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The Neuroprotective Effect of Rooibos Herbal Tea Against Alzheimer's Disease: A Review

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Received: 20 August 2024 | **Revised:** 19 November 2024 | **Accepted:** 2 December 2024

Funding: This study was funded by the South African Rooibos Council and Cape Peninsula University of Technology.

Keywords: Alzheimer's disease | neurodegenerative disorders | neuroprotection | Rooibos

ABSTRACT

The world is experiencing a demographic shift toward an increasing proportion of elderly persons. Alzheimer's disease (AD) and other neurological disorders are far more likely to develop as people age. AD is a gradual, irreversible, and degenerative brain disorder that progressively deteriorates memory and cognitive function, eventually leading to death. Treatment for AD is the most significant unmet clinical need in neurology. There are no effective treatment options to prevent or reverse the degenerative process. The current medical management focuses primarily on temporarily easing symptoms, with little or no overall improvement. Although genetic predisposition and lifestyle factors influence the risk of neurodegenerative disorders, recent research suggests that dietary polyphenols with solid antioxidant capacities play crucial roles in determining brain health and aging. *Aspalathus linearis* is used to produce Rooibos, a popular South African herbal tea, which may modulate neurodegenerative mechanisms such as oxidative stress, tau protein, amyloid plaques, inflammation, and metals, all of which have been associated with AD. We reviewed the literature to evaluate the potential neuroprotective effects of Rooibos and its major flavonoids and to understand the underlying molecular mechanisms.

1 | Introduction

Neurodegenerative disorders (NDDs), such as AD and Parkinson's disease (PD), are becoming increasingly common, especially in aging populations. This trend is expected to reach pandemic levels and is influenced by genetics, aging, lifestyle, and environmental factors [1, 2].

Alzheimer's disease (AD), a leading cause of dementia among older adults, affects over 50 million people globally [2, 3]. Its development is associated with multiple factors, including oxidative stress (OS), inflammation, dietary habits, and mental imbalances [4, 5]. It is important to note that the key pathological hallmarks of AD are the accumulation of hyperphosphorylated tau protein and amyloid-beta (Aβ) plaques, which ultimately lead to neuronal cell death [6], Figure 1.

AD is characterized by accumulating two abnormal structures: extracellular amyloid plaques and intracellular neurofibrillary tangles. These structures, driven by the activation of glycogen synthase kinase 3 beta (GSK-3β), are composed of tightly packed, highly insoluble filaments. Amyloid plaques consist of Aβ peptides derived from an amyloid precursor protein (APP), while neurofibrillary tangles comprise hyperphosphorylated tau protein. Both Aβ and tau contribute to neuronal dysfunction and death, and their accumulation is exacerbated by OS, metal dyshomeostasis, and inflammation.

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Summary

- Rooibos modulates γ-secretase, reducing pathogenic Aβ peptides.
- Aβ plaque deposition reduced by Rooibos, aiding neuroprotection.
- Neuroprotective effects of Rooibos via GABAergic neurotransmission.
- Rooibos mitigates neuroinflammation and oxidative stress in AD.
- Multifaceted therapeutic benefits of Rooibos for Alzheimer's disease.

Although current pharmaceutical treatments like galantamine, rivastigmine, and donepezil can provide symptomatic relief for NDDs, they often come with side effects such as depression, bradycardia, nausea, and vomiting [5]. Given the irreversible nature of neurodegeneration, prevention and disease-modifying therapies are crucial to mitigating their impact [4]. As a result, exploring natural compounds is gaining significant attention for their potential neuroprotective benefits [7, 8].

Rooibos tea, a South African herbal infusion, is celebrated for its diverse range of beneficial compounds. Unlike caffeine-rich yerba mate (*Ilex paraguariensis*) and traditional teas (white, green, and black) with caffeine concentrations ranging from 14 to 61 mg per serving (6 or 8 oz) [9, 8], Rooibos is naturally caffeine-free, though trace amounts of the alkaloid sparteine have been detected. Although Rooibos is often considered a low-tannin tea, approximately half of its water-soluble components are tannin-like substances. However, compared to black tea (*Camellia sinensis*), Rooibos contains significantly fewer tannins [10].

Essential bioactive compounds in Rooibos, including aspalathin, nothofagin, and linearthin, have demonstrated neuroprotective effects in various in vitro and in vivo models of neurodegenerative diseases [7, 11, 12]. For instance, aspalathin and its derivative, linearthin, have shown promise in mitigating neurotoxicity induced by OS and mitochondrial dysfunction in PD models [12]. Furthermore, given the potential link between diabetes, cardiovascular disease (CVD), and AD [13], incorporating Rooibos into the diet may offer protective benefits. Rooibos, known for its ability to mitigate diabetes and cardiovascular risk factors [14–16], could be a valuable dietary strategy for AD prevention.

According to a recent review on the neuroprotective effects of Rooibos, rutin and quercetin, an isomer of rutin, can readily pass the blood–brain barrier (BBB) and offer neuroprotection with many mechanisms of action [17]. The well-established bioactivity of Rooibos makes it a good candidate for NDD intervention.

The bioavailability of Rooibos compounds is supported by studies using the Brain Or IntestinaL EstimateD absorption (BOILED-egg) model, which suggests that these compounds can be absorbed in the gastrointestinal tract and cross the BBB [18]. Furthermore, research on the pharmacokinetics of Rooibos metabolites indicates that consuming Rooibos tea leads to the absorption and subsequent excretion of various bioactive compounds [19, 20]. It is suggested that consuming six cups of Rooibos tea daily may offer potential health benefits, including neuroprotection [16]. Therefore, the growing body of evidence supporting the neuroprotective potential of Rooibos tea highlights its promise as a natural intervention for NDDs.

2 | Effects of Rooibos on the Endogenous Defense System

Several antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), work together to neutralize harmful reactive oxygen species (ROS) and protect cells from OS [21, 22].

Glutathione (GSH), an essential antioxidant, exists in reduced (GSH) and oxidized (GSSG) forms. Maintaining the balance between these two forms is crucial for cellular redox homeostasis. During OS, GPx catalyzes the oxidation of GSH to GSSG, disrupting this balance and impairing cellular function [23, 24]. However, GPx also utilizes GSH to reduce harmful hydrogen peroxide (H_2O_2) in water [25]. Glutathione reductase (GR) maintains the balance between GSH and GSSG by using nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) as a cofactor [24]. It is important to note that GSH can also bond with protein cysteine residues, known as glutathionylation. This reversible modification can alter protein function and contribute to neurodegenerative diseases such as AD [26].

