International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

Check for updates

Allium cepa peel-derived quercetin and polyphenols: Mechanistic evidence for neuroprotection in epilepsy

Abhay L. Rathod *, Sagar N. Ande and Pramod V Burakle

Department of Pharmacology, Dr. Rajendra Gode Institute of Pharmacy, Mardi Road, Amravati, Maharashtra-444602.

International Journal of Science and Research Archive, 2026, 19(01), 725-749

Publication history: Received on 09 March 2026; revised on 18 April 2026; accepted on 20 April 2026

Article DOI: https://doi.org/10.30574/ijsra.2026.19.1.0805

Abstract

Allium cepa peel, commonly discarded as waste, is a rich source of bioactive phytoconstituents with potential therapeutic benefits. Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and epilepsy are increasing globally and are associated with oxidative stress, inflammation, and neuronal loss. Due to the limited effectiveness of current treatments, plant-derived compounds are gaining attention for their neuroprotective potential. Onion peels are particularly rich in quercetin, its glycosides, and other flavonoids and phenolic compounds known for their antioxidant and anti-inflammatory properties. This review summarizes existing scientific evidence on the neuroprotective effects of Allium cepa peel, based on studies retrieved from PubMed, Google Scholar, and ScienceDirect. Preclinical studies indicate that onion peel extracts can reduce oxidative stress, modulate inflammation, support mitochondrial function, and improve cognitive performance. Quercetin is identified as the primary active compound, along with minor contributions from other phenolics and sulphur-containing compounds. Overall, Allium cepa peel shows promising neuroprotective potential; however, further human studies are required to confirm its mechanisms and clinical applicability.

Keywords: Onion Peels; Phytoconstituents; Epilepsy; Quercetin and Derivatives; Neuroprotective Mechanisms

1. Introduction

Allium cepa (onion) is well known vegetable that is used daily in our meals due to its vast nutritious values. Onions are native to Asia, and varieties like red, yellow, white are widely use.as a food item, onion is generally used as vegetable ingredient in cooking.it can also be eaten in raw form as a salad, used in spice .as an herbal medicine onion is used for treating cough. Asthma. Bronchitis, etc. Several benefits of onion are due to potential phytocompounds such as flavonoids, anthocyanins, organ sulphur compounds, phenolic acids, etc[1], [2] .The lacrimatory effect of onion is due to enzymes like alliinase and sulphur compounds[3]. Onion contains several important phytoconstituents such as quercetin, quercetin glycosides and kaempferol. This phytoconstituents exhibits several pharmacological activities like antioxidant, anti-inflammatory, anti-allergenic, neuroprotective, cardioprotective, anti-diabetic, antifungal, etc[4]. Outer peel of onions contains more flavonoids than edible bulb[5]. Quercetin is major flavanol present in outer peel as compared to edible flesh[6]. There are several quercetin derivatives identified in outer peel such as quercetin 3,4'-diglycoside, quercetin-7,4'-diglycoside, iso rhamnetin-3,4'diglycoside, quercetin-3-glycoside, quercetin-4'-gluco side, isorhamnetin-4'-glycoside, protocatecoyl quercetin, quercetin dimer 4'-glycoside, quercetin dimer hexoxide, quercetin dimer, and quercetin trimer, etc[7]. Presence of these important phytoconstituents in onion outer peel possess neuroprotective potential. Thus, powder form or extract of onion peel can be used in neurodegenerative diseases. Consumption of allium cepa for long term can produce preventive effect on the incidence of neurodegenerative diseases[8].

* Corresponding author: Abhay Lalsing Rathod

Allium cepa and its outer peel contains several bio constituents and have been extensively studied and several original and review articles were published on their pharmacological, nutritious effects and health benefits. The present article is compilation of data on neuroprotective potential of allium cepa peel enriched with quercetin derivatives and other coactive in neurodegenerative diseases. This review will provide mechanistic studies of neuroprotective effects of allium cepa peel which is regarded as a waste product and further, can be used therapeutic agent.

Figure 1 *Allium cepa* L (onion)

2. Botanical overview[9]

The genus *Allium* l. Consists of 1100 recognised species, makes it one of the biggest genera of the family Amaryllidaceae and taxonomically significant group in the order asparagales[10]. Allium cepa is the biennial herbaceous plant and cultivated annually. It has tunicated bulb, hollow cylindrical leaves, terminal umbels bearing white to purple flowers[11].

Table 1 Botanical overview of *Allium* cepa.

Kingdom	**Plantae**
Division	Magnoliophyta
Class	Liliopsida
Order	Asparagales
Family	Amaryllidaceae
Genus	*Allium*
Species	*A. cepa* L
Edible parts	leaves, flowers, seed, root

3. Morphological characters[12], [13]:

Table 2 Morphological characteristics features of onion peel.

S. No.	**Morphological characters**	**Description**
1	Family	Amaryllidaceae
2	Habit	Perennial herb
3	Stem	Underground modified stem forming a fleshy bulb
4	Root system	Fibrous, adventitious
5	Leaves	Sheathing leaves with parallel venation
6	Bulb	Fleshy, underground, cylindrical to globose
7	Inflorescence	Umbel

8	Scape	Leafless, hollow flowering stalk (75–180 cm)
9	Flowers	Small, bisexual, actinomorphic, hypogynous
10	Perianth	Six white tepals arranged in two whorls; valvate aestivation
11	Androecium	Six epipetalous stamens
12	Gynoecium	Syncarpous, tricarpellary
13	Ovary	Superior, trilocular with axile placentation
14	Fruit	Loculicidal capsule
15	Seed	Endo spermous

4. Bio compounds in *allium* cepa peels

Onion peel i.e. Outer skin of onion is considered as solid waste and these peels consists of various phytochemicals[14], [15]. Studies have reported presence of flavonoids[16], phenolics[16], [17], [18], [19] flavanols [14], anthocyanins [20], [21], [22] vanillic acid[23]ferulic acid[23]. Phytochemical profile of allium cepa peel is given in table 2, and some structures of important bio compounds given in fig2.

Highest concentration of phenolics, flavonoids were observed in onion peel as compared to onion bulb[16], [24]. Outer peel of onion, top bottom part, brown skin had higher number of total phenolics (19.7, 30.5, 52.7 mg GAE/g), total flavonoids (19.5, 25.9, 43.1 QE/g), total flavanols (19.27, 15.29, 7.89 mg/g) as compared to inner scales (9.4 mg GAE/g; 7.0 mg QE/g; 6.19 mg/g)[14]. Onion peel and skin of yellow onions cultivated in farms of southern Sweden had total phenol (mg GAE/g) content ranging from 27.8 to 51.1 and 54.7–68.2 based on dry weight, respectively[25]. Yellow peels of onions from the local market of Galati, Romania, reported for having slightly higher total polyphenolic compound (97.28 mg GAE/g dw). These onion peels were also reported to have good flavonoid content[23]. Peel extract from the onions of Nigerian local market gave yield of 98.52 µ g QE/ml total flavonoids and 664.30 µ g/ml GAE total phenols[18]. Ethanolic extract of onion peels obtained from yellow onions had cultivated in Korea had higher amount of phenolic and flavonoid compounds, like *p* -coumaric acid and vanillic acid, epicatechin, morin [26]. However, flavonoids in red onion peel (20.22 mg/g), had higher as compared to pearl (19.64 mg/g), and white (0.08 mg/g) variety[16]. Other than this, differences in varieties and regions of cultivation the concentrations of phenolic and flavonoid compounds in onion peel may also different based on the extraction methods used[27]. Studies concluded that ethanolic extraction resulted in yielding highest amount of total flavonoid and phenolics (372.50 mg GAE/g extract; 183.95 mg qe/g extract)[27]. Dried red onion skin reported for containing (82.99 to 431.08 mg cyanidin 3-o-glycoside/100 g)[28]. Albishi et.al confirmed that red onion skin contains highest number of anthocyanins (10.04mg anthocyanidin-3-glucoside/100g) as compared to yellow, white variety[16]. Despite various extraction techniques the main and major flavonoid compound identified was quercetin. The compound identified was quercetin and its glycosides derivatives such as quercetin 4'-o –glucoside, quercetin 3,4'-diglucoside, and kaempferol were reported for highest amount present in onion skin[29]. Ethanolic extraction of onion peel contains (62.39mg/g dw), hot water extraction contains (25.78mg/g dw), swe-110 ◦ c contains (44.40mg/g dw), and swe-165 ◦ c contains (12.26mg/g dw) quercetin and this was determined by lee et al[27]. Onion peel extracts (acetonic; ethanolic; methanolic) contains several other compounds such as morin(298.37; 158.74; 341.23µ g/g dm),quercitrin (04.55; 21.49; 31.78µg/g dm),myricetin(00.95; 00.10; 0.46µg/g dm),epicatechin(111.05; 274.98; 534.86µg/g dm)[24].thus due to rich flavonoids, phenolics compounds having strong antioxidant activity , neuroprotective potential onion peels can be used in neurodegenerative disorders as a vital ingredient in herbal therapeutic medicine[30].

5. Phytochemical profile of *Allium* cepa peel

Table 3 Phytoconstituents present in onion peel.

Variety (region)	Extraction method	Bioactive compounds identified	Yield /concentration of bio actives	References
Yellow onion peel (Galati, Romania)	Ultrasound-assisted extraction (UAE) at 100 W, 40	Total flavonoids content (TFC) Total polyphenolic content (TPC)	55.27 mg QE/g dw 97.28 mg GAE/g dw	Milea et al. [25]

	kHz; for 30 min, using 70% ethanol			
Onion solid wastes	Ultrasound-assisted extraction	Total polyphenols Protocatechuic acid, protocatechuic acid derivative, 2-(3,4-dihydroxy benzoyl) 2,4,6-trihydroxybenzofuran-3(2 H)-one, quercetin 7,4'-O,O-diglucoside, cyanidin 3-O-glucoside, quercetin 3,4'-O,O-diglucoside, cyanidin 3-O-malonylglucoside, quercetin 4'-O-glucoside, isorhamnetin 3-O-glucoside, quercetin, quercetin 4'-O-glucoside/quercetin dehydrate adduct, quercetin 4'-O-glucoside/quercetin adduct, quercetin dehydrodimer	21.57–64.91 mg GAE/g dw	Katsampa et al [29]
Onion peel (South Korea)	Ethanol extraction	TPC TFC Quercetin	372.50 mg GAE/g 183.95 mg QE/g 62.39 mg/g dw	Lee et al [27]
Onion peel (South Korea)	Hot water extraction	TPC TFC Quercetin	120.6 mg GAE/g 54.50 mg QE/g 25.78 mg/g dw	Lee et al [27]
Onion peel (South Korea)	Subcritical water extraction: SWE (at 110ºC and 165ºC)	TPC TFC Quercetin	218.73 & 56.68 mg GAE/g 119.5 & 27.10 mg QE/g 44.4 & 12.26 mg/g dw	Lee et al [27]
Onion skin (South of Sweden)	50% ethanol containing 0.05 M ortho-phosphoric acid	Total phenols Quercetin-3,7,4-triglucoside, p-hydroxybenzoic acid, quercetin-7,4-diglucoside, vanillic acid, quercetin-3,4-diglucoside, quercetin-3-O-glucoside, ferulic acid, kaempferol-3-O-glucoside,	54.7–68.2 mg GAE/ g dw 26.3 mg/g dw 12.2 mg/g dw 366.4 mg/g dw 20.0 mg/g dw 444.7 mg/g dw 301.8 mg/g dw Below detection levels 32.2 mg/g dw	Burri et al. [23]

		isorhamnetin-3-Oglucoside, quercetin-4-O-glucoside, quercetin, kaempferol.	10.7 mg/g dw 1767.6 mg/g dw 1779.8 mg/g dw 263.9 mg/g dw	
Onion peel (South of Sweden)	50% ethanol containing 0.05 M ortho-phosphoric acid	Total phenols Quercetin-3,7,4-triglucoside, p-hydroxybenzoic acid, quercetin-7,4-diglucoside, vanillic acid, quercetin-3,4-diglucoside, quercetin-3-O-glucoside, ferulic acid, kaempferol-3-O-glucoside, isorhamnetin-3-Oglucoside, quercetin-4-O-glucoside, quercetin, kaempferol.	27.8–51.1 mg GAE/ g dw 173.5 mg/g dw 4.1 mg/g dw 416.2 mg/g dw 12.1 mg/g dw 952.8 mg/g dw 729.5 mg/g dw 30.7 mg/g dw 129.7 mg/g dw 113.7 mg/g dw 1936.6 mg/g dw 623.8 mg/g dw 93.2 mg/g dw	Burri et al. [23]
Red onion (Allium cepa L) solid waste (Muan, South Korea)	Distilled water (DWE), 80% aqueous methanol (ME), 80% aqueous ethanol (EE), diethyl ether (DEE), ethyl acetate (EAE), n-butanol (BE)	TPC TFC quercetin-3,4′-O-diglucoside, Quercetin-3-O-glucoside (isoquercetin) Quercetin-4′-O-glucoside (spiraeoside) isorhamnetin-4′-glucoside, quercitrin glycoside, quercetin aglycone	30.5–415.3 mg GAE/g 10.6–120.6 mg QE/ g 32.8 mg/100 g 9.1 mg/100 g 41.6 mg/100 g 6.3 mg/100 g 57.5 mg/100 g	Nile, et al. [30]
Onion waste (outer scales, top, bottom, brown skin) (Spain)	70% acidified methanol extract	Total phenolics Total flavonoids Total flavanols Quercetin, quercetin 3'-glucoside, quercetin 4'-glucoside, quercetin 3,4'-diglucoside, isorhamnetin 3,4'-diglucoside, isorhamnetin 4'- glucoside	19.7–52.7 mg GAE/ g dw 19.5–43.1 mg QE/g dw 7.89–19.27 mg/g dw 0.59–1.61 mg/g dw 0.31–0.42 mg/g dw 0.32–1.03 mg/g dw 0.34–9.49 mg/g dw	Benítez et al. [14]

