

Quercetin as a Multi-Target Neuroprotective Adjunct for Spinal Muscular Atrophy: Mechanisms, Pharmaceutical Challenges and Translational Perspectives – A Thorough Review

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Abstract: Spinal muscular atrophy (SMA) is a devastating autosomal recessive neuromuscular disorder primarily caused by deficiency of the survival motor neurone (SMN) protein resulting in progressive degeneration of lower motor neurones, skeletal muscle atrophy, respiratory dysfunction, and premature mortality. Despite recent advances in treatment strategies targeting SMN gene replacement and RNA approaches, which have dramatically changed the disease landscape, significant challenges still persist such as incomplete restoration of function, restricted access, cost of treatment, and inability to halt progressive neurodegeneration. The search for safe and inexpensive adjunctive therapies that can act on several pathogenic pathways has therefore become a major area of investigation. Quercetin is a natural plant-derived flavonoid, which has been considered as a promising neuroprotective phytochemical for its potent antioxidant, anti-inflammatory, anti-apoptotic and mitochondrial protective effects. However, evidence regarding its potential therapeutic role in SMA is limited and has not been exhaustively synthesised. This review critically appraises the existing knowledge on quercetin in SMA by synthesising molecular mechanisms, pre-clinical data, pharmacological properties, formulation challenges and translational perspectives. Special emphasis is given to the modulation of oxidative stress, neuroinflammation, mitochondrial dysfunction, autophagy, apoptosis and crucial signalling pathways — including Nrf2/ARE, NF- κ B, PI3K/Akt, MAPK and SIRT1 — that together contribute to motor neurone survival and disease progression. Moreover, the review highlights the major pharmaceutical problems of quercetin such as low aqueous solubility, poor oral bioavailability, rapid metabolism, and low blood-brain barrier permeability and emerging formulation strategies such as lipid-based delivery systems, polymeric nanoparticles, nanoemulsions, liposomes, and other nanocarrier platforms to enhance its therapeutic efficacy. The current evidence is critically reviewed to identify knowledge gaps, limitations of preclinical and barriers for clinical translation. Future perspectives on biomarker driven evaluation, advanced drug delivery systems, combination therapy with SMN-targeted treatments and well-designed clinical studies are also discussed. This review integrates mechanistic, pharmaceutical and translational perspectives to offer a comprehensive scientific rationale for the assessment of quercetin

as a potential adjunct therapy for spinal muscular atrophy and highlights critical research needs for the future development of neuroprotective drugs.

Keywords: Spinal muscular atrophy; Quercetin; Plant-derived flavonoids; Survival motor neuron protein; Neuroprotection; Oxidative stress; Neuroinflammation; Mitochondrial dysfunction; Nrf2; NF-κB; PI3K/Akt; Autophagy; Nanotechnology; Drug delivery systems; Bioavailability; Blood–brain barrier; Translational medicine; Pharmaceutical sciences.

1. Introduction

Spinal muscular atrophy (SMA) is one of the most common inherited causes of infant mortality caused by homozygous deletion or mutation of the survival motor neurone 1 (SMN1) gene on chromosome 5q13[1, 2]. This lack of SMN protein results in the selective degeneration of lower motor neurones in the anterior horn of the spinal cord, denervation atrophy of skeletal muscle and in the most severe forms, death in the first years of life due to respiratory failure[2,3].

The natural history of SMA has been revolutionised with the approval of three disease-modifying SMN-targeted therapies, intrathecal antisense oligonucleotide nusinersen, onasemnogene abeparvovec gene-replacement therapy and oral small-molecule splicing modifier risdiplam, particularly when initiated pre-symptomatically[10,11,12]. However, real-world and post-marketing data show that a significant proportion of treated patients still have residual weakness, incomplete motor recovery, plateauing of function and disease progression in non-neuronal tissues, while access to treatment is limited by extremely high cost, invasive administration and the need for early diagnosis[11,12,13,14].

The lack of a complete therapeutic floor has generated increasing interest in pharmacological strategies that are SMN-independent and/or adjunctive and can modulate the secondary pathogenic cascades—oxidative stress, neuroinflammation, mitochondrial dysfunction, aberrant proteostasis, and skeletal muscle atrophy—which amplify neurodegeneration once SMN levels drop below a critical threshold[6,7,8]. Quercetin, a common dietary flavonol, is one of the candidate phytochemicals investigated for this purpose, and has received significant interest because a seminal mechanistic study directly involved a quercetin-modulated pathway -- ubiquitin homeostasis and β -catenin signalling -- in SMA neuromuscular pathology, and because pharmacological β -catenin inhibition with quercetin attenuated disease phenotypes in zebrafish, Drosophila and mouse models of SMA[6,7].

