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Quercetin as a Multi-Target Therapeutic Candidate in Amyotrophic Lateral Sclerosis: From Molecular Mechanisms to Nano-Delivery and Senolytic Strategies

Rufina Pricy S[1]*, Harini S[2], Dr. Chamundeeswari M[3]

Department of Biotechnology, St. Joseph's College of Engineering, Chennai, Tamil Nadu 600119, India
*Corresponding author: rufinaastephen@gmail.com

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that destroys motor neurons, leading to progressive paralysis and death usually within 2–5 years. Current drugs such as riluzole and edaravone offer only modest benefit, making new treatments urgently needed. Quercetin, a natural plant-derived flavonoid found in everyday foods, acts on multiple disease mechanisms at once — it fights oxidative stress, reduces neuroinflammation, prevents toxic protein clumping, protects mitochondria, and can even selectively destroy harmful senescent cells ("zombie" cells) that drive inflammation in the spinal cord. However, quercetin poorly dissolves in water, is rapidly broken down in the gut and liver, and barely crosses the blood-brain barrier (BBB). This review explains what makes quercetin scientifically promising for ALS, how nano-engineered drug carriers such as PLGA nanoparticles, lipid carriers, and exosomes can overcome these delivery problems, and how combining quercetin with the senolytic drug dasatinib might slow ALS progression. Key research gaps and steps needed before quercetin-based therapies can enter clinical trials for ALS patients are also discussed.

Keywords: *Amyotrophic lateral sclerosis; quercetin; neuroprotection; neuroinflammation; oxidative stress; TDP-43; SOD1; Nrf2/ARE; blood-brain barrier; nano-delivery; PLGA nanoparticles; senolytics; senescence; dasatinib; polyphenol; flavonoid*

1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) — also known as Lou Gehrig's disease or motor neuron disease — is a progressive and invariably fatal neurological condition. [1] It was first described by the French neurologist Jean-Martin Charcot in 1869 and is characterised by the gradual death of both upper motor neurons (in the brain) and lower motor neurons (in the brainstem and spinal cord). [2] As these neurons die, patients lose the ability to move, speak, swallow, and eventually breathe, with death typically occurring within 2–5 years of onset. [1,2]

ALS affects approximately 2–3 people per 100,000 every year worldwide, with over 200,000 patients living with the disease at any given time. [1] Around 90% of ALS cases are sporadic (no clear family history), while the remaining 10% are familial, caused by mutations in genes such as *C9orf72*, *SOD1*, *TARDBP* (encoding TDP-43), and *FUS*. [3] Despite intense research, the only widely available treatments are riluzole (approved 1995), edaravone (approved 2017), and the more recent AMX0035 — none of which halt or reverse the disease. [4]

ALS is not caused by a single defect but by many interacting problems at the same time. These include: excessive free radicals damaging cells (oxidative stress), chronic inflammation driven by overactivated immune cells in the brain (neuroinflammation), nerve cells being overstimulated by glutamate (excitotoxicity), faulty energy production by mitochondria, and the accumulation of misfolded proteins that clump

together and poison cells. [5,6,7] This complexity means a treatment that hits only one target is unlikely to make a significant difference — and helps explain why so many clinical trials have failed.

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a naturally occurring plant compound (flavonoid polyphenol) found in everyday foods such as onions, apples, berries, capers, and green tea. [5] What makes quercetin particularly exciting for ALS is that it simultaneously addresses almost every one of the disease mechanisms listed above. It is a powerful antioxidant, an anti-inflammatory agent, an inhibitor of toxic protein aggregation, a protector of mitochondria, and — uniquely among natural compounds — a senolytic agent that can selectively destroy the harmful zombie cells whose inflammatory secretions worsen ALS. [6,7,8]

Despite its impressive biological profile, quercetin faces a fundamental clinical challenge: it is very poorly absorbed, rapidly metabolised in the liver and gut, and barely enters the brain due to the BBB. [9] To solve this, scientists are engineering tiny drug-delivery vehicles — nanoparticles — that protect quercetin, carry it through the bloodstream, and smuggle it across the BBB into the spinal cord and brain where it is needed most. [8,10]

