# Benefits of aged garlic extract on Alzheimer's disease: Possible mechanisms of action (Review)

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Received September 26, 2019; Accepted November 1, 2019

DOI: 10.3892/etm.2019.8390

**Abstract.** Alzheimer's disease (AD) is the most common form of dementia and has become a growing health concern in aging societies. β-amyloid (Aβ) formation in vulnerable brain regions, such as the hippocampus and cerebral cortex is a major neuropathological feature of the disease. Currently, there is no specific drug available for the treatment of AD. However, due to its high antioxidant activity, aged garlic extract (AGE) has been widely used to prevent chronic diseases, such as cancer and cardiovascular disease. A number of studies on the benefits of AGE against cognitive and memory deficits have also been published. This review aimed to summarize the information related to the effects of AGE on learning memory in order to obtain a better understanding of its mechanisms of action. This review also presents an overview of the pathogenesis of AD, and summarizes the main ingredients and neuroprotective effects of AGE against cognitive and learning memory deficits. The mechanisms of action of AGE are also discussed.

**Contents**



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*Key words:* Alzheimer's disease, aged garlic extract, cognitive and learning memory, neuroinflammation, antioxidant, cholinergic, glutamatergic, GABAergic

## 1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that commonly occurs among elderly with dementia (1). Currently, AD poses a serious threat to human health among the aging population. The disease is clinically diagnosed by a loss of cognitive function and memory, and pathologically by the deposition of senile plaque rich in the insoluble aggregation of β-amyloid (Aβ) and neurofibrillary tangles in the brain (2,3). The development of the disease is due to multiple factors, including both genetic and epigenetic factors. Diet, lifestyle and chemical exposure play important roles in the pathogenesis of the disease (4-6).

Aβ is a 40-42-amino acid residue of a transmembrane amyloid precursor protein that is cleaved by the enzymatic action of β-secretase and γ-secretase (7). Following polymerization, the Aβ oligomeric assemblies become a toxic molecule to form the deposited plaques, then activate the microglia and generate reactive oxygen species (ROS) and cytochemokines, leading to severe neuronal damage (8,9). Several studies have demonstrated that the intra-cerebral injection of Aβ causes neurodegeneration and an impairment of learning and memory (10,11). Aβ injection has been shown to induce radical-mediated neurotoxicity and an increase in lipid peroxidation. In animal models of AD, Aβ binds to nicotinic acetylcholine receptors, which is abundantly expressed in the brain regions vulnerable to AD, including the hippocampus and basal cholinergic forebrain (12-14). Apart from causing cholinergic degeneration, Aβ leads to the disruption of signaling that is involved in long-term potentiation and memory in the hippocampus (15,16).

Currently, there is no standard treatment or specific drug available for the treatment of AD. Drugs known to be associated with some parts of the pathogenesis and to reduce Aβ formation by restoring cholinergic deficits, such as cholinesterase inhibitors (e.g., donepezil and rivastigmine) are used. Other drugs related to neuroinflammatory processes, such as cyclooxygenase-2 (COX-2) inhibitors (e.g., celebrex) and non-steroid anti-inflammatory drugs (NSAIDs; e.g., ibuprofen and indomethacin) are also used.

## 2. Aged garlic extract

Garlic (*Allium sativum* Linn., Alliaceae) has long been known, not only as a food ingredient, but also as a herbal

medicine. Previous studies on garlic have emphasized its antioxidant properties against atherosclerosis and cancer (17-20). However, the consumption of raw garlic can cause various side-effects, including anemia, growth retardation and the destruction of the gut microflora, and can also alter serum protein levels (21,22). Moreover, fresh garlic may cause indigestion and its pungent odor may linger on the breath, which may be a social barrier. To overcome these unwelcome effects, an alternative product from garlic that has less odor, but is rich in antioxidants has been produced and is known as aged garlic extract (AGE). AGE is an extract from garlic powder in a non-toxic solvent. It is derived from a prolonged extraction time at room temperature, generally >15 months. The aging process converts unstable compounds, such as allicin, to stable substances and several water-soluble organosulfur compounds, including the two major compounds, S-allylcysteine (SAC) and di-allyl-disulfide (DAD). AGE also contains other phytochemicals, such as ajoene, allixin, flavanoids, polyphenols and thiosulfinates (23,24). Aged garlic extract has a very potent antioxidant activity, as well as numerous bio-activities, conferring several health benefits to humans (20). Recently, the potential activity of AGE to ameliorate cognitive impairment has attracted some interest.

