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Enhancing Quercetin's Neuroprotective Effects in Alzheimer's Disease Through Advanced Nano formulations

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ABSTRACT

Alzheimer's disease (AD) is a crippling neurological illness characterized by a steady loss of memory and cognitive impairment. Strong antioxidant and anti-inflammatory qualities make Quercetin a flavonoid that has gained resistant as a potential neuroprotective agent for AD. Unfortunately, its poor bioavailability, fast metabolism, and restricted solubility limit its therapeutic potential by preventing it from reaching the brain at levels that are useful. Nano-formulation methods such nanoparticles, liposomes, and nanoemulsions have been used to improve quercetin delivery in order to overcome these obstacles. By enhancing quercetin's stability and facilitating its targeted release in the brain, these cutting-edge delivery methods boost the drug's effectiveness in treating AD-related diseases such oxidative stress and amyloid-beta aggregation. This abstract provides a prospective approach for more successful management of Alzheimer's disease by examining the role of quercetin in modifying neurodegenerative pathways in AD and highlighting how nano-formulations can maximize its protective benefits.

Keywords: Quercetin, Alzheimer's Disease, Nano-formulations, Neuroprotection, Targeted Drug Delivery, Antioxidant, Cognitive Health.

Introduction

Different neurodegenerative disorders have different etiologies and clinical consequences. Numerous risk factors, including age, genetic defects, excitotoxicity, oxidative stress, abnormalities of antioxidant enzymes, deficiencies in neurotransmitters, metabolic toxicity, autoimmunity, and hypertension, have been linked to neurodegenerative disorders in epidemiological and experimental studies (1). Aloes Alzheimer, a German physician, is credited with first describing Alzheimer's disease (AD) in 1906. An estimated 50–60% of dementia cases are thought to be caused by AD, a progressive neurological disease that usually affects those over 65 (2). According to estimates, there are currently 35.6 million dementia sufferers globally, and by 2030, that number will rise to 65.7 million, with developing nations accounting

for the majority of the growth (3). Clinically, it manifests as cognitive deficiencies, progressive memory impairments, and reduced learning capacity. AD may arise as a result of a number of conditions, including a decrease in physical activity, infection, smoking, and the prevalence of disorders like obesity and diabetes (4).

Extracellular neuritic plaque aggregates and intracellular hyper-phosphorylated microtubule-associated Tau protein accumulations, or neurofibrillary tangles, are the histopathologic hallmarks of AD. Proteolytic cleavage of the amyloid precursor protein, a large type I integral membrane protein with 695–770 amino acids expressed in many organs but mostly concentrated at the synapse of neurons, results in the formation of neuritic plaques, which are primarily composed of Aβ peptides (5).

The greatest recognized effect of phytochemicals is their ability to lower the risk of chronic illnesses like cancer, diabetes, hypertension, and cardiovascular disorders. The most varied class of phytochemicals are flavonoids, which are found in many higher plants and have exceptional medicinal potential. Based on their chemical structure, flavonoids are further classified into six classes: isoflavonoids, anthocyanidins, flavanols, flavanones, and flavones. They have been shown to be helpful in preventing neurodegenerative illnesses and may slow the progression of neurodegeneration even though they target several targets at once. Since flavonoids have anti-inflammatory and antioxidant properties that are key in initiating the pathophysiology of AD, they have been the subject of much research. Research has indicated that flavonoids possess the ability to penetrate the blood–brain barrier (BBB), indicating their potential as agents in the prevention of neurodegenerative illnesses. Nevertheless, the degree to which flavonoid subclasses are able to traverse the BBB varies. Their effectiveness in the case of AD is linked to a decrease in oxidative stress and a reduction in Aβ toxicity (6).

Szent-Gyorgyi discovered and recognized quercetin (3,30,40,5,7-pentahydroxyflavone) as a flavonol for the first time in 1936. Fruits and vegetables include a flavonoid called quercetin, which has special biological qualities that may enhance mental and physical function and lower the risk of illness. These characteristics serve as the foundation for potential advantages to general health and resistance to disease, such as antiviral, anti-inflammatory, anticarcinogenic, antioxidant, and psychostimulant effects; they can also be used to suppress platelet aggregation, lipid peroxidation, and capillary permeability, as well as to promote mitochondrial biogenesis (6). One of the most powerful antioxidants derived from plants, quercetin is a major flavonoid that is more frequently present in edible plants. It is a member of the flavonol class of flavonoids, which is a significant class of polyphenols (7).

