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Quercetin as an Epilepsy Disease Treatment and Its Nanotechnological Perspective

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ABSTRACT:

A polyphenolic bioactive substance that is abundantly found in berries, nuts, vegetables, and fruits is quercetin. Many neurological disorders, including epilepsy, are known to benefit from quercetin and its derivatives, such as rutin and hyperoside. The clinical studies of quercetin and its derivatives in relation to epilepsy are limited. This review provides the evidence of most recent knowledge of anticonvulsant properties of quercetin and its derivatives on preclinical studies. Additionally, the studies demonstrating antiseizure potential of various plants extracts enriched with quercetin and its derivatives has been included in this review. Here, we've also covered the bioactive compounds neuroprotective effects and provided a brief overview of the underlying processes causing their anticonvulsant effects. Lastly, the limits of quercetin and its derivatives as drugs that prevent seizures as well as potential methods to increase their effectiveness have also been covered.

1. Introduction

Epilepsy is a neurological condition characterized by recurrent unprovoked seizures, which are caused by sudden and excessive electrical discharges in the brain. It is defined by the tendency to have unprovoked seizures, which can manifest in various ways ranging from momentary lapses of awareness to convulsions and loss of consciousness[1]. The condition can develop due to various factors such as genetics, brain injury, infections or other medical conditions[2]. While epilepsy cannot be cured, it can often be effectively managed with medication, surgery or other treatment options allowing individuals with epilepsy to lead normal lives.The diagnosis and treatment of seizures and epilepsy are common tasks for physicians[3]. Approximately 1 in 10 people will experience a seizure during their lifetime. Globally, epilepsy is the fourth most common neurological disorder affecting approximately 65 million people[4]India is home to approximately one-sixth of the global population, with an estimated 10–12 million people living with epilepsy in the country.Despite its prevalence, misconceptions and stigmas surrounding epilepsy often hinder proper diagnosis, treatment and support for those affected.The treatment of epilepsy has evolved significantly since the introduction of phenobarbital in 1912[6]. Recent years have witnessed remarkable advancements in the pharmacological management of epilepsy, characterized by the development of new antiepileptic drugs (AEDs) and a deeper understanding of the disorder's underlying mechanisms. A significant area of progress lies in the development of novel AEDs with enhanced efficacy and safety profiles.The mainstream treatment for epileptic seizures involves over 30 antiepileptic drugs (AEDs)**(Table 1)**[7]. However, these drugs only provide symptomatic relief and fail to modify disease progression. Additionally, drug-resistant epilepsy affects about one-third of epilepsy patients[8]. This underscores the complexity of epilepsy's pathogenesis and the urgent need for disease-modifying therapeutic strategies that can halt disease progression and alleviate neurobehavioral

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comorbidities associated with epilepsy. In this context, there has been growing interest in exploring novel antiepileptic therapeutic compounds from natural sources. Quercetin, a flavonoid compound found in various fruits, vegetables, leaves and grains, has garnered attention for its potential in epilepsy treatment. Quercetin has been shown to possess neuroprotective effects against various neurological disorders, including epilepsy[9]. Animal studies have reported that quercetin exerts antiepileptic effects primarily by ameliorating oxidative damage and reducing inflammatory responses[10]. Importantly, quercetin is capable of penetrating the blood-brain barrier, making it a suitable therapeutic candidate for various brain disorders, including epilepsy[11]. While further preclinical and clinical studies are needed to fully understand quercetin's efficacy and safety in managing epilepsy, its antioxidant, anti-inflammatory properties and ability to modulate neurotransmitter systems and ion channels involved in seizure generation and propagation make it a promising candidate for further investigation in this field.

Nanotechnology has transformed drug delivery and treatment enhancement by providing precise control over drug release, improved targeting and enhanced therapeutic effectiveness. Engineered nanoparticles can target specific cells or tissues, reducing systemic side effects while increasing drug concentration at the desired site[12]. Additionally, these nanoparticles enhance drug solubility and stability, thereby improving drug bioavailability and efficacy[13]. Nanotechnology enables controlled and sustained drug release, overcoming biological barriers such as the blood-brain barrier and expanding the range of accessible drug targets[14]. Furthermore, it allows for combination therapy, delivering multiple drugs simultaneously within a single nanoparticle to enhance synergistic effects and combat drug resistance. Nanoparticles functionalized with imaging agents also enable early disease detection, diagnosis and monitoring, thus advancing personalized medicine and improving patient outcomes[15].

