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REVIEW

Metalloflavonoid strategy: enhancing quercetin efficacy through conjugation

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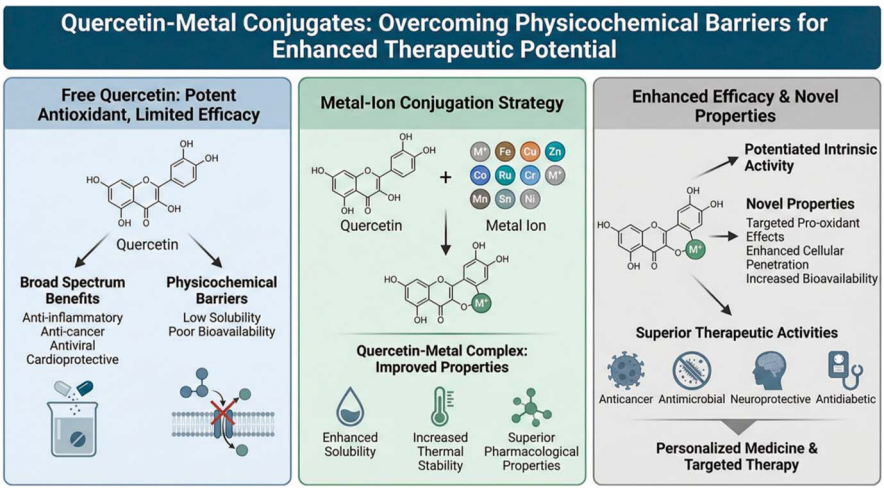
Graphical abstract



Abstract

Quercetin, one of nature's most potent antioxidants, exhibits a broad spectrum of biological benefits, including anti-inflammatory, anti-cancer, anti-viral, and cardioprotective properties. However, the full therapeutic potential of this natural compound is partially restricted by fundamental physicochemical barriers, primarily low solubility and poor bioavailability. This review thoroughly investigates the potential of metal-ion-conjugated quercetin as a strategy to overcome these limitations and unlock its full efficacy. This review uniquely extends beyond quercetin's established bioactivities to detail the specific therapeutic enhancements conferred by complexation with diverse metal ions. These complexes can significantly improve the solubility, thermal stability, and overall pharmacological properties of the parent compound. Conjugates formed with various metal ions – including iron, copper, zinc, cobalt, ruthenium, chromium, manganese, tin, and nickel – not only potentiate quercetin's intrinsic antioxidant capacity but also introduce novel, enhanced properties that transcend non-conjugated quercetin. Extensive *in vitro* and *in vivo* studies confirm that metal complexation yields superior results, unlocking unique effects that surpass quercetin alone. Notably, their ability to modulate specific pathways, such as offering targeted antioxidant effects and exhibiting enhanced cellular penetration and bioavailability, positions these conjugates as a critical strategy for developing next-generation therapeutics.

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Such enhancements highlight the potential of these complexes in exhibiting improved anti-cancer, anti-microbial, neuroprotective, and anti-diabetic properties. In conclusion, quercetin–metal conjugates offer a means to enhance the compound's preclinical efficacy by precisely modulating its effects on oxidative stress and free radical formation. This possibility holds the potential to revolutionize the fields of personalized medicine and targeted therapy.

Keywords: antioxidant effect; bioavailability; metal complexes; oxidative stress; quercetin

Introduction

The polyphenol quercetin (3,5,7,3′,4′-pentahydroxyflavone) is a flavonoid classified as a flavonol, one of the subclasses of flavonoids (Alharbi *et al.* 2025). The name 'quercetin' has been in use since 1857 and derives from the Latin word 'quercetum' (meaning 'oak forest'), referring to the genus Quercus. The International Union of Pure and Applied Chemistry (IUPAC) nomenclature for quercetin is 3,3′,4′,5,7-pentahydroxyflavanone (or its synonym 3,3′,4′,5,7-pentahydroxy-2-phenylchromen-4-one). Quercetin has an OH group attached at positions 3, 5, 7, 3′, and 4′ (Carrillo-Martinez *et al.* 2024). Quercetin ($C_{15}H_{10}O_7$) exists in nature mostly as an aglycone. It is a vibrant citron-yellow crystalline compound with high insolubility in cold water and limited solubility in hot water, although it is readily soluble in alcohol (e.g. 9.5 mg/mL in ethanol at 37°C; converted from mole fraction data in Razmara *et al.* (2010)) and lipids (e.g. 0.3 mg/mL in olive oil at 37°C) (Rich *et al.* 2017).

The endogenous antioxidant network provides cells and tissues with an adequate protection against reactive species, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). However, when the production of reactive species overcomes defenses. A condition called oxidative stress arises. Oxidative stress can lead to irreversible oxidative damage to tissue and may result from excessive production of free radicals and/or impaired degradation of ROS or reduction of the endogenous antioxidant defense system (Alharbi *et al.* 2025). Due to their ability to remove free radicals and reactive derivatives, and consequently reduce oxidative stress and related damage, exogenous antioxidants have been recommended for various health benefits (Rodríguez-Arce & Saldías 2021).

Quercetin has been shown to possess a variety of biological activities (Fig. 1), including antioxidant, anti-inflammatory, anti-apoptotic, anti-cancer, anti-aging, immunomodulatory, anti-viral, cardioprotective, anti-obesity, and anti-allergy effects (Ulusoy & Sanlier 2020, Shabir *et al.* 2022).

