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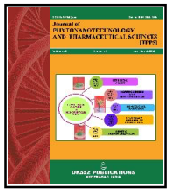

Review Article : Open Access

Role of polyphenols in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a complex and multifactorial neurodegenerative condition. The complex pathology of this disease includes oxidative stress, metal deposition, formation of aggregates of amyloid and tau, enhanced immune responses, and alter cholinesterase levels. Drugs targeted toward the reduction of amyloidal load have been discovered, but there is no effective pharmacological treatment for combating the disease so far. Natural products have become an important avenue for drug discovery research. Polyphenols are natural products that have been shown to be effective in the modulation of the type of neurodegenerative changes found in AD, suggesting a possible therapeutic role. This article focuses on the role of polyphenols in modulating the most important, *i.e.*, amyloid precursor protein (APP) processing. We also provide new hypotheses on how these therapeutic molecules may modulate APP processing, prevent Aβ aggregation, and favor disruption of preformed fibrils. Finally, the role of polyphenols in modulating Alzheimer's pathology is discussed.

1. Introduction

It is widely acknowledged that nutrition plays a key role in the occurrence and progression of non-communicable diseases. A body of epidemiological evidence shows that a diet rich in fruit and vegetables reduces the incidence of cardiovascular diseases, type 2 diabetes, stroke, and numerous cancers (Lacroix *et al.,* 2017). Other studies find an inverse association between the consumption of green tea and cognitive decline. These observed health benefits are thought to be at least partly attributable to a class of non-essential nutrients named polyphenols, found abundantly in fruits and vegetables (Jiang *et al.,* 2017).

Together with cancer and cardiovascular diseases, neurodegenerative disorders constitute a potential application for the benefits of polyphenols (Choi *et al.,* 2012). This includes Parkinson's and Alzheimer's diseases which lack clear etiopathogenetic origins and arise from the interaction between ageing, environment, and genetic risk factors. Polyphenols are reported to improve many of these factors at a cellular level, which makes their use in complex neurodegenerative disorders compelling (Rengasamy *et al.,* 2019).

In this review, the properties that may influence the functionality and bioavailability of dietary polyphenols in the central nervous system. Foods are rich in polyphenols have been positively correlated to a reduced risk of several non-communicable diseases, including Alzheimer's disease. The aim of this paper is to collect and evaluate the relevant studies on the beneficial effects of polyphenols on Alzheimer's disease (Estruch *et al*., 2013).

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2. Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder, which is known to develop clinically only in humans and unknown in other mammalian species. It is one of the most common forms of dementia accounting for about 60% to 70% of all cases, and it causes interference with memory, thinking, and behavior. Alzheimer's disease is a chronic disease, which progresses and worsens over several years. People living with Alzheimer's disease can live on average 8 years after the detection of symptoms, but their survival rate may differ, reaching up to 20 years, depending on an individual's age and other health conditions.

Alzheimer's disease (AD) is a process in which uncontrolled cleavage of amyloid precursor protein (APP) by unknown inducing factors, and toxic amyloid beta fragments are generated. Alzheimer's disease is also characterized by amyloid fibril and phosphorylated tau aggregates and tangles.

2.1 Unavailability of suitable animal models

It reflects all the events seen in AD human brain. Other limitations of mouse models are expected as a result of their smaller and less-developed prefrontal cortex and a shorter lifespan that may not be useful in studying age-related neurodegenerative diseases such as AD. Critically, there are also substantial differences between mouse and human immune systems

2.2 Lack of reliable biomarkers

To detect and understand the progression of AD (Vauzour *et al*., 2012). Polyphenols have antioxidant activity, *i.e.*, their ability to inhibit oxidative damage within the cells by mopping up reactive oxygen species. Current evidence strongly supports and it contributes to the prevention of certain disorders like cardiovascular, cancer, and neurodegenerative disorder including Alzheimer's disease (Vauzour *et al*, 2012).

3. Stages and pathogenesis

Till date, three stages of Alzheimer's disease were reported, although the progression of the disease may be faster or slower depending on the individual's health history and underlined disorder. Early symptoms are associated with symptoms of short-term memory loss, meaning difficulty in remembering recent events, forgetfulness, and feeling lost in unfamiliar places.

