by decreased expression of pro-caspase-3, Parp-1 and Bcl-2, and increased expression of active caspase-3 and Bax; reduced the migration of A2780 cells; decreased the protein expression of Wnt5a, p-AKT and c-Jun	Xu et al. (2014)
		A2780	SAC	Inhibited the proliferation of A2780 cells	Resulted in G1/S phase arrest; global DNA methylation levels; decreased the levels of 5-methylcytosine, DNMT activity, messenger RNA (mRNA) and protein levels of DNMT1; resulted in re-expression of the mRNA and proteins of silenced tumor suppressor gene CDKN1A accompany with reduced cell division control 2 expression	Xu et al. (2018)
		SKZOV3	Allicin	Inhibited cell proliferation	JNK activation induced Bcl-2 family activation, triggered mitochondria mediated signaling pathways, and led to the translocation of a considerable amount of Bax and cytochrome c release	Xu et al. (2014)
		HO8910, SKOV3	SAMC	Inhibited proliferation and invasive capability		Wu et al. (2016)
	Vivo	HO8910, HO8910PM, SKOV3 In female BALB/c nu/nu mice	SAMC	Reduced tumor volume for HO8910 and SKOV3 lines		Wu et al. (2016)
Pancreatic cancer	*Vitro*	PANC-1	Z-ajoene	The apoptosis of Panc-1 cells was induced	Inhibited Gli transcriptional activity in Sonic Hedgehog (Shh) stimulated C3H10T1/2 mesenchymal stem cells; suppressed Gli transcriptional activity and Gli-target protein expressions in PANC-1 human pancreatic cancer cells; reduced expression of FoxM1, one of Gli-target proteins; down regulated expressions of cell cycle related proteins; reduced cell proliferation and increased G2/M phase of PANC-1 cells	Lee, Jeong, and Ryu (2019)
		MIA PaCa-2	Allicin	Induced apoptosis of MIA PACA-2 cells	Induced caspase-3 expression; DNA fragmentation, cell cycle arrest, p21Waf1/Cip1	Chhabria et al. (2015)

				cyclin-dependent kinase inhibitor expression, ROS generation, GSH depletion and led to various epigenetic modifications		
Sarcoma	*Vitro*	U2OS and MG-63	DADS	Inhibited the proliferation and invasion	Partially reversed by miR-134 inhibitor transfection	Li et al. (2019)
		MG-63	DADS	Increased apoptotic ratio	Induced G2 /M arrest, apoptosis, and autophagic death of human osteosarcoma cells by inhibiting the PI3K/Akt/mTOR signaling pathway	Yue et al. (2019)
		U2-OS, SaOS-2, and MG-63	DATS	Suppressed cell survival, wound-healing capacity, invasion and angiogenesis in osteosarcoma cells	Decreased expression of Notch-1 and its downstream genes; increased expression of a panel of tumor- suppressive microRNAs; re-expression of miR-34a and miR-200b	Li et al. (2013)
		MG63 and MNNG/HOS cells	DATS	Inhibited cancer cell growth	Inhibition of the PI3K/Akt signaling pathway and through the mitochondrial apoptotic pathway	Wang et al. (2016)
		Saos-2	DATS	Suppressed cell proliferation of Saos-2 cells; blocked cell cycle progression and induced apoptosis		Zhang, Zhang, Li, Yang, & Diao (2009)
		U2-OS	DATS	Inhibited the proliferation of cancer cells	NF-κB activity was inhibited while expression of IκB was increased	Wang et al. (2014)
		Saos-2	DATS	Changed the morphology; inhibited the growth of the Saos-2 cells	Demonstrated to upregulate the expression of calreticulin (CRT)	Zhang et al. (2009)
		Saos-2	DATS	Inhibited the growth of the Saos-2 cells	Down regulated the expression of GRP78	Zhang et al. (2018)
	Vivo	Sarcoma-180 (allogenic) cells transplanted into mice	AGE	Inhibited tumor cell growth	Increased NK activities; enhanced phagocytosis of peritoneal macrophages	Kyo et al. (1998)
		Sarcoma-180 ascites tumor cells inoculated into CFW Swiss mice	Allicin	Inhibited tumor growth		Weisberger and Pensky (1957)
		Sarcoma-180 ascites tumor cells inoculated into CFW Swiss mice	Alliin + alliinase	Inhibited of tumor growth		Weisberger and Pensky (1958)
		Sarcoma-180 solid tumor cells in CFW Swiss mice and Murphy-Sturmlymphosarcoma in Wistar rats	Allicin	Inhibited of tumor growth; prolonged survival		Weisberger and Pensky (1958)
		WEHI-164 fibrosarcoma tumor in BALB/c Mice	Garlic extract	Inhibited tumor growth		Shirzad, Taji, and Rafieian-Kopaei (2011)
		WEHI-164 fibrosarcoma cells were implanted subcutaneously into BALB/c mice	AGE	Inhibited tumor growth	Significantly increased the splenocytes	Li et al. (2019)
		MCF-7	DADS	Induced apoptosis in the MCF-7 breast-cancer cell line	Interfered with cell-cycle growth phases in a way that increased the sub-G0 population and substantially halted DNA synthesis	Xiao et al. (2014)
		MCF-7 and MDA-MB-231	DADS	inhibited the proliferation, invasion and migration of breast cancer cells	Down regulation of upA and MMP-9 protein expression; up-regulated TTP expression	Xiong et al. (2018)
		human breast cancer cells (MCF-7 and MDA-MB-231	DADS	Inhibited of cell viability that was accompanied by apoptosis induction	Induced ROS production and apoptotic cell death; caused ROS generation, but not activation of Bax or Bak	Chandra-Kuntal, Lee, and Singh (2013)
		MDA-MB-231	DADS	Inhibited the proliferation of MDA-MB-231 cells migration and		Nakagawa et al. (2001)

(*continued*)

Table 1. Continued.

Cancer type		Models	Components of garlic	Effects	Anticancer mechanisms	References
				invasion were significantly inhibited		
		MDA-MB-231	DADS	Decreased viability, increased apoptosis and suppression of metastatic	Induced dysregulation of Bcl-2 family members; down regulation of matrix metalloproteinase-9 reversal of the epithelial-mesenchymal transition	Xiao et al. (2014)
		MDA-MB-231	SAC	Induced anchorage -dependent and -independent growth of MDA-MB-231	Increased expression of E-cadherin; reduced MMP-2 expression and activity	Gapter, Yuin, and Ng (2008)
	Vivo	MDA-MB-231 xenograft BALB/c nude mice	DADS	Reduced the size of the tumor		Pinto et al. (2000)
		MDA-MB-231 xenograft BALB/cnude mice	DADS	Reduced the mass and volume of the tumor		Nakagawa et al. (2001)
		MCF-7 cell xenografts in female BALB/c mice	DATS	Reduced the size of the tumor		Na et al. (2012)
		xenograft tumor models were created by subcutaneously injecting MCF-7 and MDA-MB-231 breast cancer cells	DADS	Reduced tumor size and weight	Down regulated uPA and MMP-9 protein expression; up-regulated TTP expression	Huang et al. (2015)
		MDA-MB-231 xenograft mice.	DADS	Reduced tumor volume and weight and increased apoptosis	Decreased expression of active β-catenin and the downstream molecules were dysregulated	Xiao et al. (2014)
Lung cancer	*Vitro*	A549	DADS	Inhibited cell growth		Sundaram and Milner (1996)
		H460 and H1299	DADS, DAS	Inhibited cell proliferation	Induced a rise in the level of Bax and a fall of Bcl-2 level; reduction of anti-proliperative gene in NSCLC	Hong et al. (2000)
		MRC-5	DATS	Inhibited cell proliferation	Increased DNA fragmentation and intracellular Ca^{2+}	Sakamoto, Lavvson, & Milner (1997)
		A549	DADS	Inhibited cell proliferation	Induced cell cycle arrest and apoptosis incancer cells, cell cycle arrest at G2/M and increase of intracellular ROS	Wu, Kassie, and Mersch-Sundermann (2005)
	Vivo	LL/2 lung carcinoma (syngenic) cells transplanted into mice	AGE	Inhibited tumor growth		Kyo et al. (1998)
		A549 into female BALB/c nude mice	DATS	Retarded growth of A549 xenografts in nude mice		Li et al. (2012)
		4-(methyhiitrosaniino)-l-(3-pyridyl)-l-butanone (NNK) in A/J mouse lung	DAS	Reduce the incidence and diversity of tumors	Keto aldehyde, keto alcohol, NNK-A'-oxide and NNAL-N-oxide) in the lung microsomes were decreased	Hong et al. (1992)
Gastric cancer	*Vitro*	SNU-1	SAMC	Induced apoptosis	Induced Bax and p53	Lee (2008)
		MGC803	DADS	Inhibited cell growth	Inhibited the phosphoryation of ERK and the activation of ERK1/2	Ling et al. (2006)
		MGC803	DADS	Inhibited cell proliferation	Up-regulated of miR-200b and miR-22 expression	Tang, Kong, et al. (2013)
		SGC7901	Allicin	Reduced cell viability; inhibited proliferation and induced apoptosis in SGC-7901 cancer cells	Induced cytochrome c release from the mitochondria and increased caspase-3, -8, and -9 activation, with concomitant upregulation of bax and fas expression intrinsic mitochondrial and extrinsic Fas/FasL-mediated pathways of apoptosis	Zhang et al. (2010)
		SGC-7901	DATS	Inhibited tumor growth and promoted tumor apoptosis		Jiang, Zhu, Huang, et al. (2017)