This review is written for undergraduate students and early-career researchers. It explains, in plain terms, the science behind ALS, how quercetin works against each disease mechanism, how nanoparticles can be designed to deliver it to the brain, and how senolytic strategies using quercetin and dasatinib could represent a new class of ALS therapy. Key knowledge gaps and what must be done before this approach reaches patients are also highlighted. [10]

2. PATHOPHYSIOLOGY OF ALS: WHAT GOES WRONG?

2.1 Oxidative Stress and Antioxidant Failure

Every cell in the body produces small amounts of reactive oxygen species (ROS) — chemically unstable molecules sometimes called "free radicals" — as a normal by-product of energy metabolism. [11] Under healthy conditions, antioxidant enzymes such as superoxide dismutase 1 (SOD1), catalase, and glutathione peroxidase neutralise these molecules before they can cause harm.

In ALS, this balance is broken. Motor neurons face an unusually high ROS load while their antioxidant capacity is diminished. [11,12] The most direct evidence comes from SOD1 mutations: over 180 different mutations in the *SOD1* gene have been identified in familial ALS. [3] Mutant SOD1 protein does not just lose its antioxidant function — it gains a toxic new function, producing harmful hydroxyl radicals through abnormal chemical reactions and misfolds into shapes that damage mitochondria. [12]

One of the cell's most important protective responses to oxidative stress is the Nrf2/ARE pathway. Nrf2 is a transcription factor that, when activated, travels to the nucleus and switches on a battery of protective genes (including HO-1, NQO1, and glutathione-synthesising enzymes). [11] In ALS motor neurons, Nrf2 activity is significantly reduced, meaning the cell cannot mount an adequate defence against oxidative damage. This makes Nrf2 a prime drug target. [12]

2.2 Neuroinflammation: Microglia and Astrocytes

The brain and spinal cord have their own immune cells — microglia (the resident macrophages of the CNS) and astrocytes (support cells that normally protect neurons). [13] In early ALS, these cells try to be helpful, secreting anti-inflammatory signals and trophic factors that protect motor neurons. As disease progresses, however, they become chronically overactivated in a harmful state, flooding the spinal cord with pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. [6,13]

This chronic inflammation is driven primarily through the NF-κB signalling pathway, which acts like a master switch for pro-inflammatory gene expression. [14] In ALS spinal cords, NF-κB is

constitutively (always) switched on in both neurons and glia, creating a sustained inflammatory environment that directly damages motor neurons. [6,14]

ALS astrocytes also lose their housekeeping function: they reduce their expression of the EAAT2 glutamate transporter, meaning they no longer efficiently clear glutamate from synapses — a key driver of the excitotoxicity discussed in the next section. [13] Patient-derived ALS astrocytes have been shown in laboratory experiments to actively secrete toxic factors that kill motor neurons — an alarming finding because it means astrocytes themselves become part of the disease process. [13]

2.3 Excitotoxicity

Excitotoxicity refers to neuronal death caused by excessive stimulation through the neurotransmitter glutamate. [9] Motor neurons are particularly vulnerable because they carry high densities of calcium-permeable glutamate receptors (AMPA receptors lacking the GluA2 subunit) and have relatively limited calcium-buffering capacity. [9] When glutamate builds up in the synapse (partly due to impaired astrocyte clearance), it overstimulates these receptors, flooding the neuron with calcium ions. This calcium overload activates destructive enzymes — proteases, lipases, and nucleases — triggers mitochondrial breakdown, and initiates programmed cell death (apoptosis). [4,9]

This mechanism is already the therapeutic target of riluzole, which reduces glutamate release. However, riluzole only modestly slows disease progression, suggesting that excitotoxicity must be tackled alongside other pathological mechanisms simultaneously. [4]

2.4 Protein Misfolding and Aggregation

A hallmark of ALS at the microscopic level is the presence of abnormal protein clumps (inclusions) inside motor neurons and their supporting cells. [7] The most important of these involves TDP-43 (TAR DNA-binding protein 43), an RNA-binding protein that is normally found in the nucleus. In approximately 97% of all ALS cases, TDP-43 mislocalises from the nucleus into the cytoplasm, where it becomes chemically modified (phosphorylated and cleaved) and forms toxic fibrillar inclusions. [7] These inclusions disrupt RNA processing and are directly toxic to cells.

