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Antioxidant and neuroregenerative roles of *Allium sativum* L. in promoting central nervous health

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Abstract

This review examines the antioxidant properties of *Allium sativum* L. (*A. sativum*) and its implications for tissue regeneration, with a specific focus on the central nervous system (CNS). This review explores the existing research to highlight the antioxidant, anti-inflammatory, neuroprotective and regenerative effects of bioactive compounds within *A. sativum*, particularly allicin and its derivatives. Recent studies demonstrate that *A. sativum* has the potential to enhance the production of neurotrophic factors, promote neurogenesis, and improve overall neural function, which are essential parameters for the maintenance and recovery of the CNS. The key emphasis of this review is to highlight that *A. sativum* can support tissue regeneration in the CNS by modulating biochemical pathways involved in reducing oxidative stress and inflammation, which are essential for fighting neurodegenerative diseases such as Alzheimers, Parkinsons and Huntington diseases. The review also emphasizes the need for more robust clinical trials, improved formulations for enhanced bioavailability, and deeper investigations into the mechanisms of action of *A. sativum* on neural tissues. Conclusively, *A. sativum* diversity of roles in promoting the health of CNS offers promising aspects for developing natural, cost-effective therapeutic strategies for neurological conditions. Future research is encouraged to further validate garlic's benefits, optimize dosages, and integrate its use into conventional medical practices, enhancing outcomes for patients with CNS disorders.

1. Introduction

For centuries, *Allium sativum* L., commonly known as garlic, has been widely used for culinary components, flavouring, and pharmaceutical purposes, as well as to treat a wide variety of diseases, including cancer (Durak *et al.*, 2004). The medicinal applications of *A. sativum* are well-established across various cultures and historical periods. Ancient civilizations such as Egypt, Greece, and Rome extensively utilized *A. sativum*, particularly during epidemics of diseases like typhus, dysentery, and cholera. It has also played a significant role in various traditional healing practices (Sayed, 2023). Its therapeutic benefits of *A. sativum* are largely due to allicin, its primary active compound, and related derivatives (Salehi *et al.*, 2019). Traditionally, *A. sativum* has been used to manage conditions like high blood pressure, high cholesterol, and coronary artery disease (Alali *et al.*, 2017). It is also renowned for its antioxidant characteristics, which are significant in improving general health and preventing various diseases. Its antioxidants are particularly effective in neutralizing oxidative stress caused by free radicals, which are linked to ageing and cognitive decline. Contemporary research has confirmed the efficacy of *A. sativum* in preventing conditions like

alzheimer's disease (Luo *et al.*, 2021), reducing blood pressure, lowering cholesterol levels, and providing protection against the common cold (Ried, 2016). Over time, scientific studies continued to validate *A. sativum* health benefits, demonstrating its related significance in treating a wide range of illnesses and promoting overall health. The purpose of this review is to address the impact of *A. sativum* components on tissue regeneration, with a specific emphasis on their effects on the central nervous system (CNS) in both experimental models and humans. This review aims to summarize the findings of existing literature to better understand how the biologically active compounds in *A. sativum*, particularly antioxidant agents, contribute to neural regeneration. By examining a wide range of studies and outcomes, this review seeks to highlight potential therapeutic applications of *A. sativum* in managing neurological conditions and enhancing CNS recovery and maintenance.

This review can provide insights into novel therapeutic strategies for enhancing neuroprotection and promoting tissue regeneration within the brain and spinal cord. This could lead to improved outcomes in the treatment and management of various neurodegenerative conditions. Additionally, understanding these relationships may guide dietary recommendations and supplementation practices aiming at optimizing neurological health through natural dietary components. Thus, this scoping review consolidates existing knowledge and identifies research gaps that could direct future studies, thereby contributing to the broader field of neurology and public health.

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2. Antioxidant properties of *A. sativum*

2.1 Chemical structure of *A. sativum* and metabolites

The chemical compositions of fresh *A. sativum* are widely variable and provide different biological properties such as antimicrobial, antioxidant, anti-inflammatory, and cardioprotective effects. The main

constituents are water which is about 65% and carbohydrates which form 28%. The remaining goes for organosulfur compounds 2.3%, proteins 2%, free amino acids 1.2%, and fiber 1.5%. In addition, *A. sativum* contains multivitamins (such as B complex and vitamin C) and minerals (such as Zn, Mg, Fe, Cu, and Se) (Melguizo-Rodríguez *et al.*, 2022).

Table 1: The major organosulfur compounds in garlic and their metabolites, highlighting the transformation processes and their contributions to garlic's properties and effects

Compound	Chemical structure	Metabolite	Notes
Allicin	$(\text{CH}_2=\text{CHCONH}_2)_2\text{S}$	Sulfenic acids	Formed when garlic is chopped or crushed; responsible for the initial pungent aroma. Converts into other sulfur-containing compounds.
Diallyl disulfide	$\text{CH}_2=\text{CHCH}_2\text{SCH}_2\text{CH}=\text{CH}_2$	Allyl methyl sulfide	Produced during the breakdown of allicin; contributes to garlic's lingering taste and smell.
S-allyl cysteine	$\text{H}_2\text{NCOCH}_2\text{CH}_2\text{SCH}_2\text{CH}=\text{CH}_2$	Urinary excretion products	Water-soluble, considered a stable garlic metabolite with various health benefits.
Alliin	$\text{C}_6\text{H}_{11}\text{NO}_3\text{S}$	Allicin	The stable precursor to allicin; transformed into allicin <i>via</i> the enzyme alliinase when garlic cells are disrupted.
Diallyl trisulfide	$\text{CH}_2=\text{CHCH}_2\text{S}(=\text{S})\text{SCH}_2\text{CH}=\text{CH}_2$	Allyl methyl sulfide	A volatile compound formed from allicin decomposition; known for its strong odour and health-promoting properties.