					Increased in the expressions of cyclin A2 and cyclin B1; increased the cytokine secretions of IL-12, TNF-α and IFN-γ	
	Vivo	KMN-45 and MKN-45 injected nude mice	SAMC	Inhibited tumor growth	Lowered ratio of bcl-2/bax	Lee et al. (2011)
		SGC-7901 xenograft mice	DATS	Inhibited tumor growth		Jiang, Zhu, Huang, et al. (2017)
		MGC-803 cells were subcutaneously injected into nude mice	DADS	Inhibited tumor growth		Tang, Kong, et al. (2013)
		SGC-7901 xenograft BALB/c nude mice	SAMC	Delayed the growth SGC-7901	Reduced expression of Bcl-2 and Increased Bax expression; caspase-9 and caspase-3 as well as cleavage of PARP	Zhu et al. (2017)
Prostate cancer	*Vitro*	CRL-1740	SAMC	Inhibited cell proliferation		Sigounas et al. (1997)
		PC-3 and DU-145	SAC and SAMC	Inhibited cell proliferation and invasion	Led to restoration of E-cadherin expression at transcription and protein levels; suppression of invasive growth through restoration of E-cadherin expression in cancer cells	Chu et al. (2006)
		LNCaP	DADS; DAS	Inhibited cancer cell growth		Pinto et al. (1997)
		PC-3 and DU145	DADS	Suppressed proliferation of cancer cells	Reduced Bcl-2, Bax interaction, and cleavage of procaspase-9 and -3, Bcl-2 over expressing	Xiao et al. (2004)
		PC-3	DADS	Suppressed of cell growth	Increased the expression of apoptotic protein Bax and reduced the expression of antiapoptotic protein Bcl-2, and activating caspase-3, final caspase in the apoptotic pathway	Arunkumar et al. (2005)
		LNCaP	DADS	Inhibited cell proliferation	Reduced the secretory activity of LNCaP cells	Gunadharini et al. (2006)
		PC-3	DADS	Inhibited cell growth and induced apoptosi	Decreased the survival rate of androgen independent prostate cancer cells; inhibited cell cycle progression and survival by lowering the expression of cyclin D1, NFkB and anti-apoptotic Bcl-2 molecule and increasing the level of pro-apoptotic (Bad and Bax)	Arunkumar et al. (2012)
		PC-3 and DU145	DATS	Inhibited cell proliferation	Induced ROS generation and consequently the cell cycle arrest in DU145 and PC-3 cells is caused by an increase in labile iron due to ferritin degradation	Shin et al. (2012)
		PC-3 and DU145	DATS	Induced apoptosis	Inactivated Akt to trigger mitochondrial translocation of BAD and caspase-mediated apoptosis	Xiao and Singh (2006)
		PC-3 and LNCaP	DATS	Inhibited prostate cancer growth	Down-regulated the expressions of Bcl-2, Bcl-XL and Mcl-1; up-regulated the expressions of Bax, Bak, PUMA, Noxa, and Bim protein levels; less expression of Bcl-2 and Bcl-XL and induced expression of Bax and Bak	Shankar et al. (2008)
		PC-3	DATS	Cytotoxic to Prostate Cancer Cells PC-3 than to Noncancerous Epithelial Cell Line PNT1A	Decreased in the level of ferritin H; induced Akt inactivation and Erk1/2 activation is attenuated in PNT1A; induced serine 36 phosphorylation of p66Shc is attenuated in PNT1A cells	Herman-Antosiewicz and Singh (2005)
		LNCaP; LNCaPC81 and LNCaPC4-2	DATS	Induced of apoptosis	Increased protein level of Bak and down-regulation of Bcl-2 and Bcl-xL protein levels; induced apoptosis was significantly attenuated by knockdown of Bax and Bak	Kim et al. (2007)

(*continued*)

Table 1. Continued.

Cancer type		Models	Components of garlic	Effects	Anticancer mechanisms	References
					proteins; caused generation of ROS in LNCaP cells disruption of the mitochondrial membrane potential and apoptosis	
		PC-3, DU145, LNCaP	DATS	Caused G2-M phase cell cycle arrest	Inhibited cyclin-dependent kinase 1 activity and hyperphosphorylated Cdc25C at Ser21	Herman-Antosiewicz and Singh (2005)
		DU145	DADS	Inhibited the growth; induced of apoptosis	mediated through the activation of JNK and the inhibited the PI3K/Akt signaling pathway	Borkowska, Knap, and Antosiewicz (2013)
		PC-3	DADS	Induced apoptosis	Induced cell cycle arrest and the activation of caspases; increased the expression of caspases (3, 9, and 10); increased proapoptotic protein Bax and decreased Bcl-2 protein	Gayathri et al. (2009)
		PC-3	DADS	Inhibited cell growth and proliferation	Induced cell cycle arrest at G2/M transition in PC-3 cells; inhibited the cell cycle by downregulating CDK1 expression; inhibited proliferation of prostate cancer cells through cell cycle arrest	Arunkumar et al. (2006)
		PC-3	SAC	Suppressed the proliferation and induced cell apoptosis	led to cell cycle arrest at the G0/G1 phases; decreased expression of Bcl-2 and increased expression of Bax and caspase 8	Liu et al. (2012)
	Vivo	PC-3 prostate carcinoma in nude mice	DATS	Inhibited of tumor growth	Inhibited prostate tumor growth and induced DR4 and DR5 expression, caspase-8 activity; inhibited expression of antiapoptotic Bcl-2, Bcl-XL, and induced expression of proapoptotic Bax, Bak; reduced in microvessel density and the expression of VEGF, IL-6 and IKK activity; down-regulated the expression of MMP-2, MMP-7, MMP-9 and MT-1 MMP	Shankar et al. (2008)
Liver cancer	*Vitro*	HepG2	SAC	Inhibited proliferation of tumor cells		Bagul, Kakumanu, and Wilson (2015)
		Hep3B and Huh-7	SAMC	Inhibited cell proliferation; reduced cell viability and cell adhesion;disrupted cell cycle distribution; reduced cell migration,	Reduced the cell number and Ki-67 fluorescent signal density	Xiao et al. (2018)
		MHCC97L	SAC	Inhibited cell proliferation, colony forming ability, migration and invasion	Suppressed Bcl-xL and Bcl-2; activated caspase-3 and caspase-9; induced the S phase arrest;down-regulated of cdc25c, cdc2 and cyclin B1	Ng et al. (2012)
	Vivo	1, 2- dimethylhydrazine-injected male Fischer 344 rats	DAS	Inhibited of cancer cell proliferation	Inhibitory effect on the numbers of 7-GT positive foci and reduced numbers of GST-P foci reduce DMH binding	Hayes, Rushmore, and Goldberg (1987)

arrest in G2/M phase and inhibit the proliferation of colon cancer cells (Q. Zhang et al. 2018). Allyl mercaptan is a kind of metabolite of DADS. It inhibits the histone acetylase and increases the histone acetylation in HeLa nuclear extract and human colon cancer cell lysates. The expression of p21 can be increased by the binding of SP3 transcription factor to p21WAF1 gene promoter region, resulting in cell cycle arrest in HT29 colon cancer cells (Nian et al. 2008). DATS increased the activity of caspase-3, which induced cell cycle arrest and successive apoptosis (Hosono et al. 2005). In addition, DAS reduced the frequency of colorectal adenocarcinoma (Wargovich 1987). Based on the results in vitro and in vivo, DAS, DADS and DATS affected the gene expression of the multidrug resistance in COLO 205 human colon cancer cells in vitro and in vivo (Lai et al. 2012). AGE inhibited the invasive activity of SW480 and SW620 cells, but had no influence on the invasion of HT29 cells. In SW480 and SW620, G2/M phase cell cycle was arrested, cyclin B1 and CDK1 were decreased, and nuclear factor kappa B was inactivated (Jikihara et al. 2015; Matsuura et al. 2006). The mechanistic roles of SAMC have been extensively studied in colon cancer treatment and it was reported that SAMC was able to upregulate the Bax/Bcl-2 ratio and p53 (Li et al. 2017).

3.2. Hematological cancers-leukemia

The sulfur-containing compounds found in garlic, such as DADS, DATS and DAS may induce the apoptosis of human leukemia cells through activating the peroxides, NF-$\kappa\beta$, caspase-3 and caspase-8, arresting cell cycle in G2/M phase, and inhibiting the function and expression of P-glycoprotein (Arora, Seth, and Shukla 2004; Choi and Park 2012; Dasgupta and Sengupta 2013; Xia et al. 2012). Ling et al. (2017) observed that DADS showed antiproliferative effect on HL-60 cells, induced cell cycle arrest and granulocyte differentiation, inhibited invasion and migration, and reduced mRNA levels of DJ-1, cofilin1, RhoGD12 and calreticulin differentially expressed proteins. It was reported that DATS could reduce the viability of leukemia cells, and caused DNA fragmentation, the formation of apoptotic bodies and morphological changes after treating four leukemia cell lines (THP-1, U937, K562 and HL-60) with DATS in a concentration and time dependent manner. Moreover, apoptosis induced by DATS required the generation of reactive oxygen species (ROS) in the specific cell line (Choi and Park 2012). As a water-soluble component of garlic, N-acetyl-L-cysteine (NAC) has an antioxidant activity (Shih et al. 2018). It was observed that the cytotoxicity of NAC on human acute promyelocytic leukemia HL-60 cells in vitro was exerted by up regulation of endogenous antioxidant activity (with the increase of superoxide dismutase level and total antioxidant capacity) and blocking H_2O_2 induced ROS production. NAC also up regulated glutathione (GSH)/glutathione disulfide (GSSG) ratio, which could further support NAC and help to counteract the oxidative stress (Shih et al. 2018). Ajoene, a compound of garlic, might induce apoptosis in human leukemic cells via stimulation of peroxide production and activation of NF-$\kappa\beta$ (Dirsch, Gerbes, and Vollmar 1998). Jeong et al. (2014) isolated the novel phenylamine derivative N-benzyl-N-methyldecan-1-amine from garlic cloves and found that it induced G2/M phase arrest and apoptosis in U937 human leukemia cells.

3.3. Bladder cancer

The growth of bladder cancer T24 cells could be significantly inhibited by treating with DATS in a concentration-dependent manner (Wang, Hsieh, et al. 2012). DATS induced caspase dependent apoptosis and cell cycle arrest in G2/M phase. Meanwhile, apoptosis Bax was up-regulated and antiapoptotic Bcl-2 was down-regulated. T24 cell proliferation was inhibited through P13K/Akt pathway inactivation, caspase dependent apoptosis and activation of JNK signaling pathway by DATS treatment (Shin et al. 2014). Lu et al. (2004) found that DADS increased cyclin E but decreased CDK2 gene expression which might lead to the G2/M arrest of T24 human bladder cancer cells. Oral administration of garlic extract can inhibit the growth of T24 in vivo, increase the expression of radixin gene and AKAP12, and decrease the expression of RAB13 (W. T. Kim, Yu, et al. 2017), which participate in the protein kinase A signaling pathway and may be potential targets for tumor inhibition. SAC, the most abundant organosulfur compound in AGE, is a potential therapeutic agent for the treatment of bladder cancer. SAC promoted a cell cycle arrest in the S phase and induced the apoptosis of human bladder cancer cells by increasing the expression of apoptosis-related genes, including caspases, poly (ADP-ribose) polymerase and cytochrome C (cyt-c) (Ho et al. 2018).

