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REVIEW

Ameliorative properties of quercetin in the treatment of traumatic brain injury: a mechanistic review based on underlying mechanisms

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Abstract
Traumatic brain injury (TBI) is a leading cause of disability worldwide, with an estimated annual incidence of 27–69 million. TBI is a severe condition that can lead to high mortality rates and long-term cognitive, behavioral, and physical impairments in young adults. It is a significant public health concern due to the lack of effective treatments available. Quercetin, a natural flavonoid found in various fruits and vegetables, has demonstrated therapeutic potential with anti-inflammatory, antioxidant, and neuroprotective properties. Recently, some evidence has accentuated the ameliorating effects of quercetin on TBI. This review discusses quercetin's ability to reduce TBI-related damage by regulating many cellular and molecular pathways. Quercetin in vitro and in vivo studies exhibit promise in reducing inflammation, oxidative stress, apoptosis, and enhancing cognitive function post-TBI. Further clinical investigation into quercetin's therapeutic potential as a readily available adjuvant in the treatment of TBI is warranted in light of these findings. This review adds to our knowledge of quercetin's potential in treating TBI by clarifying its mechanisms of action.

Keywords Traumatic brain injury · Pathogenesis · Quercetin · Molecular pathway · Second injury

Introduction

Traumatic brain injury (TBI) poses a significant threat to public health, impacting individuals across various demographics, including civilians, military personnel, and athletes. While the neurological and psychiatric consequences of TBI are well-established, recent research suggests a potentially understudied link between TBI and the development of chronic cardiovascular diseases and associated risk factors, particularly in individuals exposed to repeated or single brain injuries. This link adds another layer of complexity to the already devastating impact of TBI, which significantly contributes to mortality rates and long-term physical, cognitive, and behavioral impairments, especially among young adults in economically developed nations [1, 2]. Considering that young adults (aged 20–30)

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often constitute the primary workforce and driving force behind economic and social progress, the societal burden of TBI becomes even more concerning [3]. Epidemiological studies estimate that around 5% of the US population lives with TBI, while global projections suggest over 60 million individuals may experience permanent disability due to TBIs of varying severity [4, 5]. Despite advancements in diagnosis, neurosurgical care, and cognitive rehabilitation, a definitive cure for TBI remains elusive [6]. Current treatment strategies primarily focus on minimizing secondary damage and its consequences, reducing inflammation, and promoting neuroprotection [7].

Herbal medicine has emerged as a complementary approach to conventional treatments, offering potential benefits such as enhancing efficacy, mitigating side effects, and addressing limitations in conventional therapies, even in TBI [8]. Studies suggest that herbal medicines may alleviate symptoms by improving blood-brain barrier permeability, reducing brain water content, and potentially downregulating the expression of inflammatory markers like tumor necrosis factor-α and nitric oxide [8]. Notably, the antioxidant properties of certain flavonoids are also being investigated for their potential neuroprotective effects [4].

Quercetin, a naturally occurring flavonoid widely found in fruits and vegetables, has garnered significant attention due to its diverse medicinal properties [9]. Its Latin name, "quercetum," meaning "oak forest," reflects its classification as a flavonol—one of the six subgroups of flavonoid compounds [10]. This bioactive compound boasts a range of health benefits, including antioxidant, anti-inflammatory, anti-proliferative, anti-carcinogenic, anti-diabetic, and antiviral capabilities [11]. However, it is crucial to acknowledge that quercetin's efficacy may be limited by its short half-life and rapid metabolism in the body [12]. Additionally, studies have shown that it may suppress the function of immunostimulatory dendritic cells [10].

Despite these limitations, preliminary data suggests that quercetin possesses potential neuroprotective benefits in the context of TBI, warranting further exploration [13]. This review aims to shed light on quercetin's therapeutic potential as an adjunctive therapy for TBI by comprehensively examining published research and delving into the molecular mechanisms underlying its antioxidant, anti-inflammatory, and neuroprotective properties.

The pathogenesis of traumatic brain injury

TBI is a leading cause of disability and death, particularly among individuals under 45 years old [14]. The Global Burden of Disease (GBD) projections anticipate a rise in TBI prevalence due to population growth and increased use of motorized vehicles. Notably, TBI can contribute to the development of neurodegenerative disorders like dementia, Parkinson's disease, and Alzheimer's disease [15]. The diverse pathophysiology of TBI presents a challenge in establishing standardized treatment approaches. The extent, location, and individual characteristics of TBI can vary significantly. Injuries can be categorized as either primary (e.g., bleeding, contusion) or secondary (e.g., edema, increased intracranial pressure) based on the mechanism of injury [16]. However, cellular and molecular processes involved in TBI pathogenesis are broadly classified into primary and secondary damage mechanisms [17]. Another classification system differentiates between local (focal) and diffuse (global) damage, with the latter demonstrating a stronger clinical-pathological association (Fig. 1) [17].

Tissue damage and cellular processes

Following TBI, a complex cascade of molecular and cellular events unfolds, involving neurotransmitters, inflammatory mediators, cytokines, and genetic abnormalities [18], as indicated below:

Primary injury

The immediate impact of a collision results in primary mechanical damage to the brain, leading to localized or diffuse injuries such as contusions, hematomas, and axonal shearing [17]. These injuries can disrupt the blood-brain barrier (BBB), causing cerebral edema and altered blood flow [15, 19].

Secondary injury

Secondary injury processes, lasting for varying durations, follow the initial impact. Mechanisms contributing to neuronal injury and death include oxidative stress, neuroinflammation, excitotoxicity, BBB disruption, and apoptosis [15, 16, 18].

Oxidative stress TBI triggers the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to lipid peroxidation, worsening neuroinflammation, and synaptic dysfunction [20]. The brain's compromised antioxidant defense mechanisms exacerbate oxidative stress, contributing to continued secondary brain damage [20]. Mitochondrial dysfunction and oxidative stress are tightly linked in TBI, with mitochondrial oxidative stress playing a role in various types of brain damage [21]. Exacerbating oxidative damage, neuronal impairment, and mitochondrial dysfunction post-TBI can cause increased ROS generation [21]. Recent research suggests that antioxidant

