MADYNIAK, Katarzyna and CIECIERSKI, Piotr. Coffee and Alzheimer's Disease: Reviewing the Neuroprotective Effects of Bioactive Compounds. Quality in Sport. 2024;29:55649. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.29.55649
https://apcz.umk.pl/QS/article/view/55649

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.10.2024. Revised: 20.10.2024. Accepted: 26.10.2024. Published: 26.10.2024.

Coffee and Alzheimer's Disease: Reviewing the Neuroprotective Effects of Bioactive Compounds

Katarzyna Madyniak
Medical University of Warsaw
kasiamadyniak@onet.pl
ORCID: 0009-0003-6927-3832

Piotr Ciecierski
Medical University of Warsaw
piotr.ciecierski06@gmail.com
ORCID: 0009-0005-7225-7918

Abstract

Alzheimer's disease (AD) is a common neurodegenerative disorder primarily managed with symptomatic treatments. Coffee, a popular beverage, contains bioactive compounds like caffeine, chlorogenic acid, quercetin, trigonelline, caffeic acid, and kaempferol, which may offer neuroprotective benefits. These compounds could potentially address AD-related pathologies such as amyloid-beta accumulation, tau hyperphosphorylation, oxidative stress,

and inflammation. This review explores the neuroprotective potential of coffee's bioactive components in AD.

Aim of the Study

This study aims to review research on the neuroprotective effects of coffee and its bioactive compounds in Alzheimer's disease. It seeks to understand how these compounds may mitigate AD-related pathologies and their potential in preventive and therapeutic applications. The study also identifies knowledge gaps and suggests future research directions.

Material and Methods

We reviewed literature from PubMed, Google Scholar and other scientific sources using keywords: Alzheimer's disease, coffee, neuroprotective, caffeine, chlorogenic acid, quercetin, trigonelline, caffeic acid, and kaempferol.

Conclusions

Emerging evidence indicates that coffee's bioactive compounds may offer neuroprotective benefits against Alzheimer's disease. Compounds such as caffeine, chlorogenic acid, quercetin, trigonelline, caffeic acid, and kaempferol show potential in mitigating key AD pathologies. However, the current evidence is preliminary, and more research is needed to fully understand their cognitive benefits and mechanisms. Investigating these properties is particularly relevant given the aging global population and the age-related nature of AD.

Keywords: coffee, Alzheimer’s disease, neuroprotective, caffeine, chlorogenic acid, quercetin, trigonelline, caffeic acid, kaempferol

Introduction:

1. Alzheimer’s Disease

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is a common cause of cognitive impairment occurring in midlife and late life. It is the main cause of dementia, estimated to be responsible for 60-80% of cases [1, 2, 3]. It usually begins with a gradual loss of episodic memory and cognitive function, leading to difficulties with language and spatial awareness [4]. Communication problems and behavioral changes such as aggression or apathy, may occur in the later stages of the disease. Subsequently, difficulties with walking, speaking, and swallowing may appear [3].

Various factors contribute to the risk of developing the disease, including advanced age, genetic predisposition, female gender, cardiovascular risk factors, and an unhealthy lifestyle [5]. The pathogenesis of Alzheimer’s disease is associated with two main factors: the accumulation of beta-amyloid protein outside neurons and the accumulation of abnormal tau protein inside neurons. These lead to neuronal death and brain tissue damage due to the neurotoxicity of these proteins. Additionally, chronic inflammation associated with the activation of microglia and atrophy caused by cell death can contribute to AD [3].

Currently available treatments are only symptomatic, meaning they do not eliminate the causes of the disease but only combat or alleviate its symptoms to improve quality of life. Pharmacological treatments include cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine. Memantine, an NMDA receptor antagonist, can also be used to help regulate glutamate activity in the brain and improve cognitive function [6].

To conclude, despite significant efforts to understand the etiology and pathophysiology of Alzheimer's disease (AD), scientists have yet to develop medications that can definitively halt its progression. Consequently, contemporary research has increasingly focused on the potential role of natural products in the treatment and prevention of AD, garnering substantial interest in this field.

2. Coffee

Coffee is one of the most widely consumed beverages in the world, and its consumption has become a regular part of many people's lives. It is a mixture of many bioactive ingredients, and it also contains minerals and vitamins [7].

According to studies, the leading motives for coffee consumption are functional benefits, taste and pleasure, routine, tradition, and social factors. On the other hand, primary factors discouraging people from drinking coffee include a dislike of its taste and concerns regarding potential adverse health effects. Thus, it can be inferred that coffee consumption is not typically viewed as health-conscious behavior, despite scientific evidence suggesting that coffee can be included as part of a balanced diet [7].