3.4. Ovarian cancer

SAC can induce apoptosis of A2780 ovarian cancer cells and inhibit the proliferation. SAC can also increase the levels of Bax, caspase-3 and Akt, promote G0/G1 cell cycle arrest, and down-regulate Bcl-2, PARP-1, Wnt5a and c-Jun (Xu et al. 2014). Furthermore, SAC can promote G0/G1 cell cycle arrest and inhibit A2780 cell proliferation. DNA methylation level and DNMT activity level decreased with the increase of SAC concentration (Xu et al. 2018). Wu et al. (2016) investigated the inhibitory effect of SAMC, a garlic derivative, on ovarian cancer, they found that SAMC decreased the volume of subcutaneous transplanted tumor of SKOV3 and HO8910 ovarian cancer cells after giving mice 300 μmol/L SAMC by gavage for 8 days, but demonstrated no influence on HO8910PM ovarian cancer cells. In SKOV3 and HO8910 cells, SAMC decreased the expression of adhesion factor integrin β1, but increased caspase-3 activity and the level of E-cadherin. There was no such mechanism in HO8910PM cells because its high level of survivin was resistant to SAMC. Allicin induced the apoptosis and inhibited the proliferation of human ovarian cancer cells in a time and concentration-dependent manner (Xu et al. 2014). The enhanced cytoplasmic levels of cyt-c and Bax were associated with the activation of JNK pathway.

3.5. Pancreatic cancer

Alliinase can react with alliin to produce allicin in situ. MIA PaCa-2 cells can be recognized by the chemically combined alliinase with a monoclonal antibody specific to pancreatic cancer marker CA19-9 (Chhabria et al. 2015). Allicin produced from the added alliin can increase DNA fragmentation and ROS production, decrease intracellular glutathione, induce cell cycle arrest in G1 phase, and induce apoptosis. *Glioma*-associated *oncogene* is a gene associated with pancreatic cancer. It was found that z-ajoene reduced cell viability, decreased *Gli* transcription activity, decreased the expression level of *Gli* mediated proteins (Ptch FoxM1, Gli1 and Gli2), increased the number of cells in G2/M phase and induced cell cycle arrest in G2/M phase when z-ajoene was applied to PANC-1 human pancreatic cancer cells (Lee, Jeong, and Ryu 2019). In addition, GO showed a cycle arrest effect on pancreatic cells, especially in G2/M phages. It significantly inhibited the proliferation of ASPC-1, MIA PACA-2 and PANC-1 pancreatic cancer cells. After exposure to GO, almost all pancreatic tumor cells showed a tendency to shrink and aggregate. At the same time, GO prevented the metastasis of cancer cells (Lan et al. 2013).

3.6. Sarcoma

It is found that sarcomas can be utilized to exhibit the antiproliferative effect of garlic ingredients (Kyo et al. 1998). Weisberger and Pensky (1957) investigated whether garlic-induced sarcomas could have an antitumor effect in vivo and found that allicin could delay the formation of ascites and inhibit the growth of tumors (Weisberger and Pensky 1958). Shirzad, Taji, and Rafieian-Kopaei (2011) studied fibrosarcomas by giving fresh garlic extracts containing allicin, phenols, flavonoids and other substances to mice inoculated with fibrosarcoma cells from WEHI-164 mice. After a few weeks, it was found that tumor growth was inhibited and slowed significantly. Oil-soluble compounds have been found to have anticancer effects on osteosarcoma cells in vitro. DADS inhibited the cellular activity of MG-63 osteosarcoma cells, and the degree of DADS inhibition was related to the level of DADS concentration, which also increased the expression of miR-134 (Li et al. 2019). Studies have shown that when cancer cells are exposed to DADS or DATS, DADS or DATS induced G2/M arrest, apoptosis, and autophagy death of human osteosarcoma cells by inhibiting the PI3K/Akt/mTOR signaling pathway (Wang et al. 2016; Yue et al. 2019). In addition, DATS can reduce mitosis of tumor cells, histone deacetylase activity and tumor volume, and inhibit cell cycle progression (Wallace et al. 2013). DATS inhibits the growth of human cancer cells by upregulating the calreticulin CRT mRNA and protein levels of SAOS 2 cells, inhibits proliferation of osteosarcoma by down-regulating Notch-1 and reexpression of miRNAs, induces cell apoptosis by blocking the cell cycle process, and inhibits the growth and proliferation of SAOS 2 cells by down-regulating the expression of GRP78 (Zhang, Zhang, Li, Yang, & Diao, 2009; Li et al. 2013; Zhang et al. 2009; Zhang et al. 2018). Additionally, DATS reduces multidrug resistance and induces apoptosis in human osteosarcoma cells by inhibiting NF-κB (Wang et al. 2014).

3.7. Breast cancer

The oil-soluble compound DADS extracted from garlic has a better inhibitory effect on breast cancer than the water-soluble compound. DADS is mainly involved in regulating cell cycle arrest, inhibiting the formation of DNA adducts and inducing apoptosis (Chandra-Kuntal, Lee, and Singh 2013; Shih et al. 2018). In addition, DADS inhibits the proliferation, invasion and migration of breast cancer cells by down-regulating the expression of uPA and MMP-9 protein and up-regulating the expression of TTP (Xiong et al. 2018). At the same time, in vivo studies have shown that DADS can reduce the size and weight of breast tumors (Huang et al. 2015; Kim et al. 2016; Nakagawa et al. 2001; Xiao et al. 2014; Xiong et al. 2018). While allicin can prevent the proliferation of human breast cancer cells (MCF-7), DAS can prevent the lipid peroxidation and DNA damage of breast cancer (Hirsch et al. 2000; Pinto et al. 2000). DATS can reduce the incidence of breast cancer by regulating cell cycle and inhibiting cell proliferation (Nkrumah-Elie et al. 2012). Nakagawa et al. (2001) studied the anticarcinogenic effect of DADS on MKL-F and McF-7 breast cancer cell lines, proving that DATS could reduce the activity and induce the apoptosis of cancer cells. Additionally, DADS could reduce the incidence of breast cancer via increasing Mir-34A levels in vitro (Xiao et al. 2014). Furthermore, DATS could reduce the proliferation of MDA-MB-231 triple negative breast cancer cells (Liu et al. 2015; Malki, El-Saadani, and Sultan 2009; Na et al. 2012). Increased expression of E-cadherin promotes cell adhesion and prevents breast tumor cells from detaching from the primary tumor, while reduced adhesion to type I collagen hinders metastasis through the stroma. SAC affects the migration, attachment and invasion of breast cancer cells by altering the expression of E-cadherin in breast cancer cells (Gapter, Yuin, and Ng 2008).

3.8. Lung cancer

The carcinogen benzopyrene can promote the occurrence and metastasis of lung cancer by inducing DNA insertion, oxidative damage, mutations and dominant tumorigenesis. SAMC could play a role in preventing against lung cancer, and it could also inhibit the proliferation of A549 cells, which might explain the certain potential treatment for human lung cancer (Wu et al. 2016). Garlic compounds (DADS and DATS) were found to be effective in the treatment of lung cancer. DADS inhibited the growth of A549 cells and inhibited the proliferation of A549 cells by inducing the increase of intracellular ROS (Sundaram and Milner 1996; Wu, Kassie, and Mersch-Sundermann 2005). It also inhibits the proliferation of H460 and H1299 cells, resulting in the increase of Bax and the decrease of Bcl-2 levels. DATS can inhibit the proliferation of MRC-5 cells and increase the intracellular Ca^{2+} level (Hong et al. 2000; Sakamoto, Lawson, and Milner 1997). It can inhibit the cell

activity of large-cell lung cancer cell H460 and H358 non-small-cell lung cancer cell lines in a time-dependent manner, and it can also significantly inhibit the growth of transplanted tumor in A549 nude mice (Lan et al. 2013; Li et al. 2012). In addition, AGE and DAS also have certain effects on lung cancer. AGE can inhibit the growth of tumor cells, while DAS can reduce the incidence of tumors (Kyo et al. 1998; Hong et al. 1992).

3.9. Gastric cancer

Garlic has a certain preventive effect on gastric cancer, which may be related to its antibacterial effect. SAMC can increase p53 activity and inhibit the proliferation of SNU-1 gastric cancer cells, and also inhibit the growth of KMN-45 and MKN-45 tumor cells, thus reducing the Bcl-2/Bax ratio (Lee 2008; Lee et al. 2011). Zhu et al. (2017) investigated the anti-tumor effect of SAMC on gastric cancer transplanted tumor SGC-7901 in BALB/c nude mice, and found that SAMC could delay the growth of SGC-7901. Ling et al. (2006) studied whether DADS had an antiproliferation effect on MGC-803 gastric cancer cells, and the results showed that DADS could inhibit cell growth and induce cell apoptosis through ERK1/2 pathway. In addition, MGC-803 cells were subcutaneously injected into nude mice, and DADS was found to be able to inhibit tumor growth in mice (H. Tang et al. 2013). Another study has revealed that allicin can inhibit the proliferation of SGC-7901 cancer cells by reducing cell viability, and induce the apoptosis of gastric cancer cells SGC7901 (Zhang et al. 2010). DATS can inhibit the growth of SGC-7901 tumor cells, promote cell apoptosis, and increase the expression of cyclin A2 and B1 (Jiang, Zhu, Huang, et al. 2017). It can also induce the apoptosis of gastric cancer cells BGC-823 and GSE-1 by decreasing proliferating cell nuclear antigen and increasing cyclin content, demonstrating its good anticancer role (Jiang, Zhu, Huang, et al. 2017). Additionally, DAS could reduce the occurrence probability of gastric tumor induced by carcinogen DMBA in mice and inhibit tumor expression (Nagabhushan et al. 1992).

3.10. Prostate cancer

Prostate cancer is a urogenital cancer and is one of the common cancers in men. Currently, there are a large number of studies related to the antiproliferative effect of garlic on prostate cancer, demonstrating that SAMC can reduce testosterone metabolism of decomposition rate and the cell vitality by inhibiting cell growth (Majewski 2014). Human prostate cancer cells (LNCaP) treated with garlic water-soluble ingredients SAC and SAMC demonstrated no significant change initially, but they obviously inhibited the cell growth with the extended processing time, and SAMC exhibited a stronger inhibitory action (Pinto et al. 1997). SAC and SAMC can also act on PC-3 and DU-145 of prostate cancer cells, and restore the expression of E-cadherin at the transcriptional and protein levels by inhibiting the proliferation and aggressive growth of cancer cells (Chu et al. 2006; Liu et al. 2012; Sigounas et al. 1997). Another study showed that DADS induced apoptosis of prostate cancer cells DU145 and PC-3, up-regulated apoptosis of Bax and down-regulated antiapoptosis of Bcl-XL (Borkowska, Knap, and Antosiewicz 2013; Xiao et al. 2004). DADS also inhibited the proliferation and growth of LNCaP cancer cells by increasing p21WAF 1/CIP1 protein (Gunadharini et al. 2006; Pinto et al. 1997). Furthermore, it was found that DADS could also act on PC-3 cancer cells by inducing cell cycle arrest and reducing the expression of apoptotic protein Bcl2, and could inhibit the proliferation and growth of PC-3 cancer cells and lead to the apoptosis of cancer cells (Arunkumar et al. 2005, 2006, 2012; Gayathri et al. 2009).