Quercetin reverses the neurotoxicity caused by Aβ by interfering with the development of neurotoxic oligomeric Aβ species and exhibiting fibril destabilizing effects on preformed fibrillary Aβ. A minimum of three hydroxyl groups are present in aromatic rings, and these groups are crucial in inhibiting fibrils because they create hydrogen bonds with β-sheet structures through hydrophobic contact. The aromatic rings' electron density is raised by the phenolic hydroxyls, potentially improving quercetin's ability to attach to the aromatic amino acids in peptide beta-sheet structures. Because quercetin meets these structural requirements and has hydrophobic moieties, it prevents the development of fibrils. The modulation of BACE-1 Expression, the reduction of tau protein phosphorylation, and the suppression of NFT formation are all impacted by quercetin-induced NF-kB inhibition. In HT22 cells, quercetin reverses the hyperphosphorylation of tau proteins through the PI3K/Akt/GSK3β and MAPK signaling pathways (8).

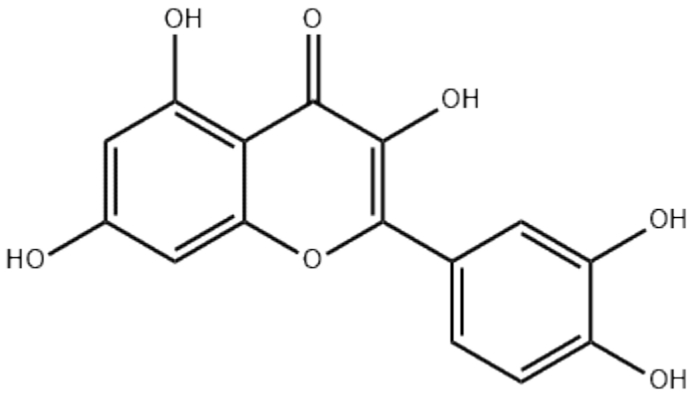

Figure 1: Quercetin chemical structure

Literature review regarding Quercetin's Nano-formulations used in AD

Qi, Yujie, et al. (2020) synthesize nanocomposites of P80-Que@Se. The two pathological hallmarks of Alzheimer's disease (AD) are abnormal aggregation of amyloid-β (Aβ) particles and oxidative stress. A popular flavonoid antioxidant called quercetin (Que) has the ability to reduce oxidative stress and has been shown to prevent the production of Aβ fibrils. Its therapeutic use is, however, restricted by its poor water solubility, high first-pass metabolism, and limited blood-brain barrier (BBB) permeability. In order to create nanocomposites (NC) for drug delivery, we present a straightforward method here. In order to create selenium nanoparticles, this approach combines Que with Na2SeO3. Polysorbate 80 (P80-Que@Se NC) and acacia are then used to modify these nanoparticles. The blood-brain barrier (BBB) may be more effectively crossed by this newly created nanocomposite, and polysorbate 80 functions as a

pharmaceutical excipient to make Que more soluble in water. The in vitro results showed that P80-Que@Se could successfully prevent Aβ fibrillation and had a high aqueous solubility when compared to individual Que. According to an examination using the In vitro Cell Counting Kit (CCK)-8, P80-Que@Se nanocomposites might shield PC12 cells from H2O2-induced cell death. Furthermore, P80-Que@Se demonstrated strong antioxidant activity and significant 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity (9).

The efficacy of quercetin-loaded nanoparticles to enhance neuroprotective effects was explored in this **Pinheiro, R. G. R., et al. (2019)** study employing an in vitro model of Alzheimer's disease with Aβ (1-42) peptide. When compared to the control sample with the Aβ (1-42) sample alone, it was shown that quercetin-loaded nanoparticles, particularly transferrin-functionalized NLC, were able to inhibit fibril formation, reverse the aggregation effect of unloaded nanoparticles, and also decrease peptide aggregation. Consequently, because of their greater ability to deliver quercetin to specific brain sites and their enhanced ability to inhibit amyloid-beta aggregation, the developed nanosystems functionalized with transferrin and loaded with quercetin appear promising for the treatment of neurological diseases, including Alzheimer's disease, primarily NLC. These nanosystems may offer a fresh approach to enhancing the current treatment, providing significant data and raising new expectations for Alzheimer's patients (10).

