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# From gut to brain: formulation and transporter-guided approaches to maximise rutin central nervous system delivery

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## ABSTRACT





Neurological disorders, including Alzheimer's and Parkinson's disease, are characterised by high morbidity and disability, representing a major global health challenge. A central obstacle in their treatment is the *blood-brain barrier*, a highly selective interface that limits drug delivery to the central nervous system. Rutin, a naturally occurring flavonoid, exhibits potent antioxidant, anti-inflammatory, and neuroprotective activities, yet its clinical utility remains constrained by poor solubility, low oral bioavailability, and restricted *blood-brain barrier* permeability. Recent advances in drug delivery and formulation science offer promising solutions. Nanoparticle encapsulation, peptide conjugation, intranasal delivery, and co-administration with absorption enhancers have been shown to improve rutin's solubility, metabolic stability, and central nervous system penetration in preclinical models. Mechanistic studies further reveal that rutin can modulate efflux transporters, regulate tight-junction proteins, and influence microglial activity and cellular metabolism, collectively contributing to enhanced neuroprotection. Experimental evidence highlights its potential to mitigate key neurodegenerative processes, particularly in Alzheimer's disease. This review synthesises current knowledge on rutin's pharmacological effects, limitations in bioavailability, and innovative strategies to improve *blood-brain barrier* penetration. By integrating mechanistic insights with advances in delivery technologies, this review underscores rutin's translational potential. Priority next steps include optimising delivery systems, establishing long-term safety, and conducting well-designed clinical trials to define efficacy and dosing.

## KEYWORDS

Rutin; flavonoids; neurological disorders; neurodegenerative diseases; bioavailability; nanoparticle delivery; neuroprotection; drug delivery strategies

## 1. Introduction

The burden of neurological disorders is rising in parallel with global population ageing, posing an escalating challenge to public health. Neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and epilepsy, rank among the leading global causes of disability and mortality [1–3]. Neurodegenerative diseases such as AD and PD, along with cerebrovascular conditions including ischaemic stroke and cerebral infarction, significantly compromise patients' quality of life and generate a substantial socio-economic burden. In China, for instance, the prevalence of PD among individuals aged over 65 years is approximately 1.7% [4]), and the overall incidence of AD is 3.48% in the population aged above 55 years and increases to 5.98% in those aged 75 years and above [5], and other neurodegenerative disorders continue to increase. Globally, an estimated 57.4 million people were living with dementia in 2019, with cases projected to rise to 152.8 million by 2050 driven largely by population growth and ageing [6]. PD affected

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about 11.77 million people worldwide in 2021, with higher age-standardised prevalence in men; modelling projects the number living with PD will climb to ~25.2 million by 2050 [7,8]. More broadly, neurological disorders are now the leading global cause of ill-health and disability, underscoring the accelerating burden of neurodegeneration [9]. These conditions commonly manifest through cognitive impairment, motor dysfunction, and emotional disturbances, underpinned by complex pathological mechanisms involving neuronal degeneration, neuroinflammation, and oxidative stress. Although a range of pharmacological and supportive therapies are currently available, their effectiveness is frequently constrained by the blood–brain barrier (BBB), which restricts efficient drug delivery to the central nervous system (CNS). Thus, developing strategies that can bypass or overcome BBB-associated challenges is critical for improving the treatment of neurological diseases.

Rutin (quercetin-3-O-rutinoside), a naturally occurring polyphenolic flavonoid widely found in citrus fruits, buckwheat, and several medicinal plants, has gained increasing attention for its diverse pharmacological properties, including antioxidant, anti-inflammatory, vasoprotective, and neuroprotective activities [10–12]. Nevertheless, its therapeutic application in clinical settings is restricted by poor oral bioavailability and limited permeability across the BBB. This review critically evaluates current evidence on rutin, with a focus on its pharmacokinetics, bioavailability, BBB penetration, neuroprotective mechanisms, and formulation strategies, while highlighting its translational potential in neurological disease management.

## 2. Rutin, pharmacological properties, and significance in research

### 2.1. Chemical structure and natural sources

Rutin is a naturally occurring flavonoid glycoside, also called vitamin P, chemically defined as 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[ $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranosyloxy]-4H-chromen-4-one. It consists of the flavonol aglycone quercetin linked to the disaccharide rutinose via a glycosidic bond. In its pure form, rutin appears as an odourless yellow crystalline powder that is practically insoluble in water but partially soluble in alcohol [13]. As humans cannot synthesise rutin endogenously, it must be obtained through dietary intake of plant-based sources. Rutin is widely distributed in the plant kingdom. It is particularly abundant in citrus fruits, tea leaves, buckwheat, and medicinal plants such as *Sophora japonica* [14,15]. It also occurs in apples, mulberries, cranberries, ash tree fruits, and the flowers and fruits of the pagoda tree (*Sophora japonica*) [16,17]. Since the mid-twentieth century, buckwheat (*Fagopyrum* spp.) has been cultivated as a commercial source of rutin for herbal medicine production, and today it is recognised as a major dietary source worldwide. Rutin is also referred to by several synonyms, including rutoside, quercetin-3-O-rutinoside, vitamin P, and sophorin. These names reflect both its chemical composition and its botanical origins, particularly from rue plants (*Ruta graveolens*) (Table 1).

**Table 1.** Food sources rich in rutin.

Food Item	Rutin Content (mg/100 g)	References
Roasted Tartary buckwheat	389 (bran) 68 (grain) 36 (flour)	Noda et al. [125]
Thyme	87.5	Babotă et al. [126]
Black olives (raw)	4.6	Rocha et al. [127]
Green tea (Matcha, fresh)	62.3	Sivanesan et al. [128]
Amaranth	800 (seed) 2450 (dry leaves)	Kalinova et al. [129]
Asparagus (raw)	99–177	Di Matteo et al. [130]
<i>S. nigra</i> flowers	939	Ibragic et al. [131]
Golden berry leaves	499.6	Ivanova et al. [132]
Lettuce (leaves, fresh)	~75.1	Tobar-Delgado et al. [133]
Broccoli (stored)	10.2	Tobar-Delgado et al. [133]
Cauliflower	55.1	Rahman et al. [134]
Parsley (dried leaves)	19–630	Waheeba et al. [135]
Citrus	3200–4900 (Peel) 1100 (leaves) 700 (lime)	Gómez-Mejía E et al. [136]

**Table 2.** Pharmacological properties and therapeutic potential of rutin.

Property	Description / Mechanism	Therapeutic relevance	References
Anti-inflammatory	Inhibits pro-inflammatory cytokines and signalling pathways	Reduces systemic and neuroinflammation	Saha et al. [18]; Gabriele et al. [19]; Gur et al. [20]
Antioxidant	Scavenges free radicals and enhances endogenous antioxidant enzymes	Protects against oxidative stress in tissues and neurons	Singh et al. [16]
Vasoprotective & Anti-hypertensive	Improves endothelial function and regulates vascular tone	Benefits cardiovascular and cerebrovascular health	Goyal et al. [15]; Gur et al. [20]
Anti-apoptotic & Anti-autophagic	Modulates apoptotic and autophagy-related pathways	Prevents neuronal cell death and degeneration	Singh et al. [16]; Chen et al. [12]
Neuroprotective	Crosses the blood–brain barrier; modulates signalling and metabolism	Therapeutic potential in Alzheimer's, Parkinson's, and cerebrovascular disorders	Pan et al. [23]; Sharma et al. [24]; Mao et al. [22]; Chen et al. [12]
BBB permeability modulation	Influences endothelial signalling and transport	May enhance delivery of co-administered drugs into the brain	Naeem et al. [25]
Drug delivery potential	Microencapsulation, nanodelivery, emulsions, enzymatic modification improve bioavailability	Expands clinical utility of rutin in CNS disorders	Mel et al. [26]; Zhao et al. [27]; Pandian et al. [28]
Evidence from in vitro BBB models	ECV304 and RBE4 endothelial cell lines show limited but measurable transport	Supports translational research on CNS-targeted flavonoid delivery	Chunmei and Shuai [30]; Wu et al. [29]

## 2.2. Pharmacological properties and therapeutic significance

Rutin is recognised for its broad pharmacological profile, encompassing anti-inflammatory, antioxidant, vasoprotective, anti-hypertensive, anti-apoptotic, and anti-autophagic effects [10,12,15,16,18–20]. Of particular interest is its neuroprotective potential, with increasing evidence supporting its role in mitigating the pathophysiology of neurodegenerative diseases. Studies have demonstrated that rutin and its metabolites can cross the BBB and exert protective effects within the CNS, thereby offering therapeutic opportunities for AD, PD, and cerebrovascular disorders [12,21–24]. Mechanistically, rutin can modulate efflux transporters (e.g. P-gp/BCRP), support barrier integrity by influencing tight-junction proteins (e.g. claudin-5/and occludin), and temper microglial activation, thereby aligning permeability control with neuroinflammatory restraint [25].

Importantly, rutin has been reported to influence BBB permeability by modulating signalling pathways and cellular metabolism, which may enhance drug transport into the brain [25]. This property highlights its unique value for the development of novel drug delivery systems targeting the CNS. However, despite these promising features, the clinical application of rutin has been limited by its poor water solubility, low oral bioavailability, and rapid metabolism.

To address these challenges, various technological strategies have been developed, including microencapsulation, nanodelivery systems, microemulsions, and enzymatic modification. These approaches aim to improve intestinal absorption, metabolic stability, and overall bioavailability of rutin and related bioactive compounds [26–28]. In vitro BBB models, such as ECV304 and RBE4 endothelial cell lines, have further confirmed that flavonoids, including rutin, can traverse endothelial cell layers, albeit with limited efficiency [29,30]. Collectively, these findings underline both the promise and the limitations of rutin in clinical applications, reinforcing the need for continued investigation into optimising its pharmacological potential in neurological disease management (Table 2).

## 3. Pharmacokinetics and bioavailability of rutin

### 3.1. Absorption and metabolism

Rutin is poorly absorbed after oral dosing because its hydrophilicity and relatively high molecular weight hinder passage across the intestinal epithelium [31]. Following ingestion, a substantial fraction reaches the colon, where intestinal enzymes and gut microbiota deglycosylate the rutinose to yield quercetin aglycone, which is more readily absorbed [32–35]. Once absorbed, quercetin is rapidly subjected to phase-II conjugation in enterocytes and liver – predominantly O-glucuronidation (UGTs), O-sulfation (SULTs), and O-methylation (COMT) – so that the circulating forms are mainly quercetin conjugates (e.g. quercetin-3-O-glucuronide, quercetin-3'-O-sulfate, isorhamnetin conjugates) rather than free quercetin or rutin [36–39]. Microbial taxa implicated include *Bifidobacterium* spp. and *Lactobacillus* spp., which express

$\alpha$ -L-rhamnosidase/ $\beta$ -glucosidase activity, and the flavonoid-degrading anaerobe *Eubacterium ramulus*, which carries out ring-fission of quercetin-type aglycones [34,35]. Accordingly, inter-individual differences in the abundance and enzymatic capacity of these microbes drive variability in the extent and rate of rutin  $\rightarrow$  quercetin conversion and downstream exposure to conjugated metabolites [40].