DATS displays an excellent anticancer activity. DATS has little toxicity to prostate cells, but it can induce apoptosis of PC-3 and DU-145 of human prostate cancer cells lines through the inactivation of Akt signal axis (Xiao and Singh 2006; Antosiewicz et al. 2006; Borkowska, Knap, and Antosiewicz 2013; Shin et al. 2012). Besides, DATS also has a certain inhibitory effect on the proliferation of LNCaP prostate cancer cells by inhibiting the activity of cyclin-dependent kinase 1, which leads to apoptosis of LNCaP cancer cells (Herman-Antosiewicz and Singh 2005; Kim et al. 2007). After treating PC-3 nude mouse tumors with DATS, the expression of Bcl-2 and Bcl-XL was down-regulated, while the protein expressions of Bax and Bim were up-regulated, and finally the tumor growth rate slowed down, indicating that DATS could inhibit tumor growth and proliferation (Shankar et al. 2008). It is concluded that garlic active ingredient has certain preventive and therapeutic effects on prostate cancer.

3.11. Liver cancer

There are many causes of liver cancer, but it is mainly caused by liver cirrhosis, which is related to long-term alcohol drinking. Several experimental studies have revealed that the active ingredients in garlic have certain preventive and inhibitory effects on liver cancer. SAC can inhibit the proliferation of HepG2 cells (Bagul, Kakumanu, and Wilson 2015), induce cell cycle stagnation, inhibit the proliferation of HCC cells MHCC97 L, and reduce the levels of Bcl-XL and Bcl-2 to induce cell apoptosis (Ng et al. 2012). Xiao et al. (2018) found that SAMC could inhibit the proliferation of Hep3B and Huh-7 cells, reduce cell viability, reduce cell migration, inhibit the levels of Bcl-XL and Bcl-2, and activate caspase-3 and caspase-9. Hayes, Rushmore, and Goldberg (1987) studied mechanisms of DAS on the male Fischer 344 rats injected with 1, 2-dimethylhydrazine and they found that the number of Gst-P sites was significantly reduced, thus reducing the binding of dimethyl hydrazine which had a certain inhibitory effect on the proliferation of hepatoma cells. The current studies found that garlic active ingredient DATS could better inhibit tumor growth by using nanotechnology. A new type of DATS embedded using nanotechnology indicated that diallyl trisulfide poly butyl cyanoacrylate nanoparticles (DATS-PBCA-NP) could increase the DATS concentrations in the liver, improve the

stability and the bioavailability of DATS, provide a better DATS distribution in the liver, thus DATS-PBCA-NP could inhibit tumor growth more efficiently than DATS (Zhang et al. 2007).

4. Other functional properties of garlic

4.1. Antimicrobial function

Garlic is resistant to fungi, bacteria, viruses and parasites (Salehi et al. 2019). The antibacterial components in garlic are mainly allicin and sulfur-containing compounds including DAS, DADS and ajoene. Allicin can inhibit many gram-negative bacteria and gram-positive bacteria, such as *Salmonella, Helicobacter pylori, Pseudomonas, Escherichia coli, Staphylococcus aureus, Proteus*, *Klebsiella*, *Bacillus subtilis, Micrococcus*, *Clostridium*, *Mycobacteria*, *Lactobacillus casei* (Goncagul and Ayaz 2010a). Allicin also has inhibitory effects on beneficial intestinal microbes and potentially harmful intestinal bacteria, and is more effective in inhibiting harmful intestinal bacteria (Bayan, Koulivand, and Gorji 2014; Müller et al. 2016). The inhibition of *H. pylori* can reduce the risk of gastric tumor formation. However, DATS, DADS, DAS and ajoene showed a greater antifungal activity than allicin, and Eruboside-B showed an antifungal activity against *Candida albicans* (Corzo-Martínez, Corzo, and Villamiel 2007).

Allicin, ajoene and other sulfides are resistant to parasites. Allicin can inhibit the cysteine protease of some parasites and react with the sulfhydryl group of cysteine residue of pathogen enzyme, resulting in its inactivation. Allicin treatment can enhance the innate or adaptive immunity of mice on *Plasmodium yoelii* 17XL infection, increase the number of cytokines, $CD4^+$ T cells and macrophages, promote the maturation and expansion of dendritic cells, and initiate the adaptive immunity (Feng et al. 2012). Garlic extract can treat *Eimeria vermiformis*-infected mice, increase the quantity of $CD8^+$ T lymphocytes in the epithelium without increasing the production of interferon gamma (IFN-γ), thus enhancing the immunity of mice, protecting the host, enhancing the immune defense against helminth infection, preventing chemotherapy and enhancing the drug resistance of *E. vermiformis* (Khalil et al. 2015).

4.2. Antioxidant function

Free radicals are unhealthy substances with strong oxidation characteristics, which are generated in the oxidation reaction of body. They can hurt human cells and tissues, leading to cancer, atherosclerosis and aging. The antioxidant activity of flavonoids and phenolic compounds is confirmed by monitoring the free radical scavenging capacity and lipid peroxidation inhibition ability of garlic extract (Bozin et al. 2008). Polysaccharides have the ability of scavenging hydroxyl free radical and superoxide anion. The antioxidation mechanism of polysaccharides is as follows: polysaccharides directly act on antioxidant enzymes, which can demonstrate the antioxidant activity by enhancing the activities of antioxidant enzymes including glutathione peroxidase, catalase and superoxide dismutase. The hydroxyl structure of polysaccharides can combine metal ions producing hydroxyl radicals, such as Fe^{2+} and Cu^{2+}, inhibit the production of free radicals and block the reaction of metal ions; and directly take action on free radicals and scavenge free radicals (Cheng and Huang 2018).

DAS and AMS also have antioxidant effects. In the rat aortic smooth muscle cells model, the antioxidant mechanism of DAS and AMS is not by inducing apoptosis of cancer cells, but by inhibiting cell-cycle progression and migration stimulated by aortic smooth muscle cell angiotensin II. It can avoid down-regulation of $p27^{Kip1}$ (p27) and activation of protein kinases (MAPKs) activated by mitogen, reduce the production of reactive oxygen species induced by Ang II and the phosphorylation of ERK1/2. AMS and DAS can also prevent cardiovascular diseases related to vascular remodeling (Castro et al. 2010).

AGE has a significant antioxidant activity, while raw or heated garlic stimulates oxidation. The antioxidant mechanisms of AGE and SAC include: (1) the ability to remove reactive oxygen species and nitrogen species; (2) increase the levels of both enzymatic and non-enzymatic antioxidants; (3) activate Nrf2, the main regulator of cell redox state; (4) inhibit some oxidase, such as xanthine oxidase, COX and NADPH oxidase (Colín-González et al. 2012; Suleria et al. 2015).

The animal model of Type 2 diabetes was used to compare the free radical scavenging activities of garlic and black garlic. The trolox equivalent antioxidant capacity value of black garlic is 3.5 times higher than that of normal garlic. Consumption of aged black garlic can increase the activities of glutathione peroxidase, superoxide dismutase and catalase, and prevent diabetes. This is attributed to the increase of SAC and polyphenols in black garlic (Lee et al. 2009).

4.3. Antiinflammatory effect

Alliin has an antiinflammatory effect. Quintero-Fabián et al. (2013) took the 3T3-L1 cell line induced by lipopolysaccharide (LPS) as an inflammatory model. After adding alliin, they found that the expression of proinflammatory genes MCP-1, IL-6 and EGR-1 was decreased, and ERK1/2 in 3T3-L1 adipocytes was inhibited, which inhibited inflammation and prevented obesity. Alliin treatment significantly inhibited the expression of inflammatory cytokines induced by dextran sulfate sodium in RAW264.7 cells and the phosphorylations of c-Jun N-terminal kinase and protein 38, as well as the proliferator-activated receptor γ activation regulated by ERK1/2 to inhibit ulcerative colitis (Shi et al. 2017). Alliin reduces acute lung injury induced by LPS through activating proliferator-activated receptor γ, which subsequently blocks NF-κB activation induced by LPS and inflammatory responses (Wang et al. 2017). Alliin blocked the c-Fos-NFATc1 signaling pathway, reduced the expression of osteoclast specific genes TRAP, DC-STAMP and OC-STAMP, and inhibited the expression of NADPH oxidase 1 (Nox1) and the generation of reactive oxygen species,

thus inhibiting the formation, fusion and differentiation of osteoclast mediated via the receptor activator of nuclear factor-κB ligand (RANKL) (Chen et al. 2016).

The single GO can reduce inflammation through decreasing the activity of NF-κB and its proinflammatory cytokines including interferon-gamma (IFN-γ) and tumor necrosis factor alpha. It can reduce inflammation and prevent atherosclerosis in mice on a high-fat diet (Lestari et al. 2020). AGE treatment can diminish the neurological alterations, the infarct area and the cerebral ischemia-induced histological damage. AGE administration can also attenuate the increase in 8-hydroxy-2-deox-yguanosine levels, in tumor necrosis factor alpha levels, and in COX-2 protein levels and activity. Additionally, AGE has a neuroprotective effect and can alleviate the inflammation caused by cerebral ischemia (Colín-González et al. 2011). AGE can inhibit the activation of NF-κB, which is a chief factor associated with the expression of proinflammatory enzymes including COX-2 and nitric oxide synthase. NF-κB factors are also involved in HIV gene expression and atherosclerosis induction (Santhosha, Jamuna, and Prabhavathi 2013).

Macrophages are considered as target immune cells to fight against infection and inflammation, and their activation can improve the immune system of the host. Fresh garlic polysaccharides can increase the immune function of mouse RAW 264.7 macrophages, including phagocytosis, production of nitric oxide and expression of various cytokines. However, black garlic polysaccharides had no immunomodulatory effect due to the degradation of fructosan by fermentation (Li et al. 2017).

4.4. Prevention and treatment of cardiovascular diseases

In the mouse myocardial ischemia-reperfusion model, alliin can reduce the risk area and myocardial infarction area, increase the ejection fraction, and enhance cardiac function by inhibiting apoptosis and increasing autophagy (Zhao et al. 2019). Therefore, alliin can protect mice from heart injury induced by myocardial infarction through activating autophagy and exerting anti-necrosis factor activity (Yue et al. 2019). Allicin can improve antioxidant status, prevent hyperlipidemia and cardiac hypertrophy, induce vasodilation, and inhibit angiogenesis and even platelet aggregation (Salehi et al. 2019). The study of rat middle cerebral artery occlusion model revealed that allicin could prevent cerebral ischemia injury in vivo and in vitro through activation of sphingosine kinases 2, which was beneficial to neuroprotection (Lin et al. 2015).