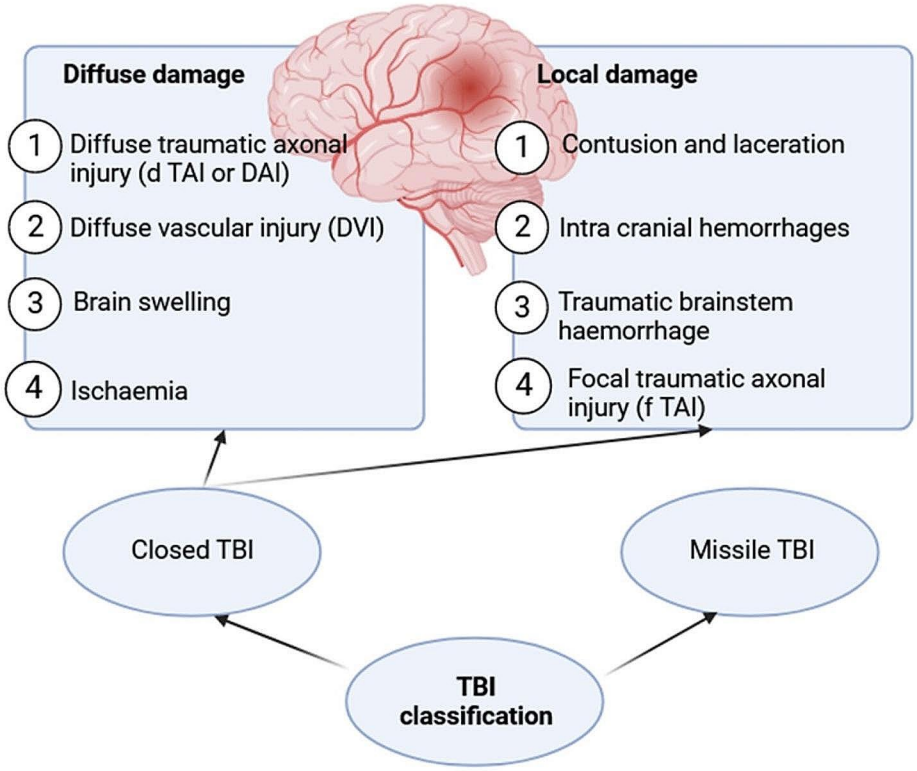

Fig. 1 Classification of ethology of TBI (adopted and redisgned from Al-Sarraj, 2016 [17]), Created with biorender (https://biorender.com/)

therapies may offer a new treatment option for preventing further damage by reducing oxidative stress in TBI, demonstrating potential in both laboratory and human studies to improve cognitive and functional abilities [20, 22].

Neuroinflammation Neuroinflammation, a complex and multifaceted process, plays crucial role in secondary injury following TBI [23]. This response, characterized by a series of immunological events, can be beneficial or detrimental, acting as a double-edged sword [23]. While acute neuroinflammation, initiated by release danger signals and activation the innate immune system, is essential for post-TBI healing, an unchecked immune response can turn destructive, exacerbating tissue damage [24]. Microglial and astrocyte activation, combined with infiltration of peripheral immune cells, results in a pro-inflammatory environment characterized by the production of damage-associated molecular patterns (DAMPs) and pro-inflammatory mediators [25]. This inflammatory environment further activates immune cells, leading to tissue damage and exacerbating the overall injury [24].

Chronic neuroinflammation following TBI is closely linked to the development of long-term cognitive impairments and even chronic neurodegenerative diseases [23, 26]. This chronic phase is characterized by sustained glial cell activation, continued production of inflammatory mediators within the brain, and ongoing recruitment of peripheral immune cells [26]. Therefore, targeting and regulating neuroinflammation after TBI presents a promising avenue for developing new treatment strategies. By understanding the intricate mechanisms involved, including the roles of resident glia, inflammatory mediators, and peripheral immune cell recruitment, we can identify potential intervention targets and advance translational and clinical research in TBI management [26]. Additionally, the development of precise proteomic and transcriptomic tools has opened doors to discovering novel inflammatory pathways with therapeutic potential [23]. Ultimately, the goal is to minimize secondary injury, enhance healing processes, and harness the power of inflammation in a personalized manner to improve patient outcomes [24].

Excitotoxicity A surge in extracellular glutamate levels following TBI triggers excitotoxic processes, significantly contributing to secondary brain injury [27]. Understanding and addressing this disruption of glutamate homeostasis and subsequent excitotoxicity is crucial for developing effective therapeutic strategies. While glutamate receptor antagonists have shown limited success in TBI treatment, the need for alternative approaches

to effectively control excitotoxicity and minimize its detrimental impact on neuronal survival and function is increasingly recognized [27]. Excitotoxicity is characterized by neuronal death triggered by excessive stimulation of excitatory neurotransmitters, primarily glutamate [16, 18]. Research suggests that elevated glutamate levels can overstimulate NMDA receptors, particularly synaptic NMDA receptors, leading to an influx of calcium and sodium ions into neuronal compartments [28]. This abnormal glutamate release from both neurons and glial cells further exacerbates the situation. The influx of calcium ions through various glutamate receptors ultimately activates programmed cell death pathways, contributing to neuronal damage [28]. Following TBI, a decrease in astrocytic glutamate transporters, responsible for regulating glutamate levels in the extracellular space, further contributes to excitotoxicity [27].

Calcium dysregulation Calcium dysregulation plays a central role in the devastating cascade of secondary damage following TBI [29, 30]. This disruption is characterized by abnormal calcium signaling and persistently elevated intracellular calcium levels within neurons, upsetting the delicate balance essential for their proper function [29, 30]. This imbalance triggers a chain reaction of detrimental events, including the activation of degradative enzymes, impairment of normal cellular functions, and ultimately, the initiation of cell death pathways [29]. Several mechanisms contribute to calcium dysregulation in TBI:

- **Increased expression of calcium sensor proteins**: Proteins like stromal interactive molecule 2 (STIM2) act as calcium sensors, and their increased expression in TBI amplifies the calcium imbalance [31].
- **Hyperactive voltage-gated calcium channels**: L- and N-type calcium channels, responsible for regulating calcium influx into cells, become hyperactive after TBI, leading to excessive calcium entry and worsening the injury [32].
- **BBB disruption**: the BBB breakdown allows activated white blood cells to infiltrate the damaged brain tissue. These cells can generate harmful reactive oxygen species and inflammatory substances, further contributing to calcium-induced neuronal damage [32].

The consequences of disrupted calcium homeostasis in TBI survivors are far-reaching and long-lasting. Cognitive impairments, behavioral issues, and even post-traumatic stress disorder (PTSD) can persist for years after the initial injury [30]. Understanding the long-term alterations in neuronal calcium dynamics and the underlying causes of this disruption is crucial for developing new therapeutic strategies to alleviate the debilitating effects of TBI [30].

BBB disruption Disruption of the BBB is a hallmark of severe TBI and plays a critical role in the neuroinflammatory processes that lead to brain swelling and cell death [33]. The BBB acts as a highly selective gatekeeper, meticulously controlling the exchange of substances between the bloodstream and the brain, maintaining a stable and healthy brain environment. Following TBI, the BBB becomes compromised, increasing its permeability and allowing the influx of harmful elements like immune cells, toxins, and other substances into the delicate brain tissue. This disruption exacerbates and prolongs the cascade of secondary damage [34]. Studies show that BBB breakdown occurs within hours of TBI and can persist for extended periods [34]. This disruption triggers a devastating chain reaction, including:

- **Tissue destruction**: Leaked harmful substances directly damage brain tissue.
- **Edema (fluid buildup)**: Increased permeability allows fluid to accumulate in the brain, causing swelling and pressure.
- **Inflammation**: Immune cells infiltrate the brain, contributing to further tissue damage.
- **Neuronal dysfunction**: Disrupted communication and function of brain cells.

The leakage of specific proteins like fibrinogen and immunoglobulin G into the brain parenchyma is a marker of BBB damage and is associated with poor outcomes in TBI patients [34]. Additionally, the heightened permeability can lead to cerebral edema, further amplifying the damage and jeopardizing recovery.

Apoptosis Apoptosis, or programmed cell death, plays a critical role in the devastating cascade of secondary brain injury following traumatic brain injury (TBI). Extensive research, from laboratory models to human studies, has solidified its significance in the pathogenesis of TBI. Extensive research, from laboratory models to human studies, has solidified its importance in the pathogenesis of TBI [35]. Detecting apoptotic cell death in both contusional brain lesions (directly impacted areas) and distant regions highlights a dynamic mechanism contributing to progressive neuronal deterioration over time [36]. Understanding and targeting this process is crucial, as neuronal apoptosis is critical in TBI management. This includes identifying its

initiators, modulators (e.g., the Bcl-2 family), and executors (e.g., the caspase family) [35].