In the later stages of the disease, more problems arise that can seriously interfere with an individual's life. For instance, the middle stage of AD usually presents symptoms such as feeling lost at home, needing help with personal care, forgetting family names, increasing difficulty with communication, experiencing repetition, and continuous questioning.

3.1 Amyloid hypothesis

Amyloid plaques are extracellular accumulations, mostly composed of abnormally folded antibodies (Aβ) with 40 or 42 amino acids. ($A\beta_{40}$ and $A\beta_{42}$), two by-products of APP metabolism (Baum *et al.,* 2004). Due to mutations in the APP or PSEN1 or PSEN2 genes, there is increased production of $\mathbf{A\beta_{42}}$ throughout life. The imbalance between Aβ production and Ab clearance is therefore thought to be the main pathologic process (Lane *et al*.,2013).

3.2 Tau hypothesis

The tau hypothesis claims that threads of tau protein twist and tangle together, starting this way the neurodegenerative process of Alzheimer's disease. When tangles are formed inside the bodies of nerve cells, the microtubules disintegrate, destroying the structure of the cells. This eventually leads to the collapse of the support and transportation system, in which tau protein threads are responsible for interference and malfunction in the communication between neurons. Most current reviews suggest that tau protein alone does not cause Alzheimer's disease and that both Ab and tau protein abnormalities are required to provide an accurate diagnosis of the disease. Several studies have explored the progression and interaction of these two pathologies *in vivo*, and have provided further evidence that amyloid pathology develops many years before clinical symptoms, whereas tau pathology develops later on leading to clinical symptoms (Lane *et al*., 2013).

3.2.1 Pathogenesis of Alzheimer's disease

When an Alzheimer's diseased brain is examined under the microscope, two defining neuropathological features of AD are observed:

- Extracellular β-amyloid plaques
- Intracellular neurofibrillary tangles (Estruch *et al*., 2013).

3.3 Formation of β-amyloid plaques

β-amyloid plaques are formed by abnormal processing of its parent protein called AMYLOID PRECURSOR PROTEIN (APP), composed of β-amyloid peptides (Swerdlow *et al*., 2007; Ortega *et al*., 2013).

3.4 Formation of neurofibrillary tangles

Neurofibrillary tangles are the chief component of the tau protein. The function of tau in healthy neurons was to bind to microtubules and stabilizes them. In healthy neurons, microtubules help in the transport of nutrients and cellular components along an axon. In Alzheimer's disease, hyperphosphorylation of tau proteins, detached from microtubules and aggregated together to form neurofibrillary tangles. Microtubule disintegration leads to the collapse of the neuron's internal transport network (Vazour *et al*., 2012).

4. Polyphenols

These are groups of a class of organic compounds characterized by the presence of more than one phenol, structural unit phytochemicals have a protective role in plants. They were present in plant-based diets.

4.1 Role of polyphenols in the prevention of Alzheimer's disease

Several epidemiological studies suggest that diets rich in polyphenols beneficially affect human brain function:

- Improving memory and cognition in normal ageing
- Delaying the onset of neurodegenerative diseases, including Alzheimer's disease
- Halting the progression of Alzheimer's disease

4.2 Epidemiological studies illustrating the role of polyphenols in the prevention of Alzheimer's disease

When a cross-sectional study was carried out to investigate the relation between intake of three common foods which are high in flavonoids (chocolate, red wine, and tea) and cognitive performance, it was clear that:

- Those who consumed all 3 food items had the highest cognitive test scores
- Association was dose-dependent, with maximum effect at intakes of 10 g chocolate/ day 75-100 ml wine/ day.

The relationship was approximately linear for tea (Nurk *et al*., 2009). This relationship was observed even after adjusting for confounding factors.

