The Immunomodulation and Anti-Inflammatory Effects of Garlic Organosulfur Compounds in Cancer Chemoprevention

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Abstract: Garlic (*Allium sativum*) has been used for centuries as a prophylactic and therapeutic medicinal agent. Importantly, garlic has been suggested to have both cancer-preventive potential as well as significant enhancing effects on the immune system. While these observations are supported experimentally both *in vitro* and *in vivo*, the impact of garlic in assisting the immune system in the prevention of cancer still lacks experimental confirmation. Studies addressing the immunomodulatory effects of garlic reveal conflicting data as to pro- or anti-inflammatory responses depending on the particular experimental set-ups and the garlic preparation used (*i.e.* garlic extract versus chemically pure garlic compounds). Here we provide an overview of the chemistry of the major garlic organosulfur compounds, summarize the current understanding and propose a link between the immunomodulating activity of garlic and the prevention of cancer. We hypothesize that garlic rather elicits anti-inflammatory and anti-oxidative responses that aid in priming the organism towards eradication of an emerging tumor.

INTRODUCTION

The health effects of dietary garlic have been utilized throughout the centuries to offer protection against infections, heart disease and cancer. Crushed cloves are rich in sulfur containing compounds collectively termed garlic organosulfur compounds (OSCs) which are the active principles responsible for the biological activity of garlic. Regarding cancer, the face of garlic is multi-faceted being capable of eliciting both preventative and therapeutic effects. In cancer treatment, garlic organosulfur compounds have been shown to inhibit proliferation and induce apoptosis of cancer cells both in culture as well as in mouse xenograft models [1, 2]. Central to this effect are G_2/M cell cycle arrest and activation of the mitochondrial-dependent caspase cascade [1, 2]. In cancer prevention, numerous epidemiological studies have demonstrated a link between garlic consumption and decreased risk of cancer especially cancer of the colon and stomach [3]. Some of these observed effects may be explained from the ability of garlic OSCs to inhibit tumorigenesis arising from exposure to chemical carcinogens as demonstrated in experimental animals [2, 4]. On the other hand, garlic OSCs are reported to exert an immunological effect by eliciting diverse immune responses depending on the particular experimental setting. We propose that garlic OSCs obtained through the diet, may aid in cancer prevention by shifting the overall balance from a tumor-mediated pro-inflammatory to a host-mediated anti-tumor response which may stimulate the immune system towards eradication of an emerging tumor.

THE ORGANOSULFUR COMPOUNDS IN CRUSHED GARLIC

The beneficial health effects of garlic are attributed to the organosulfur compounds found in crushed cloves. The principle organosulfur compound in intact cloves is (+) *S*-allyl-L-cysteine sulfoxide (alliin) which is compartmentalized away from the vacuolar enzyme alliinase (EC 4.4.1.3). Upon damaging of the clove (*i.e.* by chewing or crushing), alliinase comes into contact with its substrate and an elimination reaction ensues to form 2-propenesulfenic acid, which self-condenses to form diallyl thiosulfinate (allicin) (Fig. **1**). Allicin, therefore being a constituent of freshly crushed cloves, is an anti-microbial agent possibly generated by the plant as a defence against pathogen invasion. Allicin, however, is chemically unstable and degrades and rearranges over time to form a collection of second generation allyl sulfides and polysulfides (commonly termed garlic organosulfides), through pathways which were elegantly elucidated by Eric Block in the 1980's [5]. These second generation organosulfides are constituents of fresh, but have increased concentrations in aged, garlic preparations. The chemical structures of the predominant second generation organosulfides are displayed in Fig. **2**. Allicin is only found in fresh, raw garlic preparations in a reported amount of 3.1 mg.g^{-1} [6]. Garlic preparations vary in concentration of secondary organosulfur compounds, which can be isolated by steam distillation or oil extraction, sometimes with heat, to be (in micrograms per gram of garlic preparation) diallyl sulfide (DAS) 20-240; diallyl disulfide (DADS) 280-900; diallyl trisulfide (DATS) 40-200 and *E/Z*-4,5,9-trithiadodeca-1,6,11-triene 9-oxide (*E/Z*-ajoene) 130-480 [7-10]. The other organosulfur compounds listed in Fig. **2** are only present in concentrations < 50 µg.g^{-1}. As can be seen from above, the exact amount of compound in a preparation is subject to high variability. *In vivo*, allicin is never detected after ingestion of garlic supporting experimental evidence that allicin is both chemically and metabolically unstable. It is likely that the ingested allicin rapidly degrades into the second generation organosulfur compounds (as observed *in vitro* in garlic preparations), as well as participates in the rapid thiolation of plasma proteins (discussed in the next section). This has been demonstrated in the very rapid first pass effect observed for allicin in a perfused rat liver [11]. In this experiment, only allicin metabolites were detected after the first pass and these were identified to be DADS, ajoene, the vinyl diithins and allyl mercaptan. In addition, no allicin has been detected in blood after oral ingestion of a large amount of raw garlic (25g) [12]. Three studies have identified the organosulfur compounds present in the breath after ingestion of raw garlic by either GC-MS [13, 14] or proton-transfer-reaction mass spectrometry [15]. Again, only allicin metabolites were detected and these are collectively listed to be: DADS, AMS, AMDS, DAS, DADS, DATS, dimethyl sulfide, acetone and allyl mercaptan. It is therefore likely that the second generation allicin products DAS, DADS, DATS and *EZ*-ajoene are responsible for the biological activity of

