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Genetics, Pathophysiology, Various Targets and Role of Flavonoids for the Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is a neurodegenerative disorder caused by the progressive, recurrent, and irreversible loss of neuronal cells from certain areas of the brain. Alzheimer's disease happens through either genetic, cellular, or multifactor pathophysiological mechanisms. There are three genes have been identified in inherited autosomal dominant cases of AD. Amyloid precursor protein (APP), Presenilin 1 (PS-1), and Presenilin 2 (PS-2) geared nes located on chromosomes- 21, 14 and 1 respectively. Flavonoid contents have differential efficacy against age-related toxic pathways within neurodegenerative disorders. Flavonoids are right health-promoting products and serve as a vital constituent in a wide variety of nutraceuticals, pharmaceuticals and therapeutic. The mechanisms of flavonoids are mediated through the inhibition of cholinesterase including acetylcholinesterase (AChE), butyrylcholinesterase (BChE), β-secretase (BACE1), free radicals and modulation of signalling pathways, that are implicated in cognitive and neuroprotective functions. Flavonoids interact with various signalling protein pathways like ERK and PI3-kinase/Akt and modulate their actions, thereby leading to beneficial neuroprotective effects. Moreover, they enhance vascular blood flow and instigate neurogenesis, particularly in the hippocampus. This literature reviewed the flavonoids evaluated in various possible mechanisms with multiple targets with significant effects.

INTRODUCTION

AD was first described in 1901 by the German psychiatrist and neuropathologist Alois Alzheimer. Dr Alois Alzheimer identified amyloid plaques and NFTs in the autopsied brains of a 55-year-old woman with progressive dementia. Amyloid plaques are extracellular deposits of Aβ in the brain parenchyma and in the cerebral blood vessels where it's known as congophilic angiopathy also known as cerebral amyloid angiopathy (CAA). NFT is composed largely of paired helical filaments with hyperphosphorylated tau proteins and neuronal and synaptic loss (Kumar *et al.*, 2014) [50].

AD is a progressive neurodegenerative disorder characterized by initial memory impairment and cognitive decline that can ultimately affect behaviour, speech, visuospatial orientation, and motor system and it is the most common form of dementia (DeTure and Dickson 2019) [22]. Dementia is an acquired deterioration of cognitive function that impairs one's ability to successfully perform daily living activities. It is characterized by memory loss and increasing age is the most important risk factor (Umar J T *et al*., 2011) [90].

Genetics of AD:

There are three genes have been identified in inherited autosomal dominant cases of AD. On chromosomes 21, 14, and 1, respectively, the genes for the amyloid precursor protein (APP), presenilin 1 (PS-1), and presenilin 2 (PS-2) are found (L H Honig and R Mayeux 2001) [40].

APP GENE:

Glenner and Wong cloned the Aβ sequence in 1987 and mapped it to chromosome 21. The cloning of this gene revealed that the Aβ peptide produced a larger precursor protein called β amyloid precursor protein or APP (Alonso Vilatela *et al.*, 2012) [107]. B-APP present on chromosome 21 in the region of 21q11.2-q213. The APP gene undergoes two independent proteolytic pathways: the non-amyloidogenic pathway is controlled by α- secretase. This enzyme cleaves β APP within the Aβ peptide sequences and releases amino terminals of β-APP. The amyloidogenic pathway combines the sequential action of β and γ secretase generating Aβ peptides of 40 to 43 amino acids at intracellular sites such as the Golgi apparatus and endoplasmic reticulum. The cleavage of the β-site of APP by β secretase generates a C-terminal C99 peptide and γ-secretase generates amyloid fragments Aβ (Aβ-40 OR Aβ-42). These fragments misfold and form extracellular fibrils. The most common form of Aβ in humans is Aβ 40-42 amino acids. Aβ 42 is less abundant than Aβ 40 (Alonso

Vilatela *et al*., 2012, Tomiyama *et al*., 2008; Iwatsubo *et al.*, 1995; Tandon A *et al.*, 2000) [46, 102, 104,107].