Histological and experimental evidence reveals that various types of brain cells undergo apoptosis after TBI [36]. While neuronal apoptosis can act as a protective mechanism by eliminating damaged neurons, its overactivation can be detrimental, especially in situations like TBI [32]. Therefore, targeting apoptotic pathways presents a promising therapeutic approach for improving outcomes in TBI patients. By halting the excessive degeneration of neurons and glial cells, we can potentially mitigate the damage caused by this process [32]. Additionally, encouraging evidence suggests that apoptotic markers in cerebrospinal fluid could be valuable biomarkers for predicting patient prognosis after TBI [37]. Glutamate, acting on N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, plays a crucial role in triggering neurochemical changes following TBI [38]. When glutamate concentration in the synaptic cleft remains elevated due to impaired clearance mechanisms, it can trigger neuronal apoptosis [38]. This excitotoxic process is further exacerbated by the overstimulation of NMDA receptors, leading to calcium influx, mitochondrial dysfunction, and ultimately increased oxidative damage through mechanisms like reactive oxygen species production and lipid peroxidation [39, 40]. Astrocytes, a type of glial cell in the brain, play a complex role in neuronal survival and inflammation after TBI. While they can produce various substances that support neuronal health, reactive astrocytes, often associated with TBI, can also contribute to neurodegenerative processes [41].

TBI is a dynamic condition characterized by time-dependent alterations following the initial injury [42]. This necessitates the evaluation of diagnostic and prognostic tools that can adapt to this evolving context. Biomarkers, measurable indicators of biological processes, have emerged as valuable tools for understanding TBI and guiding clinical decision-making [42, 43]. Several biomarkers, including GFAP, tau, neurofilament light chain, S100B, and ubiquitin carboxy-terminal hydrolase-L1, are under extensive research for their potential in TBI diagnosis, prognosis, and treatment monitoring [43]. Blood tests for these biomarkers can offer valuable insights into the severity of neuronal injury and the extent of BBB disruption [42, 43].

Despite the promise of these biomarkers, significant knowledge gaps still need to be discovered regarding their optimal application. A deeper understanding of their kinetics, the pathways they take from the brain to the blood, is crucial for maximizing their effectiveness [43]. It is important to remember that biomarkers are not replacements for clinical evaluation and imaging tests but complementary tools that can provide valuable information for guiding clinical decisions [42]. As our understanding of TBI, particularly its neuroinflammatory aspects, continues to evolve, these biomarkers hold immense potential for developing novel therapeutic strategies.

Quercetin, an herbal compound with wide benefits

Quercetin, with the chemical formula $C_{15}H_{10}O_7$, is classified as an aglycone due to its absence of a sugar moiety. This compound presents a vivid citron-yellow coloration in the form of needle-shaped crystals and is entirely insoluble in cold water [44]. Quercetin constitutes approximately 75% of the flavonoids consumed [11]. Dietary intake of quercetin varies across countries, accounting for a significant portion of daily flavonoid intake, estimated to range from 50 to 800 mg [44]. Research studies have unveiled various potential benefits of quercetin across diverse health domains. Da et al. reported that quercetin increased bone density and strength in mice that underwent orchiectomy. This suggests that it may be used in the osteoporosis treatment [45]. Hu et al. demonstrated that quercetin's inhibition of breast cancer might be linked to promoting TFEB-mediated lysosomal activation and subsequent ferritin degradation [46]. A recent study by Hogaboam et al. indicated that quercetin suppressed lung fibrosis progression, decreased senescent cell markers, and enhanced health outcomes in mice with experimental fibrosis [47]. Additionally, quercetin has been identified as an inhibitor of LPS-induced microglial activation, a significant contributor to neuronal apoptosis [48]. Quercetin's suppression of PI3K/AKT in renal tissue has been associated with increased pro-apoptotic gene expression and decreased anti-apoptotic gene expression, indicating its potential to mitigate renal fibrosis and apoptosis in animals with chronic renal failure [49]. Kuang and colleagues (2021) investigated the function of the PI3K signaling pathway in ovarian function, revealing that quercetin inhibited follicle activation via the PI3K/Akt/Foxo3a pathway, a known protein phosphorylation target [10]. The versatile herbal compound quercetin manifests a broad spectrum of benefits, positioning it as a promising candidate for diverse applications in health and wellness. This section delves into its well-established antioxidant, anti-inflammatory, and neuroprotective properties.

Antioxidant properties

Antioxidants protect cells by neutralizing free radicals, which could otherwise cause cell injury. The accumulation of free radicals in the body causes oxidative stress, which may lead to many chronic diseases; therefore, the

antioxidant properties of quercetin may contribute to their prevention and treatment [50]. Quercetin's reputation as a potent antioxidant capable of combating oxidative stress and neutralizing free radicals has garnered significant scientific interest [51]. Both in vitro and in vivo studies have highlighted quercetin's antioxidant prowess, highlighting its potential in mitigating age-related ailments and diseases [11]. However, its oxidative byproducts, such as semiquinone radicals and quinones, must be considered when investigating its medicinal potential [52]. Research by Smith et al. revealed that quercetin primarily exerts its antioxidant activity through its effects on glutathione (GSH), enzymatic activity, signal transduction pathways, and ROS resulting from toxicological and environmental exposures. GSH, a potent intracellular antioxidant composed of cysteine, glutamic acid, and glycine, has crucial role in immune function and body detoxification [53]. Animal and cell studies have demonstrated that quercetin induces GSH synthesis, enhancing the antioxidant capacity of cells and preventing oxidative damage [54]. Furthermore, Erkasap and colleagues conducted an in vivo investigation to explore how quercetin affected kidney ischemia/reperfusion damage. The results showed that renal tissues treated with quercetin had significantly elevated GSH levels and decreased oxidative stress and inflammatory events compared to the control group [55].

Cellular damage and oxidative stress can be caused by ROS and RNS, both generated during enzyme activity. In the neurological system, acetylcholinesterase and butyrylcholinesterase degrade the neurotransmitter acetylcholine. Quercetin can bind to other compounds with its -OH group on the lateral benzene ring [56, 57]. Quercetin's ability to attach to the active sites of these enzymes has been associated with its capacity to suppress their oxidative activities. This property suggests potential benefits for conditions like Alzheimer's disease and other neurodegenerative disorders linked to acetylcholine breakdown [58]. Research conducted by Odbayar et al. indicates that quercetin can stimulate the production of antioxidant enzymes such as glutathione S-transferase (GST) and aldose reductase. In their study, mice fed a quercetin-enriched diet for two weeks showed increased liver GST and reductase enzyme activity. Moreover, indicators of inflammation and oxidative stress decreased [59].