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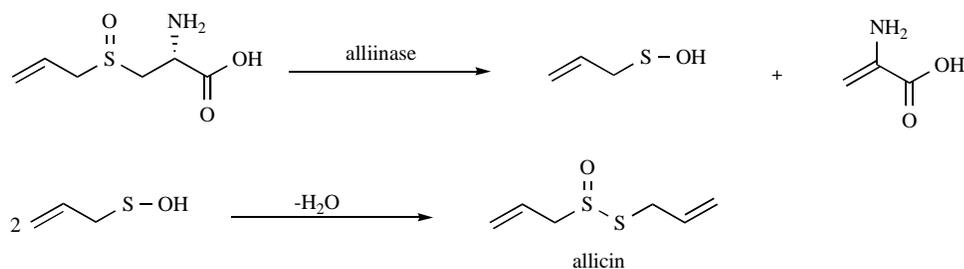
Fig. (1). The enzymatic conversion of alliin to 2-propenesulfenic acid which then undergoes self-condensation to produce allicin.
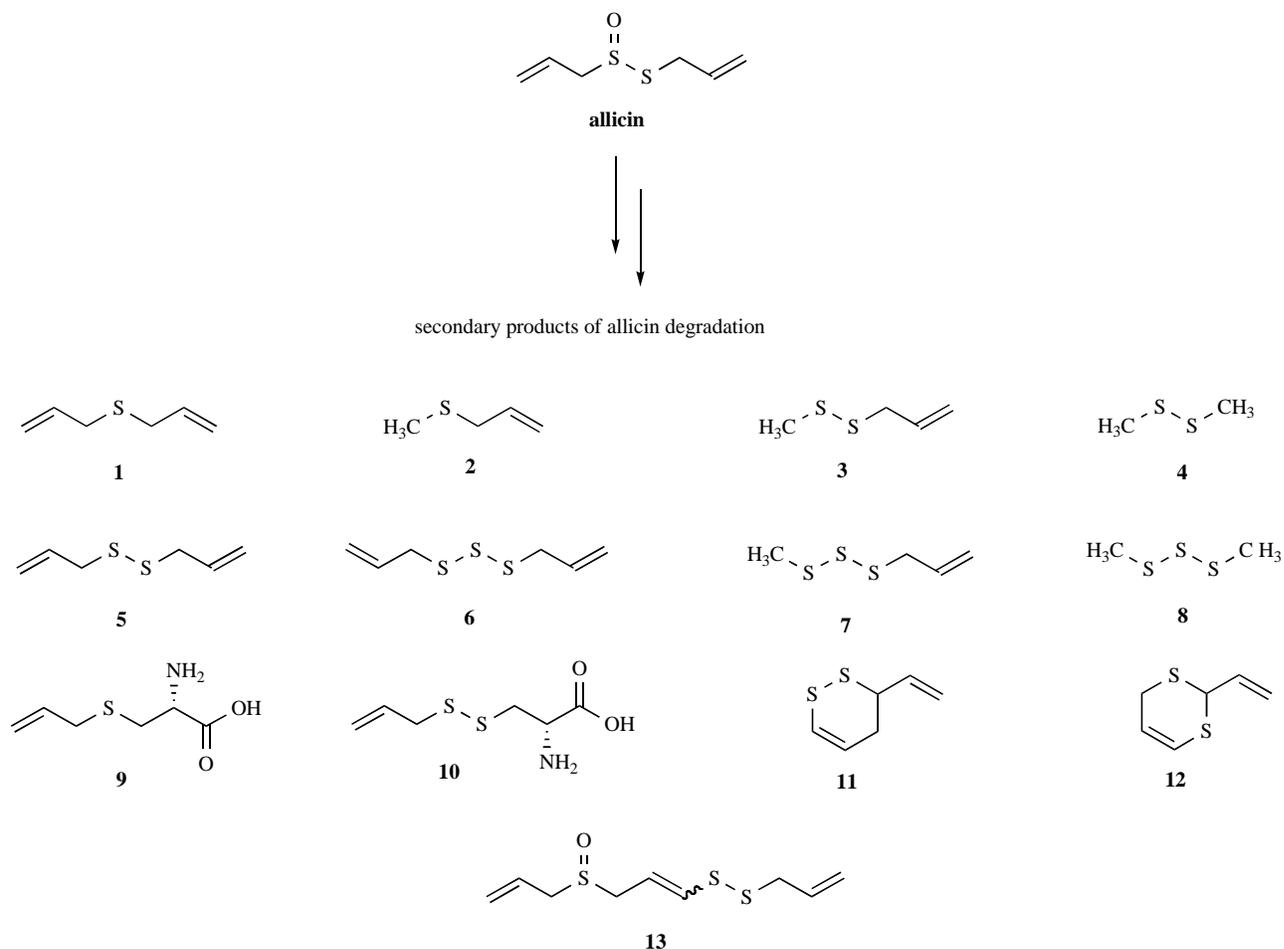