Mechanisms in antioxidant defense and cellular signaling

Antioxidant mechanisms

The molecular mechanism involved in quercetin's antioxidant activity is associated with its ability to bind to enzymes, receptors, transporters, and signal transduction systems changing the cell's ability to generate ROS and RNS (Shabir *et al.* 2022). Biophysical characteristics, such as the dispersion in the membrane lipid bilayer, orientation, and affinity, are crucial determinants of quercetin's antioxidant efficacy. Given that available quercetin molecules concentrate at the cell membrane, investigating the biophysical characteristics connected to the cell membrane's varied lipid compositions may be key to understanding the membrane's involvement in these activities. Quercetin is also an efficient iron chelator. Through its iron chelation capability, quercetin protects cells against oxidative damage caused by iron overload. Quercetin's anti-carcinogenic effect is linked to both its antioxidant and iron-chelating effects; furthermore, quercetin–metal complexes have been reported to possess even greater anti-cancer and anti-bacterial activities than free quercetin (Xiaoa *et al.* 2018). Quercetin's antioxidant efficacy is fundamentally rooted in the radical-scavenging capacity of the B-ring catechol moiety, complemented by electron delocalization through the 3-OH/4-oxo system and resonance stabilization across its conjugated framework (Perron & Brumaghim 2009*b*, Corrente *et al.* 2025).

Regulatory effect on core signaling pathways of oxidative stress and inflammation

Quercetin exerts a complex and dual-directional immunomodulatory effect (Alharbi *et al.* 2025), defined by its ability to modulate both pro-inflammatory signaling pathways and cellular functions, thereby suppressing inflammation while supporting proper immune function. Its primary mechanism involves directly targeting the two master regulators of cellular defense and inflammation: NRF2/ARE and NF-κB.

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Quercetin effectively counteracts redox homeostasis by activating the nuclear factor erythroid 2-related factor 2 (NRF2)–antioxidant response element (ARE) pathway (Marunaka 2017). NRF2 binds to AREs, which induces the expression of crucial antioxidant enzymes, including catalase, glutathione peroxidase, HO-1, and superoxide dismutase (SOD) (Alharbi *et al.* 2025). Preclinical evidence in diabetic rats supports the antioxidant potential, demonstrating that quercetin increased SOD activity and total antioxidant capacity while decreasing plasma levels of oxidative stress markers (malondialdehyde (MDA)) and 4-hydroxyalkyne (4-HNE)) (Ulusoy & Sanlier 2020). Recent meta-analyses confirm that redox-modulating therapies significantly reduce MDA levels ($P < 0.0001$) and restore antioxidant profiles (glutathione (GSH) and total antioxidant capacity (TAC)), thereby accelerating wound closure. In particular, a quercetin–oleic acid nano-hydrogel demonstrated superior healing rates and reduced infection incidence in diabetic ulcers. These findings underscore quercetin's clinical potential to translate molecular signaling modulation into improved re-epithelialization by mitigating peroxidative damage (Arnal-Forné & Borrás 2025). Simultaneously, quercetin exerts potent anti-inflammatory effects by downregulating the nuclear factor-kappa B (NF-κB) pathway, a fundamental regulator of pro-inflammatory genes expression (Chiang *et al.* 2023, Alharbi *et al.* 2025). Quercetin modulates the NF-κB signaling pathway by directly interacting with TNF-α, which leads to the stabilization of NF-κB α (IκBα) and the subsequent blockade of P65 nuclear translocation and its transcriptional activity (Chen *et al.* 2025). Further molecular targets include the MAPK signaling pathway, where quercetin reduces the activation of ERK and MAPK, and the AMPK and NLRP3 inflammasome pathways (Chiang *et al.* 2023). Quercetin also directly inhibits pro-inflammatory mediators, such as TNF-α (Chen *et al.* 2025) and the PUFA-metabolizing enzyme lipoxygenase (LOX) (Ramzan *et al.* 2025).

At the intracellular level, quercetin's immunomodulatory effects involve regulating specific immune cell functions. It increases antioxidant capacity by inducing an anti-inflammatory effect through the polarization shift of macrophages from the pro-inflammatory M1 state toward the anti-inflammatory M2 state (Tsai *et al.* 2021). It exerts an immunosuppressive effect on dendritic cells by reducing their production of pro-inflammatory cytokines and chemokines, as well as the expression of MHC class II and co-stimulatory molecules (Huang *et al.* 2010). It inhibits the proliferation and activation of T-lymphocytes in peripheral blood mononuclear cells without inducing apoptosis in normal cells (Alharbi *et al.* 2025). These actions collectively underscore quercetin's multifaceted and essential role as a central cellular modulator of inflammatory and oxidative processes.

Dual role in cell survival and death

Quercetin is a versatile flavonoid that displays complex, context-dependent effects on programmed cell death (Shabir *et al.* 2022), offering critical selective toxicity for non-cancerous versus cancerous cells. In non-cancerous cells, particularly during neurodegenerative processes such as traumatic brain injury or Alzheimer's disease, quercetin acts as an anti-apoptotic agent, preventing cell death by reducing oxidative stress, maintaining mitochondrial integrity, and activating pro-survival pathways, such as PI3K/AKT (Yang *et al.* 2014, Carrillo-Martinez *et al.* 2024). In contrast, regarding cancer cells, quercetin acts as a potent pro-apoptotic agent by employing mechanisms (Rather & Bhagat 2020). It triggers apoptosis and autophagy in cancer cells by activating caspases (notably CASP3), regulating the BAX/BCL-2 balance, and downregulating mutant P53 proteins, all while inhibiting key proliferative signaling pathways, such as PI3K/AKT/MTOR, WNT/β-catenin, and MAPK/ERK1 (Lotfi *et al.* 2023, Sethi *et al.* 2023, Tubtimsri *et al.* 2025). In addition, quercetin exhibits therapeutic potential by inhibiting metastasis through reduced MMP and VEGF secretion, arresting the cell cycle at the G1 phase, and targeting mitochondrial bioenergetics (Reyes-Farias & Carrasco-Pozo 2019). While preclinical studies confirm quercetin's anti-cancer effects and its potential to enhance the efficacy of other drugs (Azeem *et al.* 2023), there are currently few clinical studies to support these applications (Lotfi *et al.* 2023).