Anti-inflammatory properties

Quercetin has been extensively studied for its health benefits, particularly its capacity to reduce inflammation [44, 60]. Inflammation is a natural response to harmful stimuli, such as infections, cellular damage, or irritants, and it plays a crucial role in the body's immune defense mechanisms. However, persistent inflammation can lead to various health complications, including cardiovascular diseases, cancers, and neurological disorders. The remarkable antioxidant and anti-inflammatory properties of quercetin contribute to its ability to mitigate inflammation [44, 60, 61]. Quercetin's anti-inflammatory properties have been shown to reduce inflammation and support the immune system [44]. In human hepatocyte-derived cell lines, it has been demonstrated to inhibit the production of inflammatory mediators, including nitric oxide synthase, cyclooxygenase-2, and C-reactive protein [60]. Its anti-inflammatory actions are linked to its ability to inhibit enzymes like lipoxygenase and cyclooxygenase (COX-2), which are responsible for the body's inflammatory responses [62]. Quercetin exerts potent anti-inflammatory effects by suppressing COX-2 protein expression and associated pathways [63]. Furthermore, quercetin has been found to decrease nitric oxide production and the secretion of tumor necrosis factor-alpha (TNF-α) by LPS-stimulated macrophages, further supporting its anti-inflammatory potential [64, 65]. In a study involving diabetic rats treated with quercetin at 25 mg/kg, accelerated wound healing was observed, attributed to reduced synthesis of prostaglandin E-2, IL-1, and leukotriene B-4 [66].

Quercetin's potential impact on obesity and atherosclerosis, two conditions closely associated with chronic low-grade inflammation, has been explored [67]. Quercetin shows promise in alleviating insulin resistance, a common feature in obesity, by reducing the generation and/or expression of proinflammatory cytokines and enzymes [67]. Moreover, research has provided insights into the therapeutic potential of quercetin in atherosclerosis, an inflammatory disorder of artery walls, and its molecular and cellular regulation [67]. Despite these promising findings, further studies are necessary to fully understand the mechanisms of action and address challenges related to quercetin's bioavailability and potential interactions with other compounds when used for anti-inflammatory therapy [68].

Neuroprotective activity

As previously mentioned, quercetin, a naturally occurring flavonoid found in various fruits and vegetables, has numerous health benefits, including a potential role in addressing neurodegenerative disorders [69, 70]. The progressive loss of neuronal structure and function, characteristic of neurodegenerative illnesses, leads to significant cognitive impairments [69]. Quercetin's effective antioxidant and anti-inflammatory properties may contribute to lowering the risk of certain diseases [69]. Quercetin has demonstrated neuroprotective properties and offers protection against neurodegenerative diseases by downregulating two significant contributors to their development—oxidative

stress and inflammation [69, 71] in neurons by significantly restoring p53 and downstream apoptotic markers, such as Cyto C, *Bax*, and caspase cascades. Moreover, quercetin restores the elements that activate p53. Therefore, neuroprotection may have a substantial impact by reducing levels of apoptotic markers in brain tissue [71]. Quercetin reduces inflammation in the neurological system by decreasing the levels of mediators and proinflammatory cytokines (TNF, ILs, IFN, etc.) [71]. Specifically, quercetin has been found to shield neurons from damage induced by oxidative stress [72]. Additionally, it serves as an effective natural antioxidant and anti-inflammatory agent, reducing inflammatory markers, minimizing microgliosis and astrogliosis, and contributing to overall homeostasis [71]. In the context of specific neurodegenerative disorders, researchers have explored quercetin's potential role in Alzheimer's disease and Parkinson's disease. In Alzheimer's disease, quercetin has demonstrated the ability to defend against Aβ(1–42), a peptide responsible for forming plaques in the brains of Alzheimer's patients [71]. In Parkinson's disease, quercetin has been found to possess therapeutic potential, shedding light on its molecular and cellular regulation [69, 70]. However, despite these promising findings, the therapeutic potential of quercetin in treating neurodegenerative diseases is significantly constrained by the BBB [72]. To address this limitation, researchers have investigated quercetin nanoparticle formulations, which enhance quercetin accumulation in brain tissue and yield more substantial effects at the tissue and cellular levels [72]. Given its potent antioxidant and anti-inflammatory qualities, quercetin holds significant promise as a potential therapeutic agent in neurodegenerative disorders.

Quercetin and traumatic brain injury: therapeutic aspects with focus on mechanisms

The impact of quercetin on TBI has been discussed, as outlines in Table 1. The research reveals its ability to reduce oxidative-nitrosative stress in both periodontal and cerebral tissues post-TBI in rats [73]. Additionally, it has demonstrated efficacy in preserving nerve cells and preventing a decline in erythropoietin (EPO) levels after acute severe TBI in rodent models [74]. As a result, quercetin demonstrates promise in addressing various neurological disorders [75] due to its neuroprotective mechanisms [76]. Its role in neuroprotection following TBI may be attributed to its capacity to diminish neuronal autophagy and apoptosis by enhancing the PI3K/Akt signaling pathway [77]. Elevated PIP3 levels may activate AKT in a feedback loop, influencing metastasis. Moreover, in various studies the PI3K/AKT signaling pathway has been implicated in cancer development and prognosis. Suppression of PI3K and/or AKT results in cancer cells undergoing apoptosis and growth inhibition [78]. Du et al. (2016) investigated Akt phosphorylation following TBI using Western blotting and immunofluorescence, determining that quercetin's action against neuronal autophagy is primarily linked to Akt activation [77]. Their findings indicated that the PI3K inhibitor LY294002 or the TrkB receptor antagonist K252a countered quercetin's neuroprotective effects, highlighting the mediation of quercetin's protective effects on neurons through the PI3K/Akt signaling pathway. The results suggest that quercetin can alleviate neuronal apoptosis and autophagy in rat TBI models by enhancing the PI3K/Akt signaling pathway [77]. Autophagy, a conserved mechanism that degrades proteins and organelles in stressed cells [79], was shown by Zubčić et al. (2020) to be positively influenced by quercetin. It enhances P19 neuron survival in oxidative stress induced by hydrogen peroxide through regulation of Akt and ERK1/2 signaling. Given the multifaceted contributions of the PI3K/Akt and the ERK1/2 pathways to neuronal function, these pathways present potential therapeutic targets in neurodegeneration [80].

Quercetin's neuroprotective effects in TBI are attributed to its activation of the Nrf2 pathway, a critical regulator of the cellular response to oxidative stress [81, 82]. This pathway plays a pivotal role in orchestrating various cellular processes, including synthesis of antioxidant enzymes that combat oxidative damage and inflammation [82]. Notably, Nrf2 emerges as key target of quercetin, as it regulates the expression of these cytoprotective enzymes, thereby exerting neuroprotective, detoxifying, and antioxidative effects [81]. Studies have demonstrated that quercetin treatment not only increases Nrf2 expression but also prevents neuronal death and structural alterations in the hippocampus, further highlighting its potential in mitigating TBI-induced damage [81]. Moreover, the Nrf2 pathway has been implicated in improving mitochondrial function and biogenesis, which are often compromised after TBI [82]. Some therapeutic potentials of quercetin are illustrated in Fig. 2.

