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Review

Antioxidant properties of flavonoid metal complexes and their potential inclusion in the development of novel strategies for the treatment against neurodegenerative diseases

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ABSTRACT

The increased oxidative stress in the acceleration of the aging process and development of the neuronal disorder are the common feature detected in neurodegenerative illness, such as Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis. Searching for new treatment against these diseases, the inclusion of exogenous antioxidant agents has shown good results. Flavonoids are polyphenols compounds present in plants, fruits and vegetables that exhibit potent antioxidant and biological properties, which are related to their chemical structure that to confer an excellent radical scavenging ability. The design of metal-flavonoid complexes allows to obtain compounds with improved biological and physicochemical properties, generating important increase of the flavonoid antioxidant properties. This evidence we motive to propose that antioxidant properties of the metal flavonoids compounds can play an important role in the design of potential novel therapeutic strategies. This review presents the structure-activity relationship on the antioxidant properties of three series of metal-flavonoid complexes: M-(quercetin), M-(morin), and M-(rutin). In general, we observed that the coordination sites, the metal ion type used, and the molar ratio metal:flavonoid present in the complexes, are important factors for to increase the antioxidant activity. On these evidences we motive to propose that the development of metal-flavonoid compounds is a potentially viable approach for combating neurodegenerative diseases.

1. Introduction

Neurodegenerative diseases are characterized by slowly progressive damage in neuronal cells and neuronal loss, which leads to compromised motor or cognitive function. Common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), among others [1,2]. These illnesses represent a significant health problem worldwide, especially for the aging population. The etiology of neurodegenerative diseases has not yet been fully elucidated; however, increased oxidative stress has been suggested as one of the potential common etiologies in these diseases. Oxidative stress may induce cellular damage, impairment of the DNA repair system, and mitochondrial dysfunction, which are key factors in the acceleration of the aging process and the development of neuronal disorders [3,4]. For this reason, the discovery and development of agents that can protect against oxidative stress damage are being actively pursued, and treatment with antioxidant molecules has shown good results.

It is widely accepted that a plant-based diet involving a high intake of fruit, vegetables, and other nutrient-rich plant foods may reduce the risk of oxidative stress related diseases [5,6]. Indeed, numerous plants have long been used as safe, effective, and sustainable sources of natural antioxidants, particularly phenolic compounds, such as phenolic acid, tannins, stilbenes, anthocyanins and flavonoids [7]. These phytochemical molecules can eliminate free radicals and other reactive oxygen species (ROS) and are thus beneficial in the fight against many pathological conditions, such as cancer, diabetes, and neurodegenerative diseases [8,9]. Antioxidants originating from foods may function as antioxidants in their own right *in vivo*, as well as bring about beneficial health effects through other mechanisms, including acting as inducers of

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mechanisms related to antioxidant defense, longevity, cell maintenance, and DNA repair [8,10,11].

In this review, we focus on the antioxidant activities of flavonoids and the increase in their antioxidant activity upon coordination with metal ions to generate metal-flavonoid complexes. The metal complexes design offers an efficient approach for the development of potential new drugs for the treatment of neurodegenerative diseases, especially Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

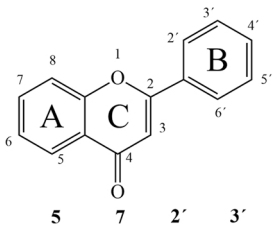
Polyphenols are a group of biologically active compounds that found abundantly are in plants and have shown a significant protective effect against injuries and degeneration neural. Flavonoids are polyphenol compounds that exhibit potent antioxidant and anti-inflammatory properties [12,13]. Flavonoids are low molecular weight molecules constituted by a diphenylpyran backbone (C6-C3-C6), comprising two phenyl rings (A and B) linked through a heterocyclic pyran C ring (Fig. 1). The biological properties of flavonoids and their dietary importance have motivated various research groups to investigate their structure-antioxidant activity relationship, in particular, evaluating their ability to act as free radical scavenging agents [14]. This characteristic may offer an effective strategy for the development of new drugs for the treatment of illnesses affected by oxidative stress, including neurodegenerative diseases.

Oxidative stress is the result of unregulated production of ROS [15], highly reactive molecules that have at least one unpaired electron in the outermost shell, which have been implicated in the pathogenesis of neurodegenerative diseases [2]. Although ROS may not be the triggering factor for neurodegenerative diseases, they are likely to exacerbate AD, PK, and ALS progression through oxidative damage and interaction with mitochondria [17] (Scheme 1). Indeed, high levels of oxidative stress are commonly observed in the brains of patients with neurodegenerative conditions [2,17].

Neuron cells are particularly vulnerable to oxidative damage due to their high polyunsaturated fatty acid content in membranes, high oxygen consumption, and weak antioxidant defense [2]. The most commonly reported cellular free radicals are hydroxyl radical (OH·), superoxide radical (O_2^{-}), nitric oxide radical (NO·) [18], and molecules no-radicals as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) can easily lead to free radical reactions in the living organisms [19].

