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# Neuroprotective Role Of Quercetin In Alzheimer's Disease

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**ABSTRACT:** Increase in the case of neurogenerative diseases and aging population indicates the necessity for developing new methods to prevent or treat brain dysfunction and associated cognitive decline. Quercetin a polyphenolic flavonoidis found to be protective against many degenerative diseases by preventing lipid peroxidation. By its powerful antioxidant properties, it hinders the fibril formation of amyloid-β proteins and counteractinflammatory cascade pathways. This review highlights the pharmacological effects of quercetin and details various quercetin nanoparticles which can be used to cure alzheimers disease.

**KEYWORDS:** Flavonoids, quercetin, neuroprotection, alzheimer's disease, nanoparticles

## I. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that contributes to about 50% of dementia cases worldwide.[1].Dementia is a clinical syndrome characterized by progressive cognitive decline[2].The shrinkage of the cerebral cortex and the medial temporal lobe is a characteristic feature of Alzheimer's disease along with the enlargement of brain ventricles. The extracellular amyloid plaques and intraneuronal tangles of hyperphosphorylated tau protein are the central markers of Alzheimer's disease [3].

Current treatments available include anticholinesterase drugs like tacrine, caproctamine, and memantine, for people with moderateto-severe AD dementia. These medications are shown to reinforce the standard of life for both patient and caregiver when prescribed at the acceptable time during the course of illness; however, they will not change the course of illness or the speed of decline. They have side effects like hepatotoxicity, gastrointestinal disturbance, dizziness, diarrhea, vomiting, and nausea, and this has led to the look for molecules from natural sources with fewer side effects.[4,5]

Recently, studies shows that the dietary flavonoids are often suggested to stop and treat neurodegenerative diseases. Flavonoids are secondary metabolites found in numerous plants, fruits, and vegetables and described as potent antioxidant, radical scavengers, and metal chelators. They also posess anticholinesterase, antiaging, neuroprotective and anti-inflammatory properties, and neurotrophicroles, ameliorating learning and memory, possessing potent antidepressant and antiamyloidogenic effects, suppressing the activation of microglia, and mediating inflammatory processes within the central systema nervosum (CNS). Flavonoids can readily cross the barrier with chronic or acute administration suggesting that these compounds can feasibly have an immediate effect on the brain. This chemical compounds might be used as a prophylactic, so as to hamper the progression of diseases like AD and PD .[6]

Quercetin (3,5,7,30,40-pentahyd roxyflavone) is a well-known natural flavonoid abundantly found in fruits and vegetables like apples, berries, onions and capers. A traditional human diet includes a daily intake of up to 25 mg of this compound. Quercetin possesses numerous biological activity like antitumoral, antithrombotic, anti-inflammatory and antiapoptotic activities. Quercetin protects against neuroinflammation by inhibiting gas (NO) production in microglial cells, which further results in the inhibition of NF-κB signals and prevents inflammatory-related neuronal injury.[7]

### SOURCES OF QUERCETIN

Quercetin a potent antioxidant flavonoid, more specifically a flavonol, is found mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits. It is a flexible antioxidant known to possess protective abilities against tissue injury induced by various drug toxicities.[8]

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| Common Name | Botanical Name | Family | Parts used | Pharmacological activity |
|---|---|---|---|---|
| Red onions | Allium cepa | Amaryllidaceae | Fruits | Antioxidant, Antibacterial, Cardioprotective, Immunostimulant |
| Maidenhair Tree | Ginkgo biloba | Ginkgocea e | Leaves | Antioxidant, Antiasthmatic, Wound-healing properties |
| Grape vines | Vitis vinifera | Vitaceae | Fruits | Anti- inflammatory, Cardioprotective, Neuroprotective |
| Blue berries | Vaccinum angustifolium | Ericaceae | Fruits | Anti-oxidant, Decrease the risk of heart disease and cancer |
| Honey | Apis mellifera | Apidae | Honey comb | Antibacterial, Antioxidant, Anticancer activity |
| Tomato | Solanum lycopersicum | Solanaceae | Fruits | Antidiabetic, Cardioprotective, Anticancer property |
| Pomegranate | Punica granatum | Lythraceae | Fruits | Anti-inflammatory, Antidiarrheal,Immune modulatory, Antitumour |
| Apple | Malus domestica | Rosaceae | Fruits | Antioxidant, Antiproliferative, Antimicrobial |
| Broccoli | Brassica oleracea var. italic | Brassicaceae | Flowerbuds and stalk | Antioxidant, anticancer |
| Pepper | Piper nigrum | Piperaceae | Fruits | Antihypertensive, Antitumor, Antioxidant,Anticonvulsant |
| Green tea | Camellia sinesis | Theaceae | Leaves | Antioxiative, Anticarcinogenic, Antiatherosclerotic |
| Gotu kola | Centella asiatica | Apiaceae | Whole plant | Wound healing, CNS disorders |
| Garden asparagus | Asparagus officinalis | Asparagaceae | Root and shoot | Antineoplastic, antiulcer, antitussive |
| Coriandrum | Coriandrum Sativum | Apiaceae | Leaves | Reduce blood pressure, cholesterol, and dyspepsia |
| Small cranberry | Vaccinium oxycoccos | Ericaceae | Berries | Urinary tract infections |
| White mulberry | Morus alba | Moraceae | Leaves | Antioxidant, Aid in digestion |
| Mango | Mangifera indica | Anacardiaceae | Mango | Antibacterial, anti HIV |
| Chicory | Cichorium intybus | Compositae | Leaves | Gastroprotective, Wound healing, analgesic |
| Sweet cherry | Prunus avium | Rosacea | Flowers and leaves | Tonic, astringent, Diuretic |
| Passion flower | Passiflora incarnate | Passifloraceae | Leaves | Antiasthmatic, Anticough, Analgesic |