4.3 Pharmacokinetics and bioavailability

To be effective in the prevention or amelioration of neurodegenerative diseases, polyphenols must be bioavailable. Extensive reports on the bioavailability of the most common dietary polyphenols can be found elsewhere. In this review, we will initially discuss the obstacles that hinder polyphenol bioavailability and address CNS permeability in particular

4.4 Food matrix or vehicle

Oral administration is the most usual route if polyphenols are given pharmacologically but this often conflicts with bioavailability. Particular factors include interaction with the vehicle, transformations by digestive and microbial enzymes, and absorption by the gastrointestinal tract. Few studies have been conducted and inconsistent results have been obtained, demonstrating either a negligible or a significant contribution of the food matrix to polyphenol absorption. Indeed, peculiar factors such as the type of lipid matrix used may mediate in the release of polyphenols in the gastrointestinal tract (Huang *et al*., 2009).

4.5 Gastrointestinal transformations and absorption

Absorption and metabolism of polyphenols have been extensively studied. Whereas, aglycones are normally well absorbed by the small intestine, nutritional polyphenols are more commonly present as

glycosides, esters, and polymers, which cannot be efficiently assimilated in the upper portion of the gut. Molecules not absorbed in the upper gastrointestinal tract continue to the colon to become substrates for the gut microbiota, responsible for a very wide array of reactions, some of which yield monomers or aglycones from glycosylated polyphenols. Smaller, better-absorbed phenolic acids may also be produced by the gut microbiota. For example, macrobiotic degradation of quercetin mainly generates 3,4-dihydroxyphenylacetic, 3-methoxy-4-hydroxyphenyl acetic (homovanillic acid), and 3-hydroxyphenyl acetic acid (Williams *et al*., 2017).

4.6 Plasma bioavailability, transformations, and cellular uptake

Once in the bloodstream, enzymes in the liver and kidneys further modify polyphenols into various conjugated forms, a process that serves to detoxify potentially harmful substances. Molecules are rendered more hydrophilic in order to facilitate their urinary elimination, which usually lowers bioavailability. While metabolites usually constitute the greatest fraction of circulating polyphenolic species, some forms undergo enterohepatic recirculation *via* biliary secretion, followed by deconjugation into free polyphenols by the gut microbiota and reabsorption in the colon. Additional hepatic reactions may also occur which revert circulating metabolites back to the free form, as is the case for the conversion of resveratrol sulfate to bioactive resveratrol by sulphatases in humans (Walle *et al*., 2011).

4.7 Accumulation in the brain parenchyma

Drugs targeting the brain must ultimately be able to accumulate in the brain parenchyma, in a biologically active form, and in sufficient concentrations. Three important obstacles stand in the way of this:

The blood-brain barrier (BBB), efflux transporters, and multidrug resistance-associated proteins. Youdim and colleagues were the first to demonstrate polyphenols crossing the BBB in an *in vitro* model, describing superior penetration of lipophilic (methylated conjugates) in comparison to hydrophilic molecules (sulfated or glucuronidated). Another study identified a stereoselective process in the passage of flavonoid catechins across the BBB. Yet, the exact mechanisms polyphenols use to traverse the BBB *in vivo*, either *via* diffusion or *via* transporters, remains to be elucidated. Although, the information on the transport of polyphenols into the brain is limited compared to the measurement of plasma levels, an increasing number of studies have measured polyphenols and metabolites in the brains of rodents and pigs (Figurira *et al*., 2017).

4.8 Side effects from dosage and chronicity

Virtually all investigations performed in humans using a wide array of polyphenol preparations found that they are safe and tolerable in the short, medium, and long term. Generally, side effects are uncommon and are mild and transient and include minor gastrointestinal problems and, more rarely, headaches, dizziness, and rashes. A great number of investigations have addressed the safety of specific diets enriched in polyphenol-rich foods. Of particular interest, black cohosh, soy, and red clover regimens aimed at reducing menopausal symptoms in women have proven to be safe, with occasional mild gastrointestinal issues, musculoskeletal and connective tissue troubles, as well as weight gain (Boocock *et al*., 2017).

4.9 Mechanisms of neuroprotection (Estruch *et al.*, 2013)

There are several theories which can explain the neuroprotection mechanism of different drugs acting on CNS, but neuroprotection mechanism of polyphenols is well described *via* following mechanisms:

- Protection *via* radical scavenging activity
- Metal chelation
- Modulation of enzyme activity
- Effect on neuronal signaling pathways

4.9.1 Protection *via* antioxidant capabilities

The brain is particularly susceptible to oxidative stress because of oxidative stress plays a major role in the pathogenesis of AD (Massad *et al.,* 2011). When green tea polyphenol was investigated, it was observed to be capable of reducing the death of cultured hippocampal neuronal cells exposed to β-amyloid (Choi *et al.,* 2001).