A. sativum mainly contains organosulfur compounds like allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, E/Z-ajoene, S-allyl-cysteine, and S-allyl-cysteine sulfoxide (alliin). Allicin is the chief sulfur-containing composite in intact *A. sativum* and is highly accountable for its fragrance and taste characteristics. Allicin is produced when the enzyme alliinase catalyzes alliin, a process that is triggered by the crushing or damaging of an *A. sativum* bulb. Moreover, *A. sativum* contains more phenolic compounds essential for biological activity and maintaining health (Shang *et al.*, 2019; Subroto *et al.*, 2021). Most of the intermediate products that results from the biosynthesis of different *A. sativum* components were extensively studied. These include C-glutamyl peptides, which are thought to be the reservoirs for storing nitrogen and sulfur in the cell (Colín-González *et al.*, 2012).

2.2 Biological mechanisms

A. sativum offers several health benefits due to its antioxidant properties, including anti-inflammatory, anticarcinogenic, and anti-hypertensive effects (Rahman, 2007). It also has antilipidemic, anti-diabetic, immune promoting, and tissue-protective activities (Capasso, 2013; Borlinghaus *et al.*, 2014; Bisen and Emerald, 2016). The beneficial outcome of *A. sativum* supplementation on human health is owing to its antioxidant potential activity (Kopec *et al.*, 2013). The biological mechanisms through which the antioxidants in *A. sativum* potentially support tissue regeneration, particularly in the central nervous system include:

2.2.1 Oxidative stress reduction

A. sativum is well-known in traditional medicine, and its sulfur compounds are accountable for their anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and anticancer properties. Several studies

demonstrate the different antioxidant techniques of *A. sativum* extract, including its capacity to (1) neutralize reactive oxygen species and free radicals; (2) increase the levels of intrinsic antioxidants including both enzymatic and nonenzymatic factors; (3) trigger the Nrf2 factor; and (4) block certain prooxidant enzymes such as xanthine oxidase (Colín-González *et al.*, 2012). Specifically, sulfur compounds in *A. sativum* can inhibit the activity of HMG-CoA reductase, a key enzyme in the mevalonate pathway which is critical for cholesterol synthesis. Although, raw *A. sativum* is a potent antioxidant, many conflicts were raised about its side effects, such as the destruction of gut microflora, growth retardation, and anaemia (Shashikanth *et al.*, 1984). Aged garlic extract (AGE) has been prepared to overcome the side effects of raw garlic by removing many irritant sulfur compounds and stabilizing unstable components such as allicin (Morihara *et al.*, 2006; Morihara *et al.*, 2006).

2.2.2 Anti-inflammatory effects

Chronic inflammations are known for their contribution to the development of neurodegenerative diseases and can impede the progress of neural regeneration. Antioxidant compounds in *A. sativum* also exhibit anti-inflammatory properties by modulating the activity of inflammatory cytokines and enzymes such as cyclooxygenase and lipoxygenase. This modulation helps to reduce inflammation around neural tissues, facilitating a more conducive environment for regeneration. Compounds derived from *A. sativum*, such as caffeic acid, SAC, and DATS, inhibit the NF- κ B transcription factor, which plays a key role in regulating genes encoding proinflammatory cytokines. *A. sativum* extracts have been shown to inhibit the production of inflammatory mediators such as NO, prostaglandins, and cytokines by immune cells, thereby reducing inflammation. A meta-analysis reveals that supplementation of *A. sativum* significantly

lowers the circulating C and TNF- α in serum (Mirzavandi *et al.*, 2020). AGE notably reduced the inflammatory response by suppressing the activation of microglia and lowering IL-1 β levels of TNF α in the cerebral cortex and hippocampus (Nillert *et al.*, 2017).