Disposition is further shaped by transporters, with uptake via OATP1A2/2B1 and efflux by BCRP, MRPs, and P-gp; notably, BCRP limits net intestinal uptake by apical efflux of quercetin glucuronides *in vivo* [41,42]. In practical terms, intact rutin contributes little to transporter-mediated flux, whereas circulating quercetin conjugates are the principal substrates – taken up mainly via OATP1A2/2B1 and effluxed at the luminal membrane by BCRP/MRPs, with P-gp acting chiefly on quercetin aglycone (and some conjugates). Consistent with this, uptake via OATP1A2/2B1 applies predominantly to quercetin conjugates rather than intact rutin (owing to rutin's high polarity), while BCRP/MRPs preferentially efflux quercetin glucuronides/sulfates and P-gp engages quercetin aglycone and some conjugates at the luminal membrane [41,42]. Accordingly, intact rutin is a weak transporter substrate and contributes minimally to trans-epithelial or trans-endothelial flux compared with quercetin conjugates [41,43,44].

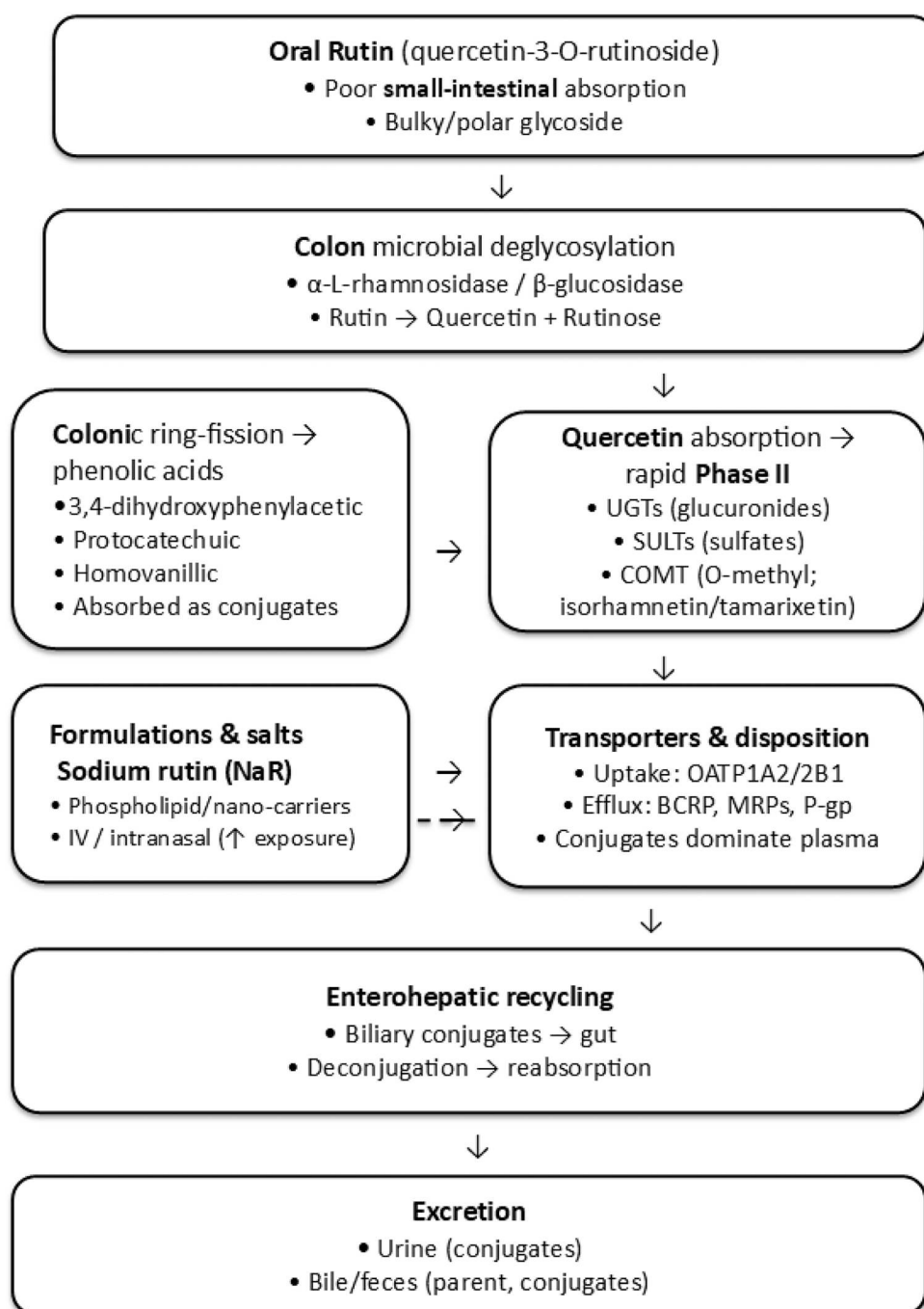
Additional colonic ring-fission generates smaller phenolic acids that are absorbed and conjugated, while enterohepatic recycling prolongs low-level exposure [37,38]. Clinically, this leads to low parent-level plasma concentrations of rutin and a short half-life, although salts/formulations (e.g. sodium rutin (NaR), nano-systems) can raise systemic levels; *in vivo* pharmacodynamic effects often reflect quercetin conjugates and related metabolites rather than intact rutin [35,45]. In summary, the circulating and brain-accessible species are predominantly quercetin conjugates, and BBB/intestinal transporter interactions largely reflect the handling of these conjugates rather than parent rutin [41–44]. In human time – concentration profiles, enterohepatic recycling is evidenced by reproducible 'secondary peaks' over ~6–12 h and a multi-exponential decline, indicating biliary excretion of conjugated quercetin metabolites followed by intestinal deconjugation and reabsorption; this recycling sustains low-level plasma concentrations and extends the terminal disposition phase [37,38]. Consistent findings in controlled kinetic studies (with high urinary recovery of conjugates and prolonged low-concentration tails) further support recycling as a key driver of exposure maintenance beyond the absorption window [46,47] (Figure 1).

### 3.2. Bioavailability challenges

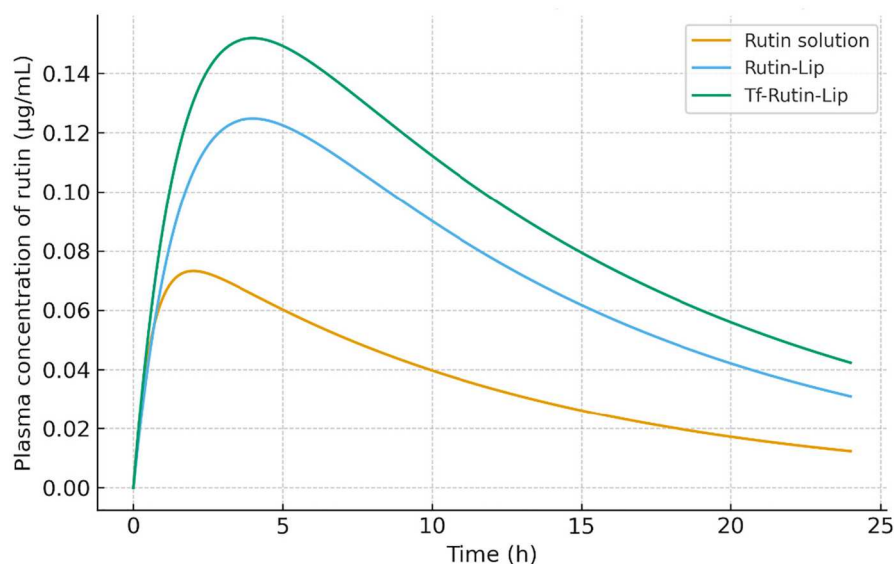
Several pharmacokinetic factors restrict the bioavailability of rutin. Inter-individual variability in gut microbiota composition strongly affects hydrolysis efficiency and quercetin release, leading to inconsistent systemic exposure [40]. In humans, only approximately 20% of an orally ingested 500 mg dose of rutin is absorbed and subsequently excreted in urine [48]. Animal studies similarly report poor oral absorption and rapid clearance, with bioavailability values as low as 0.13% in rats following administration of rutin-rich extracts [49,50]. Compared with quercetin glucosides, rutin is absorbed more slowly and inefficiently, partly due to the rhamnose moiety that resists hydrolysis in the small intestine [51]. As a result, much of the absorption occurs later in the large intestine, where microbial rhamnosidases cleave the disaccharide, releasing quercetin for absorption [52]. This delayed absorption contributes to a time to peak plasma concentration of approximately nine hours [53]. Plasma profiles showing secondary peaks and a sustained low-concentration tail reflect this recycling and its contribution to an extended terminal half-life [37,38]. Nevertheless, significant interspecies and inter-individual differences persist, highlighting the complexity of rutin pharmacokinetics. Quantitatively, enterohepatic recirculation contributes to an 'apparent' half-life that is longer than would be predicted from first-pass elimination alone, because reabsorption of biliary conjugates (after intestinal deconjugation) prolongs the terminal phase; studies tracking plasma/urine conjugates and observing secondary peaks over 0–24 h are consistent with this mechanism and its effect on  $t_{1/2}$  [37,38] (Figure 2).