Table 1:Years of Introduction of Currently Available Antiseizure Medications in the Market

1900	1951	1986	2001	2015
1950	1985	2000	2015	2022
Phenobarbital	Carbamazepine	Felbamate	Eslicarbazepine acetate	Brivaracetam
Phenytoin	Clobazam	Fosphenytoin	Lacosamide	Cannabidiol
	Clonazepam	Gabapentin	Perampanel	Cenobamate
	Diazepam	Lamotrigine	Pregabalin	Everolimus
	Ethosuximide	Levetiracetam	Rufinamide	Fenfluramine
	Midazolam	Lorazepam	Stiripentol	Brivaracetam
	Primidone	Oxcarbazepine	Eslicarbazepine	
	Valproic acid	Tiagabine		
		Topiramate		
		Vigabatrin		
		Zonisamide		

2. Chemistry of Quercetin

Quercetin **(Figure 1)**, a flavonol found abundantly in nature, belongs to the polyphenol flavonoid group. It is widely distributed in various fruits, vegetables, seeds and grains with capers, red onions and kale being notable sources[16]. Renowned for its bitter taste, quercetin is a popular addition to dietary supplements, beverages and numerous food products. Its name, derived from the Latin "quercetum," meaning oak

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forest, reflects its association with the oak genus Quercus[17].

According to the International Union of Pure and Applied Chemistry (IUPAC), quercetin is formallyknownas3,3',4',5,7pentahydroxyflavanoneor3, 3',4',5,7-pentahydroxy-2-phenylchromen-4-one. The quercetin molecule contains five hydroxyl groups located at positions 3, 5, 7, 3', and 4', allowing for the formation of various pentamethyl derivatives[18].Quercetin is also known by several other names, including 5,7,3′,4′-flavon-3-ol, Sophoretin, Meletin, Quercetine, Xanthaurine, Quercetol, Quercitin, Quertine, and Flavin meletin[19]. It presents as a yellow crystalline powder with a chemical formula of C15H10O7 and a molar mass of 302.236 g/mol. With a density of 1.799 g/cm^3 and a melting point of 316 °C (601 °F; 589 K), quercetin is practically insoluble in water but soluble in aqueous alkaline solutions[20].

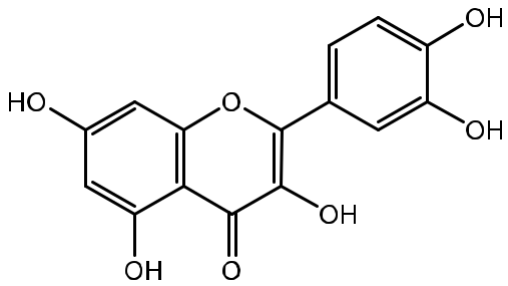

Figure 1. Structure of Quercetin

3. Antiepileptic effects of Quercetin

The antiepileptic effects of quercetin have been demonstrated in various *in vivo* studies. In one study using a KA-induced epilepsy model in BALB/c mice, quercetin treatment (50 and 100 mg) dose-dependently reduced KA-induced seizures as indicated by a decreased seizure

score compared to the KA-treated group[21].Similarly, in a study involving Wistar rats the seizure-protective effects of quercetin obtained from *Heterothecainuloides* plant were investigated in a KA-induced epilepsy model. Oral administration of quercetin at doses of 30, 100 and 300 mg/kg resulted in a dose-dependent reduction in seizure severity [22]. Additionally, quercetin treatment delayed seizures in the KA group.In another experiment using a KA-induced epileptic seizure model in BALB/c mice, quercetin treatment (10 mg/kg) significantly reduced KA-induced seizure activity, as evidenced by a decreased seizure score in the quercetin-treated group compared to the KA-treated group [23].

Quercetin is essential in the regulation of neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate[24]. GABA acts as a primary inhibitory neurotransmitter in the centralnervous system regulating neuronal excitability via GABAA receptors[25]. Experimental findings indicate that quercetin may possess antiepileptic properties by modulating GABAA receptors, potentially offering a therapeutic approach for temporal lobe epilepsy (TLE)[26]. In an animal model of KA-induced seizures (10 mg/kg, I.P.), aimed at investigating the GluR1 subunit of the AMPA receptor and the NR2A and NR2B subunits of the NMDA receptor, quercetin treatment (100 mg/kg, I.P.) led to an increase in the gene expression of GluR1, NR2A and NR2B subunits of glutamate receptors[27].Similarly, in another study using the same KA-induced seizure model (10 mg/kg, I.P.), quercetin treatment (100 mg/kg, I.P.) significantly reduced the gene expression of the AB1 and AB3 subunits of the GABAA receptor in the hippocampus[28].Furthermore, in the same KA-induced seizure animal model, there was an observed increase in the expression of the GABAA α-5 receptor gene. Interestingly, treatment with quercetin at doses of 50 and 100 mg/kg significantly decreased the expression of the GABAA α-5 receptor gene[29].