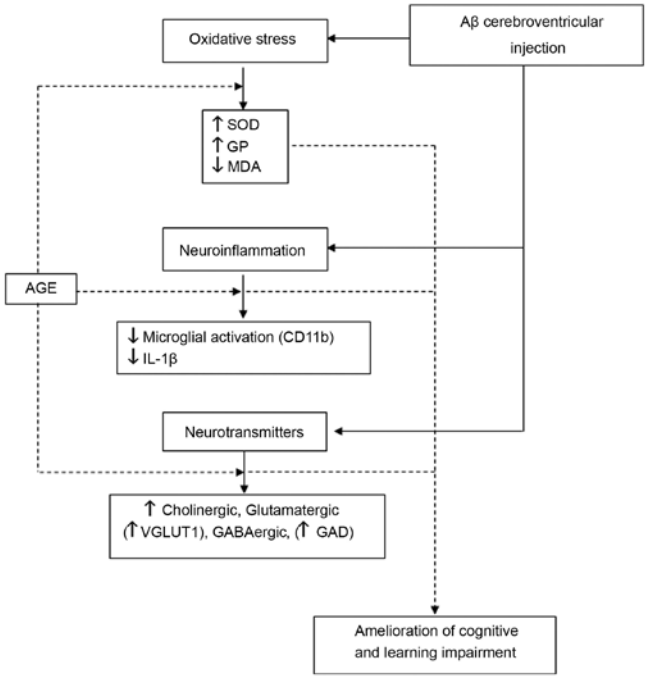


Figure 1. Possible mechanisms of action of AGE to ameliorate the cognitive impairment in rats with Aβ-induced neurotoxicity. AGE, aged garlic extract; Aβ, β-amyloid; SOD, superoxide dismutase; GP, glutathione peroxidase; MDA, malondialdehyde; IL, interleukin; VGLUT1, vesicular glutamate transporter 1 protein; GAD, glutamate decarboxylase.

## 3. Known neuroprotective effects of aged garlic extract

Aβ is known to exert cytotoxic effects on cultured neurons (25). There are multiple events culminating in neuronal death. The increased levels of ROS promote neuronal death (26,27). Lipid peroxidation products are also increased in the brains of patients with AD (28). On the other hand, SAC, the major compound of AGE, has been shown to protect against the Aβ- and tunicamycin-induced death of differentiated PC12 cells (29).

Aβ induces neurotoxicity to hippocampal cells and increases the levels of ROS. Aβ also induces the expression of the 78-kDa glucose-regulated protein (GRP-78), a molecular chaperone that regulates protein folding and translocation into the endoplasmic reticulum (ER), as well as the activation of caspase-12, which is localized predominantly at the ER (30,31). SAC has been shown to decrease the levels of ROS and its neuroprotective effects are mediated predominantly through the caspase-12-dependent pathway in a concentration-dependent manner, but does not prevent the 4-hydroxynonenal-induced death of hippocampal neurons (32). These findings suggest that SAC exerts a unique effect on the ER and that it can protect against neuronal cell death that is triggered by ER dysfunction in the rat hippocampus. Moreover, a previous study on organotypic hippocampal slice cultures indicated that Aβ potentiated the ER stress-induced neuronal death elicited by tunicamycin and that SAC exerted a significant neuroprotective effect against ER stress-induced neuronal death (33).

## 4. Known effects of aged garlic extract on learning memory

The attenuating effects of AGE on Aβ-induced neurotoxicity and cognitive impairment have been previously demonstrated (34). The ethyl acetate fraction of AGE reduces cellular oxidative stress, increases the viability and decreases the death of PC12 cells subjected to Aβ-induced cytotoxicity. Pre-treatment with AGE has been shown to attenuate Aβ-induced learning and memory deficits in mice, as detected by the Y-maze test and a passive avoidance test. Dimethyl disulfide anhydrous has been identified to be a main thiosulfate of the ethyl acetate fraction of AGE that was obtained by subsequently partitioned of the ethanol extract of garlic at room temperature (20˚C). Experiments using transgenic mice have revealed the amelioration of early cognitive deficits by AGE (35). A comparative study was conducted in two models of transgenic mice, i.e., Tg2576 (slow plaque development with a predominance of Aβ 40) and TgCRND8 (accelerated plaque development with a predominance of Aβ 42) (35). The feeding of AGE to the mice for 5 months was shown to prevent the deficits of spatial acquisition learning in both transgenic mouse models. AGE significantly reduced cerebral Aβ build up and prevented the progressive deterioration of hippocampal-based cognitive tasks. In the senescence-accelerated mouse (SAM), which was established as a genetic murine model for studying spontaneous senescence (36), these mice have been characterized to be a prone strain in which the impairment of learning and memory with brain atrophy is accelerated (37). In addition, the chronic administration of AGE has been previously reported to prevent brain atrophy and improve learning memory, suggesting the anti-aging effects of AGE on SAM (38).

