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# Alzheimer's Disease: Analysis of Flavonoids with Mechanism Focusing Upon Targeting Aβ- Deposition and BDNF/Trkb Along with Other Signalling Pathway

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**ABSTRACT**:
Alzheimer's disease (AD) affects 60–70% of the global population and is one of the most common, severe, and progressive neurodegenerative illnesses in the elderly. Many signaling pathways are implicated in AD development, and while focusing on one pathway may reduce symptoms, it cannot offer a long-term solution. It has been discovered that using flavonoids to treat Alzheimer's disease is very beneficial. In addition, flavonoids have a variety of neuroprotective effects on the brain including defense of the brain against numerous neurotoxins and inhibition of the neuro-inflammatory process, as these actions will improve memory, learning, and other understandable. Plant parts such as berries, vegetables, roots, stems, flowers, and other sections include flavonoids, which are a group of naturally occurring chemicals with different phenolic structures. The flavonoid's mechanism of action in AD involved the inhibition of acetylcholinesterase, butyryl cholinesterase, Tau protein aggregation, β-secretase, oxidative stress, inflammation, and apoptosis through modulation of signaling pathways which are implicated in cognitive and neuroprotective functions, such as ERK, PI3-kinase/Akt, NFKB, MAPKs, and endogenous antioxidant enzymatic systems. Flavonoids communicate with different signalling pathways and adjust their activities, accordingly prompting valuable neuroprotective impacts. Flavonoids likewise hamper the movement of obsessive indications of neurodegenerative disorders by hindering neuronal apoptosis incited by neurotoxin substances. In this review, we briefly discussed about the classification of flavonoids and their neuroprotective properties that could be used as a potential source for the treatment of AD. We also highlight the structural features of flavonoids.

## Introduction

AD is one of the most prevalent neurodegenerative disorders that affect millions of people all over the world [1]. The social and economic burden of AD is high and the number of cases is rising dramatically and may reach to 88 million by 2050 [2]. During the onset and progression of AD, various neurological dysfunctions take place that ultimately leads to loss of memory and cognitive deficits that cause interference in daily life of the individuals [3]. Plenty of significant resources have been exhausted to date in its treatment, but the overall results are still disappointing and challenging. AD occurs due to disturbance of multiple pathways therefore, the multi-target approached through whole plant extract will be more promising among the possible therapies. Ongoing analyses have demonstrated that consumption of flavonoids-rich diet can actually improve mental health and cognitive ability in people [4-7]. The flavonoids-rich foods like cocoa, citrus, green tea, and berry can be ascribed to the

