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QUERCETIN AS A MULTIFUNCTIONAL METAL CHELATOR: NEUROPROTECTIVE MECHANISMS IN METAL-INDUCED NEURODEGENERATION

Ali Zarbaliyev[1], Gulnur Arabaci*[2]

[1]Chemistry, Institute Of Natural Sciences, Sakarya University, Sakarya, Turkey.

[2]Department of Chemistry, Faculty of Science, Sakarya University, Sakarya, Turkey.

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***Corresponding Author: Gulnur Arabaci**
Department of Chemistry, Faculty of Science, Sakarya University, Sakarya, Turkey.
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ABSTRACT

Relevance – A key pathogenic factor in neurodegenerative diseases, most notably Alzheimer's disease and Parkinson's disease, is the dyshomeostasis of heavy and transition metal ions, namely iron (Fe), copper (Cu), cadmium (Cd), manganese (Mn), and zinc (Zn). Heavy metals induce mitochondrial dysfunction, oxidative stress, and neuroinflammation, leading to damage to nerve cells. Synthetic chelators have a number of drawbacks: pronounced side effects, toxicity, and restricted permeability through the blood-brain barrier. This highlights the need to identify alternative, safe chelating agents. The objective of this study was to substantiate the potential of quercetin as a neuroprotective agent for future clinical trials by systematizing data on its biochemical mechanisms of heavy metal ion chelation. A literature review was conducted in the PubMed database using the keywords "the role of quercetin as a heavy metal chelator," "flavonoids as antioxidants," "neuroprotection," "heavy metal neurotoxicity," "neurodegeneration," and combinations thereof. Studies from 2017 to 2025 were analyzed, primarily those with quantitative biochemical data on metal-induced neurotoxicity. **Results –** An analysis of 17 sources revealed that quercetin chelates metals via structural elements, specifically the catechol group of the B-ring and the 3-OH/4-oxo system of the C-ring. It also exerts a neuroprotective effect by inhibiting the Fenton reaction in iron (Fe) dyshomeostasis, normalizing antioxidant status in manganese (Mn) toxicity, restoring cholinergic neurotransmission in cadmium (Cd) accumulation, and by activating the PI3K/Akt and ERK1/2 signaling pathways in copper (Cu)-induced apoptosis. Bioavailability analysis revealed that it is significantly increased upon conjugation with superparamagnetic nanoparticles (QCSPIONs) and in combination with piperine. **Practical significance:** This work establishes a theoretical basis for the development of new quercetin-containing neuroprotective drugs for heavy metal-induced neurodegenerative diseases. **Target Audience:** This work is of interest to neurologists, neurobiologists, pharmacologists, pharmacists, and biochemists involved in the study of metal-induced neurodegeneration and the development of alternative chelating agents.

KEYWORDS: Quercetin; heavy metal chelation; neuroprotection; flavonoids; metallothioneins; oxidative stress; Alzheimer's disease; Parkinson's disease.

INTRODUCTION

According to the World Health Organization (WHO), Alzheimer's disease is responsible for 60–70% of all cases of dementia on a global scale. Meanwhile, Parkinson's disease is considered the second most prevalent neurodegenerative disease. These conditions are characterized by progressive neuronal loss and the lack of effective etiological treatments.[1]

Particular attention is paid to the accumulation of heavy and transition metal ions in nervous tissues in these conditions. A large European cohort study, EPIC4PD, involving 220,494 participants from seven countries, demonstrated a link between high levels of heavy metals in the blood and the risk of developing Parkinson's disease, specifically highlighting the role of cadmium as an environmentally prevalent heavy metal.[4] Dyshomeostasis — a disruption in the balance of ions within the cell — of metals such as iron (Fe), copper (Cu), zinc (Zn), and the accumulation of toxic metals — cadmium (Cd) and manganese (Mn) — lead to multiple cellular dysfunction:, protein aggregation, mitochondrial dysfunction, oxidative stress and neuroinflammation.[1] Iron and zinc levels exceed normal ranges in the substantia nigra in Parkinson's disease, while copper levels are, conversely, reduced.[2] It has been established that iron, copper, and zinc bind excessively to amyloid-beta proteins, enhancing peptide aggregation and the toxicity of senile plaques in Alzheimer's disease patients.[3]