Quercetin's powerful antioxidant properties hold promise for epilepsy treatment by enhancing cellular antioxidant capacity, effectively reducing epilepsy-related oxidative stress and preventing neuronal cell damage and subsequent neurodegeneration[30,31]. Further research is essential to explore novel antioxidant compounds for epilepsy treatment. Numerous preclinical studies have investigated quercetin's impact on oxidative processes in animal epilepsy models. In rodent models of KA-induced seizures, quercetin significantly increased the activity of antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and superoxide dismutase (SOD), while concurrently reducing malondialdehyde (MDA) and carbonylated protein levels in the brain[2]. Similarly, in

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a PTZ-kindled model, quercetin treatment led to a significant decrease in malondialdehyde (MDA) levels in the hippocampus and cerebral cortex, revealing the intricate prooxidative and antioxidative effects of quercetin[32].

Neuro inflammation plays a big role in epilepsy. Drugs that fight inflammation can help prevent long-term problems[33]. When seizures happen, microglial cells in the brain get activated and release inflammatory chemicals. These chemicals can make neurons too active and cause damage. Substances like TNF-α, IL-1β and HMGB1 are part of this process[34-36]. They can also make the brain's protective barrier weak, letting in harmful cells[37]. Quercetin and other flavonoids can reduce inflammation by controlling a protein called NF-κB[38]. Quercetin also lowers the levels of inflammatory chemicals like TNF-α and IL-1β released by microglial cells, which helps to reduce epilepsy. High levels of IL-1β in the brain can trigger seizures, especially febrile seizures[39,40].In a rat model of prenatal febrile seizures induced by KA, researchers investigated the therapeutic effect of quercetin. They found that quercetin administration alleviated febrile seizures and reduced IL-1β levels. However, when combined with lipopolysaccharide (LPS) injection, quercetin's ability to suppress IL-1β was limited due to an exaggerated inflammatory response triggered by LPS. This suggests that quercetin may have a limited effect in controlling the systemic release of IL-1β and other pro-inflammatory cytokines that cross the blood-brain barrier[41]. Nanotechnology-based drug delivery systems have emerged as a novel and promising strategy to enhance drug bioavailability[42].Intranasal administration of a mucoadhesive nano-emulsion containing quercetin has been shown to enhance the bioavailability of quercetin and its transport across the blood-brain barrier[43].Research has demonstrated that silica nanoparticlesloaded with quercetin can effectively decrease the production of proinflammatory cytokines by cultured macrophages[44].The effectiveness of nanoparticles loaded with quercetin was evaluated in a chronic epilepsy model induced by PTZ (36.5 mg/kg). Thesenanoparticles, made by conjugating quercetin with Fe3O4– cyclodextrin nanoparticles, significantly reduced seizure behaviour, neuronal loss and astrocyte activation compared to free quercetin in the PTZ model. Overall, quercetin–Fe3O4– cyclodextrin nanoparticles offer a promising therapeutic approach for epilepsy[45].To enhance quercetin's ability to penetrate the blood-brain barrier (BBB), it is essential to improve its bioavailability through the development of innovative nanoparticles[46].

4. Nanotechnology approaches for Quercetin delivery

a. Encapsulation technique: Quercetin have weak solubility in water, also chemical stability in food and the human stomach frequently restrict its bioavailability. encapsulation techniques that can be applied to raise Quercetin's bioavailability. To enhance its bioavalibilty, encapsulation often entails trapping an active agent inside another material[47]

b. Liposome: Liposomes are vesicular systems for drug delivery that contain lipid bilayers generally comprising cholesterols and phospholipids. The cytotoxicity and stability of quercetin can be increased by incorporating it into liposomes. Liposomes loaded with quercetin demonstrated a low hygroscopicity, a decreased propensity to absorb water, and a favourable stability profile. [48]. *Seong et al.*formulated multidimensional liposomes that were shown to be stable when coated with chitooligosaccharide and N-succinyl-chitosan. When compared to uncoated liposomes, these liposomes displayed increased drug release at pH 5.5. At pH 5.5, these liposomes showed higher drug release compared with uncoated liposomes [49]. Encapsulation of quercetin using long circulating liposomes formed using film ultrasound reversed multidrug resistance