Previous studies have explored the correlation between coffee consumption and human health. Besides its neuroprotective effects, these studies have noted a lower risk of cardiovascular diseases, a lower risk of liver conditions, a reduced risk of type-2 diabetes, and positive effects on mental health [7, 8, 9]. However, it should be noted that drinking excessive amounts of coffee may lead to adverse effects. Caffeine consumption has been linked to elevated total cholesterol levels and reduced high-density lipoprotein in the bloodstream. Moreover, excessive coffee intake may result in hypertension, tachycardia, and arrhythmia [10].

State of knowledge:

Coffee consumption has been the subject of numerous studies investigating its potential effects on Alzheimer's disease. It contains various bioactive compounds, such as caffeine, chlorogenic acid, quercetin, trigonelline, caffeic acid and kaempferol, which are believed to

have physiological effects. Here we outline the possible mechanisms by which selected compounds of coffee may provide neuroprotection.

1. Caffeine

Caffeine, the most commonly consumed psychoactive substance, improves attention and alertness, stabilizes mood, and may independently boost cognitive performance [11].

The structural similarity between caffeine and adenosine allows caffeine to bind to adenosine receptors, particularly adenosine A2A receptors, due to their similar chemical structures [12]. This is crucial for understanding caffeine's effects on the brain. Caffeine acts as a competitive antagonist, meaning it blocks the action of adenosine, which normally influences sleep and reduces neuronal activity [12]. In Alzheimer's disease, where there is loss of neurons and decreased neuronal activity, this action of caffeine can have a beneficial effect by helping to maintain healthy synaptic function. Caffeine's blockade of adenosine A2A receptors also contributes to its neuroprotective properties. Synaptotoxicity, or damage to synapses, is a significant issue in neurodegenerative diseases like Alzheimer's. By blocking adenosine A2A receptors, caffeine can reduce excessive neurotransmission and inflammation associated with synaptic damage. This action helps to support synaptic health and may protect against mood disorders and cognitive impairments related to Alzheimer's disease [13].

Furthermore, the amyloid-beta (Aβ) theory involves an imbalance between the production and clearance of Aβ. Caffeine reduces the activity of β-secretase and γ-secretase, enzymes responsible for producing amyloid-beta through the proteolysis of amyloid precursor protein (APP). This suggests that caffeine may reduce the risk of Alzheimer's disease by decreasing pathological cerebral amyloid deposition [14].

Moreover, the tau protein theory indicates that caffeine, by preventing the expression of enzymes responsible for tau hyperphosphorylation, may reduce the accumulation of

neurofibrillary tangles within neurons. This implies a potential protective effect of caffeine against tau-related neurodegeneration [14].

Caffeine is the most extensively investigated bioactive compound in coffee. The beneficial effects of coffee consumption are largely attributed to caffeine; however, there are reports suggesting that decaffeinated coffee could also possess neuroprotective properties [15, 16].

2. Chlorogenic acid

Chlorogenic acid (CGA) is recognized for its significant antioxidant properties, which play a crucial role in combating oxidative stress- a key factor in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease. CGA effectively neutralizes oxidative stress by reducing the production of reactive oxygen species (ROS) and inhibiting lipid peroxidation, a process that can lead to cellular damage through the degradation of cell membranes. This inhibition of lipid peroxidation by CGA is particularly important, as it prevents the formation of malondialdehyde (MDA), a byproduct of lipid peroxidation and a well-established marker of oxidative stress. Elevated levels of MDA are indicative of increased oxidative damage, which can exacerbate neuronal injury and contribute to the progression of Alzheimer's disease [13, 17, 18]. By reducing oxidative stress, CGA helps protect neuronal cells in critical regions of the brain, such as the hippocampus and frontal cortex, which are particularly vulnerable to oxidative damage. This protective effect underscores the potential role of CGA in neuroprotection, particularly in the context of neurodegenerative diseases where oxidative stress is a pathological factor [18].

In addition to its antioxidative effects, CGA has been shown to inhibit acetylcholinesterase, an enzyme responsible for the breakdown of acetylcholine, a neurotransmitter that plays a vital role in memory and cognitive function. The inhibition of acetylcholinesterase by CGA leads

to increased levels of acetylcholine in the brain, which may contribute to improved cognitive functions, especially in areas such as the hippocampus and frontal cortex [10]. This mechanism is particularly relevant in Alzheimer's disease, where acetylcholine levels are often reduced, leading to cognitive decline.