Here, we collate the scattered literature linking quercetin pharmacology to SMA pathobiology. It synthesises (i) the molecular pathophysiology of SMA, (ii) the multi-target pharmacology of quercetin, (iii) direct and indirect pre-clinical evidence relating quercetin to SMN-related and SMN-independent disease pathways, (iv) the pharmaceutical limitations that currently hinder its clinical translation, (v) nanotechnology-based strategies to overcome these limitations, and (vi) a proposed translational roadmap for evaluating quercetin as an adjunctive neuroprotective therapy in SMA.

2. Spinal Muscular Atrophy: Epidemiology, Genetics and Pathophysiology

2.1 Epidemiology and clinical classification

SMA occurs in an estimated 1 in 6000–10,000 live births and the carrier frequency is around 1 in 40–60 in most populations [2,3]. SMA is classified clinically into Types 0–IV according to the age of onset of symptoms and the highest motor milestone achieved. This phenotypic spectrum is inversely correlated with the copy number of the modifying gene SMN2 [3, 4]

SMA Type	Onset	Typical SMN2 copies	Highest motor function	Untreated prognosis
Type 0	Prenatal	1	None; severe hypotonia, respiratory failure at birth	Death within weeks
Type I (Werdnig–Hoffmann)	0–6 months	2	Never sits independently	Death/ventilator-dependence by 2 years
Type II	6–18 months	3	Sits independently, never walks	Survival into adulthood with disability
Type III (Kugelberg–Wielander)	Childhood/adolescence	3–4	Walks independently (may lose ambulation)	Normal-to-reduced lifespan
Type IV	Adulthood	4–5+	Normal ambulation, mild proximal weakness	Normal lifespan

Table 1 . Spinal muscular atrophy classification according to phenotype and SMN2 copy number [2,3,4].

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2.2 Molecular genetics: the SMN1/SMN2 axis

About 95% of SMA cases are caused by homozygous deletion or conversion of SMN1 exon 7, resulting in the loss of production of stable, full-length SMN protein[3,5]. Humans have the paralogue SMN2, which differs from SMN1 by a single C to T transition in exon 7, which disrupts an exonic splicing enhancer. As a result, ~90% of SMN2 transcripts undergo exon 7 skipping to produce a truncated protein product (SMN Δ 7) that is rapidly degraded; only ~10% of transcripts produce functional full-length SMN[3,5,6]. The copy number of SMN2 varies and inversely correlates with disease severity, thus constituting both a natural genetic modifier and the primary molecular target of all three approved disease-modifying drugs (Figure 1).

Figure 1. Molecular pathophysiology of spinal muscular atrophy (SMA)

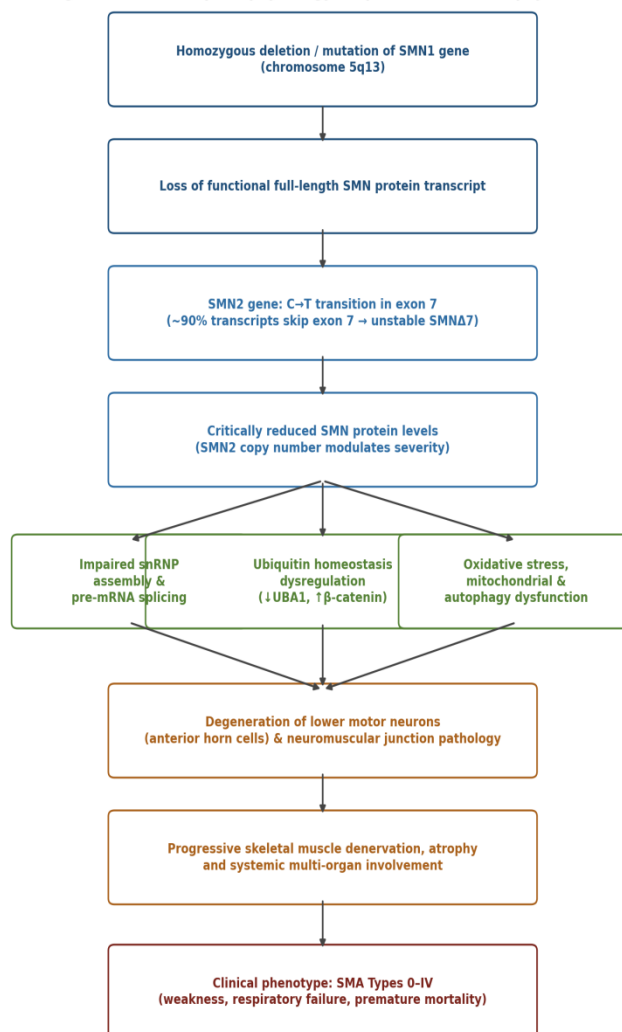


Figure 1. Molecular pathophysiology of spinal muscular atrophy: from SMN1 loss to clinical phenotype [3, 5,6,7,8]