2.2.3 Improved blood flow and circulation

The ability of *A. sativum* to improve blood flow and circulation can also contribute to tissue regeneration in the CNS. *A. sativum* showed promising effects in promoting vascular health, especially in people prone to cardiovascular diseases (Sundarrajan, 2023). This indicates that *A. sativum* might play a beneficial role in maintaining and improving the function of blood vessels, potentially aiding in the prevention and management of heart-related conditions (Emamat *et al.*, 2020). *A. sativum* may be an effective element in diets aimed at preventing atherosclerosis, when consumed in appropriate amounts (Wang *et al.*, 2019; Wang *et al.*, 2017). Recent studies indicated that *A. sativum* has properties that lower plasma lipids and enhance plasma anticoagulant and antioxidant activities. Additionally, it was shown to ameliorate compromised endothelial function (Gorinstein *et al.*, 2007). Evidence suggests that *A. sativum* supplementation appears to enhance tissue blood flow, potentially through the action of interleukin-6 (IL-6) (Anim-Nyame *et al.*, 2004). Improving blood supply delivers essential nutrients and oxygen to the brain, supporting the repair and regeneration of neural tissue. *A. sativum* can help lower cholesterol and triglyceride levels. Studies have shown that consuming *A. sativum*, either in fresh or supplemental form, can reduce total cholesterol, LDL cholesterol, and triglycerides by regulating different signaling pathways, such as AMPK/TLRs, Keap1/Nrf2, PI3K/AKT and, GEF-H1/RhoA/Rac. Yet, the molecular mechanism for clinical atherosclerosis patients remain unclear (Li *et al.*, 2022). This can help in preventing the buildup of plaque in the arteries. *A. sativum* has anti-inflammatory properties that can slow the atherosclerotic process. *A. sativum* has also been shown to reduce levels of inflammatory markers like VCAM-1 and ICAM-1, which are involved in the development of atherosclerosis (Wlosinska *et al.*, 2020; Li *et al.*, 2022). AGE, in particular, has been found to inhibit the progression of coronary artery calcification and lowers IL-6 a marker of atherosclerosis. Wlosinska *et al.* (2020) reported that patients taking AGE supplements had an 80% reduction in the buildup of “soft plaque” in their arteries compared to the placebo group.

2.2.4 Neurogenesis and neuroplasticity

Emerging evidence suggests that *A. sativum* 's antioxidants may stimulate neurogenesis, the process of generating new neurons, and enhance neuroplasticity, improving the brain's ability to reorganize and adapt (Alipour *et al.*, 2014; Zhuang *et al.*, 2023).

Many studies explored the neurogenic and neuroplastic properties of *A. sativum*, focusing on its influence on neurite outgrowth and new synaptic formation in primary hippocampal neuronal cells of rats (Gavilán *et al.*, 2023; Munni *et al.*, 2023). *A. sativum* ethanol extracts were found to stimulate neurite outgrowth in a dose-dependent manner, enhancing axonal and dendritic growth and maturation, as well as the formation of functional synapses. Some studies highlighted the neurotrophic activity of *A. sativum*, particularly the compound linalool found in both extracts, which can play a significant role in promoting neurite outgrowth. Linalool has influenced neuronal development by modulating the key molecules

in neurotrophic signalling pathways like glycogen synthase kinase 3 (GSK3 β) and extracellular signal-regulated protein kinase (Erk1/2), as confirmed by immunocytochemistry (Munni *et al.*, 2023).

3. Impacts on central nervous system (CNS) health

3.1 Neuroprotective effects

The beneficial health effects of *A. sativum* are mostly because it contains compounds that display a robust antioxidant endeavour (Kopec *et al.*, 2013). A study has shown that *A. sativum* extract enhances short-term memory and prevents pyramidal cells in the medial part of the prefrontal cortex from induced monosodium glutamate cytotoxicity (Nurmasitoh *et al.*, 2018). *A. sativum* has shown protective effects against lead toxicity in the developing hippocampus of rat pups, mainly by preventing neuron apoptosis. It has been found that *A. sativum* reduces the development of free radicals and lowers lead levels in the blood and brain, which are important factors in lead-induced neurotoxicity. The supplementation of *A. sativum* effectively decreases the number of TUNEL-positive cells, which is indicative of apoptosis, particularly in the hippocampal regions CA1, CA3, and the dentate gyrus (Ebrahimzadeh-Bideskan *et al.*, 2016). Black *A. sativum* extract has been shown to protect the hippocampal pyramidal cells in rats from damage caused by monosodium glutamate (MSG). This protection is evident through improved spatial memory performance and an increased number of pyramidal cells in the hippocampus, particularly in the CA1 region (Hermawati *et al.*, 2015). Diallyl sulfide promotes microglial process elongation and induces an anti-inflammatory phenotype. The elongation of microglial processes, which is reversible and dose-dependent, enhances brain function regulation by improving the environmental skimming abilities of microglia. Therefore, it modulates inflammatory responses by decreasing pro-inflammatory cytokines like TNF- α and IL-1 β and increasing anti-inflammatory markers such as IL-10 and CD206. Additionally, Diallyl sulfide has been found to prevent behavioural changes associated with neuroinflammation in animal models, suggesting its potential utility in treating neurodegenerative diseases where inflammation is a key factor (Xu *et al.*, 2020). Research indicated that diallyl sulfide prevents the brains of rat models from iminodipropionitrile-induced cytotoxicity, attributed to its antioxidant capacities, free radical quenching, and anti-inflammatory properties (Zhang *et al.*, 2016). Diallyl trisulfide effectively reduces oxidative stress markers like reactive oxygen species and malondialdehyde, decreases apoptosis levels in neural cells, and is particularly effective when administered early and in optimal doses (Xu *et al.*, 2015). S-allyl-cysteine (the predominant compound in aged *A. sativum* extract) has a mitochondrial and cell protective effect and attenuated the pyknotic changes towards normality in experimental autoimmune encephalomyelitis in rat models. This suggests that S-allyl-cysteine may have a potent neuroprotective effect against multiple sclerosis disease (Escribano *et al.*, 2018). S-allyl-cysteine, a composite within *A. sativum*, helps protect neurons and preserves the structural integrity of several brain regions from damage induced by stress. It reduces the number of damaged cells and mitigates reactive gliosis, a process involving the proliferation of glial cells that typically signifies neuronal damage and inflammation (Becerril-Chávez *et al.*, 2017). Also, S-allyl-cysteine effectively protects neuronal death caused by reactive oxygen species (H₂O₂). Additionally, aged *A. sativum* extract was shown to maintain the pre-synaptic synaptosome-associated peptides from oxidative stress damage (Ray *et al.*, 2011).