AGE has also been reported to prevent the lipopolysaccharide-induced cognitive deficits in rats via a reduction of lipid peroxidation markers, an increase in the activities of superoxide dismutase (SOD) and catalase, and an increase in the level of reduced glutathione, as well as a decrease in acetylcholinesterase activity, a downregulation in the expression of hippocampal nuclear factor-κB, Toll-like receptor 4, glial fibrillary protein and interleukin (IL)-1β and an upregula-

tion of nuclear factor (erythroid-derived 2)-like 2 (39). These findings suggest that AGE mitigates LPS-induced cognitive deficits and neuroinflammation, oxidative stress, astrogliosis and acethylcholinesterase activity.

## 5. Overview of the mechanisms of action of aged garlic

To better understand the beneficial effects of AGE, its mechanism of action should be clarified. However, as the pathogenesis of AD is complex (it is derived from both genetic and epigenetic factors), mechanisms of action of AGE on the improvement of cognitive and memory loss are also very complex. Clearly, its mechanisms of action are multifactorial and involve several pathways. In general, the high antioxidant activity of AGE is a critical element since there is evidence to support this. Our research group has previously reported that pre-treatment with AGE prevents the learning and short-term memory impairment caused by Aβ-induced neurotoxicity rats (40). In parallel, AGE can reverse neuronal loss in the CA1 and CA2 regions of the hippocampus, increase the activity of antioxidant enzymes, including SOD and glutathione peroxidase (GP), as well as decrease the malondialdehyde (MDA) level in the Aβ-exposed rat brain homogenate. Therefore, AGE, through its antioxidant activities, can scavenge free radicals through antioxidant enzyme activity to decrease the oxidative stress condition and help regain the spatial learning and memory performance in animal models with Aβ-induced AD.

The neurotoxicity of Aβ has been reported to involve a number of neuronal events, such as the deficiency of neurotransmitters, and a decrease in vesicular transporters and synaptic transmissions, leading to neuronal cell death (41-44). In addition, the effects of AGE on cholinergic, glutamatergic and GABAergic systems have been shown in rats with Aβ-induced cognitive impairment (45). AGE can significantly improve the working memory, as well as the reference memory of rats with Aβ-induced cognitive impairment in association with the amelioration of the loss of cholinergic neurons. It also increases the vesicular glutamate transporter 1 protein (VGLUT1) and glutamate decarboxylase (GAD) levels in the hippocampus (45). These findings suggest that AGE attenuates the impairment of working memory via the modification of cholinergic neurons, VGLUT1 and GAD in the hippocampus of rats with Aβ-induced cognitive impairment. Since Aβ formation, as a major neuropathological feature of AD, has been shown to trigger a series of inflammatory processes; it can thus initiate the host defense response to damage neurons, contributing to neuronal degeneration (46,47). Moreover, the activation of the microglia has been reported to promote the neurodegenerative process through the release of a number of pro-inflammatory cytokines that may lead to neuronal cell damage and eventual cell death (48-50). Based on these findings, the possible mechanisms of action of AGE on the process of neuroinflammation in Aβ-induced AD have been proposed (51). It is noteworthy that pre-treatment with AGE significantly improves short-term recognition memory in rats with Aβ-induced neurotoxicity along with the reduction of the activation of microglia in the cerebral cortex and hippocampus via the decrease in the immunohistological staining of integrin aM or CD11b protein. Furthermore, the levels of IL-1β was also decreased in the hippocampus region (51). These studies suggest the possible roles of AGE as an antioxidant and anti-inflammatory agent. It is also suggested that it can act as a modulator of the activity and transportation of certain neurotransmitters to ameliorate the cognitive and learning memory deficits of Aβ-induced rat neurotoxicity (Fig. 1).

## 6. Conclusions

AGE is a potentially valuable product which can be used to prevent the deficits of cognitive and learning memory. *In vitro* and animal studies *in vivo* have demonstrated the mechanisms of action of AGE, which involve its antioxidant, anti-inflammatory and modulatory effects on neurotransmitter function in the brain regions that are associated with the pathogenesis of AD. However, as multiple factors are involved in the development of AD, more pathways related to the disease pathogenesis need to be further investigated.

## Acknowledgements

The author would like to thank Dr Suwannee Saenthaweesuk, all the co-authors of her publications on AGE and the authors of all the cited articles in this review. The stimulation to provide the review article from the organizing committee of International Aged Garlic Conference 2019 is also greatly appreciated.

## Funding

No funding was received.

## Availability of data and materials

Not applicable.

## Authors' contributions

BS was responsible for the conception and design of this review article. BS also performed the literature search and edited and revised the article. The author has read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The author declares that there are no competing interests.

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