4.9.2 Metal chelation

When curcumin polyphenol was tested on animal models of AD, it was found to decrease the levels of β-amyloid plaques and prevent cognitive deficits This was attributed to its ability to bind metal ions in the brain, such as Fe^{+II} and Cu^{+II} ions. These ions form part of the structure of β-amyloid plaques. Metal chelation. reduces the amount of ROS generated from reactions and reduces the oxidative stress, thus low availability of metal ions for the formation of β-amyloid. Plaques for the upregulation of translation of APP (Mandel *et al.,* 2006).

4.9.3 Modulation of enzyme activity

Green tea polyphenol EGCG was reported to promote the non-amyloidogenic processing of APP by up-regulating alpha-secretase. Suppressing beta- and gamma-secretase. This shifts the pathway from β-amyloid plaque formation towards the formation of sAPP-alpha, which promotes neuronal growth and survival (Smith *et al.,* 2010).

4.9.4 Effect on neuronal signaling pathways

Polyphenols also act by altering the expression of anti-apoptotic and pro-apoptotic genes as shown in Figure 1 (Weinreb *et al.,* 2004).

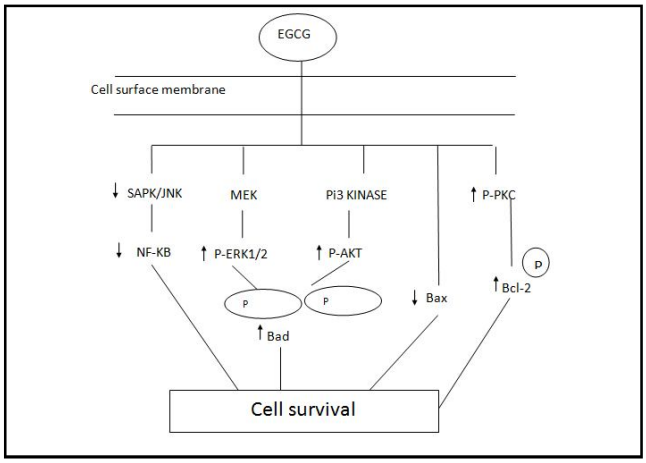

Figure 1: Role of polyphenols in cell survival.

4.10 Examples of polyphenols

Structure of resveratrol is shown in Figure 2.

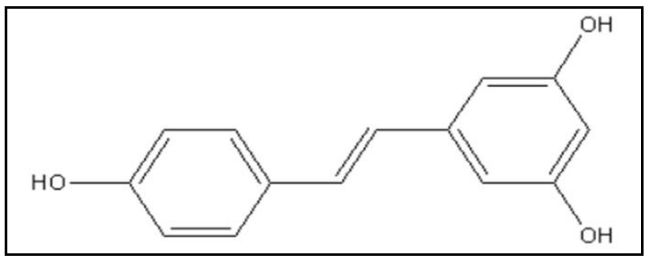

Figure 2: Structure of resveratrol.

4.10.1 Occurrences

First isolated in 1943, has been found in over 70 plant species, including herbs and human food. Different sources of resveratrol shown in Table 1 and Table 2.

Table 1: Resveratrol content in foods

Food	Serving	Total resveratrol (mg)
Peanuts (raw)	1 cup (146 g)	0.01-0.26
Plants (butter)	1 cup (258 g)	0.04-013
Red grapes	1 cup (160 g)	0.24-1.25
Cocoa powder	1 cup (200 g)	0.28-0.46

Table 2: Resveratrol concentration in beverages

Beverage	Resveratrol (mg/100 ml)	
	Mean	Range
Red wine	0.27	0-2.78
Wine and grape juice	0.12	5.00×10^{-03}-0.29
Rose wine	0.04	0.00-0.17
White wie	0.009	8.00×10^{-03}-1.00×10^{-2}
Sparkling wine	0.00508	0.00-1.00-10^{-02}
Green grape juice		

4.10.2 Metabolism

Resveratrol is extensively metabolized in the body with the liver and lungs as the major site of its metabolism. Resveratrol and conjugated metabolites exit the apical membrane of the small intestine and move towards the large intestine where they can be metabolized by the gut microbiota to generate dihydroresveratrol (DHR), lunularin (L) and 3,4'-dihydroxy-trans-stilbene.