3.2 Neuroregenerative effects

Several articles have also reported that *A. sativum* sulfur compounds can promote neurotrophic factors production and stimulate neurogenesis, in addition to enhancing synaptic plasticity in the brain. Emerging evidence suggests that *A. sativum*-derived compounds such as diallyl disulfides and diallyl trisulfides may also have the potential to induce neuroplasticity and neovasculogenesis and to improve cognitive and motor function in both healthy animals and pathological models (Zhuang *et al.*, 2023). More findings indicate that *A. sativum* oil notably enhances novel object recognition and increases both cell proliferation and neuroblast differentiation. This effect was achieved through the modulation of hippocampal BDNF protein levels and AChE activity (Jung *et al.*, 2016). *A. sativum* essential oil alleviates depression induced by mild stress in rats by increasing the expression of hippocampal brain-derived neurotrophic factor (BDNF), c-AMP response element binding protein (CREB), and protein kinase B (AKT), demonstrating its effects through the modulation of monoamine neurotransmitters and the BDNF-associated signaling pathway (Huang *et al.*, 2019). It was observed the estimated total number of Purkinje cells of the cerebellum was significantly higher in experimental rat models exposed to monosodium-glutamate cytotoxicity which indicate that supplementation of black *A. sativum* may enhance the neurogenesis process (Aminuddin *et al.*, 2015).

3.3 Clinical outcomes

Based on the search results provided, the key clinical trials and

research findings related to *A. sativum* antioxidant properties and impact on the central nervous system and overall health: A randomized, double-blind, placebo-controlled clinical trial is currently investigating the “Effect of *A. sativum* extracts on changes in cerebral blood flow” in healthy participants. This study evaluates the impact of *A. sativum* extracts on regional cerebral blood flow, which is an important indicator of neuroplasticity and brain function (Baik *et al.*, 2022). Preclinical studies have shown that *A. sativum* -derived compounds, such as allicin and S-allyl cysteine, can promote the production of neurotrophic factors, stimulate neurogenesis, and enhance synaptic plasticity in both healthy animal models and models of neurological damage, suggesting their potential to induce neuroplasticity (Farooqui and Farooqui, 2018; Maccioni *et al.*, 2022; Shohag *et al.*, 2022). Published research in health and ageing showed that *A. sativum* could potentially aid in maintaining cognitive functions and delay cognitive decline in the elderly due to its antioxidant properties (Rahman, 2003; Wichai *et al.*, 2019; Shukla *et al.*, 2024). A randomized controlled trial indicated that *A. sativum* supplementation enhances immune cell function and reduces the severity of colds and flu. This study supports the role of *A. sativum* in boosting the immune system and mitigating inflammatory responses (Nantz *et al.*, 2012). A systematic review and meta-analysis published in 2016 reported that *A. sativum* supplementation significantly reduces blood pressure in individuals with hypertension, compared to standard antihypertensive medications (Ried, 2020).

Table 2: The impact of *A. sativum* on the central nervous system, highlight on its various neuroprotective and regenerative capabilities, as evidenced across multiple studies and experimental models

<i>A. sativum</i> impact/effect	Authors	Key findings/conclusions
Antioxidant properties of <i>A. sativum</i>	Melguizo-Rodríguez <i>et al.</i> , 2022	<i>A. sativum</i> contains a variety of sulfur compounds that provide strong antioxidant benefits, essential for reducing oxidative stress which is crucial for combating neurodegenerative diseases.
Neuroregenerative effects	Alipour <i>et al.</i> , 2014	<i>A. sativum</i> enhances neurogenesis and neuroplasticity, suggesting potential benefits in neuroprotective therapies.
Neuroprotective effects	Ebrahimzadeh-Bideskan <i>et al.</i> , 2016	Garlic exhibits protective effects against lead toxicity in the developing hippocampus by preventing neuron apoptosis and reducing lead levels in the brain.
Effects on CNS health	Jung <i>et al.</i> , 2016	<i>A. sativum</i> essential oil influences brain-derived neurotrophic factor (BDNF) and acetylcholinesterase activity, promoting neuroblast differentiation in the dentate gyrus.
Clinical outcomes	Baik <i>et al.</i> , 2022	A study on the effects of fermented garlic extract showed it improves regional cerebral blood flow, indicating enhanced neuroplasticity and brain function.
Anti-inflammatory effects	Mirzavandi <i>et al.</i> , 2020	Garlic supplementation significantly lowers circulating inflammatory markers in serum, such as C-reactive protein and TNF- α , suggesting its role in reducing systemic inflammation.
Neurogenesis and neuroplasticity	Zhuang <i>et al.</i> , 2023	Garlic's antioxidants may stimulate neurogenesis and enhance neuroplasticity, improving the brain's ability to reorganize and adapt, crucial for recovery from CNS injuries.
Neuroprotective effects in neurodegeneration	Becerril-Chávez <i>et al.</i> , 2017	S-allyl-cysteine, a compound in garlic, protects against neuronal death caused by oxidative stress and preserves the structural integrity of brain regions.