Rifaai, Rehab Ahmed, et al. (2020) explored the quercetin nanoparticles (QNPs) neuroprotective role in Alzheimer’s. AD hippocampi displayed a significant amount of extraneuronal and neuronal structural and ultrastructural abnormalities. comprising astrogliosis, downregulation of tyrosine hydroxylase (TH), neuronal degeneration, AP and NFT formation, and suppression of proliferative activity (all $P \leq 0.05$). Using electron microscopy, neuronal degeneration was observed together with astrocyte and microglia activation, myelination disruption, and disruption of the blood-brain barrier (BBB). Interestingly, the treatment of QNPs significantly decreased the production of APs, NFTs, and neuronal degenerative alterations (all $P \leq 0.05$). Moreover, there were indications of regeneration (all $P < 0.05$) and increased TH expression. In the group receiving preventative treatment, the impact was significant. Therefore, QNPs mitigated the deleterious impact of AlCl3 on hippocampus neurons on a molecular, cellular, and subcellular level and an adjuvant therapy for AD (11).

Priprem, Aroonsri, et al. (2008) Quercetin liposomes demonstrated anxiolytic and cognitive-enhancing effects and could be reliably synthesized from EPC/chol at a 2:1 ratio. The anxiolytic and cognitive effects

of quercetin, a potent flavonol utilized as an antioxidant, were studied in male Wistar rats. Oral and intranasal quercetin liposomes (20 μg/day) were compared with oral quercetin (300 mg/kg body weight/day). When quercetin liposomes were dissolved in 50% polyethylene glycol in water and mixed with egg phosphatidylcholine, cholesterol, and quercetin (2:1:1), they had a mean particle diameter of about 200 nm, a negative surface charge, and an encapsulation effectiveness that ranged from 60% to 80%. Morris water maze and elevated plus maze tests were used to assess the cognitive-improving and anxiolytic effects of conventional and liposomal quercetin, respectively. Anxiolytic and cognitive-enhancing effects were demonstrated by conventional and quercetin liposomes. Quercetin can be effectively delivered to the central nervous system using intranasal quercetin liposomes and it can be a potentially novel strategy for AD (12).

According to **Pinheiro, R. G. R., et al. (2020)** RVG29-nanoparticles below 250 nm had a spherical morphology and size, making them suitable for use in brain applications. The values of the zeta potential ranged from -20 to -25 mV. In general, quercetin entrapment efficiency was greater than 80%, while NLC nanoparticles could encapsulate up to 90% of the drug. The LDH experiment demonstrated that the hCMEC/D3 cell line is not cytotoxic, and after 4 hours of incubation, RVG29-functionalized nanoparticles significantly increased the permeability across the in vitro blood-brain barrier by 1.5 times when compared to non-functionalized nanoparticles. In conclusion, the thioflavin T binding experiment demonstrated that our nanosystem may suppress amyloid beta aggregation, indicating a significant potential for neuroprotection. Delivering quercetin effectively and offering hope for future therapies to Alzheimer's disease are RVG29-nanoparticles, which simultaneously target the blood-brain barrier and stimulate neuronal protection against amyloid-beta fibrillation and provide better protection in AD (13).

Table 1: Quercetin based drug delivery system and their application in Alzheimer's

Formulation	**Model**	**Route of administration**	**Pharmacological benefit**	**Outcome**	**Reference**
Liposomes	Rats	Intranasal	Increased solubility	Anxiolytic and cognitive benefits	(12)
		Oral	Enhanced plasma concentration	QT-SPIONs prevent neural cell	(14)

				apoptosis and improves learning and memory.	
SLNs	Rats	Intravenous	Drug entrapment increased	Behavioural improvement in memory retention	(15)
NPQ	SAMP8 mice	Oral	Enhanced bioavailability	Increased memory and cognition	(16)
Silica nanoparticles	Hippocampal cells	Peripheral	Retain physiochemical integrity	Improves antioxidant activity potential	(17)
Polymeric NPs	SH-SY5Y cells		sustainable release	disassembles Aβ fibrils	(18)

Conclusion

Quercetin, a flavonoid known for its antioxidant and neuroprotective properties, has shown promising therapeutic potential in managing Alzheimer's disease when delivered through advanced nanotechnology-based formulations. The efficacy of numerous quercetin formulations, including silica nanoparticles, polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), and nano-encapsulated quercetin (NPQ), in diverse animals and administration routes, is demonstrated by this. Utilizing these nanocarriers improves the pharmacological advantages of quercetin by addressing issues such as its low bioavailability and poor solubility. Increased drug entrapment through intravenous SLNs led to greater memory retention, while liposome-based intranasal and oral delivery markedly enhanced cognitive outcomes. An important pathology in Alzheimer's disease, amyloid-beta fibrils, was successfully disassembled and quercetin was stabilized and released over time with the use of polymeric and silica nanoparticles. The above study highlights quercetin's potential for better administration and efficacy as a neuroprotective drug in Alzheimer's therapy.

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