Effects of aged garlic extract on macrophage functions: a short review of experimental evidence (Review)

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Abstract. Macrophages play crucial roles in both the innate and adaptive immune systems, contributing to the removal of pathogens and subsequent immune responses. Conversely, aberrant macrophage functions are associated with the onset and progression of various diseases, highlighting macrophages as potential therapeutic targets. Aged garlic extract (AGE) is derived from garlic that has undergone a maturation process of over 10 months in an ethanol solution and contains a variety of bioactive components which are produced in the aging process. Previous animal studies and clinical trials have demonstrated that AGE and its constituents exert a range of health benefits, including immune modulation and amelioration of disease conditions. Experimental studies indicate that AGE modulates macrophage functions associated with pathological conditions. To facilitate understanding of AGE's potential as a functional alleviation for macrophage-associated diseases, the present short review summarizes experimental evidence supporting the notion that AGE and its components modify macrophage functions, including phagocytosis, production of reactive oxygen species and polarization.

Contents

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Abbreviations: AGE, aged garlic extract; Fru-Arg, fructosyl arginine; IFN-γ, interferon-γ; IL, interleukin; NO, nitric oxide; iNOS, inducible NO synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor-kappa B; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; S1PC, *S*-1-propenylcysteine; SAC, *S*-allyl cysteine; SMC, *S*-methyl-L-cysteine; TNF-α, tumor necrosis factor-α

Key words: AGE, macrophage, innate immunity, inflammation, ROS

1. Introduction

Macrophages play important roles in the innate immune system, primarily through phagocytosis of pathogens, antigen presentation and immune modulation (1). They are also responsible for the removal of dead or dying cells, tissue repair and tissue remodeling (1). Additionally, tissue-resident macrophages have physiological functions that depend on their tissue distribution, maintaining tissue homeostasis (2). In contrast to their homeostatic functions, macrophages can exhibit pathological roles in various tissues, including cardiovascular, neuronal, bone, gastrointestinal and immune systems. This suggests that modulating macrophage functions could be a promising strategy for the prevention and treatment of numerous diseases (1,3).

Aged garlic extract (AGE) is obtained from garlic that has been aseptically matured in an ethanol solution for at least 10 months (4). AGE contains a variety of bioactive sulfur-containing compounds, including *S*-allyl cysteine (SAC), *S*-1-propenylcysteine (S1PC) and *S*-methyl-L-cysteine (SMC) (4). The aging process and intrinsic enzyme activity produce these compounds while reducing the levels of stimulative components, such as allicin, in AGE (5). Clinical trials have demonstrated the health benefits of AGE and its components (6-13), highlighting the need to understand the detailed mechanisms by which AGE affects health and disease conditions for more effective usage. A substantial body of evidence from numerous studies indicates that AGE exerts modulatory effects on macrophage function, indicating that macrophages are one of the crucial target cell types in AGE treatment. The present short review explains the experimental evidence showing that AGE affects macrophage function and summarizes current knowledge regarding the potential of AGE as a preventive or therapeutic option for macrophage-associated pathologies.

2. Effect of AGE on macrophage phagocytosis

Phagocytosis is one of the fundamental physiological functions of macrophages. This process removes invading pathogens, dead cells, or tumor cells and drives subsequent antigen presentation and the production of various cytokines that regulate the immune system (14,15). Some *in vitro* studies have indicated that AGE or its components promote phagocytic activity in cultured macrophages. In mouse peritoneal macrophages, AGE has been shown to induce phagocytosis against latex beads (16). Fructans, contained in AGE, are shown to be related to phagocytosis activation. They have been demonstrated to enhance the phagocytosis of lipopolysaccharide (LPS)-stimulated rat peritoneal macrophages against yeast cells (17). Oxidative burst is a crucial process during macrophage phagocytosis, enabling the elimination of pathogens and the initiation of cellular signaling (18). Both AGE and its protein fraction have been reported to induce oxidative burst in culture systems, including J774 cells, a mouse macrophage cell line, and thioglycollate-elicited mouse peritoneal macrophages (19). This suggests that AGE could enhance host protection by eliminating non-self and self-pathogens and facilitating subsequent signal transduction. Indeed, a previous randomized controlled trial indicates that AGE has a preventative effect on colds and flu (6). However, that study focused on lymphocyte activity rather than macrophage functions. To fully understand the protective roles of AGE in infections, further examination is necessary to determine whether AGE or its constituents affect each process in the adaptive immune system. This includes macrophage phagocytosis, which initiates subsequent immune responses.