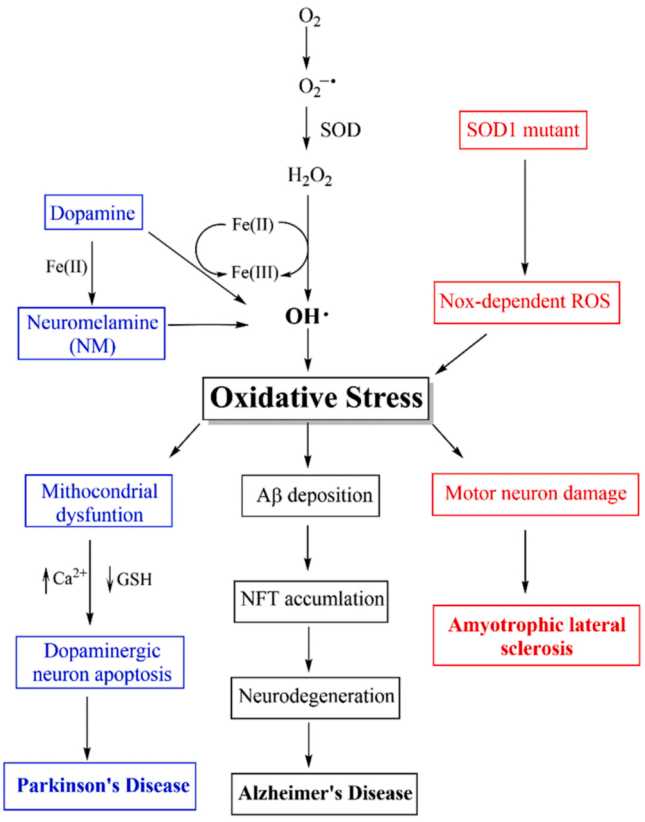
Cellular ROS are generated by exogenous sources, such as xenobiotics, viral and bacterial infections, ionizing radiation, ultrasound or photo-oxidation, poor diet, alcohol consumption, and smoking, as well as also by endogenous sources. In particular, the endogenous production of ROS is mediated by mitochondrial and non-mitochondrial ROS-generating enzymes including NADPH oxidase (Nox), xanthine oxidase (XO), and the cytochrome P450 system [1,20]. The major sources of ROS production are the mitochondrial respiratory chain and Nox system [1].

Oxygen is the most significant and essential element present in aerobic biological systems. Neuronal cells utilize 20% of respired oxygen,



	3	5	7	2′	3′	4′
Quercetine:	-OH	-OH	-OH	-	-OH	-OH
Morin:	-OH	-OH	-OH	-OH	-	-OH
Rutin:	-Glucose-rhamnose	-OH	-OH	-	-OH	-OH

Fig. 1. Basic chemical structure of flavonoids and of the selected flavonoids.



Scheme 1. : Oxidative stress in neurodegenerative disease. Blue: Parkinson's disease, black: Alzheimer's disease, and red: amyotrophic lateral sclerosis.

even though the brain represents only 5% of the body [18]. As previously mentioned, a percentage of the O_2 consumed is converted to ROS, leading to unfavorable oxidative effects on relevant for cell life biological molecules, including DNA, protein, unsaturated lipids, and enzymes [21]. The oxidative stress process leads to impaired cellular function and the formation of toxic species, such as peroxides, alcohols, ketones, and others [15]. The increased neuronal ROS production and accumulation of oxidative damage that occurs with age correlates well with the extent of neurodegeneration. Many studies have confirmed a direct relationship between oxidative stress and the development of neurodegenerative diseases, such as AD, PD, and ALS [22].

Alzheimer's disease is the most common neurodegenerative disease, which is characterized by progressive memory loss, dysfunctions in cognitive abilities, and personality changes [2,18,22,23], and leads to death within five to nine years post-diagnosis [22]. The pathophysiology of AD is mainly associated with the extracellular deposition of amyloid beta (Aβ) plaques and the accumulation of intracellular tau neurofibrillary tangles (NFT) [24–26]. Aβ plaques can deplete calcium ions (Ca^{2+}) storage in the endoplasmic reticulum, resulting in cytosolic Ca^{2+} overload. In response to cytosolic Ca^{2+} increase, endogenous GSH levels are reduced, and ROS can be over accumulated inside the cells [27]. Thus, ROS-induced oxidative stress is emerging as an important factor in the pathogenesis of AD, as ROS overproduction is thought to play a critical role in the accumulation and deposition of Aβ plaques in this disease (Scheme 1).

Parkinson's disease is the second most prevalent neurodegenerative disease, characterized by dopaminergic neuron loss in the substantia nigra pars compacta of the brain [1,22,28,29]. Approximately 1–2% of the population over 65 years of age is affected by PD and this rate increases to 4% in persons above 85 years of age [22,30]. Clinical manifestations of PD include resting tremor, muscle rigidity, bradykinesia, and a tendency to fall [22]. The pathological mechanism underlying the degeneration of dopaminergic neurons has been correlated with the

over-accumulation of ROS or other free radical species. In the brain, the primary ROS generation sites include mitochondria in the neurons and glia [16]. In PD, the production of these radicals is exacerbated by neuroinflammation, mitochondrial dysfunction, aging, dopamine degradation, GSH depletion, and high levels of Ca^{2+} or Fe(II). Moreover, this suggests that the loss of dopaminergic neurons could also be associated with the presence of neuromelanin, as highly pigmented neurons are more susceptible to damage. Neuromelanin is a dark brown pigment that accumulates metal ions, principally ferrous ion [18]. Neuromelanin formation could be related to dopamine auto-oxidation, a process induced by ROS overproduction [2]. An important increase of iron levels has been reported in dopaminergic neurons of patients with PD, which may facilitate the interaction of ferrous ion with hydrogen peroxide (H_2O_2) and enhance the production of highly toxic hydroxyl radicals (OH·) [31]. Although the exact mechanism remains unclear, significant evidence indicates that enhanced oxidative stress levels are associated with PD, and therefore this is considered as one of the major pathophysiological mechanisms underlying the disease. This is because the markers of oxidative damage to biological structures, such as lipids, proteins, and DNA oxidation, are found to be increased in patients with PD.

The amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, is a severe neurodegenerative disease characterized by progressive upper motor neuron loss in the cerebral cortex and lower motor neuron loss in the brainstem and spinal cord [18,32]. It is classified as either familial or sporadic, depending on whether it is clearly defined by inherent genetic characteristics. Sporadic ALS commonly emerges in persons between 50 and 60 years of age [33]. The symptoms observed in patients with ALS include spasticity, muscle wasting, and weakness, leading to paralysis and difficulties with speech, swallowing, and breathing. The principal pathological hallmark observes in ALS is the formation of cytoplasmic aggregates in degenerating motor neurons and surrounding oligodendrocytes, although the aggregates are also present in the frontal and temporal cortices, hippocampus, and cerebellum [34]. The mechanisms of ALS development include various factors, such as mitochondrial dysfunction, excitotoxicity, neuroinflammation, and oxidative stress. One of the common genetic mutations identified in ALS occurs in the superoxide dismutase-1 (SOD1) gene [35]. The functions of SOD1 are diverse and include scavenging excessive superoxide radicals ($O_2^{\bullet-}$), converting this radical anion into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2). SOD1 mutants enhance the production of Nox2-dependent ROS, which is thought to be the cause of motor neuron death in ALS; therefore, SOD1 functional loss can lead to increased levels of oxidative stress. [36].

It has been suggested that oxidative imbalance and resultant neuronal damage may play a critical role in the initiation and progression of neurodegenerative diseases. Considering the important role of oxidative stress in these diseases, the decrease of ROS levels may represent a promising treatment option for slowing down neurodegeneration and alleviating the associated symptoms.

Flavonoids play an essential role in protection against phenomena of oxidative damage. They have a high capacity for scavenging free radicals, primarily hydroxyl and superoxide radicals, which are highly reactive species involved in neurodegenerative diseases [12]. The antioxidant properties of flavonoids are related to their radical scavenging capacity, metal-reducing activity, and chelation of metals, which are involved in the generation of reactive hydroxyl radicals. These properties arise from the polyphenolic chemical structure constitutes by the C_6-C_3-C_6 ring system (Fig. 1). In particular, the antioxidant activity depends on the number and position of the hydroxyl groups in the structure. For example, some radicals are reduced via proton transfer through of the homolytic cleavage of the catechol group (3′-OH and 4′-OH) present in some flavonoid structures [37]. However, although the catechol moiety is an important requirement for antioxidant activity, some flavonoids devoid of catechol groups also display remarkable radical scavenging performances due to the ability to transfer hydrogen atoms, or the simultaneous hydrogen/electron transfer or sequential electron transfer with proton loss [39].

2. Flavonoid metal complexes

The poor water solubility and low bioavailability of flavonoids have limited their biological evaluation studies for the development of potential new drugs [39]. This behavior is due to the presence of hydroxyl and carbonyl groups in their structure, which allow for the chelation of biological metal ions and interaction with biomolecules, that could be important effects on their pharmacological and pharmacokinetic properties [40,41]. Therefore, this structural characteristic of flavonoids could be used for the design of metal complexes with improved and novel biological properties.

In the last three decades, inorganic medicinal chemistry has become relevant in the development of prospective metal-based drugs for the treatment of various diseases [42–44]. Since the inclusion of cisplatin in cancer therapy, the design of novel metal complexes with pharmacological properties has become an important approach for the treatment of these and other pathologies, such as parasitic diseases [45–47], bacterial affections [48], Alzheimer's disease [49,50], among others. The inclusion of a metal center in the scaffold of an organic molecule (bioactive ligand) could lead to enhanced pharmacological properties. The metal-bioactive ligand interaction would increase the bioavailability of the organic molecule because this union modifies the solubility, lipophilicity, and stability in biological systems, thus allowing for the therapeutic targets to be reached more efficiently. Thus, the therapeutic index can be improved by increasing in the biological activity, decreasing toxicity, or both. Furthermore, the coordination of a bioactive ligand can achieve metal-drug synergism through dual or multiple mechanisms of action [42].

Flavonoids are excellent ligands for designing metal complexes. Hydroxyl-substituted flavonols, such as phenolic compounds, have favorable structural characteristics for coordinating metal ions [39]. There are three potential coordination sites (Fig. 1): (1) between the 3-OH and 4-C═O groups in the C ring, (2) between the 5-OH (in the A ring) and 4-C═O groups (in the C ring), and (3) between the 3′-OH and 4′-OH groups in the B ring.

Flavonoids are weak acids that undergo deprotonation, which strongly favours their coordination to metal ions [41]. In particular, the acidity of the 3-OH protons is the highest; therefore, 3-OH and 4-C═O groups are the first sites to be implicated in the complexation process. In complexes that include flavonoids with 3′- and 4′-OH groups, it was observed that the catechol moiety acts as a second metal ion binding site [51]. The 5-OH group is not involved because of the lower proton acidity and steric hindrance caused by the first complexation. In addition, experimental evidence has shown that 3-OH has a higher chelation capacity because the delocalization of the oxygen electron occurs to a greater extent compared to that of 5-OH, which facilitates the delocalization of π electrons over the molecular structure [52].

As mentioned, the featured flavonoid properties are their capacity to act as antioxidants and free radical scavengers [53]. The coordination of metal ions with flavonoid ligands can affect the kinetic factors as well as the thermodynamics of the reaction, which causes that the reaction with free radicals are probably easier and faster to occur [39]. In addition, metal coordination can change the redox potential of a ligand and thus affect the flavonoid antioxidant activity. For example, Pekal et al. reported an increase in the radical scavenging activity of the Cu (II)-quercetin complex, which showed a lower redox potential values compared to free quercetin. The more facile oxidation of flavonoids in the coordination sphere of copper was due to the destabilization of their structure upon coordination [54].

Flavonoid metal complexes have demonstrated enhanced free radical scavenging activities in assays as DPPH and $ABTS^{+}$, among others [40]. However, the observation that metal complexes increase the antioxidant properties of flavonoids is not a rule; for example, the Fe(III)-luteoline

complex displays a lower scavenging activity in the DPPH assay than the free ligand [55]. Studies on the antioxidant properties of metal-flavonoid compounds have demonstrated that the increase in the activity depends on the central metal ion and flavonoid type used, and the metal:flavonoid molar ratio present in the compound [40,56–60].