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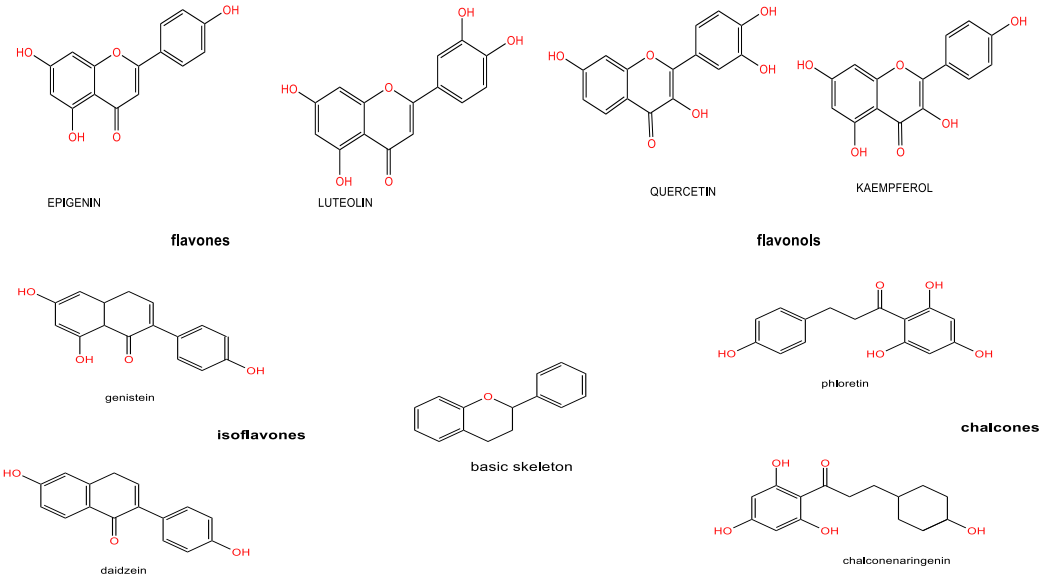
connections of flavonoids and their metabolites with various sub cellular targets [8-9]. Flavonoids overview a broad and varied range of organic chemicals produced by plants, the vast majority of which do not appear to be directly involved in growth and development. Historically, these compounds have been referred to as secondary metabolites specially flavonoids. During the last few years, a myriad of studies has ignited the attention of polyphenolic compounds in the treatment of AD because of their possible therapeutic applications [10]. Flavonoids belong to one of the diverse groups of plant polyphenols, and more than 10,000 flavonoids have been extracted to date from natural resources including wines, vegetables, restorative plants, and organic products [11]. Flavonoids have emerged as a promising leading molecule either alone or in association with other compounds for showing the effective plan and improvement as anti-alzheimer's disease drugs [12]. The flavonoids are having connection with a broad-spectrum well-being result and found to be an essential element in an area of pharmaceuticals, medicals, and various face-related demulcents. It takes place because of integrity with the capacity in modulating key cellular enzymatic functions with a combination of anti-oxidative, anti- inflammatory, anti-mutagenic, and anti-carcinogenic activities. Flavonoids have one more property as active inhibitors in a majority of enzymes xanthenes Oxidase, cyclooxygenase (COX), lipoxygenase (LOX), and phosphoinositide 3-kinase [13]. In combination with nature, these flavonoids are also found in food and liquid containing drinks such as tea, wine due to this, they are known as dietary flavonoids. They are divided into many sub-groups that are chalcones, flavones, flavonols, and isoflavones. In Alzheimer's disease (AD), its current therapeutic methods the uses of flavonoids in the form of plant secondary metabolites are used in the treatment of this disease with its mechanism involvement. Acute or chronic administration of flavonoids crosses through the blood-brain barrier suggesting that these compounds can feasibly have a direct effect on the brain and hence could be used as a prophylactic agent [14]. Furthermore, natural and synthetic flavonoids have gained substantial attention not only because of their antioxidative, anti-inflammatory, and anti-amyloidogenic properties [15]. But also because of multiple range of pharmacological effects that ameliorate learning and memory in the AD patients [16]. In this review, various ventures are made in discussing today's trends in areas of research for flavonoids, its use in the form of dietary forms, and its benefits on the health of individual comes with a broader classification and its future research directions.

**Classification of flavonoids.**

More than 10000 different flavonoids have been identified to dates which have enormous therapeutic potential. Despite having great diversity, the classification of flavonoids has restricted into six groups based on their molecular structure [17]. By seeing upon the Carbon of C ring on which B ring is attached and oxidation of C ring with degree of unsaturation, on these points the subdivision of Flavonoids into different sub-groups is done. The corresponding flavones are flavonols, flavanones, flavanonols, anthocyanins, and chalcones.



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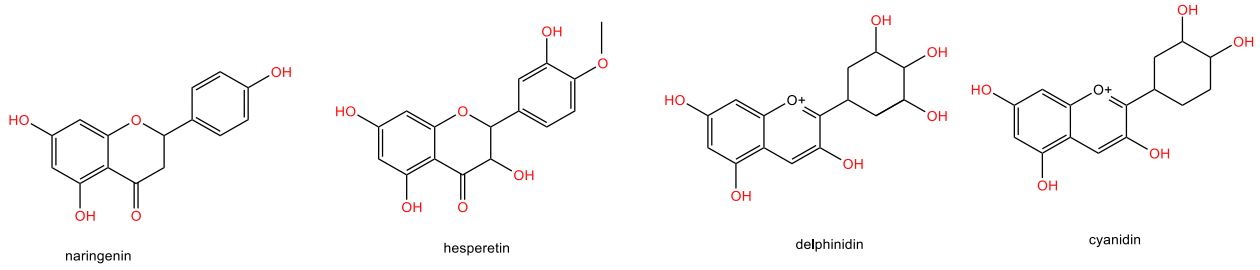


**Flavones**

They are major sub-groups of flavonoids. Majorly they are found in flowers, fruits, and leaves in the form of glucosides. The main sources are celery, parsley, chamomile, mint, etc. The subclass of these flavones is luteolin, apigenin, and tangeritin.

**Flavanols**

These are those flavonoids which contains a ketone group and as well as also essential components of proanthocyanins. They are found profusely in a number of fruits and vegetables. As majorly studied flavonols are kaempferol, quercetin, fistin. The prosperous origins and in certain sources like tea, red wine, vegetables also show some origins of flavonols. There are many health benefits associated with Flavanols, e.g., antioxidant potential and decreased risk of vascular diseases. These compounds have a high diversity in methylation and hydroxylation patterns. Due to this, they are one of the major common and largest sub-groups found in fruits as well as leafy vegetables.