Other important aggregating proteins in ALS include FUS (Fused in Sarcoma), which forms inclusions in approximately 5% of familial ALS cases, and mutant SOD1, whose misfolded forms aggregate in SOD1-linked familial ALS. [7,3] Cells have quality-control systems — molecular chaperones (heat shock proteins) and the autophagy pathway — to handle misfolded proteins, but these systems are overwhelmed in ALS, allowing toxic aggregates to accumulate. [15,16]

2.5 Mitochondrial Dysfunction

Mitochondria are the energy factories of the cell, and motor neurons — among the most metabolically demanding cells in the body — are highly dependent on mitochondrial function. [17] In ALS, mitochondria in motor neurons show numerous abnormalities: their internal membranes (cristae) are disrupted, their electron transport chain activity is reduced (especially complexes I and IV), ATP production falls, and ROS generation increases. [17,18] Mutant SOD1 protein physically accumulates on mitochondrial membranes, impairing their function. The mitochondrial permeability transition pore (mPTP) — a channel that, when opened, collapses the mitochondrial membrane potential and releases death signals — is a key mediator of motor neuron death in ALS. [18,19]

3. QUERCETIN: A MULTI-TARGET NATURAL COMPOUND

3.1 What is Quercetin?

Quercetin (molecular formula $C_{15}H_{10}O_7$, molecular weight 302 Da) is a yellow-pigmented flavonoid

polyphenol belonging to the flavonol subclass. [5] It is found in abundance in everyday plant foods — onions, apples, capers, berries, green tea, broccoli, and various traditional medicinal herbs. [5] Structurally, its key feature is a catechol group (two adjacent hydroxyl groups) on its B-ring, combined with a conjugated double-bond system, which together give it exceptional ability to neutralise free radicals. [5,20]

What makes quercetin stand out from most natural compounds is that it does not just do one thing — it simultaneously engages multiple cellular pathways relevant to ALS. This is exactly what a disease as complex as ALS requires. [6] Table 1 below summarises quercetin's key mechanisms in ALS alongside the pathological process each one targets.

Table 1. Summary of ALS Pathological Mechanisms and Quercetin's Therapeutic Actions

Oxidative stress	Excess ROS damages motor neurons; SOD1 mutations impair antioxidant defence	Scavenges ROS; activates Nrf2/ARE pathway; upregulates HO-1 and NQO1	[1,5,11,12]
Neuroinflammation	Activated microglia/astrocytes release TNF-α, IL-1β, IL-6 via NF-κB	Inhibits IKK/NF-κB; suppresses NLRP3 inflammasome; reduces COX-2	[6,13,14]
Protein aggregation	TDP-43, FUS, SOD1 misfold into toxic cytoplasmic inclusions	Inhibits fibril formation; induces HSP70/HSP90 chaperones; promotes autophagy	[7,15,16]
Excitotoxicity	Excess glutamate overactivates AMPA/NMDA receptors; Ca^{2+} overload kills neurons	Upregulates EAAT2 transporter; blocks Ca^{2+} channels; reduces caspase-3	[4,9,20]
Mitochondrial dysfunction	Impaired electron transport, reduced ATP, fragmented mitochondria	Inhibits mPTP; activates SIRT1-PGC-1α; promotes PINK1/Parkin mitophagy	[17,18,19]
Cellular senescence (SASP)	Senescent astrocytes/microglia secrete neurotoxic IL-6, IL-8, MMP-3	Senolytic: eliminates senescent cells by inhibiting PI3K/Akt and BCL-2/BCL-XL	[22,23,24]

ROS = Reactive Oxygen Species; SASP = Senescence-Associated Secretory Phenotype; EE = Encapsulation Efficiency

3.2 Antioxidant Action: Activating the Nrf2/ARE Pathway

Quercetin is one of the most potent natural antioxidants known. [5] It works in two ways: (1) directly, by donating hydrogen atoms to neutralise ROS and chelating (binding) metal ions like Fe^{2+} and Cu^{2+} that would otherwise generate more free radicals; and (2) indirectly, by switching on the cell's own antioxidant defence systems. [11,12]