The 3' and 4' ortho-dihydroxyl groups are the most significant contributors to the antioxidant activity of flavonoids. These catechol moieties form ortho-semiquinone radicals that are highly stabilized by electron delocalization and intramolecular hydrogen bonding. The combination of the C2 =C3 and 4-C=O groups in the C ring also assists in the delocalization of the π-electrons in the B ring. This in turn influences the dissociation of phenolic hydroxyl groups, as well as the stability of the phenoxy radicals formed on the B ring [61].

The *meta*-hydroxyl groups present in the A ring are less important than the B ring dihydroxy groups, which are more readily oxidized [62]. (Fig. 2).

Thus, the principal factor to consider in the design of metal-flavonoid complexes with high antioxidant activity is the coordination site between the flavonoid structure and the central metal ion. It is important that the flavonoids possess the 3´-OH and 4´-OH groups in their structure, and that coordination occurs preferably at the 5-OH, 4-C=O, and/or 3-OH groups. For these reasons, in this review, we focus on metal-based compounds that include flavonoid ligands with these structural characteristics, hence, we selected flavonoids quercetin, morin, and rutin (Fig. 1). Thereby, we want to show that metal-flavonoid complexes with enhanced antioxidant properties can emerge as good candidates for the design of novel agents for the treatment of neurodegenerative diseases.

In the literature, the antioxidant properties of metal-flavonoid complexes have been analyzed using various analytical techniques. The antioxidant activities of the selected complexes are summarized in Table 1.

The radical scavenging ability was evaluated employing electronic transfer (ET) and hydrogen atom transfer (HAT) assays using the following methodologies:

i) ***DPPH assay*:** This is a spectrophotometric technique based on a non-enzymatic method used to provide basic information on the reactivity of compounds for scavenging free radicals. This study evaluated the decrease in the absorbance of the DPPH radical (or ABTS radical) resulting from the presence of antioxidant molecules. The methodology allows for the determination of scavenging ability by monitoring the decrease in the absorbance of the radical with varying antioxidant concentrations; radical scavenging is expressed as a percentage of samples compared to antioxidant standard (usually Trolox); the EC_{50} is the amount of antioxidant needed to reduce the initial DPPH concentration by 50%, and the assay results can be determined as a function of time relative to the action of an antioxidant standard, usually Trolox [63].

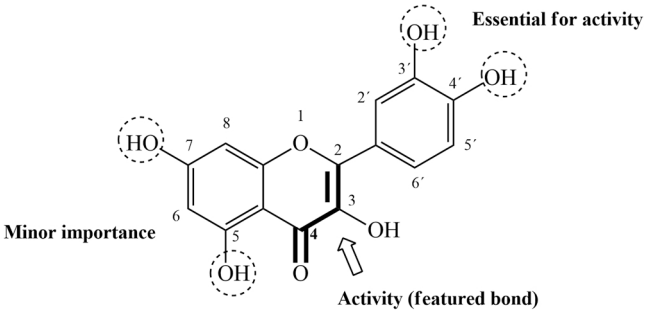


Fig. 2. Main structural features responsible for the antioxidant activity of flavonoids.

Table 1
Antioxidant activities of metal-flavonoid complexes and of free flavonoids.

Antioxidant assay	Compounds	Antioxidant activity	Reference
QUERECTIN METAL COMPLEXES			
	(nmol (TE[a])/mL)		Bratu et al.
Spectrophotometric Techniques (DPPH)	[Zn^{II}-quercetin]	0.872*	[74]
	[Cu^{II}-quercetin]	1.368	
	quercetin	1.327	
	(mg (TE[a])/Kg)		Mutlu Gençkal
Spectrophotometric Techniques (ABTS)	[Co^{II}(queH-1)Cl(phen)(H_2O)]•$2H_2O$	0.31	et al. [72]
	[Ni^{II}(queH-1)Cl(phen)(H_2O)]•$2H_2O$	0.35	
	[Cu^{II}(queH-1)Cl(phen)] •$2.5H_2O$	0.37	
	[Cu^{II}(queH-1)Cl(bpy)] •$2H_2O$	0.61*	
	***(%)*[b]**		Chen et al.
Spectrophotometric Techniques (DPPH)	[Cr^{III}(quercetin)$_2$]	88*	[73]
	quercetin	76	
	***(%)*[c]**		Dehghan
Spectrophotometric Techniques (DPPH)	[Sn^{II}_2(quercetin)]	45	et al. [52]
	quercetin	70*	
	***(%)*[c]**		
Spectrophotometric Techniques (ABTS)	[Sn^{II}_2(quercetin)]	~55	
	quercetin	~70*	
	***(mmol Fe^{+2}/L)*[d]**		
Spectrophotometric Techniques (FRAP)	[Sn^{II}_2(quercetin)]	1.0	
	quercetin	1.5*	
	***(TE)*[e]**		
Chronoamperometric Technique (CRAC)	[Fe^{II}-quercetin]	11.10*	Porfírio
	quercetin	8.42	et al. [75]
	***EC_{50} (μM)*[f]**		
Spectrophotometric Techniques (DPPH)	[Cu^{II}_2(quercetin)(H_2O)$_4$]Cl_2	2.29	De Souza et al. [37]
	[Fe^{II}_2(quercetin)(H_2O)$_8$]Cl_2	2.11	
	[Al^{III}_2(quercetin)(H_2O)$_8$]Cl_4	1.67*	
	[Zn^{II}_2(quercetin)(H_2O)$_4$]Cl_2	1.92	
	quercetin	2.79	
MORIN METAL COMPLEXES			
		***(TE)*[e]**	Porfírio
Chronoamperometric Technique (CRAC)	[Fe(II)-morin]	13.58*	et al. [75]
	morin	11.78	
RUTIN METAL COMPLEXES			
		***EC_{50} (μM)*[f]**	De Souza
Spectrophotometric Techniques (DPPH)	[Cu^{II}_3(rutin)$_2$(H_2O)$_6$]Cl_2	5.02	et al. [37]
	[Fe^{II}_3(rutin)$_2$(H_2O)$_{12}$]Cl_2	4.67	
	[Al^{III}_3(rutin)$_2$(H_2O)$_{12}$]Cl_5	3.76*	
	[Zn^{II}_3(rutin)$_2$(H_2O)$_6$]Cl_2	4.27	
	rutin	18.23	

* Highest radical scavenging activity in each series of complexes.