**Isoflavonoids**

It is a large and very particular subgroup of flavonoids. There major contribution is found in the plant kingdom and mainly in soyabeans and leguminous plants. There are also present in microbes [18]. During plant microbe interaction they show a major role as precursor in the development of phytoalexins [19].

**Neoflavonoids**

It is a class of poly-phenolic compounds. The difference between flavonoids and neoflavonoids is backbone structure in one it is 2-phenylchromen4-one and other 4-phenylchromen with number hydroxyl group at position second substitution. The 1st neoflavone detected from environmental source in the year 1951 was calophyllolide from Calophylluminophyllum seeds.

**Flavanols, Flavon-3-Ols, or Catechins**

Flavanonols are 3-hydroxy derivatives of flavanones, frequently named as dihydroflavonols or catechins. They are multi-substituted and extremely diverse subclass due to this hydroxyl GP is always attached to post. 3 of the C-ring, flavanols are also known as flavan-3-ols. As well as there not any kind of double bond between positions second and third. Bananas, apples, blueberries, etc., contain more amounts of flavonols [20].

**Anthocyanins**

They are pigments that provide colour to plants, fruits, and flowers in nature. The highly studied anthocyanins are cyanidin, delphinidin, malvidin, pelargonidin, and peonidin. They are majorly seen in cell external layer of red grapes, raspberries, and many more. Their stability as well as its health benefits make it useful in a high majority of areas in the areas of food distribution [20]. The colour is affected by pH and methylation or acylation of the hydroxyl groups on the A and B rings.

**Chalcones**

Chalcones are a flavonoid subclass. The absence of ‘ring C’ of the basic flavonoid skeleton structure depicted in distinguishes them. Due to this nature, they come under open-chain flavonoids. Some of its examples are Phloridzin, arbutin, phloretin, and chalconaringenin. Tomatoes, pears some products of wheat all contain substantial levels of chalcones. Due to their multiple nutritional and biological benefits, chalcones, and their derivatives are known to gather major concern and attention. The simplest and safest strategy to prevent diseases and adjust activities may be to consume flavonoids through food sources.

**Hallmarks of Alzheimer’s Disease**

Positive lesions including amyloid plaques, neurofibrillary tangles, and cerebral amyloid angiopathy, as well as negative lesions such neuronal and synaptic loss, are the neuropathological hallmarks of AD [21].

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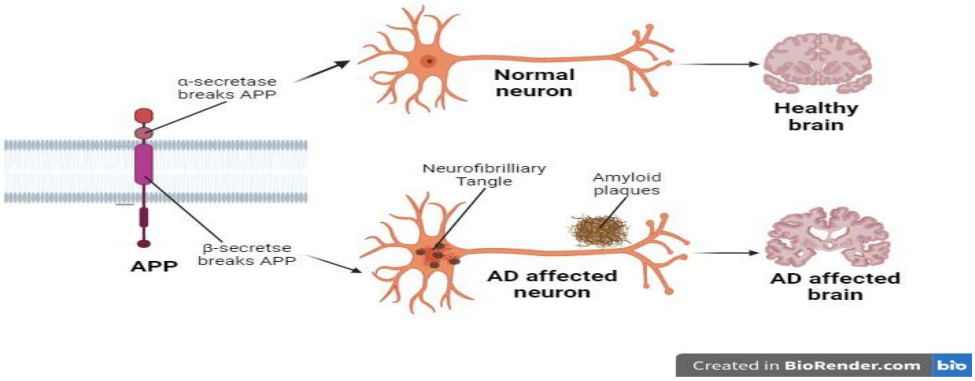