S-propyl cysteine, SAC and S-ethyl cysteine can inhibit the cholesterol synthesis up to 40–60%, and SAC can reduce the activity of 3-hydroxyl 3-methyl-glutaryl COA reductase by increasing thiol oxidation (Suleria et al. 2015). S-methyl cysteine sulfoxide can also reduce blood cholesterol and atherosclerosis (Thomson and Ali 2003).

Streptozotocin-induced hyperglycemic mice treated with aged black garlic rich in SAC can reduce the islet degradation, β-cell apoptosis, and insulin deficiency in mice (J. H. Kim et al. 2017). Alliin showed no effects on body weight, obesity and energy balance in diet-induced obesity in mice, but enhanced glucose homeostasis, reduced fasting glucose level in blood, and increased insulin sensitivity. Total triglycerides and free fatty acids were decreased, while high-density lipoprotein was increased and lipid distribution was improved. This is due to alliin-induced structural regulation of intestinal microbiota (Zhai et al. 2018).

5. Stability and bioavailability of garlic components

5.1. Stability of garlic components

Among the bioactive ingredients of garlic, all substances except allicin are relatively stable. Allicin can be easily converted into more stable substances, such as DADS, DAS and DATS. The precursor of allicin is alliin, which is found in garlic in a stable odorless form. When garlic tissue is damaged, alliin forms a colorless oily substance called allicin under the catalysis of allinase (Lee, Kim, and Kyung 2014).

5.1.1. Thermostability

The stability of allicin is greatly affected by temperature, and the stability of allicin becomes worse at higher temperatures. Different studies have shown that the content of allicin decreased with time at differing temperatures; when temperature is >100 °C, allicin content drops faster with the higher temperature. This indicates that allicin is unstable at a high temperature; the possible reason is that the disulfide bond is broken due to the reaction of allicin at a high temperature, resulting in more sulfur-containing compounds. The half-life of allicin is about 15 days at 25 °C; while only 15% allicin is degraded after a month of storage at 4 °C; and the loss of allicin is close to 90% in >3 days at 40 °C (Wang et al. 2015; Chong et al. 2015; Lee, Kim, and Kyung 2014). Thus, allicin should be stored at a low temperature as much as possible.

5.1.2. Ph stability

Garlic itself has an unmixed natural pH of around 6, and it is more stable when it is kept in an acidic environment. But it can be more easily broken down when kept in an alkaline environment (pH > 7). After garlic homogenate was placed under pH 3.0, 4.0, 5.0, 6.0, 7.0 at 30 °C for 24 h, the degradation of allicin exhibited a consistent trend with the increasing pH; and the degradation rate becomes faster and faster, but the degradation amounts of the first four groups did not vary significantly (Lee, Kim, and Kyung 2014). The same pattern was also found by another group, and allicin was very unstable in solutions with a pH <1.5 or > 11 and the best storage pH was 5–6 (Wang et al. 2015).

5.1.3. Concentration stability

The stability of allicin is also related to its own concentration. Its stability increases with the enhancing concentration, which might be related to the variety of garlic. However, the influence of the concentration of allicin on the stability is

less than that of temperature and pH (Wang et al. 2015). Therefore, the effect of allicin concentration on the stability needs to be further studied.

5.1.4. Solvent stability

Solvent can affect the stability of allicin. The concentrated garlic water extract is diluted using different solvents with different polarity (water, dimethylsulfoxide and acetone) to investigate the stability of allicin. The degradation process is affected by the different properties of allicin in different polar solvents, and it is generally better to dilute the concentrated extract with water (Chong et al. 2015). Furthermore, the solubility of allicin in polar solutions is higher than that in non-polar solutions, which is possibly due to hydrogen bonds among allicin and polar solutions (Lee, Kim, and Kyung 2014).

5.1.5. Effects of food matrix on the stability

5.1.5.1. Effects of amino acids and protein on the stability. It is believed that amino acids and proteins can affect the stability of allicin because garlic greening requires the involvement of amino acids. However, experiments have shown that the addition of glycine and protein to garlic homogenates has no effect on the stability of thiosulfonates (mostly allicin), although there is a large amount of blue-green color (Lee, Kim, and Kyung 2014). Further research is needed to explain this mechanism.

5.1.5.2. Effects of lipid on the stability. Lipids have a negative effect on the stability of allicin, especially liquid and vegetable oils. The negative effect on allicin is increased with the degree of unsaturated oil. Allicin can be degraded into different degrees in different solvents. As vegetable oil is a non-polar solvent, allicin can produce a polar solvent ratio effect, thus making the stability of allicin worse (Lee, Kim, and Kyung 2014).

5.1.5.3. Effects of saccharides on the stability. Saccharides can improve the stability of allicin. The β-cyclodextrin uses its empty structure to entrap allicin molecule, and stabilizes the disulfide bond in allicin molecule by hydrogen bond and *Van der Waals* forces, thus improving the stability of allicin. The network structure formed by soluble starch dissolved in water can absorb allicin molecules and also increase the stability of disulfide bond to make allicin difficult to be decomposed (Wang, Shao, et al. 2012).

5.2. Bioavailability of garlic composition

Among the biological active components of garlic, sulfur compounds especially allicin have antioxidant, anticancer and antibacterial functions and thus are considered as the main pharmacological active components in garlic. These pharmacologically active ingredients need to be absorbed by the body, and the degree of absorption reflects the bioavailability of the active ingredient, which can be studied by using in vivo or in vitro experiments.

Freeman and Kodera (1995) simulated the reaction of allicin in intestinal juice (pH 7.5) and gastric juice (pH 1.2), and the reaction temperature was controlled at 37 °C with an aqueous solution at the same pH. The results showed that 90% of allicin was retained in the aqueous solution after 5 h; 80% of allicin was retained in the simulated gastric juice after 1 day; and 62% of allicin was retained in the simulated intestinal juice. This suggests that pH in the gastrointestinal tract (GIT) is not a key factor affecting the bioavailability of allicin. Alliin and allinase only produce allicin after digestion when the digestive enzymes are inhibited, because the optimum pH of allinase is 7.0. Therefore, the excessive acidity in the stomach might inactivate alliinase and affect the bioavailability of allicin. In order to better play the role of allicin to prevent the inactivation of alliinase in the stomach, it is essential to develop enteric garlic products or to use lactose as a stabilizer to encapsulate alliin and alliinase with nanotechnology. However, when alliin is not inactivated, the bioavailability of allicin is not changed with the alliinase activities Six brands of allicin enteric-coated tablets exhibited that allicin could exert its highest bioavailability at both the highest and lowest enzyme activity. But the lowest alliinase activity was sufficient to achieve the maximum alliin conversion (Bangham and Horne 1964; Freeman and Kodera 1995).

In a continued experiment with allicin performed by Freeman et al. (1995), allicin was reacted with milk for an hour, and then incubated in the blood for 5 min to test its composition. Allicin was in low levels, but its degradation products were present. Egen-Schwind, Eckard, and Kemper (1992) did a similar experiment with the rat liver isolated from the body and injected with allicin. The results showed that allicin was metabolized to DADS and else in liver. In vivo experiments demonstrated that allicin was detected in serum and urine after taking raw garlic for 24 h (Lawson and Hughes 1992). The metabolism of radioactive labeled DADS in mouse livers showed that 70% of the radioactivity material was detected in the cytoplasm of the liver, but the radioactive material was not in the form of DADS, about 80% of these were DADS sulfates (Lawson and Hughes 1992). These experiments suggested that allicin is metabolized into other sulfur compounds to function in the body. Another report confirmed this speculation. These substances are capable of forming hydrogen sulfide that has a wide range of functions in biology, which is also a signal transduction substance in human body (Lefer 2007).

As a stable water-soluble sulfide, SAC is the most important indicator of garlic bioavailability. The bioavailability test of oral SAC in mice, rats and dogs showed that the bioavailability was 103.0%, 98.2% and 87.2%, respectively, which were relatively high; and the n-acetyl capsule, a metabolized product of SAC, was detected in dog urine (only found in human and dog urine) (Nagae et al. 1994). SAC could be detected in the blood after oral administration and the content gradually increased and then decreased, thus SAC was generally considered as a signature component of garlic organic sulfide activity and the only reliable human

compliance marker for garlic intake studies at present (Steiner and Li 2001).

In conclusion, bioavailability is mainly related to the metabolic absorption in the digestive system. But other factors, such as food substrates, can also affect the bioavailability. In vitro digestion experiments of sulfur compounds in different garlic substrates showed that garlic powder had the highest bioavailability among garlic cloves and garlic powder; when allicin was eaten with foods containing high protein, allicin's bioavailability was decreased by the slow gastric emptying (Torres-Palazzolo et al. 2021; Lawson and Hunsaker 2018).

Garlic can produce a variety of organic sulfides in different processes. These organic sulfides have many important biological and pharmaceutical functions. The further study of bioavailability of various organic sulfides is of great significance for developing garlic health products and pharmaceutical markets.

6. Application of functional components of garlic in nanotechnology

Common biodegradable nanoparticles with biocompatibility include liposomes, nano-emulsions, solid lipid nanoparticles (SLN), micelles, nano-spheres and nano-capsules, dendrimers, carbon nanotubes, protein-based nanoparticles, biopolymeric particles, nanocrystals, microcapsules, inorganic nanoparticles and phyto-phospholipid complexes (Figure 2). A lot of phytochemicals, nutrients and other compounds extracted from garlic can be incorporated into biodegradable and biocompatible nanoparticles, which would enhance their stability, aqueous solubility, bioavailability, target specificity and circulation time (Figure 3). Hence, more nanoparticles would get into disease tissues owing to the leaky vasculature, while fewer nanoparticles enter normal tissues.

6.1. Application of garlic functional components in nanoliposomes

Liposomes have a phospholipids-containing lipid bilayer structure, including a hydrophilic head and a hydrophobic fatty acid tail. In the mid-1960s, liposomes were used in the study of biofilms (Lasic 1998). Then liposomes have been used in various fields, such as cosmetic formulation, drug delivery, diagnostics and the food industry (Newman and Huang 1975). The US Food and Drug Administration (FDA) has approved some liposome-based drugs which can be used on the market to treat a great number of diseases (Harrison, Tomlinson, and Stewart 1995). Because of their biphasic properties, liposomes can be used to embed both hydrophilic compounds (in the central chamber) and to transport hydrophobic compounds (in the lipid bilayer) (Langer 1990).

The common methods of nanoliposome synthesis include ultrasonic treatment, extrusion, ether injection, freeze-thawing, and micro-fluidization. Ultrasonic processing and extrusion are extensively utilized in the laboratory (Mozafari 2010; Reza Mozafari et al. 2008). Small size nanoliposomes can be produced with high power, long time and small pore diameter extruder filtration. However, industrial manufacturers commonly use microfluidization. It involves high pressure techniques, which use microfluidizers to decrease the particle size of liposomes (Reza Mozafari et al. 2008; Mozafari 2010). The significant advantage of this method is that nanoliposomes of different sizes can be prepared on a large scale without exposing to the toxic agents (Mozafari 2010).