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| | | | | |
|---|---|---|---|---|
| Drumstick tree | Moringa oleifera | Moringaceae | Leaves | Anti-inflammatory, Antihypertensive, Antibacterial, Wound healing |
| Lettuce | Lactuca sativa | Asteracea | Leaves | Iron deficiency anemia, Osteoporosis |

**Table 1: Sources of quercetin**

## PHYSICAL PROPERTIES OF QUERCETIN

Quercetin is categorized as a flavonol, one of the six sub classes of flavonoid compounds. The name has been used since 1857, and springs from quercetum (oak forest), after Quercus. It is a present polar auxin transport inhibitor. The International Union of Pure and Applied Chemistry (IUPAC) nomenclature for quercetin is 3, 31, 41, 5, 7-pentahydroxyflvanone (or its synonym 3, 31, 41, 5, 7-pentahydroxy-2-phenylchromen-4-one). This means that quercetin has an OH group attached at positions 3, 5, 7, 31, and 41. [9]

| | |
|---|---|
| Category | Flavanol |
| IUPAC Nomenclature | 3, 31, 41, 5, 7-pentahydroxyflvanone (or its synonym 3, 31, 41, 5, 7-pentahydroxy-2-phenylchromen-4-one) |
| Molecular Formula | $C_5H_{10}O_7$ |
| Melting Point | $316^oC$ |
| Molar mass | 302. 236 g/mol |
| Colour | Brilliant citron yellow needle crystal |
| Taste | Bitter |
| Solubility | Entirely insoluble in cold water, poorly soluble in hot water but quite soluble in alcohol and lipids |

**Table 2: Physical properties of quercetin**

## CHEMISTRY

Quercetin ($C_5H_{10}O_7$) is an aglycone, lacking a sugar group. A quercetin glycoside is formed by attaching a glycosyl group as a substitution for one of the OH groups which is mainly at position 3. The attached glycosyl group (a sugar suchas glucose, rhamnose or rutinose) can change the solubility, absorption and invivo effects. As a general rule of thumb, the presence of a glycosyl group(quercetin glycoside) results in increased water solubility compared to quercetin aglycone.[10,11]. Besides antioxidant activities, multiple OH groups in the structure of quercetin may also lead to its photodegradation. Dall'Acqua et al (2012) described that OH groups at positions 3,30, and 40 are mostly involved in photolability, while OH groups at positions 5 and 7 do not play a crucial role in the photo-oxidative mechanism.[12].Methylation at the 4' or (and) 7 positions by replacing OH group was important in maintaining antiproliferative potency while dimethylation enhanced activity [13].

When the flavonol quercetin (3, 5, 7,3',4'-pentahydroxyflavone) reacts with a free radical, it donates a proton and becomes a radical and the resulting unpaired electron is delocalized by resonance. Thus making the quercetin radical too low in energy to be reactive. Three structural groups support the quercetin's capability to maintain its stability and act as an antioxidant by reacting with free radicals: the B ring o-dihydroxyl groups, the 4-oxo group coupled with 2,3-alkene, and the 3- and 5-hydroxyl groups. The functional groups can donate electrons to the rings and thus increase the number of resonance forms available in addition to those generated by the benzene structure.[14]

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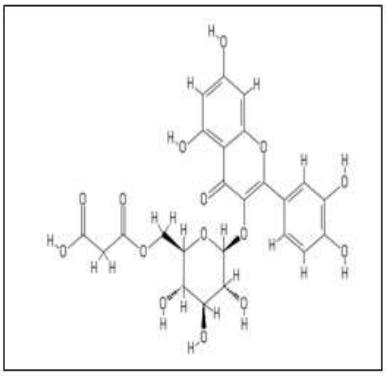
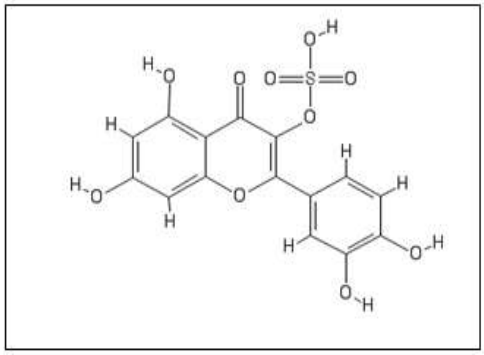


(A)