The indirect mechanism is arguably more important. Quercetin modifies specific cysteine residues on the Keap1 protein — the "gatekeeper" that normally keeps Nrf2

switched off. [11] By doing this, quercetin frees Nrf2 to travel into the nucleus, where it activates the Antioxidant Response Element (ARE) and switches on the production of protective proteins including HO-1 (haem oxygenase-1), NQO1 (an antioxidant enzyme), and glutathione-synthesising enzymes. [12] In SOD1-G93A transgenic mice (the most widely used animal model of familial ALS), quercetin treatment significantly reduces markers of oxidative damage in the spinal cord and upregulates Nrf2/HO-1 signalling. [12,21]

3.3 Anti-Inflammatory Action: Blocking NF-κB

Quercetin suppresses the NF-κB pathway — the main driver of chronic neuroinflammation in ALS — by inhibiting IKK, the enzyme that kicks off NF-κB activation. [6,14] Without IKK activity, the inhibitory protein IκBα is not broken down, so NF-κB remains trapped in the cytoplasm and cannot reach the nucleus to switch on inflammatory genes. [14] The end result is a significant reduction in the production of TNF-α, IL-1β, IL-6, NO, and COX-2 by microglia and astrocytes.

Additionally, quercetin inhibits the NLRP3 inflammasome — a multiprotein complex that activates caspase-1 and triggers the release of particularly potent inflammatory cytokines (IL-1β and IL-18). [6] The NLRP3 inflammasome is increasingly recognised as a contributor to ALS neuroinflammation, making quercetin's ability to suppress it an important mechanistic advantage. [13,14]

3.4 Anti-Aggregation and Proteostasis Enhancement

Quercetin directly interacts with the misfolded forms of TDP-43 and SOD1, binding to their hydrophobic regions and inhibiting the nucleation and growth of toxic protein fibrils. [15,16] Computational modelling studies (molecular docking) suggest that quercetin binds to the RNA recognition motifs of TDP-43, interfering with the protein-protein interactions that drive pathological aggregation. [15]

Beyond this direct effect, quercetin also boosts the cell's protein quality-control systems. It activates heat shock factor 1 (HSF1), which in turn increases the production of molecular chaperones — HSP70 and HSP90 — that act like cellular "repair technicians", refolding misfolded proteins before they can aggregate. [15,16] Quercetin also promotes autophagy (the cell's recycling system for damaged proteins and organelles) by inhibiting mTORC1 and activating the AMPK-ULK1 pathway. [16] In cell culture models expressing ALS-linked TDP-43 mutations, quercetin treatment significantly reduces cytoplasmic TDP-43 inclusions and improves cell survival. [15]

3.5 Neuroprotection Against Excitotoxicity

Quercetin targets excitotoxicity through multiple angles. Most importantly, it upregulates the expression of EAAT2 — the main glutamate transporter on astrocytes — thereby restoring the normal clearance of glutamate from the synapse. [9,20] This is particularly relevant because EAAT2 is downregulated in ALS astrocytes, and its loss is a major driver of excitotoxic motor neuron death. [9]

Quercetin also inhibits voltage-gated calcium channels, reducing the calcium influx that triggers the cascade of neurotoxic events. [20] In motor neuron cultures exposed to toxic glutamate doses, quercetin pretreatment significantly reduces calcium

overload, preserves mitochondrial membrane potential, and reduces caspase-3 activation (a marker of cell death). [9,20]

3.6 Mitochondrial Protection

Quercetin preserves mitochondrial health through several mechanisms. [17,18,19] First, it inhibits the opening of the mPTP, which, if opened, rapidly kills the cell by collapsing the mitochondrial membrane potential and releasing death signals such as cytochrome c. [17] Second, it activates the SIRT1-PGC-1α-TFAM signalling axis, which stimulates the growth of new mitochondria (mitochondrial biogenesis) and improves overall respiratory capacity. [18] Third, it promotes mitophagy — the selective removal of damaged mitochondria by the cell's autophagy system — through activation of the PINK1/Parkin pathway. [19] In SOD1-G93A cell models, quercetin restores complex I activity, improves oxygen consumption, and reduces apoptotic markers. [19,21]

4. SENOLYTIC PROPERTIES OF QUERCETIN IN ALS

4.1 What is Cellular Senescence?

Cellular senescence is a state in which a damaged cell permanently stops dividing but refuses to die. [22] Think of it as a cell going into "retirement" — it stops working properly but stays in the tissue, releasing a constant stream of inflammatory signals. This collection of secreted molecules is called the Senescence-Associated Secretory Phenotype, or SASP. [22,23] The SASP includes cytokines (IL-6, IL-8, IL-1β), matrix metalloproteinases, and growth factors that create a toxic environment for neighbouring healthy cells.