Nanoliposomes can be introduced into the body through parenteral, oral or nasal administration (Shoji and Nakashima 2004). The nanoliposomes in the circulatory system are quickly cleared by the reticuloendothelial system because they are considered as foreign substances (S. Tang et al. 2013). In addition, *Van der Waals* and electrostatic forces can decompose nanoliposomes (Lasic et al. 1991; Papahadjopoulos et al. 1991). Hence, inert polymers are needed to be coated with nanoliposomes to enhance their stability (Momekova et al. 2007; Woodle and Lasic 1992). In 1995, the first liposomal drug, a PEGylated liposome containing doxorubicin for treating Kaposi's sarcoma was approved by FDA (Harrison, Tomlinson, and Stewart 1995). Polyethylene glycol (PEG) liposomes significantly reduced the cardiotoxicity of Adriamycin and extended the circulating half-life of Adriamycin from a few minutes to over 20 h (Coukell and Spencer 1997; Harris et al. 2002). As a result of the success of Adriamycin liposome, many liposomal preparations have been established and are tested in clinical trials currently.

Firstly, nanoliposomes have a large dissolution area and can be rapidly absorbed, resulting in a large absorption concentration gradient (Chan and Kwok 2011). Secondly, nanoliposomes have a small size, which can increase the area of biological tissues and embedded compounds, increase the permeability of drugs, and prevent enzyme degradation, which provides potential for improving oral bioavailability (Mozafari et al. 2009). At present, studies on liposomes mainly focus on their applications. Liposomes can be modified with PEG to reduce their conditioning effect in plasma, and transformed into suitable carriers for targeted cancer drug delivery (Bunker 2012; Xie et al. 2012; Kurmi et al. 2020). Nanoliposomes can be used for embedding garlic extract, which can protect their antioxidant activity and reduce the bad flavor (Pinilla and Brandelli 2016). Nanoliposomes can also be used in health care products, which can prevent premature degradation of health care products and improve the quality of health care products (Harde, Das, and Jain 2011; Xu et al. 2013). It has been found that garlic essential oil (GEO, 2% v/v) can be loaded into nanoliposomes. The embedding of GEO has great potential, and now can be used as a food preservative (Khatibi et al. 2014). Allicin is formed via allinase when garlic is crushed (Arzanlou and Bohlooli 2010), which has a strong antibacterial activity, thus it may have an inhibitory effect on *Listeria* monocytogenes. Research has shown that bacteria, fungi, protozoa and viruses are sensitive to the garlic extract (Goncagul and Ayaz 2010b; Wallock-Richards et al. 2014). The nanoliposome embedding milk peptide chain

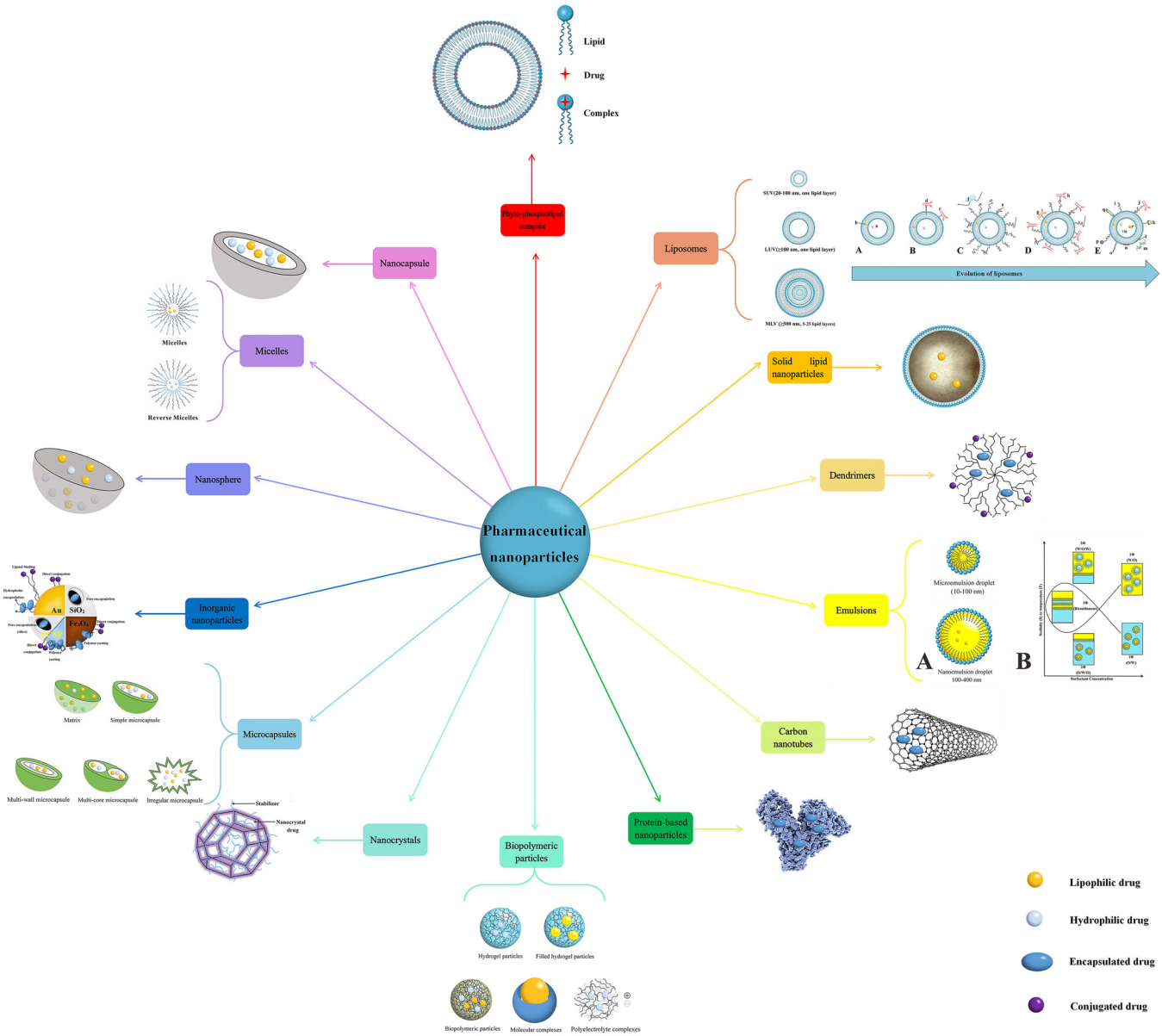

Figure 2. Classification of nanotechnology.

bacteria and garlic extract can be used to better control the growth of *Salmonella enteritidis,* E. *coli,* L. *monocytogenes* and S. *aureus*. Liposome and coating garlic extract can also weaken the bad smell and protect its antioxidant activity.

6.2. Application of garlic functional substance in nanoemulsion

Two insoluble liquids can form emulsion. As the oil disperses, it passes through the water phase to form droplets, which is named oil-in-water (O/W) emulsion. By contrast, aqueous solutions disseminated in the oil phase are named water-in-oil emulsions (W/O) (Liu and Liu 1995). However, surfactants or emulsifiers are required to disperse the two immiscible liquids and stabilize the structure of emulsions. Surfactants or emulsifiers exhibit an amphiphilic structure, with one segment being hydrophilic and the other hydrophobic (McClements, Decker, and Weiss 2007; Mun, Decker, and McClements 2005). The emulsifier can decrease the interfacial tension, form a thin film on one phase to repel the other, increase the viscosity of the medium and maintain and stabilize the emulsion structure. Most emulsions, especially those designed for oral or parenteral use, are O/W type (McClements, Decker, and Weiss 2007). In 1972, the first intravenous fat emulsion, Intralipid, consisting of lecithin, soybean oil, and glycerin, was approved by FDA. For patients who cannot absorb these nutrients through diet, essential fatty acids can be delivered via intralipid intravenous injection (McNiff 1977). The successful clinical trial of this emulsion laid the foundation for the encapsulation and dissolution of hydrophobic substances into the inner oil core of the emulsion for curing other diseases (Press et al. 1974). Emulsions can be utilized to transport various biologically active lipids or hydrophobic compounds, such as carotenoids, omega-3 fatty acids, flavonoids, phytosterols and other phytochemicals (McClements, Decker, and Weiss 2007). To prepare nanoemulsions with