Inhibition of viral entry and replication

Recent research has highlighted quercetin's significant potential as an anti-viral agent, primarily due to its ability to interfere with multiple stages of the viral life cycle (Di Petrillo *et al.* 2022, Nguyen & Bhattacharya 2022). The anti-viral effects of quercetin are mainly attributed to its capacity to inhibit various viral processes, including viral entry, replication, and protein assembly (Nguyen & Bhattacharya 2022). A key mechanism of action involves inhibiting crucial viral enzymes, such as polymerases, reverse transcriptase, and proteases, including 3CLpro, RdRp, and PLpro (Gasmi *et al.* 2022). Furthermore, quercetin can modulate the host immune response by reducing excessive inflammation often caused by infection. Preclinical studies conducted in animal models have demonstrated that quercetin supplementation significantly decreases viral load and mortality rates in respiratory tract infections (Brito *et al.* 2021). Complementary to these findings, emerging clinical evidence in humans suggests that quercetin may help reduce the risk of severe clinical outcomes, such as hospitalization and intensive care unit (ICU) admission, in infected patients (Cheema *et al.* 2023).

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Therapeutic potential and prevention of cardiovascular diseases

The core pathophysiological processes underlying many chronic cardiovascular pathologies, such as atherosclerosis, hypertension, myocardial ischemia, and heart failure, are chronic inflammation and oxidative stress (Ozorowski *et al.* 2025). Oxidative stress contributes to endothelial dysfunction and the development of atherosclerosis by damaging cellular components (Azizidoost *et al.* 2025). Similarly, chronic inflammation facilitates the accumulation of inflammatory cells in the vascular walls and the formation of atherosclerotic plaques. Quercetin is considered a promising cardioprotective candidate due to its ability to modulate chronic inflammation and oxidative stress. Its beneficial effects on the cardiovascular system are linked to complex and multifaceted mechanisms, notably the modulation of oxidative stress, inhibition of inflammatory pathways, improvement of endothelial function, and reduction in lipid accumulation (Ozorowski *et al.* 2025). Epidemiological data consistently support this protective role, showing that a diet rich in fruits and vegetables significantly reduces the risk of cardiovascular diseases (CVDs) (Bondonno *et al.* 2015). The protective effect is attributed mainly to the biological activity of flavonoids, particularly quercetin. For instance, one cohort study revealed that men consuming more than 29 mg of flavonols daily had a 68% lower risk of coronary deaths compared to those consuming less than 10 mg per day (Serban *et al.* 2016). Clinical studies have demonstrated quercetin's ability to lower blood pressure significantly. Furthermore, current reviews highlight that quercetin significantly reduces concentrations of atherogenic oxidized LDL (Ozorowski *et al.* 2025). Such findings have intensified interest in investigating quercetin as a potential therapeutic agent for the prevention and management of CVDs.

Anti-allergic effect via mast cell stabilization

Allergic reactions are characterized by an overreaction of the immune system to typically harmless triggers (antigens). Central to these reactions are mast cells, a type of white blood cell produced in the bone marrow, which play critical functions in allergy, anaphylaxis, immune tolerance, and pathogen defense (van Anrooij *et al.* 2013). Quercetin's most recognized anti-allergic mechanism is its function as a mast cell stabilizer. This effect is achieved by preventing mast cells from degranulating and consequently inhibiting the release of inflammatory mediators, such as histamine and tryptase (Weng *et al.* 2012). Quercetin also acts as a natural antihistamine, directly inhibiting histamine release. These two actions are part of interrelated pleiotropic mechanisms: inhibition of calcium influx, suppression of inflammatory signaling pathways (NF-κB and AKT), and cytoskeleton modulation (Zhao *et al.* 2024). Quercetin's capacity to regulate these multiple targets simultaneously makes quercetin a broader and potentially more effective anti-allergic agent than conventional drugs that typically rely on a single mechanism (Zhao *et al.* 2024).

Modulation of obesity and lipid metabolism

Given its documented antioxidant and anti-inflammatory properties, quercetin is being extensively investigated as a potential therapeutic agent for obesity and related metabolic disorders. Its anti-obesity effects are primarily linked to its ability to influence adipocyte formation (adipogenesis) and regulate lipid metabolism. Quercetin has been shown to reduce fat mass, increase lipolysis (fat breakdown) (Wang *et al.* 2024), and inhibit the formation of new adipocytes (Alharbi *et al.* 2025). In particular, during adipocyte differentiation, quercetin impairs lipid accumulation in a dose-dependent manner. This effect is mediated by complex regulatory actions on key signaling pathways and transcription factors. Quercetin modulates the expression of master transcription factors critical for adipogenesis, such as C/EBPα, PPARγ, and SREBP-1c (Yun-Soo *et al.* 2015). It regulates the expression of lipases, including adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), thereby enhancing lipolysis. Preclinical evidence suggests that quercetin's anti-obesity effects are mediated through the mitogen-activated protein kinase (MAPK) and AMPK signaling pathways (Solnier *et al.* 2021). Quercetin has also been shown to inhibit the activation of key factors in the PI3K/AKT/mTOR pathway, which plays a crucial role in adipocyte differentiation and lipid accumulation (Seo *et al.* 2015). These findings highlight quercetin's potential for therapeutic use in the prevention and management of obesity.

Impact on aging and senescence

Quercetin shows significant potential in gerontology and dermatology due to its comprehensive anti-aging effects. This activity targets the fundamental biological hallmarks of aging, specifically cellular senescence, oxidative stress, and chronic inflammation (Deepika & Maurya 2022). One of quercetin's most notable effects is its function as a senotherapeutic agent. This means it exhibits both senolytic (selectively eliminating senescent cells) and senomorphic (modulating the harmful effects of these cells) capabilities (Medoro *et al.* 2025). Senescent cells, often referred to as 'zombie cells', are dysfunctional cells that resist programmed cell death (apoptosis) and release

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a range of pro-inflammatory molecules, thereby causing damage to neighboring cells and propagating chronic inflammation (Scudellari 2017). Quercetin acts through a dual mechanism to combat aging: through senolytic action and senomorphic effect. For senolytic action, it triggers apoptosis in senescent cells by inhibiting anti-apoptotic proteins (Medoro *et al.* 2025). For senomorphic effect, it functions by suppressing the senescence-associated secretory phenotype (SASP) (Csekes & Račková 2021, Medoro *et al.* 2025). This effects are specifically associated with the suppression of inflammatory pathways, such as NF-κB and the NLRP3 inflammasome, which play a key role in the neuroinflammation observed in age-related neurodegenerative diseases (Cui *et al.* 2022) (Table 1).

