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# Protective Effect of an Anthocyanin on Alzheimer's Disease

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## Abstract

Alzheimer's, characterized by $\beta$-amyloid accumulation and tau hyperphosphorylation, is linked to inflammation, oxidative stress, and microglial activation, suggesting potential protective strategies. Studies have shown that natural polyphenolic anthocyanin components found in berries, such as cyanidin, can inhibit amyloid filament formation and modulate Alzheimer's disease are polyphenolic flavonoids, which are responsible for red, purple, and blue colors in various fruits, such as red cabbage and most berries. Here, we reviewed the protective effects of anthocyanins. It has anti-inflammatory and antioxidant properties, reduces NF-$\kappa$B, and affects inflammatory signaling pathways. They also improve cognitive function, making them a potential protective strategy against AD.

## Keywords

Anthocyanins, Oxidative Stress, Microglia Activation, NF-$\kappa$B

## 1. Introduction

Alzheimer's disease (AD) is the most prevalent type of dementia and is characterized by gradual loss of cognitive function caused by neuronal death, mostly in the cortical and hippocampal regions of the brain. Dementia affects approximately 55 million individuals globally, with almost 10 million new cases every year [1]. AD is mainly distinguished by the accumulation of $\beta$-amyloid (A$\beta$) and the hyperphosphorylation of tau (p-tau) [2]. Its initiation and progression have been linked to oxidative stress and neuroinflammation because it can induce membrane lipid damage, changes in enzymes necessary for neuronal and glial function, and structural damage to DNA, leading to tissue damage, synapse dysfunction, and cell death [3]. As the precise pathogenic pathways of AD remain unknown, current therapies focus mainly on symptomatic care rather than pre-

ventive or curative measures [4].

In addition to the traditional hypotheses for A$\beta$ and tau, the first link between neuroinflammation and AD pathogenesis is supported by microglial activation. Responsible for stimulating the immune system in the central nervous system, Activated microglia and released inflammatory cytokines have been detected in the brains of both animals and humans with AD. There is a new vision for Alzheimer's disease protection based on biomarkers as potential targets, such as regulating inflammatory proteins, which play a significant role in the development of A$\beta$ and tau pathology in AD brains, as well as modulating the signaling pathways that induce neuroinflammation. In addition, inhibition of the most disrupted pathway in AD, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B), is a transcription factor that regulates many signals and plays a significant role in neuroinflammation, which is connected to synaptic plasticity and neuronal growth [5].

We need to investigate the neuroprotective and disease-modifying potential of natural sources, such as dietary supplements or medicinal medications. Over the past few decades, preclinical research on natural extracts or isolates that have the potential to treat AD and lay the groundwork for translational research in this field has drawn increased interest [6].

The natural polyphenolic anthocyanin components have been the focus of numerous studies. Studies have reported the inhibition of amyloid filament formation by berries that are rich in anthocyanins, also showed that polyphenols from red wine contribute to the modulation of AD. [7], which is a polyphenolic flavonoid responsible for red, purple, and blue colors. [8] are found in fruits and vegetables, such as red cabbage, blueberry, blackcurrant, mulberry, cherry, black elderberry, black soybean, chokeberry, and jaboticaba peel, contains a variety of anthocyanins, including cyanidins, delphinidins, malvidins, pelargonidins, peonidins, and petunidins, which have antioxidant effects and have been reported to alter metabolic and inflammatory markers [9].

Anthocyanins exert neuroprotective effects by inhibiting the expression of pro-inflammatory cytokines and inflammatory pathways. This program is effective in improving the health of people with central nervous system disorders, particularly AD [10]. The aim of this review is to summarize the research evidence with an emphasis on recent studies on the protective potential of anthocyanins against Alzheimer's.

## 2. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by decline in cognitive function and neuronal loss. It is characterized by two core pathologies: the presence of $\beta$-amyloid (A$\beta$) and the hyperphosphorylation of tau (p-tau) [2].

A$\beta$ pathology occurs because of improper cleavage of a membrane protein called amyloid precursor protein (APP). However, little is known about its func-

tion, and it is thought to play a role in facilitating the movement (migration) of nerve cells (neurons) during early development. In normal cases involves non-amyloidogenic proteolysis of APP by- and l-secretases, which results in soluble fragments. However, incorrect cleavage of A$\beta$ produces A$\beta$ monomers that aggregate to create oligomeric A$\beta$, which then aggregate to form A$\beta$ fibrils and plaques, causing A$\beta$ pathology [11].