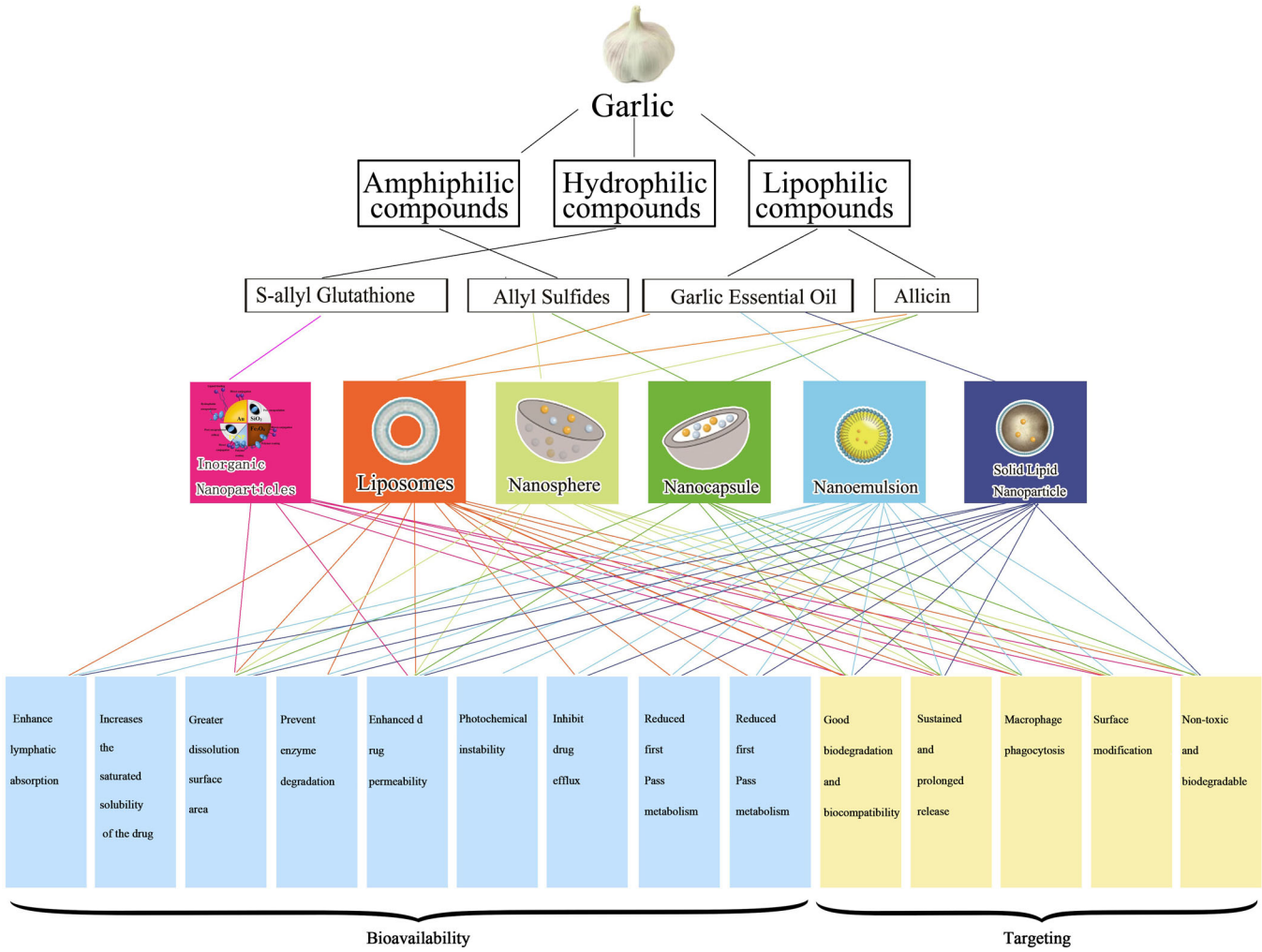

Figure 3. Improving the bioavailablity and bioactivity of garlic ingredients using nanotechnology.

diameters < 100 nm, it requires more surfactants or auxiliary surfactants and high energy inputs to reduce surface tension and thus make them small and thermodynamically stable (Tadros et al. 2004).

Homogenization and ultrasonic treatment are general methods for preparing nanoemulsions on a laboratory scale (Anton and Vandamme 2011). Micro-fluidization and high pressure homogenization can be utilized for mass production of nanoemulsions (Pinnamaneni, Das, and Das 2003). Nanoemulsions have a large dissolution area, which can enhance the chemical stability of the drug with a rapid effect (Corzo-Martínez, Corzo, and Villamiel 2007). It can also enhance the drug permeability and reduce the size of emulsion particles to nanosize, which is conducive for improving the emulsion stability, and increase the oral bioavailability of the encapsulated drug. Nanoemulsions can promote lymphatic absorption and bypass the liver to deliver nutrients to the whole body for circulation, avoid the first metabolism of the liver, prolong the time of drugs in the body, and thus improve the bioavailability (Porter, Trevaskis, and Charman 2007). Nanoemulsions can improve gastrointestinal digestibility, thus nanoemulsions have more digestive enzyme binding sites (Salvia-Trujillo et al. 2013). Experiments have shown that nanoemulsions can enhance the antioxidant effect of drugs. The antioxidant ability of nanoemulsion drug carriers is much higher than that of free drugs, thus the properties of nanoemulsion drug carrier are more stable (Nagi et al. 2017). Nanoemulsions play a key role in drug control release and improve the targeting specificity due to the low toxicity, good biocompatibility and biodegradability. Nanoemulsions can also be used in GO products. Studies have found that nanoemulsion of GO has a good lipid-lowering effect, and can prevent and treat dyslipidemia diseases. In addition, GO itself is toxic, but its nanoemulsion can reduce the toxicity to human body (Ragavan et al. 2017). GO can reduce the level of cholesterol in the blood and enhance immunity, along with other advantages such as antitumor and protecting liver abilities. But the applications in industry are limited by the poor aqueous solubility (Zheng et al. 2013), leading to the poor oral bioavailability. To improve the disadvantages of GO, GO and nanoemulsion can be combined to improve the solubility, stability and oral bioavailability.

6.3. Application of garlic functional substances in nanospheres and nanocapsules

Nanospheres can be divided into nanospheres and nanocapsules. The difference of nanospheres and nanocapsules lies in their different skeletons, which are solid scaffolds and

drug storehouses with membrane shells. Both of them can be used as drug carrier, because the balls and nanocapsules have a larger dissolution area. They can increase permeability, reduce drug dosage, improve patient compliance, and enhance the oral bioavailability (Chan and Kwok 2011). Nanospheres and nanocapsules can be coated to target specific tissues and organs, crossing the blood-brain barrier from circulation through intracellular transport (Fillebeen et al. 1999). Nanospheres and nanocapsules have good biocompatibility and biodegradability, which can decrease the drug toxicity to normal tissues and organs, play a key role in drug controlled release, and improve the targeting specificity. Paclitaxel is one of the most effective anticancer drugs, and Cremophor EL is used as adjuvant for its solubilization in current commercial formulation. A novel surfactant, D-α-tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS), and matrix material with other biodegradable polymers are proposed by Mu and Feng (2003) for fabricating nanoparticle formulation of paclitaxel. The results suggested that Vitamin E TPGS could be used as an efficient emulsifier to fabricate polymeric nanoparticles via the single emulsion technique. TPGS might also have the potential to enhance the hemodynamic properties of the nanoparticles in the blood flow and the nanoparticle adhesion to cells. It is inferred that Vitamin E TPGS is advantageous to prepare nanoparticles for controlled release of paclitaxel either as emulsifier or as matrix material mixed with PLGA. As an antitumor compound, allicin is considered as the most plentiful thiosulfinate in freshly crushed garlic (Hirsch et al. 2000). Hence, researchers have synthesized facile and low cost garlic clove extract-based silver nanoparticles (G-AgNPs) and have evaluated the broad spectrum of therapeutic activity, such as antibiofilm, anti-breast cancer and antiparasitic activity. These particles have exhibited a significant anticancer activity against breast cancer cell MCF-7 lines without resulting in any notable cytotoxicity to the normal embryonic cells HEK293 (Vijayakumar et al. 2019). During nanoparticle synthesis, garlic extract performed a role as the silver salt reducing agent and the postsynthesis stabilizing ligands. The presence of organosulfur compounds in the form of allyl sulfides is considered as the reason for the strong oxidation resistance of silver nanoparticles prepared with garlic extract (Von White et al. 2012).

Nanospheres and nanocapsules can be surface modified by specific substances to extend their circulation time in vivo and improve their efficacy to effectively target tumor sites (Kurmi et al. 2020). Xu et al. (2005) studied the sustained and targeted delivery of paclitaxel using PEG-coated biodegradable polycyanoacrylate nanoparticle (PEG-nanoparticles) conjugated to transferrin. The release profile of paclitaxel- nanoparticle was maintained more than 30 day (81.6%). Nanoparticles were also observed to demonstrate a significantly delayed blood clearance in mice. Compared with the level of free drug from paclitaxel injection, the level from conjugated nanoparticles retained much higher at 24 h. Therefore, it could be an effective carrier for paclitaxel delivery using PEG-coated biodegradable polycyanoacrylate nanoparticle conjugated to transferrin. Additionally, Zhang and Feng (2006) studied the delivery of paclitaxel using poly(lactide)-tocopheryl polyethylene glycol succinate (TPGS) (PLA-TPGS) as newly developed copolymers with advantageous hydrophobic-hydrophilic balance. Paclitaxel containing nanoparticle prepared with PLA-TPGS copolymer was identified in vitro and ex vivo. Comparing with the commercial paclitaxel, the anticancer activity and cellular uptake of nanoparticle paclitaxel demonstrated a remarkably higher anticancer activity and decreased cytotoxicity in HT-29 and Caco-2 cells according to MTT assay. Garlic extract can be embedded with nanoparticles to form GE-NP gel nanoparticles. This GE-NP sol-gel nanoparticle system can improve the stability and antibacterial activity of garlic extract for a long time, and also protect them from degradation. Furthermore, Jurcisek et al. (2011) evaluated the ability of GE-NP to destroy bacterial biofilm and found it had an antibiofilm effect.

6.4. Application of garlic functional components in SLN

The structures of SLNs are similar to that of O/W nanoemulsions, such as hydrophobic lipid cores and solid hydrophilic shells at room temperature (Puri et al. 2009). As an alternative to traditional nanocarriers including polymer nanoparticles, nanoliposomes and nanoemulsions, SLNs was established in the early 1990s (Müller et al. 1996). A relatively high melting temperature of lipids in SLNs is helpful to realize and maintain the structure of SLNs. Common lipids contain triglycerides (e.g., triglycerides), waxes, fatty acids (stearic acid), or mixtures of these lipids (Mehnert and Mäder 2012; Üner 2006). Generally, lipid dispersions are stabilized using surfactants, such as phospholipids, bile salts, fatty acid ethoxylates, dehydrated sorbitol esters, or a mixture of these compounds (Mehnert and Mäder 2012). Although SLNs are one of the extensively used lipid-based nanocarriers in nutrition care and drug research, there are some drawbacks including low substance load and leakage during storage. To overcome these limitations, an improved new generation of nanostructured lipid carriers (NLCs) have been recently developed (Üner 2006). Traditional methods for preparing SLN and NLC include cold homogenization, high pressure homogenization, phase conversion, thermal homogenization/ultrasound and solvent emulsification/evaporation (Das and Chaudhury 2011). The relatively simple and most cost-effective method for mass production is the high-pressure homogenization method (Jenning, Lippacher, and Gohla 2002). While ultrasound/emulsification is a regular laboratory method for producing SLN and NLC, SLN and NLC have been extensively studied for pharmaceutical, cosmetic, food and agricultural products (Puri et al. 2009).

Solid lipid particles are a kind of colloidal system used for delivering unstable drugs, which can embed the drug to the target site through oral administration. Oral solid lipid particles can increase the stability, solubility and permeability of drug, prevent enzyme degradation, prolong half-life, and play a role in controlled-release drugs (He and Hwang 2016). By studying valsartan solid lipid particles, Parmar et al. (2011) found that solid lipid particles can bypass the first

metabolic effect, reduce drug outflow, enhance lymphoid absorption and improve oral bioavailability, which is widely used as a nanocarrier for embedding. Solid lipid particles have the advantages of small volume, large dissolution area, good biocompatibility and biodegradability, high nontoxic safety, and improved targeting specificity (Puri et al. 2009). SLNs can embed GO, a nutraceutical with medicinal properties, whose applications have been limited by its poor solubility. This drug carrier has good effects on sustained-release drugs, because it can improve the bioavailability, target liver organs, and improve the targeted specificity of compounds to disease tissues (Müller, Mäder, and Gohla 2000). As an organosulfur ingredient of garlic, DADS exhibits the activity against breast cancer, as well as the cytotoxic activity. To overcome its bioavailability problems, Siddhartha et al. (2018) developed SLNs loaded with DADS (DADS-SLN). To deliver drugs specifically to the receptor for advanced glycation endproducts (RAGE) which is the target of triple-negative breast cancer cells, it was expected to specifically target DADS to triple-negative breast cancer (TNBC) cells to minimize the off-target cytotoxic effects on healthy cells using the surface modification of DADS-SLN with anti-RAGE antibody owing to the overexpression of RAGE receptor on TNBC cells.