3. Effect of AGE on nitric oxide (NO) production in macrophages

NO plays various biological roles, including mediating vasodilation, synaptic plasticity and cellular signaling transduction (20). In macrophages, NO is crucial for eradicating pathological microorganisms and inducing inflammation (21-23). It is also regarded as an indicator of macrophage activation (24). However, excessive NO production can lead to the generation of reactive nitrogen species, which are cytotoxic and contribute to the development of inflammatory diseases (24-26). Therefore, modulating excessive NO production is considered a potential therapeutic strategy for inflammatory diseases (26-28). AGE has been shown to inhibit NO production in J774 cells induced by interferon-γ (IFN-γ) and LPS (29). SAC, a component of AGE, has been shown to attenuate IFN-γ and LPS-induced NO production in RAW264.7 cells (30). SAC inhibits the promoter activity of inducible NO synthase (iNOS), one of three NOS isotypes expressed in inflammatory contexts (30). However, it does not affect the activity of iNOS and endothelial NO synthase, a constitutive NOS isotype that induces arterial relaxation (30,31). These studies indicate that AGE and its components suppress inflammation-related NO production following increased iNOS expression in macrophages, without disturbing constitutive NO synthesis. This highlights the potential benefit of AGE in treating inflammatory diseases associated with dysregulated NO production.

4. Antioxidant effects of AGE in macrophages

AGE is known to attenuate the accumulation of reactive oxygen species (ROS) through multiple mechanisms, including upregulation of the nuclear factor erythroid-2-related factor 2 pathway, which is a key regulator for the antioxidant response, direct ROS scavenging, chelation of metal ions associated with ROS production and downregulation of ROS-generating enzymes (32). Macrophage-derived ROS play a key role in the antimicrobial functions of macrophages and act as cellular signaling molecules, contributing to appropriate immune responses (33,34). However, excessive ROS accumulation in macrophages, resulting from overproduction and dysfunction in redox systems, is associated with various inflammatory diseases. In atherosclerosis, ROS in macrophages plays a significant role in plaque formation by activating macrophages, inducing inflammatory cytokine production, and inhibiting reverse cholesterol transport (35,36). Oxidized low-density lipoprotein (oxLDL), an atherogenic modification of LDL, induces ROS production in macrophages (37,38). AGE has been shown to suppress oxLDL-induced ROS production in J774 cells (29). SAC and fructosyl arginine (Fru-Arg), a Maillard reaction product isolated from AGE, have demonstrated redox effects in macrophages (39,40). These compounds have been shown to reduce hydrogen peroxide levels in a cell-free system and attenuate the release of peroxides by macrophages in response to oxLDL stimulation in a dose-dependent manner (39,40). In the skeletal system, ROS act as important signaling molecules that induce the differentiation of osteoclasts from the monocyte/macrophage lineage (41). Receptor activator of nuclear factor-kappa B (NF-κB) ligand, a key regulator of osteoclastogenesis, induces ROS production via nicotinamide adenine dinucleotide phosphate oxidase (42). The induced ROS activate mitogen-activated protein kinase pathways associated with osteoclast differentiation (42). Alliin, one of the components of AGE, has been shown to inhibit receptor activators of NF-κB ligand-induced osteoclastogenesis in RAW264.7 cells (43). Alliin reduces the expression of nicotinamide adenine dinucleotide phosphate oxidase and suppresses ROS production induced by receptor activator of NF-κB ligand stimulation (43). This suggests that alliin inhibits osteoclastogenesis, possibly by decreasing ROS production. Since excessive bone resorption by osteoclasts is linked to osteoporosis, the inhibitory effect of AGE on osteoclastogenesis through ROS reduction could be a potential strategy for maintaining bone homeostasis.