[50-52]. *Santos et al.*developed magnetoliposomes that demonstrated enhanced in vitro effects on rat glioma cell survival and were shown to be useful as an anticancer treatment [53-54]. Based on dipalmitoyl lecithin, stable liposomes containing quercetin with a regulated release pattern were also produced [56-58]. Additionally, incorporating quercetin into succinylchitosan liposomes improved its stability and release at gut pH.

c.Nanoemulsion: Nanoemulsions are colloidal biphasic dispersions comprising two immiscible liquids which are water in oil (w/o) or oil in water (o/w) droplets stabilized by a surfactant. Stable emulsions with enhanced solubility and bioaccessibility were formulated using natural milk protein surfactants [59]. Furthermore, red pepper seed oil was used to prepare a

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double emulsion of quercetin, which showed increased stability compared with an emulsion prepared using olive and sunflower oil [60-63]. The antioxidant activity, stability, and solubility of quercetin was improved by formulating its nanoemulsion using linseed, olive, and fish oil [64]. Quercetin-loaded solid self-emulsifying delivery systems (SEDs) showed a delayed release pattern and higher stability compared with liquid SEDs [65-67]. **d. Micelles:**Drug carrier that are lipophilic can be delivered using polymeric micelles. *Srisa-nga et al.* used film hydration to create supramagnetic micelles that were loaded with quercetin. The spherical-shaped prepared micelles exhibited more cytotoxicity than free quercetin when they entered HepG2.2.15 cells. Due to their ability to halt the proliferation of cancer cells, these micelles show promise as a treatment for hepatocellular carcinoma [68]. In simulated gastrointestinal fluid, quercetin-loaded micelles demonstrated efficient solubility and prolonged drug release [69]. When compared to free quercetin, quercetin loaded into micelles showed markedly increased solubility, prolonged release behaviour, and anticancer potential [70]. CD44-overexpressing tumour cells were suppressed by hyaluronic acid-quercetin bioconjugatedmiceelles, which also displayed pH-dependent and prolonged drug release [71].

e. Conjugate-based delivery systems:A

chitin-glucan-aldehyde-quercetin conjugate was synthesised by *Dutta et al.* via a condensation procedure, and it demonstrated improved antioxidant capacity as well as DPPH and 2,2'-azino-bis(3-ethylbenzothiazoline-6- sulfonic acid) (ABTS) scavenging characteristics. When applied to the J774 cell line, the conjugate demonstrated significant antioxidant potential [87]. In one investigation, quercetin that had been modified by conjugating with glutamic acid was more effective than quercetin that was left free in reversing multidrug resistance [72]. *Zhang et al.* produced quercetin-glutathione conjugates and came to the conclusion that quercetin contributes to the glutathione depletion in human aortic endothelial cells by promoting the formation and export of quercetin-glutathione conjugates throughout the cells[73-74].

f. **Nanostructured lipid carriers:**Liquid lipids (oils) and solids distributed in an aqueous solution including a surfactant are the components of nanostructured lipid carriers (NLCs), which exhibit exceptional stability, minimal cytotoxicity, and good biocompatibility[75]. When compared to a quercetin solution, Liu et al.'s quercetin NLCs showed a slower rate of release and accumulated in the kidney, liver, and lungs. As

a result, NLCs were suggested as a possible nanocarrier technology for quercetin oral administration [76]. NLC, solid lipid NPs (SLNs), and nano lipid emulsions (NLE) loaded with quercetin were compared by Aditya et al. When compared to SLNs, NLCs and NLEs had

a higher bioaccessibility. Moreover, NLCs had the highest encapsulation effectiveness of >90% and were the shortest in size [77-80]. According to a recent study, quercetin's antioxidant properties, penetration, and ability to stay in the dermis and epidermis

g. Polymeric nanoparticle: Polymeric nanoparticles can be made of a variety of biomaterials, including polymers and lipids. Scientists are generally interested in polymeric nanoparticles[81-83]. Numerous bioactive substances (proteins, APIs, genetic material) can be included into the interior or outer surface of NPs[84]. The substance may be transferred to the intended site of action by NPs because of their small size and ability to provide a sustained molecule release. By changing the external stimuli, such as pH, temperature, irradiation, etc., the controlled release may be accomplished[85]

h. **Hydrogel:**Another category of polymeric compositions that may be employed as Quercetin delivery systems are hydrogels. Depending on where they came from, they are categorised as natural, synthetic, or hybrid. Their capacity to absorb large volumes of aqueous liquids into their polymeric network is the consequence of the cross-linking of polymers, which gives them their three-dimensional shape. *Bashir et al.* (2018) created hydrogels based on karaya gum-g-poly(acrylic acid) as effective delivery systems for the hydrophobic medication Quercetin [86]. The hydrogels demonstrated a porous structure and demonstrated resilience against mechanical strain[87]. They presented a superior profile in acidic pH settings than in neutral pH situations, and their swelling characteristics varied in water and buffer solutions. The