allicin

secondary products of allicin degradation

Fig. (2). The predominant secondary products of allicin degradation in crushed garlic. (**1**) diallyl sulfide (DAS), (**2**) allyl methyl sulfide (AMS), (**3**) allyl methyl disulfide (AMDS), (**4**) dimethyl disulfide (DMDS), (**5**) diallyl disulfide (DADS), (**6**) diallyl trisulfide (DATS), (**7**) allyl methyl trisulfide (AMTS), (**8**) dimethyl trisulfide (DMTS), (**9**) *S*-allyl cysteine (SAC), (**10**) *S*-allyl mercaptocysteine (SAMC), (**11**) 2-vinyl-2,4-dihydro-1,3-dithiin, (**12**) 3-vinyl-3,4-dihydro-1,2-dithiin, (**13**) *E/Z*-4,5,9-trithiadodeca-1,6,11-triene 9-oxide (*E/Z*-ajoene). Note that compounds **9** and **10** are the only water soluble compounds.

garlic with the minor constituents, due to their lower concentrations, playing a lesser role.

The garlic organosulfides are all sulfur-rich containing either a sulfide, disulfide or polysulfide functional group in their backbone which is likely the pharmacophore responsible for their biological activity. In support of this, the disulfide bond in ajoene was found to be important for both anti-microbial and anti-cancer activities where removal of the disulfide to the sulfide rendered the analog inactive in both cases [16, 17]. Disulfides and polysulfides can be considered as thiol oxidising agents, able to thiolate cysteine residues in proteins to form mixed disulfides. In a thiol-disulfide exchange reaction, a disulfide RSSR reacts with a thiol R'SH to form a mixed disulfide RSSR' and a thiol RSH. For this reaction to occur, a thiolate anion first needs to be generated. In the cell, cysteine normally has a pK_a significantly higher than the physiological range; however, active site cysteines in enzymes usually provide an unusually basic microenvironment in which cysteine dissociates more readily to form a thiolate. Experimentally, this reaction has been demonstrated to occur by the ajoene thiolation of glutathione reductase at the active site Cys58 to form the modified protein CH_2=CH-CH_2-SO-CH_2-CH=CH-S-Cys58-GR revealing the vinyl sulfur to be the preferred site of enzyme thiol sulfur attachment [18]. We have demonstrated the feasibility of this sulfenylating reaction through the formation of *S*-