The rational design of metal–flavonoid complexes offers a promising strategy to obtain compounds with enhanced biological and physicochemical properties, thereby substantially boosting flavonoid antioxidant potential. This evidence suggests that the superior antioxidant properties of metal–flavonoid compounds can play a crucial role in the development of potential novel therapeutic strategies (Rodríguez-Arce & Saldías 2021).

The quercetin–metal complex strategy: a paradigm shift

Quercetin is of great interest in the field of medicinal chemistry due to the wide range of biological activities it exhibits, as detailed above. Its low aqueous solubility and poor bioavailability significantly limit its effective absorption and delivery to target tissues. To overcome these limitations, the complexation of quercetin with metal ions can be considered a more reliable and sensitive strategy (Ramzan *et al.* 2025). Notably, quercetin–Fe(III) complexes have demonstrated markedly increased solubility and improved dissolution behavior compared to free quercetin, supporting the fundamental premise that metal coordination can overcome solubility-dependent bioavailability limitations (Vrzal *et al.* 2016). More broadly, metal coordination transforms quercetin into a distinct chemical entity with modified physicochemical and pharmacological properties, representing a shift toward optimized drug-like behavior (Trifunschi & Munteanu 2018). This represents a transition to a potentially more effective ‘drug’ form with optimized pharmacokinetic and pharmacodynamic characteristics. In particular, metal complexes have become a focal point of increasing interest due to their biocompatibility and a wide range of biological potentials (Lawson 2025). Collectively, this situation enables the development of strategies for synthesizing metalloflavonoid structures rather than individual flavonoids, presenting a significant paradigm shift in traditional approaches.

In addition to these pharmacokinetic advantages, the capacity of quercetin to form structurally diverse coordination complexes originates from its unique chemical architecture (Corrente *et al.* 2025). The molecule contains five phenolic hydroxyl groups and one carbonyl group, creating several chemically distinct metal-binding domains (Corrente *et al.* 2025). From a quercetin-specific structural perspective, antioxidant activity is primarily associated with the catechol moiety located on the B-ring (3′,4′-dihydroxyl groups), which constitutes the main redox-active site of the molecule (Perron & Brumaghim 2009*a*, Corrente *et al.* 2025). This structural unit enables efficient radical scavenging through electron or hydrogen atom donation, while resonance stabilization across the conjugated flavonoid framework preserves molecular integrity and the 3-OH/4-oxo system further supports electron delocalization and contributes to the overall redox behavior of quercetin (Perron & Brumaghim 2009*a*, Corrente *et al.* 2025). Depending on the metal ion and coordination mode, complexation may either preserve catechol-based radical-scavenging activity or shift antioxidant behavior toward metal-centered redox processes, thereby modulating the overall redox profile of quercetin (Fig. 2) (Perron & Brumaghim 2009*a*, Corrente *et al.* 2025).

Differences in acidity, resonance stabilization, and electron-donating capacity across the available binding sites enable quercetin to act as a multidentate ligand capable of chelating a wide range of metal ions (Perron & Brumaghim 2009*a*). Metal coordination generally occurs through deprotonation of phenolic hydroxyl groups, followed by O → M interactions that lead to the formation of stable chelate structures (Perron & Brumaghim 2009*a*). Such metal complexation is known to influence the physicochemical properties of quercetin, including its stability, solubility, electronic characteristics, and biological activity (Perron & Brumaghim 2009*a*).

The variability in biological effects observed among different quercetin–metal complexes can be attributed to differences in metal ion properties and their preferential interactions with specific oxygen-donor binding sites on the quercetin molecule (Corrente *et al.* 2025). Metal ions, such as Fe^{3+}, are known to coordinate primarily with phenolic hydroxyl and carbonyl oxygen donor atoms, leading to the formation of stable complexes that can modulate redox behavior (Corrente *et al.* 2025). These interactions influence the stability, solubility, and biological activity of quercetin–metal complexes (Perron & Brumaghim 2009*a*, Corrente *et al.* 2025).

Consequently, the formation of quercetin–metal complexes does not merely enhance the intrinsic properties of the parent flavonoid but results in a new chemical entity with distinct physicochemical and pharmacological characteristics (Ramzan *et al.* 2025).

Table 1 Comprehensive biological activity spectrum of quercetin.