As a key regulator of cellular metabolism and energy balance, AMPK phosphorylates and modulates the activity of downstream targets in mitochondrial biogenesis, autophagy, glucose and lipid metabolism, and autophagy. There is evidence that quercetin can enhance cellular energy generation, decrease oxidative stress, and inhibit the release of pro-inflammatory cytokines via activating AMPK. By blocking NF-kB and NLRP3 inflammasome pathway activation, quercetin achieves neuroprotective effects [83] (Fig. 2). A study by Lee et al., showed that quercetin reduced localized ischemia-induced BBB breakdown by inhibiting MMP-9 activity [84]. Building upon previous findings, Song et al. revealed that quercetin's

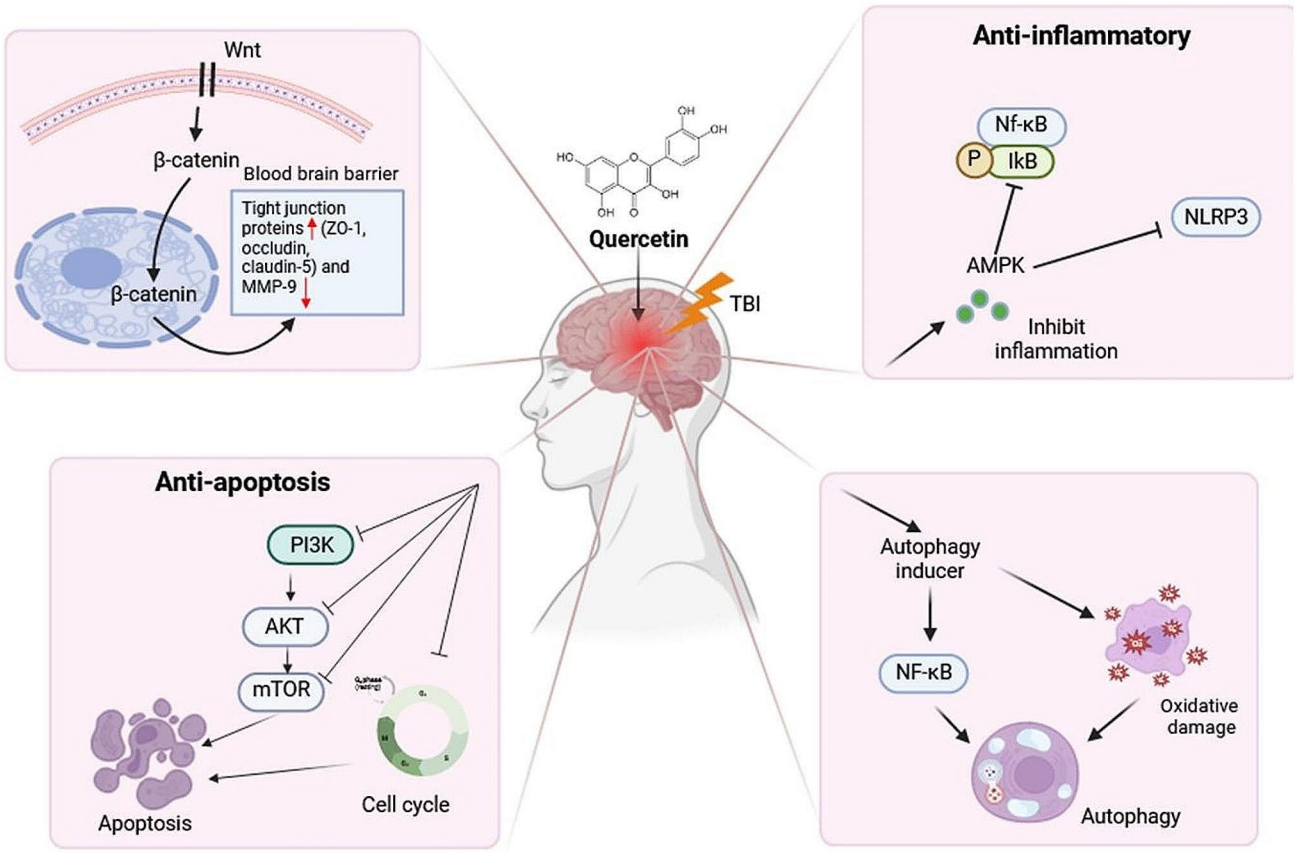

Fig. 2 The influence of quercetin on TBI, Created with biorender (https://biorender.com/)

neuroprotective effects involve the activation of Nrf2/HO-1, leading to reduced cortical neuroinflammation and oxidative stress following TBI [85]. Notably, TBI triggers the translocation of Nrf2 from the cytoplasm to the nucleus, a process further enhanced by quercetin treatment. This observation aligns with the established mechanism of Nrf2 activation, where cytoplasmic Nrf2 protein levels decrease significantly after TBI, with an even more significant reduction observed with quercetin therapy. Interestingly, the total Nrf2 protein levels remain relatively unchanged. These findings suggest that quercetin primarily influences Nrf2 activity by promoting its translocation to the nucleus rather than increasing protein expression. This aligns with previously reported post-translational Nrf2 regulatory mechanisms [82]. Figure 3 depicts the potential quercetin action mechanism in TBI.

Quercetin's neuroprotective effects extend beyond Nrf2 activation and encompass the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway, which plays a crucial role in regulating mitochondrial function [13]. PGC-1α, the first member of the PGC1 family, is implicated in various neurological disorders [13]. Studies employing a mouse model of TBI have shown that quercetin treatment upregulates PGC-1α expression and restores levels of key mitochondrial markers, including cytochrome c, malondialdehyde (MDA), and superoxide dismutase (SOD) [13]. These findings suggest that quercetin may enhance PGC-1α activity, potentially improving mitochondrial function and mitigating oxidative stress in the brain following TBI. This further highlights the multifaceted mechanisms underlying quercetin's protective effects against traumatic brain injury, as detailed in Table 1.

Further supporting quercetin's neuroprotective potential, various studies have documented its multifaceted effects in TBI models [73, 74, 88]. One study observed a significant reduction in superoxide radical production, increased nitric oxide synthase activity, and decreased superoxide anion production upon quercetin administration [73]. Additionally, Kalmeci et al. demonstrated that both quercetin and mannitol effectively reduced malondialdehyde levels, increased antioxidant enzyme activity (catalase and glutathione peroxidase), and did not significantly impact erythropoietin levels. However, mannitol administration transiently lowered hematocrit levels [74]. Furthermore, Yang et al. reported that quercetin treatment enhanced antioxidant