The excitatory amino acid carrier 1 (EAAC1) is essential for neuronal GSH synthesis. Glutamate transport-associated protein 3–18 (GTRAP3-18) and miR-96-5p, which exhibit a diurnal rhythm, regulate EAAC1 expression. Upregulating miR-96-5p increases GTRAP3-18 expression by 1.26-fold ($p = 0.0081$), leading to increased GSH levels and potential neuroprotection [27]. In vivo studies have shown that inhibiting miR-96-5p can increase EAAC1 expression and GSH levels, particularly in regions vulnerable to OS, such as the substantia nigra. For instance, inhibiting miR-96-5p increased EAAC1 expression by 0.2-fold ($p < 0.05$) and elevated GSH levels to match peak levels observed at specific times of day when biological processes may be more active (0.2-fold change, $p < 0.05$) [28].

Rooibos herbal tea, a potent antioxidant, offers significant neuroprotective benefits by mitigating OS, enhancing antioxidant enzyme activity, and restoring redox balance. In vitro studies have shown that green Rooibos extract reduces intracellular OS in Neuro-2a cells. Treatment with increasing concentrations of the extract (25, 50, and 100 μg/mL) significantly lowered ROS production ($p < 0.0001$) compared to the control when cells were exposed to OS induced by 250 or 125 μM H_2O_2 for 90 min, indicating its effectiveness in modulating OS and protecting cells from ROS-mediated damage. Additionally, green Rooibos extract exhibited a dose-dependent inhibitory effect on the neuroenzyme monoamine oxidase-A (MAO-A). However, this activity was inferior to the reference selective inhibitor clorgyline [11]. Rooibos tea pretreatment significantly increased antioxidant enzymes (SOD and CAT, $p < 0.001$ and $p < 0.01$, respectively)

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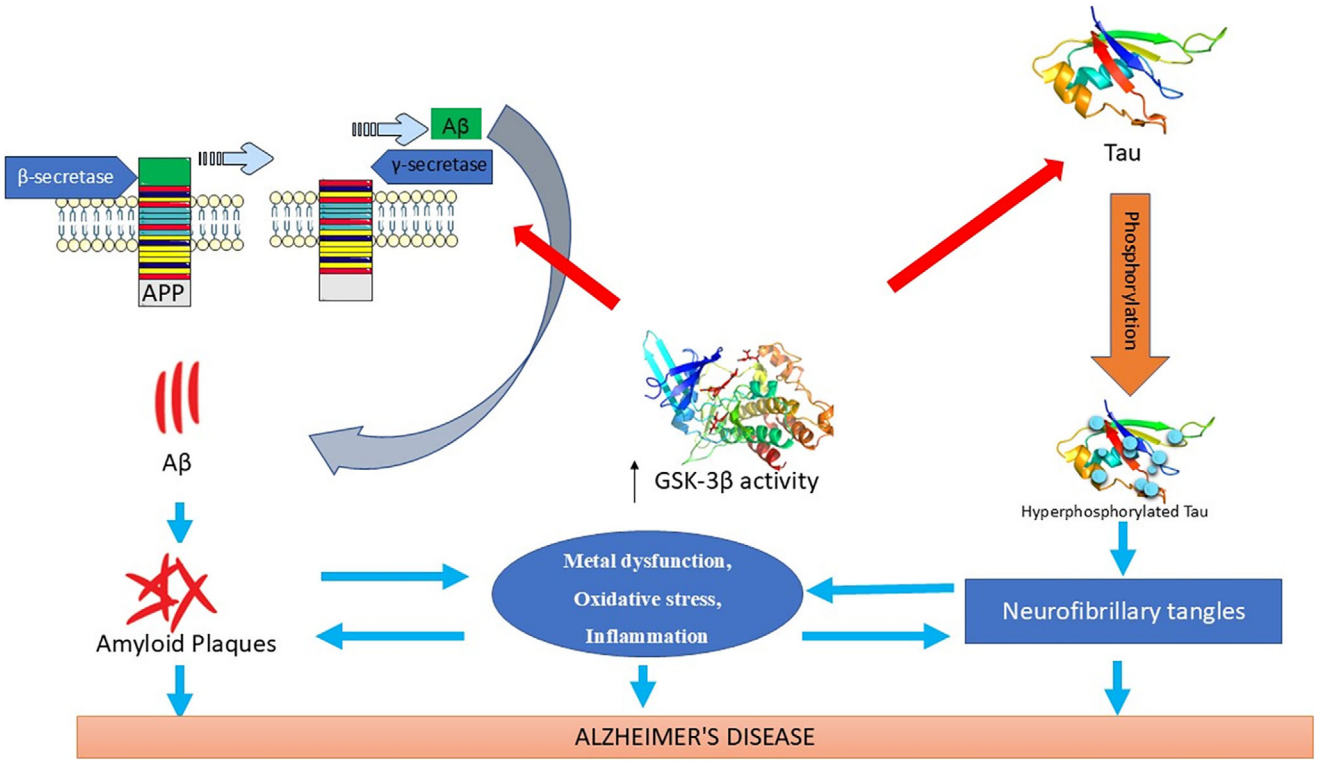


FIGURE 1 | The most prominent clinical biomarkers of Alzheimer's disease.