Biological activity	Key mechanisms and targets	Outcome/clinical implication	References
Antioxidant effect	Scavenges free radicals (ROS/RNS, e.g., O2−, NO−, ONOO−). Induces endogenous antioxidant enzymes (catalase, *SOD, GR, GST, HO-1*) by activating the NRF2–ARE signaling pathway. Acts as an effective iron chelator	Reduces oxidative stress and associated damage. Forms the basis of its anti-aging profile and anti-carcinogenic effect	Marunaka (2017), Xiaoa *et al.* (2018), Shabir *et al.* (2022), Alharbi *et al.* (2025)
Anti-inflammatory effect	Inhibits activation and recruitment of the NF-κB transcription factor to pro-inflammatory genes. Suppresses pro-inflammatory cytokines (*TNF-α, IL-6, IL-1β*). Inhibits the PUFA-metabolizing enzyme 'lipoxygenase', blocking associated metabolites	Reduces chronic inflammation and the progression of inflammatory diseases (e.g. rheumatoid arthritis, skin inflammation)	Chiang *et al.* (2023), Chen *et al.* (2025), Ramzan *et al.* (2025)
Immunomodulatory effect	Blocks NF-κB activation and modulates the MAPK signaling pathway (P38*,* MAPK*, ERK*). Shifts macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2. Inhibits T-lymphocyte proliferation and activation	Regulates immune responses, alleviating autoimmune and inflammatory conditions	Huang *et al.* (2010), Tsai *et al.* (2021)
Cardioprotective effect	Inhibits oxidative stress and inflammatory pathways. Improves endothelial function and reduces lipid accumulation. Lowers systolic blood pressure (*SBP*) and concentrations of atherogenic oxidized LDL	Reduces the risk of cardiovascular diseases, such as atherosclerosis, hypertension, and myocardial ischemia	Serban *et al.* (2016), Alharbi *et al.* (2025), Ozorowski *et al.* (2025)
Anti-cancer effect	Regulates signaling pathways, such as PI3K/AKT/MTOR, Wnt/β-catenin, and MAPK/ERK1. Enhances apoptosis and autophagy by activating CASP3. Inhibits metastasis by reducing the secretion of MMP and VEGF. Downregulates mutant TP53 proteins	Selective toxicity targeting multiple pathways against various cancers (e.g. prostate, lung, leukemia, colon)	Reyes-Farias & Carrasco-Pozo (2019), Rather & Bhagat (2020), Tubtimsri *et al.* (2025)
Anti-apoptotic effect (neuro-/healthy cells)	Inhibits cell death by reducing oxidative stress, preserving mitochondrial integrity, and modulating pro-survival PI3K/AKT signaling pathways	Prevents tissue damage and functional loss in neurodegenerative conditions such as traumatic brain injury and Alzheimer's disease	Yang *et al.* (2014), Carrillo-Martinez *et al.* (2024)
Anti-viral effect	Interferes with viral entry, replication, and protein assembly. Inhibits viral enzymes including polymerases, reverse transcriptase, and key proteases such as 3CLpro, RdRp, and PLpro. Modulates immune response by reducing infection-induced inflammation	Reduces viral load and mortality rates in respiratory tract infections; lowers the risk of severe clinical outcomes (e.g. hospitalization/ICU admission)	Di Petrillo *et al.* (2022), Gasmi *et al.* (2022), Cheema *et al.* (2023)
Anti-allergy effect	Mast cell stabilization (prevents degranulation and release of histamine/tryptase). Acts as a CLM-1 agonist, inhibiting MRGPRX2-mediated mast cell degranulation. Suppresses inflammatory signaling pathways (*NF-κB,* AKT)	More effective than cromolyn in reducing cytokine release; alleviates histamine release, contact dermatitis, photosensitivity, and associated pruritus	Weng *et al.* (2012), Zhao *et al.* (2024)
Anti-obesity effect	Impairs lipid accumulation by regulating key transcription factors (*C/EBPα, PPARγ, SREBP-1c*) and lipases (*ATGL, HSL*). Mediated via MAPK and AMPK signaling pathways. Inhibits the PI3K/AKT/MTOR pathway	Reduces fat cell formation and fat mass; improves obesity-related insulin resistance and systemic inflammation	Seo *et al.* (2015), Solnier *et al.* (2021), Wang *et al.* (2024)
Anti-aging effect	Functions as a senolytic and senomorphic agent. Suppresses SASP (senescence-associated secretory phenotype). Suppresses inflammatory pathways (NF-κB and NLRP3 inflammasome). Strengthens antioxidant defense by activating NRF2	Targets fundamental hallmarks of aging: cellular senescence, oxidative stress, and chronic inflammation	Scudellari (2017), Cui *et al.* (2022), Medoro *et al.* (2025)

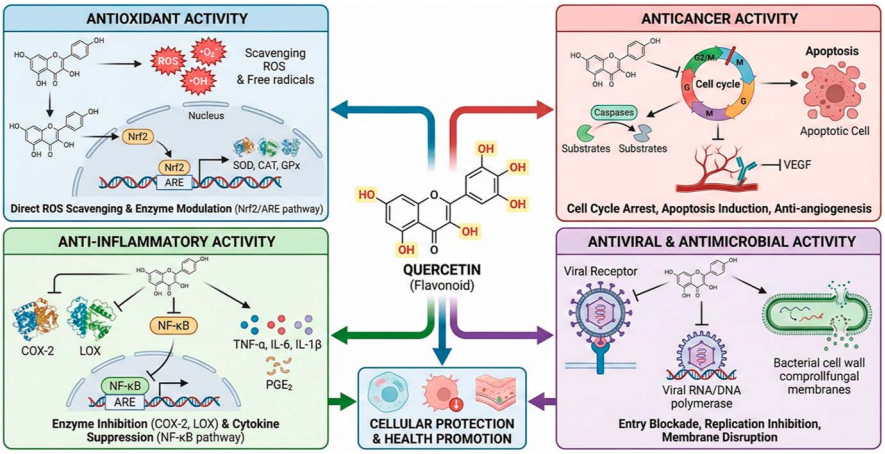

Figure 1

Main biological activities of quercetin and its mechanism.

Metal coordination alters key pharmaceutical parameters, including aqueous solubility, pH-dependent ionization behavior, thermal stability, and molecular conformation, which can directly translate into improved pharmacokinetic profiles.

Iron–quercetin complex

Iron–quercetin complex conjugates represent a burgeoning area of pharmacological research aimed at overcoming the limitations of their individual components (Lucas Prestianni *et al.* 2023). Conversely, while iron is vital for human biology, its presence in excess can trigger free radical production and lead to toxic effects (Silvestri *et al.* 2023). The formation of a complex between these two components addresses both challenges: it not only mitigates the harmful pro-oxidant effects of excess iron but may also modulate and potentially enhance selected pharmacological properties of quercetin (Innuan *et al.* 2025). These conjugates exhibit superior therapeutic properties, including enhanced antioxidant activity, targeted pro-oxidant effects, and markedly increased bioavailability (Lucas Prestianni *et al.* 2023). Furthermore, the integration of these complexes with advanced formulation strategies, such as nanoparticles, further improves the complex's stability and tissue penetration. This strategy shows significant promise for the treatment of various conditions, including iron overload and neurodegenerative diseases, and even for use as a new generation of magnetic resonance imaging (MRI) contrast agents (Dechsupa *et al.* 2022). Supporting this pharmacological rationale, *in vitro* antioxidant assays (DPPH, ABTS, and FRAP) and metal chelation studies indicate that metal–quercetin complexes can reduce Fenton-related oxidative processes by limiting metal-catalyzed radical formation (Fig. 2) when compared to free metal ions (Ramzan *et al.* 2025). Furthermore, *in vivo* models of iron overload have shown a marked reduction in oxidative tissue damage following administration of iron–quercetin conjugates (Perron & Brumaghim 2009*a*).