[a] : TE = Trolox equivalent.

[b] : % = 100 * (Ac-As)/Ac; Ac: absorbance DPPH pure, As: reduction of DPPH absorbance in the presence of samples (metal-flavonoid complexes) in the monitoring time.

[c] : % = 100 * (1-A_f)/A_0; A_0 is the absorbance of the ABTS cation and A_f is the absorbance after sample addition in the monitoring time.

[d] : values obtained from a standard calibration curve generated using varying concentrations of $FeSO_4$ * 7 H_2O.

[e] : $[Ce^{3+}]_{sample}$ /$[Ce^{3+}]_{Trolox}$; $[Ce^{3+}]_{sample}$: concentration of cerium ion produced via reaction with the sample antioxidant; $[Ce^{3+}]_{Trolox}$: concentration of cerium ions produced using the Trolox standard.

[f] : EC_{50} = antioxidant concentration needed to reduce the initial DPPH concentration by 50%.

ii) ***FRAP assay*:** The ferric reducing antioxidant ability (FRAP) assay is an ET-based method that measures the reduction of ferric ions in the $Fe(TPTZ)_2Cl_3$ complex by antioxidant molecules, which generates the intensely blue-colored ferrous (Fe(II)) complex in an acidic medium. Antioxidant activity is determined based on the increase in the absorbance at 595 nm, and the results are expressed as Fe^{2+} equivalents or relative to the activity of an antioxidant standard [64].

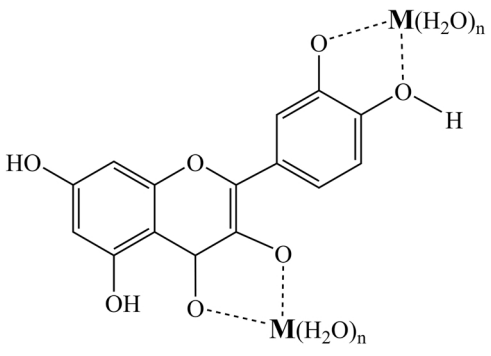
iii) ***CRAC assay*:** This is an electrochemical assay that utilizes chronoamperometry technique for directly quantify the antioxidant ability of compounds. The assay utilizes an acid solution of cerium (IV) sulfate as the oxidant. This technique evaluates the decrease in the Ce(IV) concentration at specific time points following the reaction with the added antioxidant sample. Chronoamperometric results are commonly analyzed based on the linear relationship between the instantaneous current (*I*) and time of monitoring (*t*), the slope of which, in turn, is directly proportional to the remaining bulk concentration of the Ce(IV) species for a given antioxidant [63,75].

2.1. Quercetin metal complexes

Quercetin (3,3´,4´,5,7-pentahydroxyflavone, Fig. 3) is one of the most common flavonoids present in nature and it has attracted considerable attention owing to its biological and pharmaceutical properties [65]. It is a potent antioxidant and a major dietary flavonoid commonly found in various foods, such as apples, tea, onions, nuts, berries, cauliflower, and cabbage [66]. The biological properties of quercetin arise from the presence of hydroxyl and carbonyl groups in the molecular structure, which enable to coordinate to several endogen metal ions [51].

Flavonoid metal complexes are generally synthesized by dissolving the flavonoid salt in an aqueous or alcoholic solution, followed by the addition of a metal salt dissolved in the same solvent. The reaction is performed under varying conditions, such as stirring or heating; normally, a base is added to deprotonate the hydroxyl groups and thus facilitate coordination [40]. Metal complexes that include quercetin as ligand have shown various binding sites and distinct metal/quercetin stoichiometries due to the variation in the experimental conditions employed in specific synthetic methodologies [67–70]. For example, in the complexes of Fe(III)–quercetin, synthesized in an acid solution, the catechol group is the major chelation site [49]. However, Markovic et al. reported the formation of a 1:2 (metal: ligand ratio) complex in an acid solution with coordination via 3-OH/4-C═O or 4-C═O/5-OH sites, and Fe(III) binding to the catechol group in a 1:1 metal: ligand ratio at higher pH values [71].

The antioxidant properties of metal-quercetin complexes have been



M = Co(II), Cu(II), Mg(II), Fe(II), Al (III), Zn(II)

n = 2 or 4

Fig. 3. Schematic representation of metal-quercetin complexes.

studied employing DPPH assays, measuring their hydrogen donating or radical scavenging ability using UV–vis spectroscopy. The reaction between quercetin and DPPH occurs in two steps indicated by: (1) a rapid decay in DPPH absorbance (λ_{max} = 515 nm in methanol) decays quickly and (2) a slow decay in DPPH absorbance over ~ 1 h to reach a constant value. The fast step is associated with the abstraction of the most labile H-atoms, being of the 3´-OH and 4´-OH groups of quercetin [52]. The authors studied the antioxidant activities of different metal complexes, including those of Cr(III), Co(II), Cu(II), Mg(II), Al (III), Fe(II), and Zn(II) ions, and found that complexation with metal ions increased the antioxidant activity of quercetin. [37,52,70–75].