allylmercaptocysteine from the reaction between cysteine and ajoene in solution although this reaction was found to proceed *via* regioselective attack at the non-vinyl sulfur [19]. In another cell free system, DADS has been demonstrated to alkylate β-tubulin at cysteine residues Cys-12β and Cys-354β in the protein [20] lending support to the hypothesis that garlic organosulfur compounds induce apoptosis in cancer cells by destabilizing the microtubule network [21]. The biological chemistry of garlic organosulfur compounds probably involves more than a simple thiolation reaction with an enzyme as this should be reversible in cells which contain 2-10 millimolar concentrations of cytosolic glutathione [22, 23] compared to the micromolar concentrations [23] of garlic compounds which are required to bring about a biological effect. In the absence of oxidative stress, these cells should overcome the effects of micromolar concentrations of garlic organosulfur compounds. The biological chemistry of garlic likely involves various types of oxidation, radical generation, protein modification and enzyme inhibition reactions.

EPIDEMIOLOGICAL AND EXPERIMENTAL EVIDENCE FOR CANCER CHEMOPREVENTION BY GARLIC

Over the last thirty years there have been numerous reports linking the etiology of cancer to the consumption of *Allium* vegetables. Some of the first evidences came from case-control studies in China [24] and Italy [25] where consumption of *Allium* vegetables was found to be negatively correlated with incidence of gastric cancer. Since then there have been in excess of 20 additional publications documenting the outcome of various case-control and cohort studies. These studies cover populations from China, Europe, South America and the United States and have looked at the incidence of many cancers but predominantly stomach and colorectal cancers. There are four systematic reviews or meta-analyses which critically scrutinise the vast amount of literature on the subject. Fleischauer and Arab critically reviewed nineteen articles documenting garlic consumption to the incidence of stomach, colorectal, head and neck, prostate, breast and lung cancers reported for the period 1966 - 1998 [3]. Site specific case-control studies of stomach and colorectal cancers were analyzed to suggest a protective effect for high intake of raw and / or cooked garlic with cohort studies confirming this inverse relationship for colorectal cancer. However, garlic supplementation as opposed to dietary intake was not found to be related to cancer risk, as analysed by four cohort studies and one case-control study, from two distinct populations. Kim and Kwon performed their own analysis of the published epidemiological literature for the period 1955 - 2007 using the US Food and Drug Administration's evidence-based review system [26]. Nineteen studies were identified and evaluated to conclude that limited evidence exists to support a relation between garlic consumption and reduced risk of colon, prostate, oesophageal, larynx, oral, ovary or renal cancers with no credible evidence for gastric, breast, lung or endometrial cancers. A systematic meta-analysis by Ngo *et al.*, [27] of 7 colorectal studies confirmed an inverse association with cancer risk. Zhou *et al.*, conducted a meta-analysis of 21 cohort and case-control studies published for the period 1966 - 2010. The relative risks from individual studies were pooled using a random effects model and performed a dose-response, heterogeneity and publication bias analysis to conclude that consumption of high levels of *Allium* vegetables reduces the risk of gastric cancer. Taken together, critical review of the epidemiological literature supports a link between the consumption of *Allium* vegetables including garlic and decreased risk of colorectal and gastric cancers.

Numerous studies in the 1980s and 1990s investigated the cancer chemopreventative activity of garlic OSCs against chemically-induced cancers in experimental animals. Research into this topic has culminated in over 40 publications that have been comprehensively reviewed [2, 4]. In these investigations, a mouse or rat is pre-treated with the garlic extract or pure garlic compound (topically or orally) followed by tumor induction by a chemical carcinogen. Some of the chemical carcinogens that have been used for this purpose include nitrosamines [28, 29], azides [30, 31], aromatic hydrocarbons including benzo[a]pyrene [32] and anthracenes [33] which are administered either topically, by intraperitoneal injection or orally. The outcome of these studies, excluding one [34] claims a reduction in tumor size and tumor number in the garlic pre-treated animals. More specifically and as expected, the pure garlic compounds DADS and SAC were found to exert an increased effect relative to the extract [35]. There are several lines of evidence to suggest that these observed effects may be related to the ability of garlic OSCs to inhibit phase I enzymes (such as the cytochrome P450-dependent monooxygenases [36, 37]) which are responsible for activation of a number of carcinogens; as well as to enhance detoxification processes by inducing expression of phase II enzymes to include glutathione *S*-transferases [38], quinone reductase [39] and epoxide hydrolase [40].