### 3.3. Factors influencing bioavailability

The bioavailability of rutin is influenced by multiple physiological and dietary factors. Rutin is poorly soluble in water, resulting in a low concentration gradient between the intestinal lumen and blood vessels, thereby limiting passive diffusion. Food matrices also play a significant role; co-consumed macronutrients and micronutrients can alter rutin metabolism and absorption [54,55]. The intestinal mucus layer



**Figure 1.** Metabolism and disposition of rutin (and sodium rutin). After oral dosing, rutin (quercetin-3-O-rutinoside) is poorly absorbed in the small intestine. In the colon, microbial  $\alpha$ -L-rhamnosidase/ $\beta$ -glucosidase release quercetin, which is absorbed and rapidly conjugated (UGTs  $\rightarrow$  glucuronides; SULTs  $\rightarrow$  sulfates; COMT  $\rightarrow$  O-methylated forms). Circulating species are therefore mainly quercetin conjugates. Disposition is transporter-mediated (uptake: OATP1A2/2B1; efflux: BCRP, MRPs, P-gp), with enterohepatic recycling prolonging exposure. Excretion is chiefly urinary (conjugates) and biliary/faecal (parent and conjugates). Side pathways: (i) microbial ring-fission to phenolic acids (e.g. 3,4-DHPA, protocatechuic, homovanillic), which are re-conjugated and cleared; (ii) formulation/route (e.g. sodium rutin, phospholipid/nano-carriers, parenteral/intranasal) increases exposure but follows the same downstream handling. Those abbreviations are, UGTs, UDP-glucuronosyltransferases; SULTs, sulfotransferases; COMT, catechol-O-methyltransferase; OATP1A2/2B1, organic anion transporting polypeptides 1A2 and 2B1; BCRP, breast cancer resistance protein (ABCG2); MRPs, multidrug resistance-associated proteins (ABCC family); P-gp, P-glycoprotein (ABCB1); 3,4-DHPA, 3,4-dihydroxyphenylacetic acid.



**Figure 2.** Rutin pharmacokinetics in rats after an oral  $100 \text{ mg}\cdot\text{kg}^{-1}$  dose: solution, liposome and transferrin-liposome (model-based reconstruction). Plasma concentration – time profiles reconstructed from reported summary PK (AUC,  $T^{\text{max}}$ ,  $t_{1/2}$ ) in Wu et al., [29] using a one-compartment oral (Bateman) model. Liposomal delivery increases exposure versus solution, with higher  $C^{\text{max}}$  and larger AUC, and the transferrin-modified liposome shows the greatest and most sustained levels (delayed  $T^{\text{max}}$  consistent with slower absorption). Curves illustrate relative performance of formulations rather than raw means; parent rutin concentrations remain low compared with circulating conjugates. The abbreviations are: AUC, area under the curve;  $T^{\text{max}}$ , time to peak concentration;  $t_{1/2}$ , elimination half-life;  $C^{\text{max}}$ , maximum concentration.

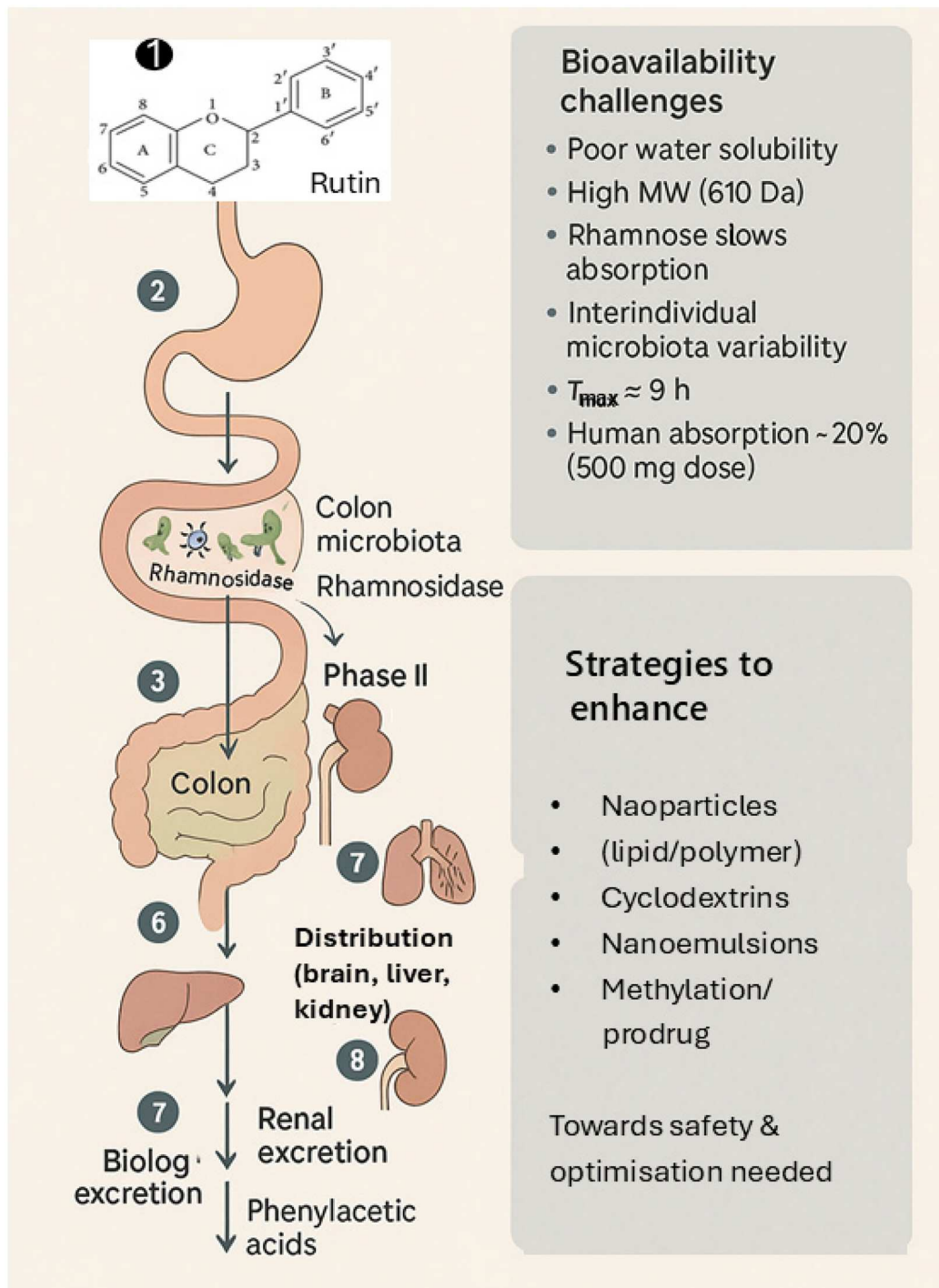
represents another barrier: soluble glycosides such as quercetin glucosides may penetrate the mucus and undergo enzymatic cleavage at the brush border, whereas rutin, which contains rhamnose, largely bypasses this route and instead relies on microbial fermentation in the colon [52]. Some studies suggest that rutin may also be absorbed in the small intestine via sodium–glucose cotransporter 1 (SGLT1), although the involvement of active transporters in flavonoid glycoside uptake remains uncertain.

Metabolism further complicates bioavailability. Once absorbed, quercetin undergoes conjugation in enterocytes and hepatocytes, yielding glucuronides, sulfates, and methylated derivatives that are distributed systemically by albumin and can reach multiple organs, including the brain [46]. Most metabolites are ultimately excreted via the kidneys [47]. Interestingly, microbial degradation of rutin in the colon also generates phenylacetic acids, which possess antioxidant activity comparable to vitamin E [47]. Thus, both direct and microbial metabolites contribute to its biological effects.

### 3.4. Strategies to Enhance Bioavailability

Given its poor solubility, low absorption, and extensive metabolism, numerous strategies have been investigated to enhance the bioavailability of rutin. These include formulation-based approaches such as encapsulation in nanoparticles [56], microencapsulation, nanoemulsions, and complexation with cyclodextrins [57,58]; biochemical modifications, including enzymatic methylation to improve intestinal absorption and metabolic stability [59]; and nanodelivery systems, in which food-grade engineered nanomaterials and novel natural compound-loaded carriers have been proposed to increase CNS delivery [60]. Although promising, these approaches require further optimisation and safety evaluation for clinical application.

It is noteworthy that rutin does not comply with Lipinski's 'rule of five' for oral drug-likeness, as it possesses more than five hydrogen-bond donors and more than ten hydrogen-bond acceptors, along with a molecular weight exceeding 500 Da. Nevertheless, exceptions to this rule are common, as only about half of FDA-approved oral drugs fully adhere to it. Importantly, studies using *in vitro* BBB models, such as ECV304 and RBE4 cells, have confirmed that rutin and related flavonoids are able to cross the endothelial barrier, albeit inefficiently [61]. Therefore, enhancing oral bioavailability remains essential for maximising rutin's therapeutic potential in neurological disorders (Figure 3).



**Figure 3.** Rutin pharmacokinetics (left) and bioavailability levers (right): absorption, metabolism, distribution, and enhancement strategies. Rutin exhibits poor oral absorption owing to low aqueous solubility, relatively high molecular mass, and the rhamnose moiety. After gastric transit, uptake in the small intestine is limited; most reaches the colon, where microbial rhamnosidases cleave rutinose to release quercetin, which is more readily absorbed. Absorbed quercetin undergoes rapid Phase II conjugation (glucuronidation, sulfation, O-methylation), circulates largely albumin-bound, distributes mainly to liver and kidney with only trace brain penetration, and is cleared predominantly by the kidney. Microbial catabolites (e.g. phenylacetic/phenylpropionic acids) are also formed and excreted. Human studies indicate delayed absorption ( $T_{\max} \approx 9$  h) and roughly 20% urinary recovery after a 500 mg dose, while reported oral bioavailability in animals can be very low ( $\approx 0.1$ – $0.2\%$ ). The right panel summarises exposure-enhancement strategies – nanoparticles/nanoemulsions, cyclodextrin inclusion complexes, lipid/polymer carriers, and prodrug or methylation approaches – which can improve solubility, stability, transport, and/or lymphatic uptake; safety and optimisation are still required. The abbreviations are:  $T_{\max}$ , time to maximum plasma concentration; Phase II, conjugative metabolism (UGT/SULT/COMT); UGT, UDP-glucuronosyltransferase; SULT, sulfotransferase; COMT, catechol-O-methyltransferase.