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drug encapsulation was attained to a maximum of 88%. Drug release experiments conducted in vitro showed that pH[88]

5. Future direction of Quercetin

Quercetin has surfaced as a promising alternative for brain tumors due to its antioxidant, anti-cancer and anti-inflammatory properties. Moreover, it is a natural compound with low toxicity and a suitable safety profile. Even though Que demonstrates significant antitumor activity, its application for further pharmacological benefits is limited due to its low solubility, bioavailability, and instability in different in vitro and in vivo experimental models[89].The encapsulation of Quercetin into nano-formulations, which enhanced its biological activity and therapeutic potential, is notably the significant advance for Quercetin. Nevertheless, there haven't been any documented therapeutic trials that use nano-delivery methods to provide Quercetin to patients with CNS tumours. Treating any sickness in humans efficiently depends on the capacity to deliver extremely potent therapeutic chemicals precisely to the sites of disease. Unfortunately, because unbound drug molecules are rapidly metabolised before they reach their targeted locations and because biodistribution is non-specific, current treatment techniques need an excessively high systemic dose. These innovative drug delivery systems are smaller than conventional large-scale systems and provide better benefits, such modified pharmacokinetic behaviour and enhanced payload[90].

Based on an evaluation of scientific observations, Quercetin is usually considered safe. According to existing reports, safety evaluation of Quercetin usage was carried out in adult individuals. Children and adolescents as well as pregnant and breastfeeding women were not included in the target population[91]. These specific vulnerable groups were excluded due to some safety concerns because of certain hormonal effects of Quercetin that were observed in animal studies (variation of testosterone levels), which requires further elucidation. In general, there is insufficient relevant safety data from human studies which could appeal to strong conclusions regarding safety concerns for this population group[92].

However, certain potential risk categories have been identified in relation to the findings from animal research, taking into account limitations arising from inadequate human data and the difficulties in extrapolating findings from animal studies to people. Given the potentially nephrotoxic effects of quercetin that have been shown on the pre-damaged kidney in mouse models, patients with renal dysfunction may represent a potential risk category for long-term use of quercetin at high dosages. Furthermore, a study conducted on animals revealed that quercetin may have the ability to promote tumour growth in cancers that are estrogen-dependent. These results, nevertheless, require further explanation[93].

Across several studies, adverse effects after Quercetin intake have been rarely reported and such effects are usually mild. However, few reports indicated some potential risk groups. Therefore, the future investigation should be conducted in order to ensure the clinical safety of Quercetin usage[94].

6. Conclusion

According to the previously published data, quercetin is a strong antioxidant that improves neurons' ability to survive a range of oxidative stressors in culture. Remarkably, in contrast to other flavonoids, antioxidation seems to be a prerequisite for neuroprotection, but not an adequate one, and activities on transcription factors and intracellular signalling seem to be essential for the preservation of neurons in culture.Particularly significant is the activation of Nrf2, which promotes the translocation of the protein to the nucleus and increases the production of survival and antioxidation-related proteins. One outcome of this action is an increase in glutathione concentrations, which is essential for the survival and repair of intracellular redox. Activation of other transcription factors such as NF-κB or key molecules for survival such as sirtuins, as well as kinase inhibition and modulation of intracellular signaling are part of the complex pro survival profile of quercetin. Accordingly, in vitro studies show a great potential of quercetin as a multi-target neuroprotective molecule. The chronic administration of quercetin as part of complex natural mixtures would assure low amounts of the molecule in the brain where a low level of its pro-oxidant profile could potentiate antioxidant defenses. The in-vitro and in-vivo outcomes of the study provide a hope for better brain delivery of neuro-protective agents for various neurological disorders, which constitute a huge burden on humanity. Quercetin's strong and wide range of direct and indirect antioxidant effects would be helpful

in the early stages of CNS disorders when redox imbalance is present. Consequently, quercetin would play a significant function as a preventative nutraceutical agent when included in plant matrices. Its possible use as a therapeutic agent in advanced chronic neurodegenerative illnesses or in acute circumstances like stroke still requires a great deal of investigation.

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