3. Quercetin

Quercetin, a prominent flavonoid found in various plants and dietary sources, demonstrates significant potential in combating Alzheimer's disease through several mechanisms.

Quercetin exhibits strong antioxidant activity, which helps reduce oxidative stress and inflammation. Its antioxidant properties support the protection of nerve cells from damage caused by reactive oxygen species and other free radicals [19].

In addition, quercetin inhibits the formation of amyloid-β protein fibrils, a key factor in the pathology of Alzheimer's disease. By blocking amyloid-β aggregation, quercetin may help reduce cellular damage and inflammatory processes associated with the disease [20, 21]. Furthermore, quercetin acts as a competitive inhibitor of acetylcholinesterase, an enzyme targeted by current symptomatic treatments for Alzheimer’s disease. This suggests that quercetin could play a role in managing Alzheimer's symptoms [21].

Research into quercetin-1,2,3-triazole hybrids, which are modified forms of quercetin, explores their potential for enhancing neuroprotective effects. These hybrids aim to address limitations such as low bioavailability and permeability, thereby improving the therapeutic efficacy of quercetin [22].

4. Trigonelline

Trigonelline is a naturally occurring alkaloid predominantly found in coffee beans [23]. Emerging research highlights its potential neuroprotective effects, particularly in managing

neurodegenerative conditions such as Alzheimer's disease. Current studies suggest several significant benefits of trigonelline.

Trigonelline demonstrates potent antioxidant activity, which reduces oxidative stress and enhances the antioxidant defense system. This reduction in oxidative stress mitigates damage caused by reactive oxygen species, thereby preserving neuronal health and supporting cognitive function. Additionally, trigonelline lowers levels of neuroinflammatory markers, including glial fibrillary acidic protein (GFAP), S100b, COX-2, TNF-α, and IL-6 [24]. By decreasing neuroinflammation, trigonelline contributes to the protection of neurons and supports improved cognitive performance, including spatial recognition memory in animal models [24].

Trigonelline also plays a role in maintaining mitochondrial health by improving mitochondrial membrane potential. Mitochondrial integrity is crucial for cellular energy production and overall neuronal function. By supporting mitochondrial function, trigonelline helps sustain neuronal health and counteract the energy deficits often associated with neurodegenerative diseases [24].

Trigonelline has been reported to lower acetylcholinesterase (AChE) levels in the brain. AChE is an enzyme responsible for the breakdown of acetylcholine, a neurotransmitter essential for memory and learning. Inhibiting AChE can lead to increased levels of acetylcholine, which may improve cognitive symptoms associated with Alzheimer's disease. This suggests that trigonelline could play a role in managing Alzheimer's symptoms through its effects on neurotransmitter dynamics [25].

Furthermore, trigonelline helps normalize levels of brain-derived neurotrophic factor (BDNF). BDNF is critical for neuronal survival, growth, and synaptic plasticity. In neurodegenerative conditions, BDNF levels are often depleted, contributing to cognitive decline and neuronal

loss. By restoring BDNF levels, trigonelline supports neuroprotection and enhances neuronal resilience, further contributing to its potential therapeutic effects in Alzheimer's disease [25].

5. Caffeic acid

Caffeic acid, a polyphenolic compound found in coffee and a significant metabolite of chlorogenic acid, has garnered attention for its potential neuroprotective properties in Alzheimer's disease. This compound appears to exert its effects through several mechanisms. One of the key benefits of caffeic acid is its ability to inhibit acetylcholinesterase and butyrylcholinesterase activities. In Alzheimer's disease, these enzymes are often dysregulated, negatively affecting cognitive function. Caffeic acid’s inhibition of these enzymes may help counteract these changes and support cognitive health [26].

Additionally, caffeic acid plays a protective role against oxidative stress, a condition that contributes to the progression of Alzheimer's disease. It reduces the production of reactive oxygen species (ROS) and helps prevent the depletion of glutathione, a crucial antioxidant. By mitigating oxidative stress, caffeic acid helps protect brain cells from damage caused by factors like acrolein [27].

The compound also influences key signaling pathways involved in inflammation and neurodegeneration, such as NF-κB and GSK3β. These pathways are critical in the disease's progression, and caffeic acid’s modulation of these pathways may further contribute to its neuroprotective effects [27, 28].