2.3 Downstream Pathogenic Mechanisms: SMN and Beyond

Critical SMN deficiency causes a cascade of secondary, SMN-independent pathogenic events directly relevant to the pharmacology of quercetin. Wishart et al showed disruption of ubiquitin homeostasis in the SMA mouse spinal cord, including a decrease in ubiquitin-like modifier activating enzyme 1 (UBA1) which physically interacts with SMN in neurones, and suppression of UBA1 alone was sufficient to cause a SMA-like neuromuscular phenotype in zebrafish[6]. Pharmacological or genetic reversal of this accumulation ameliorated neuromuscular pathology in *Drosophila*, zebrafish and mouse models robustly, due to loss of UBA1-dependent ubiquitination leading to pathological accumulation of β -catenin[6,7].

Furthermore, in addition to the ubiquitin– β -catenin axis, SMA pathology is further exacerbated by neuromuscular junction (NMJ) dysfunction, with pre-synaptic denervation often occurring before overt motor-neuron cell death[8]; impaired mitochondrial bioenergetics and increased oxidative stress in motor neurones and skeletal muscle; and dysregulated autophagic and apoptotic signalling contributing to both neuronal loss and muscle fibre atrophy[8,38,39]. These SMN-independent mechanisms are the very molecular nodes where the best-characterised pharmacological actions of quercetin take place (see Section 5), and this is the main mechanistic rationale for its assessment as an adjunctive therapy.

3.The Present Therapeutics Arena and Rationale of Adjunctive Therapy

At present, there are three approved SMN-targeted therapies for SMA (Table 2). Each has led to clinically meaningful improvements in survival and motor function, particularly when provided early, before symptom onset[10,11,13]. However, none is curative, and significant gaps remain: plateauing or incomplete motor gains in patients treated later, the need for repeated invasive administration (nusinersen), a narrow therapeutic and immunological window for one-time gene therapy (onasemnogene abeparvovec), the theoretical risk of off-target splicing effects of a systemically distributed small molecule (risdiplam) and treatment costs among the highest of any approved medicine, limiting global access[11,12,14,15].

Therapy	Class / mechanism	Route	Key trials	Principal limitations
Nusinersen (Spinraza®)	Antisense oligonucleotide; promotes SMN2 exon-7 inclusion	Intrathecal, repeated dosing	ENDEAR, CHERISH	Invasive lifelong dosing; incomplete response in later-onset disease
Onasemnogene abeparvovec (Zolgensma®)	AAV9 gene-replacement; delivers SMN1 transgene	Single IV infusion	START, STRIVE	One-time window; immune/hepatotoxicity risk; extremely high cost
Risdiplam (Evrysdi®)	Oral small-molecule SMN2 splicing modifier	Oral, daily	FIREFISH, SUNFISH	Systemic exposure; long-term safety data still maturing

Table 2. Approved SMN-targeted disease-modifying therapies for SMA [10,11,12,13,14,15].

Such residual gaps justify the need to identify safe, orally available, low cost adjunctive agents that can act on SMN-independent neurodegenerative and myodegenerative pathways in parallel to SMN-restorative therapy; a role for which multi-target phytochemicals such as quercetin are increasingly being considered[6,16,22].

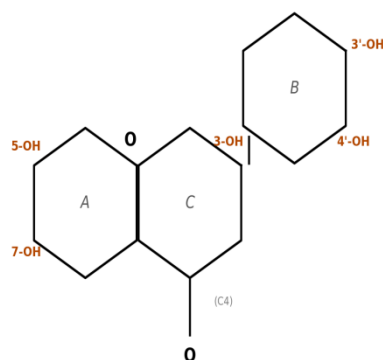
4. Quercetin: A multi-faceted dietary flavonoid

4.1 Chemistry and Natural Occurrence

Quercetin (3,3',4',5,7-pentahydroxyflavone; C₁₅H₁₀O₇; molecular weight 302.24 g/mol) is a flavonol subclass polyphenol that is abundant in onions, apples, berries, grapes, citrus fruits, broccoli, capers and tea[16,17]. Its pharmacophore (Figure 2) — a B-ring with a catechol moiety, a 2,3-double bond conjugated to the 4-carbonyl and hydroxyl groups at positions 3, 5 and 7 — is responsible for its potent metal-chelating and free-radical-scavenging capacity and for most of its downstream signal-modulating activity[16,20].