Given the important role of heavy metals in the development of neurodegenerative diseases, the use of synthetic chelators in the treatment of these conditions is severely limited. Serious problems with synthetic chelators include: systemic toxicity, lack of selectivity, and most importantly, extremely low penetration across the blood-brain barrier (BBB). These shortcomings complicate the use of these chelators in long-term therapy for chronic neurodegenerative diseases and highlight the relevance of the ongoing search for natural alternative chelating agents. The focus of this study is quercetin (3,3',4',5,7-pentahydroxyflavone) — a natural flavonol commonly found in plants. In addition to its ability to chelate metal ions via structure-specific coordination centers, it also exerts significant antioxidant and neuroprotective effects.[5] Systematic data on studies of quercetin's chelating properties and neuroprotective mechanisms are scarce in the literature. The question of the mechanisms through which quercetin's neuroprotective activity manifests — whether through direct chelation of heavy metal ions or through modulation of intracellular signaling pathways — and the role of these mechanisms with different types of metal ions remains poorly understood.

It should also be noted that quercetin has low bioavailability when taken orally and limited penetration across the blood-brain barrier.[5,13] This narrative mini-review systematizes preclinical data on the mechanisms of chelation of five metal ions — Fe, Cu, Cd, Mn, and Zn — by quercetin, as well as a justification of its potential as a multipurpose neuroprotective agent for future clinical developments in metal-induced neurodegenerative diseases.

MATERIALS AND METHODS

This study is a narrative mini-review of the literature aimed at evaluating the potential of quercetin as a chelating and neuroprotective agent. Due to the theoretical nature of the study, no practical laboratory methods or techniques were used. The search for publications was conducted in the PubMed electronic database, recognized as the most authoritative database on our subject. The following keywords and their combinations were used in the search: "the role of quercetin as a heavy metal chelator," "flavonoids as antioxidants," "neuroprotection," "heavy metal neurotoxicity," "neurodegeneration."

Article selection criteria: articles published between 2017 and 2025 were considered. Preference was given to articles that provided quantitative biochemical data — specifically, the dosage of quercetin and heavy metals — as well as those that described the mechanisms of metal ion neurotoxicity, the chelating ability of quercetin, and comparisons of quercetin with other chelators. As a result of the review, 17 publications were selected.

RESULTS

1. Neurotoxicity of metals: the mechanism of molecular pathogenesis

The accumulation of heavy and transition metals — iron (Fe), copper (Cu), zinc (Zn), cadmium (Cd), and manganese (Mn) — is recognized as the root cause driving the pathogenesis of neurodegenerative diseases (EPIC4PD studies). Three interrelated molecular mechanisms of neurotoxicity are known:

A. Amyloidosis and proteopathy

Fe^{2+}, Cu^{2+}, and Zn^{2+} ions are high-affinity ligands for the histidine residues of the amyloid-beta (Aβ) peptide. As a result of their binding, the energy barrier required for the conformational transition from the α-helix to the β-sheet structure is sharply reduced, which catalyzes the irreversible oligomerization of peptides and the formation of senile plaques in Alzheimer's disease. Excess Fe^{2+} ions similarly accelerate the fibrillation of α-synuclein in the substantia nigra in Parkinson's disease.

B. Oxidative stress

Cadmium and manganese ions have a high affinity for the sulfhydryl (–SH) groups of cysteine in glutathione, thereby reducing the amount of antioxidant buffers within the cell. This triggers a cascade of lipid peroxidation in the membranes of neurons and microglia.