4.10.3 Biosynthesis

Resveratrol is produced in plants by the action of the enzyme, resveratrol synthase.

4.10.4 Stability

One study showed that UV irradiation to Cis-resveratrol induces further photochemical reaction, producing a florescent molecule named resveratrone.

Trans-resveratrol in the powder form was found to be stable under Accelerated stability conditions of 75% humidity and 40^0C in the pressure of air. The transisomer is also stabilized by the presence of transport proteins. Resveratrol content also was stable in the skins of groups and pomace was taken after fermentation and stored for a long period. ^{1}H and ^{13}C NMR data for the four most common forms of resveratrol are reported in the literature (Li *et al.*, 2012).

4.10.5 Role of resveratrol in Alzheimer's disease

Increasing evidence has pointed to resveratrol's usefulness in testing cardiovascular diseases, cancers, pain and in laminates injuries of the tissue, and in lowering the risk of neurodegenerative disorders such as Alzheimer's disease. Resveratrol can induce protective effects. In neurodegenerative conditions such as AD. Surface plasmon resonance (SPR) and proton nuclear resonance (^{1}H NMR) methods showed direct binding of resveratrol to A-BETA. It was also shown that resveratrol binds to the N-terminus (residues S-20) $\mathbf{A\beta_{42}}$ monomers. Resveratrol promotes the non-amyloidogenic cleavage of the amyloid precursor protein, enhances clearance of amyloid beta peptials, and reduces neuronal damage. Because it has no effect on the **A**β producing enzymes α and γ secretase, resveratrol does not inhibit **A**β production, rather it promotes intracellular degradation of **A**β *via* a mechanism that involves the proteasome. Neither resveratrol nor its conjugates metabolites were detectable in the brain.

Resveratrol diminished plaque formation in a region-specific manner; the largest reduction in percentage occupied by plaques was observed in the medial cortex 48%, and hypothalamus (90%) (Li *et al.,* 2012).

4.11 Some other important compounds useful in the treatment of Alzheimer's disease

4.11.1 Curcumin

Structure of curcumin is shown in Figure 3.

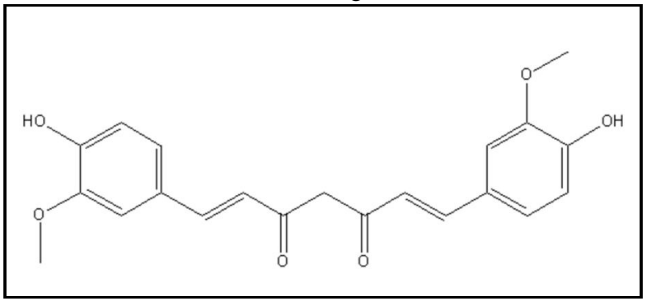

Figure 3: Structure of curcumin.

Curcumin was named in 1815 when Vogel and Pierre Joseph Pelletier reported the first isolation of a "yellow coloring matter" from the rhizomes of turmeric. Although, curcumin has been used historically in Ayurvedic medicine, its potential for medicinal properties remains unproven as a therapy when used orally. Curcumin is a bright yellow chemical produced by *Curcuma longa* plants. It is the principal curcuminoid of turmeric (*Curcuma longa*), a member of the ginger family, Zingiberaceae (Yousuf *et al*., 2005).

4.11.1.1 Mechanism of action

The process through which Alzheimer's disease degrades the nerve cells is believed to involve certain properties: inflammation, oxidative damage, and most notably, the formation of beta-amyloid plaques, and metal toxicity. There have been several studies on the effects of curcumin on AD. Outlined below are some of the studies and their conclusions.