Figure 2. Schematic structure and key pharmacophoric features of quercetin

Catechol (3',4'-diOH) B-ring and 3-OH/4-oxo/5-OH system enable metal chelation, hydrogen-bond donation and radical scavenging (antioxidant pharmacophore)



Quercetin (3,3',4',5,7-pentahydroxyflavone)
Molecular formula: C₁₅H₁₀O₇ | Molecular weight: 302.24 g/mol

Fig. 2. Quercetin schematic structure showing the antioxidant pharmacophore [16,20]

4.2 General Pharmacological Profile

Quercetin has a remarkably wide range of pharmacological properties, such as antioxidant, anti-inflammatory, anti-apoptotic, antiviral, cardioprotective, anti-diabetic and, most importantly here, neuroprotective and myo-protective activity

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[17,36]. Consistent systematic and mechanistic reviews across Alzheimer's, Parkinson's, Huntington's disease, multiple sclerosis and stroke models identify a recurring set of molecular targets – Nrf2/ARE, NF- κ B, PI3K/Akt, MAPK, AMPK and SIRT1 – through which quercetin exerts convergent cytoprotective effects on neurons[18,19,22], providing strong mechanistic plausibility for extrapolation to the motor-neuron and skeletal-muscle pathology of SMA.

5. Molecular mechanisms of quercetin in the SMA pathobiology

Quercetin is not a single receptor drug but modulates a network of interrelated survival pathways (Figure 3), several of which map directly to the secondary pathogenic mechanisms of SMA described in Section 2.3.

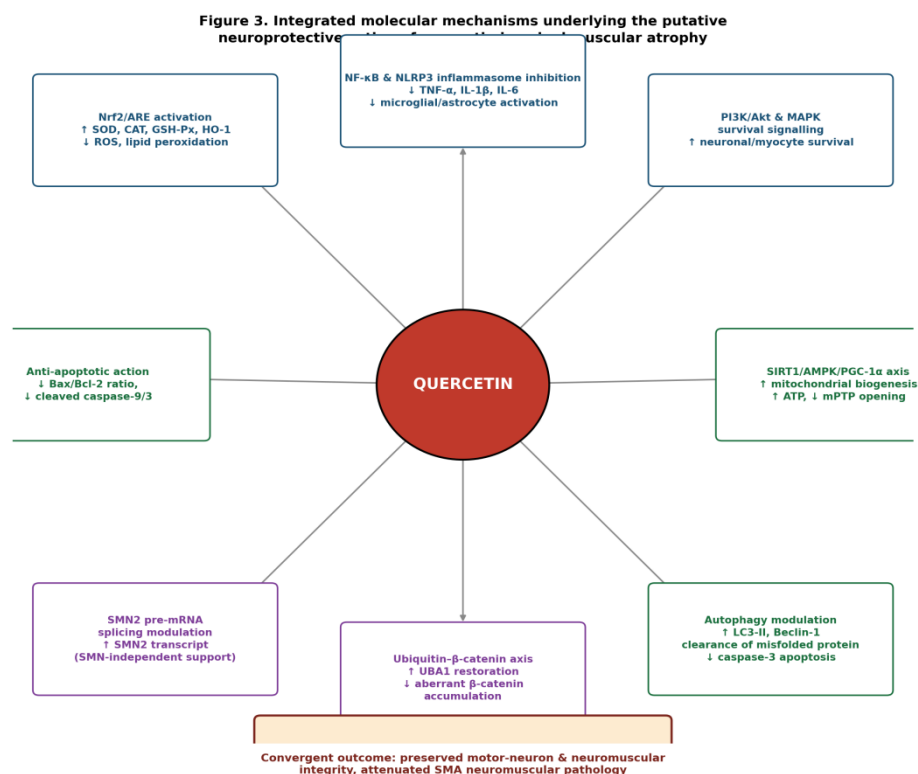


Figure 3. Integrated molecular mechanisms of the potential neuroprotective activity of quercetin in SMA [6,7,9,17,18,19,20,21,22,23,24,25,26,27,28,38,39].