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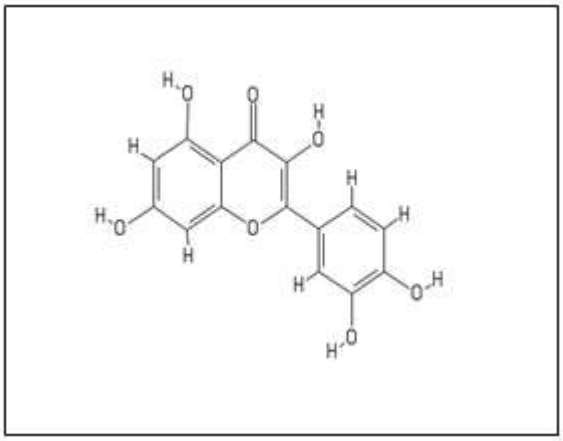
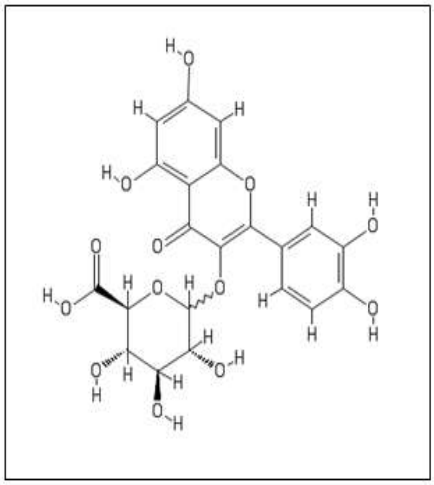
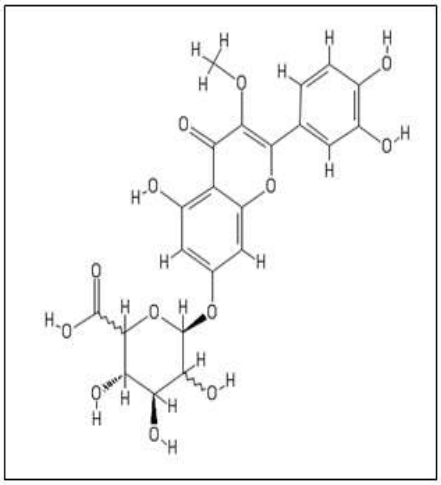


Quercetin





(C) (D)

**Fig 1: Chemical structure of quercetin and its derivatives. (A) Quercetin glucoside, (B) Quercetin- 3- O-sulphate, (C) Quercetin-3-O-glucuronide, and (D) 3-O- methyl quercetin**

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## PHARMACOKINETICS AND BIOAVAILABILITY OF QUERCETIN

**Absorption:** Quercetin glycosides is differently absorbed based on the type of sugar attached . Available evidence indicates that quercetin glucosides (like those found mostly in onion or shallot flesh) are well absorbed than its rutinosides (the major quercetin glycoside in tea). The glucosides are hydrolyzed in the small intestine by beta-glucosidases to the aglycone form, much of which is then absorbed. Quercetin glucuronic acid and its sulfuric acid derivatives are rapidly absorbed than quercetin. Therefore, its absorption is affected by several factors like difference in its glycosylation, the food matrix from which it is consumed, and the co-administration of dietary components such as fiber and fat. Thus different sugar types and sugar group conjugation sites leads to absorption variation.[15].

**Transformation, Transportation and Excretion:** After absorption, quercetin becomes metabolized in various organs like the small intestine, colon, liver and kidney.[16] The quercetin aglycone undergoes extensive biotransformation reactions to form glucuronidated, sulfated, and methylated metabolites, indicating an involvement of the phase II enzymes UGT (uridine 5'-diphosphoglucuronosyltransferase), SULT (sulfotransferase), and COMT (catechol-O-methyltransferase).In general, bioavailability of quercetin is low, and it variesnotablyamongindividuals and limits the use for therapeutic purposes. [17]

Previously, Day et al. (2001) while studying the identification of quercetin metabolites in plasma have reported that quercetin is found mainly as a glucuronated or sulfate conjugate in plasma after oral administration.Quercetin was administered to subjects in doses of 500 mg thrice daily, and the plasma and urine samples were collected from subjects to analyze the concentration of quercetin aglycone and metabolites. The average peak plasma concentration reported after the administration of quercetin at 500 mg thrice daily was 463ng/mL at 3.5h. The oral clearance of quercetin was found to be high(3.5×104 L/h)with an average half life of 3.5 h. The urinary recovery percentage of quercetin aglycone and conjugated metabolites were 0.05% to 3.6% and 0.08% to 2.6%,consecutively.[18]

An important issue for the potential use of quercetinin vivo is whether it can pass the blood-brain barrier (BBB) and what amount of quercetin and/or its metabolites are present in brain tissue. In vitro studies with BBB models shows that quercetin can enter the brain. Upon administration of quercetin in vivo to rats and pigs only low levels are found in brain tissue. Thus recent successful efforts are developed to increase bioavailability of quercetin. By formulating quercetin into lipid nanoparticles increases its permeability into the brain.[19]