PSEN1 GENE (PRESENILIN 1)

Mutation in the PSEN1 gene is the most common cause of AD. PSEN1 is located on chromosome 14q 24.2. This gene consists of 12 exons that encode 467 amino acid proteins with 50kda. PSEN1 is a polytrophic membrane protein that forms a catalytic core on the γ secretase complex. γ secretase is found at the cell surface, Golgi apparatus, endoplasmic 21SS2121reticulum, and mitochondria. Mutations in PSEN1 cause the most severe form of AD, occurring in the early stages such as 30 years > 58 years. In the PSEN1 gene, more than 180 mutations have been reported (Strooper et al 1998; Baulac *et al.*, 2003; Kimberly *et al*., 2003; Murrell J *et al*., 1991) [9, 16, 21, 53].

Mutation in the PSEN 2 gene rarely causes AD. It contains 12 exons and encoded 448 amino acid proteins. It is a component of γ secretase and it is responsible for Aβ. PSEN-2 increases Aβ generation in the AD protein brain. Mutant PSEN 2 increases β secretase activity through reactive oxygen species-dependent activation (Levy-Lahad *et al.*, 1995; Rogaev *et al.*, 1995; Cruts *et al.*, 1998; Binetti *et al.*, 2003; Park *et al* 2014) [11, 19, 65, 83, 89].

Pathophysiology of AD

Cholinergic hypothesis:

The activity of choline acetyltransferase in the amygdala, hippocampus, and cortex was reduced, in which the concentration of acetylcholine was decreased in synaptic regions of the brain (Liu *et al.*, 2019) [67]. Acetylcholine esterase inhibitors prevent the degradation of acetylcholine in AD patients. The efficacy of acetylcholine inhibitors for treating the cognitive symptoms of dementia, acetylcholine esterase inhibitors possess modest effects on dementia but the effect is not continuous (Francis *et al.*, 1999; Fotiou *et al.*, 2015; Vieira *et al*., 2016) [31, 32. 39].

Amyloid hypothesis:

John Hard and David Allsop found a pathogenic mutation in the Aβ precursor protein (APP) gene on chromosome 21. Mis-metabolism of APP protein and Aβ deposition are the primary events in AD. APP consists of 695 amino acids and a glycosylated receptor located on the cell surface Aβ composed of 39-43 amino acids derived from multiple proteolytic cleavages

of APP. It is cleaved in two ways: the first method is: APP hydrolyzed by α-secretase followed by γ- secretase, this pathway does not produce insoluble Aβ. The second pathway is through β-secretase. APP hydrolyzed by β secretase (BACE-1) and then γ secretase to produce insoluble Aβ (Kang *et al.*, 1987; St George- Hyslop, 1987; Mullan M, 1992; Karran *et al.*, 2011) [42, 50, 75, 100].

In normal conditions Aβ produced by α- the secretase pathway and a small amount of insoluble Aβ produced by β secretase pathway. But the insoluble Aβ eliminated by the immune system some metabolism such as Lys 670, Asn/Met 671, Leu, and Ala 673 near the BACE-1 cleavage site, APP prone to hydrolysis by β secretase pathway resulting in excessive accumulation of insoluble Aβ and it causes AD (Goedert *et al.*, 2009; Lee *et al.*, 1988; Andreadis A *et al.*, 1992) [3, 33, 60].

Tau propagation hypothesis:

Tau proteins are a group of soluble protein isoforms produced by alternative splicing from the gene MAPT. They help for the stability of microtubules in axons. Intracellular tau contains NFT are composed of hyperphosphorylated tau proteins (Adams *et al.*, 2010) [1]. Tau proteins are phosphorylated at 3 different positions, threonine, serine, and proline. The phosphorylated amino acid residues attach to microtubules and hyperphosphorylation of proteins occurs at T231, S235, and S 265 (Rapoport *et al.*, 2002; Lefebvre T; 2003; Gong C X *et al.*, 2005) [34, 63, 85]. These proteins lose their ability to attach to microtubules and form NFT. NFTs are formed by aggregation of hyperphosphorylated tau threads that disintegrate the nerve cells. Microtubules inhibit the transmission within and between neurons (Buea *et al.*, 2000; Merrick S E *et al.*, 1997; Wittmann C W *et al.*, 2001) [12, 48, 72].