5.1 Nrf2/ARE pathway in antioxidant function

Quercetin activates nuclear factor erythroid 2-related factor 2 (Nrf2) to translocate to the nucleus and bind to the antioxidant response element, increasing the production of the endogenous antioxidant enzymes superoxide dismutase (SOD), catalase, glutathione peroxidase and haeme oxygenase-1 (HO-1), which in turn reduces reactive oxygen species and lipid peroxidation[18,19,20]. Quercetin and chitosan-nanoencapsulated quercetin normalised the levels of glutathione, malondialdehyde and pro-inflammatory cytokines in cyclophosphamide-induced oxidative brain injury through Nrf2/HO-1/Keap1 signalling[20]. Isoquercitrin/quercetin also protected HT22 hippocampal neurones against glutamate-induced oxidative death through Nrf2/HO-1 activation[21]. This pathway is directly relevant to disease-modifying potential as oxidative stress is a known contributor to motor-neuron vulnerability in SMA[8].

5.2 Anti-neuroinflammatory effect through NF- κ B and NLRP3 inflammasome Quercetin inhibits nuclear translocation of NF- κ B and subsequent transcription of TNF- α , IL-1 β and IL-6 and reduces activation of microglia and astrocytes in neurodegenerative models[17, 18]. The NLRP3 inflammasome is a known driver of inflammation-associated atrophy in skeletal muscle via pyroptosis through caspase-1 activation and activation of the ubiquitin–proteasome system[39] and quercetin has been shown to mitigate obesity-induced skeletal muscle inflammation and atrophy through inhibition of inflammatory receptor signalling[38]. This anti-inflammatory, anti-atrophic effect is mechanistically important for the peripheral, non-neuronal component of the disease because inflammation associated with denervation contributes to muscle wasting in SMA.

5.3 PI3K/Akt and MAPK survival signalling

Quercetin modulates phosphoinositide-3-kinase (PI3K)/Akt/protein kinase B signalling to promote neurogenesis and inhibit glycogen synthase kinase-3 β (GSK-3 β)-mediated pro-apoptotic signalling, and MAPK/ERK and CREB cascades[17,20,22]. GSK-3 β and β -catenin turnover are functionally interlinked, these convergent survival pathways complement the ubiquitin- β -catenin mechanism described below.

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5.4 SIRT1/AMPK/PGC-1 α axis-mediated mitochondrial protection

Sirtuin-1 (SIRT1) has been demonstrated to be a key mediator of the cytoprotective effect of quercetin and acts as an antioxidant (SIRT1/Keap1/Nrf2/HO-1), anti-inflammatory (SIRT1/NF- κ B), mitochondrial biogenesis (SIRT1/PGC-1 α) and autophagy (SIRT1/FoxO, SIRT1/AMPK) responses[23]. Quercetin activated AMPK/SIRT1 signalling in models of osteoarthritis and retinal degeneration, improving mitochondrial membrane potential, ATP production and mitochondrial copy number and reducing reactive oxygen species by deacetylation of SOD2[26,27], mechanisms directly relevant to the mitochondrial bioenergetic deficits documented in SMA motor neurones and muscle[8].

5.5 Regulation of autophagy and apoptosis

Quercetin has an effect on autophagic flux in a context-dependent manner, generally playing a cytoprotective role, inducing the expression of LC3-II and beclin-1, the clearance of misfolded or aggregated proteins through SIRT1/AMPK-dependent autophagy and downregulating the Bax/Bcl-2 ratio and cleaved-caspase-3/9 activity to limit apoptosis[24,25,28]. Autophagy–apoptosis balance pharmacological tuning may also be a plausible avenue of benefit, since the excessive apoptosis of motor neurones and defective proteostasis are both implicated in SMA pathogenesis[6,8].

5.6 SMA-specific evidence: the ubiquitin– β -catenin axis and SMN2 modulation

The most direct mechanistic link between quercetin and SMA is predicated on the work of Wishart et al. who demonstrated that SMN-dependent loss of UBA1 results in pathological β -catenin accumulation that drives neuromuscular pathology, and that pharmacological inhibition of β -catenin signalling, using quercetin, a cell-permeable flavonoid β -catenin/TCF pathway inhibitor, robustly improved neuromuscular phenotypes in Drosophila, zebrafish and mouse models of SMA[6,7].

Separately, Uzunalli et al. investigated the direct effect of quercetin on SMN2 gene expression in fibroblasts from two SMA type I patients and found that quercetin increased SMN2 mRNA by up to four-fold, but this transcriptional increase did not translate into a similar increase in SMN protein, a difference the authors attributed to post-transcriptional regulation[9]. Combined, these findings support the therapeutic relevance of quercetin in SMA more strongly at the level of SMN-independent downstream pathology (ubiquitin– β -catenin signalling) than as a direct SMN2-inducing splicing modifier, supporting its role as an adjunctive, rather than disease-reversing, intervention.