Senescent cells are defined by a set of molecular markers: upregulation of p21*CIP1/WAF1* and p16*INK4a* (cell cycle arrest proteins), enlarged and flattened cell morphology, resistance to apoptosis (programmed death), and the SASP. [22] Cells can enter senescence due to DNA damage, oxidative stress, telomere shortening, or oncogene activation — all processes that are accelerated in the ALS spinal cord microenvironment. [23]

4.2 Senescent Cells in ALS

Until recently, senescence was primarily studied in the context of cancer and ageing. However, accumulating evidence now implicates senescent cells as active participants in ALS pathology. [23,24] Studies in SOD1-G93A transgenic mice have identified a significant accumulation of p21+ and p16+ senescent cells in the spinal cord, with senescent astrocytes being the predominant cell type. [24]

ALS patient-derived astrocytes show markers of stress-induced senescence, including DNA damage foci at telomeres and elevated SASP production (particularly IL-6, IL-8, and MMP-3). [23] The SASP from these senescent astrocytes has been shown in laboratory experiments to be directly toxic to motor neurons — providing a clear mechanistic link between glial senescence and motor neuron death in ALS. [24] Senescent microglia also contribute to this toxic microenvironment, amplifying chronic neuroinflammation through sustained NF-κB activation. [23,24]

4.3 Quercetin as a Senolytic Drug

Senolytics are drugs designed to selectively destroy senescent cells without harming normal cells. [22] The key insight is that senescent cells upregulate specific anti-apoptotic (anti-death) survival pathways to resist dying — they become dependent on these pathways to stay alive. [22,23] If these pathways are blocked by a drug, the senescent cells are no longer protected and undergo apoptosis, while normal cells (which do not rely on these same pathways) survive. These survival pathways are called SCAPs (Senescent Cell Anti-apoptotic Pathways). [22]

In a landmark 2015 study, quercetin was identified as a potent senolytic agent. [22] Its senolytic mechanism targets SCAPs directly: quercetin

inhibits PI3K/Akt signalling (which senescent cells use to keep the pro-death protein BAD switched off), reduces expression of BCL-2 and BCL-XL (anti-death proteins), and activates p53-driven apoptosis. [22,23] The result is that senescent cells die while their normal neighbours survive. Importantly, senolytics work best when given intermittently (a few days on, then weeks off), rather than as continuous daily therapy. [22]

4.3.1 The Dasatinib + Quercetin (D+Q) Combination

Quercetin is most potent as a senolytic when combined with dasatinib, a tyrosine kinase inhibitor originally used to treat leukaemia. [22,23] Their mechanisms are complementary: dasatinib preferentially targets Src kinase-dependent SCAPs prominent in certain cell types, while quercetin targets PI3K/Akt and BCL-2 pathways. Together, they cover a broader range of SCAP networks than either drug alone. [22]

In ageing mouse models, D+Q treatment reduces senescent cell burden in multiple tissues, attenuates SASP markers, and improves physical function. [23] A first-in-human clinical trial in patients with idiopathic pulmonary fibrosis (another senescence-driven disease) showed that just 3 days of D+Q treatment measurably reduced senescent cell markers in fat tissue biopsies and improved walking performance. [23] In preliminary SOD1-G93A mouse experiments, D+Q treatment reduced senescent cell burden in the spinal cord, preserved motor neuron numbers, and modestly extended survival. [24] These results strongly support further investigation of D+Q as an ALS therapy.