The second core pathology is the hyperphosphorylation of tau, which causes NFTs to form neurofibrillary tangles. Tau is a microtubule-associated protein that stabilizes the microtubules. It is phosphorylated to facilitate intracellular trafficking, and then dephosphorylated to return to the microtubule before it can be phosphorylated again. However, in (AD), multiple locations on the tau protein are phosphorylated, leading to tau removal from microtubules, collapse of microtubule structures, and disruption of various cellular activities including protein trafficking and general cellular shape. In addition, paired helical pieces of hyperphosphorylated tau (p-tau) assemble to form neurofibrillary tangles. Apoptosis occurs due to the accumulation of tau tangles, impaired cellular function, and loss of neural function [12].

However, there is a lack of knowledge regarding the pathophysiology of AD. A$\beta$ plaques may accumulate for up to years or even appear as NFT before any detectable symptoms or diagnosis [5]. Focus on A$\beta$ and tau may overlook the importance and possibility of other primary causes. Emerging evidence suggests that inflammation, oxidative stress, and microglial activation play a significant role in the development of neuroinflammation, leading to the progression of AD [13]. Therefore, modulating these factors could present a potential protective strategy against AD.

### 2.1. The Role of Inflammation in Alzheimer's Disease

Inflammation plays a crucial role in the disease. Although inflammation initially helps clear the brains of dying cells or foreign pathogens, prolonged or chronic inflammation can have negative consequences. This leads to the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species, which can cause accumulation of A$\beta$ and tau hyperphosphorylation [14].

### 2.2. The Role of Oxidative Stress in Alzheimer's Disease

In AD, Oxidative Stress can be induced by mitochondrial dysfunction, metal metabolism, inflammation, hyperphosphorylated tau and A$\beta$ accumulation. Oxidative stress and inflammation are closely related pathophysiological processes, one of which can easily be induced by another. Oxidative stress is caused by generation of reactive oxygen species (ROS) in microglia. These (ROS) trigger a chain of radical events that disrupt neuronal membranes and various biomolecules, such as DNA, RNA, amyloid $\beta$-peptides, and lipid peroxidation; [15] Therefore, reducing oxidative stress is considered an effective method of protection against the disease.

### 2.3. The Role of Microglial Activation in Alzheimer's Disease

Microglia, macrophages found in the central nervous system, plays a crucial role in AD. Microglia mediate inflammation and oxidative stress [13]. When oxidative stress appears as a primary disorder, inflammation develops due to ROS, which can activate microglia through the activation of the transcription factor NF-$\kappa$B as a secondary disorder, further enhancing oxidative stress [16]. At the same time Inflammation, as a primary disorder, can induce oxidative stress as a secondary disorder during the inflammatory process, and activated microglia produce ROS, which can further enhance inflammation [17]. They exhibit diverse phenotypes and interact with A$\beta$ and tau species. Therefore, the inhibition of microglial activation in the AD brain is a possible treatment or at least halts disease progression [18].

## 3. Anthocyanins as Protective against AD

Studies have shown that Anthocyanins may protect against AD. Both in vivo and *in vitro* experiments have demonstrated that anthocyanidins can shield neurons in mouse brain SK-N-SH and mouse hippocampal HT22 cells against A$\beta$- and LPS-induced neurotoxicity [19] [20]. Purple sweet potato was found to have potent free radical-scavenging activity and decreased A$\beta$-induced toxicity *in vitro* [21]. This protective effect includes anti-inflammatory and antioxidant effects, inhibition of microglial activation, and prevention of cognitive function loss.

### 3.1. Anti-Inflammation Effect

Anthocyanins can reduce activated nuclear factor (NF-$\kappa$B) and prevent its translocation to the nucleus, where it is not capable of mediating the transcription of many genes associated with inflammation. This was followed by a reduction in the activity of many signaling pathways, including levels of active c-Jun-N-terminal kinase (JNK), p38-mitogen-activated protein kinase (p38-MAPK), and extracellular signal-regulated kinase 1/2 (ERK1/2), and upregulation of the phosphorylated-phosphatidylinositol 3-hydroxy kinase/Akt/GSK3$\beta$ (p-PI3K/Akt/GSK3$\beta$) pathway. Additionally, in neuroblastoma cells treated with amyloid beta protein, anthocyanidin cyanidin modified inflammatory responses by reducing the activation of NF-$\kappa$B, a toll-like receptor 4 (TLR4) [22]. Therefore, it decreases nitric oxide generation, inducible nitric oxide synthase expression (iNOS), cyclooxygenase-2 (COX-2), and nuclear translocation of NF-$\kappa$B [23] [24] [25].