Free radicals are able to induce damaging effects which may lead to tumorigenesis. Garlic extracts and pure garlic organosulfur compounds are reported to have radical scavenging and anti-oxidant activity as demonstrated by their ability to inhibit lipid peroxidation [41]. It has been hypothesized that increased activity of anti-oxidant enzymes namely catalase [42], superoxide dismutase [43] and glutathione peroxidase [42, 44], as well as increased glutathione content [42, 45, 46] may be responsible for these observed effects. On the other hand, garlic OSCs are reported to induce ROS in cultured cancer cells in a dose-dependent manner and this effect has been linked to the therapeutic action of garlic. Some studies have demonstrated a link between ROS generation and apoptosis induction in cancer cells [47-49] although other studies have failed to find this link [50]. The contrasting effects of ROS generation versus ROS scavenging by the individual garlic organosulfur compounds may be explained from the redox chemistry of the thiol-disulfide exchange or through homolytic cleavage of the disulfide to generate a reactive thiyl radical. It is still debated whether there is an overall generation of ROS that is linked to the therapeutic action of garlic against growing tumor cells. It is possible that ROS as well as Reactive Nitrogen Species (RNS) are implicated in the immunomodulating activity of garlic by acting as signal transducer in the immune defence mechanism involved in the killing of malignant cells. However, excessive levels (for example due to inflammatory reactions, see section below) can damage DNA and proteins leading to impaired cellular functions and an enhanced inflammatory response.

THE IMMUNOMODULATORY EFFECTS OF GARLIC

Although the cancer-preventative properties of garlic may be ascribed in part to the anti-carcinogenic and anti-oxidant activities of garlic, they might, at least in part be explained by underlying effects on the immune system. While acute inflammatory responses promote the elimination of growing tumor cells, chronic inflammation and the presence of inflammatory cells, particularly tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), at tumor sites is strongly associated with specific malignancies and influences both tumor initiation as well as tumor promotion and progression [51-53]. Indeed, inflammation is considered a double-edged sword in neoplasia as the immune cells exert rather paradoxical effects during cancer development: they play important roles both in host-mediated anti-tumor immunity as well as in tumor-mediated immunosuppressive activity [52-54]. A delicate balance between these immune responses determines the overall outcome of the carcinogenic process and depends on different mediators released by host inflammatory cells, cancer cells and cancer-associated cells in the tumor micro-environment [55]. This is best illustrated by activated macrophages and neutrophils that are able to kill tumor cells, but can also release

reactive oxygen species, angiogenic, proliferative, pro-inflammatory as well as immunosuppressive substances [56].

The complex role of the different cytokines that are produced upon innate immune activation and inflammation exerts opposing activities in tumor suppression and progression and is thought to be stage and cancer cell type dependent. Generally, activation of the NFκB signaling pathway and expression of pro-inflammatory cytokines such as IL6, IL1β, TNFα and IL17 promote tumor development while pro-apoptotic and anti-inflammatory cytokines such as TRAIL, IL10 and TGF-β inhibit carcinogenesis depending on the particular tumor microenvironment [54]. As mentioned above, the generation of ROS and RNS is another important immune defence mechanism in killing of malignant cells. Indeed, both oxidative stress and overexpression of the inducible form of nitric oxide synthase (iNOS) are common phenomena during chronic inflammatory conditions and play fundamental roles in the initiation of cancer, promotion of tumor growth and progression [57, 58]. As signal transducers, ROS and RNS can stimulate NFκB which leads to the expression of numerous genes encoding proteins in immune function [59]. Macrophages represent the typical source for both oxidative burst in immune responses as well as for iNOS. iNOS expression can be transcriptionally upregulated (*via* NFκB signaling) by pro-inflammatory cytokines such as IFN, IL1, IL2 and TNFα, as well as LPS and hypoxia; it can be downregulated by anti-inflammatory cytokines such as TGFβ and IL10, the tumor suppressor gene p53 and NO (nitric oxide) itself [60].

Immune responses are regulated by intrinsic and extrinsic factors; but diet also plays an important role in the proper functioning of the immune system [54]. There are numerous studies addressing the effect of garlic on the immune system. However, dependent on the particular experimental set-ups and the garlic preparation used (such as fresh garlic juice, garlic powder extract or chemically purified compounds), these studies revealed conflicting data as to garlic being able to stimulate pro- or anti-inflammatory responses as outlined below.