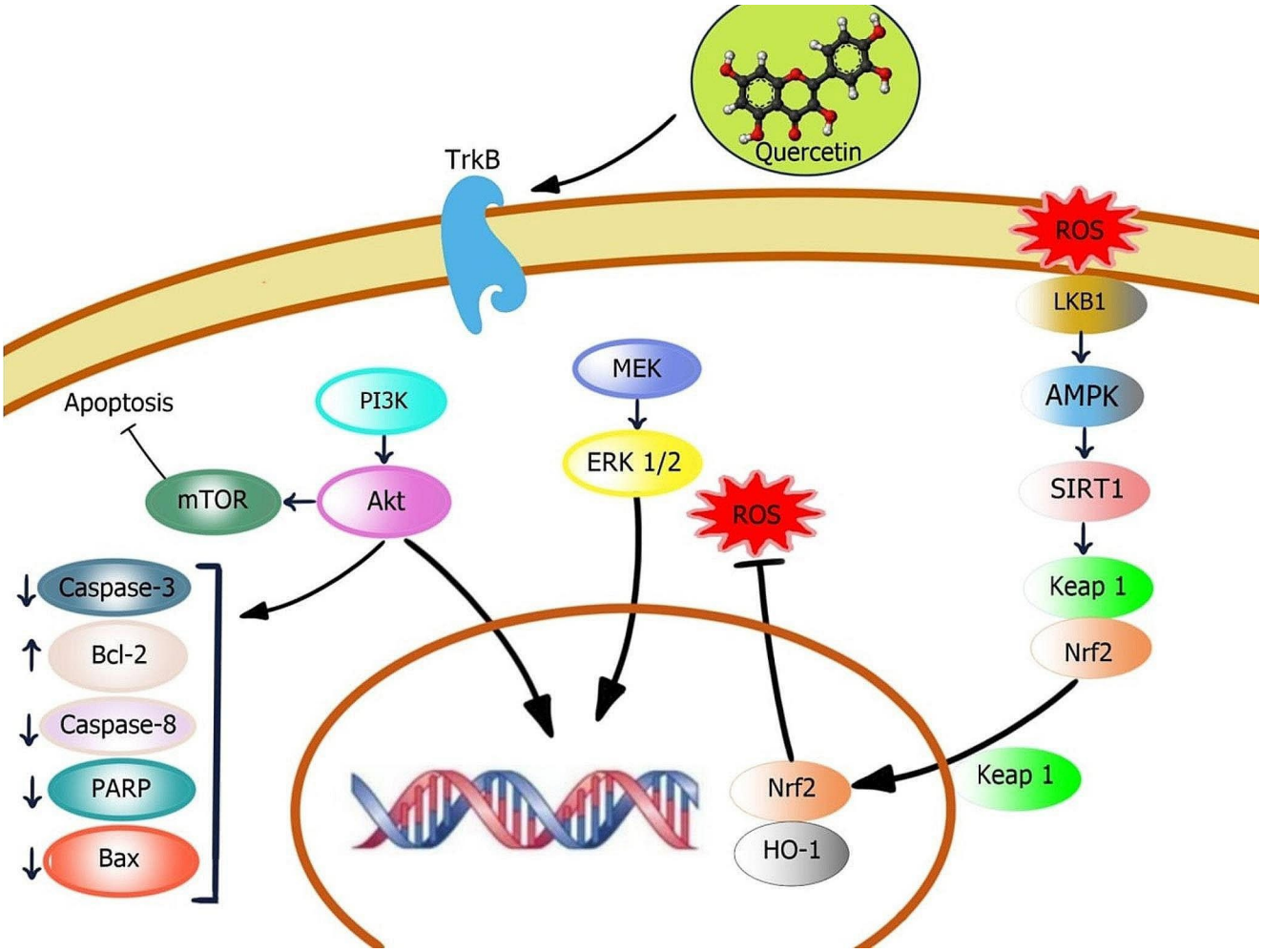

Fig. 3 The possible action mechanism of quercetin in traumatic brain injury. TrkB, Tropomyosin-related kinase B; PI3K, Phosphatidylinositol-3-kinase; PARP, PARP, Poly ADP-ribose polymerase; ERK, Extracellular signal-regulated kinase; mTOR, Mammalian target of rapamycin; MEK, Mitogen-activated protein kinase kinase; AMPK, AMP-activated protein kinase; LKB1, Liver kinase B1; Bax, Bcl-2 Associated X-protein; Nrf2, Nuclear factor erythroid 2-related factor 2; SIRT1, Sirtuin 1; Keap1, kelch like ECH associated protein 1; HO-1, Heme oxygenase-1

enzyme activity, reduced oxidative stress and inflammation, and improved cognitive function in rats with TBI, suggesting potential cognitive recovery benefits [88]. It is essential to acknowledge that while these preclinical studies are encouraging, further clinical trials are necessary to establish the safety and efficacy of quercetin for treating TBI in humans [89].

Conclusion

In conclusion, research on quercetin suggests its potential therapeutic benefits in treating TBI. Quercetin exhibits promise in reducing inflammation, oxidative stress, apoptosis, and enhancing cognitive function post-TBI. Its antioxidant and anti-inflammatory properties position it as a potential candidate for neuroprotection in TBI, paving the way for exploring new therapeutic strategies. Although the potential of quercetin as a TBI intervention is promising and merits further investigation, recent studies have started to unveil some molecular pathways associated with its protective effects, yet the underlying processes remain unclear. Nevertheless, quercetin has demonstrated efficacy in diminishing inflammation, neuronal apoptosis, and oxidative stress in animal models of TBI. The challenge for the future is to delve deeper into quercetin's optimal advantages, especially considering suggestions for prolonged consumption. However, further research is imperative to comprehend the underlying mechanisms and optimize their benefits.

Table 1 Quercetin can be effective against traumatic brain injury by various mechanisms in vivo and in vitro

Dose	Target (s)	Effect (s)	Model	Ref.
20–100 mg/kg	PGC-1α and caspase-3	Boosting mitochondrial biogenesis through the PGC-1α pathway. Only 50 mg/kg showed neuroprotective effects after TBI.	in vitro	[13]
50 mg/kg	Nrf2, HO-1, NF-κB, caspase 3	Quercetin reduced the harmful neurodegenerative and apoptotic processes linked to TBI, demonstrating antioxidant capabilities.	in vivo	[86]
20 mg/kg	lipid peroxidation level, SOD, catalase, glutathione peroxidase activities, and histological analysis	Quercetin treatment significantly reduced lipid peroxidation, increased superoxide dismutase, catalase, glutathione peroxidase, and histological changes in the cerebral cortex compared to the inflammation group.	in vivo	[87]
10 mg/kg	SOD, catalase, and NOS	Quercetin administration resulted in a decrease in peroxynitrite content and lipid peroxidation, indicating a reduction in oxidative stress, also reduced the activity of NOS, including iNOS, and increasing cNOS. Quercetin enhanced the SOD activity and catalase.	in vitro	[73]
50 mg/kg	LC3, caspase-3, Bax, Bcl-2, and p-Akt	Repressing neuronal apoptosis and autophagy and promoting cognitive function	in vitro	[77]
50 mg/kg	Malondialdehyde, catalase, EPO, and GSH-Px	lowering malondialdehyde and promoting catalase and GSH-Px	in vitro	[74]
30 mg/kg	Caspase-3, SOD, GSH-Px, Bax, TNF-α, IL-1β, IL-6, and IL-10	Enhancing cognitive function, decreasing cell death, oxidative stress, and inflammation	in vivo	[88]

NOS: nitric oxide synthesis; iNOS: inducible NOS; cNOS: constitutive NOS; SOD: superoxide dismutase; TNF-α: Tumor necrosis factor-α; IL: Interleukin; LC3: Light chain 3; GSH-Px: Glutathione peroxidase

