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Review of the Therapeutic Potential of Flavonoids in Alzheimer's Disease: Insight from Molecular Docking Validation

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Abstract-

There are a million patients with Alzheimer's Disease (AD) according to international data in September 2021. AD is a progressive neurodegenerative disorder characterized by cognitive decline, neuronal loss, and the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles. Current therapeutic strategies primarily offer symptomatic relief, underscoring the urgent need for novel, disease-modifying treatments. Flavonoids, a diverse class of polyphenolic compounds found in plants, have shown promising neuroprotective properties due to their antioxidant, anti-inflammatory, and anti-amyloidogenic effects. This review examines the therapeutic potential of flavonoids in AD, focusing on molecular docking studies that elucidate their interactions with key AD targets, such as Aβ peptides, tau proteins, acetylcholinesterase (AChE), and other relevant enzymes. Computational docking analyses highlight the binding affinities and inhibitory mechanisms of various flavonoids, demonstrating their potential to disrupt Aβ aggregation, inhibit AChE activity, and mitigate oxidative stress. These findings provide compelling evidence for further preclinical and clinical investigations, suggesting flavonoids as promising candidates for AD therapy. Future research should aim to validate these in silico results through in vivo studies and explore the bioavailability and pharmacokinetics of flavonoid-based interventions. This review focuses on flavonoids and their role in AD, in terms of therapeutic potentiality for human health, antioxidant potential, and specific AD molecular targets.

Keywords: Molecular Docking, Alzheimer's disease, Flavonoids, Acetylcholinesterase, Acetylcholine

INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder and a leading cause of dementia. AD is an irreversible disease that acts on the cells of the brain and causes impairment of intellectual functioning and damages the ability to reason, remember, imagine and learn. Alzheimer disease neuropathology is characterized by Hydrolysis of Ach , Extracellular accumulation of Peptide, intracellular aggregative of hyper -phosphorylated tau, Neuronal loss, Synaptic death[1]. The histological features of AD are the extracellular deposits of the amyloid beta peptide (Aβ), in the form of neuritic plaques. The intraneuronal neurofibrillary tangles (NFTs) constitute aggregates of hyperphosphorylated Tau protein. The social and economic burden of

AD is high and the number of cases is rising dramatically and may reach 88 million by 2050[2]. Its pathology is complex, characterized by a decline in memory that, in its most usual form, arises after 60 years of age. More rarely, the symptomatology can initiate between 40 and 50 years, and in this case, the disease has a very rapid progression[3]. Generally, the early-onset form, called "familial", is related to specific mutations in the gene's encoding. presenilin1 (PS1) and 2 (PS2) and amyloid precursor protein (APP), while sporadic late-onset disease is associated with mutations in the gene encoding apolipoprotein E (ApoE), and includes several environmental risk factor.

Till now, more than 9000 flavonoids have been reported, and their daily consumption varies between 20 mg and 500 mg, mainly from dietary supplements such as apples, grapes, berries, tea, tomatoes and onions[4]. Recent studies have shown that regular use of flavonoid-rich foodstuffs can effectively enhance cognitive capabilities in humans (Macready et al., 2009;Socci et al., 2017;Bakoyiannis et al., 2019). Additionally several flavonoids have been reported to restrain the progression of pathologies of Alzheimer's disease (AD) and this has been stem from their ability to quash the cognitive deficits in numerous normal and transgenic preclinical animal models. The flavonoids rich foods such as green tea, cocoa, blueberry and other foods improve the various states of cognitive dysfunction, AD and dementia-like pathological alterations in different animal models. Flavonoids thus mediate their neuroprotective effects by maintaining the neuronal quality and number in the key brain areas and thus prevent the onset/progression of diseases responsible for the decrease in the cognitive function.

FLAVONOIDS

Flavonoids are an essential category of natural products; especially, they belong to a class of plant secondary metabolites having a polyphenolic structure, widely found in fruits, vegetables and certain beverages. They have miscellaneous favourable biochemical and antioxidant effects associated with various diseases such as cancer, Alzheimer's disease (AD), atherosclerosis, etc[5]. Furthermore, epidemiologic research suggests a protective role of dietary flavonoids against coronary heart disease[6]. Most of the flavonoids are widely accepted as therapeutic agents. These are naturally produced through the phenyl-propanoid pathway with bioactivity dependent on its absorption mechanism and bioavailability[7]. Flavonoids are associated with a wide range of health-promoting effects and are an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is because of their antioxidative, anti-inflammatory,anti-mutagenic and anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme functions. It is a more potent inhibitor for several enzymes, such as xanthine oxidase (XO),cyclooxygenase (COX), lipoxygenase and phos-phoinositide3-kinase[8-10]. In nature, flavonoid compounds are products extracted from plants and they are found in several parts of the plant. Flavonoids are used by vegetables for their growth and defence against plaques[11]. They belong to a class of low-molecular-weight phenolic compounds that are widely distributed in the plant kingdom. They constitute one of the most characteristic classes of compounds in higher plants. Many flavonoids are easily identified as flower pigments in most angiosperm families. However, their presence is not restricted to flowers but are found in all parts of plants.