In all the reviewed cases, the presence of metal ions led to a more rapid decay in DPPH absorbance than observed with free quercetin. This suggests that the radical scavenging activity of quercetin increases when it is included in the coordination compound.

The stoichiometric composition of the metal-quercetin complexes was 2:1 (metal: ligand), and in most cases, this was obtained by Jobs method [76]. The metal compounds were characterized using various techniques, and in all cases, the authors proposed the same structure for the complexes. The coordination of quercetin toward the metal ion center occurred through the 3´-OH and 4´-OH groups in the B ring, and the 3-OH and 4-C═O in the C ring, as shown in Fig. 3. Except in the Cr (III)-quercetin complex, that using DFT calculations, the authors proposed coordination between the 5-OH (in the A ring) and 4- C═O (in the C ring) groups [73].

It was assumed that for quercetin, 3´-OH and 4´-OH are primarily involved in H-atom transfer reactions to DPPH, and/or that each –OH group facilitates H-abstraction from the adjacent hydroxyl group by stabilizing the corresponding radical through a combination of electronic and H-bonding effects. This reaction is favored because the 3-OH moiety interacts with the B ring through hydrogen bonding with 6´-H, thereby "fixating" the B ring in the same plane as the A and C rings [37,77,78]. The increase in the antioxidant activity of flavonoid complexes suggests that the metal ions generate a positive effect on the physicochemical properties of flavonoids. The bond dissociation enthalpy (BDE) obtained from DFT calculations for quercetin and the Cr(III)-quercetin complex [73] evidenced the lowest energy value in the 4´-OH site in both molecules. The obtained BDE values were 74.59 kcal/mol and 75.20 kcal/mol for the complex and flavonoid, respectively. These results confirm that the coordination of Cr(III) ions favors the reactivity of the catechol site in quercetin, and therefore enhances its ROS scavenging ability.

The HAT mechanism was also studied by de Souza et al. [37], who determined the radical scavenging activities of Cu(II), Fe(II), Al(III), and Zn(II)–quercetin complexes (Table 1). The results were obtained as EC_{50} radical scavenging on DPPH and TEC_{50} (as the time needed to obtain the EC_{50} concentration). $[Al^{III}_2(quercetin)(H_2O)_8]Cl_4$ was the most active complex with the lowest EC_{50} value and the shortest radical scavenging time, which was directly dependent on both parameters. The activity of the Al(III)-quercetin complex increased by 40% and 59% in EC_{50} and TEC_{50} values, respectively, in comparison to that of the free ligand, being attributable to the vacant p-orbitals of the aluminum cation, which are good π acceptors. Therefore, de Souza et al. also evaluated the antioxidant efficiency (AE), obtained from the ratio between EC_{50} and TEC_{50} values, and thus classified the complexes as highly active antioxidants in the following order: Al(III)-quercetin > Zn(II)- quercetin > Fe(II)- quercetin > Cu(II)- quercetin. Fig. 4 shows the mechanism proposed for the reaction between the metal-quercetin complexes and the DPPH radical.

A hydrogen atom is abstracted from the complex to give a semiquinone complex stabilized by the metal center and by conjugation with the 3-OH group. Due the 4´-OH bond is homolytically cleaved in this step, the EC_{50} values depend on the differences between the energies of the semiquinone complex (II) and the ground state energies of the metal complexes (I) (expressed as ΔE). The stabilization of complex I increased the ΔE and decreased antioxidant activity, while complex II stabilization

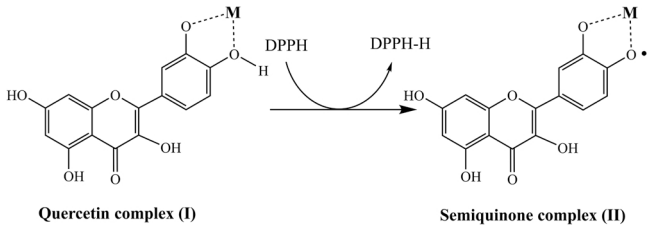


Fig. 4. Proposed pathway of metal–quercetin complex oxidation by a DPPH radical via a semiquinone radical intermediate.

decreased ΔE and increased antioxidant activity. Moreover, the higher antioxidant activities of the metal complexes compared to that of free quercetin could be due to the acquisition of an additional radical scavenging metal center in the complexes, as mentioned by the authors, likely being a superoxide-dismounting center [37,79,80].

On the other hand, Bratu et al. studied the antioxidant capacity of Zn (II)- and Cu(II)-quercetin employing photochemiluminometric techniques [74]. Only the copper complex showed a slight increase in the antioxidant activity compared with that of free quercetin, and the Zn(II) complex showed an antioxidant capacity 10-fold lower than that of the free ligand.

The antioxidant activities of these complexes differed from the results previously described. This could be due to the coordination by the 3-OH and 4-C═O groups in quercetin and to the choice of evaluation method reported in the literature. The method used by Bratu et al. to assess the antioxidant activity entails photosensitized chemiluminescence, which is based on multiple accelerations of a natural reaction leading to the generation of a superoxide anion radical. Instead based on the principle of the DPPH method, the oxidation process of the complex occurs more readily than the flavonoid due to the destabilization of their structure. However, these results lead to the same conclusion concerning the lack of stability of flavonoid structures subsequently to the coordination [74].