Antioxidant and antiaging effects	Rahman, 2003	Garlic's antioxidant properties help maintain cognitive functions and delay cognitive decline, particularly beneficial in aging populations.
Role in cardiovascular health related to CNS	Emamat <i>et al.</i> , 2020	Garlic enhances vascular health, which is indirectly beneficial to CNS health by improving blood flow and nutrient delivery to the brain.
Protective effects against MSG cytotoxicity	Hermawati <i>et al.</i> , 2015	Black garlic extract protects hippocampal pyramidal cells in rats from damage caused by monosodium glutamate, demonstrating improved spatial memory performance.
Effects on neuronal development	Munni <i>et al.</i> , 2023	Garlic ethanol extracts stimulate neurite outgrowth in rat primary hippocampal neurons, enhancing axonal and dendritic growth and maturation.
Impact on neuroinflammation	Xu <i>et al.</i> , 2020	Diallyl sulfide promotes an anti-inflammatory phenotype in microglia, modulating brain function and potentially treating neurodegenerative diseases with inflammatory components.
Neuroprotective and mitochondrial effects	Escribano <i>et al.</i> , 2018	S-allyl-cysteine exhibits neuroprotective effects against multiple sclerosis by attenuating pyknotic changes and preserving neuronal integrity.

4. Research limitations and future prospects

The key limitations encountered the research on the effects of *A. sativum* on the human CNS include: Lack of high-quality clinical trials, variability in *A. sativum* preparations, clear understanding of the mechanisms of action, potential confounding factors such as dosage, duration of administration, and potential interactions with other medications or supplements which need to be more extensively studied and finally there are safety concerns. Based on these findings, several areas for future research have been identified to further explore and verify the benefits of *A. sativum* in central nervous system health. Addressing these research directions could significantly advance our understanding of *A. sativum* role in CNS health and potentially develop new viable complementary or alternative therapies for neurological disorders. Future research should focus on several key areas: The evidence from experimental animal studies is promising, but human clinical trials are limited and often methodologically weak. To conclusively determine the efficacy of *A. sativum* in neurological disorders, more robust, well-designed clinical trials with adequate sample sizes and durations, including placebo-controlled studies, are necessary. The specific biological mechanisms through which *A. sativum* and its compounds provide neuroprotective effects remain unclear. Future studies should aim to identify the specific pathways and molecular targets involved, which could enhance the therapeutic use of *A. sativum*. The preliminary evidence suggests potential benefits of *A. sativum* in neurodegenerative disorders like Alzheimer Parkinson, and Huntington diseases. Consequently, comprehensive research is needed to thoroughly assess *A. sativum* neuroprotective effects in these conditions. The variety of manufacturing processes for different *A. sativum* products (e.g., raw *A. sativum*, powder, oil extract, aged extracts) can significantly influence the composition and thus the biological effects of the *A. sativum* making it challenging to compare results across studies and draw definitive conclusions. There is a need for long-term safety studies, particularly in sensitive populations like pregnant or breastfeeding women and children, to fully comprehend the potential side effects of chronic *A. sativum* consumption and establish its clinical utility. Investigating *A. sativum* as an adjuvant therapy, in combination with standard treatments for neurological disorders, could potentially enhance therapeutic efficacy

and provide significant benefits. The rapid metabolism and poor bioavailability of *A. sativum* compounds may restrict their therapeutic potential. Research should focus on developing novel formulations or delivery methods that improve the bioavailability of *A. sativum* active ingredients.

5. Conclusion

This review has explored the existing literature to reveal the significant roles of *A. sativum* in promoting tissue regeneration and enhancing CNS health. The key findings indicate that *A. sativum*'s rich array of sulfur-containing compounds, notably allicin, provides potent antioxidant and anti-inflammatory properties. These properties are important for mitigating oxidative stress and inflammation, which are pivotal factors in the pathogenesis and progression of various neurodegenerative diseases. Moreover, *A. sativum* has been shown to enhance neurotrophic factors, support neurogenesis, and improve vascular health, which are essential for maintaining and improving neurological functions.

The findings from this review have emphasised the implications for future research, clinical practices, and dietary guidelines. Further investigations are encouraged to clarify the mechanisms through which *A. sativum* bioactive compounds influence neuroprotective activities and to explore the therapeutic potential of *A. sativum* in more targeted clinical settings. Healthcare providers might consider the integration of *A. sativum* supplements or dietary recommendations into preventive and therapeutic strategies for patients at risk or those suffering from cognitive decline and other neurodegenerative conditions.