## PATHOGENESIS OF ALZHEIMERS DISEASE

Mainly six hypothesis have been proposed that explain AD pathogenesis

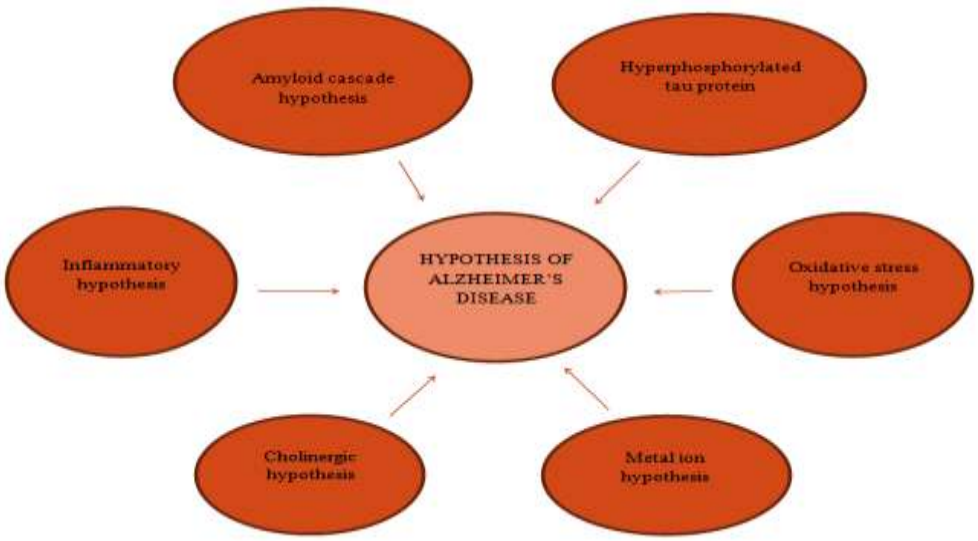


**Fig1: Hypothesis of alzheimer's disease**

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**Amyloid cascade hypothesis**: One of the characteristic feature of AD is the formation of senile plaques (SP), which caused by amyloid beta (Aβ) deposition. Aβ is a soluble small peptides, which is produced by cleavage of the amyloid precursor protein (APP) by the action of three enzymes : α-secretase, β-secretase and γ-secretase.The imbalance between β-amyloid (Aβ) production and clearance give rise to various types of toxic oligomeric, namely protofibrils. Fibrils and plaques depends upon the extent of oligomerization. The reason for the formation of Aβ is still unknown. Some studies suggested that neurotoxicity required assembly of the peptide into oligomers,and other evidences suggested that soluble oligomers forms of Aβ could produce more neurotoxicity. A thorough study shows that amyloid toxicity is associated with both protein-specific and conditional which is determined by the function of vascular endothelial growth factor receptor 2 (VEGFR2) loss. It is essential for target protein in a biological context.A recent work is suggesting that amyloid dyshomeostasis has emerged as the most extensively validated and compelling therapeutic target.[20]

**Hyperphosphorylated Tau protein:**Tau protein is a highly soluble microtubule-associated protein (MAP) which on excessive or abnormal phosphorylation results in the formation of PHF-tau (paired helical filament) and NFTs. By isoforms and phosphorylation tau protein link with tubulin and stabilize microtubule assembly. There are six tau isoforms present in an hyper phosphorylated state of paired helical filaments , in which the longest isoform has four repeats (R1, R2, R3, and R4) and two inserts (441 amino acids total), and the shortest isoform has three repeats (R1, R3, and R4) and no insert (352 amino acids total).[21]

The normal level of tau phosphorylation is an out- turnof dynamic regulation of both tau kinases and tau phosphatase. Glycogen-synthase kinase-3β (GSK-3β), cyclin-dependent protein kinase 5 (cdk5), cAMP-dependent protein kinase (PKA), and stress-activated protein kinases were found to be the most active tau kinases.. However the causes leading to abnormal hyperphosphorylation of tau are till now not fully understood.Down-regulation of PP2A activity in AD leads to deregulation of two endogenous PP2A inhibitors, namely $I_1^{PP2A}$ and $I_2^{PP2A}$. Due to the relatively broad substrate specificity of PP2A, specific neuronal proteins, such as neurofilaments, MAP1B, β-tubulin, and β-catenin, are also hyper phosphorylated in AD brain. [22]

In addition to phosphorylation, the serine/threonine residues of tau are altered by a monosaccharide called β-N-acetylglucosamine (GlcNAc) via a glycosidic bond, and this modification is called O-GlcNAcylation. It manages phosphorylation of tau inversely both in vitro and in vivo . Tau O-GlcNAcylation was found to be decreased in AD brain, and this decrease was correlated to tau hyperphosphorylation. This same phenomenon has also been seen for neurofilaments. O-GlcNAcylation is directly regulated by glucose metabolism which supplies Uridine diphosphate (UDP)–GlcNAc as a donor for protein O-GlcNAcylation, the above observations led us to suggest a novel hypothesis that explains the molecular mechanism by which impaired glucose uptake/metabolism in AD brain contributes to neurodegeneration. In AD brain, impaired glucose metabolism leads to decreased tau O-GlcNAcylation which facilitates hyperphosphorylation of tau and generates neurofibrillary degeneration.[23]