6.5. Application of garlic functional components in micelles

Micelles are amphiphilic colloid consisting of amphiphilic monomers such as phospholipids and other polymers. The diameter of micelles is commonly between 20 and 80 nm. Conventional micelles are lipid based (Torchilin 2007). Micelles are generally formed when the temperature gets to the critical micelle transition temperature and the amphiphilic phospholipid concentration attains the critical micelle concentration (Lim, Banerjee, and Önyüksel 2012; Torchilin 2007). The micellar shells are formed by hydrophilic heads of phospholipids, while the hydrophobic nuclei are formed by the fatty acid tails of phospholipids to contain phytochemicals or other hydrophobic components. Recently, polymer micelles have aroused much attention among researchers. Polymeric micelles are prepared from block copolymers consisting of hydrophilic and hydrophobic monomer units (Torchilin 2001). Core-shell micelle structures can be formed by conjugating two monomers with differing hydrophobicity, in which hydrophobic and hydrophilic blocks form nuclei and micelle shells, respectively. The extensively used nucleating blocks are polycaprolactone, polypropylene oxide, poly L-aspartic acid and poly D, L-lactic acid, and the usually utilized hydrophilic monomer is PEG (Gong et al. 2012; Torchilin 2001). Micelles have been utilized as carriers of diverse hydrophobic compounds for topical, oral, ocular and parenteral use (Torchilin 2001).

As an aggregation of surfactant molecules, micelles can prevent chemical degradation and metabolism and perform a solubilizing role for drugs with poor water solubility. Thus it can be used as a drug carrier for oral administration of low water solubility (Sharma and Garg 2010). Micelles have a large dissolution area, which can accelerate the absorption rate and increase the permeability of drugs to improve the oral bioavailability (Chan and Kwok 2011). Micelles can reduce toxicity of compounds, prolong blood circulation time, target certain disease sites, and improve drug concentration and targeting specificity (Kwon et al. 1995; Oerlemans et al. 2010). The advantages of micellar targeted drug delivery are nontoxic and biodegradable. Their good biocompatibility and the effect of controlled-release drugs can control the continuous or prolonged release of drugs to improve the targeting specificity. It has been proved that there was a biodegradable micelle that could be used in actively targeted chemotherapy for liver cancer (Zou et al. 2014). And Yang et al. (2020) prepared a stable hybrid micelle for active targeted drug delivery in treating triple negative breast cancer. Pan et al. (2016) determined the antitumor activity and toxicity of the bladder cancer-specific nanoscale micelles incorporated the chemotherapeutic drug paclitaxel. The antitumor activity and in vivo targeting were characterized in immunodeficient mice with patient-derived bladder cancer xenografts. Paclitaxel-loaded disulfide-cross-linked PLZ4 nanomicelles (DCPNM) overcame cisplatin resistanceand improved the anticancer efficacy of paclitaxel by targeting the bladder cancer xenografts in vivo.

6.6. Application of garlic functional substances in inorganic nanoparticles

In the nanosystem, inorganic nanoparticles have various sizes and shapes, and their unique properties also depend on the crystallographic properties, shapes and sizes of the particles (Asta et al. 2007). Nowadays, inorganic nanoparticles are extensively used in developing therapeutic drug delivery systems. G-AgNPs based on low cost and facile garlic clove extract were synthesized to evaluate their anti-breast cancer activity. G-AgNPs significantly inhibited the MCF-7 human breast cancer cell viability, demonstrating a remarkable anticancer effect (Vijayakumar et al. 2019). As an analog of glutathione (GSH), S-allyl glutathione (SAG) is synthesized using the allyl group to alkalate the thiol group of GSH. Topoisomerase, which is an important target protein of cancer treatment, could be potentially inhibited in vitro by SAG. *Spermacoce hispida* L. (Rubiaceae) aqueous leaf extract was used to synthesize SAG conjugated selenium nanoparticles (SAG-Sh-SeNPs), which was studied for anticancer potential against hepatocarcinoma cell line (HepG2). Cell cycle arrest was induced by the SAG-Sh-SeNPs treatment at sub-G1 phase, followed by apoptosis which was detected using acridine orange/ethidium bromide staining (Krishnan, Loganathan, and Thayumanavan 2019).

6.7. Applications of other nanomaterials

Currently, several other nanomaterials, including dendrimers, carbon nanotubes, protein-based nanoparticles, biopolymeric particles, nanocrystals, microcapsules and phyto-phospholipid complexes, have been relatively

infrequently used, especially in garlic. However, these nanomaterials are currently being studied for use in Chinese herbal medicines. Despite various effective anticancer characteristics of curcumin, its application is limited owing to the hydrophobic structure. PAMAM dendrimers encapsulating curcumin increased the inhibitory effect on telomerase activity, decreased IC_{50} for proliferation, but demonstrated no cytotoxicity on cancer cells (Mollazade et al. 2013). As a drug delivery system incorporating various compounds, protein-based nanoparticles have been greatly rated for their capability. For example, alpha-mangosteen-contained nanoparticles were produced for anticancer purposes by cross-linking alpha-mangosteen extracted from mangosteen pericarp. These particles demonstrated a capability to enhance the alpha- mangosteen solubility, reduce the drug hematopoietic toxicity by 90%, sustain release for over 72 h, and keep the effect of drug treatment (Pham, Saelim, and Tiyaboonchai 2019). In addition, the delivery of quercetin incorporated to SWCNTs was performed by Dolatabadi et al. using covalent PEGylation. It enhanced the biocompatibility and solubility, followed by conjugating with arginine-aspartate-glycine peptide to selectively target to integrin receptors on cancer cells, and finally loaded quercetin into SWCNTs-RGD. To realize the controlled release of quercetin, its high solubility could be achieved by SWCNTs that could also increase its hydrophilicity at a low pH, which is helpful due to the acidic microenvironment of tumor cells. Raman imaging and photoacoustic imaging revealed that delivery of quercetin based on CNTs exhibited a high selectivity to cancer cells (Dolatabadi et al. 2011). Rutin is a plant active ingredient with various therapeutic effects, but its bioavailability is low due to its hydrophobicity. To overcome this problem, Raeesi (2020) prepared rutin nanocrystals and investigated their physicochemical properties. Because the toxicity increase of nanorutin was 100 times more than that of rutin on oral cancer cells, this substance can be a suitable option in the design of anticancer drugs, especially in combination with chemical anticancer drugs.

As a promising system, microcapsules can selectively deliver hydrophobic drugs including camptothecin to tumor cells. The poly (vinyl alcohol) microcapsules are prepared as carriers to deliver an anticancer drug camptothecin with a poor solubility in water. The camptothecin-loaded chitosan-folate microcapsules can remarkably decrease the proliferation of HeLa tumor cells (Galbiati et al. 2011). As an herbal drug isolated from *Glycyrrhiza glabra* (L.), glycyrrhizic acid has been found to have an anticancer activity due to its protection of DNA in cancerous cells and the effective inhibitor of MMPs A sustained release that 88% (w/w) of glycyrrhizic acid and 14% (w/w) of silibinin were released more than 48 hours in in vitro release study. The coencapsulated nanophytosomes of glycyrrhizic and silibinin were three times more potent than those of individual glycyrrhizic acid (75% w/v) and silibinin (25% w/v) in the cell viability study on HepG2 cell lines. In another word, the bioavailability of silibinin was improved by phytosome, demonstrating the ability of phytosome technology in developing coencapsulated systems that improved the therapeutic effects of silibinin with the help of the synergistic effects of glycyrrhizic acid (Babazadeh, Zeinali, and Hamishehkar 2018). Biopolymeric particles quercetin is a kind of Chinese herbal medicine with very low water solubility (Zheng et al. 2005), poor stability and low antioxidant performance under alkaline conditions. Studies have found that quercetin can be wrapped in biopolymer particles to improve its poor performance, stability and bioavailability (Shoji and Nakashima 2004). In summary, nanotechnology has a promising future, and these materials could be used for garlic applications in the future.

7. Conclusive remarks/conclusion

Garlic has been used as ingredients in food elaboration or direct consumption for thousands of years. In recent years, researches on garlic for its medicinal purposes have attracted much attention for its anticancer properties. Garlic and its products are frequently used for treating certain diseases due to the belief that these therapies have fewer side effects than pharmaceutical products, though it demonstrates instability, low aqueous solubility, strong gastrointestinal irritation and low bioavailability. However, nanotechnology and other embedding technology have promisingly overcome the limitations of conventional garlic preparation. GO nanoemulsion generated with ultrasonic emulsification can improve efficacy and reduce toxicity in treating or preventing dyslipidemia (Ragavan et al. 2017). Nanoencapsulation of GEO with chitosan and persian gum as wall materials has a good stability and low dispersibility (Raeisi et al. 2019). GEO encapsuled in nanophytosomes as a novel phytoconstituents delivery system demonstrated powerful antibacterial effects against food-borne pathogens i.e. *Staphylococcus aureus* and *E. coli* (Nazari et al. 2019). However, the nanoscale reduction of droplet size alone will not be sufficient to improve their biological activity. The GO nanoemulsion using calcium nano-particles has a lower antibacterial activity than regular GO (Hassan and Mujtaba 2019). Nanoencapsulation on garlic was mainly based on its antibacterial effects, and the anticancer study was still limited.

First and foremost, in vivo and in vitro studies have demonstrated the applications and advantages of garlic biologically active compound individually or in combination in treating cancers. However, what is more interesting is that the future work remains to be done to provide a comprehensive understanding for the interactions of the bioactive phytochemicals in garlic in the human body system through *in-vivo* preclinical trials. In addition, since garlic has been traditionally used for anticancer, more human clinical trials are needed to verify the exact dosage and mode of administration as traditional practice to determine its efficacy and observe any possible adverse reactions. Last but not least, with the increasing scale of nanotherapy, the design of patient-specific drug delivery system would in turn contribute to the personalization and management of treatment based on the clinical phenotype of the patient. Nonetheless, further pharmacodynamic and pharmacokinetic studies are needed to determine the molecular pathway exhibited by these nano-formulations and their bioavailability.

Nanomedicine is expected to become the next wave of global transition in cancer therapeutics which would transform the therapeutic front through early identification of tumor and patient management at an early stage.

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Disclosure statement

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