The broader implications of leveraging natural antioxidants like *A. sativum* in medicinal practices spotlight a paradigm shift towards more holistic approaches in healthcare. Utilizing natural products like *A. sativum* can support the intrinsic healing of the body and protective mechanisms, which offers a complementary strategy that works alongside conventional medicine to enhance overall health outcomes. This review highlights the potential of natural substances, such as *A. sativum*, to play a more significant role in modern medical practices, advocating for greater integration of nutritional and lifestyle factors in the prevention and management of diseases, especially those related to ageing and the central nervous system.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

- Alipour, F.; Bideskan, A. E.; Fazel, A.; Sadeghi, A.; Hami, J.; Kheradmand, H. and Haghiri, H. (2014). Protective effects of ascorbic acid and garlic extract against neurogenesis inhibition caused by developmental lead exposure in the dentate gyrus of rat. *Comp. Clin. Pathol.*, **23**:1681-1687.
- Aminuddin, M.; Partadiredja, G. and Sari, D.C. (2015). The effects of black garlic (*Allium sativum* L.) ethanol extract on the estimated total number of purkinje cells and motor coordination of male adolescent wistar rats treated with monosodium glutamate. *Anat. Sci. Int.*, **90**(2):75-81.
- Anim-Nyame, N.; Sooranna, S.R.; Johnson, M.R.; Gamble, J. and Steer, P.J. (2004). Garlic supplementation increases peripheral blood flow: A role for interleukin-6? *The J. Nutr. Biochem.*, **15**(1):30-36.
- Baik, J.S.; Min, J.H.; Ju, S.M.; Ahn, J.H.; Ko, S.H.; Chon, H.S.; Kim, M.S. and Shin, Y.I. (2022). Effects of fermented garlic extract containing nitric oxide metabolites on blood flow in healthy participants: A randomized controlled trial. *Nutr.*, **14**(24):5238.
- Becerril-Chávez, H.; Colín-González, A.L.; Villeda-Hernández, J.; Galván-Arztate, S.; Chavarria, A.; Eduarda de Lima, M.; Túnez, I. and Santamaría, A. (2017). Protective effects of s-allyl cysteine on behavioral, morphological and biochemical alterations in rats subjected to chronic restraint stress: Antioxidant and anxiolytic effects. *J. Funct. Foods*, **35**:105-114.
- Borlinghaus, J.; Albrecht, F.; Gruhlke, M.C.; Nwachukwu, I.D. and Slusarenko, A.J. (2014). Alliin: Chemistry and biological properties. *Mol.*, **19**(8):12591-12618.
- Capasso, A. (2013). Antioxidant action and therapeutic efficacy of *Allium sativum* L. *Mol.*, **18**(1):690-700.
- Colín-González, A.L.; Santana, R.A.; Silva-Islas, C.A.; Chánez-Cárdenas, M.E.; Santamaría, A. and Maldonado, P. D. (2012). The antioxidant mechanisms underlying the AGE -and s-allylcysteine-induced protection. *Oxidative medicine and cellular longevity*, **2012**:907162.
- Durak, I.; Kavutcu, M.; Aytac, B.; Avcı, A.; Devrim, E.; Özbek, H. and Öztürk, H.S. (2004). Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. *The J. Nutr. Biochem.*, **15**(6):373-377.
- Ebrahimzadeh-Bideskan, A.R.; Hami, J.; Alipour, F.; Haghiri, H.; Fazel, A.R. and Sadeghi, A. (2016). Protective effects of ascorbic acid and garlic extract against lead-induced apoptosis in developing rat hippocampus. *Metab. Brain. Dis.*, **31**(5):1123-1132.
- Emamat, H.; Tangestani, H.; Totmaj, A.S.; Ghalandari, H. and Nasrollahzadeh, J. (2020). The effect of garlic on vascular function: A systematic review of randomized clinical trials. *Clin. Nutr.*, **39**(12):3563-3570.
- Escribano, B.M.; Agüera, E.; Aguilar-Luque, M.; Luque, E.; Feijóo, M.; LaTorre, M.; Giraldo, A.L.; Galván-Jurado, A.; Caballero-Villarraso, J.; García-Maceira, F. I.; Santamaría, A. and Túnez, I. (2018). Neuroprotective effect of s-allyl cysteine on an experimental model of multiple sclerosis: Antioxidant effects. *J. Funct. Foods*, **42**:281-288.
- Farooqui, A. A. and Farooqui, T. (2018). Antiaging and neuroprotective properties of mediterranean diet components in humans. *Molecular Basis and Emerging Strategies for Anti-ageing Interventions*, pp:237-252.
- Gavilán, J.; Mardones, C.; Oyarce, G.; Triviño, S.; Espinoza-Rubilar, N.; Ramírez-Molina, O.; Pérez, C.; Becerra, J.; Varas, P. and Duran-Arcos, R. (2023). Elephant black garlic's beneficial properties for hippocampal neuronal network, chemical characterization and biological evaluation. *Foods*, **12**(21):3968.
- Gorinstein, S.; Jastrzebski, Z.; Namiesnik, J.; Leontowicz, H.; Leontowicz, M. and Trakhtenberg, S. (2007). The atherosclerotic heart disease and protecting properties of garlic: Contemporary data. *Mol. Nutr. Food Res.*, **51**(11):1365-1381.
- Hermawati, E.; Sari, D. C. and Partadiredja, G. (2015). The effects of black garlic ethanol extract on the spatial memory and estimated total number of pyramidal cells of the hippocampus of monosodium glutamate-exposed adolescent male wistar rats. *Anat. Sci. Int.*, **90**(4):275-286.
- Huang, Y.-J.; Lu, K.-H.; Lin, Y.-E.; Panyod, S.; Wu, H.-Y.; Chang, W.-T. and Sheen, L.-Y. (2019). Garlic essential oil mediates acute and chronic mild stress-induced depression in rats *via* modulation of monoaminergic neurotransmission and brain-derived neurotrophic factor levels. *Food Funct.*, **10**(12):8094-8105.
- Jung, H. Y.; Lee, K. Y.; Yoo, D. Y.; Kim, J. W.; Yoo, M.; Lee, S.; Yoo, K.-Y.; Yoon, Y. S.; Choi, J. H. and Hwang, I. K. (2016). Essential oils from two *Allium* species exert effects on cell proliferation and neuroblast differentiation in the mouse dentate gyrus by modulating brain-derived neurotrophic factor and acetylcholinesterase. *BMC Complementary and Alternative Medicine*, **16**:1-10.
- Kopec, A.; Piatkowska, E.; Leszczynska, T. and Sikora, E. (2013). Healthy properties of garlic. *Cur. Nutr. Food Sci.*, **9**(1):59-64.
- Li, M.; Yun, W.; Wang, G.; Li, A.; Gao, J. and He, Q. (2022). Roles and mechanisms of garlic and its extracts on atherosclerosis: A review. *Front. Pharmacol.*, **13**:954938.
- Luo, J.-F.; Dong, Y.; Chen, J.-Y. and Lu, J.-H. (2021). The effect and underlying mechanisms of garlic extract against cognitive impairment and alzheimer's disease: A systematic review and meta-analysis of experimental animal studies. *J. Ethnopharmacol.*, **280**:114423.
- Maccioni, R. B.; Calfio, C.; González, A. and Lüttges, V. (2022). Novel nutraceutical compounds in alzheimer prevention. *Biomole.*, **12**(2):249.
- Melguizo-Rodríguez, L.; García-Recio, E.; Ruiz, C.; De Luna-Bertos, E.; Illescas-Montes, R. and Costela-Ruiz, V. J. (2022). Biological properties and therapeutic applications of garlic and its components. *Food Funct.*, **13**(5):2415-2426.
- Mirzavandi, F.; Mollahosseini, M.; Salehi-Abargouei, A.; makiabadi, E. and Mozaffari-Khosravi, H. (2020). Effects of garlic supplementation on serum inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab. Syndr. Clin. Res. Rev.*, **14**(5):1153-1161.