**Oxidative stress hypothesis**: Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play dual role as they both have beneficial functions in cellular signalling pathways and harmful processes that can lead to damage of cellular structures (including cell membrane, lipid, fattyacids, protein, and DNA). The high oxygen demand of the brain, utilizes 20% more oxygen than other mitochondrial respiratory tissues. It means that the brain is more susceptible to oxidative stress. The neuron contains a large number of polyunsaturated fatty acids. It can react with ROS, leading to the lipid peroxidation reaction and molecular apoptosis. The less glutathione in neurons is also one of the causes of oxidative stress injury.[24]

**Metal ion hypothesis**: The amyloid cascade hypothesis, states that excessive production of Aβ is sufficient to cause AD. But the problem of this hypothesis is that, in most forms of AD the self-aggregating properties of Aβ alone are not sufficient to explain the accumulation of the peptide in specific brain regions of AD patients. Healthy people normally have soluble Aβin their brains. They will interact with specific metals (particularly copper and zinc)and downstreams AD pathology. It is marked by raised brain iron levels and deposition of copper and zinc in cerebral beta-amyloid deposits (e.g., senile plaques). Both ionic zinc and copper are able to accelerate the aggregation of Aβ, the principle component of

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beta-amyloid deposits. Copper and iron can also aid the neurotoxic redox activity of Aβ and induce oxidative cross-linking of the peptide into stable oligomers. Recent reports have reported the release of Aβ together with ionic zinc and copper in cortical glutamatergic synapses after excitation. This, in turn, give rise to the formation of Aβ oligomers, which, in turn, attenuates long-term potentiation by controlling synaptic levels of the NMDA receptor. The excessive accumulation of Aβ oligomers in the synaptic cleft is then predicted to adversely affect synaptic neurotransmission.[25]

**Cholinergic hypothesis:** Acetyl-cholinesterase inhibitors (AchEI) medications are the core of the treatment of AD, and apo-lipo-protein E (APOE) genotype is the most important factor associated with AD. The effects of APOE genotype on the useful effect of AChEIs in patients with Alzheimer's disease is studied.The lack of major effect of APOE is examined with respect to the "Cholinergic Hypothesis" of AD through the identification that cholinergic neurons are not the main target of AD.

Cholinergic receptor binding is decreased in specific brain regions with mild to moderate AD and is linked to neuropsychiatric symptoms. Among healthy older adults, decreased receptor binding may be associated with slower processing speed. Cholinergic receptor binding in vivo may disclose links to other key brain changes associated with aging and AD and may provide a promising molecular treatment target.Clinical decrease is related to considerable loss of cholinergic neurons formed in the forebrain nuclei (medial) and a related decline in acetylcholine-mediated neurotransmission. Drugs tending to modulate acetylcholine transmitter level, such as cholinesterase inhibitors (ChEIs) and donepezil served as the foundation of symptomatic therapy for AD. [26]

**Inflammatory Hypothesis:** A number of investigations indicated that in addition to Aβ plaques and NFT, the brains of patients with AD revealed confirmation of a sustained inflammatory response. The inflammatory response has now been mentioned in multiple studies of postmortem tissues of AD patient samples and is consistently observed in preclinical model systems of AD.

Acute inflammation in the brain is standard defence against infection, toxins, and injury, but when a disturbance in the equilibrium of anti-inflammatory and pro-inflammatory signaling occurs, as seen in AD, it results in chronic inflammation (neuroinflammation). This chronic neuroinflammation is allocated to activated microglia cells and the release of numerous cytokines. The existence of a sustained immune response in the brain is not unique to AD. A number of studies have indicated elevated markers of inflammation in the brain of patients with Parkinson's disease (PD), and traumatic brain injury associated with chronic traumatic encephalopathy (CTE), amyotrophic lateral sclerosis (ALS) and Multiple Sclerosis (MS). It is progressively recognized that a sustained immune response is a keynote of neurodegenerative disorders.

The appearance of a sustained inflammatory response in the brain of patients with AD was, at one point, thought to be reactive to the neuronal loss happening in the disorder. However, substantial body of research has now shown that a constant immune response in the brain is not only associated with neurodegeneration but it also facilitates and intensifies both Aβ and NFT pathologies. Moreover it has been suggested that the inflammatory response may provide a connection between the initial Aβ pathology and the later development of NFT.[27]

## NEUROPROTECTIVE MECHANISM OF QUERCETIN

**Inhibition of Aβaggregation and tau phosphorylation:** Tau is a microtubule-associated protein. It will physiologically, binds to microtubules predominanty in axons and helps in its stabilisation and organisation. In AD, tau is hyperphosphorylated, and dissociates from the microtubule. Hyperphosphorylation of tau promotes its mislocalization to the somatodendritic region where it impair nuclear import, and synaptic function. Severalkinasesarethoughttocontribute tothe hyperphosphorylated state of tau in AD, especially the proline directed kinases; GSK-3, CDK5299 and members of the MAPK family.

By inhibiting JNK in primary cortical neurons, a transgenic mouse model and human fibroblasts obtained from AD patients all showed a decrease in phosphorylation of tau at Ser202, Ser205 and Ser422. Several flavonoids have been shown to inhibit JNK activity315 in vitro, although not typically at 316 found in vivo. [28]

**Acetylcholinesterase Inhibition:** The inhibition of AChE and BChE enzyme activities has been extensively established as a first-line treatment/management for the symptoms of neurodegenerative condition[29].