5.7 Effects on skeletal muscle atrophy pathways

In addition to primary motor-neuron loss, SMA also presents a significant degree of skeletal muscle atrophy due to denervation and disuse. Quercetin's ability to inhibit NLRP3-inflammasome driven proteolysis and preserve muscle mass in obesity- and inflammation-induced atrophy models[38,39] suggests another peripherally mediated mechanism of potential benefit that remains specifically untested in SMA muscle.

6. Preclinical Evidence for Direct Role of Quercetin in SMA

Few studies provide direct experimental evidence of quercetin in SMA disease models (Table 3). This absence of disease-specific data, in contrast to the wealth of literature on quercetin in other neurodegenerative diseases, is a significant gap in knowledge and is discussed further in Section 9.

Study / model	Intervention	Key findings	Ref.
Fibroblasts from 2 SMA type I patients	Quercetin treatment in vitro	SMN2 mRNA upregulated up to 4-fold; SMN protein level unchanged, suggesting post-transcriptional limitation	[9]
Drosophila, zebrafish and SMN Δ 7 mouse models of SMA	Pharmacological β -catenin inhibition with quercetin	Reversal of UBA1-loss-driven β -catenin accumulation; robust amelioration of neuromuscular pathology across species	[6,7]
Zebrafish UBA1-knockdown model	Genetic/molecular restoration of UBA1 (mechanistic validation of the target pathway modulated by quercetin)	UBA1 suppression alone reproduced an SMA-like neuromuscular phenotype, confirming pathway relevance	[6]

Table 3. Summary of preclinical studies directly linking quercetin or its target pathway to SMA models [6,7,9].

7. Pharmacokinetic and Pharmaceutical Limitations

Notwithstanding the favourable pharmacology, the clinical translation of quercetin is essentially hindered by unfavourable biopharmaceutical properties. Quercetin is a BCS Class II/IV drug with very low aqueous solubility (~0.01–0.1 mg/mL)[29,34]. Only a small proportion of the oral dose reaches the portal circulation unchanged, with estimates of absorption as low as 6–7%, with most being lost to intestinal metabolism[35]. The absorbed fraction undergoes extensive first-pass glucuronidation, sulfation and methylation in the intestine and liver. Circulating quercetin is almost entirely in the form of conjugated metabolites

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(principally quercetin-3-glucuronide and quercetin-3'-sulfate) with biological activity distinct from the parent aglycone[35]. In human pharmacokinetic studies, quercetin exhibits a short terminal half-life of 2-4 hours and high variable clearance after oral administration [34,35]. The penetration of intact quercetin into the blood-brain barrier (BBB) is limited, and therefore the exposure to the central nervous system (CNS) is limited at conventional oral doses [30,31]. These limitations are shown in Figure 4.

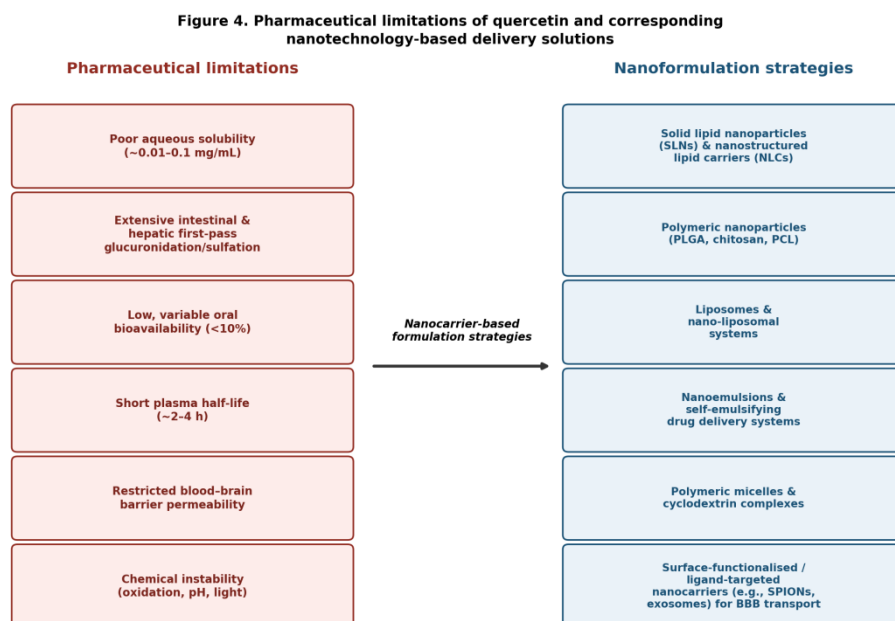


Figure 4. Pharmaceutical limitations of quercetin and its delivery solutions based on nanotechnology [29,30,31,32,33,34,35,36,37].