C. Mitochondrial dysfunction

Metal ions trigger apoptosis by penetrating the mitochondrial matrix, depolarizing the inner membrane, inhibiting electron transport chain complexes, and opening the mitochondrial porin.

2. Structure and Mechanisms of Quercetin Chelation

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonoid containing five hydroxyl groups in its chromone skeleton. It is a polydentate ligand capable of forming chelates with metal ions, with an efficacy comparable to that of popular synthetic chelators. The chelation process occurs via two mechanisms related to its structure. It should be noted that the pH of the medium strongly influences the chelation process and is often a decisive factor in determining to which part of the molecule the metal ion will bind.[5,6]

A. Ortho-dihydroxyl (catechol) group of the B-ring (positions 3' and 4')

The formation of high-affinity complexes with Fe^{3+}, Cu^{2+}, and Cd^{2+} ions is accompanied by the deprotonation of hydroxyl groups and the formation of a five-membered chelate ring with high thermodynamic stability.

B. 3-hydroxy-4-carbonyl system (C-ring) and 5-hydroxy-4-carbonyl system (A-C rings)

These centers additionally form complexes with divalent metal ions: Fe^{2+}, Zn^{2+}, and Mn^{2+}. Of particular note is the study by Glykofridi et al. (2023), in which stable quercetin complexes with rhenium of the fac-[Re(CO)3(FI)(sol)] type were synthesized, providing direct physicochemical evidence of its role as a polydentate ligand. In this complex, quercetin encapsulates the metal ion, shields the valence orbitals, and completely suppresses redox activity.[14]

3. Specific mechanisms of quercetin neuroprotection in certain metal-related pathologies

The neuroprotective effects of quercetin are mediated by several well-studied mechanisms: reduction of free radicals through direct chelation, neutralization of reactive oxygen species (ROS) via hydrogen atom donation, and activation of cytoprotective cascades.[5,6]

A. Iron (Fe) Neurotoxicity

Iron dyshomeostasis is a critical factor in the pathogenesis of Parkinson's disease. An excess of iron ions in the brain initiates the Fenton reaction, in which iron (II) ions catalyze the decomposition of hydrogen peroxide, forming highly reactive hydroxyl radicals. Bardestani et al. (2021) describe that quercetin neutralizes this effect through four mechanisms: direct chelation of iron, regulation of iron homeostasis genes, inhibition of protein aggregation, and direct neutralization of ROS.[5] It is noted that quercetin's chelating activity toward iron (Fe^{2+}) at pH 7.2 is stronger than that of the well-known chromophore chelator ferrozine.[5] Another study states that at normal physiological pH levels (~7.0), Fe^{3+} ions may precipitate, which hinders binding; however, quercetin can maintain iron ions in a soluble form by forming complexes.[15] In a study by Sharma et al. (2020), Parkinsonism was modeled in rats using rotenone and an iron dietary supplement. The use of quercetin (25 and 50 mg/kg) significantly reduced the severity of motor impairments, demonstrating a neuroprotective effect. In addition to directly chelating iron ions, quercetin combined with piperine increases the activity of mitochondrial complexes I and IV, interrupts radical oxidation chain reactions, and protects the dopaminergic pathways of the striatum.[8]

B. Copper (Cu) Neurotoxicity

Copper is an essential component of many neuroenzymes, but in excess, it has a pronounced neurotoxic effect due to increased oxidative stress. Zubčić et al. (2020) describe the mechanisms of quercetin neuroprotection in vitro in the context of damage to P19 neurons by Cu^{2+} ions: at a concentration of 150 μM, quercetin activates the PI3K/Akt and ERK1/2 signaling pathways, reduces the expression of the pro-apoptotic protein PUMA, increases the level of the anti-apoptotic protein NME1, and inhibits the activity of caspase-3/7.[6] Additionally, the same study reports estimated binding constants for copper ions with quercetin at a physiological pH of 7.4: 180±34×103 M−1.[6] In the modulation of cerebral ischemia, quercetin (20 mg/kg) also normalized the Cu/Zn ratio in the rat cerebral cortex, reduced markers of oxidative stress, and increased total antioxidant activity.[12]