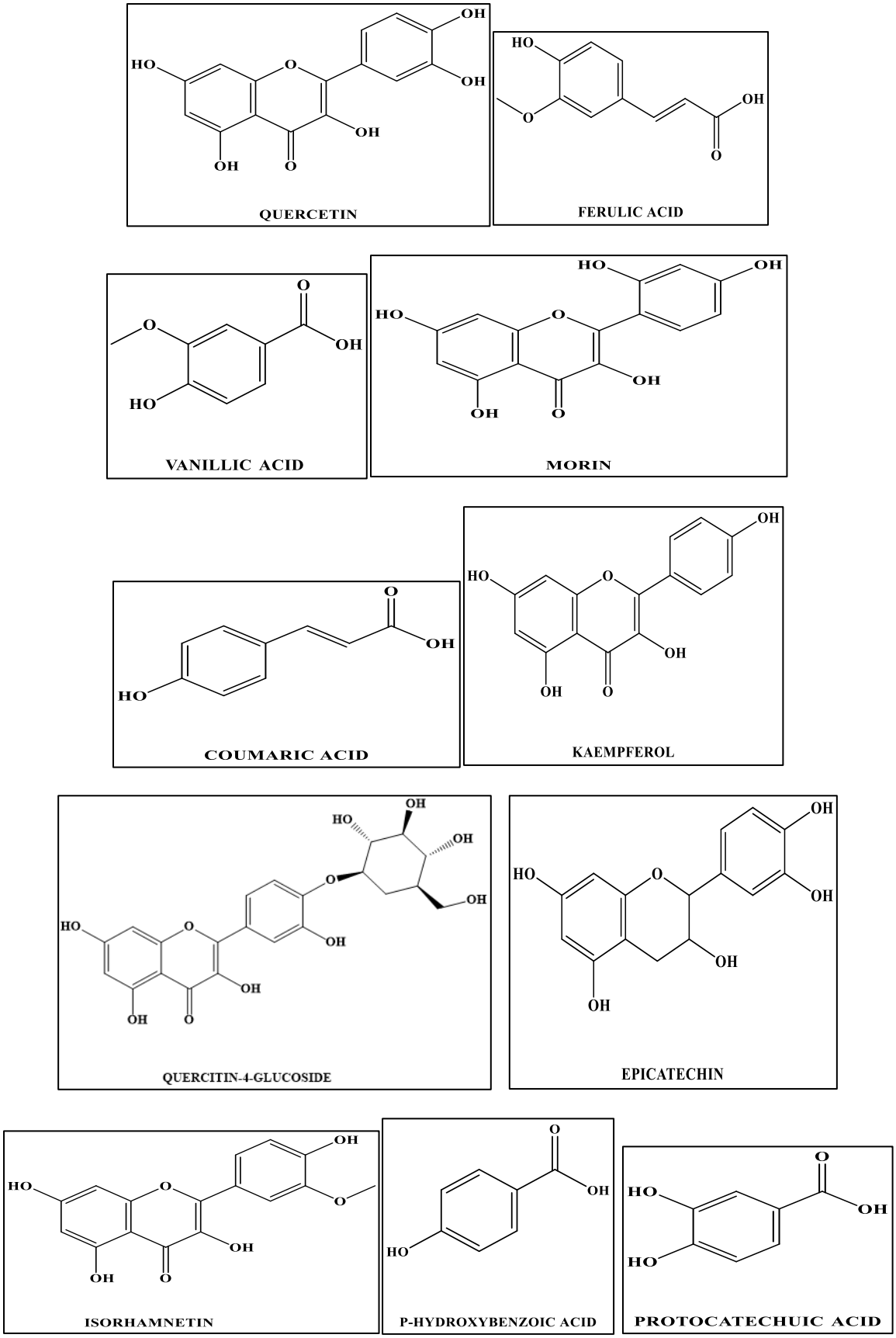

Figure 2 Some important structures of Bio compounds present in *Allium* cepa peels

6. Quercetin as neuroprotective agent

Dietary flavonoids have neuroprotective properties (fig no.3) it also includes protection from amelioration of memory, learning, cognitive function, protection from neuronal injury by traumatic injury[31], [32]. Quercetin and its glycosides are the most commonly occurring flavonoids in abundant amount in onion peels[29]. Quercetin has been reported to exert neuroprotective effects against a wide range of neurodegenerative disorders such as Alzheimer's disease (AD)[33], Parkinson disease (PD)[34], Epilepsy[35]. Animal models studies reported that quercetin possesses antiepileptic effect ameliorating the oxidative stress, downregulates the inflammatory response[35], [36]. The most important feature of quercetin is it can penetrate the blood-brain-barrier (BBB)[37], [38]. Thus, quercetin is a suitable therapeutic candidate for various neurological disorders.

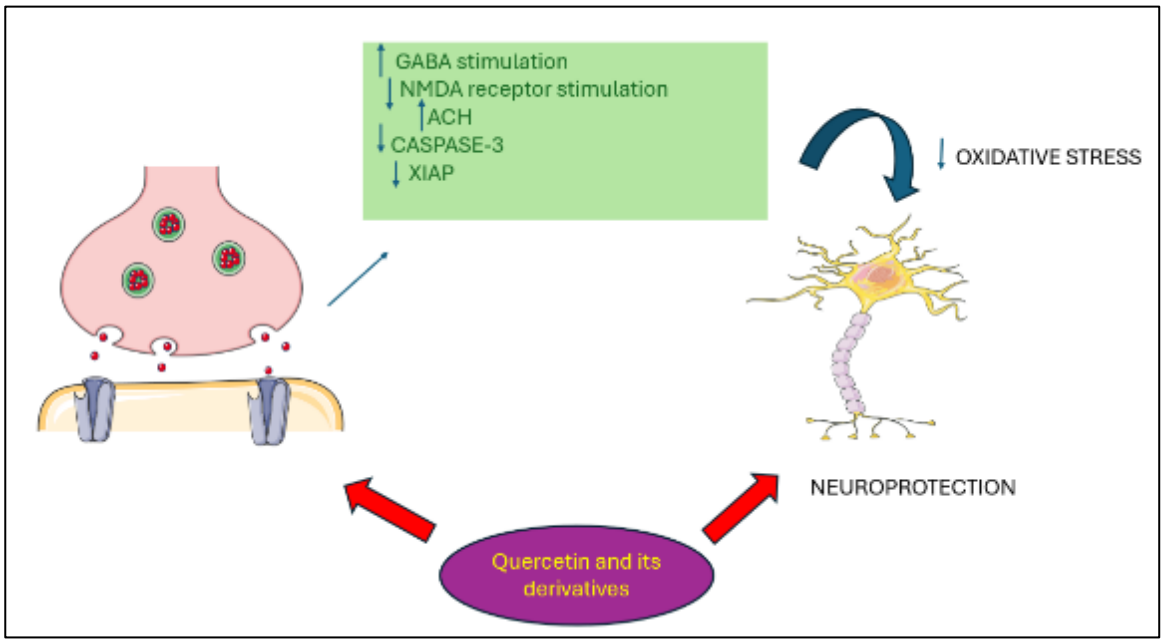

Figure 3 Quercetin and its derivatives effect on neurotransmitters and oxidative stress

7. Quercetin neuroprotective potential in epilepsy

Quercetin effects on seizure onset, seizure frequency, and duration: update from experimental findings:

Antiepileptic activity of quercetin has been investigated in several *in vivo* studies. In kainic acid (KA) induced seizures in BALB/c mice (10 mg/kg), quercetin significantly reduces the KA induced seizure activity determined by decrease in seizures scores in quercetin treatment group as compared to ka treated group[35]. Antiepileptic effect of quercetin obtained from the plant *heterotheca inuloides* was also reported in ka induced seizures model in Wistar rats. Oral administration of quercetin at the doses of 30,100and300mg/kg there is a dose -dependent reduction in seizures scores was observed, also seizure delaying effect were reported in ka group after quercetin treatment[39]. Quercetin at the dose of 50 ,100mg/kg dose dependently reduced the seizures scores[40].

The antiseizures effect of quercetin was reported in pentylenetetrazol (PTZ) (45mg/kg) and picrotoxin(5mg/kg) induced epileptic animal model in male albino rats. Quercetin in the dose of 10mg/kg significantly delayed the onset of seizures, reduced the seizures stage and also reduced the generalised seizures duration in (PTZ) group[41]. Quercetin (20mg/kg) significantly reduced the onset of seizure in picrotoxin induced seizures group: however, it is observed that quercetin (10mg/kg) treated group does not show significant results in delaying onset of seizures. Quercetin in 10,20mg/kg did not reduce the seizures scores in picrotoxin treated group[41].

The antiepileptic effect of quercetin has been studied in several models of epilepsy, it includes model of psychomotor seizures induced by 6-hz stimulation, maximal electroshock (MES) and PTZ [42]. During 6- Hz seizure test in mice quercetin showed anticonvulsant effect 30-60 min post injection. However, in MES test in mice quercetin (100–800 mg/kg) did not significantly change the seizure threshold. Also, quercetin (100-800 mg/kg) did not significantly change any parameters of first myoclonic twitches, generalized clonus, and forelimb tonus seizures in PTZ infusion test[42].

The seizure preventive effect of quercetin at single dose and multiple doses were also investigated in acute and chronic model of PTZ induced seizures where , PTZ (90mg/kg) is administered via intraperitoneal(i.p.), quercetin given in (50-100mg/kg) dose delayed the latency of generalized tonic -clonic seizures onset(GTCS).however, quercetin (25mg/kg) at multiple oral and intraperitoneal administration for 7days 30min before PTZ) delayed seizure onset and decreased GTCS duration[43]. In PTZ kindling chronic seizure model, quercetin (25, 50, 100, and 200 mg/kg) pretreated prior to each kindling differentially altered the stages kindling development stages[43]. All these studies reflect that acute intraperitoneal and multiple oral administration of quercetin did not affect the PTZ-induced GTCS.

Table 4 Summarizing effect of quercetin in epilepsy

Sr.no	Animal model	Treatment regimen	Observation	References
1.	KA (10mg/kg, I.P.)-induced seizure in male BALB/c mice	Quercetin (50 and 100 mg/kg I.P.) daily for 7 days; on the last day, KA was injected 30 min after the administration of quercetin.	Quercetin reduced the seizure severity score in animals in a dose dependent manner. Quercetin significantly decreased the overexpression of GABAA a5 receptor gene.	[40]
2.	KA (10mg/kg I.P.)-induced seizure in male BALB/c mice	Quercetin (50 and 100 mg/kg, I.P.) for 6 days and, on the 7th day injections of KA were administered 30 minutes after the quercetin injections	The mRNA levels of the GABAA receptor b3 subunit were higher in the KA group. Pretreated quercetin prevented increase in the mRNA levels of the b1 and the b3 subunits of the GABAA receptor.	[47]
3.	KA (10mg/kg, I.P.)-induced seizure in male BALB/c mice	Quercetin (50 and 100 mg/kg, I.P.) was administered daily for 7 days, and on the last day, KA was injected 30 minutes after administration of quercetin.	GluR1 gene expression levels in the KA group were decreased after 7 days. It was observed that quercetin at a dose of 100 mg/kg increases the overexpression of GluR1 subunit gene in the hippocampus. Quercetin (100 mg/kg) significantly increased the level of NR2AandNR2Bsubunit gene expression in the hippocampus.	[51]
4.	Psychomotor seizures (6-Hz seizures) were induced via corneal stimulation on male Swiss mice (0.2 ms square pulse at 6 Hz for 3 s) using Grass S48 stimulator coupled with a constant current unit	In order to determine the time-course of anticonvulsant effect of quercetin (400 mg/kg, I.P.) in the 6 Hz test in mice, quercetin was injected and tested at 15, 30, 60, 120, and 240 min post injection time points.	Quercetin gave anticonvulsant effect 30-60min after their injection in the 6-Hz seizures taste in mice. Statistical analysis did not demonstrate differences between seizure thresholds determined 30 and 60 min after quercetin administration.	[44]
5.	PTZ (35 mg/kg, I.P., 15 injections total)-induced seizure in Wistar rats	25, 50, or 100 mg/kg of quercetin I.P. was given 30 min before administration of PTZ every other day.	Pretreatment with 50 mg/kg of quercetin attenuated the seizure severity of the kindling procedure. Quercetin 50 mg/kg significantly enhanced memory retrieval in the retention tests of a passive avoidance task compared to the control. MDA levels were significantly increased in the quercetin groups in the hippocampus and cerebral cortex following PTZ kindling.	[79]