8. Nanotechnology Based Delivery Strategies for CNS Targeted Quercetin

To address these challenges, various nanocarrier systems have been investigated in order to improve quercetin solubility, protect it from first-pass metabolism, extend systemic exposure and, importantly for a neuroprotective indication, enhance BBB penetration (Table 4).

Nanocarrier platform	Representative system	Reported benefit	Ref.
Solid lipid nanoparticles (SLN)	Compritol/Tween-80 quercetin SLN (i.v.)	Particle size <200 nm, ~86% entrapment; improved brain delivery and behavioural outcomes in an Alzheimer's rat model	[29]
Polymeric nanoparticles	PCL quercetin–biapigenin nanoparticles	Enhanced apparent BBB permeability versus free compound; reduced cytotoxicity	[30]
Liposomes / modified liposomes	Menthol-modified and glucose-modified quercetin liposomes	Superior BBB penetration and brain accumulation versus free/standard quercetin	[31]
Nanoemulsions	Quercetin nanoemulsion (QCNE)	Improved solubility and BBB penetration; enhanced neuroprotective activity	[31]
Superparamagnetic iron-oxide nanoparticles (SPIONs)	Quercetin–SPION conjugate (oral)	Significantly higher plasma and brain quercetin concentration versus free quercetin	[33]
Exosomes / functionalised nanocarriers	Exosome-loaded quercetin (Exo-Que)	Markedly enhanced BBB penetration and particle stability	[31,32]

Table 4. Nanoformulation strategies developed to enhance quercetin bioavailability and CNS delivery [29–37].

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Collectively, these nanoformulation strategies have shown improved brain accumulation, prolonged release and diminished susceptibility to efflux transporters(ABCB1/ABCG2) and first-pass conjugation as compared to free quercetin[31,37]. However, none have been specifically designed or tested for spinal-cord targeted delivery relevant to SMA, a clear translational opportunity discussed in Section 10.

9. Translational Challenges and Knowledge Gaps

There are several important gaps that need to be filled before quercetin can be considered a rational adjunctive therapy for SMA. First, direct experimental evidence is limited to a single in vitro fibroblast study and pathway-level validation in non-mammalian and mouse models[6,7,9]; pharmaceutically optimised quercetin formulations have not been tested in dedicated dose–response and efficacy studies in established SMA mouse models (e.g. SMN Δ 7, Taiwanese SMA mice). Secondly, the difference between SMN2 transcriptional induction and SMN protein output observed by Uzunallı et al.[9] raises the question of whether the benefit of quercetin in SMA is mainly mediated through SMN-independent pathways (ubiquitin– β -catenin, oxidative stress, mitochondrial protection) rather than SMN restoration itself, which has direct implications for how efficacy should be measured in future studies.

Third, SMA is mainly a paediatric disease, and in its most severe forms a neonatal disease; the pharmacokinetics, safety and appropriate dosing of quercetin and its nanoformulations have not been established in this vulnerable population, and juvenile toxicology data are largely lacking[34,35]. Fourth, in the absence of a validated pharmacodynamic biomarker to confirm target engagement of the ubiquitin– β -catenin pathway in living patients, an early-phase adjunctive trial could not readily discriminate a true biological effect from background variability in the natural history of treated SMA[13]. Finally, formulation standardisation, scalability and regulatory characterisation of nanocarrier-based quercetin are all still in their infancy, as are safety data for chronic paediatric administration of novel nanocarriers (SLNs, SPIONs, exosomal systems)[32,37].

10. Outlook

Direct clinical evaluation of unformulated quercetin is not the way forward to address the gaps above, but rather a staged, biomarker-driven translational strategy is needed (Figure 6).

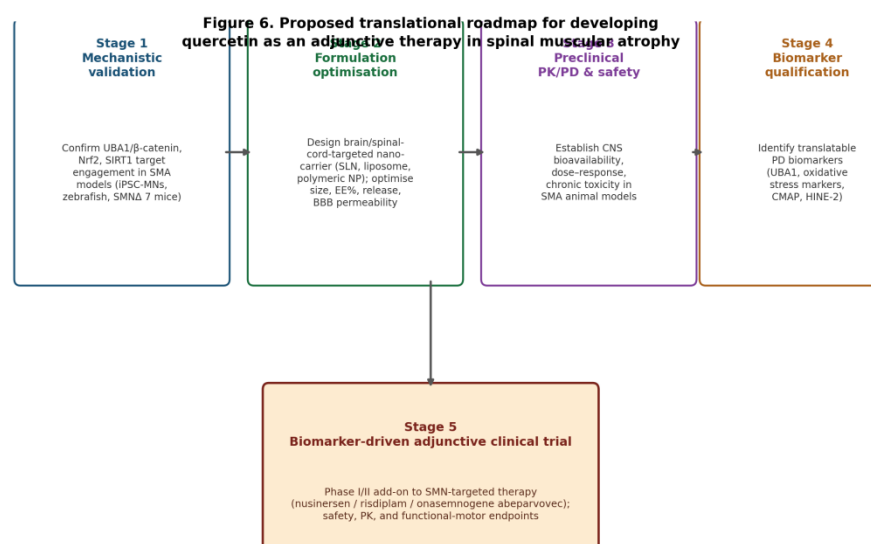


Fig. 6. Suggested translational roadmap for quercetin as adjunctive therapy in SMA.