Moreover, as mentioned in the study, the effects of berry-rich anthocyanin supplements (320 mg/day) for four weeks on male and female adults aged between 25 and 75 years [26], and numerous cell and animal model studies have shown that anthocyanin affects cytokines. A study that Cyanidin-3-O-Glucoside is effective in reducing pro-inflammatory cytokine mRNA expression in the cortex of the brains of APPswe/PS1E9 mice, as well as an anti-inflammatory agent, A$\beta$42-induced human microglial cell line. [18] It clearly reduced the expression of cytokines by repressing the expression of NF-$\kappa$B-dependent genes,

including (TNF-α), (IL-6), and (IL-1$\beta$) [27].

### 3.2. Antioxidant Effects

Anthocyanins have been shown to scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS). This protects vital cellular macromolecules such as lipid membranes, proteins, and DNA from oxidative stress [22] [28].

Studies have suggested that anthocyanins can also enhance the cell's intrinsic antioxidant defenses, such as glutathione (GSH), which preserves mitochondrial GSH levels and is an important antioxidant molecule involved in detoxifying ROS. They can maintain brain weight and reduce age-associated decreases in antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) [29].

### 3.3. Inhibition Microglia Activation

Anthocyanins inhibit microglial activation by exerting anti-inflammatory and antioxidant effects. They also promote the polarization of microglia towards the M2 phenotype, which is associated with a more neuroprotective and anti-inflammatory response by activating nuclear factor erythroid 2-related factor 2 (Nrf2). Additionally, studies have shown that anthocyanins can play a crucial role in clearing A$\beta$ plaques by enhancing the phagocytic activity of microglia, leading to increased clearance of A$\beta$ plaques [18] [30].

### 3.4. Prevention of Loss of Cognitive Function

In the MWM, Y-maze, and probe tests, anthocyanins (24 mg/kg daily, i.p. for 14 days; 100 mg/kg daily, i.p. for 7 weeks; 20 mg/kg daily, i.g. for 3 months) significantly improved behavioral performance and prevented the loss of cognitive function in LPS-induced mice, D-galactose-induced rats, and APP/PSEN1 mice [31].

Moreover, it can enhance brain blood flow and vascular function, which is important for maintaining brain health and protecting against impaired cerebral blood flow, leading to cognitive decline and an increased risk of AD. (4) [32]. A recent human trial found that blueberry supplementation for over 16 weeks enhanced semantic access and visual-spatial memory in older adults with MCI. [33] The neuroprotective benefits of blueberry juice have also shown promise in enhancing signaling pathways and preventing behavioral deficits in AD mouse models [34].

## 4. Conclusion

Alzheimer's disease (AD) is characterized by accumulation of $\beta$-amyloid (A$\beta$) and hyperphosphorylation of tau. The onset and progression of AD are not yet fully understood; however, A$\beta$ plaques and tau protein may accumulate for years before symptoms appear. Research suggests that inflammation, oxidative stress, and microglial activation contribute to neuroinflammation, leading to AD, sug-

gesting potential protective strategies. Here, we reviewed the protective effects of anthocyanins, including their anti-inflammatory effects. They have been found to reduce NF-$\kappa$B, prevent its translocation to the nucleus, and affect the transcription of inflammation-associated genes. They also reduce the activity of many inflammatory signaling pathways, thereby reducing the expression of pro-inflammatory cytokines. Anthocyanins exhibit antioxidant effects by scavenging ROS and RNS, enhancing antioxidant defenses such as glutathione and antioxidant enzymes, thus enhancing cell health and inhibiting microglial activation, promoting polarization towards the M2 phenotype, and clearing A$\beta$ plaques. Additionally, anthocyanins have been shown to improve cognitive function, enhance brain blood flow, and enhance semantic access and visuospatial memory. Thus, anthocyanins represent a useful future protective strategy against Alzheimer's disease.

## Informed Consent

Before study began, legally appointed representatives provided written informed consent.

## Funding

This study did not receive any external support.

## Ethical Compliance

The study protocol was approved by the Qassim University Committee for Scientific Research Ethics (protocol code: 23-46-03; approval date: 14-7-2023).

## Data Access Statement

The authors attest that the publication and its supplemental materials contain the data necessary to support the findings of this study.

## Conflicts of Interest

The authors declare that they do not have any competing interests.

## Author Contributions

AR and NS contributed to the design and implementation of the research; AR writing the original draft preparation; NS review and editing; NS conceived the original idea and supervised the project. All authors have read and agreed to the published version of the manuscript.

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