**Figure 1:** The following figure shows comparision between healthy and AD affected brain.

**Amyloid Plaques:**

The accumulation of amyloid plaques, sometimes referred to as senile plagues, is one of the main markers of AD pathogenesis. These plaques are primarily composed of Aβ [22]. Differentially, APP is cleaved while ill. BACE-1, an a spartyl protease that crosses membranes and has its active site in the lumen, and γ-secretase, an intramembrane protease made up of four complex proteins presenilin, nicastrin, anterior pharynx-defective 1 (Aph1), and Psen2—cleave Aβ from APP in a series of consecutive cleavages [23]. This combination helps γ-secretase produce neurotoxic and insoluble Aβ fragments. The initial and most crucial stage is the cleavage of β-secretase, leading to a cut at the N-terminus of Aβ. Only the C-terminal of APP remains after the extracellular portion of the protein is largely eliminated [24]. After then, Aβ cleaves again at its C-terminus to produce Aβ oligomers, which polymerize to create aggregated plaques. The two main subtypes of Aβ polymers that cause neurotoxicity and directly contribute to the development of plaque are Aβ40 and Aβ42. Aβ40 is more common and less neurotoxic than Aβ42, which serves as a toxic building block of Aβ assembly and is extremely insoluble, severely neurotoxic, and more aggregation-prone. The aggregation of Aβ40/Aβ42 results in ion channel obstruction, disturbed calcium homeostasis, elevated oxidative stress within the mitochondria, and compromised glucose regulation and energy metabolism. These events deteriorate the health of neurons and ultimately cause the death of neurons.

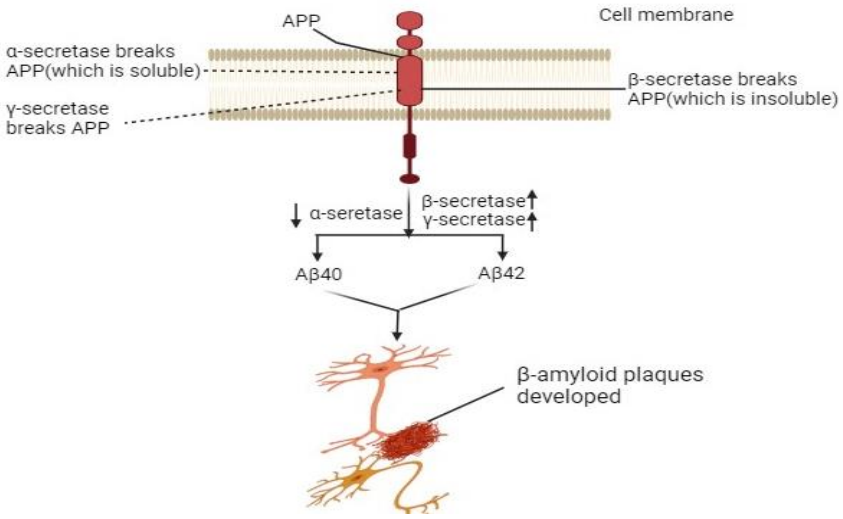


**Figure 2:** Amyloid Plaques as a Hallmark of Alzheimer's disease.

**Neurofibrillary Tangles**:

NFTs are considered to be yet another important pathogenic sign of AD. The microtubule-associated τ protein undergoes hyperphosphorylation, which causes these tangles [25]. The quantity of Aβ in the environment causes the kinase to be released, which

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causes the τ protein to become hyperphosphorylated when it comes into touch with them. Due to its hyperphosphorylation, it becomes oligomerized. The dissociation of tubule subunits causes the tubule to become unstable. These subunits break apart and transform into large τ filament pieces, which then further aggregate into NFTs. These NFTs, which are straight, fibrillary, and extremely insoluble patches in the cytoplasm and processes of neurons, cause aberrant loss of neuron-to-neuron connection, incorrect signal processing, and ultimately, neuronal apoptosis [26]. It has been reported that soluble Aβ regulates the phosphorylation and cleavage of τ to generate NFT [27].