Glutamate and Calcium Homeostasis:

Glutamate is a neurotransmitter that stimulates the brain's activity. An excessive amount of glutamate cause excitotoxicity and leads to cell death. Memantine is a non-competitive NMDA receptor antagonist and regulates glutamate over-secretion. It also blocks the $5HT_3$ receptor and nicotinic acetylcholine receptor. Inhibition of the NMDA receptor reduces the inhibition of α-secretase and the production of Aβ (Johnson J W and Kotermanski S E, 2006; Guo S and Lo E H, 2010) [37, 74].

Calcium homeostasis was proposed by Mattson *et al.*, in 1992. According to the calcium homeostasis hypothesis; Aβ can increases the intracellular Ca^{2+} levels and the neurons

become more vulnerable to environmental stimuli (Norris C M; 2005) [38]. In AD patients inflammatory processes in astrocytes are triggered by calcineurin. Aβ mediated cognitive decline and alteration of T-cell signalling are more common in AD patients (Demuro A *et al.*, 2010; Berridge M J, 2013) [10, 20].

Inflammatory hypothesis:

Inflammatory responses of microglia and astrocytes play an important role in the development of AD (Bagyinszky E *et al.*, 2017; Latta C H *et al.*, 2015) [6, 57]. Microglial cells are brain-specific macrophages and they exhibit higher activity in AD patients (McGeer *et al.*, 1988) [70]. Aβ binds to microglia cells through CD 36-TLR 4- TLR 6 receptors and releases inflammatory factors like TNF-α, IL-1β, TGF-1, IL-12, and IL-18. CD-22 is a β cell receptor that negatively regulates phagocytosis (McGeer E G and McGeer P L, 2010; Michaud M *et al.*, 2013) [69, 73].

Metal ion hypothesis:

Disease results from any metal ion's dyshomeostasis in the body. Free metal ions are tightly controlled and kept at very low levels in healthy brains. Aβ aggregation and toxicity are caused by biometals. Zinc and copper are directly coordinated by Aβ and ions can reach a high concentration in plaques (Duce and Bush, 2010; Spinello, A *et al.*, 2016; Roberts, B. R. *et al.*, 2012) [88, 96, 99].

Recently, studies showed considerable efforts in searching for antioxidant plant-derived polyphenol compounds with neuroprotective potential for treating neurodegenerative diseases. Dietary flavonoids have been suggested to prevent and treat neurodegenerative diseases (Grosso *et al.*, 2013) [36].

`Role of flavonoids for AD

Flavonoids are natural products; they belong primarily to secondary metabolites of plants through a phenolic compound, commonly present in medicinal plants, green leaves, and fruits. In addition to being strong antioxidants, free radical scavengers, and metal chelators, secondary metabolites also have anticholinesterase, anti-ageing, neuroprotective, anti-inflammatory, and neurotrophic properties. They also improve learning and memory, have strong antidepressant and anti-amyloidogenic effects, suppress microglia activation, and mediate inflammatory processes in the central nervous system (CNS). (Khoo HE *et al.*, 2017;

Lee YK *et al.*, 2009) [52, 62]. Additionally, flavonoids can pass across the blood-brain barrier after chronic or acute administration, indicating that they may directly impact the brain. As a result, these chemical compounds may be employed as a preventative measure to slow the onset of disorders like AD. Flavonoid compounds are also responsible for inhibiting numerous cellular enzymes, such as phosphoinositide-3-kinase, xanthine oxidase, Cycloxygenase, and lipoxygenase (Iio M *et al.*, 1985, Walker EH *et al.*, 2019) [43, 109].