6.	PTZ (35 and 90mg/ kg, I.P.)-induced seizure in male Wistar rats	Quercetin (25, 50, 100, 200 mg/kg, I.P. or gavage) was administered for 7 days and on the last day PTZ was administered 30 min after the administration of quercetin.	Quercetin significantly increased time to death compared with that of the control. On the test day (day 33), 100 mg/kg quercetin significantly increased GTCS onset compared with the control. 100 mg/kg quercetin significantly reduced GTCS duration compared with the control. 200 mg/kg quercetin did not show an anticonvulsive effect, and the duration of GTCS was not significantly reduced.	[43]
7.	One week after surgery and animal recovery, using stimulus isolated from amygdala of male Wistar rats kindling model was prepared	Quercetin (40 mg/kg/day, I.P., dissolved in propylene glycol) was received for three weeks.	Quercetin administration inhibited amygdala electrical kindling in all respects including its seizure severity and duration. Quercetin pretreatment caused lower seizure intensity.	[81]
8.	KA (10mg/kg, I.P.)-induced seizure in BALB/c mice	Quercetin-3-O-rutinoside (rutin) (100 and 200 mg/kg, I.P.) for 7 d, and on the last day, KA was injected 30 min after administration of rutin.	Quercetin reduces the occurrence of seizures and the MDA substance involved in oxidative stress in the hippocampus.	[82]
9.	KA (10mg/kg I.P.)-induced seizure in Wistar rats	In the groups treated with methanolic and acetonic extracts of *H. inuloides* and quercetin (30, 100, and 300 mg/kg, orally) for six days prior to KA administration for assessment of their protective effects.	Dose-dependent effects on the all-natural product groups vs. the control group, with decreases in seizure severity and increases in seizure latency on lipid peroxidation and carbonylated proteins in all brain tissues.	[39]
10.	Lithium chloride (125 mg/kg, I.P.)-pilocarpine (10 mg/kg, I.P.)-induced SE in male SD rats	The rats in the quercetin-treated SE group received quercetin treatment (50 mg/kg I.P.) 15 min after SE onset. All SE rats received chloral hydrate (10%, 3 ml/kg, I.P.) to terminate epileptic attacks.	Study found expression alterations of X-linked inhibitor of apoptosis protein and caspase-3 protein in post SE hippocampus, along with an alteration in the number of apoptotic and surviving neurons.	[83]
11.	KA (10mg/kg, I.P.)-induced seizure in BALB/c mice	In the KA+quercetin group, the mice were injected with quercetin (10 ml, 100 mg/kg, I.P.) daily for one week and on the last day, KA was administered 30 min following injection with quercetin.	Microglia cells in the KA group had higher TNF a and IL-1b expression levels in the culture medium and then decreased with quercetin. The expression levels of the molecule IBA1 involved in NF-jB and microglia phagocytosis increased in microglia cells in the KA group treated with quercetin.	[35]

12.	PTZ (36.5mg/kg, I.P.)-induced seizure in male NMRI mice	Quercetin-loaded NPs were prepared using an iron oxide core coated with bCD and pluronic F68 polymer. Quercetin or its nano-formulation (25 or 50mg/kg I.P.) were administered 10 days before PTZ injections.	Compared to free quercetin, quercetin NPs were observed to significantly reduce seizure behaviour, neuronal loss, and astrocyte activation in the PTZ model.	[84]

8. Quercetin modulates neurotransmitters

Flavonoids can modulate the activity of neurotransmitters in central nervous system (CNS). Quercetin plays a significant role in multiple cellular and molecular mechanisms; it also regulates the neurotransmitters in the brain[36]. The most imp action of quercetin is it can modulate gamma -aminobutyric acid (GABA), glutamate, adenosine, acetyl choline, serotonin, glycine receptors[42]. Because of their central involvement in controlling neuronal excitation and inhibition, GABA and glutamate have attracted significant research interest. Among them, gamma-aminobutyric acid (GABA) serves as the principal inhibitory neurotransmitter in the central nervous system (CNS). It exerts its effects primarily through receptors associated with chloride (Cl^-) ion channels. Activation of GABA (a) receptors increase chloride influx into neurons, leading to membrane hyperpolarization and a reduction in neuronal excitability. In this way, GABAergic signaling plays a critical role in maintaining the balance between excitation and inhibition within neural circuits[44].

Experimental studies suggest that flavonoids possess antiepileptic properties, partly through their interaction with the GABA-a receptor–chloride channel complex. Owing to certain structural similarities with benzodiazepines, flavonoids are believed to modulate this receptor system, thereby enhancing inhibitory neurotransmission and reducing neuronal hyperexcitability[45]. Schipper and colleagues proposed that GABA-a receptors may represent a promising therapeutic target in the management of temporal lobe epilepsy (TLE). Given their central role in mediating inhibitory neurotransmission, modulation of these receptors could help restore the imbalance between excitation and inhibition that characterizes temporal lobe epilepsy (TLE)[46]. In a kainic acid (ka, 10 mg/kg, i.p.)–induced seizure model, an upregulation of the GABA-a α5 receptor subunit gene expression was observed. Notably, administration of quercetin at doses of 50 and 100 mg/kg significantly attenuated this elevated expression. Furthermore, quercetin treatment produced a dose-dependent reduction in behavioral seizure scores, indicating its potential modulatory effect on GABAergic signaling and seizure severity [46]. Consistent with these findings, another study reported that quercetin (100 mg/kg) significantly downregulated the gene expression of the GABA-a receptor β1 and β3 subunits in the hippocampus in a kainic acid (ka, 10 mg/kg, i.p.)–induced seizure model. These results further support the modulatory role of quercetin on GABAergic signaling pathways during seizure conditions[47]. The upregulation of GABA receptor expression observed in epilepsy may reflect an adaptive or compensatory response to ongoing neuronal hyperexcitability. This increased expression likely represents an intrinsic attempt of the brain to restore the disrupted balance between excitation and inhibition that characterizes epileptic pathology[48]. This elevated receptor expression may represent an intrinsic neuroprotective response aimed at counteracting the excitotoxic damage associated with recurrent seizure activity. By enhancing inhibitory signaling, the brain may attempt to limit excessive neuronal firing and reduce seizure-induced neuronal injury[49].

L-glutamate is the principal excitatory neurotransmitter in the central nervous system (CNS), playing a crucial role in maintaining synaptic plasticity and facilitating processes such as learning, memory formation, and the development of new neural networks. Upon release from presynaptic terminals, glutamate binds to postsynaptic receptors, including ionotropic receptors—AMPA and NMDA—as well as g protein–coupled metabotropic glutamate receptors. Through activation of these receptor systems, glutamate regulates excitatory neurotransmission and synaptic signaling [50]. Following its release from presynaptic terminals, glutamate binds to postsynaptic receptors, including ionotropic receptors such as AMPA and NMDA, as well as g protein–coupled metabotropic glutamate receptors. Activation of these receptor systems mediates excitatory synaptic transmission and plays a central role in regulating neuronal communication[50]. In a kainic acid (ka, 10 mg/kg, i.p.)–induced seizure model, the expression of specific glutamatergic receptor subunits was investigated, including glur1 of the AMPA receptor and nr2a and nr2b of the NMDA receptor. Administration of quercetin (100 mg/kg, i.p.) Was found to significantly upregulate the gene expression of glur1, nr2a, and nr2b subunits. These findings suggest that quercetin may modulate glutamatergic receptor dynamics in the context of seizure activity[51]. The observed upregulation of glutr1, nr2a, and nr2b subunits may indicate that quercetin

contributes to the regulation of synaptic plasticity. By modulating the expression of key glutamatergic receptor components, quercetin could influence synaptic remodeling and functional recovery in seizure conditions.

Quercetin's impact on neurotransmission goes beyond simply altering receptor expression levels. It also plays an important role in regulating the functional activity of NMDA receptors. When NMDA receptors are excessively activated, they cause prolonged neuronal depolarization and allow an abnormal influx of calcium ions (Ca^{2+}) into postsynaptic neurons (fig.4). This rise in intracellular calcium disrupts cellular balance and triggers a cascade of harmful events, including oxidative stress, mitochondrial dysfunction, and activation of cell death pathways. Over time, these processes contribute to neuronal degeneration and loss, which are key features of epileptic brain injury.

By moderating NMDA receptor activity, quercetin helps prevent calcium overload and reduces excitotoxic damage, thereby supporting neuronal survival and maintaining synaptic stability during seizure conditions[52]. Pentylenetetrazol (PTZ) is a widely used chemical convulsant in experimental epilepsy models. It induces seizures primarily by antagonizing GABA-a receptors, thereby reducing inhibitory neurotransmission. This imbalance enhances neuronal excitability, indirectly facilitating glutamatergic overactivation, including NMDA receptor stimulation. The resulting excessive activation promotes increased Ca^{2+} influx into neurons, contributing to neuronal hyperexcitability and seizure generation[53]. Quercetin has been reported to act as a functional antagonist of NMDA receptors. By modulating NMDA receptor activity, it helps limit excessive calcium influx into neurons, thereby reducing excitotoxic damage. This inhibitory effect on NMDA-mediated signaling contributes to its neuroprotective potential, particularly in conditions such as epilepsy where glutamate-induced excitotoxicity plays a central role[45]. NMDA receptor antagonists are well-recognized for their potent anticonvulsant properties and are also employed in certain clinical settings. By inhibiting NMDA receptor activity, these agents reduce the excessive influx of Ca^{2+} into neurons. This limitation of calcium entry prevents abnormal neuronal hyperstimulation, thereby protecting against excitotoxic damage and seizure propagation [54]. Since glutamate is the principal excitatory neurotransmitter in the central nervous system, excessive glutamatergic signaling plays a pivotal role in seizure initiation and propagation. Overactivation of ionotropic glutamate receptors—particularly the n-methyl-d-aspartate (NMDA) receptor—leads to increased intracellular calcium influx, neuronal hyperexcitability, oxidative stress, and ultimately excitotoxic neuronal damage, all of which are central to epileptogenesis.

In this context, quercetin, a bioactive flavonoid abundantly present in onion peel, demonstrates promising antiepileptic potential. Experimental evidence suggests that quercetin can attenuate glutamate-mediated excitotoxicity by modulating NMDA receptor activity, reducing calcium overload, and suppressing downstream oxidative and inflammatory cascades. By limiting NMDA receptor overactivation, quercetin may help restore the balance between excitatory (glutamate) and inhibitory (GABAergic) neurotransmission—an imbalance that is a hallmark of epilepsy.

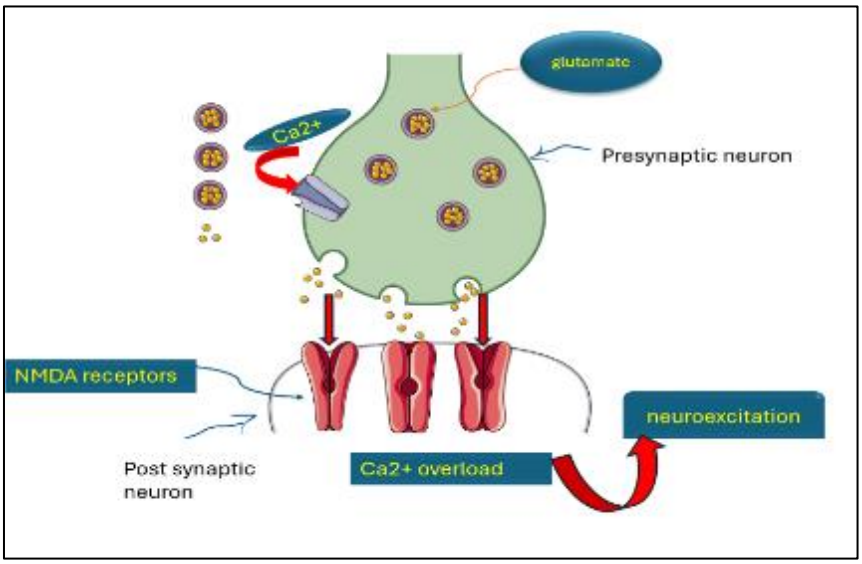

Figure 4 Glutamate binds to NMDA receptor led to overload of calcium ions that causes neuronal excitation

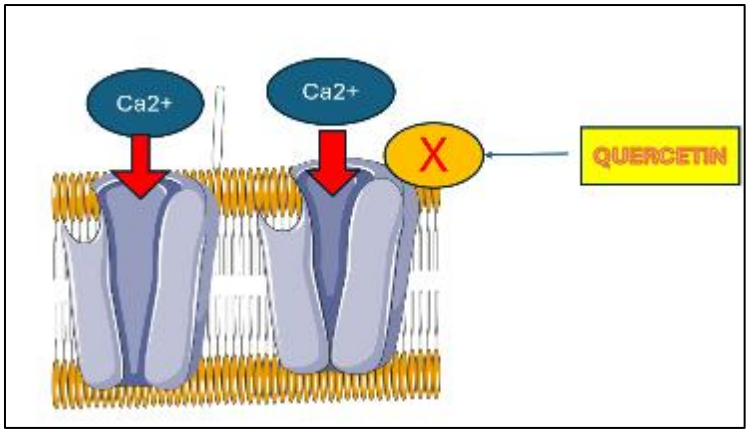

Figure 5 Quercetin blocks the Ca^{2+} ion channels, reduce calcium influx leading to prevent neuroexcitation