and restored redox balance by increasing GSH levels and the GSH:GSSG ratio ($p < 0.01$ and $p < 0.05$, respectively) in immobilized rats [23]. Long-term consumption significantly increased ferric-reducing antioxidant power (FRAP) values (2.12 ± 0.16 vs 0.63 ± 0.11) and decreased malondialdehyde (MDA) levels (0.017 μmol/g ± 0.0008 vs 0.029 μmol/g ± 0.0014) in cerebral ischemia models compared to controls [29]. Human clinical trials have shown that Rooibos tea consumption significantly enhances lipid profiles and redox status. After Rooibos consumption, total polyphenols increased (from 79.8 ± 16.9 mg/L to 89.8 ± 14.1 mg/L), and biomarkers of lipid peroxidation decreased. Conjugated dienes (CDs) decreased from 167.3 ± 29.5 nmol/mL to 108.8 ± 20.1 nmol/mL, and MDA from 1.9 ± 0.6 μmol/L to 0.9 ± 0.3 μmol/L. Additionally, GSH levels increased from 797 ± 238 μmol/L to 1082 ± 140 μmol/L, and the GSH:GSSG ratio improved from 41 ± 14 to 76 ± 17. The lipid profile also improved, with "bad" low-density lipoprotein (LDL)-cholesterol decreasing from 4.6 ± 1.3 mmol/L to 3.9 ± 0.7 mmol/L, triacylglycerols from 1.7 ± 0.8 mmol/L to 1.2 ± 0.7 mmol/L, and "good" high-density lipoproteins (HDLs)-cholesterol increasing from 0.9 ± 0.1 mmol/L to 1.2 ± 0.2 mmol/L [16]. These findings align with a recent study by Hartnick et al. [15] demonstrating that a 12-week Rooibos herbal tea intervention significantly reduced key cardiac parameters like left atrial size, interventricular septum diameter, and left ventricular posterior wall thickness. A separate study compared the effects of green, black, and Rooibos tea on angiotensin-converting enzyme (ACE) activity. Participants consumed 400 mL of each tea brewed similarly. Rooibos tea significantly inhibited ACE activity by 5% at 30 min ($p < 0.01$) and 3% at 60 min ($p < 0.05$), while green and black tea had no significant effect [30]. These findings suggest that Rooibos tea can significantly enhance lipid profiles and redox status, which is crucial for heart health, especially in individuals at risk of CVD and NDDs like AD.

Two-month-old male Wistar rats (200–250 g) administered 25 g of *I. paraguariensis* in 500 mL of 70°C hot water for 4 weeks at a 2.31 g/kg/day dose showed no significant change in TBARS levels. Additionally, while selegiline, a known MAO inhibitor, significantly reduced MAO-B activity ($F(2,11) = 78.80$, $p < 0.05$), *I. paraguariensis* did not affect the activity of either MAO-A or MAO-B [31]. Vargas et al. [32] found that microencapsulating yerba mate enhanced its ability to combat OS in male Wistar rats. Compared to the control, yerba mate extract, and empty microparticle groups, only the yerba mate microparticle group showed increased plasma antioxidant activity (0.2 ± 0.1 μg GAE/mL). It decreased brain lipid peroxidation (0.9 ± 0.3 nmol MDA/mg protein). Importantly, plasma lipid peroxidation levels remained consistent across all groups. The disparity in the potential to reduce lipid peroxidation markers between Rooibos and yerba mate could be attributed to bioavailability. When 300 mL of yerba mate infusions were consumed over 2 h, the bioavailability of yerba mate polyphenols in plasma was 49.3% ± 11.9% [33], which is lower than the 54% observed for Rooibos polyphenols after consuming 500 mL of Rooibos tea over 3 h [19]. Furthermore, the apparent bioavailability of green coffee polyphenols (cinnamic moieties) ranged from 7.8% to 72.1% in plasma, with a mean of 33.1% ± 23.1% [34].

Rooibos tea's cytoprotective effects stem from activating the NRF2(nuclear factor erythroid 2-related factor 2)/KEAP1(Kelch-like ECH-associated protein 1) pathway, which upregulates antioxidant enzymes. Aspalathin, an essential compound, significantly enhances NRF2 nuclear translocation in INS1E β cells

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at a concentration of 60 μM ($p < 0.01$) [35]. Male Wistar rats given Rooibos extract for 4 weeks showed improved antioxidant defense by increasing γ-glutamyl cysteine synthetase production and reducing oxidative damage (lipid peroxidation). Rooibos mitigated lipopolysaccharide-induced liver damage, reducing aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alanine transaminase (ALT) levels ($p < 0.05$ and $p < 0.1$), decreasing MDA levels ($p < 0.05$), and improving the GSH:GSSG ratio ($p < 0.05$). It also suppressed inflammation by inhibiting tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) production ($p < 0.05$) [36]. Isoorientin, a Rooibos component, protected SH-SY5Y cells from oxidative damage caused by methylglyoxal by increasing γ-glutamate-cysteine ligase activity ($p < 0.05$). This protection depended on NRF2 activation and the AMP-activated protein kinase (AMPK)/phosphatidylinositol 3-kinase (PI3K)/protein kinase (Akt) pathway [37].

Rutin can influence glutamate metabolism by upregulating EAAC1. Treatment with rutin (0.5 μM) significantly increased EAAC1 mRNA levels ($p < 0.001$) and modulated glutamine synthetase expression ($p < 0.05$) [38]. Rooibos, rich in polyphenols like quercetin, exhibits antioxidant properties by regulating microRNAs. Combining polyphenols may enhance neuroprotection. For instance, quercetin and (−)-epigallocatechin-3-gallate (EGCG) synergistically suppressed hepatic insulin resistance, increasing miR-96-5p expression by 0.2-fold compared to quercetin alone and 0.3-fold compared to EGCG alone ($p < 0.05$) [39]. This suggests that Rooibos' diverse polyphenol content may offer neuroprotective benefits by preventing glutamate-induced cell death and modulating GSH synthesis [40, 41].

3 | Rooibos Modulates γ-Secretase

The APP undergoes sequential proteolytic processing. It is first cleaved by α-secretase (nonamyloidogenic pathway) or β-secretase (BACE1) (amyloidogenic pathway) within the luminal region [42, 43]. In the amyloidogenic pathway, BACE1 cleaves APP, producing the C-terminal segment (C99). γ-Secretase then processes C99, forming heterogeneous Aβ species. ε-Cleavage between amino acids 50 and 59 produces ζ- and γ-cleavages (Aβ-49, -43, -40, and -37 peptides), while cleavage between -49 and -48 results in Aβ-48, -45, -42, and -38 peptides. Aβ-40 and Aβ-42 are linked to AD, with Aβ-42 being more prone to aggregation and thus more pathogenic [43].