Multi-targeting natural compounds based on pure pharmacological moieties that are less dangerous and seem to have promising cognitive enhancing characteristics are among the potential treatments. (Baptista *et al.*, 2014; Khan *et al.*, 2018) [8, 51]. Epicatechin-3-gallate, gossypetin, quercetin, and myricetin are examples of flavonoids that have been demonstrated to reduce the aggregation of tau and -amyloid, scavenge free radicals, sequester metal ions, and have also been shown to inhibit MAO and AChE enzymes at clinically low quantities (Zhang *et al.*, 2006; Khan *et al.*, 2009; Jayasena *et al.*, 2013) [47, 110, 112]. Therefore, flavonoids represent a promising lead class of chemicals for efficiently designing and developing multi-potent anti-AD therapies.

Our work is a comprehensive evaluation of pharmacological findings regarding the use of flavonoids on neurodegenerative illnesses, specifically for Alzheimer's disease (AD). Neurodegenerative diseases represent some of the greatest challenges for basic science and clinical medicine.

Chemistry

The term 'flavonoid' is implemented to molecules structurally propyl benzene derivatives with C15, and C16 skeleton molecules. In plants, the byproducts of secondary metabolites are rich in polyphenols, which are flavonoids. Flavonoids' fundamental chemical structure consists of two benzene rings (A and C) connected by a pyran ring B. One of the benzene rings (A) and the pyran ring are fused, while the other benzene ring (C) is attached to the pyran ring as a substituent. Different patterns of benzene ring substitution, as well as patterns of pyran ring substitution, oxidation, and saturation, can be used to synthesize numerous derivatives of flavonoids that have distinct physicochemical properties and biological functions suitable for the effective treatment of neurodegenerative diseases (Ayaz M *et al.*, 2019) [4].

PATHOLOGICAL ASPECTS AND TARGETS OF AD

Flavonoids as Cholinesterase Inhibitors

Cholinesterase like AChE and BChE62 degrade acetylcholine (ACh), which is necessary for impulse propagation across many synapses. (Voet 1995) [108]. Cholinesterase inhibitors are a helpful therapeutic approach to maintain the concentration of neurotransmitters for a long time at the synapse because ACh is scarce in AD (Bachman *et al.*, 1992) [5]. Results for the already available pharmaceuticals demonstrate that this approach is the most beneficial target in the treatment of AD symptoms, simplifying the final clinical approval of four treatments (Atta-Ur-Rahman *et al.*, 2004) [77]. This approach is also successfully employed in the management of Parkinson's disease, ataxia, and dementia (Ahmad *et al.*, 2003) [2]. There is an urgent need to create more safe and more efficient medications due to the side effects and limited efficacy of the ones that are currently on the market (Schneider, 2001) [91]. Several flavonoids, including genistein, kaempferol, apigenin, naringin, quercetin, diosmin, and silibinin, were examined for their capacity to inhibit cholinesterases (AChE, BChE). Quercetin was discovered to be the most active of these flavonoids and showed a 76.2% suppression of AChE. Other substances, such as genistein, luteolin, and silibinin, inhibited BChE by 65.7, 54.9, and 51.4%, respectively (Orhan *et al.*, 2007) [27]. In a published report, Uriarte-Pueyo and Calvo (2011) summarized 128 flavonoids concerning their AchE inhibitory potentials [105]. They were regarded as prospective therapeutic agents in the development of novel anti-Alzheimer medicines due to their efficacy as cholinesterase inhibitors.

Flavonoids as Tau Modifying Agents

Several reported studies describe the effects of flavonoids in the formation of highly phosphorylated tau proteins, a pathological hallmark of AD (Calcul *et al.*, 2012; Baptista *et al.*, 2014) [8, 15]. For instance, myricetin and epicatechin-5-gallate have been reported to avert heparin-mediated tau formation (Taniguchi *et al.*, 2005) [103]. Epicatechin-5-gallate has been demonstrated to alter tau profiles in transgenic animal models of AD by preventing the production of sarkosyl-soluble phosphorylated tau isoforms (Rezai-Zadeh *et al.*, 2008) [86]. Through the prevention of tau peptide aggregations, its instability, and eventual clearance, tau neuropathology was greatly decreased in animal models of AD in previous investigations utilizing grape seed proanthocyanidin extract (GSPE) (Pasinetti *et al.*, 2010) [79]. The accumulation of NFTs as a result of tau protein hyperphosphorylation is a primary cause of