From these results, it can be inferred that could be exist a correlation between the antioxidant activity and the redox behavior of the quercetin metal complexes. In this context, Porfírio et al. [75] used the CRAC electrochemical assay to measure the antioxidant capacity of Fe (II)-quercetin and also other flavonoid metal complexes. Previously, they obtained the redox potential of quercetin (130 mV for 3´-OH and 4´-OH groups, 170 mV for the 3-OH group, and 830 mV attributed to the 5-OH and 7-OH,measured vs. Ag/AgCl electrode) and observed a new oxidation peak at ~300 mV, which is characteristic of the Fe-quercetin oxidation process. Electrochemical characterization indicated that quercetin is coordinated preferentially by the 5-OH and 4-C═O groups to the metal ion. The antioxidant capacity was then determined by the CRAC assay indicated a 32% increase in the quercetin activity after complexation. Although the redox potentials of quercetin did not shift due to the complexation, the electrochemical profile suggests that these flavonoids form stable complexes with the Fe(II) ion, and such complex formation significantly enhances their antioxidant capacity [37,75]. Pekal et al. studied the antioxidant capacity of Cu(II)-quercetin using the DPPH radical scavenging method and obtained a good correlation with the oxidation potential [54]. The cyclic voltammograms of quercetin and its solutions in the presence of Cu(II) showed well-defined peaks and practically no reverse reduction peaks, indicating an electrochemical process involving two electrons. The oxidation peak potentials for the Cu (II)-quercetin complex were observed at lower values for free quercetin, which suggests that coordination with metal ions facilitates the oxidation process due to the destabilization of the quercetin structure.

Although the coordination of quercetin leads to a significant increase in their antioxidant capacity, some metal complexes have been reported to generate the opposite effect. Dehghan et al. developed a metal complex including Sn(II) as a central metal ion, and spectroscopic characterization evidenced coordination through 3-OH and 4-C═O, as well as the 3´,4´-dihydroxyl group. Antioxidant activity was evaluated using the DPPH, $ABTS^{+}$, and FRAP assays. The results indicated that the radical scavenging activity and ferric reducing potential of free quercetin had decreased after chelation of the stannous cation, suggesting that the electron transfer ability of quercetin had diminished after complex formation, which probably decreases the redox potential of quercetin on the metal complex [52].

2.2. Morin metal complexes

Morin (3, 5, 7, 2´, 4´-pentahydroxyflavone, Fig. 1) is a yellowish pigment and a bioflavonoid constituent of many plants, such as tea, coffee, cereal grains, and a variety of fruits and vegetables [58]. Flavonols such as morin play an important role in the bioavailability of metal ions present in low amounts in the body due to their chelating ability resulting in the formation of complex structures with endogenous metal ions, which can then be readily excreted from the body [39]; their potent antioxidant activity is responsible for their various biological and biochemical effects, including anti-inflammatory, anti-neoplastic, and cardioprotective activities [38,81–83].

Morin is composed of two benzene rings (A, B), a third oxygen-containing (C) ring, and a C2 =C3 fragment, all of which are important electronic-structural features. Five hydroxyl groups at the 5, 7, 3, 2`, and 4` positions are the most significant contributors to the antioxidant activity of this flavonoid. In addition, the carbonyl and hydroxyl groups can coordinate metal ions to form coordination compounds. There are two potential coordination sites in the structure of flavonol: *(i)* between 5-OH and 4-C═O groups in the A and C rings respectively, and *(ii)* coordination site between 3`-OH and 4`-OH groups in the B ring.

Porfirio et al. studied the electrochemical stability and antioxidant capacity of Fe(II)-flavonol complexes, including morin [75]. Based on their cyclic voltammetry results, the authors inferred a unique coordination site between 3-OH and 4-C═O, as evidenced by the 100 mV shift in the oxidation peak compared to free morin. The CRAC assay showed a slight increase (up to 15%) in their antioxidant capacity compared to that of free morin, reflecting their improved ability to reduce Ce(IV) species through of single-electron transfer. According to the exposed, these results suggest that the electronic transfer mechanism could occur from the 3-OH group.

The available 5-OH and 4-C═O morin coordination sites allowed also to obtain a Cr(III)-biflavonol complex, as reported by Panhwar et al. [38]. The DPPH assay was used to measure the radical scavenging abilities of Cr(III)-$(morin)_2$ and free morin, with the complex showing superior results (radical scavenging ability was measured but antioxidant activity values were not reported). Fig. 5 shows the mechanism of homolytic cleavage proposed by Markovic for the radical scavenging process [84].

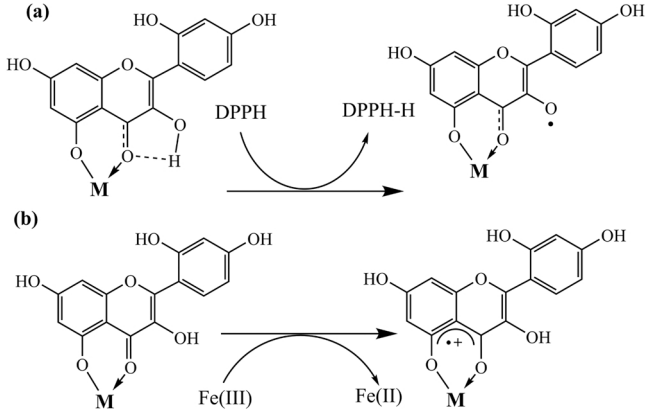


Fig. 5. (a) Homolytic cleavage of 3-OH in the DPPH assay, and (b) mechanism proposed for ferricyanide reduction in the presence of Cr(III)-$(morin)_2$.

Homolytic cleavage allows to increase the antioxidant activity by 10%, which can be attributed to the higher polyphenolic content available in the complex structure (compared with free morin); the effectiveness depends on the experimental conditions, the structural conformation adopted in the solution medium, the interactions between the radical and the reducing agent, and possible steric effects around the 3-OH active site.

In addition, the reducing power was evaluated using the FRAP assay. The Cr(III)-(morin)$_2$ complex and free morin were used as reducing agents of Fe(III) /ferricyanide to the ferrous form; being the Cr(III)-(morin)$_2$ complex that displayed the best performance, which is expected if the phenolic groups per unit are considered, being the highest in the complex.