5. Changes in cytokine production in macrophages induced by AGE

Macrophages produce a variety of cytokines to orchestrate immune responses by coordinating various cell types. Appropriate cytokine production is essential for inducing a rapid and regulated inflammatory reaction, which contributes to maintaining homeostasis through the removal of pathogens or tumor cells and facilitating tissue regeneration (44,45). However, dysregulated cytokine production-spatially, chronologically and quantitatively- is associated with the onset and progression of various inflammatory diseases, including inflammatory bowel diseases,

Table I. Effects of AGE and its constituents on macrophage functions.

First author/s, year	Macrophage function	Compounds	Action	(Refs.)
Kyo *et al*, 1998	Phagocytosis	AGE	Facilitating the phagocytosis of latex beads in mouse peritoneal macrophages.	(16)
Dupré-Crochet *et al*, 2013		Fructans	Activating LPS-induced phagocytosis of yeast cells in rat peritoneal macrophages.	(17)
Lau *et al*, 1991	Oxidative burst	AGE	Provoking oxidative burst in mouse peritoneal macrophages and J774 cells.	(19)
Ide and Lau, 1999	NO production	AGE	Reducing LPS and IFN-γ-induced NO production in J774 cells.	(29)
Kim *et al*, 2001		SAC	Downregulating LPS and IFN-γ-induced NO production by attenuating iNOS expression in RAW264.7 cells.	(30)
Ide and Lau, 1999	ROS production	AGE	Reducing ROS production induced by oxLDL in. J774 cells	(29)
Ide *et al*, 1999; Ide and Lau, 2001		SAC, Fru-Arg	Suppressing the release of ROS from J774 cells induced by oxLDL, and directly scavenges ROS.	(39,40)
Chen *et al*, 2016		Alliin	Inhibiting ROS production in RAW264.7 by the receptor activator of NF-κB ligand stimulation.	(43)
Miki *et al*, 2021	Cytokine production	S1PC	Reversing LPS-induced IL-12p70 and TNF-α expressions in bone marrow-derived macrophages.	(50)
Kaur *et al*, 2024		SAC, SMC	Suppressing LPS-induced TNF-α, IL-1β, and IL-6 production in RAW 264.7 cells via inhibiting NF-κB. expression	(51)
Song *et al*, 2016		AGE, Fru-Arg	Inhibiting LPS-induced gene expressions which is responsible for inflammatory cytokine secretions in BV-2 cells.	(53)
Ide and Lau, 1999	Polarization	AGE, SAC	Attenuating LPS and IFN-γ-induced NO production, which reflects M1 macrophage polarization, in J774 cells or RAW264.7 cells.	(29,30)
Zhang *et al*, 2022		Diallyl disulfide	Suppressing LPS-induced NO production and expression of tumor necrosis factor-α, a cytokine highly secreted by M1 macrophages, in RAW264.7 cells.	(57)
Miki *et al*, 2021		S1PC	Promoting IL-10-mediating M2 macrophage polarization.	(50)

AGE, aged garlic extract; Fru-Arg, fructosyl arginine; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible NO synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor-kappa B; NO, nitric oxide; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; S1PC, *S*-1-propenylcysteine; SAC, *S*-allyl cysteine; SMC, *S*-methyl-L-cysteine; TNF-α, tumor necrosis factor-α.

cardiovascular diseases, respiratory diseases and macrophage activation syndrome (46-49). Therefore, modulation of cytokine production is a crucial strategy for treating these diseases. Experimental evidence suggests that AGE modifies cytokine production in macrophages. S1PC in AGE has been reported to reduce LPS-induced expression of interleukin (IL)-12p70 and tumor necrosis factor-α (TNF-α) in bone marrow-derived macrophages, likely by enhancing IL-10-induced M2 macrophage polarization (50). In a recent study, SAC and SMC from snow mountain garlic, which are also abundant in AGE, have been shown to suppress LPS-induced production of TNF-α, IL-1β and IL-6 in RAW 264.7 cells (51). Additionally, SAC and SMC have been found to attenuate LPS-induced expression of NF-κB, a key mediator of pro-inflammatory cytokine expression (51). In BV-2 cells, a cell line of microglial cells, which are tissue-resident macrophages in the central nervous system (52), transcriptome analyses have demonstrated that AGE represses LPS-induced alterations in gene expression responsible for inflammatory cytokine secretion (53). As Fru-Arg, a component of AGE, exhibited similar effects on transcriptome changes in BV-2 cells under LPS stimulation (53), it is likely a key functional component of AGE in this context. Overall, AGE and its components appear to suppress the production of cytokines associated with inflammation, which may be one of the mechanisms underlying the therapeutic effects of AGE in inflammatory diseases.