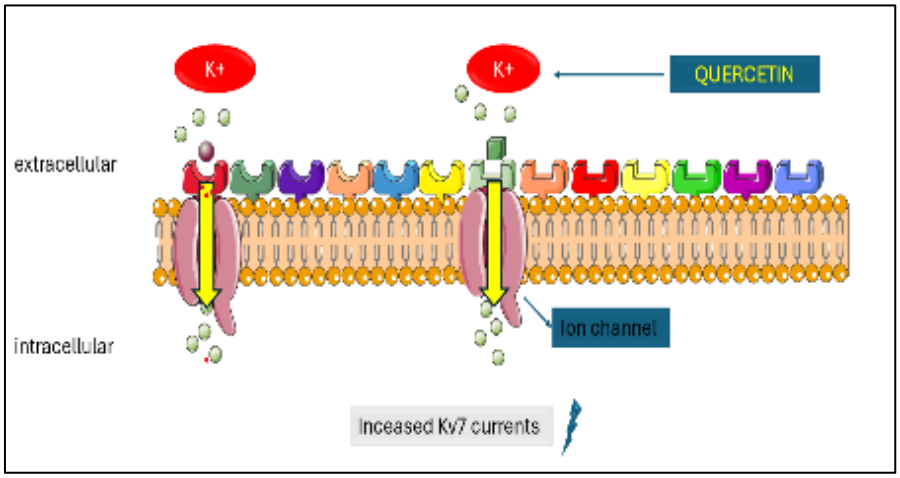

Figure 6 Quercetin stimulate k+ ion channel influx prevents seizures

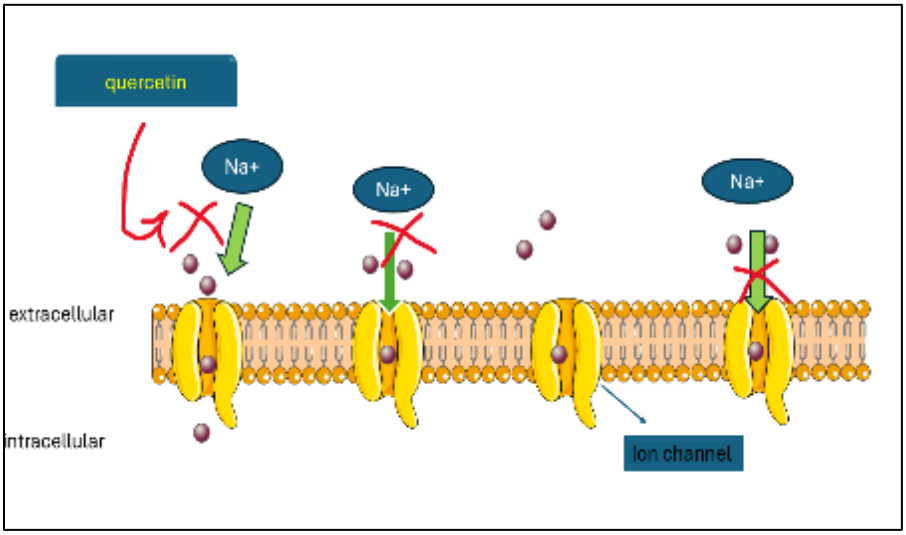

Figure 7 Quercetin blocks sodium ion channels prevent neuroexcitation

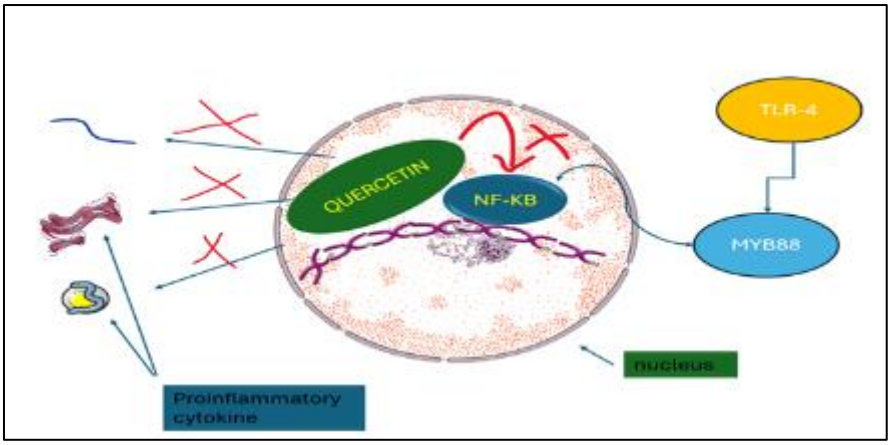

Figure 8 LPS, which binds to TLR-4 during neuroinflammation, causes cytokine production within the cell. Quercetin may inhibit the formation of cytokines by binding to NF-kB in the cell nucleus

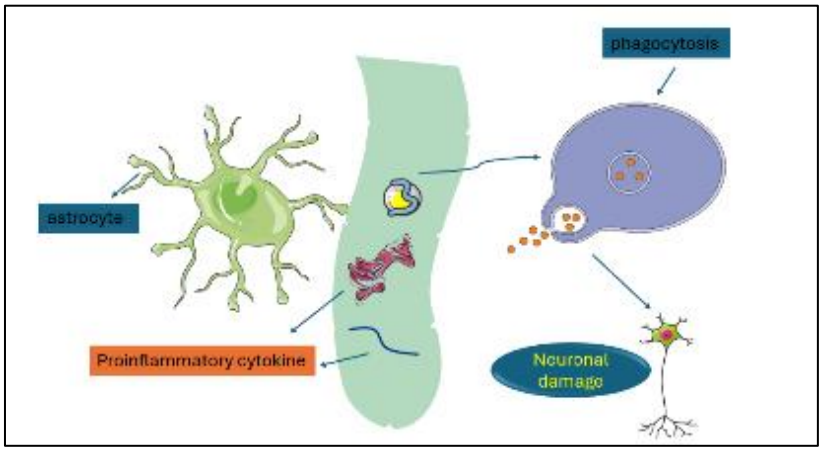

Figure 9 Inflammatory substances released into the blood cause phagocytosis and neuronal damage in the epileptogenesis

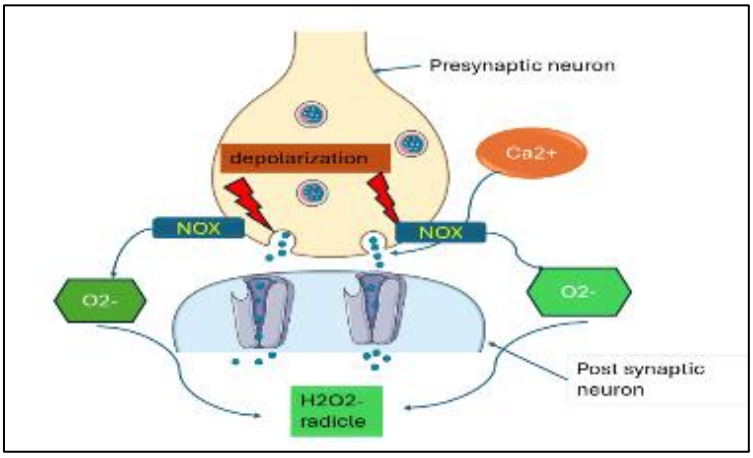

Figure 10 Quercetin prevents free radicle generation thus, prevent oxidative stress production

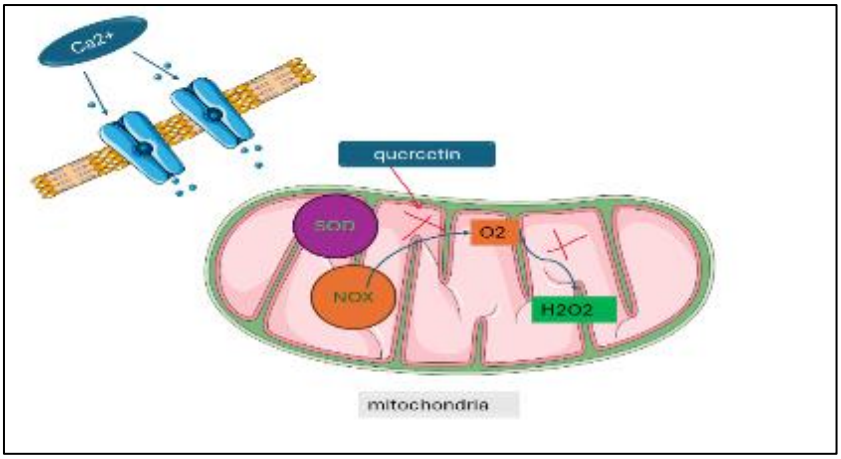

Figure 11 Quercetin binds to intracellular and extracellular pro- oxidant enzymes prevents mitochondrial damage

9. Quercetin modulates ion channels

Currently, nearly 25% of the genes implicated in epilepsy encode ion channels, underscoring the critical role of channel dysfunction in seizure pathophysiology. These genes primarily regulate voltage-gated and ligand-gated ion channels that control neuronal excitability, action potential generation, and synaptic transmission[55]. Approximately 25% of epilepsy-related genes encode ion channels, indicating that epilepsy is largely a channelopathy characterized by dysfunctional regulation of neuronal excitability. Abnormalities in sodium, potassium, calcium, and glutamate receptor channels contribute to hyperexcitability and seizure generation. In this context, quercetin may exert antiepileptic effects through modulation of ion channels and restoration of excitatory–inhibitory balance, highlighting its relevance in understanding ion channel–mediated molecular mechanisms (fig5). Acid-sensing ion channels (ASICs) are proton-gated cation channels that contribute to several physiological functions, including synaptic plasticity, learning, memory, and nociception. However, excessive activation of asics under pathological conditions—such as tissue acidosis during ischemia—can promote neuronal injury. Dysregulated ASIC activity has been implicated in neuronal death and seizure generation, particularly during ischemic stroke, highlighting their potential role in epilepsy-related pathophysiology[56].

Quercetin has been demonstrated to inhibit ph-induced currents in Chinese hamster ovary (CHO) cells expressing different rat ASIC isoforms. Furthermore, quercetin attenuates intracellular Ca^{2+} elevation and reduces cell death triggered by acidic conditions in hek-293 cells expressing asic1a and ASIC2a. These findings suggest that quercetin may exert neuroprotective effects by modulating acid-sensing ion channel activity and limiting acid-induced excitotoxic damage[57]. Investigating the effects of quercetin on seizure progression mediated through ASIC channel inhibition may provide valuable insights into its underlying molecular mechanisms[58]. Such studies could help clarify how modulation of acid-sensing ion channels contributes to its potential anticonvulsant and neuroprotective actions. Ca^{2+}activated k^+ (BK_{Ca}) channels are key regulators of neuronal excitability and play an important role in seizure pathophysiology. These large-conductance channels couple membrane depolarization with intracellular Ca^{2+} levels to control action potential repolarization and firing frequency. Interestingly, both excessive activation and inhibition of BK_{Ca} channels have been associated with epileptic seizures, reflecting their complex and context-dependent role in modulating neuronal network excitability[59]. The effects of quercetin-loaded liposomes (PCL-Q) on BK_{Ca} channel activity were evaluated in mouse myocytes under H_2O_2-induced oxidative stress. The findings demonstrated that PCL-Q enhances BK_{Ca} channel activation, suggesting a protective role against oxidative stress–mediated cellular dysfunction. This modulation of BK_{Ca} activity may contribute to the electrophysiological stabilizing and neuroprotective effects of quercetin [59]. In this context, although activation of BK_{Ca} channels by quercetin may exert protective and stabilizing effects, excessive or inappropriate activation of these channels can also contribute to seizure generation. Therefore, the precise role of BK_{Ca} modulation in epilepsy remains complex and context-dependent. Further studies are required to clarify how quercetin-mediated BK_{Ca} activation influences seizure susceptibility and epileptogenesis.

Mutations in genes encoding the voltage-gated potassium channel7(k_v7), particularly kcnq2 and kcnq3, have been strongly linked to a spectrum of epileptic disorders. These range from benign familial neonatal seizures to severe developmental and epileptic encephalopathies. Dysfunction of k_v7 channels impair neuronal repolarization and enhances membrane excitability, thereby increasing susceptibility to recurrent seizures[60]. Pharmacological stimulation of $k_v7.2$ and $k_v7.3$ potassium channels has been shown to exert significant antiepileptic effects in clinical

settings, highlighting their crucial role in regulating neuronal excitability in humans [61]. Quercetin has been reported to enhance the activity of $k_v7.1$, $k_v7.2$, $k_v7.3$, and $k_v7.4$ (fig6) potassium channel currents, indicating its modulatory influence on multiple k_v7 channel subtypes. However, this potentiating effect was not observed in kv7.5 channels, suggesting a degree of subtype selectivity in its mechanism of action[62]. Quercetin has been shown to stimulate the activity of $Na^+–k^+–2cl^-$ cotransporter 1 (NKCC1), a key ion transporter responsible for maintaining intracellular chloride homeostasis. Through activation of nkcc1, quercetin may promote an increase in cytosolic cl^- levels, thereby influencing neuronal ionic balance and excitability[63]. It has been investigated that seizures activity was delayed and it was observed that NKCC was overexpressed[64]. However, quercetin stimulates NKCC activation, it can say that the antiepileptic effect of quercetin is due to other mechanism pathway and not this.

P2x4 receptors are ATP-activated ion channels present on the cell surface as well as inside the cell in structures such as vesicles, vacuoles, lamellar bodies, and lysosomes. These receptors open when they detect extracellular ATP and allow positively charged ions to enter the cell. In epilepsy, the expression of p2x4 receptors on microglial cells is increased, indicating their involvement in seizure-associated neuroinflammation[65]. Research studies have done reporting that quercetin treatment block p2x4 expression diabetes induces rats[66]. It is important to investigate quercetin mechanism of action on p2x4 in epilepsy.