Inhibiting γ-secretase and BACE1 reduces all Aβ peptide levels but can cause neurotoxicity in vivo [44]. Therefore, drug development has shifted to small molecules that modulate γ-secretase activity. These modulators aim to lower Aβ-42 levels selectively and, to a lesser extent, Aβ-40, Aβ-38, and Aβ-37, without disrupting γ-secretase cleavage [43, 44].

Quercetin has the potential to influence γ-secretase activity. By targeting the subcellular location of γ-secretase, it may be possible to adjust its activity and specificity toward specific substrates. This approach could selectively lower the production of the aggregation-prone Aβ42, thereby reducing the levels of shorter Aβ37, Aβ38, and Aβ40 species without inhibiting the entire enzyme.

Quercetin upregulates α-secretase enzymes (a disintegrin and metalloproteinases [ADAM]-10 and ADAM 17) and downregulates amyloidogenic pathway genes (APP, BACE1, presenilin-1 [PSEN1], and anterior pharynx-defective 1 [APH-1]) in the hippocampus. In a study, rats with Alzheimer's-like symptoms treated with quercetin (25 and 50 mg/kg) showed improved cognition and reduced Aβ plaque formation. Compared to controls, quercetin-treated rats had significantly lower APP, BACE1, APH-1, and PSEN1 mRNA expression ($p < 0.05$) and higher ADAM10 and ADAM17 mRNA expression ($p < 0.05$) [45]. The higher dose had a more pronounced effect. Since APH-1 stabilizes PSEN1 and γ-secretase activity, these findings suggest Rooibos may inhibit Aβ production by modifying γ-secretase activity [45, 46] Figure 2.

4 | Clearance of Aβ: Rooibos as a Potential Intervention

In healthy individuals, Aβ peptides are cleared through receptor-mediated (nonenzymatic) and enzymatic processes [47, 48]. Glial cells, neurons, and astrocytes play a crucial role in Aβ clearance by uptake and exporting it into the peripheral circulation [47]. Apolipoprotein E (ApoE) receptors like low-density lipoprotein receptor (LDLR) and low-density lipoproteins receptor-related protein-1 (LRP1) regulate Aβ deposition in the brain [48].

ApoE, a key player in lipoprotein metabolism and transport, interacts with Aβ-peptides, influencing their metabolism, clearance, aggregation, and deposition [49, 50]. Interestingly, Aβ can cross the BBB from the periphery, and impaired Aβ clearance is a hallmark of AD pathophysiology [48]. Lambert et al. demonstrated an inverse correlation between ApoE expression and Aβ loads in early and late-onset sporadic AD [51].

Hepatocytes primarily produce ApoE4 in the liver, while astrocytes and glial cells produce it in the brain [50, 52]. Zhang et al. highlighted the potential pathogenicity of exosome-mediated ApoE4 translocation from the periphery to the brain, suggesting it is a promising therapeutic target. Exosomes, known for their ability to transport proteins and nucleic acids across the BBB, may contribute to this process [50]. In pericytes, ApoE4 activation of the cyclophilin A-matrix metalloproteinase-9 (CypA-MMP-9) pathway leads to the accumulation of proinflammatory cytokines, including TNF-α and interleukin-1β (IL-1β), BBB disruption, and subsequent impairment of synaptic and neuronal function [52, 53].

Although the specific impact of Rooibos on Aβ transport to the brain remains unclear, in vitro, 10 μg/mL quercetin significantly decreased MMP9 expression by 0.2-fold ($p < 0.05$), suggesting Aβ production inhibition [54]. In a separate study, a 28-day regimen of green Rooibos extract (1.23 Gallic acid equivalent mg/kg bw/day) significantly altered gene expression related to OS and antioxidant defense. Key findings include upregulation of Gpx2 (1.8-fold), downregulation of Gpx3 (1.2-fold), and increased expression of aminoadipate-semialdehyde synthase (Aass) (1.32-fold), isocitrate dehydrogenase 1 (Idh1) (1.3-fold), and NAD(P)H dehydrogenase, quinone 1 (Nqo1) (1.68-fold), while ApoE decreased 1.27-fold and neutrophil cytosolic factor 2 (Ncf2) decreased 4.78-fold [55, 56]. Rooibos' compound, aspalathin, offers significant cardioprotective benefits, particu-

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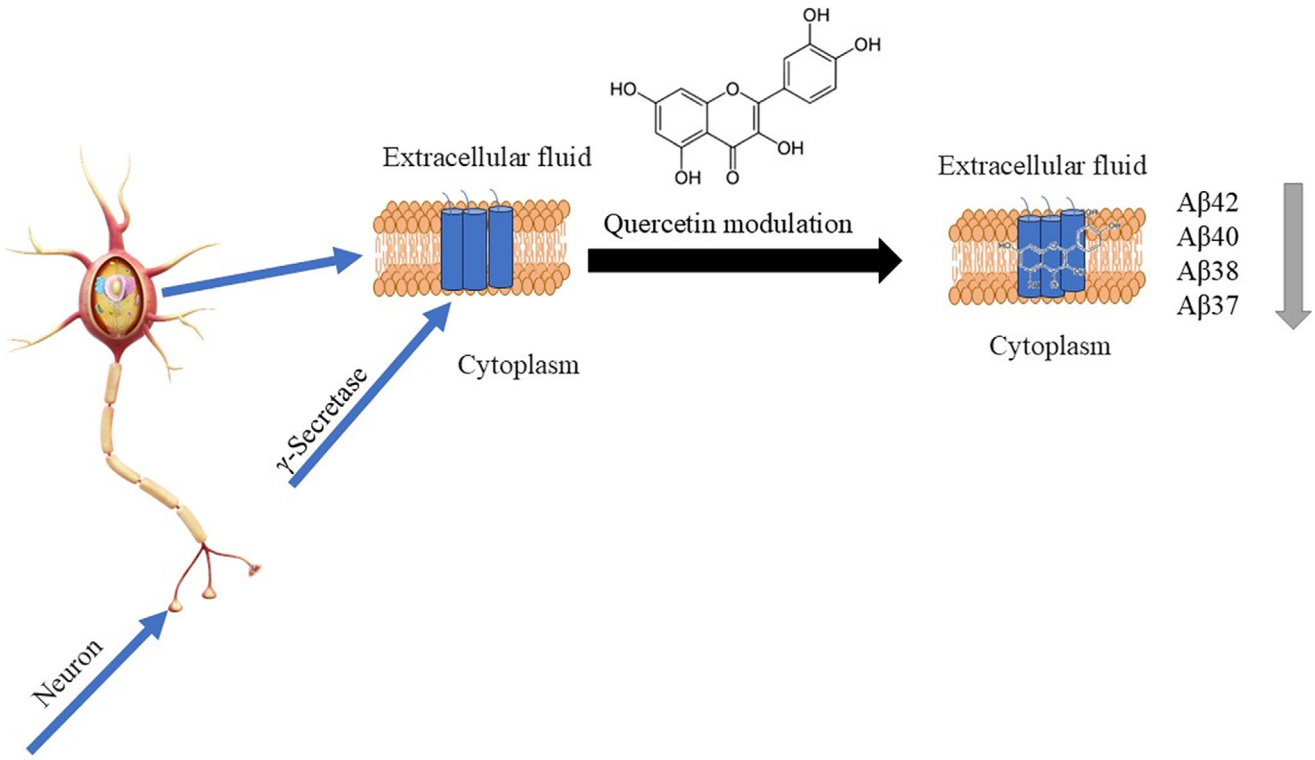