C. Cadmium (Cd) Neurotoxicity

Studies of cadmium neurotoxicity in rats reveal a multistep mechanism of toxicity of this metal's ions. Gupta et al. (2017) describe that 28-day administration of Cd (5 mg/kg) to rats leads to a decrease in the density of cholinergic-muscarinic receptors, inhibits mRNA expression of the M1, M2, and M4 in the frontal cortex and hippocampus, reduces the expression of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), and enhances ROS generation, mitochondrial dysfunction, and ultrastructural changes in neurons.[7] Administration of quercetin (25 mg/kg) restored these parameters, and the authors suggest that this is due to the flavonoid's antioxidant potential and its modulatory activity on the MAP kinase pathway.[7] Wang et al. (2022) also describe the mechanism of quercetin's action in cadmium toxicity: reduction of endoplasmic reticulum stress — inhibition of UPR activation and reduction of pro-apoptotic markers — and increased expression of Bcl-2; however, it is important to note that this study was conducted on hepatocytes.[16]

D. Manganese (Mn) Neurotoxicity

Manganism — a neurotoxic condition resulting from chronic manganese poisoning — is caused by impaired mitochondrial respiration and the oxidation of dopamine and catecholamines.[11] Adedara et al. (2017) report that experimental administration of quercetin improved neurobehavioral parameters in rats with induced manganism. Additionally, AChE activity and overall antioxidant status were restored, and levels of LPO markers were reduced.[9]

A study by Gawlik et al. (2017) compared the effects of quercetin and resveratrol on different brain regions in rats with manganese poisoning and reported that quercetin prevented the decline in SOD activity in the frontal cortex to a greater extent than resveratrol.[11]

E. Zinc (Zn) Neurotoxicity

In a study by Abdelrahman et al. (2023), ZnO nanoparticles were used to model neurotoxicity in rats. Quercetin (50 mg/kg) significantly reduced levels of MDA, TOS, and pro-inflammatory cytokines, restored calbindin D28k protein expression in Purkinje cells, and modulated the expression of miRNA-155-3p associated with NF-κB signaling.[10]

F. Molecular and signaling pathways of quercetin neuroprotection in various metal ion poisonings

Among the mechanisms described above, it should be noted that in addition to direct chelation of metal ions via its structure, quercetin also exerts a neuroprotective effect through molecular signaling pathways, the most important of which are: the PI3K/Akt and ERK1/2 pathways, whose activation prevents caspase-dependent neuronal apoptosis, as well as the mechanism of modulating the apoptotic balance (↑Bax, ↓Bcl-2, ↓caspase-3).[6,7,10] Quercetin also inhibited the initiation of the UPR cascade, interrupting the pathway from ER dysfunction to mitochondria-mediated apoptosis under conditions of Cd^{2+} -induced ER stress.[16]

Another key pathway in the neuroprotective mechanism is the Nrf2/ARE (nuclear factor erythroid 2–related factor 2/antioxidant response element) pathway. It has been demonstrated that quercetin stimulates the Nrf2-ARE axis, which restores oxidative balance and reduces neuronal damage in Alzheimer's and Parkinson's diseases; moreover, this pathway is one of the primary ones involved in Mn and Cd neurotoxicity.[10,13,16]

The NF-κB pathway (nuclear factor kappa-B) deserves special mention — Cd^{2+},Cu^{2+}, and Mn^{2+} ions can activate this pathway, thereby triggering the expression of pro-inflammatory mediators, which in turn directly damages neurons.[1,2,10,13] Quercetin inhibits this pathway by blocking IκB kinase, acting on the TLR4/MyD88/NF-κB cascade, and reducing the production of nitric oxide (NO) as well as inflammatory cytokines.[5,8,10,13]