- Morihara, N.; Sumioka, I.; Ide, N.; Moriguchi, T.; Uda, N. and Kyo, E. (2006). Aged garlic extract maintains cardiovascular homeostasis in mice and rats. *The J. Nutri.*, **136**(3):777S-781S.
- Morihara, N.; Ushijima, M.; Kashimoto, N.; Sumioka, I.; Nishihama, T.; Hayama, M. and Takeda, H. (2006). Aged garlic extract ameliorates physical fatigue. *Biol. and Pharm. Bull.*, **29**(5):962-966.
- Munni, Y.A.; Dash, R.; Choi, H. J.; Mitra, S.; Hannan, M.A.; Mazumder, K.; Timalina, B. and Moon, I. S. (2023). Differential effects of the processed and unprocessed garlic (*Allium sativum* L.) ethanol extracts on neurogenesis and synaptogenesis in rat primary hippocampal neurons. *Int. J. Mol. Sci.*, **24**(17):13386.
- Nantz, M. P.; Rowe, C. A.; Muller, C. E.; Creasy, R. A.; Stanilka, J. M. and Percival, S. S. (2012). Supplementation with aged garlic extract improves both nk and ã-t cell function and reduces the severity of cold and flu symptoms: A randomized, double-blind, placebo-controlled nutrition intervention. *Clin. Nutr.*, **31**(3):337-344.
- Nillert, N.; Pannangrong, W.; Welbat, J. U.; Chajjaroonkhanarak, W.; Sripanidkulchai, K. and Sripanidkulchai, B. (2017). Neuroprotective effects of aged garlic extract on cognitive dysfunction and neuroinflammation induced by beta-amyloid in rats. *Nutrients*, **9**(1):24.
- Nurmasitoh, T.; Sari, D. C. R. and Partadiredja, G. (2018). The effects of black garlic on the working memory and pyramidal cell number of medial prefrontal cortex of rats exposed to monosodium glutamate. *Drug Chem. Toxicol.*, **41**(3):324-329.
- QAlali, F.; El-Elimat, T.; Khalid, L.; Hudaib, R.; Saleh Al-Shehabi, T. and H Eid, A. (2017). Garlic for cardiovascular disease: Prevention or treatment? *Curr. Pharm. Desi.*, **23**(7):1028-1041.
- Rahman, K. (2003). Garlic and aging: New insights into an old remedy. *Ageing Res. Rev.*, **2**(1):39-56.
- Rahman, M. S. (2007). Allicin and other functional active components in garlic: Health benefits and bioavailability. *Int. J. Food Prop.*, **10**(2):245-268.
- Ray, B.; Chauhan, N. B. and Lahiri, D. K. (2011). Oxidative insults to neurons and synapse are prevented by aged garlic extract and s-allyl-l-cysteine treatment in the neuronal culture and app-tg mouse model. *J. Neurochem.*, **117**(3):388-402.
- Ried, K. (2016). Garlic lowers blood pressure in hypertensive individuals, regulates serum cholesterol, and stimulates immunity: An updated meta-analysis and review. *The J. Nutri.*, **146**(2):389S-396S.
- Ried, K. (2020). Garlic lowers blood pressure in hypertensive subjects, improves arterial stiffness and gut microbiota: A review and meta-analysis. *Exp. Ther. Med.*, **19**(2):1472-1478.
- S Bisen, P. and Emerald, M. (2016). Nutritional and therapeutic potential of garlic and onion (*Allium sp.*). *Curr. Nutr. Food Sci.*, **12**(3):190-199.
- Salehi, B.; Zucca, P.; Orhan, I. E.; Azzini, E.; Adetunji, C. O.; Mohammed, S. A.; Banerjee, S. K.; Sharopov, F.; Rigano, D. and Sharifi-Rad, J. (2019). Allicin and health: A comprehensive review. *Trends Food Sci. Technol.*, **86**:502-516.
- Sayed, S.F. (2023). Herbal drugs as antibiotics. In *Antibiotics-Therapeutic Spectrum and Limitations*, pp:479-532.
- Shang, A.; Cao, S.-Y.; Xu, X.-Y.; Gan, R.-Y.; Tang, G.-Y.; Corke, H.; Mayumengwana, V. and Li, H.-B. (2019). Bioactive compounds and biological functions of garlic (*Allium sativum* L.). *Foods*, **8**(7): 246.