cognitive dysfunctions. Many kinases, including GSK-3, are known to phosphorylate tau protein and are associated with the pathophysiology of AD. Flavonoids help to prevent AD by preventing the actions of numerous kinases. Indirubins, for example, prevent certain protein kinases, such as CDK5/p25 and GSK-3, from acting both of which are allegedly responsible for the aberrant phosphorylation of tau proteins seen in AD patients (Leclerc *et al.*, 2001) [58]. Morin, a different flavonoid, is said to inhibit GSK-3β activity and block GSK-3β-mediated protein phosphorylation in tau. Morin also diminishes A*β*-mediated phosphorylation of tau proteins and protects against A*β* induced cytotoxicity in human neuroblastoma cells. Furthermore, morin therapy has been shown to reduce tau hyperphosphorylation in the hippocampal neurons of transgenic animals (3xTg-AD mice; Gong *et al.*, 2011) [35]. Cyanidin 3-O-glucoside (Cy3G) has also afforded significant protection against cognitive dysfunctions induced by the administration of A*β* in animal models which is mediated by modulation of GSK-3*β*/tau (Qin *et al.*, 2013) [84].

Flavonoids as Free Radicals Scavengers

Aerobic respiration produces free radicals, which the body's varied system fights against with antioxidants. Free radicals that are produced in excess cause oxidative stress, which disrupts the processes of various proteins, lipids, and other vital components of the organism. Free radicals are involved in the inflammatory harm to neurons and the development of numerous diseases, in addition to their participation in those processes. The higher amount of oxidative stress indicators reveals that oxidative stress is a crucial component of AD (Lovell and Markesbery, 2007) [68]. Low antioxidant concentrations and antioxidant activity have also been seen in the plasma of AD patients (Mecocci *et al.*, 2002; Rinaldi *et al.*, 2003) [87. 71]. Also observed were transgenic animal models of AD with elevated lipid and protein oxidation byproducts. High amounts of AD pathogenic indicators, such as A and neurofibrillary tangles (NFTs), were found in animals with oxidative stress, which may suggest that free radicals are one of the causes of AD. The mitochondria create the majority of ROS (Kowaltowski *et al.*, 2009; Dumont and Beal, 2011) [25, 54]. A lack of cytochrome c oxidase in AD patients causes mitochondrial malfunction and an excessive amount of ROS to be produced. Aβ is also considered a mitochondrial poison and is known to initiate the excessive release of free radicals in the presence of metal ions (Butterfield *et al.*, 2007) [14]. In this context, it is known that the use of ions, such as clioquinol, has beneficial benefits in transgenic animal models of AD (Grossi *et al.*, 2009) [101].

Another defining feature of AD and other neurodegenerative diseases is the activation of glial cells (Balducci and Forloni, 2018) [7]. In addition to producing pro-inflammatory cytokines, microglial activation also promotes the production of superoxide anions by NADPH oxidase (NOX). High quantities of NOX subunits have been found in the brains of AD patients, and after the NOX gene was removed from transgenic rats, cognitive and cerebrovascular functioning improved, suggesting that NOX may play a role in the aetiology of AD (Park L. *et al.*, 2008) [82]. Additionally, inducible nitric oxide synthase (iNOS) releases NO in the activated glial cells, which then interacts with superoxide to generate peroxynitrite and exert nitrosative stress. The genetic deletion of iNOS, which improves gliosis, lowers burden, and phosphorylates tau proteins in transgenic animals, has been used to support their involvement (Nathan *et al.*, 2005) [78]. Green tea's catechins and polyphenols are potent antioxidants that neutralize free radicals and chelate metal ions by delivering an electron to the ROS-induced radical sites, EGCG inhibits DNA damage brought on by oxidative stress (Singh *et al.*, 2008) [95]. Green tea prevents the spread of chain reactions during the lipid peroxidation that iron ascorbate starts in the brain's mitochondrial membranes. EGCG is the most effective scavenger among the catechins. EGCG inhibits fibril formation during Aβ aggregation and attenuates lipid peroxidation as initiated by the Aβ. EGCG also inhibits Aβ-induced apoptosis, and caspase activity, thus enhancing the survival of hippocampus neurons (Choi *et al.*, 2001; Lee *et al.*, 2009) [117, 61].