## 4. Blood–brain barrier and rutin permeability

### 4.1. Structure and function of the blood–brain barrier

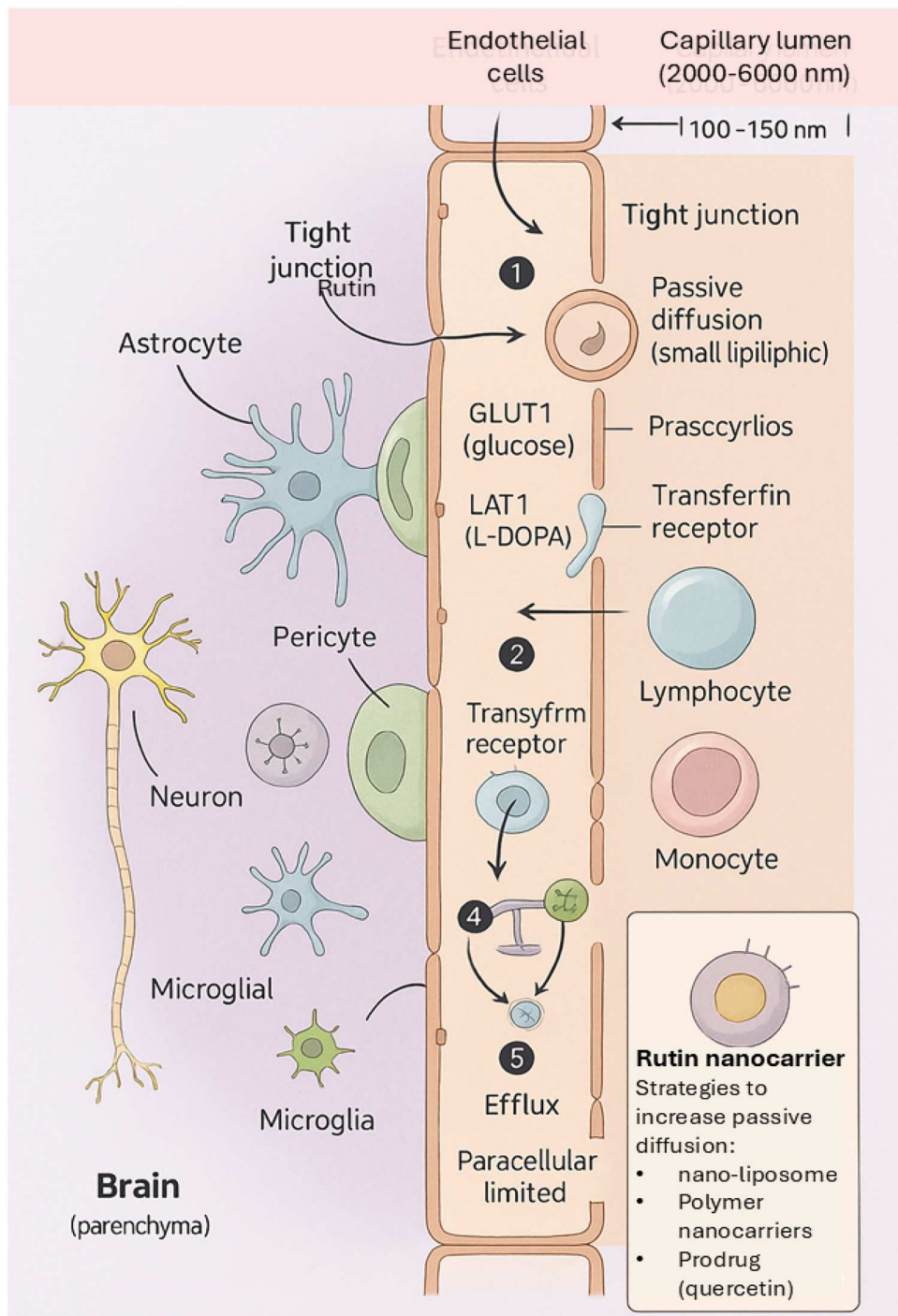
The BBB is a highly selective physiological interface that regulates molecular exchange between the systemic circulation and the brain, thereby preserving CNS homeostasis. It is formed primarily by cerebral endothelial cells sealed by tight junctions and supported by astrocytic end-feet and pericytes [62]. The combination of tight junctions and the absence of fenestrations restricts paracellular diffusion, rendering dedicated transport systems essential for the movement of nutrients, hormones, xenobiotics, and drugs across the BBB, while simultaneously limiting the passage of potentially harmful substances [63]. Functionally, the BBB acts as a dynamic, selective filter that separates the circulating blood from the CNS extracellular milieu, protecting neural tissue from exogenous agents but also impeding the entry of many therapeutic compounds [64].

Transport across the BBB occurs through five routes. First, passive transcellular diffusion allows small, lipophilic, non-ionised molecules to move down their concentration gradient. Second, carrier-mediated influx via solute carriers (uniport, symport or antiport) enables substrate-specific transport. Third, paracellular diffusion across tight junctions is effectively minimal under physiological conditions, contributing little to brain entry [44]. Fourth, vesicular transcytosis – including receptor-mediated and adsorptive-mediated endocytosis – permits uptake of larger or complex molecules [65]. Fifth, efflux transporters (e.g. P-gp, BCRP, MRPs) actively return many xenobiotics to the blood, restricting net brain exposure [44]. Together, transporter systems and tight-junction complexes maintain BBB selectivity, so only a narrow subset of low-molecular-weight compounds cross efficiently by diffusion or active transport [44]. This stringent control often prevents potentially beneficial agents from achieving therapeutic brain levels. Accordingly, recent work has pursued nanotechnology and drug-carrier modifications to enhance BBB penetration, though substantial challenges remain [65]. Within this context, rutin shows promising neuroprotective potential; the key task is to improve or facilitate its BBB transport for neurological therapy [44,65] (Figure 4).

### 4.2. Barriers to rutin permeability

Although polyphenols such as rutin demonstrate promising neuroprotective effects, their CNS delivery is severely restricted by the properties of the BBB. Rutin's bulky glycosidic structure and high polarity hinder passive diffusion across endothelial membranes [43,61]. Furthermore, active efflux transporters, including P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), act to remove flavonoids from the CNS, further reducing permeability [43]. Comparatively, its aglycone quercetin shows greater permeability but undergoes rapid metabolism into conjugated derivatives with diminished CNS activity. Consequently, only trace amounts of intact rutin reach the brain [43]. Across human brain endothelial (hCMEC/D3) monolayers, the baseline apparent permeability ( $P_{app}$ ) of rutin is  $\approx 10^{-6}$  cm/s, consistent with trace brain/plasma ratios seen in in situ perfusion studies [43]. The restricted BBB passage primarily reflects its high polarity and active efflux via P-gp/BCRP [42–44]. Where uptake occurs, it is likely mediated by OATP1A2/2B1 mainly for quercetin conjugates rather than intact rutin, owing to the latter's low membrane affinity [41]. Rutin may also modulate tight-junction proteins via PKC and Nrf2/HO-1 signalling [62]. To overcome these barriers, NaR has achieved measurable CSF and brain concentrations in rodents and improved target engagement in tauopathy models, supporting salt-/prodrug-based delivery strategies [66,67]. Co-administration with quercetin can competitively inhibit P-gp/BCRP, transiently reducing efflux and increasing transcellular passage of rutin-related conjugates, complementing any OATP-mediated uptake of quercetin conjugates noted above [62,68–70]. This effect appears model- and concentration-dependent and is consistent with short-term transporter inhibition rather than sustained changes in transporter expression.

In situ perfusion models provide complementary insights into flavonoid permeability. Radiolabelled rutin, quercetin, and naringenin have all been detected across multiple brain regions following carotid artery perfusion in rats [43]. However, rutin and quercetin showed lower permeability compared with naringenin, likely due to differences in lipophilicity and substrate affinity for efflux pumps such as P-gp. These findings highlight the need for novel delivery systems that can bypass or modulate efflux transporters to improve rutin's CNS bioavailability. In vitro BBB models indicate that quercetin acts as a competitive inhibitor of P-gp/BCRP, transiently reducing efflux and thereby increasing transcellular passage of rutin-related conjugates; this effect complements any OATP-mediated uptake of quercetin conjugates noted above.



**Figure 4.** Blood–brain barrier: structure, transport routes, and strategies to deliver rutin. The BBB consists of tightly apposed brain endothelial cells supported by a basement membrane, pericytes, and astrocytic end-feet, separating the capillary lumen from the brain parenchyma. Five routes are indicated: (1) passive transcellular diffusion, which favours small, lipophilic, non-ionised molecules; (2) carrier-mediated transport via solute carriers such as GLUT1 (glucose) and LAT1 (L-DOPA); (3) receptor-mediated transcytosis (e.g. transferrin receptor) for selected ligands and macromolecules; (4) delivery strategies for rutin that aim to enhance uptake – lipid/polymer nanocarriers, nano-liposomes, or prodrug conversion (e.g. to quercetin); and (5) active efflux by transporters such as P-gp and BCRP, which limit net CNS exposure. Paracellular movement is minimal because tight junctions seal the interendothelial space, maintaining barrier integrity and restricting entry of most therapeutics. The abbreviations are: BBB, blood–brain barrier; CNS, central nervous system; GLUT1, glucose transporter 1; LAT1, L-type amino acid transporter 1; P-gp, P-glycoprotein (ABCB1); BCRP, breast cancer resistance protein (ABCG2).

Despite its low solubility and bioavailability, rutin can cross the BBB, albeit at limited concentrations. After oral administration, plasma C<sub>max</sub> values have been reported to range from ~260 ng/ml in rabbits to ~300 ng/ml in mice [23]. Intravenous administration of 10 mg/kg in rats achieved plasma and brain levels of 1511 ± 47 ng/ml and 112 ± 12 ng/ml, respectively [71,72]. Formulation strategies enhance CNS uptake. Conjugation with apolipoprotein E-derived peptides increased brain accumulation and neuroprotection in AD mice [73], while liposomal encapsulation improved uptake in traumatic brain injury models [74]. In vitro BBB models confirm low baseline permeability (permeability coefficients ~10<sup>-6</sup> cm/s), but co-administration with quercetin enhances transport efficiency [69,70]. NaR, in particular, achieves CSF concentrations sufficient to neutralise tau pathology [67,72].

### 4.3. Mechanisms of flavonoid transport across the BBB

The mechanisms by which flavonoids traverse the BBB remain incompletely understood, and dietary or co-administered compounds may further influence their transport. For instance, α-tocopherol has been shown to enhance the transport of quercetin and rutin, possibly by modulating P-gp activity or altering phosphorylation-dependent mechanisms [62]. Importantly, chronic administration of rutin has not induced cytotoxic or pro-oxidant effects in the hippocampus, suggesting that dietary modulation may improve CNS uptake without adverse consequences [62].

A variety of in vitro models have been developed to investigate flavonoid transport across the BBB. These include ECV304 endothelial cells co-cultured with C6 glioma cells, as well as bEND5 and RBE4 endothelial cell lines [61]. Using these models, several flavonoid subclasses – including rutin – have been shown to cross endothelial cell layers, while conjugated metabolites (glucuronides and O-methylated derivatives) can be deconjugated within these cells to release aglycones, which may then enter glial cells [69]. RBE4 cell models have demonstrated that flavan-3-ols, flavonols, and anthocyanins traverse endothelial barriers in a time-dependent manner, with quercetin showing particularly low efficiency. Stereoselectivity has also been reported: for example, (+)-catechin and (–)-epicatechin display differing transport capacities, likely due to variation in efflux activity [61]. The hCMEC/D3 immortalised human cerebral endothelial cell line has also confirmed flavonoid transport and metabolism, including enhanced permeability of O-methylated derivatives compared with parent compounds [62].