5. NANO-DELIVERY STRATEGIES: GETTING QUERCETIN TO THE BRAIN

5.1 Why Does Quercetin Need a Delivery System?

Despite its outstanding pharmacological properties, quercetin faces serious obstacles when given as a conventional oral tablet or capsule. [9] First, quercetin dissolves very poorly in water (about 0.006 mg/mL at physiological pH), which means very little of it is absorbed from the gut. [9] Second, whatever does get absorbed is rapidly converted by gut and liver enzymes into conjugated metabolites (glucuronide and sulphate forms) that are far less biologically active. [9] As a result, the oral bioavailability of quercetin in humans is typically below 17% and often much less. [9]

The biggest problem for ALS, however, is the blood-brain barrier (BBB). The BBB is a highly selective barrier formed by specialised brain capillary cells joined by very tight junctions. It keeps most drugs — including quercetin — from entering the brain and spinal cord. [25] To make things worse, quercetin is a substrate for P-glycoprotein (P-gp), a molecular pump on BBB cells that actively ejects quercetin back into the bloodstream even when it does manage to cross. [9,25] The result is that very little quercetin reaches the CNS at therapeutic concentrations after conventional oral dosing.

Nanotechnology offers an elegant solution to all these problems. By encapsulating quercetin inside engineered nanoparticles (typically 50–300 nm in size), scientists can: protect quercetin from metabolism, improve solubility and absorption, extend the drug's time in the bloodstream, decorate the nanoparticle surface with molecules that trick the BBB into letting it through, and bypass P-gp efflux. [8,10] Table 2 summarises the main nano-delivery platforms used for quercetin in the context of CNS diseases including ALS.

Table 2. Nano-Delivery Platforms for Quercetin Targeting the CNS in ALS

PLGA nanoparticles	100–300 nm	Biodegradable; TfR-targeted transcytosis; sustained 7–21 day drug release	60–85%	[27,28]
Solid lipid NPs (SLN)	50–200 nm	Biocompatible lipid core; protects quercetin from oxidation; scalable production	55–78%	[29,30]
Nanostructured lipid carriers (NLC)	50–250 nm	Higher drug loading than SLN; less drug expulsion on storage; improved oral bioavailability	70–90%	[29,31]
PEGylated liposomes	80–200 nm	Stealth coating for long circulation; transferrin-conjugated form shows 4.7× higher brain AUC	50–75%	[31,32]
Exosome-based vesicles	30–150 nm	Natural BBB-crossing ability; RVG-decorated vesicles enable CNS-targeted intranasal delivery	40–65%	[33,34]
Nanoemulsions	20–200 nm	Bypasses hepatic first-pass via lymphatic absorption; greatly improves oral bioavailability	80–95%	[35]

EE = Encapsulation Efficiency; BBB = Blood-Brain Barrier; AUC = Area Under the Curve; TfR = Transferrin Receptor; RVG = Rabies Virus Glycoprotein peptide

5.2 Polymeric Nanoparticles (PLGA)

The most studied nanoparticle type for quercetin delivery is made from PLGA (poly lactic-co-glycolic acid), a biodegradable polymer already approved by the FDA for medical use. [27,28] PLGA breaks down slowly in the body into harmless lactic acid and glycolic acid, releasing its quercetin cargo in a controlled manner over 7–21 days. [27] Quercetin loading into PLGA nanoparticles achieves encapsulation efficiencies of 60–85% using methods such as nanoprecipitation or emulsion-diffusion. [27]

The major innovation for brain targeting is surface functionalisation — attaching targeting molecules to the nanoparticle surface. [28] Transferrin receptor 1 (TfR1) is highly expressed on the BBB endothelium and normally transports iron-carrying transferrin into

the brain by a process called receptor-mediated transcytosis. [28] By coating PLGA nanoparticles with transferrin or anti-TfR1 antibodies, quercetin nanoparticles can hijack this same transport route, achieving 3–5 times higher brain accumulation than non-targeted particles. [27,28] In SOD1-G93A mice, transferrin-functionalised quercetin PLGA nanoparticles achieve significantly higher spinal cord quercetin concentrations, reduce oxidative stress, and slow motor neuron loss compared to free quercetin. [21,27]

5.3 Lipid-Based Nanocarriers

Lipid-based carriers offer an alternative to polymer nanoparticles. [29,30] Solid lipid nanoparticles (SLNs) consist of a solid fat core stabilised by surfactants, with quercetin dissolved within the lipid matrix. They are easy to manufacture, biocompatible, and protect quercetin from oxidation. [29] Nanostructured lipid carriers (NLCs) are an improved version: by blending solid and liquid lipids, the resulting imperfect crystal structure holds more drug and reduces drug leakage during storage. [29,31]

PEGylated liposomes (lipid bilayer vesicles with a polyethylene glycol coating) are another important platform. [31,32] PEGylation creates a "stealth" coating that helps nanoparticles evade the immune system, extending their time in the bloodstream. [32] Transferrin-conjugated PEGylated quercetin liposomes have demonstrated 4.7-fold higher brain drug exposure compared to free quercetin in rats after intravenous administration. [32] This level of improvement could make the difference between therapeutic and sub-therapeutic CNS drug concentrations in ALS patients.

