

# Coffee Consumption Provides Therapeutic Benefits against AD through Increasing Plasma GCSF Levels and Improving Cognitive Performance

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## Abstract

Alzheimer's disease (AD) a progressive neurodegenerative disease that destroys memory and other important mental functions. More than 5 million Americans are living with AD. This number is expected to drastically increase as the baby boomer population transitions into the late-adulthood age group. Currently, the treatment for AD includes FDA drugs that focus on treating the symptoms. These types of drugs lose their efficacy as the disease progresses. Therefore, preventive measures are very critical in decreasing the incidence rate of AD. Many epidemiological studies have been conducted on the treatment of Alzheimer's that suggest enhanced coffee/caffeine intake during aging reduces the risk of AD. As one of most popular beverages in the World, many experimental studies have been done to test the effects of coffee consumption on AD. This paper will aim to review the important discoveries that have been made recently and present the possible mechanisms behind the neuroprotective effects.

**Keywords:** Alzheimer's; Immune modulation; GCSF; Cytokine; Immune system; Dementia; Caffeine

## Introduction

### Coffee

Coffee is one of the most studied and widely consumed beverages in the World [1]. Production of coffee mainly takes place in Latin America, Asia, and Africa and its trade is the second highest after only crude oil, worth more than US \$10 billion [2]. Coffee has hundreds of different species which belong to the family Rubiaceae (Coffea Genus) [3]. *Coffea arabica* and *Coffea canephora* are the two species that are cultivated for commercial purposes. As the general population becomes more conscious of their diet, many questions have been raised about the effects coffee has on their health. The common bioactive molecules in coffee are caffeine, chlorogenic acid, diterpenes, and trigonelline as shown in Figure 1 [4]. Caffeine, a neuro-stimulant, is the major bioactive molecule found in coffee that has been widely studied in scientific fields such as Neurology and Immunology. It has been linked to health benefits for cognition, alertness, and memory [5]. Due to the health benefits associated with cognition, coffee has been introduced as a therapeutic agent against Alzheimer's disease (AD). Over the past century there has been a dramatic increase in research on AD. The aim of this paper is to investigate and review the current discoveries on therapeutic effects of coffee against AD.

### Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia and its histopathological characters include: neuronal loss, deposition of extracellular amyloid- $\beta$  ( $A\beta$ ) plaques and neurofibrillary tangles (NFTs) that are composed of hyper-phosphorylated Tau protein [6]. Amyloid- $\beta$  ( $A\beta$ ) plaques, associated with the genes presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP),

are a major component of AD pathogenesis [7]. Currently, Alzheimer's dementia affects around 5.5 million Americans, of which 5.3 million are 65 years or older [8]. Due to the growing baby boomer population, this number is projected to grow to 13.8 million by 2050. These alarming statistics show the critical need for the treatment of Alzheimer's disease (Figure 1).

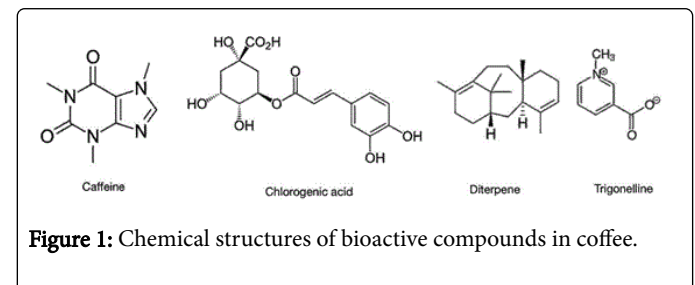
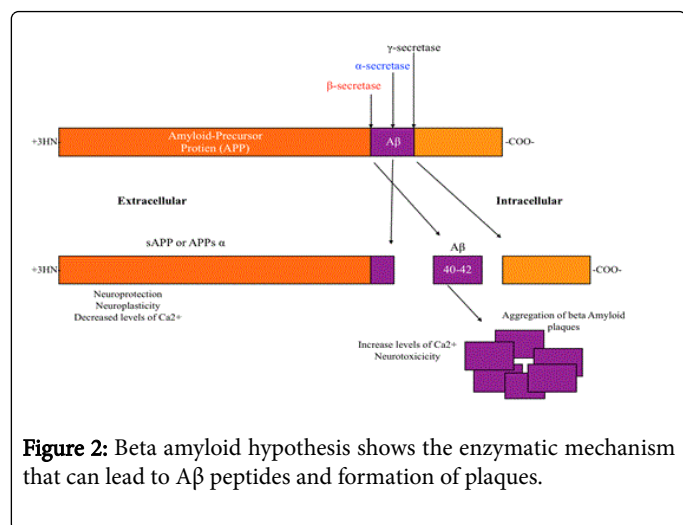


Figure 1: Chemical structures of bioactive compounds in coffee.