6. Modulating effects of AGE on macrophage polarization

Macrophage polarization is the process through which macrophages dynamically modify their phenotypes in response to their surrounding microenvironment (54). The M1 polarized macrophages are capable of promoting inflammation and play important roles in protecting the body from infections and cancers (54). Meanwhile, M1 macrophages are also known to be associated with developments of inflammatory diseases; thus, the modulation of the M1 macrophage polarization is regarded as a potential therapeutic strategy for them (54). AGE and SAC have been reported to inhibit the LPS and IFN-γ-induced NO production in macrophages (29,30). As the co-stimulation of LPS and IFN-γ is well known to polarize macrophages into the M1 phenotype and the abundant NO production is a characteristic of M1 polarized macrophages (55), that might indicate that AGE and SAC have an inhibitory effect on the M1 polarization of macrophages. In addition to SAC, diallyl disulfide, contained in AGE (56), has also been suggested to have the capability of attenuating the M1 polarization of macrophages (57). In RAW 264.7 cells, diallyl disulfide reduced LPS-induced NO production and mRNA expression of TNF-α which is highly expressed in M1 macrophages (15,57). In addition, in an LPS-induced liver injury model, the administration of diallyl disulfide to mice mitigated the upregulation of M1 macrophage marker genes in liver (57). The suppressive effect of diallyl disulfide on LPS-induced mRNA expression of TNF-α and NO production in RAW 264.7 cells was inhibited by the knockout of the nuclear erythroid 2-related factor 2 gene, suggesting the involvement of nuclear erythroid 2-related factor 2 in this effect (57). In contrast to the M1 macrophage polarization, the polarization of macrophages into the M2 phenotype plays a crucial role in resolving inflammation (54). In atherosclerosis, M2 macrophages contribute to the regression of atherosclerotic plaques (58). A recent study has indicated that promoting M2c macrophage polarization may be one of the mechanisms through which AGE reduces atherosclerotic plaque formation (50). Atherosclerosis model mice fed AGE or a diet containing S1PC exhibited less plaque formation and increased expression of M2 markers in their aortas (50). The study identified that the binding of Src homology-2-containing inositol 5'-phosphatase 1 to the IL-10 receptor α negatively regulates IL-10 signaling (50). S1PC inhibits this binding, thereby extending IL-10 signaling and promoting M2 macrophage polarization (50). Overall, these studies indicate that AGE containing SAC, diallyl disulfide and S1PC modulates macrophage polarization through multiple mechanisms. However, macrophage polarization is a complicated process which is regulated by various factors, and the roles of polarized macrophages are context-dependent. Hence, further studies in a wider range of disease models must be performed to comprehensively interpret health benefits of AGE and its constituents derived from the modulation of macrophage polarization.

7. Conclusions

As summarized in Table I, growing experimental evidence indicates that AGE and its constituents exert modulatory effects on a range of macrophage functions, implying their therapeutic potential for diseases associated with dysfunctional macrophages. AGE appears to both downregulate excessive macrophage activation, which induces inflammatory pathologies and enhance the physiological functions of macrophages critical for host defense. This underscores the necessity for further studies investigating the effects of AGE in specific pathological contexts of various diseases. Clarifying the detailed mechanisms through which AGE modulates macrophage functions, including its intracellular targets and effects on interactions between macrophages and other cell types, remains an ongoing area of research. Currently, single-cell multi-omics technologies allow for examining alterations in cellular conditions in response to diverse stimuli or pathological conditions at single-cell resolution. Single-cell omics analyses may offer new insights into the mechanisms by which AGE influences macrophage-regulated physiological or pathological processes. In summary, macrophages are a key target cell type for the beneficial effects of AGE on human health. Further elucidation of the molecular processes by which AGE modulates macrophage functions could lead to more effective applications of AGE.

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Competing interests

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Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the author revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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