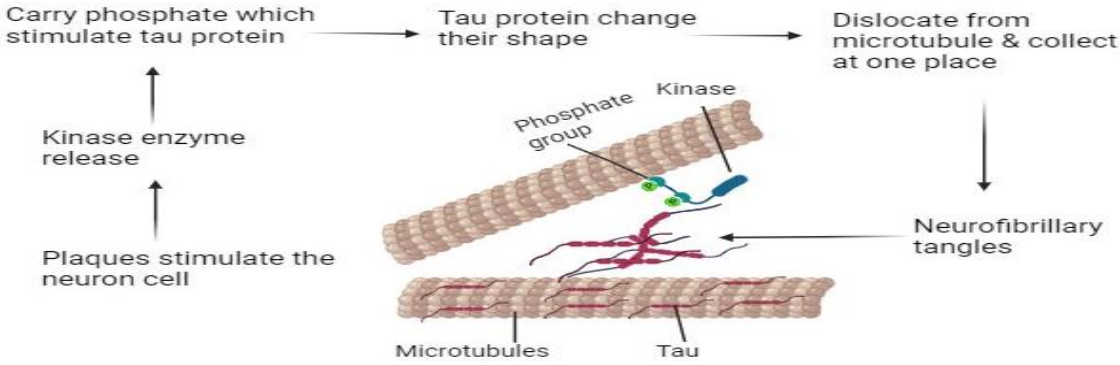


**Figure 3:** Neurofibrillary Tangles as a Hallmark of Alzheimer's disease

**Cerebral Amyloid Angiopathy (CAA):**

Although CAA is known to be one of the morphologic characteristics of AD, it has also been observed in the neurologically healthy brains of elderly patients [28]. Not only does the amyloid-b peptide accumulate in the brain parenchyma as amyloid plaques, but it can also cause cerebral amyloid angiopathy (CAA) by depositing in the artery walls. The more soluble Ab40 peptide is the primary component of CAA, mostly collecting in the interstitium between the smooth muscle cells of the tunica media, whereas the more insoluble and aggregation-prone Ab42 peptide tends to accumulate in the core of senile plaques. Even while pure CAA is rare, it is more frequent in the setting of AD, with 80% of AD patients exhibiting some degree of CAA at autopsy (typically moderate).

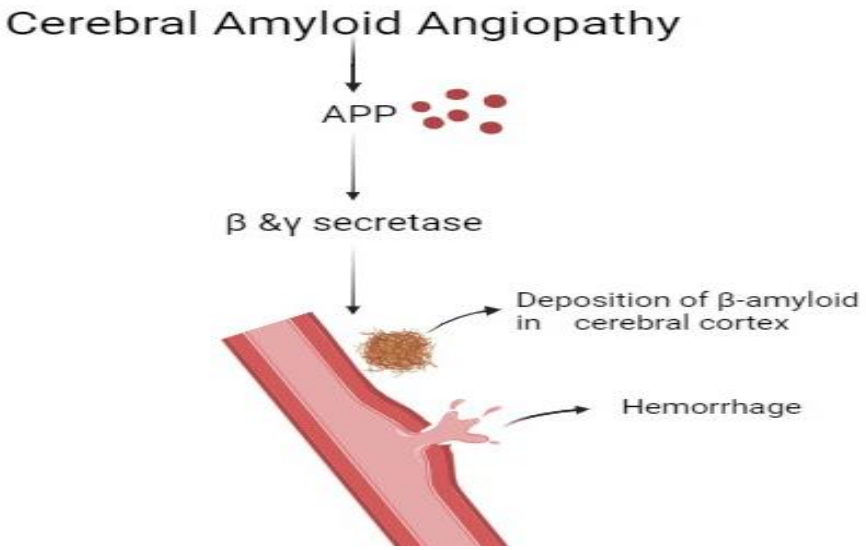


**Figure 4:** Cerebral Amyloid Angiopathy (CAA) as a Hallmark of Alzheimer's disease.

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**Inhibiting AD Pathology with Flavonoids: Mechanisms of Action**

Unfortunately, we are unable to incorporate all of the numerous research that describe the protective effects of different polyphenols against insults relevant to Alzheimer's disease after they are administered to cell lines. Similarly, a number of studies demonstrate the ability of flavonoids to function as acetylcholinesterase (Ache) inhibitors; however, since Ache inhibitors are symptomatic treatments rather than prophylactic or disease-modifying agents, they will not be covered in this context [29]. Examining flavonoids in AD-prone mice has been a significant breakthrough in the past ten years. Although the precise binding partners of the majority of flavonoids remain unknown, common molecular processes that affect neuroinflammation, oxidative stress, and ontogenesis associated with Aβ and tau pathology have been identified.