There is evidence that garlic acts as an immune booster by actively strengthening the host immune system within the tumor microenvironment against the immunosuppressive activity of an emerging tumor, the relevant literature has been summarized in Table **1**. Aged garlic extract was found to stimulate lymphocyte proliferation, macrophage phagocytosis, macrophage and lymphocyte infiltration into tumors, as well as the release of cytokines such as IL2, IL12, TNFα and IFNγ that suggests the induction of a Th1-type cellular immune response [61-63]. It was further shown to enhance NK cell number and activity [64], to increase the number of white blood cells [65], to increase NO and the anti-tumoral agent IFNα [66]. However, there are a number of reports indicating that garlic rather inhibits Th1 response and shifts towards a Th2 response. Stimulation of the anti-inflammatory cytokine IL10 was observed in LPS-stimulated human whole-blood cultures by garlic extracts while monocyte production of TNFα, IL1α, IL6 and IL8 and T-cell IFNγ, IL2 and TNFα was significantly suppressed [67].

Table 1.   Selected studies on the immunomodulatory effects of garlic.

Functional Component	Concentration	Experimental System	Reported Effect	Ref.
ajoene	5-40 μM	Human leukemic cells	Induction of apoptosis by stimulation of peroxide production and NFκB activation	[47]
AGE	500 mg daily for 6 months	Inoperable colorectal, liver or pancreatic cancer patients	Increase in NK cell number and activity	[64]
DAS, DADS, AMS	5 x 20 mg daily	BALB/c mice	Enhanced number of white blood cells and antibody titre	[65]
Fresh garlic	2g (once or daily for 7 days)	Healthy human volunteers	Increase in plasma NO and IFNα levels	[66]
Garlic extract	0.1-10 μg/ml	Whole blood and PBMCs	Decreased production of IL12, TNFα, IL1α, IL6, IL8, IFNγ, IL2; increase of IL10	[67]
Garlic extract	10-1000 μg/ml	Normal placental and preeclamptic explants	Inhibition of IL6 and TNFα production; IL10 increase (10μg/ml garlic extract) or IL10 decrease (1000μg/ml garlic extract)	[68]
Garlic powder extract DADS	10-100 mg/l 1-100 μmol/l	LPS-induced human whole blood	Reduction of NFκB activity and production of IL1β and TNFα	[69]
DAS DADS AMS	1-10 μM 0.1-0.5 μM 2-20 μM	LPS-stimulated RAW 264.7 macrophages	Reduction of iNOS expression and NO production; Reduction of COX2 expression and PGE$_2$ release (only DAS)	[70]
AGE SAC	0.1-5 g/l 0.1-20 mmol/l	Ox-LDL induced injury in endothelial cells	Prevention of membrane damage, loss of cell viability and lipid peroxidation by prevention of intracellular GSH depletion and NFκB activation	[71]
Alliin	0.05-3 μg/ml	LPS-induced PMBCs	Increase in IL1β and TNFα; Decrease in IL6 production	[73]
DADS, DATS	50-400 μM	LPS-stimulated RAW 264.7 macrophages	Reduction of iNOS expression, NO and peroxide production; Inhibition of NFκB activation	[74]
ajoene allicin	IC$_{50}$ 2.5-5 μM IC$_{50}$ 15-20 μM	LPS-stimulated RAW 264.7 macrophages	Reduction of iNOS expression and NO accumulation	[75]
DAS	1-10 μM	LPS-stimulated RAW 264.7 macrophages	Inhibition of TNFα, IL1β, IL6, IL10 production; Inhibition of NO and prostaglandin PGE$_2$ release	[76]
DADS	0.1-0.2 μM		Inhibition of TNFα, IL10 and NO release; Increase of IL1β and IL6	
AMS	2-20 μM		Inhibition of TNFα, Increase of IL10, Decrease of NO release	
ajoene	IC$_{50}$ 2.4-3.4 μM	LPS-stimulated RAW 264.7 macrophages	Inhibition of COX2 enzyme activity and PGE$_2$ release	[77]

This was confirmed on LPS-stimulated human placental explants: garlic extracts were found to stimulate the production of IL10 while decreasing TNFα and IL6 production [68]. Although garlic powder extract also inhibited LPS-induced TNFα and IL1β in human whole blood by reducing the pro-inflammatory activity of NFκB, IL10 secretion was not affected [69]. Chang *et al.*, found that garlic oil derivatives differentially suppressed the production of NO and prostaglandin E2 (PGE$_2$) in activated macrophages [70], resulting in an overall anti-inflammatory effect. On that note, the anti-oxidative effects of garlic have been suggested to be due to the prevention of intracellular glutathione depletion and to the removal of peroxides; also, inhibition of NFκB activation seems to be central to these effects [71].