**Symptoms of Alzheimer's disease:** Alzheimer's disease is a chronic neurodegenerative disorder that eventually leads to loss of memory and cognitive functions. Early onset AD is caused by several genetic factors such as PSN1, PSN2, and APP7. Late onset AD is caused by environmental factors, genetic predisposition of APOE  $\epsilon$ 4, and lifestyle choices that can combat AD or aid in its progression. AD can be genetic with an early onset or a more common late on-set that is not determined genetically [9]. The most common symptoms of Alzheimer's disease include deficits in semantic memory, language, visuospatial skills, and functional impairments that occur as the pathogenesis of AD progresses [10]. The pathogenesis of AD, such as the buildup of amyloid-beta plaques starts years before any observable symptom of cognitive decline are detected [11]. The growing prevalence of AD, the associated costs of treating AD patients, and caregiver strain magnify the importance of finding an effective treatment for AD.

**The amyloid hypothesis:** Amyloid  $\beta$  ( $A\beta$ ) hypothesis, which has been widely accepted within the scientific community as an

explanation for the pathological changes in AD, proposes that accumulation of beta-amyloid peptides results in formation of plaques [12]. The amyloid precursor protein (APP) is normally cleaved by an enzyme known as alpha-secretase [13]. However, A $\beta$  peptides that combine to form neurotoxic plaques are produced when APP is cleaved by the enzymes beta and gamma secretase. Figure 2 illustrates the cascade of events that lead to the formation of neurotoxic A $\beta$  plaques. A $\beta$  plaques can lead to neuronal damage and another abnormal protein process which results in formation of neurofibrillary tangles (NFTs). Evidence suggests that deposition of A $\beta$  along with increase in NFTs is associated with AD [14]. However, the details of how Alzheimer's disease is caused is still not certain and this uncertainty is one of the reasons why an effective treatment has not been developed yet.



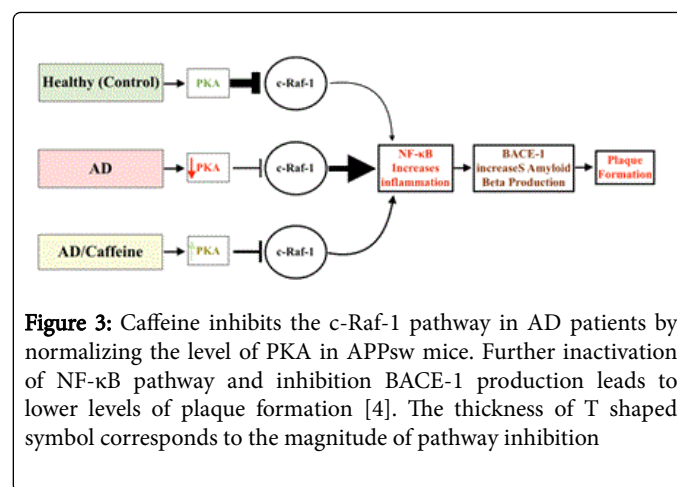
**Current treatments:** AD patients can be characterized on a spectrum from prodromal mild cognitive impairment (MCI), to mild, moderate, and severe. Currently, the treatment options for any stage of AD are limited; they treat the symptoms of the disease and not its underlying cause [15]. The treatment options include cholinesterase inhibitors (AChEIs) such as Donepezil, Galantamine and Rivastigmine and other FDA approved drugs such as Memantine and an N-methyl-D-aspartate (NMDA) receptor antagonist; none of which cure or stop the progression of AD [15-18]. Cholinesterase inhibitors can only work to improve behavioral symptoms for a limited amount of time as AD continues to progress, which varies as described in different reports, but one study estimates the efficacy of an AChEIs, Donepezil, to be around 4.9 years [19-21]. The marginal benefits that these drugs provide against Alzheimer's disease also introduce potentially harmful side effects. Currently, Research is being done on more novel treatments of AD such as vaccinations and disease modifying drugs. With treatment research under progress, it is important to identify protective factors that can help prevent certain pathways such as the toxic amyloid plaque formation which cause AD pathophysiology.