Priorities include: (i) mechanistic confirmation of UBA1/β-catenin, Nrf2 and SIRT1 target engagement in patient-derived iPSC motor neurones and contemporary SMA mouse models; (ii) rational design of a CNS/spinal-cord-targeted quercetin nanoformulation (Section 8) with paediatric-appropriate pharmacokinetics; (iii) identification and qualification of translatable pharmacodynamic biomarkers (e.g., circulating UBA1, oxidative-stress indices, compound muscle action potential, HINE-2 motor scores) capable of detecting an adjunctive effect against a background of SMN-therapy-related improvement[13]; and (iv) design of biomarker-driven, adequately powered Phase I/II trials evaluating quercetin nanoformulations as add-on therapy to nusinersen, risdiplam or onasemnogene abeparvovec, rather than as monotherapy, reflecting its most plausible clinical niche[6,10,11].

The SMN2-copy-number-dependent severity gradient that characterises SMA (Figure 5) suggests further that any adjunctive benefit of quercetin may be most detectable, and most clinically meaningful, in intermediate-severity phenotypes (Types II–III) where residual functional reserve allows measurable modulation, and in combination with early SMN-restorative treatment in Types 0–I.

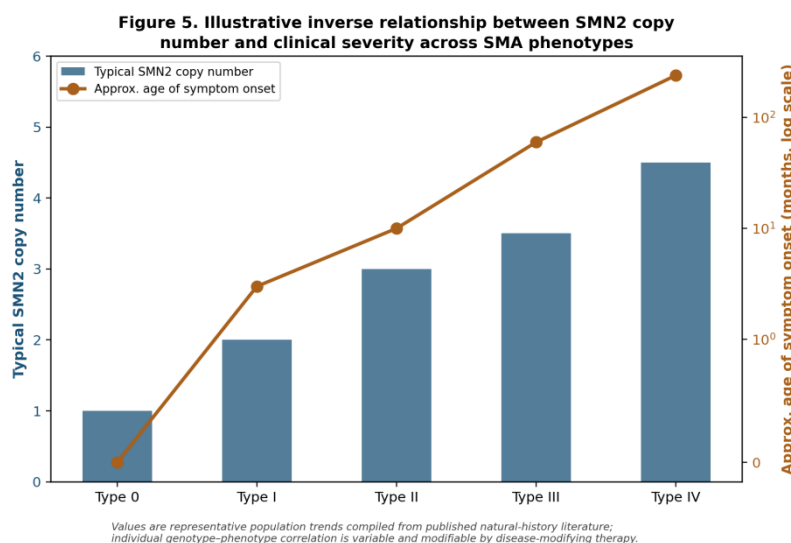


Figure 5 . [3,4] Demonstrated inverse correlation of SMN2 copy number with clinical severity in SMA phenotypes.

11. Conclusion

Quercetin is a well-characterized multi-target neuroprotective flavonoid whose effects on oxidative stress (Nrf2/ARE), neuroinflammation (NF- κ B/NLRP3), mitochondrial bioenergetics and biogenesis (SIRT1/AMPK/PGC-1 α), autophagy–apoptosis balance, and, most specifically, the UBA1– β -catenin axis directly involved in SMA pathology, provide a coherent scientific rationale for its evaluation as an adjunctive therapy in SMA . However, the evidence base specifically linking quercetin to SMA is preliminary, based on a single patient-fibroblast study and pathway-validating animal work rather than dedicated efficacy trials in optimised SMA models. Realising the translational potential of quercetin to overcome its poor solubility, low bioavailability and restricted CNS penetration will require pharmaceutical innovation, most promisingly via lipid-based and polymeric nanocarrier platforms, coupled with biomarker-driven preclinical and early clinical evaluation, always positioned as a complement to, rather than a replacement for, approved SMN-targeted disease-modifying therapy. A purposeful, staged translational program along these lines could determine if this cheap, well-tolerated dietary flavonoid has a real role in improving outcomes for patients living with spinal muscular atrophy.

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