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Acetylcholinesterase is an acetylcholine hydrolase enzyme with esterase activity. It plays crucial role in neural functioning via the cholinergic pathways. [30]Inhibition of the enzyme AChE by specific inhibitors is the therapeutic target to manage disorders such as myasthenia gravis, glaucoma, Lewy body dementia and Alzheimer's disease (AD).[31]. Quercetin inhibited AChE activity in a concentration-dependent manner[32]. Quercetin (0.1-0.4 mmol/L) has also been reported to remarkably inhibit AChE (IC50 = 0.18 mmol/L) and BChE (IC50 = 0.203 mmol/L) including a strong inhibition of Fe(2+)-induced lipid peroxidation and radical scavenging abilities in rats' brain homogenates.[33].

**Attenuation of Oxidative Stress:** Quercetin produces significant antioxidant effects in the presence of high levels of inflammation and oxidative stress . Furthermore, in an animal study, the intravenous administration of quercetin at a dose of 100–150 mg/kg body weight in rabbits caused no complication.[34]

According to studies, structural properties of quercetinthat indicates antioxidative effects include hydroxyl at position 3 of the Cring, a double bond between C2 and C3 in the C-ring, a carbonyl group at C4, and their hydroxylation pattern. Moreover, because of the presence of carbonyl at C4 and hydroxyl groups at C5/C3, chelating with iron ions allows the compound to neutralize the free radicals[35].

It was also spottedthat the antioxidant enzymes activity such as superoxide dismutase (SOD), catalase activity (CAT), and glutathione peroxidase (GPx) increase with quercetin supplementation. Quercetin can also increase the ω-oxidation of fatty acid in the liver, thus decreasing the amount of lipids in circulation. Although quercein decreases the serum level of total fatty acid, it moderately increases some of the polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid and arachidonic acid. Thus indicates a shift in the plasma fatty acids towards healthier variants. [36]

**Attenuationof neuroinflammation:** The central nervous system (CNS) contains glial cells, including astrocytes and microglia which serve as an immune system for the CNS. It defends against pathogens and maintain the normal structure of neurons. Tissue damage and systemic inflammation open on to glial cell activation, which releases inflammatory mediators and bring about inflammatory diseases in the brain, such as meningitis and multiple sclerosis and additionally non-inflammatory diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).Many studies have described that the activation of glial cells releases harmful mediators such as reactive oxygen species (ROS), nitric oxide, cytokines and inflammatory mediators, which eventually lead to neuroinflammation-mediated neuronal degeneration.

Quercetin exerts anti-inflammatory activity by inhibiting the proinflammatory cytokines that are produced by glial cells. Quercetin protects againstneuroinflammation by hindering nitric oxide (NO) production in microglial cells, which stimulate the inhibition of NF-κB signals and prevents inflammatory-related neuronal injury.[37]

It has been described that quercetin decreased manganese-induced neurotoxicity. It helps in preventing neuroinflammation-mediated neurodegeneration, which it acheived via regulating the heme oxygenase-1 (HO-1)/nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor kappa B (NF-kB) pathway [38].

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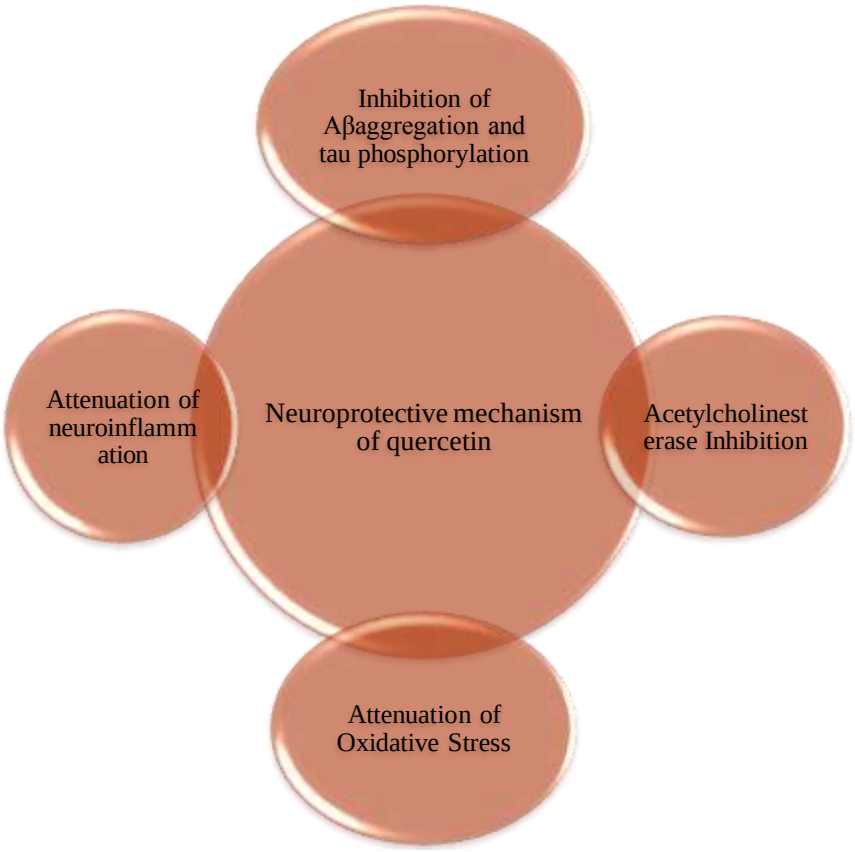