- Shashikanth, K.; Basappa, S. and Murthy, V. S. (1984). A comparative study of raw garlic extract and tetracycline on caecal microflora and serum proteins of albino rats. *Folia Microbiologica*, **29**(4):348-352.
- Shohag, S.; Akhter, S.; Islam, S.; Sarker, T.; Sifat, M. K.; Rahman, M. M.; Islam, M. R. and Sharma, R. (2022). Perspectives on the molecular mediators of oxidative stress and antioxidant strategies in the context of neuroprotection and neurolongevity: An extensive review. *Oxi. Med. Cell. Longev.*, pp:20-32.
- Shukla, D.; Jaiswal, A. K.; Suryavanshi, A.; Asati, V.; Mahapatra, D. K.; Kumar, V. and Bharti, S. K. (2024). Role of garlic and onion for better cognition and maintenance of neurodegenerative diseases. In: *Nutraceutical Fruits and Foods for Neurodegenerative Disorders*, pp:333-352.
- Subroto, E.; Cahyana, Y.; Tensiska, M.; Lembong, F.; Filianty, E.; Kurniati, E.; Wulandari, D.; Saputra, R. and Faturachman, F. (2021). Bioactive compounds in garlic (*Allium sativum* L.) as a source of antioxidants and its potential to improve the immune system: A review. *Food Res.*, **5**(6):1-11.
- Sundarrajan, P. (2023). Foods that heal: Traditional indigenous plants as bioresource for health security. *Ann. Phytomed.*, **12**(2):5-11.
- Wang, L.; Zhang, J.; Hu, Y. and Zhang, H. (2017). Effects and mechanisms of allicin on atherosclerosis in high-fat diet fed mice. *Editorial Office of Chinese Journal of Arteriosclerosis*, **25**(2):140-144.
- Wang, Q.; Ma, X.; Li, X.; Li, M.; Yu, T. and Liu, Z. (2019). Hypolipidemic effect and antioxidation mechanism of diallyl disulfide in rats with hyperlipidemia.
- Wichai, T.; Pannangrong, W.; Welbat, J.; Chaichun, A.; Sripanidkulchai, K. and Sripanidkulchai, B. (2019). Effects of aged garlic extract on spatial memory and oxidative damage in the brain of amyloid-ã induced rats. *Songklanakarin J. Sci. Technol.*, **41**(2).
- Wlosinska, M.; Nilsson, A.-C.; Hlebowicz, J.; Hauggaard, A.; Kjellin, M.; Fakhro, M. and Lindstedt, S. (2020). The effect of aged garlic extract on the atherosclerotic process-A randomized double-blind placebo-controlled trial. *BMC complementary medicine and therapies*, **20**:1-10.
- Xu, X.; Hu, P.; Ma, Y.; Tong, L.; Wang, D.; Wu, Y.; Chen, Z. and Huang, C. (2020). Identification of a pro-elongation effect of diallyl disulfide, a major organosulfur compound in garlic oil, on microglial process: *The J. Nutr. Biochem.*, **78**:108323.
- Xu, X. H.; Li, G. L.; Wang, B. A.; Qin, Y.; Bai, S. R.; Rong, J.; Deng, T. and Li, Q. (2015). Diallyl trisulfide protects against oxygen glucose deprivation-induced apoptosis by scavenging free radicals via the pi3k/akt-mediated nrf2/ho-1 signaling pathway in b35 Neural Cells. *Brain Res.*, **1614**:38-50.
- Zhang, S.X.; Niu, Y.L.; Tian, Z.Q.; He, G.R.; Wang, L.J. and Wang, J.P. (2016). Diallyl sulfide attenuates iminodipropionitrile provoked oxidative neuropathy in a rat model. *Latin Am. J. Pharm.*, **35**(5):991-1000.
- Zhuang, F.; Shi, X.; Qiao, S.; Liu, B.; Wang, Z.; Huo, H.; Liang, F.; Shen, L.; Zhu, L. and He, B. (2023). Allicin promotes functional recovery in ischemic stroke via glutathione peroxidase-1 activation of src-akt-erk. *Cell Death Discov.*, **9**(1):335.

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