In the case of mitochondrial dysfunction induced by cadmium, quercetin restores the membrane potential, and in the case of Parkinson's-like effects of rotenone and iron, it normalizes the activity of respiratory complexes I–IV.[7,8] In models of Mn^{2+}-, ZnO-NP-, and Fe/rotenone-induced toxicity, the neuroprotective activity of quercetin is demonstrated through its anti-inflammatory action, specifically by reducing the levels of TNF-α, IL-1β, and IL-6.[8,10,11]

In conclusion, we can unequivocally state that the neuroprotective effect of quercetin is due to several main mechanisms: antioxidant action, direct chelation, and anti-apoptotic and anti-inflammatory effects. The synergy of these mechanisms accounts for the unified neuroprotective effect of quercetin.

G. The Problem of Quercetin Bioavailability and Evaluation of Its Promising Nanoparticles

The main limitation in the therapeutic use of quercetin is its low bioavailability upon oral administration, as the molecule is hydrophobic. Intense metabolism in the intestine and liver, as well as limited penetration across the blood-brain barrier (BBB), may also hinder bioavailability.[5,13] Bukhari (2022) rightly notes that researchers use intravenous and intraperitoneal methods of quercetin administration, which severely limits the clinical applicability of these studies.[13]

Sharma et al. (2020) experimentally validated methods for improving bioavailability, specifically the combination of quercetin with piperine, which significantly increased the absorption and tissue distribution of the flavonoid in the treatment of Parkinson's disease.[8] Bardestani et al. (2021) propose an innovative solution: the conjugation of quercetin with superparamagnetic iron oxide particles (QCSPIONs). Paradoxically, while using this complex, significant improvements in cognitive function and stimulation of neurogenesis were documented, yet there were no signs of iron-induced toxicity, as the iron oxide core itself is neutralized by the chelating action of quercetin, forming a self-locking system.[5]

Table 1: Summary of the neuroprotective effects of quercetin in various metal-induced pathologies.

Metal	Model	Quercetin Dose	Key Effects	Source
Fe (IONPs)	In vitro / in vivo	QCSPION conjugate	Inhibition of Fenton reaction, Fe chelation, ↑neurogenesis	[5]
Fe + rotenone	SD rats, PD model	25–50 mg/kg + piperine 2.5 mg/kg	↑DA, ↑GSH, ↓MDA, ↓TNF-α, ↓IL-6, restored complexes I and IV	[8]
Cu^{2+}	P19 neurons (in vitro)	10–150 μM	Activation of PI3K/Akt and ERK1/2, ↓PUMA, ↑NME1, ↓caspase-3/7	[6]
Cd^{2+}	Rats, 5 mg/kg, 28 days	25 mg/kg	Upreg. ChAT, AChE, M1/M2/M4 receptors; ↓Bax, ↑Bcl-2; mitochondrial protection	[7]
Cd^{2+} (hepatocytes)	In vivo / in vitro (rats)	20–40 mg/kg	↓ER stress, ↓UPR activation, ↓apoptosis	[16]
Mn^{2+}	Rats	25 mg/kg	↑AChE, ↑SOD, ↓oxidative stress, neurobehavioral recovery	[9]
Mn^{2+}	Rats (FCX, STR, CER)	13–26 mg/kg	SOD protection in FCX and CER, decreased GSSG/GSH in STR	[11]
Zn (ZnONPs)	Rats, cerebellum	50 mg/kg	↓MDA, ↓IL-1β, IL-6, TNF-α; increased calbindin D28k; modulation of miRNA-155	[10]
Cu/Zn (ischemia)	Rats, SMA occlusion	20 mg/kg	Normalization of Cu/Zn ratio, ↓MDA, ↑antioxidant activity	[12]

IV. DISCUSSION

From the analysis of the studies, we can identify several key mechanisms underlying the neuroprotective potential of quercetin. The first mechanism involves the unique structure of the catechol group of the B-ring and the 3-OH/4-oxo system of the C-ring, which allows for the direct chelation of metal ions and the formation of stable complexes with both essential metals (Fe, Cu, Zn) and toxic metals (Cd, Mn), which distinguishes quercetin from synthetic chelators with narrow metal specificity.[5,14]