FLAVONOIDS CHEMISTRY

Flavonoids are abundantly present polyphenols in plants that are the products of secondary metabolites. The basic chemical structure of flavonoids contains two benzene rings (A and C) connected by a pyran ring B (Figure 2). One of the benzene rings (A) is fused with the pyran ring while the other benzene ring (C) is attached as a substituent to the pyran ring. Depending upon the pattern of substitution of benzene rings. and that of substitution, oxidation and saturation of pyran ring, various derivatives of flavonoids can be synthesized that possess unique physicochemical properties and biological activities acceptable for the efficient management of neurodegenerative diseases.

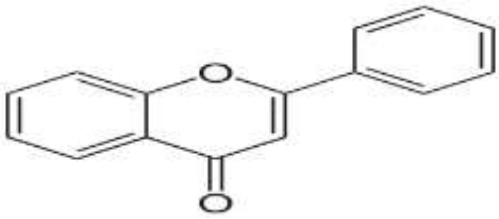

Fig no. 1

CLASSIFICATION OF FLAVONOIDS

These Subgroups are:

flavones, flavanols, flavanones, flavanonols, flavanols, anthocyanins and chalcones

I flavones

Flavones are one of the important subgroups of flavonoids.Flavones are widely present in leaves, flowers and fruits as glucosides. Most flavones of vegetables and fruits have a hydroxyl group in position 5 of the A ring,while hydroxylation in other positions, for the most part in position 7 of the A ring or 3′ and 4′ of the B ring.

II flavonols

Flavonols are flavonoids with a ketone group. They are build-ing blocks of proanthocyanidins. Flavonols occur abundantly in a variety of fruits and vegetables.Compared with flavones, flavonols have a hydroxyl group in position 3 of the C ring, which may also be glycosylated. Like Flavones, flavonols are very diverse in methylation and hydroxylation patterns as well and, considering the different glycosylation patterns, they are perhaps the most common and largest subgroup of flavonoids in fruits and vegetables. For example,quercetin is present in many plant foods[12].

III Flavanones

Flavanones are another important class which is generally present in all citrus fruits such as oranges, lemons and grapes. Hesperetin, naringenin and eriodictyol are examples of this class of flavonoid. Flavanones, also called dihydroxyflavone, have the C ring saturated; therefore, unlike flavones, the double bond between positions 2 and 3 is saturated and this is the only structural difference between the two subgroups of flavonoids.

IV Isoflavonoids

Isoflavonoids are a large and very distinctive subgroup of flavonoids. Isoflavonoids enjoy only a limited distribution in the plant kingdom and are predominantly found in soybeans and

other leguminous plants. isoflavonoids have also been reported to be present in microbes[13].

V Neoflavonoids

The first neoflavonoid isolated from natural sources in 1951 was calophyllolide from Calophyllum inophyllum seeds.Neoflavonoids are a class of polyphenolic compounds. While flavonoids have a 2-phenyl chromen-4-one backbone, neoflavonoids have a 4-phenylchromen backbone with no hydroxyl group substitution at position 2.

VI Anthocyanins

Anthocyanins are pigments responsible for colours in plants,flowers and fruits. Cyanidin, delphinidin, malvidin, pelargonidin and peonidin are the most commonly studied anthocyanins(Table. 2). They occur predominantly in the outer cell layers of various fruits such as cranberries, black currants, red grapes,merlot grapes, raspberries, strawberries, blueberries, bilberries and blackberries.

VII Chalcones

The defining feature of chalcones, a class within the flavonoids, is the open-chain nature resulting from the missing 'C ring' of the typical flavonoid skeleton. Therefore, they are also called open-chain flavonoids.