FIGURE 2 | Potential target: allosteric modulation of intact γ-secretase by quercetin.

larly against high blood sugar. It regulates cellular processes, reduces cell death, boosts survival genes (B cell lymphoma-2 [Bcl2], conserved helix-loop-helix ubiquitous kinase [Chuk]), and dampens inflammation (I16/janus kinase/signal transducer and activator of transcription [Jak/Stat] pathway).

Aspalathin also shields the heart from lipid overload by enhancing Adipoq expression and reducing lipid uptake and transport genes (*Cd36*, carnitine palmitoyl transferase 1 b [*Cpt1b*], solute carrier family, member 27,3 and 5 [*Slc27a3/5*], peroxisome proliferator-activated receptor-gamma [*PPARγ*], sterol regulatory element-binding protein 1 [*Srebf1*]), lowering cholesterol levels. High glucose triggers inflammation, upregulating cytokines (Il3 2.3-fold, Il6 2.7-fold, tumor necrosis factor superfamily [*Tnsf*] 13 4.7-fold, *Tnfsf*13b 2.1-fold, Selectin E [*Sele*] 13.8-fold, Cd44 2.3-fold) and promoting leukocyte infiltration. Aspalathin counteracts this by modulating inflammation-related genes. It also regulates lipid metabolism, influencing genes like apolipoprotein B [*Apob*] (7.7-fold), *ApoE* (4.4-fold), very LDL [*Vldlr*] (2.0-fold), apolipoprotein A-1 (*Apoa1*) (4.2-fold), ATP-binding cassette transporter 1 [*Abca1*] (2.0-fold), and adiponectin, C1Q and collagen domain containing [*Adipoq*] (−6.0-fold), reducing lipid accumulation [57]. A study by Zhang et al. [58] demonstrated that quercetin increased functional ApoE protein in the brain by 40% ($p < 0.05$) without affecting mRNA levels. This effect was comparable to bexarotene, which increased both ApoE protein (40%, $p < 0.05$) and mRNA levels (50%, $p < 0.01$). However, quercetin was more effective in reducing insoluble Aβ40 and Aβ42, with reductions of 2 ng/mg protein ($p < 0.001$) and 6 ng/mg protein ($p < 0.01$), respectively, compared to bexarotene's reductions of 1 ng/mg protein and 4 ng/mg protein ($p < 0.05$). Both treatments significantly reduced Aβ plaque burden and number ($p < 0.05$). Quercetin, a flavonoid in Rooibos tea, shows neuroprotective potential. In db/db mice, 70 mg/kg/day of quercetin significantly reduced NLR family pyrin domain containing 3 (NLRP3) inflammasome formation in the brain by 2.7-fold ($p < 0.01$) [59]. Animal doses of 25–100 mg/kg/day translate to human doses of 1–2 g/day [52].

Resveratrol, another polyphenol, also shows neuroprotective promise. It reduces retinal pyroptosis by inhibiting NLRP3. In animal studies, 25 mg/kg resveratrol significantly downregulated NLRP3 by 0.6-fold ($p < 0.01$) [60]. Human studies show that 2 g/day of resveratrol reduces CSF MMP9 levels by one-third and slows cognitive decline in Alzheimer's patients [61], with safe doses of up to 5 g/day [62]. Quercetin's ability to modulate inflammation, protect the BBB, and reduce Aβ pathology highlights its potential as a therapeutic agent for NDDs like AD.

5 | Alzheimer's Disease and Iron Overload: Rooibos as a Potential Intervention

Iron accumulation may contribute to AD through ferroptosis [63]. Ferroptosis is characterized by cumulative lipid peroxidation and depletion of antioxidants such as GSH ultimately causing oxidative cell death [64, 65]. Iron tends to easily donate its electrons, contributing to various natural biological processes in the brain [64]. Through the Fenton/Haber–Weiss reaction, Aβ binds ferric ions (Fe^{3+}), reducing them to ferrous ions (Fe^{2+}). Subsequently, Aβ binds oxygen and utilizes Fe^{2+} to convert it into H_2O_2. GSH prevents the oxidation of iron by providing a ligand for the cytosolic iron pool and a substrate for substrate in the synthesis of the Fe–S cluster proteins. Thus, iron chelation decreases ROS [64]. Therefore, iron chelators may be helpful treatments for easing AD symptoms [66].

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Crude unfermented Rooibos chelates iron and other metal ions [67]. Rooibos flavonoids (aspalathin, nothofagin, and quercetin) exhibit antioxidant activity. In cell-free systems, aspalathin and EGCG were the most potent radical scavengers (IC50 3.33 and 3.46 μM), followed by quercetin (3.60 μM) and nothofagin (4.04 μM). Quercetin (IC50 17.5 μM) and EGCG (IC50 22.3 μM) emerged as the most potent inhibitors of lipid peroxidation in biological systems. This suggests their potential as antioxidants within living organisms [68]. Long-term Rooibos consumption reduced age-related lipid peroxide accumulation in rat brains [69]. Quercetin delays neurodegeneration by chelating iron, maintaining homeostasis, and reducing oxidative damage [70, 71]. This suggests Rooibos may exhibit antiferroptotic activity in AD.