It has been studied that voltage-dependent Ca^{2+} channels regulates the neuronal excitation and blockers of this ion channel are used clinically for seizure control[67]. Studies also shown that the transient receptor potential canonical channel 3 (TRPC3), a specific type of ion channel present in brain cells may involve in epileptic seizures episodes[68]. Studies shows that quercetin can blocks l-type voltage-dependent Ca^{2+} channels and TRPC3. These channels allow calcium entry into nerve cells which is important for nerve functions. However, excessive calcium entry into nerve cells can produce nerve excitability. Thus, by blocking these ion channels quercetin may produce its neuroprotective activity[69]. In some people with epilepsy, mutations in voltage-gated na^+ (Na_v) have been identified. These channels are responsible for initiating and transmitting electrical signals in neurons. Changes (mutations) in these ion channels cause them to remain open longer or stimulate easily, they allow excessive sodium ions into nerve cells, causing neurons more excitable[70]. Studies done on isolated ca1 pyramidal neurons from the rat hippocampus, quercetin was found to reduce the amount of sodium ions entering the nerve cells during electrical activity[71]. Since, the Na^+ ion plays an important role in neuronal excitation, quercetin might be a promising neuroprotective candidate by suppressing Na_v channels(fig.7).

10. Quercetin mitigates oxidative stress in epilepsy

Oxidative stress develops when there is an imbalance between reactive oxygen species (ROS) and bodies antioxidant defence system[72]. Oxidative stress contributes a significant role in various neurological disorders such as neuro excitotoxicity, neuroinflammation, neurodegeneration[73]. It is believed that intense and abnormal neuronal excitation during seizures episodes can lead oxidative damage. Due to abnormal neuronal firing, excessive glutamate releases and activates NMDA receptors and cause oxidative stress. Due to this cellular component gets damaged. Also, overproduction of ROS can lead to dysregulate intracellular homeostasis[74], [75]. Thus, compounds like quercetin and its derivatives having high antioxidant activity can be used as therapeutic neuroprotective candidate in oxidative stress associated with epilepsy and neuroinflammation and neurodegeneration(fig10).

Quercetin and its derivatives exert its effects on various significant target molecule and various enzymes[76]. Glutathione (GSH) an antioxidant enzyme modulates the oxidative stress by changing the activity of NADPH oxidase (NOX), paraoxonase (PON) enzymes, and nuclear factor e2-related factor 2-antioxidant response element (nrf2-are) pathway. Quercetin and its derivatives having antioxidant properties has the ability to increase antioxidant cellular capacity by increasing GSH levels. GSH acts as a hydrogen donor in the conversion reactions of the formed $o_2–$ radicals to nontoxic h_2o[77], [78].

Several preclinical studies have determined effect of quercetin on oxidative stress in the animal models of seizures. In a ka induced seizures animal model in rats, quercetin significantly increases the activity of antioxidant enzymes such as catalase (CAT), superoxide dismutase (sod), glutathione peroxidase (GP_x), and significantly decreases malondialdehyde (MDA) levels in the brains of rats[39].

In a PTZ kindled model, quercetin treatment (25, 50 and 100mg/kg, i.p.) Significantly increases MDA levels in the hippocampus and cerebral cortex as compared to PTZ kindled group[79]. These studies suggest that quercetin can produce both antioxidative and prooxidative effects(fig11). Quercetin metabolites are also thought to produce prooxidative effect, mild oxidative stress production led to increase in antioxidant defence of the cell and acts as cytoprotective[80].in a study conducted on amygdala stimulus kindling model, quercetin 40mg/kg inhibited seizure

severity and seizure duration[81].in a ka(10mg/kg i.p.) Induced seizures in BALB/c mice model, quercetin-3-o glucoside(100,200 mg/kg)reduced the onset of seizures[82].in a lithium chloride(125 mg/kg i.p)-pilocarpine(10mg/kg i.p)se rat model , quercetin (50mg/kg i.p.) Altered the apoptotic neurons[83].in a ptz (36.5mg/kg i.p.) Induced seizures in NMRI mice model, quercetin nanoparticles reduced the onset of seizures , severity of seizures[84]. However, studies about the antioxidant effect of quercetin and its metabolites in epilepsy are insufficient and needs more researches on the relevant pathophysiology involved in epilepsy.

11. Quercetin supresses inflammatory responses in epilepsy

Neurodegeneration and neuroinflammation can worsen the epileptic seizures. Anti -inflammatory drugs are used in epilepsy to prevent chronic consequences[85]. Microglial cells play a significant role in neuroinflammatory pathways involved in seizures progression[86]. Seizures stimulation rapidly activates microglia's, results in neuronal excitotoxicity and neurodegeneration[87]. Arachidonic acid cascade pathway, high mobility group box protein1 (HMGB1), heat shock protein 70, interleukin-1 (il-1) and toll like receptor (TLR4) plays significant role in inflammatory progression[88], [89], [90], [91]. Seizures production for long term and release of proinflammatory cytokines can cause disruption of BBB and infiltration of leucocytes[92]. Studies have revealed that il-1b overexpression can cause epilepsy[93]. HMGB1 is a proinflammatory cytokine which is studied and used as a therapeutic target in epilepsy[94], [95], [96]. Studies reported that inflammatory biomarker associated with microglia, macrophages, antigen-presenting cells increased after seizures(fig9.)[97], [98].

Flavonoids such as quercetin and its derivatives can be an antiepileptic therapeutic candidate due to their significant anti-inflammatory, anti-oxidative, neuroprotective potential. These bio compounds act by decreasing inflammatory responses by blocking expression of proinflammatory cytokines in seizures(fig.8)[99]. Current research suggests that flavonoids beneficial effects in neurological disease such as epilepsy is associated with regulation of antioxidative and anti-inflammatory mediators such as GSH, superoxide dismutase and cytokines[100]. Flavonoids inhibit the inflammatory mediators such as ROS and no also, inhibits regulation of inflammatory enzymes such as Coxs and inducible nitric oxide synthase(iNOS), modulates transcription factors such as NF-KB[101], [102], [103].

Microglia associated neuroinflammation has been reported to show significant role in epilepsy [87]. It has been reported that microglial cells in the ka (10 mg/kg, i.p.) Had increased TNF-α and IL-1B expression, which were decreased after quercetin treatment. It was observed that ionized calcium-binding adapter molecule 1 (IBA1) is the molecule involved in the phagocytosis of microglia and NF-KB, its expression levels were increased in the microglia cells of ka group treated with quercetin. It has been reported that quercetin suppresses the ka induced epilepsy by blocking the activation of microglia cells[35].

Several research studies concluded that there is a direct correlation between IL-1 higher levels and febrile seizures in the hippocampus. Thus, il-1 is considered as one of the most important initiators of febrile response and neuronal excitotoxicity leading to generation of seizures[104], [105]. Ka (1.75 mg/kg, i.p.) Induced epilepsy model, quercetin therapeutic effect in prenatal febrile seizures associated to stress was studied. On 14^{th} day postnatal, rat pups were injected with lipopolysaccharide (lps, 200 mg/kg, 0.2 ml, i.p.) And treated with quercetin (10mg/kg i.p.).in this study, quercetin was shown to attenuates il-1b levels and treat febrile seizures.

However, LPS was unable to suppress excessive levels of il-1 in the inducer group. LPS injection caused a sudden inflammatory response characterized by an increased systemic proinflammatory cytokine. Studies have been done and shown quercetin limited effect in on released proinflammatory cytokines, exceeds bbb, activates glial cells to release more IL-1B(fig8)[106].

Quercetin treatment decreases the levels of proinflammatory cytokines in presence of both febrile seizures and prenatal stress related to epilepsy. However, quercetin can increase the proinflammatory cytokines levels in presence of only febrile seizures [106]. Currently, for increasing bioavailability of the bio compounds nanotechnology-based drug delivery systems have been used[107]. Quercetin nano-encapsulated form has been shown to lower the cellular oxidative stress and enhance neuronal protection in the hippocampus in a model of cerebral ischemia-induced brain injury[108]. Mucoadhesive nano emulsion loaded quercetin treated intranasally has been shown to increase the bioavailability of quercetin and its transport to BBB [109]. It has been concluded that nano-quercetin coated with triphenyl-phosphonium reduced the brain histopathological severity by maintaining the functionality and structural integrity of mitochondria in cerebral-ischemia -reperfusion brain injury.

It has been reported that quercetin-loaded silica nanoparticles (NPs) significantly lowered the production of proinflammatory cytokines[110]. Quercetin nanoparticles have been shown to reduce the seizure severity, neuronal

loss and astrocyte stimulation in the PTZ model. Thus, quercetin nanoparticles are novel therapeutic dosage form against epilepsy[111]. Nanoparticle's based delivery system enhances permeation of quercetin into BBB to provide neuroprotection.

12. Polyphenols in onion peel

Onion peel contains numerous polyphenolic compounds such as flavanols, anthocyanins and tannins[112], [113]. Study concluded that there are 9 main phenolic compounds present in onion peel[114]. Beside quercetin and its derivatives, ferulic acid, gallic acid, protocatechuic acid, kaempferol presence was reported in red onion peel extracts[115]. These phenolic compounds are present in minor quantity in peel as compared to quercetin and its derivatives. These polyphenols were reported to show strong antioxidant, anti-inflammatory effects[116]. They were also shown neuroprotective potential thus, these bio compounds can show synergistic effect with quercetin and its derivatives present in onion peel. In a PTZ (10mg/kg i.p.) Induced seizures rat model morin decreased TNF-α, IL-1B expression in the hippocampus and reduced the seizure score[117].Myricetin increased the GABA level while decreasing glutamate in PTZ (100mg/kg i.p) mice model[118].ferulic acid (75mg/kg i.p) decreases severity score in PTZ(30mg/kg i.p) rat mode[119]·In a pilocarpine (25mg/kg i.p.)Induced seizures in rat model protocatechuic acid downregulates the oxidative stress[120].reduced oxidative stress were observed in PTZ(50mg/kg i.p.) Induced seizures in rats by vanillic acid[121].Daily intake of cyanidin-3-0glucoside improve neurobehavioral function[122]. Kaempferol and epicatechin (100mg/kg p.o.) Decreased TNF-α, IL-6, NF-KB[123].

Table 5 Summarizing effect of polyphenols other than quercetin present in onion peels.

Sr.no	bio compounds	Animal model	Observation	References
1.	morin	PTZ induced seizures Rat model (10mg/kg i.p.)	Decreased TNF-α, IL-1B expression levels. Inhibited ep-JAK2/p-STAT3 cascade and GFAP expression in the CA1 area.	[117]
2.	myricetin	PTZ -induced mice model(100mg/kg)	Blocks the BDNF-Trkb signalling pathway, increased GABA levels while decreasing glutamate levels. MMP9 activity downregulated dose -dependently.	[118]
3.	Ferulic acid	PTZ kindling Rat model (30mg/kg i.p.)	Ferulic acid at dose of 75mg/kg,100mg/kg i.p.) reduced the seizure severity score, number of myoclonic jerks, cognitive decline, decreased oxidative stress was observed.	[119]
4.	Protocatechuic acid	Pilocarpine induced seizures in rat model (25mg/kg i.p.)	Protocatechuic acid was found to reduce neurodegeneration and oxidative stress in the hippocampus. Microglia activation was reduced.	[120]
5.	Vanillic acid	PTZ induced seizures in rat model (50mg/kg i.p.)	Upregulation of Nrf2, HO-1 and IGF-1 in CA3 hippocampal region, reduced oxidative stress, downregulation of GFAP	[121]
6.	Cyanidin 3-0-glucoside	Trimethyl tin chloride (TMT) induced neurodegeneration mice model	Daily intake of cyanidin -3-0 -glucoside improved neurobehavioral, regulate astrocyte function, reduced inflammatory cytokine levels.	[122]
7.	Kaempferol	PTZ kindled seizures rat model	Kaempferol (100mg/kg p.o.) downregulated TNF-α, IL-6, NF-KB.	[123]
8.	epicatechin	PTZ kindled seizures rat model	Epicatechin (100mg/kg p.o.) upregulated IL1Ra, IL-4, and IL-10 expression, attenuated TNF-α, IL-6.	[123]

Studies conducted on safety of onion peel concluded that there is absence of mortality at 2000mg/kg and ld50 of red onion peel extract is greater than 2000mg/kg. Mild toxicity was observed in sub-acute toxicity studies which strongly supports the therapeutic safety of red onion peel extract at moderate doses[124].

Table 6 Toxicity study of onion peels

Sr.no	toxicity models	Dose	observation	References
1.	Acute oral toxicity	2000mg/kg orally aqueous extract	No mortality was observed. LD50 dose of extract was found to be greater than 2000mg/kg. all animals were healthy and normal.	[124]
2.	Sub -acute toxicity	150, 250,500 mg/kg orally aqueous extract	Mortality was observed. 500mg/kg decreased the weight of animals. Liver function was normal.no effect on blood components. At higher dose 500mg/kg may cause mild cellular stress.	[124]

13. Discussion

Even though the current availability of antiepileptic drugs and their effects known, they do not inhibit all types of seizures. There are more than 25 antiepileptic drugs however, there drugs failed to alter disease condition [125]. Thus, investigating herbal therapeutic candidates for epilepsy is important. Red onion peel regarded as waste product consists several bio compounds having neuroprotective, strong antioxidant effects and anti-inflammatory effects. The bio compounds especially, phytochemicals viz. Flavonoids, anthocyanins, polyphenols present in onion peel make its use feasible in epilepsy. Quercetin and its derivatives in major amount and other polyphenols in small amount present in onion peel can provide synergistic neuroprotective effect in epilepsy due to strong antioxidant effects of several phytochemicals. Overall findings suggest that, rather than using quercetin alone, use of onion peel as a therapeutic candidate can provide significant effect in epilepsy. Further research studies are needed for concluding onion peel whole extract effect in epilepsy.