Caffeic acid helps manage amyloid-beta (Aβ) aggregation, a hallmark of Alzheimer's disease, by preventing the formation of Aβ1-42 fibrils and promoting the disaggregation of existing fibrils. This action reduces amyloid-beta-related brain damage. Additionally, caffeic acid lowers the expression of amyloid precursor proteins and the enzyme that cleaves them,

leading to decreased levels of Aβ1-42 in the hippocampus, which could further mitigate the progression of Alzheimer's disease [29, 30].

6. Kaempferol

Kaempferol (KMP) demonstrates significant neuroprotective potential, making it a promising candidate for Alzheimer's disease (AD) treatment.

As an antioxidant, kaempferol effectively neutralizes reactive oxygen species (ROS) and other free radicals, which helps to protect neurons from oxidative damage. Kaempferol's antioxidant activity is crucial in preserving mitochondrial function and reducing oxidative stress, which are important factors in maintaining neuronal health and mitigating neurodegenerative conditions [31, 32, 33, 35].

In terms of anti-inflammatory effects, kaempferol has been shown to lower levels of proinflammatory cytokines and neuroinflammatory markers. Jin et al. describe that kaempferol reduces the activation of inflammatory pathways and decreases markers such as glial fibrillary acidic protein (GFAP), S100b, COX-2, TNF-α, and IL-6 [33]. This reduction in neuroinflammation helps protect neurons from inflammatory damage. Furthermore, kaempferol also inhibits the activation of microglia, which are immune cells involved in neuroinflammatory responses [33].

Furthermore, KMP mitigates amyloid-beta (Aβ)-induced neurotoxicity and prevents the deposition of amyloid fibrils, tau tangles, and α-synuclein aggregates, which are hallmarks of neurodegenerative diseases [33].

Additionally, kaempferol enhances cholinergic function by inhibiting acetylcholinesterase (AChE), thus preserving acetylcholine levels crucial for cognitive processes [31, 32, 34, 35].

Conclusions:

Although coffee consumption is not typically recognized as a health-promoting habit, emerging evidence suggests that it may confer various health benefits. Extensive research has demonstrated that coffee and its bioactive compounds possess neuroprotective properties, indicating their potential for both preventive and therapeutic applications in various neurodegenerative conditions.

Among these compounds, caffeine has been the most thoroughly studied, and the beneficial effects of coffee consumption are largely attributed to caffeine. However, numerous studies have indicated that other compounds in coffee, such as chlorogenic acid, quercetin, trigonelline, caffeic acid, and kaempferol, can independently exert neuroprotective effects.

A growing body of research links Alzheimer's disease (AD) to several pathological factors, including the aberrant accumulation of amyloid-beta (Aβ) plaques, increased hyperphosphorylation of tau protein, formation of neurofibrillary tangles, mitochondrial dysfunction, excessive production of reactive oxygen species (ROS), and chronic inflammation. Coffee components may exert their neuroprotective effects by influencing these pathological processes. However, the current evidence on their cognitive benefits in humans is preliminary; and the specific mechanisms by which each component impacts the brain require further investigation.

Demographic projections indicate a rapid aging process in societies worldwide, including Poland [36]. Given that Alzheimer's disease is predominantly age-related, it is crucial to explore factors that may mitigate its risk. Therefore, further research into the neuroprotective properties of coffee and its components is warranted.

Disclosures:

Author's contribution: Katarzyna Madyniak, Piotr Ciecierski

Conceptualization: Katarzyna Madyniak, Piotr Ciecierski

Methodology: Katarzyna Madyniak, Piotr Ciecierski

Software: Katarzyna Madyniak, Piotr Ciecierski

Check: Katarzyna Madyniak, Piotr Ciecierski

Formal analysis: Katarzyna Madyniak, Piotr Ciecierski

Investigation: Katarzyna Madyniak, Piotr Ciecierski

Resources: Katarzyna Madyniak, Piotr Ciecierski

Data curation: Katarzyna Madyniak, Piotr Ciecierski

Writing - rough preparation: Katarzyna Madyniak, Piotr Ciecierski

Writing - review and editing: Katarzyna Madyniak, Piotr Ciecierski

Visualization: Katarzyna Madyniak, Piotr Ciecierski

Supervision: Katarzyna Madyniak, Piotr Ciecierski

Project administration: Katarzyna Madyniak, Piotr Ciecierski

Receiving funding: Katarzyna Madyniak, Piotr Ciecierski

Funding Statement: The Study Did Not Receive Special Funding

Institutional Review Board Statement: Not Applicable

Informed Consent Statement: Not Applicable

Data Availability Statement: Not Applicable

Conflict Of Interest: The authors declare no conflict of interest.

All authors have read and agreed with the published version of the manuscript.

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