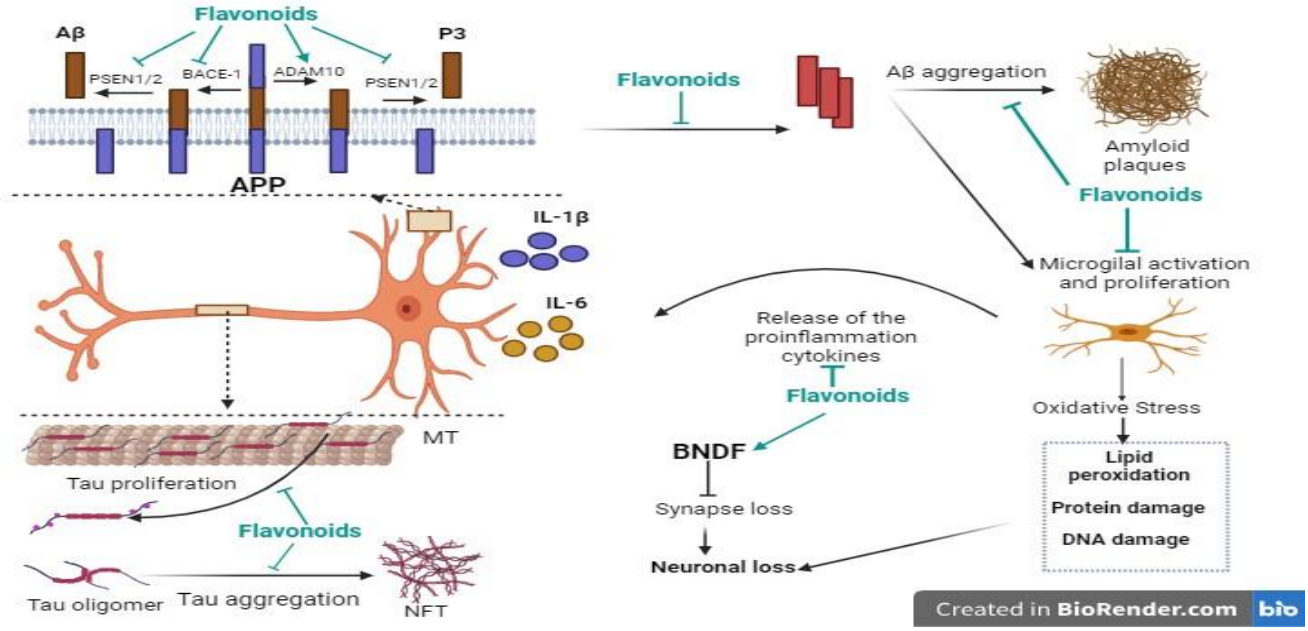


**Figure 5:** Mechanism of Action: Inhibiting Alzheimer's disease Pathology with Flavonoids

**Flavonoid inhibition of APP processing and Aβ deposition**

Numerous flavonoids have demonstrated the ability to improve Aβ pathogenesis. Increased Aβ degradation, prevention of aggregation, and a shift towards the non-amyloidogenic processing route could all contribute to this impact. There is a net decrease in Aβ-42 as a result. The well-researched catechin epigallocatechin gallate (EGCG), which is prevalent in tea, is a well-known illustration of how flavonoids hinder the processing of APP. It was discovered that EGCG increased the amount of proteolytically active mADAM10 via at least two pathways: activation of the pro-ADAM10 cleavage enzyme furin through a PI3K-independent mechanism and activation of the PI3K/Akt pathway through oestrogen receptor α (ERα)-mediated activation [30]. In vivo studies using a variety of AD mice models have validated the observation that EGCG causes APP processing to shift towards the non-amyloidogenic pathway [31,32–35]. It was found that administering EGCG orally reduced the levels of both soluble and insoluble Aβ by up regulating β-secretase activity and down regulating β- and ϒ-secretase activity. By promoting the breakdown of Aβ, flavonoids may also have the effect of lowering Aβ levels in the brain. Aβ-degrading zinc-metalloprotease called neprilysin (NEP) is reduced in AD brain regions that are impacted [36]. Exogenous A is degraded as a result of EGCG (1-3 g/ml) increasing astrocytes' NEP release in an Akt/PI3K-dependent manner [37]. Thus, NEP expression was up regulated and Aβ level was lowered in SAMP8 mice, a senescence model of AD, following intragastric delivery of EGCG [38]. Comparably, oral delivery of EGCG and other green tea catechins to a transgenic human APP over expression mice resulted in elevated NEP levels, reduced Aβ, and enhanced spatial learning. Thus, EGCG can both prevent Aβ formation and encourage its breakdown.

**Flavonoid inhibition of tau phosphorylation and aggregation**

Physiologically, tau is a microtubule-associated protein that interacts mostly to microtubules in axons [39,40]. As a result of hyperphosphorylation [41,42] tau separates from the microtubule in AD. The hyperphosphorylated tau state in AD is believed to be