5.4 Exosomes and Intranasal Delivery

Exosomes are tiny vesicles (30–150 nm) naturally released by cells as a way of communicating with each other. [33] They have a biological membrane surface that is naturally well-tolerated by the immune system and possess an inherent ability to cross the BBB, making them highly attractive as drug carriers. [33,34] When the surface of exosomes is engineered to display the RVG peptide — which binds to receptors on brain cells — quercetin-loaded exosomes show exceptional delivery to the CNS, even when given intranasally (through the nose). [33,34]

Intranasal delivery is particularly promising for ALS because the olfactory nerve pathway provides a direct anatomical route from the nose to the brain and spinal cord, completely bypassing the BBB. [34] Quercetin-loaded chitosan-coated nanoparticles given intranasally accumulate in the olfactory bulb, brainstem, and cervical spinal cord — precisely the CNS regions most severely affected in ALS. [34,35] This non-invasive route is also well-tolerated and convenient for patients, making it an attractive option for chronic ALS therapy. [35]

6. CONCLUSIONS AND FUTURE DIRECTIONS

This review has presented the case for quercetin as a scientifically rational, multi-target treatment candidate for ALS. Unlike existing ALS drugs, which target one mechanism at a time, quercetin simultaneously addresses oxidative stress (via Nrf2 activation), neuroinflammation (via NF-κB inhibition), protein aggregation (via chaperone induction and autophagy), excitotoxicity (via EAAT2 upregulation and calcium channel modulation), mitochondrial dysfunction (via mPTP inhibition and mitophagy), and cellular senescence (via senolytic SCAP inhibition).

The senolytic angle — quercetin's ability to selectively destroy harmful senescent cells in the ALS spinal cord, particularly in combination with dasatinib — represents a genuinely novel therapeutic strategy that has not yet been adequately explored in ALS clinical trials. Given that the dasatinib + quercetin combination has already shown safety and preliminary efficacy signals in humans with other senescence-driven diseases, translation to ALS trials is a logical and timely next step.

Nano-delivery platforms — especially PLGA nanoparticles functionalised with BBB-targeting ligands and exosome-based carriers given intranasally — have convincingly demonstrated that quercetin's pharmacokinetic limitations can be overcome. Achieving therapeutic quercetin concentrations in the ALS spinal cord is now a technically reachable goal.

However, significant challenges remain. Most evidence comes from cell cultures and SOD1-G93A mice, a model that does not fully represent the heterogeneity of human ALS. Future research must include studies in C9orf72, TDP-43, and FUS models, as well as iPSC-derived human motor neuron co-culture systems. Long-term safety data on nano-formulated quercetin — including nanoparticle biodistribution, immune responses, and organ toxicity — must be generated before clinical use. Reliable biomarkers (blood or CSF-based) are needed to measure quercetin's CNS activity in patients and to monitor treatment response.

In summary, quercetin-based therapies — delivered via advanced nanoparticle systems and combined with dasatinib as a senolytic — represent one of the most scientifically coherent and therapeutically promising avenues in current ALS research. ALS patients deserve urgently accelerated, well-funded investigation of this approach. The science strongly supports moving forward.

7. STATEMENTS AND DECLARATIONS

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This review received no specific funding from any public, commercial, or not-for-profit agency. No pharmaceutical or biotechnology entity influenced the content of this review.

7.2 Conflicts of Interest

The authors declare no conflicts of interest.

7.3 Author Contributions

All listed authors contributed equally to literature search, writing, critical revision, and final approval of the manuscript (CRediT taxonomy: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Visualization).

7.4 Data Availability

No primary data were generated in this review. All data discussed are available in the original studies cited herein.

7.5 Ethical Statement

This review involved no human participants, animal experiments, or biological sample collection. No ethics approval was required.

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