The second mechanism — quercetin's neuroprotective potential — is multilevel in nature, as evidenced by the study by Zubčić et al. (2020), which confirms that pharmacological inhibition of PI3K/Akt and ERK1/2 completely halts neuroprotection, even in the presence of a chelating effect.[6] This indicates a chelation-independent and autonomous

mechanism of neuroprotection via signal modulation. Mechanisms for reducing caspase-3 activity, normalizing the Bax/Bcl-2 ratio, and counteracting apoptosis in the presence of Cu^{2+}, Cd^{2+}, and Zn^{2+} nanoparticle poisoning have also been demonstrated.[6,7,10]

It should be noted that quercetin exhibits varying degrees of efficacy depending on the specific metal. Clear data have been obtained for Fe and Cu, whereas in the case of cadmium, the results were mixed — quercetin was less effective than resveratrol in terms of several parameters, namely the reduction of the GSSG/GSH ratio in the hippocampus and cerebellum.[11] This suggests a possible metal-specificity of protective mechanisms and the need for separate studies of quercetin's potential in cases of metal toxicity.

Endogenous metallothioneins (MTs) — proteins that act as chelators within the body via the sulfur-containing thiol groups of cysteine residues — also play a role.[1,17] MT-1/2 are present in astrocytes and MT-3 in neurons and participate in the coordination of Cu, Fe, and Zn homeostasis in the CNS.[1] The relationship between an external chelator (quercetin) and the internal chelation system (MT) is largely unexplored and represents a promising area for research, particularly in the context of neurodegeneration.

In addition to the above, bioavailability remains a major unresolved issue in this context. The use of nanoforms (QCSPIONs) with alkaloids (piperine) is a potential approach that could significantly improve bioavailability and overcome this problem.[5,8] Further safety assessments and preclinical studies in this area are required.

V. CONCLUSIONS

In this mini-review, we have systematized preclinical data confirming that quercetin possesses a multifaceted neuroprotective mechanism with distinct chelating properties. The main conclusions of our study are:

1. Quercetin is a broad-spectrum chelator ($Fe^{2+/3+}$, Cu^{2+}, Cd^{2+}, Mn^{2+}, Zn^{2+}) that, through its structural centers, directly inhibits the Fenton reaction and prevents neuronal damage caused by ROS.
2. In neuropathologies associated with Fe- and Cu-accumulation, quercetin exerts a neuroprotective effect via the PI3K/Akt and ERK1/2 signaling pathways, by reducing the expression of pro-apoptotic proteins (PUMA, Bax, caspase-3), and by restoring mitochondrial function. In cases of neurotoxicity caused by Fe, Cd, and Mn, it restores cholinergic neurotransmission (ChAT, AChE, M1/M2/M4 receptors), normalizes antioxidant status, suppresses neuroinflammatory markers, and stimulates the Nrf2-ARE axis, thereby reducing neuronal damage in Alzheimer's and Parkinson's diseases.
3. Quercetin inhibits the NF-κB pathway by blocking IκB kinase, acting on the TLR4/MyD88/NF-κB cascade, and reducing the production of nitric oxide (NO) as well as inflammatory cytokines.
4. In cases of Mn-ion poisoning, resveratrol exhibits superior neuroprotective properties compared to quercetin across several parameters, including a reduction in the GSSG/GSH ratio in the hippocampus and cerebellum.
5. The issue of bioavailability, which hinders its therapeutic application, remains unresolved. It is proposed to investigate a strategy combining QCSPION nanoconjugates with piperine.
6. The interaction between the body's endogenous chelating systems and external chelators — metallothioneins and quercetin — has been little studied.

It is proposed to conduct future research in the following areas: studying the synergy of quercetin with natural chelation mechanisms (MT) and developing nanoforms using piperine.

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