### 4.4. Strategies to enhance BBB penetration of rutin

Given the limited permeability of rutin across the BBB, a variety of formulation and delivery strategies have been investigated to improve its CNS availability. Nanoparticle-based systems, including polymeric nanoparticles, polylactic-co-glycolic acid (PLGA) carriers, and solid lipid nanoparticles (SLN), have demonstrated the ability to enhance stability, prolong systemic circulation, and facilitate brain delivery [71]. Liposomes and phytosomes, based on phospholipid vesicles, improve both solubility and cellular uptake, while cyclodextrin inclusion complexes increase aqueous solubility and stability, though they provide limited BBB penetration when used alone [75–77]. Alternative administration routes have also been explored. Intranasal delivery bypasses hepatic first-pass metabolism and enables direct targeting of the brain via olfactory and trigeminal pathways, offering rapid onset and high CNS bioavailability [78]. Furthermore, ligand-targeted strategies, such as surface modification of nanoparticles with transferrin, lactoferrin, or cell-penetrating peptides (CPPs), exploit

**Table 3.** Strategies to improve BBB penetration of rutin.

Approach	Key Features	Advantages	Limitations
Nanoparticles	Polymeric, SLN, PLGA	Enhanced stability, controlled release, BBB penetration	Scale-up difficulties; safety concerns
Liposomes/ Phytosomes	Phospholipid vesicles	Improved solubility, increased cellular uptake	Stability and storage issues
Cyclodextrin complexes	Inclusion complexes	Increased solubility and chemical stability	Limited ability to cross the BBB independently
Intranasal delivery	Direct brain targeting	Bypasses first-pass metabolism; rapid onset	Risk of local irritation; formulation challenges
Ligand-targeted carriers	Transferrin, lactoferrin, CPPs	Receptor-mediated transport across BBB	Complexity; high production costs

receptor-mediated transcytosis to actively transport rutin across the BBB [79–81]. Despite these advances, major challenges remain, including difficulties in large-scale manufacturing, reproducibility of formulations, and comprehensive safety validation in humans. Future research must therefore balance technological innovation with translational feasibility to enable clinical application of rutin-based neurotherapeutics [79,81] (Table 3).

## 5. Research progress of rutin in the treatment of neurological diseases

### 5.1. Alzheimer's disease

Rutin has demonstrated multi-target neuroprotective actions in preclinical AD models. In vitro studies show that rutin directly inhibits A $\beta$ 42 fibril aggregation, reducing oligomer-induced cytotoxicity and synaptic impairment [82]. Complementary in vivo findings confirm that rutin administration improves learning and memory in AD mouse models, with significantly shorter escape latencies in the Morris water maze and enhanced long-term potentiation [72,83]. Collectively, the evidence supports an indirect inhibition of GSK-3 $\beta$  by rutin via PI3 K/Akt-driven Ser9 phosphorylation of GSK-3 $\beta$  and concurrent suppression of NF- $\kappa$ B/MAPK inflammatory cascades, rather than direct ATP-competitive binding; these pathway effects converge on reduced tau phosphorylation, mitochondrial stress, and neuroinflammation in AD models. Rutin preserves BBB integrity by upregulating tight-junction proteins (e.g. claudin-5 and occludin) and supporting endothelial barrier function [66,84] and Nrf2-linked barrier protection [85].

Mechanistically, rutin mitigates AD pathology through suppression of oxidative stress and neuroinflammation, largely by downregulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) pathways [86]. Rutin also enhances endogenous antioxidant defences via activation of the Nrf2/HO-1 signalling cascade, thereby protecting neurons from reactive oxygen species (ROS)-induced apoptosis and mitochondrial dysfunction [10]. Furthermore, rutin stabilises BBB function by upregulating tight-junction proteins (e.g. claudin-5) and suppressing endothelial HDAC1 activity, thus preventing stress-induced vascular leakage and cognitive decline.

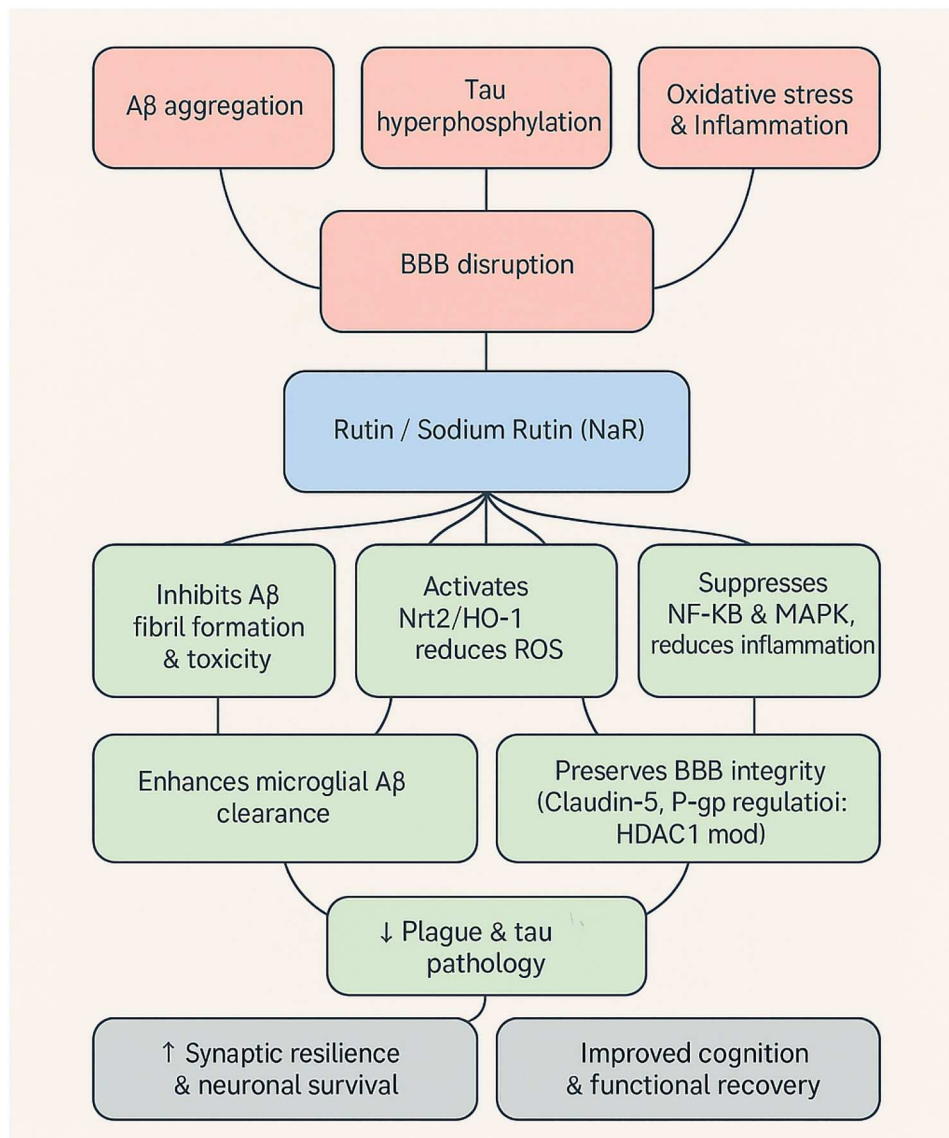
A water-soluble derivative, NaR, exhibits improved bioavailability and CNS penetration compared with native rutin. NaR crosses the BBB more effectively, attenuates A $\beta$  accumulation, and restores synaptic plasticity, leading to measurable improvements in learning and memory performance in AD mouse models [23]. Importantly, NaR facilitates microglial phagocytosis and clearance of A $\beta$  plaques, while preserving neuronal integrity and reducing synaptic toxicity [22,87]. NaR also regulates efflux transporters such as P-gp and modulates endothelial permeability, which may enhance co-delivery of other therapeutics to the brain [88, 89].

Emerging evidence indicates that rutin additionally modulates tau pathology, reducing hyperphosphorylation and aggregation through inhibition of GSK-3 $\beta$  and related kinases, key drivers of tauopathy progression [83]. These effects collectively support improved synaptic resilience, enhanced neuronal survival, and reduced apoptosis. Available data support an indirect inhibition of GSK-3 $\beta$  by rutin via upstream signalling – specifically PI3 K/Akt-driven Ser9 phosphorylation of GSK-3 $\beta$  and concurrent suppression of NF- $\kappa$ B/MAPK inflammatory cascades – rather than direct ATP-competitive binding to GSK-3 $\beta$ .

Taken together, rutin and its derivatives – particularly NaR – represent promising multi-target therapeutic candidates for AD. By simultaneously inhibiting A $\beta$  aggregation, modulating tau phosphorylation, suppressing neuroinflammation, enhancing antioxidant defence, and preserving BBB integrity, rutin-based strategies show strong translational potential for clinical management of AD. Nevertheless, limitations remain, including the poor bioavailability of native rutin, which underscores the need for optimised drug-delivery systems and clinical trials to establish efficacy and safety in humans [23,87] (Figure 5).