Flavonoids for Better Cognition

Several studies highlight the beneficial effects of flavonoid-rich foodstuffs consumption on cognition (Commenges *et al.*, 2000; Letenneur *et al.*, 2007; Spencer, 2010) [18, 64, 98]. Isoflavones from soya and soy-derived foods have been reported to improve learning and memory possibly by their potential to mimic the activity of estrogens in the brain. Additionally, these isoflavones alter the levels of ACh and neurotrophic factors in the hippocampus and frontal cortex, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) of the brain.

Foods high in flavonoids, such as grape juice, chocolate, and blueberries, have been demonstrated to have potential cognitive-improving effects (Krikorian *et al.*, 2010; Scholey *et al.*, 2010; Shukitt-Hale, 2012) [55, 92, 94]. The improvement in the overall scores of memory acquisition, short- and long-term memory, memory retention, and retrieval suggests that regular consumption of flavonoids-rich fruits, such as pomegranate, blueberry, grapes, and

strawberry, as well as pure compounds like quercetin and EGCG, can improve cognitive performance (Joseph *et al.*, 1999; Hartman *et al.*, 2006) [49, 38]. The aforementioned fruits are abundant in flavonols and anthocyanins, which in animal models help to correct cognitive and spatial working memory deficiencies. Pure EGCG can also enhance the ability to remember spatial information (van Praag *et al*., 2007) [106]. Additionally, blueberry flavonoids enhance the processing of spatial memory by acting on the dentate gyrus (DG), a brain region that is extremely vulnerable to the effects of ageing (Small *et al.*, 2004; Burke and Barnes, 2006) [13, 107]. According to studies using animal models, blueberry flavonoids have been shown to increase the proliferation of precursor cells, increasing DG neurogenesis and enhancing cognitive function (Casadesus *et al.*, 2004) [16]. To learn more about how dietary flavonoids impact memory, additional study into these dietary supplements, separation of purely natural components, and comparison to known flavonoids may be fruitful.

Signalling Pathways of Flavonoids in AD

Flavonoids can preferentially bind with the neuronal receptors including $GABA_A$, tyrosine receptor kinase B (Trk-B), *δ*-opioid, estrogen, testosterone, nicotinic, and adenosine receptors, and mediate the various neuropharmacological actions (Fernandez *et al.*, 2008; Lee *et al.*, 2010) [29, 59]. Numerous studies have examined how interactions with brain signalling pathways allow flavonoids and their metabolites to have positive neuroprotective effects. They interact with several protein kinases and lipid kinases signalling pathways like tyrosine kinase, mitogen-activated kinase (MAPK), PI3K/Akt, protein kinase C and nuclear factor *κ* B pathway (Schroeter *et al.*, 2001; Incan, 2010) [44, 93]. When flavonoids bind to these receptors, they may activate or shut down the receptors, mediating the effects of the receptors via altering gene expression or phosphorylation. The creation of synaptic proteins, brain plasticity, and other morphological changes that result in neurodegenerative illnesses and cognitive impairment are then under their control. As an illustration, it has been discovered that flavonoids and their metabolites interact with the MEK1 and MEK2 receptors of the MAPK signalling pathways, activating the cAMP response element binding protein (CREB) in the process and causing major alterations in synaptic plasticity and memory (Finkbeiner *et al.*, 1997; Impey *et al*., 1998) [30, 45]. Blueberries high in flavonols and anthocyanins have been shown to improve cognitive function in rats by activating CREB and raising BDNF levels in the hippocampus. Green tea catechins can also reduce Aβ1-42 oligomer levels, boost PKA/CREB pathway activity, and raise synaptic plasticity-related protein activity in the hippocampus nucleus when administered continuously (Li *et al.*, 2009) [66]. Additionally,