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References

1. Izzy S et al (2023) Long-term risk of cardiovascular disease after traumatic brain injury: screening and prevention. Lancet Neurol 22(10):959–970
2. Tramontano M et al (2022) Vestibular Rehabilitation improves Gait Quality and activities of Daily living in people with severe traumatic brain Injury: a Randomized Clinical Trial. Sens (Basel), 22(21)
3. Wang Y et al (2023) Target temperature management and therapeutic hypothermia in sever neuroprotection for traumatic brain injury: clinic value and effect on oxidative stress. Med (Baltim) 102(10):e32921
4. Hasan S et al (2023) Neuroprotective potential of flavonoids in Brain disorders. Brain Sci, 13(9)
5. Injury GBDTB (2019) Spinal cord Injury, *Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the global burden of Disease Study 2016*. Lancet Neurol 18(1):56–87
6. Wei C et al (2023) Therapy of traumatic brain injury by modern agents and traditional Chinese medicine. Chin Med 18(1):25
7. Crowley MG, Liska MG, Borlongan CV (2017) Stem cell therapy for sequestering neuroinflammation in traumatic brain injury: an update on exosome-targeting to the spleen. J Neurosurg Sci 61(3):291–302
8. Lee B et al (2020) Herbal Medicine for Traumatic Brain Injury: a systematic review and Meta-analysis of Randomized controlled trials and limitations. Frontiers in Neurology, p 11
9. de Oliveira MR et al (2016) Quercetin and the mitochondria: a mechanistic view. Biotechnol Adv 34(5):532–549
10. Li J et al (2021) Quercetin prevents primordial follicle loss via suppression of PI3K/Akt/Foxo3a pathway activation in cyclophosphamide-treated mice. Reprod Biol Endocrinol 19(1):63
11. Deepika, Maurya PK (2022) Health benefits of Quercetin in Age-Related diseases. Molecules, 27(8)
12. Oboh G et al (2019) Phytochemicals and Hormonal effects. Encyclopedia of Food Chemistry. Academic, Oxford, pp 550–560. L. Melton, F. Shahidi, and P. Varelis, Editors
13. Li X et al (2018) Neuroprotection by quercetin via mitochondrial function adaptation in traumatic brain injury: PGC-1alpha pathway as a potential mechanism. J Cell Mol Med 22(2):883–891
14. Huang Z, Yan L (2022) Clinical efficacy and prognosis of standard large trauma craniotomy for patients with severe frontotemporal craniocerebral injury. Am J Transl Res 14(1):476–483
15. Freire MAM et al (2023) Cellular and Molecular Pathophysiology of Traumatic Brain Injury: what have we learned so far? Biology 12(8):1139
16. Algattas H, Huang JH (2014) Traumatic brain Injury Pathophysiology and treatments: early, Intermediate, and late phases Post-injury. Int J Mol Sci 15(1):309–341
17. Al-Sarraj S (2016) The pathology of traumatic brain injury (TBI): a practical approach. Diagn Histopathology 22(9):318–326
18. Ladak AA, Enam SA, Ibrahim MT (2019) A review of the Molecular mechanisms of Traumatic Brain Injury. World Neurosurg 131:126–132

19. Werner C, Engelhard K (2007) Pathophysiology of traumatic brain injury. Br J Anaesth 99(1):4–9
20. Fesharaki-Zadeh A (2022) Oxidative stress in traumatic brain Injury. Int J Mol Sci, 23(21)
21. Nguyen A et al (2023) Mechanisms of mitochondrial oxidative stress in Brain Injury: from pathophysiology to therapeutics. Oxygen 3(2):163–178
22. Ismail H et al (2020) Traumatic Brain Injury: oxidative stress and novel anti-oxidants such as Mitoquinone and Edaravone. Antioxidants 9(10):943
23. Zheng R-z et al (2022) Neuroinflammation following traumatic Brain Injury: take it seriously or not. Front Immunol, 13
24. Simon DW et al (2017) The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Reviews Neurol 13(3):171–191
25. Liu X et al (2023) Neuroinflammation of traumatic brain injury: roles of extracellular vesicles. Front Immunol, 13
26. Xiong Y, Mahmood A, Chopp M (2018) Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities. Chin J Traumatol 21(3):137–151
27. Yi JH, Hazell AS (2006) Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. Neurochem Int 48(5):394–403
28. Baracaldo-Santamaria D et al (2022) Revisiting excitotoxicity in traumatic Brain Injury: from bench to Bedside. Pharmaceutics, 14(1)
29. Weber JT (2012) Altered calcium signaling following traumatic brain injury. Front Pharmacol 3:60
30. Sun DA et al (2008) Traumatic brain injury causes a long-lasting calcium (Ca2+)-plateau of elevated intracellular ca levels and altered Ca2 + homeostatic mechanisms in hippocampal neurons surviving brain injury. Eur J Neurosci 27(7):1659–1672
31. Rao W et al (2015) *Downregulation of STIM2 improves neuronal survival after traumatic brain injury by alleviating calcium overload and mitochondrial dysfunction* Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 1852(11):2402–2413
32. Ng SY, Lee AYW (2019) Traumatic brain injuries: pathophysiology and potential therapeutic targets. Front Cell Neurosci, 13
33. Price L, Wilson C, Grant G (2016) In: Laskowitz D, Grant G (eds) *Blood-brain barrier pathophysiology following traumatic Brain Injury*, in *Translational Research in Traumatic Brain Injury*. Boca Raton (FL), Editors
34. Cash A, Theus MH (2020) Mechanisms of blood-brain barrier dysfunction in traumatic brain Injury. Int J Mol Sci, 21(9)
35. Zhang X et al (2004) Bench-to-bedside review: Apoptosis/programmed cell death triggered by traumatic brain injury. Crit Care 9(1):66
36. Akamatsu Y, Hanafy KA (2020) Cell death and recovery in traumatic brain Injury. Neurotherapeutics 17(2):446–456
37. Jiang W et al (2020) Apoptosis in cerebrospinal fluid as outcome predictors in severe traumatic brain injury: an observational study. Medicine, 99(26)
38. Subramanian A et al (2023) Neuroprotective potential of Marsilea quadrifolia Linn against monosodium glutamate-induced excitotoxicity in rats. Front Pharmacol 14:1212376
39. Dubey Tiwari K et al (2023) Effects of high glutamate concentrations on mitochondria of human neuroblastoma SH-SY5Y cells. Ann Pharm Fr 81(3):457–465
40. Khatri N et al (2018) Oxidative stress: major threat in traumatic brain Injury. CNS Neurol Disord Drug Targets 17(9):689–695
41. Michinaga S, Koyama Y (2021) Pathophysiological responses and roles of astrocytes in traumatic brain Injury. Int J Mol Sci 22(12):6418
42. Dadas A et al (2018) Biomarkers in traumatic brain injury (TBI): a review. Neuropsychiatr Dis Treat 14:2989–3000
43. Hier DB et al (2021) Blood biomarkers for mild traumatic brain injury: a selective review of unresolved issues. Biomark Res 9(1):70
44. Li Y et al (2016) Quercetin, inflammation and immunity. Nutrients 8(3):167
45. Sun J et al (2022) Quercetin attenuates osteoporosis in Orchiectomy mice by regulating glucose and lipid metabolism via the GPRC6A/AMPK/mTOR signaling pathway. Front Endocrinol (Lausanne) 13:849544
46. An S, Hu M (2022) Quercetin promotes TFEB Nuclear translocation and activates Lysosomal Degradation of Ferritin to induce ferroptosis in breast Cancer cells. Comput Intell Neurosci 2022:p5299218
47. Hohmann MS et al (2019) Quercetin enhances ligand-induced apoptosis in senescent idiopathic pulmonary fibrosis fibroblasts and reduces lung fibrosis in vivo. Am J Respir Cell Mol Biol 60(1):28–40
48. Bureau G, Longpre F, Martinoli MG (2008) Resveratrol and quercetin, two natural polyphenols, reduce apoptotic neuronal cell death induced by neuroinflammation. J Neurosci Res 86(2):403–410
49. Tu H et al (2021) Quercetin alleviates chronic renal failure by targeting the PI3k/Akt pathway. Bioengineered 12(1):6538–6558
50. Boots AW, Haenen GR, Bast A (2008) Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol 585(2–3):325–337
51. Aghababaei F, Hadidi M (2023) Recent Adv Potential Health Benefits Quercetin Pharmaceuticals 16(7):1020
52. Hrelia S, Angeloni C (2013) Chap. 1*3 - quercetin and its metabolites in Heart Health*. Bioactive food as Dietary interventions for Cardiovascular Disease. Academic, San Diego, pp 217–228. R.R. Watson and V.R. Preedy, Editors
53. Smith AR, Visioli F, Hagen TM (2002) Vitamin C matters: increased oxidative stress in cultured human aortic endothelial cells without supplemental ascorbic acid. FASEB J 16(9):1102–1104
54. Dong Y et al (2020) Quercetin alleviates intestinal oxidative damage Induced by H(2)O(2) via modulation of GSH: in Vitro Screening and in vivo evaluation in a colitis model of mice. ACS Omega 5(14):8334–8346
55. Kinaci MK et al (2012) Effects of quercetin on apoptosis, NF-kappaB and NOS gene expression in renal ischemia/reperfusion injury. Exp Ther Med 3(2):249–254
56. Ademosun AO et al (2016) Antioxidative Properties and Effect of Quercetin and its glycosylated form (Rutin) on acetylcholinesterase and butyrylcholinesterase activities. J Evid Based Complement Altern Med 21(4):NP11–NP17
57. Jung M, Park M (2007) Acetylcholinesterase inhibition by flavonoids from Agrimonia pilosa. Molecules 12(9):2130–2139
58. Liao Y et al (2022) Exploring the inhibition of Quercetin on Acetylcholinesterase by Multispectroscopic and in Silico Approaches and evaluation of its neuroprotective effects on PC12 cells. Molecules, 27(22)
59. Odbayar TO et al (2009) Isoenzyme-specific up-regulation of glutathione transferase and aldo-keto reductase mRNA expression by dietary quercetin in rat liver. Mol Cell Biochem 325(1–2):121–130
60. Anand David AV, Arulmoli R, Parasuraman S (2016) Overviews of Biological Importance of Quercetin: a bioactive flavonoid. Pharmacogn Rev 10(20):84–89
61. Yang D et al (2020) *Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine* Oxid Med Cell Longev, 2020: p. 8825387
62. Dey R et al (2022) Natural inhibitors against potential targets of cyclooxygenase, Lipoxygenase and Leukotrienes. Comb Chem High Throughput Screen 25(14):2341–2357