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caused by a number of kinase, including proline directed kinase such as GSK-3β [43, 44], CDK5 [45, 46], and MAPK family members [47]. The possibility exists for flavonoids to influence tau phosphorylation and, in turn, the development of tau disease, given their documented involvement in MAPK and other protein kinase signalling pathways. JNK has been linked to tau phosphorylation in a number of studies [48, 49]. In vitro studies have demonstrated the inhibition of JNK activity by a number of flavonoids [50–52], albeit usually not at levels observed in vivo. In spite of this, there is proof that the treatment of oral or intragastric flavonoids can decrease JNK activity based on animal models of AD [53–55]. It has also been suggested that the MAPK member p38 kinase directly and indirectly contributes to tau hyperphosphorylation [56]. Therefore, in a tau transgenic mouse model, elevated levels of p38 kinase and CDK5 were discovered to correlate with tau hyperphosphorylation [57]. Moreover, NFTs were linked to p38 kinase and JNK in AD brains [58] as well as in a patient with P301L-associated FTDP-17 [59]. Furthermore, as will be covered in more detail later, a number of lines of evidence imply that tau is phosphorylated in a p38 kinase-dependent manner as a result of neuroinflammation [60,61–63]. There have been few attempts to directly link the two pathways, nevertheless, despite evidence supporting both flavonoid modulation of p38 kinase activity in a range of systems [64] and flavonoid interactions with p38 kinase [65,66,67]. For instance, proanthocyanidins administered orally via gavage decreased lead-induced tau phosphorylation, which was linked with JNK and activated p38 kinase levels, albeit no direct correlation was observed [68]. The few research looking to directly correlate tau phosphorylation with flavonoid therapy have produced encouraging findings. It has been demonstrated that oral administration of grape seed polyphenolic extract (GSPE), which has high concentrations of proanthocyanidins, specifically catechin and (–)-EC oligomers, inhibits tau phosphorylation at a number of critical sites, including Thr212/Ser214 (AT100) [69], Ser202/Ser205 (AT8), Ser396/Ser404 (PHF-1), and Thr181 [70]. In addition, after GSPE therapy, there are significant reductions in the amount of Sarcosyl-insoluble tau, which may indicate a reduction in aggregation [71]. As a result, a number of flavonoids have the ability to lower tau phosphorylation, either by modulating MAPKs that can phosphorylate tau directly or by inhibiting GSK-3β through activation of the PI3K/Akt pathway. Consequently, flavonoids may disrupt tau pathogenic phosphorylation as well as the development of tau oligomers and NFTs.

**Flavonoids modulation of neuro-inflammatory response in AD**

It has long been debated how neuroinflammation affects the onset and course of AD. Oral administration of flavonoids has been found to reduce neuroinflammatory markers in numerous animal models of AD. Furthermore, a number of flavonoids have been found to prevent IL-1β release and microglial activation. In primary microglia and BV2 cells, the isoflavone genistein decreased mRNA levels of IL-1β and TNF-α via a G-protein coupled oestrogen receptor (GPER)-dependent mechanism [72]. Prior administration of the flavanone pinocembrin prevented the activation of BV2 cells caused by LPS and the ensuing production of pro-inflammatory mediators, such as IL-1β [73]. Procyanidins were administered intragastrically in vivo to decrease morphine-induced activation of NLRP3 and IL-1β, most likely by inhibiting p38 kinase [74]. Several pro-inflammatory cytokines have also been proposed to be involved in AD, in addition to IL-1β. AD has also been linked to tumour necrosis factor-α (TNF-α), which flavonoids can reduce [75,76,77]. Though only in stably transfected HEK293 cells, it was discovered that TNF-α and, to a lesser extent, IL-1β, may upregulate ϒ-secretase cleavage of APP through a JNK-dependent route [78]. Additionally, primary rat hippocampus neurons exposed to baicalin eriodictyol have down-regulated levels of IL-6, which subsequently causes AD-like phosphorylation of tau. It was discovered that the phosphorylation resulted from p38 kinase activation, which raised the expression of the CDK5 activator p35. Thus, it's feasible that tau phosphorylation will decrease in AD mice models when flavonoid-induced IL-6 down regulation occurs. Determining whether flavonoid-mediated reduction of the microglial responses correlates with lower tau pathology would be of interest given the mounting data connecting pro-inflammatory cytokine release, microglial activation, and tau phosphorylation.

**Flavonoid modulation of antioxidant responses in AD**

The antioxidant potential of flavonoids is well recognised [79], since oxidative stress has been linked to neurodegeneration [80], this property may be beneficial in AD. According to reports, brain-iron imbalances have been linked to AD [81,82] and may play a role in cognitive decline [83]. This lends credence to the theory that oxidative stress fosters AD pathogenesis. It is highly probable that the inhibition of oxidative stress by flavonoids occurs via the alteration of intracellular pathways like the MAPK pathway. Via the phosphorylation or activation of transcription factors, the MAPK pathway translates changes in the cellular environment, such as oxidative stress, into