Copper–quercetin complex

Copper–quercetin complex conjugates have been a central topic of research for decades, aiming to overcome the biopharmaceutical limitations of quercetin alone (Kalinowska *et al.* 2021). These complexes demonstrate a synergistic effect by showing better antioxidant activity than free quercetin. In addition, laboratory experiments indicate that copper–quercetin complexes possess not only antioxidant properties but also pro-oxidant and DNA-damaging qualities that can be used for cancer cell therapy (Lawson 2025). This dual effect allows the complex to exhibit higher anti-tumor activity compared to quercetin alone (Kalinowska *et al.* 2021).

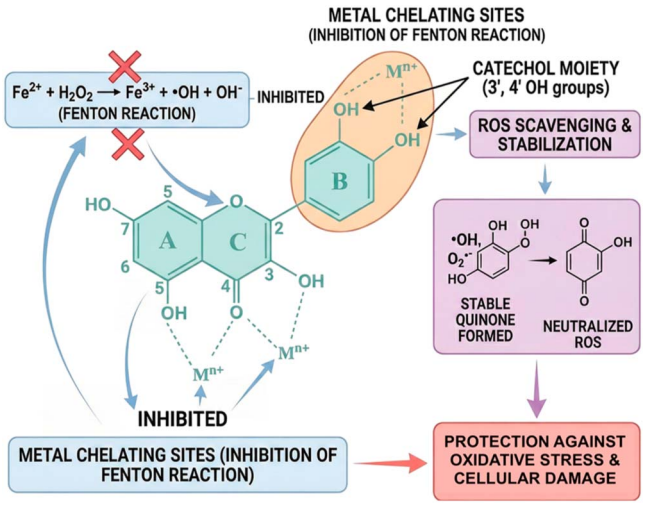

Figure 2

Chemical structure of quercetin, highlighting the metal-binding sites and the catechol moiety responsible for antioxidant activity.

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The use of advanced formulation strategies, such as nanoparticles, ensures the complex's stability, bioavailability, and clinical effectiveness, making it a promising candidate for a wide range of applications, including anti-microbial functions, osteogenesis, angiogenesis, and cancer treatment (Lawson 2025, Ramzan *et al.* 2025).

Zinc–quercetin complex

The combination of zinc and quercetin, particularly in a stoichiometric structure with a 2:1 quercetin-to-zinc ion ratio, forms a well-defined coordination complex (Uskoković-Marković *et al.* 2020). This complex has been shown to exhibit stronger antioxidant activity than free quercetin. This composition enhances the antioxidant and anti-viral effects of both zinc and quercetin (Xu *et al.* 2019). Furthermore, laboratory studies indicate that zinc–quercetin complexes have lower cytotoxic activity compared to quercetin alone (Ramzan *et al.* 2025).

Cobalt–quercetin complex

Cobalt–quercetin complex conjugates have been shown to exhibit higher antioxidant activity than quercetin alone in tests such as DPPH and FRAP (Mahar *et al.* 2018). This synergy indicates that the metal–flavonoid combination significantly enhances biological activity. Furthermore, cobalt–quercetin complexes can also demonstrate pro-oxidant properties under specific conditions, which may be useful for therapeutic purposes. Cytotoxicity studies conducted on HaCaT cell lines prove that the complex has cell-killing activity (Kalinowska *et al.* 2021). Complexation with metals that have high ionic potential increases quercetin's antioxidant properties, while advanced strategies, such as nanoparticle formulations, ensure its bioavailability and clinical effectiveness (Zahra Yarjanli *et al.* 2019). These combinations are seen as promising candidates in various clinical applications, including anti-microbial and anti-cancer therapies.

Plumbum–quercetin complex

The core mechanism of lead toxicity is the disruption of the pro-oxidant/antioxidant balance and the increased production of ROS (Flora *et al.* 2012). Quercetin plays a key role in counteracting this condition, acting as a multi-targeted therapeutic agent to address secondary cellular damage caused by lead, such as oxidative stress, inflammation, and apoptosis. Its efficacy is strongly supported by preclinical studies, particularly in mitigating lead-induced neurotoxicity, hepatotoxicity, and nephrotoxicity (Chander *et al.* 2014, Cai *et al.* 2021). On the one hand, it acts as a direct free radical scavenger, neutralizing ROS formed during lead poisoning (Ozgen *et al.* 2016). On the other hand, it strengthens the body's own antioxidant defense system by restoring the activity and levels of essential antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione (Cai *et al.* 2021). This complex function suggests that quercetin is a comprehensive therapeutic candidate rather than a simple chelating agent.

Nickel–quercetin complex

Nickel–quercetin complex conjugates represent an exciting intersection in pharmaceutical chemistry and metallo-drug design. By addressing quercetin's low bioavailability, complexation with nickel imparts powerful and multifaceted biological activities, such as inhibiting angiogenesis and apoptosis induction (Ramzan *et al.* 2025). The complex's cytotoxic activity is highlighted by its ability to intercalate between DNA base pairs and cause strand breaks through a hydrolytic mechanism (Kalinowska *et al.* 2016). Importantly, these complexes illustrate the context-dependent dual role of quercetin, whereby it functions as a ligand enhancing the biological activity of a nickel-based metallo-drug while simultaneously acting as a chelator that can limit the toxicity of free nickel ions (Yu 2023). This context-dependent behavior shows why nickel–quercetin complexes are so promising for future therapeutic designs.