flavonoids stimulate the peroxisome proliferator-activated receptor-coactivator-1 (PGC-1α) pathway, stabilize the hypoxia-inducible factor-1 (HIF-1) and Nrf2 transcription factors, and modulate the peroxisome proliferator-activated receptor gamma (PPAR-γ) (Feng *et al*., 2016) [28]. These molecular changes produced by flavonoids may improve AD pathophysiology by protecting neurons against oxidative stress, improving mitochondrial dysfunction, reducing insulin resistance, and thus ameliorating cognitive impairment.

Therapeutic Effects of Flavonoids in Neurodegeneration

Flavonoids by their low molecular weight, impact multiple cellular targets simultaneously and thus mediate their beneficial neuropharmacological effects in neurodegeneration. Flavonoids interact with several neuronal and glial signalling pathways implicated in neuronal functions and survival (Spencer, 2010; Williams *et al.*, 2004) [98, 111]. They also up-regulate the body's antioxidant system and expression of proteins related to neuronal repair and synaptic plasticity (Kong *et al.*, 2000; Eggler *et al.*, 2008) [26, 54]. They modulate cerebral blood flow and inhibit neuropathological processing in different regions of the brain (Dinges, 2006) [23].

CONCLUSION

Consuming a diet rich in foods containing flavonoids may contain flavonoids and may be able to reduce age-related cognitive decline, improve memory, and perhaps postpone the onset of dementia-related disorders. Natural products' diverse modulatory neuropharmacological capabilities have been linked to their therapeutic value in treating neurodegeneration. More study is required, especially well-designed clinical studies, to demonstrate the clinical utility of flavonoids in treating clinical signs and symptoms connected to neurodegeneration.

Additionally, numerous in vivo research ought to be planned to gain more knowledge on the effectiveness of flavonoids with regards to their bioavailability, potential toxicity, and accumulation at the target areas in the ageing brain. For example, establishing a clear link between behavioural responses in test animals and humans to changes in the cortical and hippocampal areas, the underlying molecular mechanisms underlying synaptic plasticity, effects on the proliferation of neuronal stem cells, and changes in cerebral blood flow will offer guidelines for flavonoid-based dietary applications and subsequent clinical recommendations in neurological disorders. Using imaging and spectroscopic methods like

MRI and NMR, one can gain a deeper comprehension of changes in cerebral blood flow brought on by flavonoids, quantitative changes in neural stem cells, progenitor cells, and grey matter density, as well as electrophysiological changes. All of these initiatives will provide information on the most effective doses of flavonoid therapy as well as mechanism-based linkages between flavonoid therapy and brain functions. It is crucial to investigate flavonoids' anti-amyloid and tau-modifying properties in both in vitro and in vivo models of AD and dementia. In this regard, preliminary research on the tau-modifying potentials of flavonoids is still needed. Detailed investigations on the destabilizing effects of β-amyloid, tau proteins, and the effects on microglial activation are also required. A suggestion regarding the dosage, daily intake, and duration of therapy must also be made for safe and successful results. Molecules that improve CREB function are claimed to consolidate memory by promoting the gene expression crucial for synapse architecture and long-term memory. Drugs that act on CREB upstream regulators like Akt and ERK are regarded to have a great deal of potential for improving memory. Flavonoids have been found to concentrate in the brain and promote ERK-CREB and Akt-CREB-mediated memory, making them ideal candidates for the development of memory-enhancing drugs. Despite substantial advancements in our understanding of flavonoid biology, most doctors still wrongly view them as simple antioxidants, which is a significant obstacle to the preclinical development of bioactive flavonoids. It is now widely acknowledged that flavonoids are substantially more likely to prevent both typical and disease-related decreases in cognitive abilities because they modify the cellular and molecular processes in the brain. As a result, flavonoids constitute a group of vitally important chemical building blocks in the hunt for memory-improving medications that might be able to lessen and possibly even cure declines in cognitive function caused by ageing.

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