4.11.1.2 Role of curcumin in Alzheimer's disease

Curcumin: A pleiotropic agent for treatment of Alzheimer's disease. Curcumin decreases Aβ production, inhibits Aβ aggregation, and promotes Aβ clearance. Besides, curcumin inhibits inflammatory signal pathways and decreases the production of inflammatory cytokines.

- Anti-inflammatory (Giri *et al.,* 2004).
- Curcumin as an antioxidant (Rathore *et al*., 2007).

4.11.2.1 Epigallocatechin-3-gallate (EGCG)

Human epidemiological and animal data suggest that drinking tea may decrease the incidence of dementia, AD and Parkinson's disease

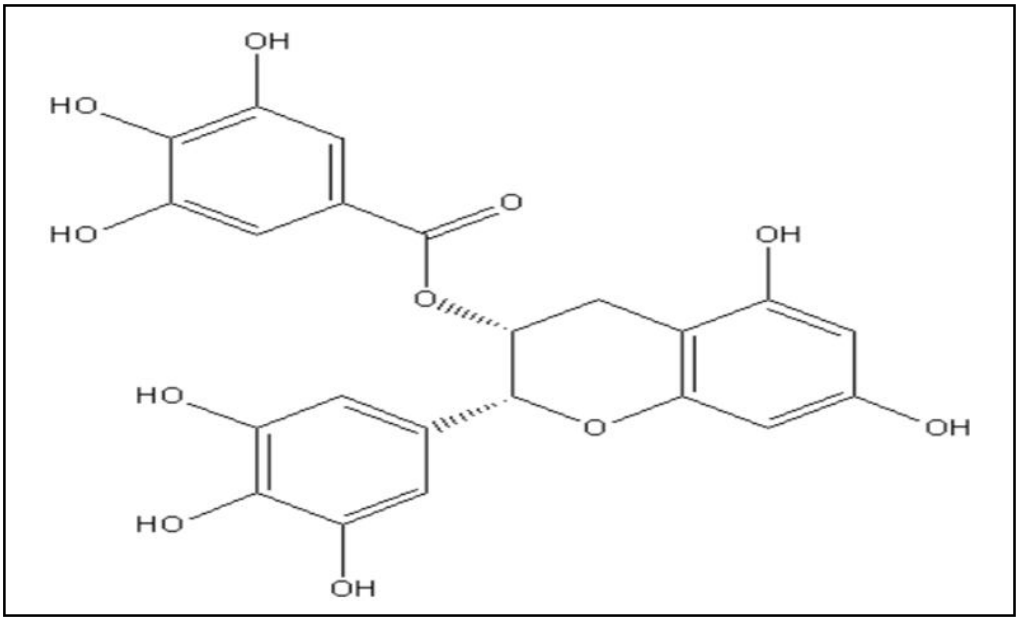

Figure 4: Structure of epigallocatechin-3-gallate.

In particular, the main catechin polyphenol constituent found in tea, (-)-epigallocatechin-3-gallate (EGCG), has been shown to exert neuroprotective activities in a wide array of cellular and animal models of neurological disorders (Awasthi *et al.,* 2016). Structure of epigallocatechin-3-gallate is shown in Figure 4.

4.11.2 Role of EGCG in Alzheimer's disease

Evidences reported that EGCG inhibits A- aggregation in animal models by activating β-secretase and disrupting unfolded peptides. In addition, EGCG has the ability to convert large, mature amyloid-β fibrils into smaller, amorphous protein aggregates that are nontoxic to mammalian cells, suggesting that EGCG is a potent remodeling agent of mature amyloid fibrils. Phase II/III clinical trials of EGCG have been reported for the same (Awasthi *et al.,* 2016).