Chemical classes	Example	Major source
flavones	Apigenin, Chrysin, Luteolin	Parsley, Thyme
flavonols	Quercetin, Rutin, Kaempherol, Myricetin, Isoquercitrin	Apple, Tea, Tomato, Red wine, Cherry, Onion, Broccoli, Fruit peels, Lettuce, Olives, Citrus fruits, Mango
Flavanones	Naringenin, Hesperidin, Fisetin, Naringin	Grapefruit, orange
Isoflavonoids	Daidzein, Formononetin, Genistein, Glycitein	Soya bean, legumes
Neoflavonoids	Calophyllolide	Green tea, apricots, cherries
Anthocyanins	Cyanidin, Malvidin, Delphinidin, Peonidin	Pomegranate, Egg plant, purple corn, cherries, plums.
Chalcones	butein, phloretin, phloridzin, chalco naringenin, xanthohumol, isobavachalcone, and aureusidin.	Citrus,apple,bean, potato, tomato

Table:2(Classification of Flavonoids)

HOW FLAVONOIDS INFLUENCE OR ACT ON ALZHEIMER'S DISEASE

Flavonoids have antioxidant, anti-inflammatory, and neuroprotective properties. Research suggests that flavonoids may play a significant role in preventing or slowing the progression of Alzheimer's disease (AD) due to their effects on brain function and neurodegeneration.

1. Antioxidant Activity

Oxidative stress was initially proposed to be a major factor in AD in 1986[14]. Oxidative stress is a key factor in AD, leading to neuronal damage and cognitive decline.Flavonoids such as quercetin, catechins (found in green tea), and anthocyanins (from berries) neutralize free radicals and reduce oxidative damage in the brain.Plasma glutathione level and antioxidant enzymes such as glutathione peroxidase catalase and superoxide dismutase and significantly decrease decrease in the earlier of Alzheimer d bn, b,. Koisease[15]. 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[16].

2. Anti-Inflammatory Effects

Flavonoids are known to have good anti-inflammatory properties. The structure of flavonoids plays an important role in anti-inflammatory activity.Catechins and quercetin could enhance IL-10 production, an anti-inflammatory compound, by the combined inhibition of IL-1β and TNF-α[17]. Chronic neuroinflammation is a hallmark of Alzheimer disease.Flavonoids like luteolin and apigenin (found in parsley, celery, and chamomile) inhibit.
Circulating neutrophils, which migrate in the brain of patients[18]. Flavonoids help maintain the integrity of the blood-brain barrier (BBB), preventing neurotoxic substances from entering the pro-inflammatory cytokines and reducing brain inflammation. Hence the anti-inflammatory activity of flavonoids helps in preventing many health disorders.

3. Reduction of Amyloid Plaques and Tau Tangles

AD is characterized by beta-amyloid plaques and tau protein tangles, leading to neurodegeneration.Various approaches that reduces Amyloid Plaques and Tau Tangles include therapy like(Antibody therapies,Antisense oligonucleotides,NAP-(AL-108), methyl blue Blarcamesin)diet and sleep.Certain flavonoids, such as epicatechin (from cocoa) and fisetin (from strawberries), have been shown to reduce amyloid plaque formation and promote the clearance of toxic proteins[19].

4. Enhancement of Neurogenesis and Synaptic Plasticity

Flavonoids support the growth of new neurons and strengthen synaptic connections, essential for memory and learning.Resveratrol (found in red grapes and wine) and curcumin (from turmeric) activate brain-derived neurotrophic factor (BDNF), which enhances brain plasticity.

5. Blood-Brain Barrier Protection

Both tau and Aβ may therefore promote the loss of BBB integrity, exacerbating the neurodegenerative process and associated inflammatory responses entering the brain. Quercetin and rutin (found in apples and citrus fruits) reinforce the BBB and protect against cognitive decline.

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MOLECULAR DOCKING IN ALZHEIMER'S DISEASE

Molecular docking is a computational technique used to predict the interaction between small molecules (ligands) and target proteins. In Alzheimer's disease (AD), molecular docking plays a crucial role in drug discovery by identifying potential inhibitors or modulators of key proteins involved in the disease's pathology[20].

Key Targets for Molecular Docking in Alzheimer's Disease

1. Beta-Amyloid (Aβ) Aggregation

Aβ plaques are hallmarks of AD, and inhibitors of Aβ aggregation could slow disease progression.Docking studies help identify molecules that can prevent or disrupt Aβ fibril formation.

2. Tau Protein and Neurofibrillary Tangles

Tau hyperphosphorylation leads to tangles, contributing to neurodegeneration[21]. Molecular docking helps screen compounds that stabilize tau or inhibit kinases responsible for phosphorylation.