**Fig 2: Neuroprotective mechanism of quercetin on Alzheimer's disease**

## IN- VITRO STUDIES ON THE EFFICACY OF QUERCETIN FOR ALZHEIMER'S DISEASE

In vitro studies conducted in neuronal cell lines and in primary neurons showed that quercetin, at low micromolar concentrations, antagonizes cell toxicity which is mainly produced by various oxidants (e.g., hydrogen peroxide, linoleic acid hydroperoxide) and neurotoxic molecules.Theyact by inducing oxidative stress (e.g., 6-hydroxydopamine and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium) [39, 40-43]. A recent study revealed that quercetin glycosides (rutin, isoquercetin) were capable of antagonizing changes in gene expression due to 6-hydroxydopamine in PC12 cells [44]. In isolated rat brain mitochondria, the toxicity of the anticancer drug oxaliplatin was counteracted by quercetin, which remarkably reduced the oxidative stress. Protection of neuronal cells from the toxicity of amyloid beta peptide toxicity has also been detailed.

Experimental conditions (e.g., end-points, duration of incubation) differs significantly in published in vitro studies; however, quercetin exerts neuroprotection in vitro at concentrations that are in the micromolar range, which is elevated than the concentration found upon in vivo administration. In addition, most of the absorbed quercetin is present as metabolites, which have gone through only limited testing in vitro. However, a number of glucuronidated, methylated, and sulfated quercetin metabolites have been shown to have neuroprotective actions in vitro, though negative results have also been reported.[45]

## IN- VIVO STUDIES ON THE EFFICACY OF QUERCETIN FOR ALZHEIMER'S DISEASE

In vivo studies using mice as an animal model have aided that quercetin increases spatial memory tasks, and decreases β-amyloidosis, tauopathies, astrogliosis, and microgliosis by increasing AMPK activity and decreasing mitochondrial dysfunction. Keddy et al.(2012) described the neuroprotective and anti-inflammatory effects of the flavonoids-enriched fraction containing quercetin and its glucosides in a mouse model of hypoxic-ischemic brain injury. The repeated administration of the flavonoid-enriched fraction prior to an experimental stroke caused by hypoxic-ischemia prevents the neuronal

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loss in the striatum and dorsal hippocampus. Due to the low bioavailability of quercetin and its glucosides, it required injection through the intraperitonial or intravenous route to produce neuroprotective effects . Tota (2010) et al. defined the effects of quercetin on cerebral blood flow and memory impairment in mice and related the ability of quercetin to improve cerebral blood flow and energy metabolism to its memory-enhancing effects. After oral administration in humans, quercetin is widely metabolized during its absorption from the gut, thus affecting its bioavailability. Moreover the metabolites of quercetin have long half-lives in vivo, and repeated dosing may lead to plasma accumulation. These are important factors, which will need to be taken into account in the design of quercetin analogs for clinical studies.[46]

**NUTRACEUTICAL LOADED NPs AND GREEN NPs**

The term "nutraceutical" was from "nutrition" and "pharmaceutical". Nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease".[47]

In the last decade, an increased interest in nutraceuticals has been noted because of the several advantages that could be associated to their application. They posess antioxidant and anti-inflammatory properties and further regulate intra- and extracellular signalling pathways. The use of nutraceuticals in AD therapy is mainly related to the high level of inflammation and oxidative stress detected as clinical hallmarks.

Nanoformulations are specifically important in this field because they can improve some chemical and biological limits of nutraceuticals like poor bioavailability, solubility and stability and pharmacokinetics feature so as to achieve brain targeting.[48]