Abbreviations

- TPC: total phenolic content,
- TFC: total flavonoid content,
- KA: kainic acid,
- PTZ: pentylenetetrazol,
- NMDA: N-methyl-D- aspartate,
- GABA: gamma amino butyric acid,
- TLE: temporal lobe epilepsy,
- AMPA: α – amino- 3- hydroxy-5 -methyl – 4- isoxazole propionic Acid receptor,
- GTCS: generalized tonic – clonic seizures,
- CNS: central nervous system,
- BBB: blood brain barrier,
- MDA: malondialdehyde,
- NKCC: Na-K- Cl cotransporter,
- TLR: toll- like receptor,
- CAT: catalase, GSH: glutathione,
- ROS: reactive oxygen species.

14. Conclusion

Allium cepa peel, often considered waste, is a rich source of quercetin and other polyphenols with promising neuroprotective effects in epilepsy. These compounds act through multiple mechanisms, including reducing oxidative stress, suppressing inflammation, modulating neurotransmitters, and regulating ion channels to control neuronal excitability and seizures. While preclinical studies show significant antiepileptic potential and possible synergistic effects of various phytochemicals, clinical evidence is still lacking. Therefore, further human studies are needed to confirm its safety, efficacy, and therapeutic application.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] M. Marrelli, V. Amodeo, G. Statti, and F. Conforti, "Biological Properties and Bioactive Components of Allium cepa L.: Focus on Potential Benefits in the Treatment of Obesity and Related Comorbidities," *Molecules*, vol. 24, no. 1, p. 119, Dec. 2018, doi: 10.3390/molecules24010119.

[2] J. D. Teshika *et al.*, "Traditional and modern uses of onion bulb (*Allium cepa* L.): a systematic review," *Critical Reviews in Food Science and Nutrition*, vol. 59, no. sup1, pp. S39–S70, Jun. 2019, doi: 10.1080/10408398.2018.1499074.

[3] *Textbook of Natural Medicine*. 2012. Accessed: Mar. 30, 2026. [Online]. Available: https://shop.elsevier.com/books/textbook-of-natural-medicine/pizzorno/978-1-4377-2333-5

[4] M.-Y. Shon, S.-D. Choi, G.-G. Kahng, S.-H. Nam, and N.-J. Sung, "Antimutagenic, antioxidant and free radical scavenging activity of ethyl acetate extracts from white, yellow and red onions," *Food and Chemical Toxicology*, vol. 42, no. 4, pp. 659–666, Apr. 2004, doi: 10.1016/j.fct.2003.12.002.

[5] Y. Duan *et al.*, "Analysis of Total Phenol, Flavonoid content and Antioxidant Activity of Various Extraction Solvents Extracts from Onion (Allium cepa L.) Peels," *Journal of Oil & Applied Science*, vol. 32, no. 3, pp. 418–426, Sep. 2015, doi: 10.12925/JKOCS.2015.32.3.418.

[6] N. Marefati *et al.*, "A review of anti-inflammatory, antioxidant, and immunomodulatory effects of *Allium cepa* and its main constituents," *Pharmaceutical Biology*, vol. 59, no. 1, pp. 285–300, Jan. 2021, doi: 10.1080/13880209.2021.1874028.

[7] L. Campone *et al.*, "Response surface methodology to optimize supercritical carbon dioxide/co-solvent extraction of brown onion skin by-product as source of nutraceutical compounds," *Food Chemistry*, vol. 269, pp. 495–502, Dec. 2018, doi: 10.1016/j.foodchem.2018.07.042.

[8] T. Albishi, J. A. John, A. S. Al-Khalifa, and F. Shahidi, "Antioxidant, anti-inflammatory and DNA scission inhibitory activities of phenolic compounds in selected onion and potato varieties," *Journal of Functional Foods*, vol. 5, no. 2, pp. 930–939, Apr. 2013, doi: 10.1016/j.jff.2013.02.005.

[9] K. P. S. Kumar, D. Bhowmik, and P. Tiwari, "Allium cepa: A traditional medicinal herb and its health benefits," 2010.

[10] D. Teotia *et al.*, "Pharmacophylogeny of genus Allium L," *Journal of King Saud University - Science*, vol. 36, no. 8, p. 103330, Sep. 2024, doi: 10.1016/j.jksus.2024.103330.

[11] B. Smith, "Onions and Other Alliums. 2nd edition. By J. L. Brewster. Wallingford, UK: CABI (2008), pp. 432, £00.00. ISBN s978-1-84593-399-9.," *Ex. Agric.*, vol. 45, no. 1, pp. 130–130, Jan. 2009, doi: 10.1017/S0014479708007199.

[12] H. A. R. Suleria, M. S. Butt, F. M. Anjum, F. Saeed, and N. Khalid, "Onion: Nature Protection Against Physiological Threats," *Critical Reviews in Food Science and Nutrition*, vol. 55, no. 1, pp. 50–66, Jan. 2015, doi: 10.1080/10408398.2011.646364.

[13] G. Griffiths, L. Trueman, T. Crowther, B. Thomas, and B. Smith, "Onions—A global benefit to health," *Phytotherapy Research*, vol. 16, no. 7, pp. 603–615, Nov. 2002, doi: 10.1002/ptr.1222.

[14] V. Benítez *et al.*, "Characterization of Industrial Onion Wastes (Allium cepa L.): Dietary Fibre and Bioactive Compounds," *Plant Foods Hum Nutr*, vol. 66, no. 1, pp. 48–57, Mar. 2011, doi: 10.1007/s11130-011-0212-x.

[15] P. Singh, D. Singh, and R. K. Goel, "PHYTOFLAVONOIDS: ANTIEPILEPTICS FOR THE FUTURE," *International Journal of Pharmacy and Pharmaceutical Sciences*, pp. 51–66, Aug. 2014, Accessed: Apr. 07, 2026. [Online]. Available: https://journals.innovareacademics.in/index.php/ijpps/article/view/1885

[16] T. Albishi, J. A. John, A. S. Al-Khalifa, and F. Shahidi, "Antioxidative phenolic constituents of skins of onion varieties and their activities," *Journal of Functional Foods*, vol. 5, no. 3, pp. 1191–1203, Jul. 2013, doi: 10.1016/j.jff.2013.04.002.

[17] B. N. Singh *et al.*, "Polyphenolics from various extracts/fractions of red onion (Allium cepa) peel with potent antioxidant and antimutagenic activities," *Food and Chemical Toxicology*, vol. 47, no. 6, pp. 1161–1167, Jun. 2009, doi: 10.1016/j.fct.2009.02.004.

[18] V. Bordin Viera *et al.*, "Ultrasonic _assisted extraction of phenolic compounds with evaluation of red onion skin (Allium cepa L.) antioxidant capacity," *Journal of Culinary Science & Technology*, vol. 21, no. 1, pp. 156–172, Jan. 2023, doi: 10.1080/15428052.2021.1910095.

[19] B. Ifesan, "Chemical Composition of Onion Peel (Allium cepa) and its Ability to Serve as a Preservative in Cooked Beef," 2017. Accessed: Apr. 07, 2026. [Online]. Available: https://www.semanticscholar.org/paper/Chemical-Composition-of-Onion-Peel-(Allium-cepa-)-a-Ifesan/b80c6c4b6c8ab0a5994570c2e2ed9fd20ee05dfa

[20] O.-H. Ali, H. Al-sayed, N. Yasin, and E. Afifi, "Effect of Different Extraction Methods on Stablity of Anthocyanins Extracted from Red Onion peels (Allium cepa) and Its Uses as Food Colorants," *Bulletin of the National Nutrition Institute*, vol. 47, no. 2, pp. 1–24, Nov. 2016, doi: 10.21608/bnni.2016.4218.

[21] Lucian Blaga University of Sibiu, Department of Agricultural Sciences and Food Products Engineering, 7-9 Ion Ratiu Street, 550012 Sibiu, Romania, S. Oancea, M. Radu, and H. Olosutean, "Development of ultrasonic extracts with strong antioxidant properties from red onion wastes," *Rom Biotechnol Lett.*, vol. 25, no. 2, pp. 1320–1327, Apr. 2020, doi: 10.25083/rbl/25.2/1320.1327.

[22] I. Chernukha, L. Fedulova, E. Vasilevskaya, A. Kulikovskii, N. Kupaeva, and E. Kotenkova, "Antioxidant effect of ethanolic onion (Allium cepa) husk extract in ageing rats," *Saudi Journal of Biological Sciences*, vol. 28, no. 5, pp. 2877–2885, May 2021, doi: 10.1016/j.sjbs.2021.02.020.

[23] S. C. M. Burri, A. Ekholm, Å. Håkansson, E. Tornberg, and K. Rumpunen, "Antioxidant capacity and major phenol compounds of horticultural plant materials not usually used," *Journal of Functional Foods*, vol. 38, pp. 119–127, Nov. 2017, doi: 10.1016/j.jff.2017.09.003.

[24] K. T. Augusti, "Therapeutic values of onion (Allium cepa L.) and garlic (Allium sativum L.)," *Indian J Exp Biol*, vol. 34, no. 7, pp. 634–640, Jul. 1996.

[25] Ştefania-A. Milea *et al.*, "Widen the functionality of flavonoids from yellow onion skins through extraction and microencapsulation in whey proteins hydrolysates and different polymers," *Journal of Food Engineering*, vol. 251, pp. 29–35, Jun. 2019, doi: 10.1016/j.jfoodeng.2019.02.003.

[26] J. Kim, J.-S. Kim, and E. Park, "Cytotoxic and anti-inflammatory effects of onion peel extract on lipopolysaccharide stimulated human colon carcinoma cells," *Food and Chemical Toxicology*, vol. 62, pp. 199–204, Dec. 2013, doi: 10.1016/j.fct.2013.08.045.

[27] K. A. Lee *et al.*, "Antioxidant activities of onion (Allium cepa L.) peel extracts produced by ethanol, hot water, and subcritical water extraction," *Food Sci Biotechnol*, vol. 23, no. 2, pp. 615–621, Apr. 2014, doi: 10.1007/s10068-014-0084-6.

[28] T. C. Lines and M. Ono, "FRS 1000, an extract of red onion peel, strongly inhibits phosphodiesterase 5A (PDE 5A)," *Phytomedicine*, vol. 13, no. 4, pp. 236–239, Mar. 2006, doi: 10.1016/j.phymed.2004.12.001.

[29] P. Katsampa, E. Valsamedou, S. Grigorakis, and D. P. Makris, "A green ultrasound-assisted extraction process for the recovery of antioxidant polyphenols and pigments from onion solid wastes using Box–Behnken experimental design and kinetics," *Industrial Crops and Products*, vol. 77, pp. 535–543, Dec. 2015, doi: 10.1016/j.indcrop.2015.09.039.

[30] A. Nile, E. Gansukh, G.-S. Park, D.-H. Kim, and S. Hariram Nile, "Novel insights on the multi-functional properties of flavonol glucosides from red onion (Allium cepa L) solid waste – In vitro and in silico approach," *Food Chemistry*, vol. 335, p. 127650, Jan. 2021, doi: 10.1016/j.foodchem.2020.127650.

[31] L. Devi and M. Ohno, "7,8-Dihydroxyflavone, a Small-Molecule TrkB Agonist, Reverses Memory Deficits and BACE1 Elevation in a Mouse Model of Alzheimer's Disease," *Neuropsychopharmacol*, vol. 37, no. 2, pp. 434–444, Jan. 2012, doi: 10.1038/npp.2011.191.

[32] J. P. E. Spencer, "The impact of flavonoids on memory: physiological and molecular considerations," *Chem. Soc. Rev.*, vol. 38, no. 4, p. 1152, 2009, doi: 10.1039/b800422f.

[33] A. M. Sabogal-Guáqueta, J. I. Muñoz-Manco, J. R. Ramírez-Pineda, M. Lamprea-Rodriguez, E. Osorio, and G. P. Cardona-Gómez, "The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice," *Neuropharmacology*, vol. 93, pp. 134–145, Jun. 2015, doi: 10.1016/j.neuropharm.2015.01.027.

[34] S. Sharma, K. Raj, and S. Singh, "Neuroprotective Effect of Quercetin in Combination with Piperine Against Rotenone- and Iron Supplement–Induced Parkinson's Disease in Experimental Rats," *Neurotox Res*, vol. 37, no. 1, pp. 198–209, Jan. 2020, doi: 10.1007/s12640-019-00120-z.

[35] D. Wu *et al.*, "Ameliorating effect of quercetin on epilepsy by inhibition of inflammation in glial cells," *Exp Ther Med*, vol. 20, no. 2, pp. 854–859, May 2020, doi: 10.3892/etm.2020.8742.

[36] N. Rishitha and A. Muthuraman, "Therapeutic evaluation of solid lipid nanoparticle of quercetin in pentylenetetrazole induced cognitive impairment of zebrafish," *Life Sciences*, vol. 199, pp. 80–87, Apr. 2018, doi: 10.1016/j.lfs.2018.03.010.

[37] K. A. Youdim, B. Shukitt-Hale, and J. A. Joseph, "Flavonoids and the brain: interactions at the blood–brain barrier and their physiological effects on the central nervous system," *Free Radical Biology and Medicine*, vol. 37, no. 11, pp. 1683–1693, Dec. 2004, doi: 10.1016/j.freeradbiomed.2004.08.002.