4.11.3 Tannin acid

Structure of tannic acid is shown in Figure 5**.**

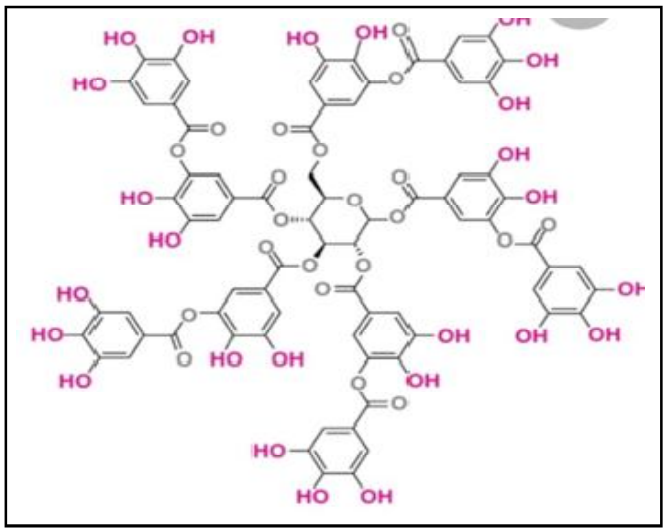

Figure 5: Structure of tannic acid.

4.11.3.1 Mode of action

Tannic acid reduces Aβ production and tannic acid significantly inhibits the aggregation of Aβ. Further, it inhibits amyloidogenic APP metabolism in neuronal cells. For example, tannic acid administered orally to transgenic PSAPP mouse models of cerebral amyloidosis for six months raises the possibility that, by inhibiting **â**-secretase activity and neuroinflammation and hence mitigating AD pathology, dietary supplementation with TA may be prophylactic for AD. Experimental results also suggest that tau peptide interacts with TA by forming a hairpin structure, a feature for inhibiting tau polymerization (Mori *et al.,* 2012).

4.11.4 Morin

Morin is a pentahydroxy flavone that is 7-hydroxy flavonol bearing three additional hydroxy substituents at positions 2' 4' and 5. Structure of morin is shown in Figure 6**.**

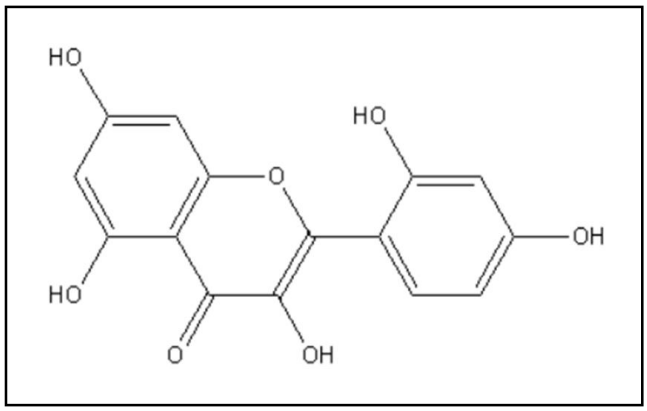

Figure 6: Structure of morin.

4.11.4.1 Mode of action

A substance that opposes oxidation or inhibits reactions brought about by dioxygen or peroxides. Atomistic, explicit-solvent molecular dynamics (MD) simulations were used to identify the mechanism through which Aβ fibril is destabilized by morin, an effective anti-aggregation flavonoid. Morin was found to bind to the ends of the fibrils, thereby blocking the attachment of an incoming peptide (Lemkul *et al*., 2010).

4.11.4.2 Role in Alzheimer's disease

Morin being a super antioxidant compound helped in preventing and curing these disorders by suppression of ROS and by inhibition of multiple targets. Morin which has antioxidant and anti-inflammatory activities has been reported to show pharmacological effects in neurodegenerative diseases (Lemkul *et al.,* 2010).

5. Conclusion

As the elderly population is rapidly increasing, age-associated neurodegenerative disorders, such as Alzheimer's disease, represent a growing public health concern, with a major socioeconomic burden. The lack of curative treatment for cognitive decline and dementia argues for the improvement of preventative strategies to include prevention through dietary measures, such as consuming a diet rich in polyphenolic compounds. Epidemiological evidence indicates a strong connection between polyphenol consumption with a condensed episode of various neurodegenerative diseases in preclinical models due to their neuroprotective properties. Some clinical trials have even been successful in revealing small but measurable improvements in human health and have confirmed the safety of polyphenols in various settings. As mentioned in this project report, polyphenols are sensitive to a great number of physiological conditions that impinge on their bioavailability and bifunctionality, which may account for the markedly high inter-individual variation observed in clinical investigations, which cannot be explained by biphasic dose-response theories.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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