### 5.2. Parkinson's disease

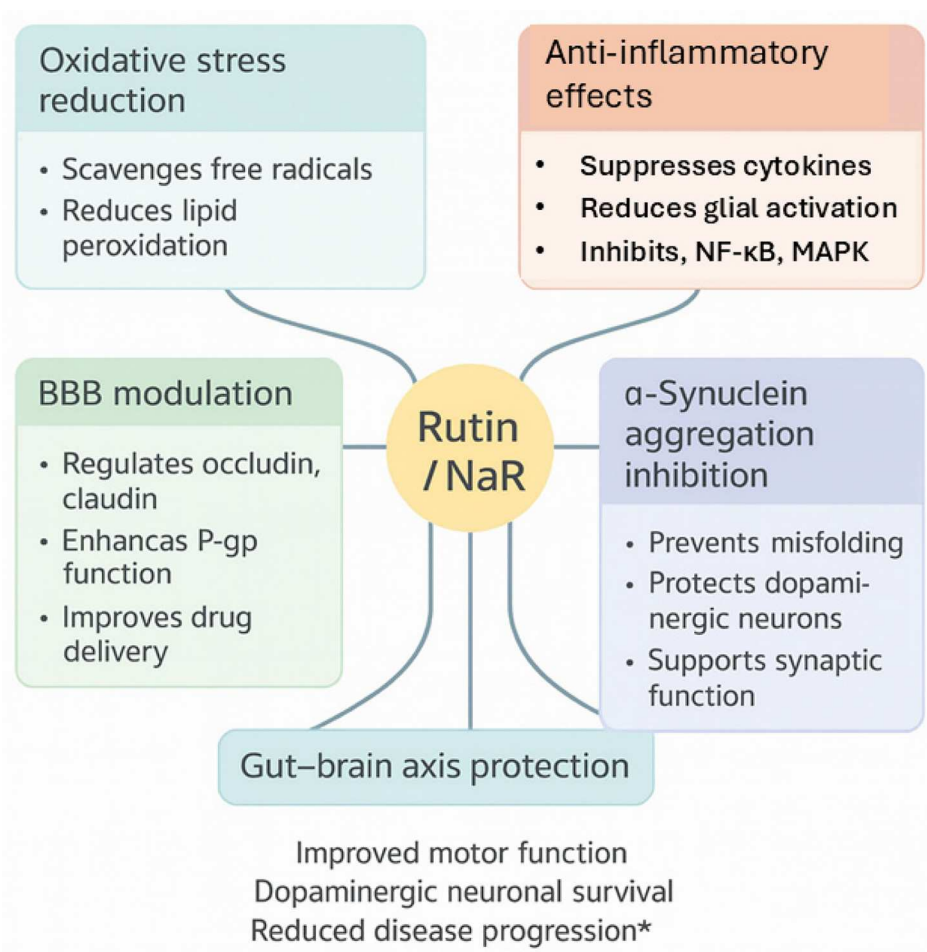
Recent studies have highlighted rutin as a promising candidate in PD therapy owing to its antioxidant, anti-inflammatory, and BBB-modulatory properties [21]. In preclinical PD models, rutin improved motor performance, enhanced dopaminergic neuronal survival, and reduced oxidative stress and neuroinflammation



**Figure 5.** Neuroprotective mechanisms of rutin and NaR in Alzheimer's disease. The core AD pathologies are A $\beta$  aggregation, tau hyperphosphorylation, oxidative stress/neuroinflammation, and BBB disruption which converge to impair synapses and cognition. Rutin/NaR counter these via multiple nodes: they inhibit A $\beta$  fibrillogenesis and oligomer toxicity; activate antioxidant defences (Nrf2/HO-1) to lower ROS and mitochondrial injury; suppress NF- $\kappa$ B/MAPK signalling to reduce neuroinflammation; and preserve BBB integrity (e.g. increased claudin-5, HDAC1 modulation, P-gp regulation). NaR improves exposure and brain entry, enhances microglial A $\beta$  clearance, restores synaptic plasticity, and yields behavioural improvement in AD models. Collectively, these actions reduce plaque/tau pathology and support synaptic resilience, neuronal survival, and cognitive recovery. The abbreviations are: AD, Alzheimer's disease; A $\beta$ , amyloid- $\beta$ ; BBB, blood-brain barrier; NaR, sodium rutin; Nrf2, nuclear factor erythroid 2 – related factor 2; HO-1, heme oxygenase-1; ROS, reactive oxygen species; NF- $\kappa$ B, nuclear factor- $\kappa$ B; MAPK, mitogen-activated protein kinase; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; P-gp, P-glycoprotein; HDAC1, histone deacetylase 1.

[90–93]. For instance, rutin administration in a 6-hydroxydopamine (6-OHDA)-induced rat model markedly protected dopaminergic neurons, restored striatal dopamine levels, and attenuated motor impairments. Mechanistically, rutin reduced lipid peroxidation, preserved glutathione levels, and enhanced the activities of glutathione-dependent enzymes, thereby preventing oxidative neuronal damage [90]. Similarly, in MPTP-induced PD mice, rutin treatment improved motor function scores by approximately 30% and increased dopaminergic neuronal survival by 25% [91]. Beyond antioxidant effects, rutin also suppressed pro-inflammatory cytokine release and glial reactivity [93,94], while modulating BBB integrity by regulating tight-junction proteins (occludin, claudin) and efflux transporters such as P-gp [95].

Notably, rutin interfered with  $\alpha$ -synuclein aggregation in the substantia nigra, a hallmark of PD pathology [96,97]. Enteric nervous system models further revealed that rutin counteracted  $\alpha$ -synuclein-induced neurotoxicity, protected enteric glial and mesencephalic neurons, and ameliorated gut dysfunctions often preceding PD symptoms [97]. Novel formulations, such as nano-rutin, demonstrated superior neuroprotective efficacy compared to conventional rutin, suggesting translational potential for clinical applications. Clinical data provide supportive evidence. In a double-blind, randomised controlled trial with 50 PD patients, rutin supplementation for 12 weeks significantly improved motor function compared with placebo ( $p < 0.05$ ) [98]. Furthermore, complex flavonoid mixtures containing rutin, such as luteolin – rutin combinations, enhanced dopaminergic markers and reduced astrocytic reactivity in PD models, suggesting synergistic benefits (Q [21]). Collectively, these findings indicate that rutin exerts multi-targeted neuroprotective effects in PD, providing both symptomatic relief and potential disease-modifying benefits (Figure 6).



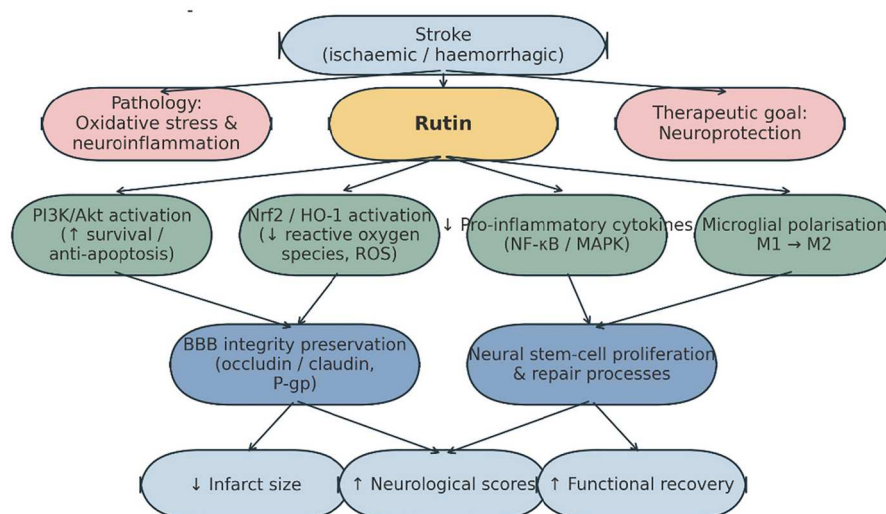
**Figure 6.** Neuroprotective mechanisms of rutin in Parkinson’s disease: antioxidant, anti-inflammatory, anti-aggregative, blood–brain barrier-modulatory and gut – brain actions. Rutin and enhanced formulations such as sodium rutin acts across five Parkinson’s disease-relevant domains. It reduces oxidative stress by scavenging reactive oxygen species and limiting lipid peroxidation while supporting endogenous defences; moderates neuroinflammation by lowering pro-inflammatory cytokines, inhibiting NF- $\kappa$ B/MAPK signalling, and dampening microglial/astroglial activation; curbs  $\alpha$ -synuclein misfolding/oligomerisation, supporting synaptic function and dopaminergic neuron survival; helps maintain blood–brain barrier integrity by preserving tight-junction proteins (occludin, claudin) and modulating P-glycoprotein, potentially aiding central nervous system drug delivery; and supports the gut – brain axis by mitigating enteric dysfunction consistent with prodromal enteric nervous system changes. Collectively, these actions improve motor outcomes and neuronal survival in pre-clinical Parkinson’s disease models, with early clinical signals suggesting translational promise. The abbreviations are: NF- $\kappa$ B, nuclear factor- $\kappa$ B; MAPK, mitogen-activated protein kinase; P-gp, P-glycoprotein.

### 5.3. Stroke

Rutin has been increasingly investigated for its potential to mitigate stroke-related brain injury. Experimental studies demonstrate that rutin reduces infarct volume, improves neurological scores, and preserves BBB integrity in models of cerebral ischaemia – reperfusion injury [81,99,100]. Mechanistically, rutin activates endogenous antioxidant pathways, including PI3 K/Akt and Nrf2 signalling, attenuates lipid peroxidation and ROS production, and upregulates antioxidant enzymes such as SOD and catalase [101]. In parallel, rutin suppresses pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) and downregulates NLRP3 inflammasome activation, thereby limiting neuroinflammation and neuronal apoptosis. Beyond acute neuroprotection, rutin appears to influence recovery processes. Evidence suggests that it promotes neural stem cell proliferation and modulates microglial polarisation towards the reparative M2 phenotype, while inhibiting M1-driven pyroptosis through regulation of the Nrf2/Mac-1/caspase-1 axis [5]. Such effects may contribute to long-term neuronal survival and improved functional outcomes.

When compared with quercetin, another well-studied flavonoid, both compounds exhibit antioxidant and anti-inflammatory effects in ischaemic stroke models. However, rutin (a glycoside of quercetin) demonstrates better BBB-protective activity and more consistent suppression of inflammasome-driven pyroptosis. Quercetin's effects are primarily attributed to radical scavenging and platelet aggregation inhibition [101], whereas rutin exerts broader multimodal actions, including modulation of microglial polarisation and neural regeneration. Thus, while structurally related, rutin may provide greater therapeutic promise in post-stroke recovery, particularly for its combined effects on vascular integrity, inflammation, and neuroplasticity. Collectively, these findings position rutin as a promising candidate for adjunctive therapy in stroke and ischaemia – reperfusion injury. Its multimodal actions – antioxidant, anti-inflammatory, and neuroregenerative – address key pathological mechanisms underlying stroke progression and sequelae. Nevertheless, translation to clinical settings requires rigorous trials to evaluate pharmacokinetics, optimal dosing, and safety in diverse patient populations (Figure 7).