### Health benefits of coffee for neurodegenerative diseases

**Research on coffee's benefits against neurodegenerative diseases:** In recent years, there has been an increasing interest in discovering preventative methods to reduce the risk of age related disorders such as AD. A considerable amount of literature has been published that associates coffee consumption with reduced risk of neurological disorders such as Alzheimer's disease - by approximately 31% in a

Canadian study, which consisted of 10, 263 men and women over the age of 65 [22-24]. When compared to those who drink less coffee, a 2010 review of longitudinal epidemiological studies stated that daily intake of 3-5 cups of coffee during middle age may lower the risk of the AD by 65% [25]. In another 2007 quantitative review of four studies (2 case controlled and 2 cohort studies conducted between 1990 and 2002), there was a pronounced protective effect of coffee consumption in the pooled estimate (risk estimate: 0.73, 95% confidence interval: (0.58-0.92) [26]. However, the design of previous studies is ambiguous as the results are based on surveys and recall. To investigate this area, researchers conducted scientific experiments to determine whether coffee has therapeutic benefits against the progression of Alzheimer's disease.

**Caffeine, a major bioactive molecule of coffee, reduces Amyloid- $\beta$  and improves cognitive performance:** In one study by Dr. Cao and Dr. Arendash, AD transgenic mice model were given oral treatment of caffeine (0.3 mg/ml - human equivalent of 5 cups per day), a major bioactive molecule of coffee [27]. The results revealed improvement in cognitive performance tasks along with reduction of hippocampal A $\beta$  due to suppression of  $\beta$ -secretase (BACE1) and presenilin 1 (PS1)/ $\gamma$ -secretase expression. Figure 3 shows how caffeine suppresses the enzymatic activity to lower the levels of plaque formation. A follow-up study was conducted to determine the effects of same amount of caffeine in 18-19-month-old mice with AD. Results revealed a substantial decrease of 40% in hippocampal A $\beta$  levels and 46% decrease in entorhinal cortex A $\beta$  levels along with a reduction in brain soluble A $\beta$ , after 4-5 weeks into the treatment. Compared to the control transgenic mice in this study, the treatment group also showed significant improvement in cognitive performance on radial arm water maze (RAWM) test. In another study, 3 month old wild-type and transgenic mice were administered crude caffeine (CC) and pure caffeine (human equivalent of 4.86 mg/kg body weight) [28]. Both caffeine treatments were beneficial, however, CC was more effective at preventing spatial memory impairment as evident by results from hidden platform test. The restoration of cognitive performance along with the reduction in pathological characteristics of AD, such as A $\beta$  plaques, suggest caffeine to be a therapeutic agent against AD and its progression.

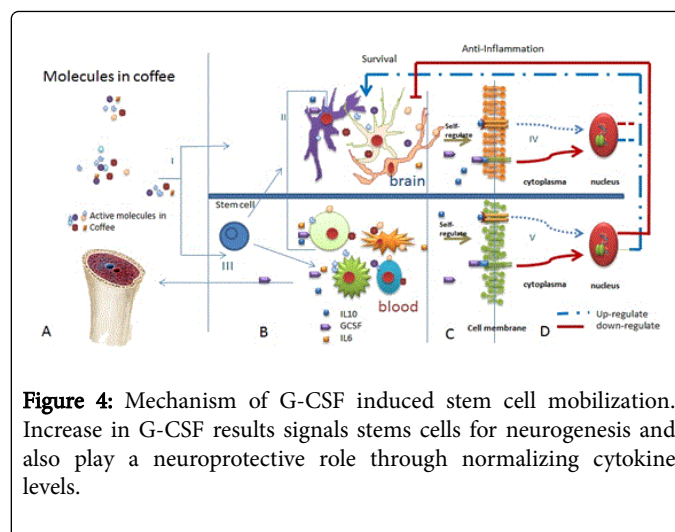


**Antioxidant properties of coffee reduce the oxidative stress associated with AD:** AD pathology has also been linked to an increase in oxidative stress: evident by the lesions present in brains of AD patients [29]. Free radicals are involved in the cascade of events that lead to neural damage. However, a bi-fold relationship exists between

amyloid- $\beta$  and production of free radicals. Oxidative stress can increase aggregated form of amyloid- $\beta$  through covalent cross-linking and amyloid- $\beta$  can also increase reactive oxygen species(ROS). The covalent cross-linking of proteins reduces the susceptibility to proteolytic degradation and induces neurotoxic effects, such as formation of plaques and NFTs, which further the oxidative stress. Caffeine along with its catabolic products, theobromine and xanthine, can serve as therapeutic to relieve the neural damage caused by oxidative stress [30-32].