Other transition metal complexes of quercetin: broadening the therapeutic spectrum

The complexation of quercetin with transition metals not only enhances quercetin's pharmacological efficacy but also leverages the unique properties of the metallic counterparts to achieve novel therapeutic profiles. This strategy has been applied to several metals. Ruthenium (Ru)–quercetin complexes are highly promising candidates for next-generation metal-based drugs (Sun *et al.* 2021). They exhibit potent and selective anti-tumor activity through a multi-targeted mechanism, including inducing apoptosis via P53 pathways, modulating signaling cascades (e.g. MTOR/AKT), and generating ROS (Roy *et al.* 2018, Žakula *et al.* 2023). Chromium (Cr)–quercetin complexes leverage the low toxicity of trivalent chromium (Cr(III)), a trace element of certain relevance for glucose and lipid metabolism (Xu *et al.* 2019, Matsia *et al.* 2022). The resulting complex exhibits stronger antioxidant activity than the free ligand (Xu *et al.* 2019) and offers potential for anti-diabetic treatments (regulating glucose homeostasis) and anti-cancer effects (Eid & Haddad 2017, Ansari *et al.* 2022). Manganese (Mn)–quercetin complexes demonstrate neuroprotective efficacy. The complex mitigates manganese-induced neurotoxicity by restoring brain antioxidant status and inhibiting apoptosis and inflammatory responses through the modulation of the HO-1/NRF2 and NF-κB pathways (Bahar *et al.* 2017). This effect also extends to

Table 2 Enhanced efficacy profile of key quercetin–metal conjugates.

Metal ion	Primary enhancement mechanism	Key enhanced biological activity	Context-specific role	References
Iron	Enhanced bioavailability, targeted pro-oxidation	Anti-cancer, neurodegenerative diseases	MRI contrast agent, controlling iron overload	Dechsupa *et al.* (2022), Lucas Prestianni *et al.* (2023)
Copper	Increased stability, DNA damage induction	Enhanced anti-tumor, anti-microbial	Synergistic effect, dual antioxidant/pro-oxidant properties	Lawson (2025)
Ruthenium	Tunable oxidation states, multi-targeted pathway modulation	Potent and selective anti-tumor, cholesterol regulation	Superior efficacy vs cisplatin; targets MTOR/AKT, TP53 pathways	Sun *et al.* (2021)
Zinc	Stronger antioxidant capacity, optimized stoichiometry	Enhanced anti-viral, cytotoxic activity	Boosting general resilience and anti-viral functions	Uskoković-Marković *et al.* (2020)
Chromium	High ionic potential, essential trace element integration	Enhanced antioxidant, anti-diabetic potential	Regulating glucose homeostasis and insulin sensitivity	Matsia *et al.* (2022)
Manganese	Toxicity mitigation, epigenetic modulation	Neuroprotection	Alleviating oxidative stress and neuroinflammation caused by toxic exposure	Bahar *et al.* (2017), Hussein *et al.* (2024)
Nickel	DNA intercalation and hydrolytic cleavage	High cytotoxicity, apoptosis induction	Paradoxical dual role: ligand efficacy and chelation mitigation	Kalinowska *et al.* (2016), Ramzan *et al.* (2025)
Cobalt	Increased antioxidant capacity, synergistic effect	Enhanced antioxidant, anti-cancer, anti-microbial	Pro-oxidant effect potential; cytotoxicity in HaCaT cells	Mahar *et al.* (2018), Kalinowska *et al.* (2021)
Lead	Multi-targeted detoxification, enzymatic restoration	Mitigation of lead toxicity (neuro-/hepato-/nephrotoxicity)	Neutralizes ROS and restores endogenous enzymes such as SOD/catalase	Chander *et al.* (2014), Ozgen *et al.* (2016)
Tin	Boosting cytotoxicity and antioxidant activity	Enhanced antioxidant, cytotoxic activity	Promising safety profile, enhancing *in vitro* efficacy	Dehghan & Khoshkam (2012)

modulating epigenetic changes, such as DNA methylation (Hussein *et al.* 2024). Tin (Sn)–quercetin complexes significantly enhance the antioxidant and cytotoxic activity of quercetin (Dehghan & Khoshkam 2012). Collectively, the development of these metal–quercetin conjugates, often coupled with advanced formulation strategies, such as nanoparticles (Ansari *et al.* 2022, Dechsupa *et al.* 2022), enables the creation of highly stable compounds with diverse therapeutic applications, positioned for future clinical development (Table 2).

Conclusion, challenges and future directions

Quercetin, as a natural compound, possesses immense therapeutic potential. However, fundamental pharmacokinetic challenges, such as low solubility and poor bioavailability, impede the full realization of this potential. This review summarized that the formation of metal complexes stands out as one of the most promising strategies to address these limitations. Conjugates formed with metals, such as iron, copper, zinc, cobalt, ruthenium, chromium, manganese, tin, and nickel, not only enhance quercetin's bioavailability but also broaden its therapeutic spectrum, improving its antioxidant, anti-cancer, anti-viral, anti-inflammatory, neuroprotective, and anti-diabetic activities compared to free quercetin. Notably, the synergistic effects of these complexes and their ability to enhance targeted tissue penetration can significantly augment quercetin's efficacy in treating various diseases.

Current limitations

Quercetin exhibits diverse therapeutic potential due to its biological activities as mentioned in this review. Despite its promising benefits, there are major limitations of quercetin, including less chemical stability and short biological half-life in mammalian tissues. These limitations challenge the development of effective clinical formulations and hinder effective therapeutic dosing. Most of the current data are based on the *in vitro* and *in vivo* studies; however, limited number of studies reported clinical trial data to confirm bioavailability improvements in humans (Mirza *et al.* 2023). Recent preclinical studies with water-soluble quercetin derivatives and advanced delivery techniques show improved pharmacokinetics; however, lack of clinical evidence limits regulatory approval (Yamaguchi *et al.* 2025).