63. Guran M et al (2019) Combined effects of quercetin and curcumin on anti-inflammatory and antimicrobial parameters in vitro. Eur J Pharmacol 859:172486
64. Manjeet KR, Ghosh B (1999) Quercetin inhibits LPS-induced nitric oxide and tumor necrosis factor-alpha production in murine macrophages. Int J Immunopharmacol 21(7):435–443
65. Wadsworth TL, McDonald TL, Koop DR (2001) Effects of Ginkgo biloba extract (EGb 761) and quercetin on lipopolysaccharide-induced signaling pathways involved in the release of tumor necrosis factor-alpha. Biochem Pharmacol 62(7):963–974
66. Ahmed OM et al (2018) Quercetin and low level laser therapy promote wound healing process in diabetic rats via structural reorganization and modulatory effects on inflammation and oxidative stress, vol 101. Biomedicine & Pharmacotherapy, pp 58–73
67. Sato S, Mukai Y (2020) Modulation of chronic inflammation by Quercetin: the Beneficial effects on obesity. J Inflamm Res 13:421–431
68. Shen P et al (2021) Potential implications of Quercetin in Autoimmune diseases. Front Immunol, 12
69. Elumalai P, Lakshmi S (2016) Role of Quercetin benefits in Neurodegeneration. Adv Neurobiol 12:229–245
70. Wróbel-Biedrawa D et al (2022) A flavonoid on the brain: Quercetin as a potential therapeutic Agent in Central Nervous System disorders. Life 12(4):591
71. Bayazid AB, Lim BO (2022) Quercetin is an active Agent in berries against neurodegenerative diseases Progression through Modulation of Nrf2/HO1. Nutrients, 14(23)
72. Goyal R et al (2023) Insights on Quercetin Therapeutic potential for neurodegenerative diseases and its Nano-technological perspectives. Curr Pharm Biotechnol
73. Yavtushenko IV et al (2020) Quercetin limits the progression of oxidative and nitrosative stress in the rats' tissues after experimental traumatic brain Injury. Wiad Lek 73(10):2127–2132
74. Kalemci O et al (2017) Effects of Quercetin and Mannitol on erythropoietin levels in rats following acute severe traumatic brain Injury. J Korean Neurosurg Soc 60(3):355–361
75. Dajas F (2012) Life or death: neuroprotective and anticancer effects of quercetin. J Ethnopharmacol 143(2):383–396
76. Ay M et al (2017) Molecular mechanisms underlying protective effects of quercetin against mitochondrial dysfunction and progressive dopaminergic neurodegeneration in cell culture and MitoPark transgenic mouse models of Parkinson's Disease. J Neurochem 141(5):766–782
77. Du G et al (2016) Quercetin attenuates neuronal autophagy and apoptosis in rat traumatic brain injury model via activation of PI3K/Akt signaling pathway. Neurol Res 38(11):1012–1019
78. Matsuda S et al (2016) Effective PI3K modulators for improved therapy against malignant tumors and for neuroprotection of brain damage after tumor therapy (review). Int J Oncol 49(5):1785–1790
79. Pozuelo-Rubio M (2011) 14-3-3zeta binds class III phosphatidylinositol-3-kinase and inhibits autophagy. Autophagy 7(2):240–242
80. Zubcic K et al (2020) PI3K/Akt and ERK1/2 signalling are involved in quercetin-mediated neuroprotection against Copper-Induced Injury. Oxid Med Cell Longev 2020:p9834742
81. Zamanian MY et al (2023) Targeting Nrf2 signaling pathway by quercetin in the prevention and treatment of neurological disorders: an overview and update on new developments. Fundam Clin Pharmacol 37(6):1050–1064
82. Li X et al (2016) Protective effects of Quercetin on mitochondrial Biogenesis in Experimental Traumatic Brain Injury via the Nrf2 Signaling Pathway. PLoS ONE 11(10):e0164237
83. Chiang M-C, Tsai T-Y, Wang C-J (2023) The potential benefits of Quercetin for Brain Health: a review of anti-inflammatory and neuroprotective mechanisms. Int J Mol Sci 24(7):6328
84. Lee JK et al (2011) *Quercetin reduces the elevated matrix metalloproteinases-9 level and improves functional outcome after cerebral focal ischemia in rats* Acta Neurochir (Wien), 153(6): pp. 1321-9; discussion 1329
85. Song J et al (2021) Protective effects of quercetin on traumatic brain injury induced inflammation and oxidative stress in cortex through activating Nrf2/HO-1 pathway. Restor Neurol Neurosci 39(1):73–84
86. Alqahtani F et al (2024) Therapeutic benefits of quercetin in traumatic brain injury model exposed to cigarette smoke. Saudi Pharm J 32(1):101895
87. Hmangte Hitler Kom MN, Srilatha K, Reddy KP (2019) *Protective effect of quercetin on weight drop injury model-induced neuroinflammation alterations in brain of mice*. Vol. Volume: 9. : Issue: 4. 096–103
88. Yang T et al (2014) Anti-apoptotic and anti-oxidative roles of quercetin after traumatic brain injury. Cell Mol Neurobiol 34(6):797–804
89. Blum B et al (2021) Melatonin in Traumatic Brain Injury and Cognition. Cureus 13(9):e17776