6 | The Role of Aβ Peptides in GABAergic Neurotransmission Inhibition: Rooibos as a Potential Intervention

Glutamatergic and gamma-aminobutyric acid (GABA)-ergic neurotransmissions are closely related to the deposition of Aβ peptides [72]. Accumulating Aβ peptide aggregates in the hippocampus interferes with GABAergic interneurons' function and promotes cognitive impairment [73]. Glutamate (the precursor of GABA) is the brain's most abundant free amino acid that functions as an excitatory neurotransmitter. It has also modulated neurogenesis, neuronal maturation, and neuronal apoptosis [74]. Specifically, GABA, GABA transporters, GABA receptors, GABAergic neurons, and neuroglia are involved in GABAergic neurotransmission. The astrocyte regulates the GABA metabolism [75]. Interneuron loss has been linked to a decline in GABAergic-mediated inhibition, which may contribute to hyperexcitability and epileptogenesis [76, 77]. Epileptogenesis is the process that leads to the development of seizures [78]. The discovery of medicines that enhance GABAergic neurotransmission has been recognized as a therapeutic target for treating AD [77].

The $GABA_A$ and $GABA_B$ receptor types are the primary mediators of GABAergic signaling. In the CNS, $GABA_A$ receptors are the most prominent inhibitory neurotransmitter receptors. They are ionotropic ligand-gated chloride channels with five subunits. $GABA_A$ receptors primarily deliver fast hyperpolarization of postsynaptic neurons [79, 80]. The overall number of allosteric binding sites has not yet been determined, even though numerous binding sites at the $GABA_A$ receptors have been identified. The radioligand binding method has been used to study the $GABA_A$ receptor binding sites most extensively in vitro. These sites include benzodiazepine (BZD), GABA/muscimol, and *tert*-butyl bicyclephosphorothionate/picrotoxin [75].

Rooibos tea has previously been shown to improve rats' cognitive function and activity in the hole-board test (measured as head-dipping and rearing) in the water maze by altering monoamine and amino acid levels in various brain regions, including the striatum, hippocampus, and prefrontal cortex [81, 82]. Similarly, in a study by López et al., the anxiolytic properties of Rooibos were demonstrated by its ability to reduce excitotoxicity induced by pentylenetetrazole (PTZ) in zebrafish larval models via regulating $GABA_A$ receptor activity [11]. By interacting with the BZD site (BZDs) of the $GABA_A$ receptor complex, the flavone vitexin (5,7,4-trihydroxy flavone-8-glucoside) demonstrates a powerful anticonvulsant effect in PTZ-induced seizures in rats [83]. The composition of the receptor subunits determines the effects of BZDs on the GABAA receptor complex. Notably, the BZD binding site is a distinct pocket formed by the intersection of α and γ subunits [75]. Quercetin acts as a negative allosteric GABAA receptor modulator in cultured cortical neurons with antipsychotic properties. Thus, the antipsychotic activity of quercetin may also justify its potential therapeutic development in AD [84]. Furthermore, Rooibos's natural flavonoid compound, luteolin, has demonstrated adverse modulatory effects on recombinant and endogenous $GABA_A$ receptors. [85]. Rutin, a flavonoid found in Rooibos, has been shown to have anxiolytic-like effects on GABAergic neurotransmission without interacting with the $GABA_A$ receptor complex's BZD site [86].

The research on the effects of *I. paraguariensis* on acetylcholinesterase (AChE) activity is inconclusive. Although some studies, such as Santos et al. [8], suggest that chronic treatment with the plant can increase AChE activity in the hippocampus, others, such as Vanin dos Santos Lima et al. [87], have not observed a direct effect. Further research is needed to clarify the relationship between *I. paraguariensis* and AChE activity.

7 | Rooibos Prevents Neuroinflammation Induced by Oxidative Stress

AD involves a complex interplay of neuroinflammatory processes, OS, and altered neurotransmitter levels. OS triggers microglial activation, leading to the release of proinflammatory cytokines and neurotoxic substances. This, in turn, contributes to the formation of neurofibrillary tangles and neuronal death [72, 88]. GABA, a neurotransmitter, stimulates microglia via nuclear factor kappa B (NF-κB) signaling, the NLRP3 inflammasome, and nucleotide-binding oligomerization domain (NOD)-like receptors, further exacerbating inflammation [72]. Amyloid-β peptide accumulation prolongs microglial activation, leading to tau protein phosphorylation [72, 88]. GSK-3β, a key kinase, regulates Aβ synthesis by preventing APP cleavage at the γ-secretase step and may suppress α-secretase activity [89]. Inhibiting GSK-3β reduces BACE1-mediated APP cleavage [90]. When GSK-3β is activated and protein phosphatase 2A (PP2A), a complex enzyme that controls the removal of phosphate groups from many serine/threonine sites, is inhibited, it results in an imbalance in tau phosphorylation [91]. Therefore, understanding the interplay between these factors is crucial for developing effective therapeutic strategies for AD.

Rooibos components, such as aspalathin and nothofagin, regulate proinflammatory genes via NF-κB and the mitogen-activated protein kinase (MAPK) pathways (see the review by [17]). Luteolin, another flavonoid, reduces GSK-3β activation and inflammatory cytokines (TNF-α, IL-1β) in traumatic brain injury (TBI) models [92]. It crosses the BBB and reaches therapeutic levels (~800 ng/mL) in the brain after 4 weeks of 5–10 mg/kg/day gavage. Quercetin inhibits tau hyperphosphorylation via MAPKs and PI3K/Akt/GSK-3β pathways [93]. Quercetin pretreatment (5 or 10 μmol/L) suppressed OA-induced tau hyperphosphorylation

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TABLE 1 | Summary of in vitro studies on the neuroprotective properties of Rooibos and bioactive plant extracts.