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physiological responses. Flavonoids provide neuroprotection against various stressors, such as oxidative stress, by activating anti-apoptotic ERK1/2 and PI3K/AKT pathways and down regulating pro-apoptotic JNK pathways at both high and physiological doses [84-87]. The MAPK pathway transforms alterations in the cellular environment, such as oxidative stress, into physiological responses through the phosphorylation or activation of transcription factors. At both high and physiological concentrations, flavonoids provide neuroprotection against a variety of stressors, including oxidative stress, by up regulating pro-apoptotic JNK pathways and activating anti-apoptotic ERK1/2 and PI3K/AKT pathways [88-92]. Moreover, it has been demonstrated that normal concentrations of (–)-EC enhance ARE activity in astrocytes in a PI3-K dependent manner [93], thereby shielding neurons from oxidative stress [94]. It has also been discovered that quercetin and EGCG enhance Nrf2 signalling in primary neurons; however, the effects at physiologically relevant doses were not studied, and the degree of Nrf2 expression in mature neurons is unknown.

**Flavonoids promote BDNF induced neurogenesis in AD**

Through binding to its receptor TrkB, brain-derived neurotrophic factor (BDNF) is known to have a significant role in neuronal development, differentiation, and synaptic plasticity. It is also known that the brains of AD patients have lower levels of BDNF than those of healthy controls [95–97]. There is proof that flavonoids can enhance downstream effects associated with BDNF/TrkB signalling. The cAMP response element binding protein (CREB) is activated by physiological concentrations of (–)-EC (100 nM), which up regulates the levels of BDNF in primary cortical neurons [98]. It has been demonstrated that oral treatment of quercetin and (–)-EC to many mouse models of AD increases the expression levels of BDNF [99, 100–102]. Furthermore, it has been demonstrated that oral administration of the TrkB agonist 7,8-dihydroxyflavone (7,8-DHF) increases long term potentiation (LTP), decreases synaptic loss, and enhances performance in the Morris water maze (MWM) in vivo [103, 104]. There have been demonstrated increases in neural progenitor cells (NPCs) and neural stem cells (NSC) linked to neuro-genesis in addition to the elevated BDNF levels observed with quercetin administration. Moreover, it has been shown that oral delivery of the TrkB agonist 7,8-dihydroxyflavone (7,8-DHF) improves performance in the Morris water maze (MWM) in vivo, reduces synaptic loss, and boosts long term potentiation (LTP) [103,104]. In addition to the increased BDNF levels shown with quercetin administration, elevations in neural progenitor cells (NPCs) and neural stem cells (NSC) associated with neuro-genesis have been demonstrated.

**Future outlooks**

Flavonoids have drawn a lot of attention in the past 10 years, and their numerous health benefits against a wide range of neurodegenerative illnesses have been clarified. More investigation is required to find novel flavonoids found in nature's abundance so that they can take the place of synthetic medications, which are bad for the body.

Natural products have been shown to have therapeutic value in Alzheimer's disease because to their diverse modulator neuropharmacological capabilities. To support the clinical effectiveness of flavonoids in the signs and symptoms of neurodegeneration, particularly well-designed clinical trials are necessary. Finding out how much flavonoids are absorbed and whether they enhance human health singly or in concert is another problem that has to be solved in the field of flavonoid research.

**Conclusion**

Natural ingredients varied modulator neuropharmacological capacities have demonstrated their therapeutic potential in Alzheimer's disease. In particular, well-designed clinical trials are required to demonstrate the clinical usefulness of flavonoids in the signs and symptoms of neurodegeneration. In the field of flavonoid research, another challenge is determining the extent of absorption and if flavonoids improve human health separately or in combination. Flavonoids regulate a number of significant physiological responses, which may contribute to their neuroprotective benefits in AD, albeit the exact mechanisms underlying these actions are yet unknown. These substances are found in a wide variety of herbal plants because of their ability to shield the brain against numerous neuronal damage. Furthermore, they have the capacity to lessen both the potential and the inflammation of neurons in supporting the processes of learning, thinking, and recalling. Consequently, flavonoids belong to the strong genera that are a significant ancestral molecule for the development of advanced generation medicinal compounds with actions that increase the brain. The ability to provide flavonoids as dietary supplements gives them an advantage over traditional targeting medications. Because of their minimal toxicity, they can also be employed without requiring a preclinical diagnosis. Undoubtedly, more long-term dietary intervention research defining the dosage and the timing of medication intake may help to thoroughly assess the efficacy of flavonoid medicines for the treatment of AD.

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**Conflict of interests**

No conflict.

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