Studies that used purified garlic compounds describe allicin as an inhibitor of NFκB activation, iNOS and TNFα production [72], while alliin was found to inhibit IL6 but increased IL1β and TNFα [73]. Both DADS and DATS decreased NO and cellular peroxide production in LPS-activated RAW264.7 macrophages by suppression of NFκB-mediated iNOS expression [74]. This effect was also seen when allicin and ajoene were studied: both compounds inhibited the expression of iNOS in activated macrophages [75]. The purified garlic derivative DAS was shown to inhibit both pro-and anti-inflammatory cytokines (TNFα, IL1β, IL6, IL10) in LPS-stimulated RAW264.7 macrophages which was closely associated with the suppression of NO and PGE$_2$ production [76]. DADS enhanced IL1β and IL6, but suppressed IL10 and TNFα, while AMS decreased NO production and TNFα but enhanced IL10 [76]. Moreover,

COX2, an enzyme that is induced under similar pathophysiological conditions as iNOS and is implicated in the pathogenesis of various inflammatory diseases as well as carcinogenesis, was found to be inhibited by ajoene in activated macrophages [77].

THE INTERRELATIONSHIP OF GARLIC AND THE IMMUNE SYSTEM IN CARCINOGENESIS

Based on the studies outlined above, it seems that the net effect of garlic elicits anti-inflammatory immune responses. This is particularly relevant in the context of the pro-inflammatory and immunosuppressive environment during chronic inflammation, a well-established factor facilitating carcinogenesis. Dampening of the tumor-mediated pro-inflammatory activity is likely induced by several active garlic compounds modulating the cytokine pattern in a way that leads to an overall inhibition of NFκB, the central regulator of pro-inflammatory gene expression and the molecular link between inflammation and tumor promotion and progression [69, 71, 78]. It could therefore be hypothesized that garlic acts as an immune modulator that can shift the balance from a pro-inflammatory and immunosuppressive environment to an enhanced anti-tumor response leading to suppression of an emerging tumor (Fig. **3**).

Although garlic seems to have an overall anti-inflammatory and immune-boosting effect, the conflicting results outlined above strongly reflect the complexity of the system: the individual components of garlic might exert immunomodulatory effects that, at least partially, act through alterations in the production of various
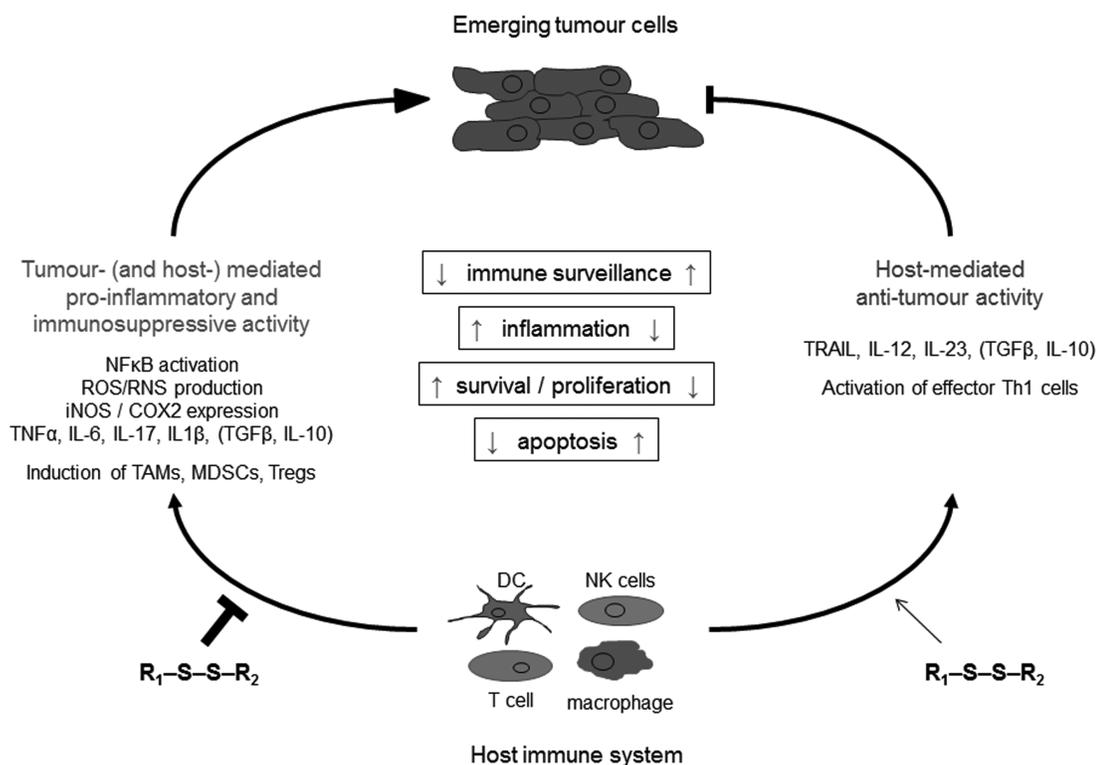