[38] M. Fiorani *et al.*, "Mitochondria accumulate large amounts of quercetin: prevention of mitochondrial damage and release upon oxidation of the extramitochondrial fraction of the flavonoid," *The Journal of Nutritional Biochemistry*, vol. 21, no. 5, pp. 397–404, May 2010, doi: 10.1016/j.jnutbio.2009.01.014.

[39] L. Carmona-Aparicio *et al.*, "Dose-Dependent Behavioral and Antioxidant Effects of Quercetin and Methanolic and Acetonic Extracts from *Heterotheca inuloides* on Several Rat Tissues following Kainic Acid-Induced *Status Epilepticus*," *Oxidative Medicine and Cellular Longevity*, vol. 2019, pp. 1–17, Dec. 2019, doi: 10.1155/2019/5287507.

[40] S. Moghbelinejad *et al.*, "The effects of quercetin on the gene expression of the GABAA receptor α5 subunit gene in a mouse model of kainic acid-induced seizure," *The Journal of Physiological Sciences*, vol. 67, no. 2, pp. 339–343, Mar. 2017, doi: 10.1007/s12576-016-0497-5.

[41] F. Sefil *et al.*, "Ameliorating effect of quercetin on acute pentylenetetrazole induced seizures in rats," *Int J Clin Exp Med*, vol. 7, no. 9, pp. 2471–2477, 2014.

[42] D. Nieoczym, K. Socała, G. Raszewski, and P. Wlaź, "Effect of quercetin and rutin in some acute seizure models in mice," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 54, pp. 50–58, Oct. 2014, doi: 10.1016/j.pnpbp.2014.05.007.

[43] M. Nassiri-Asl, F. Hajiali, M. Taghiloo, E. Abbasi, F. Mohseni, and F. Yousefi, "Comparison between the effects of quercetin on seizure threshold in acute and chronic seizure models," *Toxicol Ind Health*, vol. 32, no. 5, pp. 936–944, May 2016, doi: 10.1177/0748233713518603.

[44] S. Naqvi, A. Panghal, and S. J. S. Flora, "Nanotechnology: A Promising Approach for Delivery of Neuroprotective Drugs," *Front. Neurosci.*, vol. 14, p. 494, Jun. 2020, doi: 10.3389/fnins.2020.00494.

[45] N. Choudhary, K. R. V. Bijjem, and A. N. Kalia, "Antiepileptic potential of flavonoids fraction from the leaves of Anisomeles malabarica," *Journal of Ethnopharmacology*, vol. 135, no. 2, pp. 238–242, May 2011, doi: 10.1016/j.jep.2011.02.019.

[46] S. Moghbelinejad *et al.*, "The Role of Quercetin in Gene Expression of GluR1 Subunit of AMPA Receptors, and NR2A and NR2B Subunits of NMDA Receptors in Kainic Acid Model of Seizure in Mice," *Iran Red Crescent Med J*, vol. 19, no. 5, Nov. 2016, doi: 10.5812/ircmj.42415.

[47] X. Dong, Y. Wang, and Z. Qin, "Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases," *Acta Pharmacol Sin*, vol. 30, no. 4, pp. 379–387, Apr. 2009, doi: 10.1038/aps.2009.24.

[48] A. Y. Reid, K. Riazi, G. Campbell Teskey, and Q. J. Pittman, "Increased excitability and molecular changes in adult rats after a febrile seizure," *Epilepsia*, vol. 54, no. 4, Apr. 2013, doi: 10.1111/epi.12061.

[49] L. Vivash *et al.*, "Changes in hippocampal GABAA/cBZR density during limbic epileptogenesis: Relationship to cell loss and mossy fibre sprouting," *Neurobiology of Disease*, vol. 41, no. 2, pp. 227–236, Feb. 2011, doi: 10.1016/j.nbd.2010.08.021.

[50] U. Geronzi, F. Lotti, and S. Grosso, "Oxidative stress in epilepsy," *Expert Review of Neurotherapeutics*, vol. 18, no. 5, pp. 427–434, May 2018, doi: 10.1080/14737175.2018.1465410.

[51] A. Dhir, "Natural polyphenols in preclinical models of epilepsy," *Phytotherapy Research*, vol. 34, no. 6, pp. 1268–1281, Jun. 2020, doi: 10.1002/ptr.6617.

[52] J. Folbergrová, P. Ješina, H. Kubová, and J. Otáhal, "Effect of Resveratrol on Oxidative Stress and Mitochondrial Dysfunction in Immature Brain during Epileptogenesis," *Mol Neurobiol*, vol. 55, no. 9, pp. 7512–7522, Sep. 2018, doi: 10.1007/s12035-018-0924-0.

[53] Z. Kiasalari, M. Khalili, M. Roghani, H. Heidari, and Y. Azizi, "Antiepileptic and Antioxidant Effect of Hydroalcoholic Extract of Ferula Assa Foetida Gum on Pentylentetrazole- induced Kindling in Male Mice," *Basic Clin Neurosci*, vol. 4, no. 4, pp. 299–306, 2013.

[54] S. Subash and P. Subramanian, "Morin a flavonoid exerts antioxidant potential in chronic hyperammonemic rats: a biochemical and histopathological study," *Mol Cell Biochem*, vol. 327, no. 1–2, pp. 153–161, Jul. 2009, doi: 10.1007/s11010-009-0053-1.

[55] J. Oyrer, S. Maljevic, I. E. Scheffer, S. F. Berkovic, S. Petrou, and C. A. Reid, "Ion Channels in Genetic Epilepsy: From Genes and Mechanisms to Disease-Targeted Therapies," *Pharmacological Reviews*, vol. 70, no. 1, pp. 142–173, Jan. 2018, doi: 10.1124/pr.117.014456.

[56] E. Deval *et al.*, "Acid-Sensing Ion Channels (ASICs): Pharmacology and implication in pain," *Pharmacology & Therapeutics*, vol. 128, no. 3, pp. 549–558, Dec. 2010, doi: 10.1016/j.pharmthera.2010.08.006.

[57] M. Mukhopadhyay, A. Singh, S. Sachchidanand, and A. K. Bera, "Quercetin inhibits acid-sensing ion channels through a putative binding site in the central vestibular region," *Neuroscience*, vol. 348, pp. 264–272, Apr. 2017, doi: 10.1016/j.neuroscience.2017.02.025.

[58] P. N'Gouemo, "Targeting BK (big potassium) channels in epilepsy," *Expert Opinion on Therapeutic Targets*, vol. 15, no. 11, pp. 1283–1295, Nov. 2011, doi: 10.1517/14728222.2011.620607.

[59] M. I. Melnyk, D. O. Dryn, L. T. Al Kury, A. V. Zholos, and A. I. Soloviev, "Liposomal quercetin potentiates maxi-K channel openings in smooth muscles and restores its activity after oxidative stress," *Journal of Liposome Research*, vol. 29, no. 1, pp. 94–101, Jan. 2019, doi: 10.1080/08982104.2018.1458864.

[60] F. Miceli *et al.*, "Early-Onset Epileptic Encephalopathy Caused by Gain-of-Function Mutations in the Voltage Sensor of K_v 7.2 and K_v 7.3 Potassium Channel Subunits," *J. Neurosci.*, vol. 35, no. 9, pp. 3782–3793, Mar. 2015, doi: 10.1523/JNEUROSCI.4423-14.2015.

[61] F. Miceli *et al.*, "The Voltage-Sensing Domain of Kv7.2 Channels as a Molecular Target for Epilepsy-Causing Mutations and Anticonvulsants," *Front. Pharmacol.*, vol. 2, 2011, doi: 10.3389/fphar.2011.00002.

[62] K. E. Redford and G. W. Abbott, "The ubiquitous flavonoid quercetin is an atypical KCNQ potassium channel activator," *Commun Biol*, vol. 3, no. 1, p. 356, Jul. 2020, doi: 10.1038/s42003-020-1089-8.

[63] Y. Marunaka, "Actions of quercetin, a flavonoid, on ion transporters: its physiological roles," *Annals of the New York Academy of Sciences*, vol. 1398, no. 1, pp. 142–151, Jun. 2017, doi: 10.1111/nyas.13361.

[64] S. Eftekhari *et al.*, "BDNF modifies hippocampal KCC2 and NKCC1 expression in a temporal lobe epilepsy model," *Acta Neurobiol. Exp.*, vol. 74, no. 3, pp. 276–287, Sep. 2014, doi: 10.55782/ane-2014-1993.

[65] J. Xu *et al.*, "Imaging P2X4 receptor subcellular distribution, trafficking, and regulation using P2X4-pHluorin," *Journal of General Physiology*, vol. 144, no. 1, pp. 81–104, Jul. 2014, doi: 10.1085/jgp.201411169.

[66] R. Yang *et al.*, "Quercetin relieved diabetic neuropathic pain by inhibiting upregulated $P2X_4$ receptor in dorsal root ganglia," *Journal Cellular Physiology*, vol. 234, no. 3, pp. 2756–2764, Mar. 2019, doi: 10.1002/jcp.27091.

[67] J. H. Xu, H. Wang, W. Zhang, and F. R. Tang, "Alterations of L-type voltage dependent calcium channel alpha 1 subunit in the hippocampal CA3 region during and after pilocarpine-induced epilepsy," *Neurochemistry International*, vol. 114, pp. 108–119, Mar. 2018, doi: 10.1016/j.neuint.2018.02.005.

[68] C. Liang *et al.*, "Expression of TRPC3 in cortical lesions from patients with focal cortical dysplasia," *Neuroscience Letters*, vol. 724, p. 134880, Apr. 2020, doi: 10.1016/j.neulet.2020.134880.

[69] X. Luo *et al.*, "Polygonum aviculare L. extract and quercetin attenuate contraction in airway smooth muscle," *Sci Rep*, vol. 8, no. 1, p. 3114, Feb. 2018, doi: 10.1038/s41598-018-20409-x.

[70] M. Nakamura, J.-H. Cho, H. Shin, and I.-S. Jang, "Effects of cenobamate (YKP3089), a newly developed anti-epileptic drug, on voltage-gated sodium channels in rat hippocampal CA3 neurons," *European Journal of Pharmacology*, vol. 855, pp. 175–182, Jul. 2019, doi: 10.1016/j.ejphar.2019.05.007.

[71] Y. Yao, D. D. Han, T. Zhang, and Z. Yang, "Quercetin improves cognitive deficits in rats with chronic cerebral ischemia and inhibits voltage-dependent sodium channels in hippocampal CA1 pyramidal neurons," *Phytotherapy Research*, vol. 24, no. 1, pp. 136–140, Jan. 2010, doi: 10.1002/ptr.2902.

[72] H. Sies, "Oxidative stress: a concept in redox biology and medicine," *Redox Biology*, vol. 4, pp. 180–183, Apr. 2015, doi: 10.1016/j.redox.2015.01.002.

[73] C. Espinós *et al.*, "Oxidative Stress, a Crossroad Between Rare Diseases and Neurodegeneration," *Antioxidants*, vol. 9, no. 4, p. 313, Apr. 2020, doi: 10.3390/antiox9040313.

[74] M. Weitzmann, "Quercetin, a potent suppressor of NF-κB and Smad activation in osteoblasts," *Int J Mol Med*, Jul. 2011, doi: 10.3892/ijmm.2011.749.

[75] S. Nigar, F. Pottoo, N. Tabassum, S. Verma, and M. Javed, "Molecular Insights into the Role of Inflammation and Oxidative Stress in Epilepsy," *JAMPS*, vol. 10, no. 1, pp. 1–9, Jan. 2016, doi: 10.9734/JAMPS/2016/24441.

[76] L. G. Costa, J. M. Garrick, P. J. Roquè, and C. Pellacani, "Mechanisms of Neuroprotection by Quercetin: Counteracting Oxidative Stress and More," *Oxidative Medicine and Cellular Longevity*, vol. 2016, no. 1, p. 2986796, Jan. 2016, doi: 10.1155/2016/2986796.

[77] M. Kobori *et al.*, "Chronic high intake of quercetin reduces oxidative stress and induces expression of the antioxidant enzymes in the liver and visceral adipose tissues in mice," *Journal of Functional Foods*, vol. 15, pp. 551–560, May 2015, doi: 10.1016/j.jff.2015.04.006.

[78] A. B. Granado-Serrano, M. A. Martín, L. Bravo, L. Goya, and S. Ramos, "Quercetin modulates Nrf2 and glutathione-related defenses in HepG2 cells: Involvement of p38," *Chemico-Biological Interactions*, vol. 195, no. 2, pp. 154–164, Jan. 2012, doi: 10.1016/j.cbi.2011.12.005.

[79] M. Nassiri-Asl *et al.*, "Effects of quercetin on oxidative stress and memory retrieval in kindled rats," *Epilepsy & Behavior*, vol. 28, no. 2, pp. 151–155, Aug. 2013, doi: 10.1016/j.yebeh.2013.04.019.

[80] A. Karimi *et al.*, "A comprehensive systematic review of the therapeutic effects and mechanisms of action of quercetin in sepsis," *Phytomedicine*, vol. 86, p. 153567, Jun. 2021, doi: 10.1016/j.phymed.2021.153567.

[81] D. Yang, T. Wang, M. Long, and P. Li, "Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine," *Oxidative Medicine and Cellular Longevity*, vol. 2020, pp. 1–13, Dec. 2020, doi: 10.1155/2020/8825387.

[82] M. Nassiri-Asl *et al.*, "Effects of rutin on oxidative stress in mice with kainic acid-induced seizure," *Journal of Integrative Medicine*, vol. 11, no. 5, pp. 337–342, Sep. 2013, doi: 10.3736/jintegrmed2013042.