Troloxerutin, a semi-synthetic derivative of rutin, has been studied extensively in this context. In a clinical study of 120 patients with mild-to-moderate cerebral infarction, troloxerutin combined with standard therapy achieved a total effective treatment rate of 94.4%, approximately twenty percent higher than standard therapy alone [102]. Troloxerutin improved haemorrhological parameters, inhibited neuronal apoptosis



**Figure 7.** Neuroprotective Mechanisms of Rutin in Stroke. Stroke triggers oxidative stress, neuroinflammation, BBB disruption and neuronal loss. Rutin acts on several nodes: it activates antioxidant signalling (PI3 K/Akt, Nrf2/HO-1), suppresses pro-inflammatory pathways (NF- $\kappa$ B/MAPK) and cytokine release, promotes microglial polarisation from M1 to M2, preserves BBB integrity by maintaining tight-junction proteins (occludin, claudin) and modulating P-gp, and supports neural stem/progenitor proliferation and tissue repair. Together these actions reduce infarct size, improve neurological scores and enhance functional recovery. The abbreviations are: BBB, blood–brain barrier; PI3 K/Akt, phosphoinositide 3-kinase/protein kinase B; Nrf2, nuclear factor erythroid 2 – related factor 2; HO-1, haem oxygenase-1; NF- $\kappa$ B, nuclear factor- $\kappa$ B; MAPK, mitogen-activated protein kinase; P-gp, P-glycoprotein; M1/M2, pro-inflammatory/repair microglial phenotypes.

via NF- $\kappa$ B signalling, and reduced oxidative damage [103–106]. Clinical application of the troxerutin–cerebroprotein injection further improved neurological scores and recovery in patients with acute ischaemic stroke [107]. These findings validate the translational potential of rutin derivatives in cerebrovascular diseases.

## 6. Mechanisms of rutin in enhancing BBB penetration and neuroprotection

Rutin exerts its beneficial effects on the CNS through dual and interrelated actions: enhancing BBB penetration and providing direct neuroprotection. These mechanisms involve modulation of transport proteins, regulation of tight junctions, antioxidant and anti-inflammatory activity, and the engagement of multiple signalling pathways that support neuronal survival and vascular integrity.

Evidence from preclinical and limited clinical studies demonstrates that rutin holds significant therapeutic promise in PD, AD, and stroke (Table 4). Its beneficial effects are mediated through antioxidant, anti-inflammatory, anti-apoptotic, and BBB-modulatory mechanisms. Rutin derivatives such as NaR and troxerutin further enhance BBB penetration and pharmacokinetic properties, improving efficacy in neurodegenerative and cerebrovascular models. Mechanistic insights into microglial modulation and metabolic reprogramming provide new perspectives on its disease-modifying potential. However, limitations in bioavailability, dosing, and long-term safety remain unresolved. Rigorous clinical trials are urgently needed to translate these findings into effective therapies for neurological diseases.

Rutin and its derivative NaR exert pleiotropic neuroprotective effects across multiple neurological disorders. In PD, they protect dopaminergic neurons, inhibit  $\alpha$ -synuclein aggregation, and reduce oxidative stress and inflammation. In AD, they attenuate amyloid- $\beta$  and tau pathology, enhance microglial clearance, and restore mitochondrial oxidative phosphorylation. In stroke and cerebrovascular injury, they reduce infarct size, preserve BBB integrity, and activate PI3 K/Akt and Nrf2 signalling pathways. Mechanistic insights further highlight their roles in microglial modulation via TREM2, metabolic reprogramming from glycolysis to oxidative phosphorylation, and promotion of an anti-inflammatory M2 phenotype. Advances in pharmacokinetics and delivery, including NaR, nanoparticles, liposomes, and peptide

**Table 4.** Evidence of Rutin and its derivatives in neurological disorders.

Disease/Model	Intervention	Key Findings	Mechanisms/Pathways	References
Parkinson's disease – mouse model	Rutin	↑ Motor function (+30%); ↑ dopaminergic neuron survival (+25%)	Antioxidant, anti-inflammatory, ↓ $\alpha$ -synuclein aggregation, modulation of P-gp and tight junction proteins	Fuentes-Herrera et al. [98]; He et al. [91]; Abarikwu et al. [93]; Shanmugasundaram et al. [94]; Naren et al. [137]; Christmann et al. [96]; Guan et al. [95]
Parkinson's disease – clinical trial	Rutin (12 weeks, 50 patients)	Improved motor scores vs placebo	Symptomatic and neuroprotective effects	Fuentes-Herrera et al. [98]
Alzheimer's disease – mouse model	Rutin	↓ A $\beta$ aggregation, ↓ tau phosphorylation, ↑ memory performance (by Morris water maze)	NF- $\kappa$ B and MAPK inhibition; antioxidant; anti-inflammatory	Bermejo-Bescós et al. [83]; Sun et al. [72]; Zamanian et al. [86]; Dhakal et al. [82]
Alzheimer's disease – mouse model	Sodium rutin	↓ A $\beta$ plaques, restored synaptic plasticity, improved learning and memory	↑ BBB penetration, inhibition of P-gp efflux, ↑ microglial phagocytosis, restored OXPHOS metabolism	Pan et al. [23]; Lv et al [87]; Habtemariam et al. [138]
Stroke – animal models	Rutin	↓ Infarct size, ↑ neurological recovery, preserved BBB integrity	PI3 K/Akt and Nrf2 activation; anti-inflammatory; antioxidant; stem cell proliferation	Rana et al. [139]; Liu et al. [81]; Gao et al. [100]; Annapurna et al. [99]; Ji Q et al. [5]
Cerebral infarction – clinical study (120 patients)	Troxerutin injection + standard therapy	94.4% effective rate (~20% > control); improved hemorheology	Anti-inflammatory, antioxidant, improved blood viscosity, NF- $\kappa$ B inhibition	Zhao et al. [56]; Panat et al. [102]; Lee et al. [103]; Thomas et al. [104]; Luo et al. [107]
Traumatic brain injury – rat model	Liposomal rutin	↑ Brain uptake, ↓ oxidative damage, improved recovery	Liposome-enhanced BBB delivery	Zhang et al.
In vitro BBB models (ECV304, RBE4, hCMEC/D3)	Rutin & derivatives	Low baseline permeability; enhanced by quercetin co-administration	Passive + transporter-mediated pathways	Ishisaka et al. [69]; Kim et al. [68]; Liu et al. [70]

conjugates, enhance solubility, bioavailability, and BBB penetration. Collectively, these mechanisms demonstrate the potential of rutin and NaR as multi-target therapeutic agents in neurodegenerative and cerebrovascular disorders.

### **6.1. Regulation of transport proteins**

Studies suggest that rutin can modulate P-gp expression or function, thereby enhancing drug permeability across the BBB. In vitro experiments demonstrated that rutin inhibited P-gp activity, improving the transport of anticancer agents in brain tumour models [108]. Moreover, rutin may interact with other efflux proteins such as multidrug resistance-associated proteins (MRPs), further supporting its role as a potential penetration enhancer.

### **6.2. Modulation of tight junctions**

The structural integrity of the BBB depends on tight-junction proteins, including occludin, claudins, and ZO-1 [109]. Evidence from animal studies indicates that rutin increases the expression of occludin and claudin-5, thereby strengthening barrier function and reducing cerebral oedema in ischaemic brain injury [66]. Beyond structural stabilisation, rutin may also influence tight-junction dynamics. Activation of the protein kinase C (PKC) pathway by rutin promotes occludin phosphorylation, creating a transient and reversible tight-junction opening that facilitates paracellular transport without permanent disruption [110,111]. However, excessive modulation of tight-junction proteins could impair BBB integrity and induce neurotoxicity [112,113]. Thus, the therapeutic challenge lies in achieving sufficient BBB permeability while maintaining long-term barrier protection. Rutin modulates neuroinflammation by shifting microglia from an M1 to M2 phenotype via suppression of TLR4/NF- $\kappa$ B signalling [114,115].

### **6.3. Antioxidant and anti-inflammatory effects**

Oxidative stress and neuroinflammation are critical drivers of BBB dysfunction and neuronal injury. As a potent flavonoid antioxidant, rutin scavenges ROS, upregulates endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), and activates the Nrf2/ARE signalling pathway, thereby protecting the BBB from oxidative damage. Concurrently, rutin attenuates neuroinflammation by suppressing NF- $\kappa$ B activation and reducing the release of pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [24]. These effects contribute both to the stabilisation of BBB integrity and the reduction of secondary neuronal damage.

### **6.4. Regulation of cell survival and apoptosis**

Rutin also modulates cell survival pathways that influence both endothelial and neuronal function. Activation of the PI3 K/Akt and MAPK/ERK cascades enhances endothelial proliferation, promotes neuronal survival, and supports synaptic plasticity [116–119]. In parallel, rutin reduces apoptosis by lowering the Bax/Bcl-2 ratio, inhibiting caspase-3 activation, and preserving mitochondrial integrity. These processes are essential in maintaining cerebral microvascular health and preventing neuronal degeneration in the context of injury or disease.

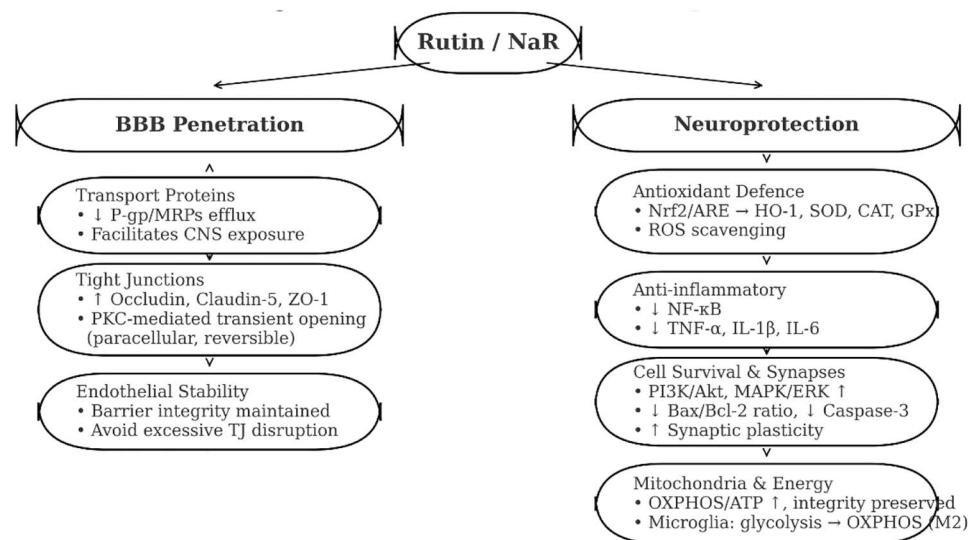
### **6.5. Metabolic and energetic support**

Microvascular and microglial cells within the CNS require substantial energy for dynamic processes such as phagocytosis, cytoskeletal rearrangement, and neurotransmitter regulation. Rutin has been shown to enhance cellular bioenergetics by modulating enzymes involved in mitochondrial metabolism, increasing ATP production, and restoring energy balance. In microglial cells, NaR was found to promote a metabolic shift from glycolysis to oxidative phosphorylation, thereby improving energy efficiency while simultaneously promoting anti-inflammatory M2 polarisation. This shift not only supports microglial clearance of  $\beta$ -amyloid (A $\beta$ ) but also reduces the release of neurotoxic metabolites such as lactate [23].