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Despite preclinical efficacy, the clinical use of quercetin metalloflavonoid complexes faces critical challenges and limitations, and here we addressed limited clinical translation, poor bioavailability, stability issues, regulatory and safety gaps, nanocarrier toxicity concerns, variety in formulations, and insufficient long-term data.

Stability and bioavailability issues

Many researchers have successfully synthesized and characterized various quercetin–metal complexes, demonstrating improved stability and bioavailability of quercetin metallocompounds in the human body system. However, quercetin complexes often exhibit instability under varying temperature, pH, and storage conditions; also, some metal complexes show toxicity in biological models, such as zebrafish embryos with Zn–QCT (Mathiyalagan & Mandal 2020). Moreover, many studies focus on short-term stability without long-term degradation data that limit translational confidence. Variations in cytotoxicity profiles and stability have also arisen from the heterogeneity in delivery system performance stem from formulation chemistry, surface modifications, particle size, and therapeutic target. Controversial studies discuss the optimal metal coordination sites and the effect of complicated quercetin's toxicity profiles and pharmacokinetics.

Clinical translation and regulatory considerations

Despite promising preclinical results, many nanoformulations, including nanoparticles, liposomes, nanocochleates, and polymeric micelles, face challenges in adaptability, reproducibility, and regulatory approval (Vishwas *et al.* 2023). The lack of standardized bioavailability metrics and dissimilarity of quercetin formulations complicate regulatory evaluation. Moreover, high doses of supplemented quercetin have adverse effects, such as gastrointestinal disturbances, headache, and tingling sensation, and can even stimulate pro-inflammatory pathways (Salehi *et al.* 2020). Furthermore, potential drug interactions remain unknown, raising concerns for long-term clinical use. Although many nanoformulations show improved bioavailability, they face production challenges, such as cost-effectiveness and reproducible large-scale manufacturing that alters clinical translation and commercial viability. All these limitations alter the improvement of quercetin-based metallodrugs and nanoformulations into verified therapeutics.

Future research perspectives

Quercetin has therapeutic advantages in cardiovascular diseases, neurodegenerative disorders, bacterial and fungal infections, viral infections, respiratory conditions, skeletal conditions, cancer, diabetes, iron-induced toxicity, and oxidative stress-mediated conditions. However, research in humans is limited and further research is necessary to establish optimal dosage and formulations to improve quercetin's therapeutic potential. Future research and development efforts should focus not only on the synthesis of novel complexes but also on understanding their physiological stability, target-specific mechanisms of action, and long-term safety profiles; in addition, they should focus on standardizing formulations and clarifying interactions with other medications to optimize quercetin's therapeutic use. Moreover, studies should be designed to improve health benefits by ensuring safe intake levels, promoting diverse polyphenol consumption, and considering individual health conditions for supplementation (Poli 2025).

The integration of quercetin–metal complexes with nanotechnology and modern drug delivery systems (e.g. MOFs and nanoparticles) will pave the way for a revolutionary new generation of therapeutic agents in the fields of personalized medicine and targeted therapy. This approach holds the potential to maximize the benefits of compounds such as quercetin while advancing clinical translation. In particular, a clearer elucidation of the complexes' stability against oxidative degradation and biotransformation pathways under physiological conditions (pH 7.4), along with their long-term toxicity and safety profiles, is critically important for human use. In addition, synergistic effects of different metal complexes (e.g., Ru and Co) on specific types of cancer or viral infections should be investigated, and *in vivo* studies are required to determine how drug delivery systems can enhance the efficacy of quercetin–metal complexes.

Innovative developments in drug delivery, including nanoformulations, could significantly improve the pharmacokinetic potential and targeted delivery of metalloflavonoids, thus maximizing therapeutic benefits while minimizing adverse effects. Furthermore, advancements in quercetin research to establish novel metal–flavonoid combinations and delivery systems could lead to the exploration of new metalloflavonoid complexes with superior pharmacological profiles and expanded therapeutic applications. Moreover, to understand mechanistic insights regarding bioavailability enhancement, precise studies should be conducted to elucidate the molecular mechanisms by which quercetin and its metalloflavonoid complexes exert their biological effects. These studies include investigating the interaction of these compounds with specific cellular targets and signaling pathways. As a result, the research, the understanding of the mechanisms of enhanced absorption, metabolism modulation, and intracellular delivery should be improved. Since the current data are insufficient for clinical translation, to design controlled clinical trials evaluating pharmacokinetics and to develop

comprehensive regulatory guidelines to ensure product consistency and patient safety can accelerate the commercialization and clinical use.

Computational studies and in silico methods, including quantitative structure–activity relationship (QSAR) models and molecular modeling, can impact the optimal design of metalloflavonoid complexes and predict their interactions with biological targets. Thus, these analyses can accelerate the transition of promising complex candidates from bench to clinical trials (Hasnat *et al.* 2024).

To conclude, research on quercetin and its metalloflavonoid strategy represents a promising frontier in the fields of natural products and therapeutics. Future perspectives on quercetin research should prioritize establishing its efficacy and safety, especially when consumed in high doses, optimal dosages, and formulations, conducting long-term safety studies, investigating drug interactions, enhancing bioavailability, and expanding human clinical trials to fully realize its therapeutic potential.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported. H Başağa is an Editor of *Redox Experimental Medicine*. H Başağa was not involved in the review or editorial process for this paper on which they are listed as an author.

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Author contribution statement

AK-M performed systematic search and prepared, reviewed, and edited the original draft of the manuscript. BV and GYA helped in manuscript preparation and reviewed and edited the manuscript. H Başağa supervised the study and administered the project. All authors have read and agreed to the published version of the manuscript.

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During the preparation of this work, the authors used GEMINI only for the purpose of language editing and figure design. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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