Fig. (3). Proposed model for the interrelationship between garlic organosulfur compounds and the immune system in carcinogenesis. In early tumorigenesis, a delicate balance exists between the tumor-mediated pro-inflammatory response of the emerging tumor and the host anti-tumor immunity. When the host-mediated anti-tumor activity is weaker than the tumor-mediated pro-inflammatory and immunosuppressive activity, tumor cells undergo immune escape and grow rapidly. By contrast, when host-mediated anti-tumor immunity is stronger than tumor-mediated pro-inflammatory and immune-suppressive activity, tumor cells are eliminated. We propose that long-term supplementation with dietary garlic organosulfur compounds contributes in shifting the balance from a pro-inflammatory to an anti-tumor response by dampening the pro-inflammatory response (left) and/or strengthening the anti-tumor immunity (right) towards tumor eradication. Note that the cytokines IL-10 and TGFβ can have dual effects in tumorigenesis depending on the context in a particular tumor microenvironment and are therefore listed in brackets.

cytokines and immune modulators. Some of the conflicting data probably relates to the complex chemical composition of garlic which is related to the method of preparation [79]. Current limitations are that most studies have been carried out *in vitro* at a cellular level, and *in vivo* animal models are lacking. It is therefore of utmost importance to design future studies using well-defined systems and chemically pure active garlic compounds at defined concentrations, and to develop animal models to demonstrate the immunomodulatory effect of garlic in cancer prevention.

Many dietary bioactive food components interact with the immune system with the potential to reduce the risk of cancer [80]. We therefore hypothesize that the organosulfur compounds of garlic contribute to the prevention or reduction of the immuno-suppressive environment during chronic inflammation with the downstream consequence of assisting the host to escape tumor-mediated immune suppression and to elicit an anti-tumor immune response. Future studies including those in animal models are required to demonstrate the role of garlic supplementation in cancer prevention. Although the effects might be subtle, garlic should be considered as a dietary anti-inflammatory supplement that in the long term might lead to the reduced risk of certain types of cancers, an effect known for long-term usage of aspirin [81].

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

LIST OF ABBREVIATIONS

OSC   =   Organosulfur compounds

NFκB   =   Nuclear Factor kappa B

IL   =   Interleukin

TNF   =   Tumor Necrosis Factor

TRAIL   =   TNF related apoptosis-inducing ligand

TGF   =   Transforming Growth Factor

ROS   =   Reactive Oxygen Species

RNS   =   Reactive Nitrogen Species

iNOS   =   (inducible) Nitric Oxide Synthase

NO   =   Nitric Oxide

IFN   =   Interferon

LPS   =   Lipopolysaccharide

Th   =   T helper cells

NK   =   Natural Killer cells

PGE2   =   Prostaglandin E2

DAS   =   Diallyl sulfide

DADS   =   Diallyl disulfide

DATS   =   Diallyl trisulfide

AMS   =   Allyl methyl sulphide

SAC   =   *S*-allyl cysteine

SAMC   =   *S*-allylmercaptocysteine

COX2   =   Cyclooxygenase-2

AGE   =   Aged Garlic Extract

PBMCs   =   Peripheral Blood Monocytes

Ox-LDL   =   Oxidized low-density lipoprotein

GSH   =   Glutathione

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