Extract	Experimental/period of treatment and dosage	Outcome relating to AD markers	Ref
Unfermented Rooibos ethanolic	Rat neuroblastoma cells (Neuro-2a cells) were cotreated for 90 min with different concentrations of extract (12.5–25–50–100 μg mL^{-1}) and 250 or 125 μM H_2O_2.	Rooibos extract (100, 50, 25 μg/mL) pretreatment Neuro-2a cells inhibited intracellular ROS formation before exposure to 250 μM and 125 μM H_2O_2 for 90 min. Additionally, green Rooibos extract demonstrated dose-dependent effects as an inhibitor of monoamine oxidase A.	[11]
Unfermented Rooibos acetone	Human neuroblastoma SH-SY5Y cells were pre-treated for two h with 12.5, 25, and 50 μg/mL Rooibos extract and 2.5, 5, and 10 μg/mL aspalathin and linearthin. Then, 2000 μM 1-methyl-4-phenylpyridinium was added and the cells were incubated for 24 h.	Increased cell viability, decreased ROS generation, raised ATP levels, and inhibited apoptosis were all observed in Rooibos extract and its bioactive components, aspalathin, and linearthin.	[12]
Quercetin	Primary microglia from P1–P2 mice and BV2 cells were pretreated with Qu (30 μM, 1 h) and/or 3-MA (5 mM, 1 h) before LPS (100 ng/mL, 24 h) and ATP (30 min) treatment.	Through mitophagy promotion, Quercetin prevents neuronal injury by inhibiting mtROS-mediated NLRP3 inflammasome activation in microglia.	[94]
Quercetin	Mouse hippocampal neuronal HT22 cells were pretreated with quercetin (1, 3, or 5 μM) for 1 h before treatment with 5 mM glutamate for 24 h.	Quercetin protects against glutamate toxicity by modulating PP2A subunit B.	[95]
Quercetin dissolved in DMSO to obtain a 100 mM stock solution.	Okadaic acid (OA) (20–160 nmol/L) induced neurotoxicity in HT22 cells. Quercetin (5 or 10 μmol/L) alleviated this neurotoxicity, and cotreatment with PI3K or GSK-3β inhibitors provided further insights into the underlying mechanisms.	Quercetin inhibited OA-induced tau hyperphosphorylation, oxidative stress, apoptosis (via Bax and cleaved caspase 3), and NF-κB activation while activating the PI3K/Akt/GSK-3β and MAPK pathways.	[93]
Luteolin	HEK293T cells.	Luteolin inhibited GABA-mediated currents and slowed GABA receptor activation kinetics in HEK cells.	[85]
Quercetin	Immortalized ApoE3, ApoE4, and primary astrocytes from newborn C57BL/6J mice (P1–P2) were treated with 20 mM quercetin or 10 mM bexarotene for 18 h in serum-free media at 37 °C, followed by an 18-h incubation with 125 nM soluble Aβ42.	Quercetin significantly increased ApoE levels in immortalized astrocytes by inhibiting ApoE degradation.	[58]

Abbreviations: AD, Alzheimer's disease; GABA, gamma-aminobutyric acid; GSK-3β, glycogen synthase kinase 3 beta; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species.

at pS396 ($p < 0.05$ at 5 μmol/L, $p < 0.01$ at 10 μmol/L), pS199, pT205, and pT231, and increased Akt phosphorylation at Ser473 ($p < 0.01$), leading to GSK-3β inactivation through increased Ser9 phosphorylation ($p < 0.01$) and decreased Tyr216 phosphorylation ($p < 0.05$ at 5 μmol/L, $p < 0.01$ at 10 μmol/L) [94]. Quercetin also inhibits mitophagy by interfering with NLRP3 inflammasome activity and controlling PP2A subunit B downregulation, preventing middle cerebral occlusion (MCAO) injury in an animal model and glutamate toxicity in HT22 cells [94, 95].

8 | Conclusion and Future Directions

A thorough understanding of the mechanisms through which Rooibos can target OS and its associated pathways in neurodegeneration will be instrumental in the development of effective interventions for individuals affected by these debilitating disorders. As each mechanism appears independent, offering potential therapeutic targets for future research [96]. Rooibos' potential to protect against NDDs in severely affected populations requires

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TABLE 2 | Summary of in vivo studies on the neuroprotective properties of Rooibos and bioactive plant extracts.

Extract	Experimental/period of treatment and dosage	Outcome relating to AD markers	Ref
Fermented Rooibos aqueous	Adult Sprague-Dawley rats (weighing 140–160 g) were pretreated with a Rooibos infusion (20 mL/100 g body weight) for 30 min before being chronically immobilized for 1 h each day for 4 weeks.	In whole brain homogenates, there was a decrease in protein and lipid peroxidation, a reversal of the increase in 5-HIAA, and a decrease in GSH and GSH/GSSG ratios, CAT, and SOD.	[23]
Fermented Rooibos aqueous	Adult Wistar rats weighing 250 g were given an aqueous extract ad libitum for 7 weeks (2% infusion) before the onset of ischemia injury as a model of ischemic brain injury.	Reduced brain edema enhanced neuronal survival in the hippocampal cornus ammonis 1 region; whole-brain homogenates significantly reduced lipid peroxidation levels, increased total antioxidant capacity, and improved neurobehavioral outcomes.	[29]
Unfermented Rooibos ethanolic	Zebrafish larval behavior model: the pentylenetetrazol (PTZ). Zebrafish larvae were subjected to Rooibos (10–25 μg mL^{-1}) for 1 or 24 h.	Green Rooibos at lower doses with a 24-h exposure period restores GABA receptor signaling.	[11]
Fermented Rooibos aqueous	Selected adult Sprague-Dawley rats were given infusions (made in 30 min) containing 1, 2, and 4% Rooibos as their only beverage for 12 weeks.	Neurotransmitter alterations in the striatum of the brain: elevated dopamine and 3-methoxytyramine; enhanced spatial memory in the Morris water maze	[81]
Fermented Rooibos aqueous	Selected adult Sprague-Dawley rats were given infusions (made in 30 min) containing 1%, 2%, and 4% Rooibos as their only beverage for 12 weeks.	Brain neurotransmitter alterations include increased taurine, decreased glutamate and aspartate in the striatum, increased taurine in the hippocampus, and decreased GABA in the prefrontal cortex. These alterations result in improved locomotion and exploration and reduced anxiety in the hole-board test.	[82]
Aqueous yerba mate extract and yerba mate microparticles	Adult male Wistar rats (180–250 g) were treated with yerba mate extract (YE), yerba mate microparticles (YM), or empty microparticles (EM) for 30 days. The control group received water, the YE and YM groups received 28.57 mg/kg of total phenolic compounds, and the EM group received empty microparticles	Microencapsulated yerba mate improved antioxidant activity, especially in the brain, by targeting antioxidant delivery to specific tissues and reducing lipid peroxidation.	[32]
Quercetin in saline	Male Wistar rats (8 weeks, 140 ± 10 g) were treated for 28 days with saline, quercetin (25 or 50 mg/kg), aluminum chloride ($AlCl_3$), or AlCl3 + Q (25 or 50 mg/kg) via oral gavage.	Quercetin treatment ameliorated cognitive deficits, enhanced cholinergic and dopaminergic function, and reduced Aβ plaque burden in AlCl3-induced AD rats by modulating the expression of genes involved in Aβ metabolism (APP, BACE1, APH1, PSEN1, ADAM10, and ADAM17).	[45]
Bexarotene and quercetin in corn oil	Male and female 5XFAD mice (C57BL/6J background) were orally gavaged daily for 10 days at 2 months old with either 100 mg/kg/day bexarotene, 500 mg/kg/day quercetin, or vehicle (corn oil).	Oral quercetin increased brain ApoE and reduced cortical Aβ levels.	[58]
Quercetin in saline	db/db and wild-type C57BL/6J-db/m mice were divided into four groups: control groups (db/m and db/db) and db/db groups treated with 35 or 70 mg/kg/day quercetin orally for 12 weeks.	Quercetin upregulated SIRT1, downregulated NLRP3, ASC, cleaved Caspase-1, IL-1β, and IL-18.	[59]