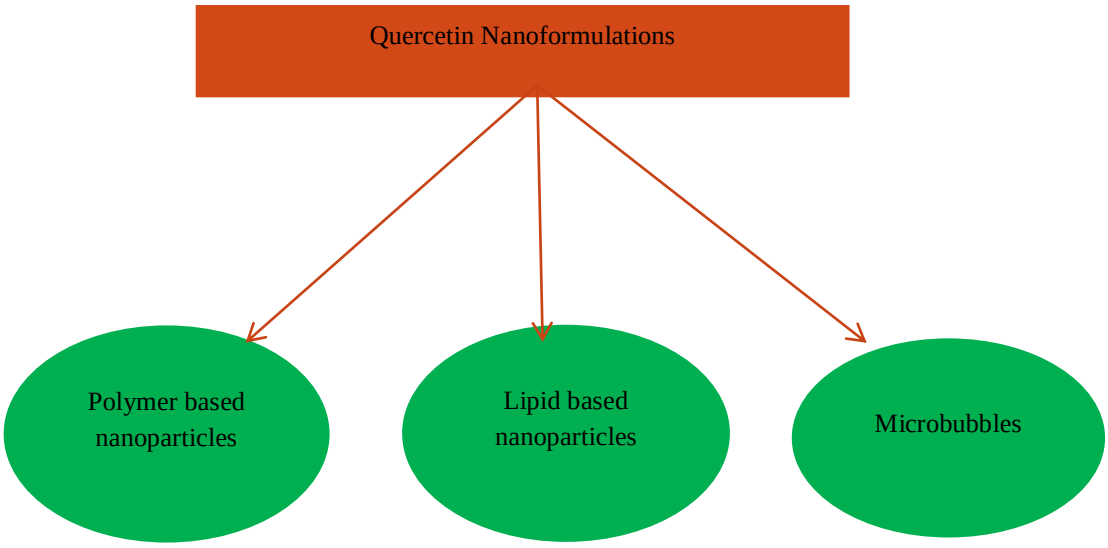


**Fig 3: Quercetin nanoformulations to treat Alzheimer's disease**

Recently, few studies have indicated that, when delivered through functionalized PLGA NPs or SLNs, quercetin act as antioxidative agent in disassembling Aβ fibrils in SH-SY5Y cells and abrogated memory impairments and ameliorated cognition in AD mice. [49, 50]

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**Polymer-Based Nanoparticles:** The characteristic features of polymeric NPs are biodegradability, biocompatibility, long shelf life, and stability during storage. They also ensure controlled and sustained release of the load. The nanoparticles are in the range of 10–1000 nm. Natural polymers used are usually polysaccharides (chitosan is the most used), while synthetic ones are poly lactic acid (PLA), poly glycolic acid (PGA), and poly D,L-Lactic-co-Glycolic acid (PLGA). According to the method of preparation, the drug can be either be loaded within the NP, that functions as a reservoir (nanocapsules), or embedded in the matrix (nanospheres). [51]

**Lipid-Based NPs**: The liposomes have size range from 100–200 nm. They provides benefits like high drug-to-lipid ratio, an excellent retention of the encapsulated drug, and a long circulation lifetime (>6 h). Their lipidic bilayer is primarily made up of of amphipathic phospholipids (phosphatidylcholines) surrounding an interior aqueous space. Phosphatidylethanolamine (PE) is included in the formulation when the target is the fusion of the liposome with cell membranes . Their spontaneous negative curvature favor this event.

Solid Lipid Nanoparticles (SLNs, size range 50–1000 nm) are based on lipid components rather than on the phospholipids (triglycerides, glyceride mixtures). They were developed as an alternative approach to liposomes. SLNs has a hydrophobic core that provides a suitable environment for better entrapment and efficient load of hydrophobic drugs, further, a finely controlled drug release, and an improved stability. Their synthesis is cheap and can be simply scaled up. [52]

**Microbubbles:** Microbubbles were at first used as diagnostic agents but are now turning up as a promising unconventional therapeutic tool because ultrasonication furnishes a non-invasive technique with unique ability to penetrate biological tissues. Bio-medically microbubbles have erythrocytes-like dimensions and consists of three phases: the innermost part is filled with gases, the middle layercontain proteins, surfactant lipids, or biodegradable polymers, and the outermost layer with the liquid phase. Microbubbles targets drugs or genes to any specific tissues; when ultrasounds are discharged, they resonate to expand, shrink and finally burst, causing site-specific delivery of bioactive materials through the opening of the BBB tight junctions. [53]

Several specific NPs loaded with flavonoids were designed, tested and studied, some of them in vitro, other in vivo, confirming their antioxidant, anti-inflammatory and neuroprotective properties. Anthocyanins encapsulated by PEG-PLGA NPs[54]and rutin-loaded lipid polymer hybrid NPs[55] be included in first group (in vitro tested flavonoids), while anthocyanin-loaded PEG-AuNPs[56,57]and hesperetin nanocrystals[58] were included in the second one as they were tested in a mouse and in a rat AD model, accordingly.

In the last five years, nanotechnologies have been impending to the “green synthesis” of NPs, in keeping with the principles of green, cost-effective, and eco-friendly chemistry. This green synthesis approach displaces the use of toxic chemicals, as reducing and stabilizing agents, with phytochemicals during NPs synthesis. [59]. Phytochemicals coating onto NPs surface assure their biocompatibility and bacteriostatic properties. Due to their antioxidant and anti-inflammatory properties, green synthetized nanoparticles may play a salient role in many therapeutic applications. New studies revealed that green zinc oxide NPs maintained their high antioxidant properties,quercetin was used in the synthesis of gold and silver NPs,put forwarding their potential application in AD.[60]

## II. CONCLUSION

Quercetin is a flavonoid with remarkable pharmacological effects and promising therapeutic potential. It is largely distributed among plants such as in fruits and vegetables. It has neuroprotective properties against general mechanisms of AD etiology in various in vitro and in vivo models. It conserve neuronal cells by attenuating oxidative stress and neuroinflammation. Quercetin inhibition

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of Aβ aggregation and tau phosphorylation proves useful for alzheimer's disease. It replaces acetylcholine levels through the inhibition of hydrolysis of acetylcholine by AChE enzyme. Despites showing neuroprotective efficacy in several in vitro and animal models they are extensively metabolized upon absorption from the gut, affecting its bioavailability. This can be overcome by formulating them into nanoparticles. Thus its low BBB penetrability can be improved. NPs have direct effects on cellular metabolism, as an increase of ROS production, inflammation and oxidative stress.

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