**Caffeine synergizes with compound(s) from coffee to provide protection against AD:** Coffee contains many other compounds in addition to caffeine. A 2011 study by Dr. Cao et al. was conducted using transgenic AD mice and non-transgenic littermates to differentiate the effects of caffeinated coffee and decaffeinated coffee against AD [33]. The treatment in this study included 200  $\mu$ l i.p injection of saline, caffeine, un-concentrated coffee (0.15 mg/100  $\mu$ l), concentrated coffee (0.75 mg/100  $\mu$ l) and concentrated decaffeinated coffee (0.03 mg/100  $\mu$ l). The cytokines in pre/post-treatment blood were measured using the Luminex assay and the post-treatment blood showed significant increase in cytokine (G-CSF, IL-10 and IL-6) levels of concentrated and un-concentrated coffee. In the 3 month long-term study, the same treatment groups were given to AD transgenic mice, only un-concentrated and concentrated coffee was able to improve performance on cognitive tasks such as 3-trial recall. The improvement in cognitive performance was also directly associated with the increase in levels of plasma G-CSF, which has been linked to a protective signaling mechanism in response to neural injury [34]. The results from this study suggest that caffeine synergizes with an unknown compound from coffee to provide benefits against AD and its progression. In addition, a study published in 2014 identified 69 discriminate metabolites in coffee [35]. This study discovered that caffeinated coffee had higher levels of 37 metabolites (benzoate and cinnamate derivatives) and decaffeinated coffee had higher levels of 32 metabolites. This study suggests that the prominent therapeutic benefits of caffeinated coffee over decaffeinated coffee can be due to the higher levels of monohydroxybenzoates, which metabolizes into other phenolic compounds through microbial degradation. Future research could further look into the interaction of caffeine with other coffee compounds to identify the specific compound(s) that provide these therapeutic benefits.

**Role of G-CSF and how it functions:** Consumption of coffee has been linked to an increase in levels of plasma Granulocyte colony-stimulating factor (G-CSF). G-CSF is a hematopoietic growth factor that has neuroprotective effects, stimulates neurogenesis, and promotes bone marrow to produce granulocytes and stem cells [36]. Human G-CSF has been used for treatment of neutropenia and mobilization of hematopoietic stem cells (HSC) from bone marrow [37]. It also plays a role in maturation of bone marrow derived granulocytes into various cellular phenotypes such as myocytes and neurons [38]. The anti-apoptotic functions of G-CSF in the human body have led to interest in G-CSF as a therapeutic agent for diseases such as AD which result from neurodegeneration. The schematic in Figure 3 shows how G-CSF stimulates other cells to provide the protective benefits against neuronal apoptosis (Figure 4).



**Figure 4:** Mechanism of G-CSF induced stem cell mobilization. Increase in G-CSF results signals stems cells for neurogenesis and also play a neuroprotective role through normalizing cytokine levels.

G-CSF is produced by the immune cells in the human body. Receptors of G-CSF have been found in bone marrow and in the central nervous system [39]. The receptors in bone marrow help mobilize stem cells and the receptors in the brain can induce neurogenesis and promote neuroplasticity. A study found that patients with AD compared to their healthy counter parts have significantly lower levels of G-CSF. The neuroprotection provided by normal levels of G-CSF is deficient in AD patients. Deficient levels of G-CSF reduce the hematopoietic brain support against progression of AD pathogenesis. In a coffee study from 2011, the levels of G-CSF post treatment and a control were measured. The study discovered the levels of G-CSF increased significantly post treatment with concentrated coffee and non-concentrated coffee. The study also observed the cognitive improvement in mice which was associated with the increase in G-CSF levels. This data shows the link between synergist effects of an unknown compound in coffee with caffeine to increase G-CSF levels, which ultimately provides the therapeutic benefits were discussed earlier.

## Summary

The therapeutic benefits of coffee consumption against AD are apparent from various recent research studies. From epidemiological studies on coffee consumption to scientific studies on transgenic mice model, the data shows an inverse relationship between coffee consumption and risk of AD. There are various hypothesis concerning the cause of AD and the most prominent one is the Amyloid hypothesis. Researches have proposed that coffee consumption provides therapeutic benefits against AD through antioxidative properties, immune modulation, and BACE-1 secretase enzyme inhibition. Further studies on interaction of caffeine with other coffee compounds can help identify the source of therapeutic benefits associated with coffee consumption.

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