(Continues)

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TABLE 2 | (Continued)

Extract	Experimental/period of treatment and dosage	Outcome relating to AD markers	Ref
Aqueous (−) catechin (*Camellia sinensis* from green tea)	Mongolian gerbils (65–90 g) were divided into four groups: sham, ischemia-reperfusion, and ischemia-reperfusion treated with 0.1 or 1.0 mg/mL (−) catechin orally for 3 weeks.	Oral (−) catechin crossed the blood-brain barrier and prevented delayed neuronal death in the hippocampus after ischemia-reperfusion via its antioxidant properties.	[69]
Fermented Rooibos aqueous	Adult male Sprague-Dawley rats were divided into four groups: control, 1:100 *A. linearis*, 2:100 *A. linearis*, and 4:100 *A. linearis* to assess the 3-month effects of fermented Rooibos tea on hypothalamic neurotransmitters and growth factors.	The effects may be linked to changes in serotonergic, glutaminergic, and BDNF/TrkB pathways, with decreased hypothalamic 5-HT and TrkB potentially modulating the HPA axis and reducing corticosterone levels.	[7]
Luteolin	Hippocampal slices prepared from 12–21-day-old ICR mice.	Luteolin inhibited GABA-mediated currents and slowed GABA receptor activation kinetics in brain slices, with effects varying by receptor subunit composition.	[85]
Hydroethanolic (HE) and aqueous (AE) extracts from leaves of *I. paraguariensis*	Male Swiss mice (3–4 months, 35–50 g) were treated with diazepam (2.5 mg/kg, p.o.) and pentylenetetrazol (20 mg/kg, i.p.) to induce anxiolytic and anticonvulsant effects. Hydroethanolic (HE) and aqueous (AE) extracts from leaves of *I. paraguariensis* were administered orally at 100, 300, or 600 mg/kg, either acutely (1 h before tests) or chronically (21 days, once daily).	Yerba mate's anxiolytic, stimulant, and neuroprotective effects may be modulated by the cholinergic system and caffeine.	[8]
Luteolin in PBS	Tg2576 mice were treated daily with 20 mg/kg ip luteolin or PBS for 15 days before TBI induction.	Luteolin treatment significantly reduced Aβ, GSK-3 activation, phospho-tau, and pro-inflammatory cytokines (TNF-α, IL-1β).	[92]
Quercetin	Hippocampal and mesencephalic tissues were collected from E14/15 C57BL/6 mice. To evaluate quercetin's neuroprotective effects in LPS-induced depression and PD models, mice were divided into five groups: saline, LPS, LPS + Qu (30 or 60 mg/kg), and LPS + Qu (60 mg/kg) + IL-1β. Qu (30 or 60 mg/kg) was administered 3 days before and during/after LPS injections, and IL-1β (15 μg/kg) was administered for 2 days after the last Qu injection. All treatments were given between 2:30 and 3:30 p.m.	Through mitophagy promotion, Quercetin prevents neuronal injury by inhibiting mtROS-mediated NLRP3 inflammasome activation in microglia.	[94]
Quercetin	Male Sprague-Dawley rats (220–230 g) were divided into four groups: vehicle + MCAO, quercetin (10 mg/kg) + MCAO, vehicle + sham, and quercetin + sham. Quercetin or vehicle was injected intraperitoneally 30 min before MCAO, which induced neurological deficits and increased infarct volume 24 h later.	Quercetin protects against MCAO injury by modulating PP2A subunit B.	[95].

Abbreviations: AD, Alzheimer's disease; CAT, catalase; GABA, gamma-aminobutyric acid; GSH, glutathione; GSK-3, glycogen synthase kinase 3; GSSG, GSH and oxidised; IL-1β, interleukin-1β; MCAO, middle cerebral occlusion; NLRP3, NLR family pyrin domain containing 3; PP2A, protein phosphatase 2A; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha.

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further investigation, focusing on the pathways highlighted in this review (Tables 1 and 2).

Preliminary cytotoxicity studies often use hepatocytes due to their role in drug metabolism [97]. Although Rooibos exhibits hepatoprotective potential, there remains a lack of in vitro studies on brain cells and animal models of neurodegeneration. Furthermore, the ability of Rooibos components to cross the BBB remains unclear [17].

Experimental studies on Rooibos and its extracts will advance our understanding of their neuroprotective potential. However, evaluating efficacy and potency requires considering the dose–response relationship. Rooibos' potential to provide resilience for AD patients necessitates clinical investigation. As a cost-effective option, Rooibos can benefit many developing countries. Future research should focus on increasing Rooibos' bioavailability in the brain to maximize its benefits, considering its dose-dependent effects observed in vitro and in vivo.

Acknowledgments

This research is supported by the Cape Peninsula University of Technology and the South African Rooibos Council.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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