Taken together, rutin acts as a multi-target agent that simultaneously enhances BBB penetration and confers direct neuroprotection. By modulating transport proteins and tight junctions, it improves its own delivery and potentially facilitates the passage of co-administered drugs. Once within the CNS, rutin exerts pleiotropic protective effects: reducing oxidative stress, attenuating inflammation, preserving mitochondrial and synaptic function, and maintaining BBB stability. Its combined regulation of signalling pathways such as NF- $\kappa$ B, PI3 K/Akt, MAPK, and Nrf2/ARE highlights its potential as both a BBB-penetration enhancer and a neurotherapeutic agent in conditions such as AD, PD, stroke, and traumatic brain injury (Figure 8).

### 6.6. Resolving the rutin bioavailability–BBB penetration paradox

Although unformulated oral rutin has low systemic exposure, this does not preclude it from enhancing brain delivery once small amounts of rutin, its better-permeating metabolites (e.g. quercetin), or the more soluble NaR reach the circulation or are given via optimised formulations (e.g. nano-carriers, intranasal or IV administration). At the BBB ‘gate,’ rutin/NaR can attenuate efflux ( $\downarrow$ P-gp/MRPs) to increase net brain entry of itself and co-therapies, and it can strengthen tight-junction structure ( $\uparrow$ occludin, claudin-5, ZO-1) while permitting brief, PKC-mediated, reversible paracellular opening for controlled passage [66,108–111]. In parallel, antioxidant and anti-inflammatory actions (Nrf2/ARE activation; NF- $\kappa$ B suppression) preserve endothelial integrity and reduce pathological leak, and mitochondrial/metabolic support – including an OXPHOS-favouring microglial shift – further stabilises the barrier and neural milieu [23,24]. Hence, despite low oral bioavailability, salts, metabolites, and formulation-enabled exposure allow rutin to modulate BBB transport and structure and thereby improve effective CNS penetration – an effect well supported preclinically, with limited but growing translational evidence. Among delivery options, Na-rutin and intranasal nano-formulations show the highest translational readiness – supported by reproducible preclinical efficacy, pharmacokinetics, and emerging safety – whereas ligand-targeted nanoparticles remain earlier-stage; key CMC/regulatory hurdles include GMP-grade scale-up and manufacture, long-term stability, sterility/endotoxin control, scalable peptide/ligand conjugation, and completion of regulatory toxicology packages.



**Figure 8.** Mechanisms of rutin in enhancing BBB penetration and neuroprotection. This schematic shows how rutin (and sodium rutin) both helps more drug reach the brain and directly protects neural tissue. On the BBB side, rutin reduces efflux by P-glycoprotein and MRPs, strengthens tight-junction proteins (occludin, claudin-5, ZO-1), and can induce a short, reversible PKC-mediated junction ‘loosening’ to allow controlled paracellular passage while preserving endothelial stability. Once inside the CNS, it mounts antioxidant defenses via Nrf2/ARE ( $\uparrow$ HO-1, SOD, CAT, GPx), suppresses inflammation by inhibiting NF- $\kappa$ B ( $\downarrow$ TNF- $\alpha$ , IL-1 $\beta$ , IL-6), promotes cell-survival signaling (PI3 K/Akt, MAPK/ERK;  $\downarrow$ Bax/Bcl-2 ratio and caspase-3;  $\uparrow$ synaptic plasticity), and supports mitochondrial function and energy metabolism ( $\uparrow$ OXPHOS/ATP; microglial shift toward an anti-inflammatory, OXPHOS-favored M2 state). Together these actions yield a tighter, more resilient BBB, improved brain exposure, and broad neuroprotection.

## 7. Challenges, limitations, and future directions

### 7.1. Potential side effects

Although rutin demonstrates considerable therapeutic promise in neurological disorders, its potential adverse effects warrant careful consideration. One major concern is its impact on normal cells, particularly with long-term administration or at high doses. Experimental studies have indicated that high concentrations of rutin may disrupt cell membrane structure and function, leading to metabolic disturbances and even apoptosis [30]. Furthermore, while its antioxidant activity underpins much of its neuroprotective action, excessive intake may paradoxically disturb redox balance, thereby inducing damage to healthy tissues. For example, in a D-galactose-induced ageing mouse model, high-dose rutin exacerbated hippocampal neuronal hyperactivation, contributing to neurodegenerative changes [120].

To mitigate such risks, several strategies have been proposed. Structural modification of rutin, such as conjugation with hyaluronic acid or other biocompatible molecules, can enhance its stability while reducing cytotoxicity. Targeted delivery systems, including nanocarriers and ligand-mediated vectors, can further improve safety by restricting drug exposure to affected brain regions [121]. In addition, careful regulation of dose and treatment duration remains crucial. Incorporating personalised treatment protocols that adjust dosing according to patient condition may optimise efficacy while minimising adverse outcomes.

### 7.2. Dose-dependent effects

The therapeutic application of rutin is further constrained by its dose-dependent characteristics, as highlighted in multiple studies [122]. Typically, its effects are limited at sub-therapeutic doses, whereas excessive doses may lead to toxicity or diminished bioavailability [123]. For instance, in stroke models, rutin exerts anti-inflammatory and signalling-modulatory effects only upon achieving a threshold plasma concentration. However, suprathreshold dosing has been associated with metabolic disruption and other adverse effects [124]. Importantly, this dose dependency is closely linked to its limited ability to cross the BBB: low doses often fail to achieve sufficient cerebral accumulation, thereby compromising efficacy.

Based on preclinical pharmacokinetic data and body surface area scaling, a pragmatic adult oral dose range of 250–500 mg/day (parent rutin) is proposed; Na-rutin and other enhanced formulations may achieve comparable systemic exposure at the lower end of this range, and – given high inter-individual variability – divided dosing with meals is advisable during early clinical evaluation.

To overcome this limitation, several optimisation strategies have been developed. Advanced drug delivery technologies, such as nanoparticle encapsulation, have been shown to enhance bioavailability, BBB permeability, and tissue targeting, thereby reducing the required therapeutic dose [79]. Combination therapies represent another promising approach. Co-administration with agents such as vitamin E has demonstrated synergistic benefits, enhancing efficacy while reducing the necessary dose of rutin and consequently mitigating risks associated with high-dose regimens. Sustained-release formulations may also offer improved safety profiles by preventing sudden spikes in plasma concentration and allowing for gradual drug release [140].

### 7.3. Future perspectives

Ageing is associated with reduced Bifidobacterium/Lactobacillus abundance and diminished  $\alpha$ -L-rhamnosidase/ $\beta$ -glucosidase activity, which can blunt rutin  $\rightarrow$  quercetin liberation and lower systemic exposure to conjugates; this microbiota-linked variability may therefore attenuate clinical response in older adults and should be considered in dose selection and trial stratification. Despite robust preclinical data, the translation of rutin into clinical settings remains challenging. Evidence for its therapeutic efficacy is currently limited almost entirely to in vitro and animal models, with little direct validation in human studies. This gap highlights a major barrier to clinical application: while rutin exhibits strong antioxidant, anti-inflammatory, and neuroprotective actions, the absence of large-scale randomised controlled trials means that its safety, efficacy, and optimal dosing in patients remain unproven. Prospective trials should stratify by gut-microbiota composition (e.g. Bifidobacterium/Lactobacillus abundance) and age, or include pre-specified PK/PD sub-studies – circulating quercetin conjugates, enterohepatic ‘secondary peaks,’ and exposure–response – to quantify microbiota-linked variability and guide dose selection.

Future research should therefore prioritise the development of innovative delivery systems, including multifunctional nanoparticles and intranasal carriers, to address limitations of solubility, stability, and BBB penetration. Systems biology and nutrigenomic approaches hold promise for tailoring interventions to individual patient profiles, particularly given inter-patient variability in gut microbiota composition and metabolic enzyme activity. Combination regimens integrating rutin with established pharmacological agents or other nutraceuticals may also provide synergistic benefits in complex neurodegenerative conditions.

Ultimately, the successful clinical translation of rutin will require rigorously designed trials that confirm efficacy, optimise dosage, and establish long-term safety. Until then, rutin should be regarded as a promising experimental compound and a valuable candidate for adjunctive strategies, but not yet a validated therapeutic agent in human neurological disorders.

In summary, while rutin presents compelling mechanistic evidence and innovative delivery strategies are under development, its translation into clinical therapy remains dependent on rigorous validation to bridge the gap between promising preclinical findings and real-world application.

## 8. Conclusion

Rutin represents a multifunctional flavonoid with considerable promise for the management of neurological disorders. Its antioxidant, anti-inflammatory, and neuroprotective activities provide a strong mechanistic foundation, yet its poor solubility, low oral bioavailability, and restricted BBB permeability remain major barriers to clinical translation. Advances in pharmaceutical science, including nanoparticle-based systems, intranasal carriers, and targeted ligand-mediated delivery, offer encouraging solutions to these limitations by improving solubility, stability, and CNS penetration. We outline a translational roadmap prioritising sodium rutin and intranasal delivery as the nearest-term candidates, with nanoparticles and ligand-targeted carriers following, pending GMP scale-up and safety validation.

At the same time, mechanistic insights continue to expand our understanding of how rutin regulates BBB transporters, modulates tight junction integrity, and influences signalling pathways that govern neuroinflammation and oxidative stress. These findings support the concept of rutin as a multi-target agent capable of addressing the complex pathophysiology of neurodegenerative diseases, particularly AD.

Nonetheless, translation to the clinic requires careful consideration of dose-dependent effects, potential side effects, and long-term safety. Integration of cutting-edge tools, such as single-cell sequencing, spatial transcriptomics, and humanised BBB models, may help clarify its molecular mechanisms and optimise delivery strategies. Ultimately, rigorously designed clinical trials are essential to establish efficacy, safety, and dosing parameters.

Taken together, rutin stands at the interface of natural product pharmacology and modern drug delivery science. With continued innovation and systematic clinical validation, it may transition from an experimental flavonoid to a clinically relevant therapeutic candidate for neurodegenerative disorders.

## Author contributions

RC and SZ are responsible for the conception of the article; HH and XY are responsible for the implementation of the study, literature retrieval, data collection, and feasibility analysis, and wrote the first draft of the paper; JG, PZ, LY, TZ, RC, and SZ were responsible for the analysis, interpretation of the results, review the paper. SZ and RC wrote and revised the paper. All authors contributed to the article and approved the submitted version.

## Disclosure statement

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