[83] K. Hu, S.-Y. Li, B. Xiao, F. Bi, X.-Q. Lu, and X.-M. Wu, "Protective effects of quercetin against status epilepticus induced hippocampal neuronal injury in rats: involvement of X-linked inhibitor of apoptosis protein," *Acta Neurol Belg*, vol. 111, no. 3, pp. 205–212, Sep. 2011.

[84] M. Hashemian *et al.*, "Fabrication and evaluation of novel quercetin-conjugated Fe_3O_4–β-cyclodextrin nanoparticles for potential use in epilepsy disorder," *IJN*, vol. Volume 14, pp. 6481–6495, Aug. 2019, doi: 10.2147/IJN.S218317.

[85] G. Terrone, F. Frigerio, S. Balosso, T. Ravizza, and A. Vezzani, "Inflammation and reactive oxygen species in status epilepticus: Biomarkers and implications for therapy," *Epilepsy & Behavior*, vol. 101, p. 106275, Dec. 2019, doi: 10.1016/j.yebeh.2019.04.028.

[86] U. B. Eyo, M. Murugan, and L. Wu, "Microglia–Neuron Communication in Epilepsy," *Glia*, vol. 65, no. 1, pp. 5–18, Jan. 2017, doi: 10.1002/glia.23006.

[87] T. Hiragi, Y. Ikegaya, and R. Koyama, "Microglia after Seizures and in Epilepsy," *Cells*, vol. 7, no. 4, p. 26, Mar. 2018, doi: 10.3390/cells7040026.

[88] V. N. De Zorzi *et al.*, "Galangin Prevents Increased Susceptibility to Pentylenetetrazol-Stimulated Seizures by Prostaglandin E2," *Neuroscience*, vol. 413, pp. 154–168, Aug. 2019, doi: 10.1016/j.neuroscience.2019.06.002.

[89] Y. N. Paudel, B. D. Semple, N. C. Jones, I. Othman, and Mohd. F. Shaikh, "High mobility group box 1 (HMGB 1) as a novel frontier in epileptogenesis: from pathogenesis to therapeutic approaches," *Journal of Neurochemistry*, vol. 151, no. 5, pp. 542–557, Dec. 2019, doi: 10.1111/jnc.14663.

[90] F. Gualtieri, M. Nowakowska, E.-L. Von Rüden, I. Seiffert, and H. Potschka, "Epileptogenesis-Associated Alterations of Heat Shock Protein 70 in a Rat Post-Status Epilepticus Model," *Neuroscience*, vol. 415, pp. 44–58, Sep. 2019, doi: 10.1016/j.neuroscience.2019.06.031.

[91] A. Vezzani, S. Balosso, and T. Ravizza, "Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy," *Nat Rev Neurol*, vol. 15, no. 8, pp. 459–472, Aug. 2019, doi: 10.1038/s41582-019-0217-x.

[92] A. Dhir, "Curcumin in epilepsy disorders," *Phytotherapy Research*, vol. 32, no. 10, pp. 1865–1875, Oct. 2018, doi: 10.1002/ptr.6125.

[93] B. Feng *et al.*, "Transient increase of interleukin-1β after prolonged febrile seizures promotes adult epileptogenesis through long-lasting upregulating endocannabinoid signaling," *Sci Rep*, vol. 6, no. 1, p. 21931, Feb. 2016, doi: 10.1038/srep21931.

[94] T. Ravizza *et al.*, "High Mobility Group Box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy," *Brain, Behavior, and Immunity*, vol. 72, pp. 14–21, Aug. 2018, doi: 10.1016/j.bbi.2017.10.008.

[95] Y. N. Paudel *et al.*, "HMGB1: A Common Biomarker and Potential Target for TBI, Neuroinflammation, Epilepsy, and Cognitive Dysfunction," *Front. Neurosci.*, vol. 12, p. 628, Sep. 2018, doi: 10.3389/fnins.2018.00628.

[96] N. M. Agalave *et al.*, "Spinal HMGB1 induces TLR4-mediated long-lasting hypersensitivity and glial activation and regulates pain-like behavior in experimental arthritis," *Pain*, vol. 155, no. 9, pp. 1802–1813, Sep. 2014, doi: 10.1016/j.pain.2014.06.007.

[97] U. Avdic, M. Ahl, M. Öberg, and C. T. Ekdahl, "Immune Profile in Blood Following Non-convulsive Epileptic Seizures in Rats," *Front. Neurol.*, vol. 10, p. 701, Jul. 2019, doi: 10.3389/fneur.2019.00701.

[98] N. Adachi, S. Tomonaga, T. Tachibana, D. M. Denbow, and M. Furuse, "(−)-Epigallocatechin gallate attenuates acute stress responses through GABAergic system in the brain," *European Journal of Pharmacology*, vol. 531, no. 1–3, pp. 171–175, Feb. 2006, doi: 10.1016/j.ejphar.2005.12.024.

[99] N. Leyva-López, E. Gutierrez-Grijalva, D. Ambriz-Perez, and J. Heredia, "Flavonoids as Cytokine Modulators: A Possible Therapy for Inflammation-Related Diseases," *IJMS*, vol. 17, no. 6, p. 921, Jun. 2016, doi: 10.3390/ijms17060921.

[100] J. Y. Kwon, M.-T. Jeon, U. J. Jung, D. W. Kim, G. J. Moon, and S. R. Kim, "Perspective: Therapeutic Potential of Flavonoids as Alternative Medicines in Epilepsy," *Advances in Nutrition*, vol. 10, no. 5, pp. 778–790, Sep. 2019, doi: 10.1093/advances/nmz047.

[101] M. Tunon, M. Garcia-Mediavilla, S. Sanchez-Campos, and J. Gonzalez-Gallego, "Potential of Flavonoids as Anti-inflammatory Agents: Modulation of Pro- Inflammatory Gene Expression and Signal Transduction Pathways," *CDM*, vol. 10, no. 3, pp. 256–271, Mar. 2009, doi: 10.2174/138920009787846369.

[102] J. Bauer, "Seizure-inducing effects of antiepileptic drugs: a review," *Acta Neurologica Scandinavica*, vol. 94, no. 6, pp. 367–377, 1996, doi: 10.1111/j.1600-0404.1996.tb00047.x.

[103] D. Ribeiro, M. Freitas, J. L. F. C. Lima, and E. Fernandes, "Proinflammatory Pathways: The Modulation by Flavonoids," *Medicinal Research Reviews*, vol. 35, no. 5, pp. 877–936, Sep. 2015, doi: 10.1002/med.21347.

[104] J. G. Heida, S. L. Moshé, and Q. J. Pittman, "The role of interleukin-1β in febrile seizures," *Brain and Development*, vol. 31, no. 5, pp. 388–393, May 2009, doi: 10.1016/j.braindev.2008.11.013.

[105] Y. Li *et al.*, "Quercetin, Inflammation and Immunity," *Nutrients*, vol. 8, no. 3, p. 167, Mar. 2016, doi: 10.3390/nu8030167.

[106] N. V. P. Mkhize, L. Qulu, and M. V. Mabandla, "The Effect of Quercetin on Pro- and Anti-Inflammatory Cytokines in a Prenatally Stressed Rat Model of Febrile Seizures," *J Exp Neurosci*, vol. 11, p. 1179069517704668, Jan. 2017, doi: 10.1177/1179069517704668.

[107] A. Alexander *et al.*, "Recent expansions of novel strategies towards the drug targeting into the brain," *IJN*, vol. Volume 14, pp. 5895–5909, Jul. 2019, doi: 10.2147/IJN.S210876.

[108] A. Ghosh, S. Sarkar, A. K. Mandal, and N. Das, "Neuroprotective Role of Nanoencapsulated Quercetin in Combating Ischemia-Reperfusion Induced Neuronal Damage in Young and Aged Rats," *PLoS ONE*, vol. 8, no. 4, p. e57735, Apr. 2013, doi: 10.1371/journal.pone.0057735.

[109] N. Ahmad *et al.*, "RETRACTED ARTICLE: Intranasal delivery of quercetin-loaded mucoadhesive nanoemulsion for treatment of cerebral ischaemia," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 46, no. 4, pp. 717–729, May 2018, doi: 10.1080/21691401.2017.1337024.

[110] T. Hatahet, M. Morille, A. Hommoss, J. M. Devoisselle, R. H. Müller, and S. Bégu, "Quercetin topical application, from conventional dosage forms to nanodosage forms," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 108, pp. 41–53, Nov. 2016, doi: 10.1016/j.ejpb.2016.08.011.

[111] S. Chauhan *et al.*, "Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications," *IJN*, p. 1761, Apr. 2012, doi: 10.2147/IJN.S29290.

[112] P. N. Sarsavadia, R. L. Sawhney, D. R. Pangavhane, and S. P. Singh, "Drying behaviour of brined onion slices," *Journal of Food Engineering*, vol. 40, no. 3, pp. 219–226, May 1999, doi: 10.1016/S0260-8774(99)00058-8.

[113] H. J. Suh, J. M. Lee, J. S. Cho, Y. S. Kim, and S. H. Chung, "Radical scavenging compounds in onion skin," *Food Research International*, vol. 32, no. 10, pp. 659–664, Dec. 1999, doi: 10.1016/S0963-9969(99)00141-6.

[114] T. N. Ly, C. Hazama, M. Shimoyamada, H. Ando, K. Kato, and R. Yamauchi, "Antioxidative Compounds from the Outer Scales of Onion," *J. Agric. Food Chem.*, vol. 53, no. 21, pp. 8183–8189, Oct. 2005, doi: 10.1021/jf051264d.

[115] A. Gülşen, D. P. Makris, and P. Kefalas, "Biomimetic oxidation of quercetin: Isolation of a naturally occurring quercetin heterodimer and evaluation of its in vitro antioxidant properties," *Food Research International*, vol. 40, no. 1, pp. 7–14, Jan. 2007, doi: 10.1016/j.foodres.2006.07.009.

[116] M. Furusawa, H. Tsuchiya, M. Nagayama, T. Tanaka, K. Nakaya, and M. Iinuma, "Anti-Platelet and Membrane-Rigidifying Flavonoids in Brownish Scale of Onion," *JOURNAL OF HEALTH SCIENCE*, vol. 49, no. 6, pp. 475–480, 2003, doi: 10.1248/jhs.49.475.

[117] S. A. Abd El-Aal, H. S. El-Abhar, and Y. S. Abulfadl, "Morin offsets PTZ-induced neuronal degeneration and cognitive decrements in rats: The modulation of TNF-α/TNFR-1/RIPK1,3/MLKL/PGAM5/Drp-1, IL-6/JAK2/STAT3/GFAP and Keap-1/Nrf-2/HO-1 trajectories," *European Journal of Pharmacology*, vol. 931, p. 175213, Sep. 2022, doi: 10.1016/j.ejphar.2022.175213.

[118] Z. Sun, F. Meng, L. Tu, and L. Sun, "Myricetin attenuates the severity of seizures and neuroapoptosis in pentylenetetrazole kindled mice by regulating the of BDNF-TrkB signaling pathway and modulating matrix metalloproteinase-9 and GABAA," *Exp Ther Med*, Feb. 2019, doi: 10.3892/etm.2019.7282.

[119] P. Hassanzadeh, E. Arbabi, F. Atyabi, and R. Dinarvand, "Ferulic acid exhibits antiepileptogenic effect and prevents oxidative stress and cognitive impairment in the kindling model of epilepsy," *Life Sciences*, vol. 179, pp. 9–14, Jun. 2017, doi: 10.1016/j.lfs.2016.08.011.

[120] S. Lee *et al.*, "Protective Effects of Protocatechuic Acid on Seizure-Induced Neuronal Death," *IJMS*, vol. 19, no. 1, p. 187, Jan. 2018, doi: 10.3390/ijms19010187.

[121] M. A. El-Hefnawy *et al.*, "Effect of vanillic acid on pentylenetetrazole-kindled rats: Nrf2/HO-1, IGF-1 signaling pathways cross talk," *J. Integr. Neurosci.*, vol. 21, no. 1, p. 15, Jan. 2022, doi: 10.31083/j.jin2101015.

[122] Y. Xi *et al.*, "Cyanidin-3- *O* -glucoside alleviates trimethyltin chloride-induced neurodegeneration by maintaining glutamate homeostasis through modulation of the gut microbiota," *Food Science and Human Wellness*, vol. 13, no. 2, pp. 1093–1107, Mar. 2024, doi: 10.26599/FSHW.2022.9250141.

[123] H. Ahmed, M. A. Khan, S. A. Ali Zaidi, and S. Muhammad, "In Silico and In Vivo: Evaluating the Therapeutic Potential of Kaempferol, Quercetin, and Catechin to Treat Chronic Epilepsy in a Rat Model," *Front. Bioeng. Biotechnol.*, vol. 9, p. 754952, Nov. 2021, doi: 10.3389/fbioe.2021.754952.

[124] Modupe Iretiola Builders, Glory Zidyep Michael, Samuel Otokpa Ede, Simeon Oyepata Joseph, and Peter Uduak Ise, "Evaluation of acute and subacute toxicity of the extract of allium cepa peels in Wistar rats," *World J. Adv. Res. Rev.*, vol. 18, no. 2, pp. 1173–1180, May 2023, doi: 10.30574/wjarr.2023.18.2.0839.

[125] C. Steriade, J. French, and O. Devinsky, "Epilepsy: key experimental therapeutics in early clinical development," *Expert Opinion on Investigational Drugs*, vol. 29, no. 4, pp. 373–383, Apr. 2020, doi: 10.1080/13543784.2020.1743678.