2.3. Rutin metal complexes

Rutin (3-(glucose-rhamnose)− 5,7,3´,4´-tetrahydroxyflavone, shown in Fig. 1, is a flavonol that includes four OH substitutions at the 5,7,3´, and 4' positions and a 3-glycoside derivative with C-3 substituted by glucose-rhamnose sugar groups. It is a compound of natural origin with a variety of pharmaceutical properties, including anti-allergic, anti-inflammatory, antiproliferative, and anti-carcinogenic activities [74].

Unlike quercetin and morin, rutin is differentiated by the lack of a hydroxyl group directly linked to the base rings and C-3 substitution. Although this glycoside substitution could avoid chelation at the 5-OH /4-C═O site, a double metallic substitution at the 5-OH/ 4-C═O site as in the 3´, 4´-OH site, has been suggested based on evidence from spectroscopic analysis [37,85]. As mentioned above, in addition to quercetin complexes, Bratu et al. reported two Zn(II)- and Cu(II)-rutin complexes (Fig. 6) with slightly higher DPPH scavenging abilities than that of free rutin. Structurally, the authors inferred that the metal center is linked to 5-OH/4-C═O, which is the only coordination proposed based on the spectroscopic evidence [74]. In both cases, the metal ion was found to be tetracoordinate, being surrounded by one rutin molecule for [Zn(rutin)(ac)] complex and two rutin in the [Cu(rutin)$_2$] complex, which would support the increase in antioxidant activity due to the double reductions available in the complex compared to the uncoordinated ligand.

On the other hand, the mechanism of reducing action is implicit, according to the available information, and it is proposed that the only site available for homolytic rupture would be the catechol group (3´, 4´-OH). Unlike in morin and quercetin, HAT, or ET followed by proton transfer cannot occur at the 3-OH/4-C═O site because of its 3-C substitution. Finally, the DPPH assay indicated that the [Zn(rutin)(ac)] complex is a better reducing agent than [Cu(rutin)$_2$], showing increases of 28% and 14% (compared to free rutin), respectively. This difference could be due to the inherent plasticity of the copper ion center, whereby the ligand arrangement around the Cu(II) can disfavor the catechol sites of the B rings, probably due to a loss of co-planarity with the rest of the molecule. The disposition of the hydroxyl groups from the glycoside fragment could be oriented towards the catechol group to stabilize the biflavonoid structure through hydrogen bonding. Thus, these interactions would block the antioxidant sites. As mentioned above, de Souza et al. evaluated the oxidant activity with respect to time of a series of biflavonoid metal complexes, including rutin 3,4-catechol complexes: [Cu_3(rutin)$_2$(H_2O)$_6$]Cl_2, [Fe_3(rutin)$_2$(H_2O)$_{12}$]Cl_2, [Al_3(rutin)$_2$(H_2O)$_{12}$]Cl_5, and [Zn_3(rutin)$_2$(H_2O)$_6$]Cl_2 [37]. The EC_{50} values obtained (Table 1) revealed that the antioxidant activity of M-rutin was higher than that of free rutin, whose activities values was the lowest in the series. Thus, it is observed that the coordination of the metal center to rutin leads to more drastic changes in activity compared to that of the other metal-flavonoid complexes. Based on the optimized metal-flavonoid structure using the DFT method [73,86], we can infer that the effect of the metal-rutin bond would partially restore the coplanarity of the flavonoid rings and reduce the interaction of the OH groups from the bulky rutinoside group (rutine-glycoside derived).

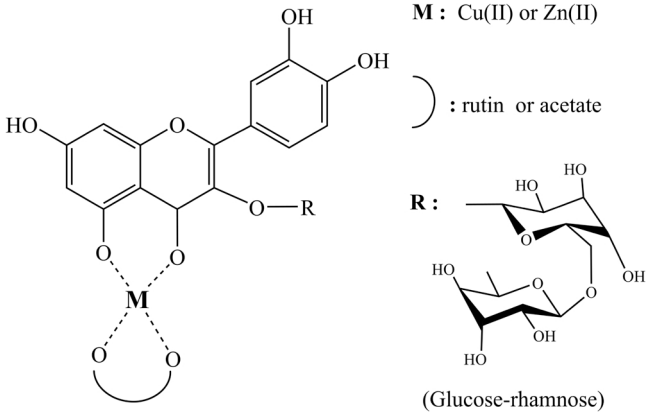


Fig. 6. Proposed structure for [Zn(rutin)(ac)] and [Cu(rutin)$_2$] complexes (Bratu et al.).

This effect was also evidenced by Gençkal et al. (Table 1) [72], who studied a series of metal-flavonoid complexes that included various planar co-ligands, such as bipyridine and phenanthroline. The square-pyramidal copper complex [Cu^{II}(queH-1)Cl(bpy)]•2 H_2O displayed a higher antioxidant activity than Co(II)-, Ni(II)-, and Cu (II)-quercetin-phenanthroline-derived complexes, confirming that the planarity of the ligand, the geometric environment adopted by the metal center, and the redox properties of each metal ion are relevant factors in the design of antioxidant metal-based agents.

2.4. Perspective

The chemical structure of flavonoids enables their efficient coordination with various metal ions. The generation of flavonoid metal complexes with improved physicochemical properties has emerged as a relevant strategy for the development of compounds with superior pharmacological profiles.

Based on the information available, in general, the inclusion of metal ions into quercetin, morin, and rutin structures enhanced the radical scavenging ability of the flavonoids.

This evidence demonstrates that metal-flavonoid compounds can play an important role in the design of potential novel therapeutic strategies based on antioxidant agents. The development of new and better antioxidant molecules is a potentially viable approach for combating neurodegenerative diseases.

CRediT authorship contribution statement

Esteban Rodríguez-Arce: Design figures, Writing the paper, Marianela Saldías: Design figures, Writing the paper.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of interest

The authors declare no conflicts of interest.

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