3. Acetylcholinesterase (AChE) Inhibitors

AChE breaks down acetylcholine, a neurotransmitter essential for memory and cognition.AChE inhibitors (e.g., Dozapine

4. Scoring and Analysis: Evaluate binding affinity and interactions.

5. In-vitro and In-vivo Validation: Confirm computational predictions with laboratory experiments[22].

Applications in Drug Discovery

Identifying natural compounds (e.g., flavonoids, alkaloids) with neuroprotective properties.Designing multi-target drugs that address multiple AD-related

pathways.Enhancing drug repurposing by testing FDA-approved drugs against AD targets.

FURTHER RESEARCH AND DEVELOPMENT IN ALZHEIMER'S DISEASE.

Flavonoids have received much attention in the literature over the past 10 years and a variety of potential beneficial effects have been elucidated. However, a number of studies carried out involved in vitro and in silico studies. Therefore, further studies are rivastigmine) are used in AD treatment, and docking studies aid in designing more effective drugs[23].

4. Beta-Secretase (BACE1) and Gamma-Secretase Inhibitors

These enzymes are involved in Aβ production.Docking assists in finding selective inhibitors to reduce toxic Aβ formation.

5. Receptor Interactions (e.g., NMDA and GABA Receptors).

Modulating neurotransmitter receptors can help manage AD symptoms.Docking studies identify ligands that enhance synaptic function and neuroprotection.

Steps in Molecular Docking for Alzheimer's disease:-

1. Protein Preparation: Obtain the 3D structure of the target protein from databases like the PDB.
2. Ligand Selection: Choose or design potential drug molecules.
3. Docking Simulation: Use software like AutoDock, Glide, or MOE to predict ligand binding.

that molecular docking studies are required to identify the potential molecules of flavonoids for their usage in the treatment of various ailments in the human health system. The interactions of flavonoids with receptor molecules during the treatment of acute and chronic diseases are an important area of future research. More and more research is needed to discover new flavonoids from nature’s bounty so that this will replace the use of synthetic medicines which are harmful to the body. In this context there is a need for research and development programmes involving invivo studies which will give a hopeful and safe picture for the future[24]. Currently, the intake of fruit, vegetables and beverages containing flavonoids is recommended, although it is too early to make recommendations on daily flavonoid intakes[25].

Current Research and Developments on Flavonoids:

As of 2024, Alzheimer's disease research is heavily focused on developing studies carried out involved in vitro and in silico studies. Therefore, further studies are needed so that the usefulness of flavonoids in the diet could be improved for better human health. The study of flavonoids is complex because of the heterogeneity of the different molecular structures and the scarcity of data on bioavailability[26]. Furthermore, insufficient methods are available to measure oxidative damage in vivo and the measurement of objective end points remains difficult. There is a need to improve analytic techniques to allow the collection of more data on absorption and excretion[27]. Data on the long-term consequences of chronic flavonoid ingestion are especially scarce.A number of reports have emphasised[28].

1. Better Understanding of Bioavailability

One major challenge is how well flavonoids are absorbed and used by the human body. Research now focuses on improving their bioavailability through food processing, supplements, or combining them with other compounds.

2. Role in Preventing Chronic Diseases

Studies suggest flavonoids may help prevent heart disease, diabetes, and even cancer by reducing oxidative stress and inflammation. Researchers are now looking at long-term human trials to confirm these benefits.

3. Molecular Docking Studies

Scientists use molecular docking (a computer-based method) to find new flavonoids that may be useful in treating diseases. This helps identify which flavonoids interact best with human cells.

4. Impact on Gut Microbiota
Some flavonoids are not directly absorbed but are transformed by gut bacteria, which can enhance or reduce their effects. Understanding this interaction is an emerging research area.
5. Natural vs. Synthetic Alternatives
Researchers are trying to extract new flavonoids from plants and even create synthetic versions that may be more stable and effective.
6. Dosage and Safety
While flavonoids from fruits and vegetables are generally safe, high doses from supplements could have unknown effects. More studies are needed to disease-modifying drugs that target the underlying pathology of the disease, particularly by tackling the accumulation of amyloid beta plaques in the brain, with several clinical trials currently testing new medications like Donanemab, which aims to remove these plaques; researchers are also investigating genetic, behavioral, and environmental risk factors, exploring improved diagnostic tools, and looking into lifestyle interventions that could potentially slow cognitive decline in Alzheimer's.
7. Use in Pharmaceuticals
Some flavonoids are being tested for their potential to replace synthetic drugs for conditions like inflammation, infections, and neurodegenerative diseases.

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