

Article

Synthesis, Characterization, Antioxidant and Antimicrobial Potentials of Novel Organometallic Compounds Derived from Quercetin

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Abstract

Quercetin, one of the most abundant flavonoids in nature, has attracted the attention of many researchers due to its chemical and biological properties. A series of metal–quercetin complexes (Cu^{2+} , Co^{2+} , Zn^{2+} , Sn^{2+} , Al^{3+} , Cd^{2+} and Mg^{2+}) were synthesized and systematically characterized by Fourier transform infrared spectroscopy (FTIR), UV-visible spectroscopy (UV–Vis) and nuclear magnetic resonance (NMR). These analyses confirmed that the complexes predominantly form through coordination with the 4-carbonyl group and adjacent phenolic hydroxyls. This induces measurable shifts in the $\nu(\text{C}=\text{O})$, $\nu(\text{O}-\text{H})$, and $\pi \rightarrow \pi^*$ transition bands relative to free quercetin. The antioxidant capacity of the complexes was evaluated using 2,2-Diphenyl-1-Picrylhydrazyl (DPPH $\bullet$) radical scavenging method, 2,2'-Azinobis(3-Ethylbenzothiazoline-6-Sulfonic Acid) (ABTS $\bullet^+$) radical activity, and Ferric Reducing Antioxidant Power (FRAP) assay. Several complexes exhibited higher radical scavenging efficiency than quercetin, with inhibition percentages exceeding 80% in the DPPH $\bullet$ and ABTS $\bullet^+$ assays. Others showed reduced activity due to the masking of redox-active hydroxyl groups during metal coordination. FRAP results corroborated these trends, indicating metal-dependent modulation of reducing power. Antimicrobial evaluation revealed that selected complexes were more active than free quercetin, particularly against *Staphylococcus aureus* and *Candida* spp., with minimum inhibitory concentrations (MICs) ranging from 75–250 $\mu\text{g mL}^{-1}$. Overall, metal complexation significantly alters the electronic structure and biological behavior of quercetin, highlighting the potential of metal–flavonoid complexes as multifunctional antioxidants and antimicrobials.

Keywords: Quercetin; synthesis; metal complexes; antioxidant potentials; antimicrobial activities



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1. Introduction

Natural products, generally secondary metabolites, are produced (with signaling or defense functions), extracted and isolated from plants, animals, microorganisms and marine organisms. These products have been continuously studied and serve as important resources for the discovery of new drugs. Among the various secondary metabolites, polyphenols stand out for their chemical and biological potential, which has been widely described in the literature. Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the most abundant flavonoids in nature and has attracted the attention of many researchers due to its chemical and biological properties. It is a member of the flavonol family, which are compounds with the 3-hydroxyflavone structure [1]. Quercetin is considered the main flavonoid found in foods with diverse pharmacological activities. It has anticancer and induces apoptosis through downregulating P4HA2, antiallergic, antiviral, antiprotozoal, antimicrobial, cardiovascular, anti-inflammatory effects [2–4]. The anti-inflammatory effect has been the subject of studies as the efficacy of quercetin has been investigated in patients with severe symptoms of the disease, including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [5,6].

The bioavailability of quercetin in the gastrointestinal tract can vary widely, but averages about 20% [7]. Furthermore, the low rate of gastrointestinal absorption, rapid metabolism, and rapid clearance result in reduced bioavailability *in vivo*, which limits their application in pharmaceuticals and functional foods [8]. The interaction of flavonoids with metal ions can alter the antioxidant properties and also the biological effects of flavonoids. It is suggested that the biological activity of an organic ligand can be enhanced when coordinated or mixed with a suitable metal ion due to its ability to act as a free radical acceptor [9]. Thus, the scope of chemistry related to metal complexation has become increasingly evident.

Organometallic compounds containing metals such as iron (Fe), arsenic (As), and silver (Ag) have been synthesized. However, their applications may be limited due to their ease of oxidation and toxicity. Ong and Gasser [10] highlighted that organometallic compounds are increasingly advancing and gaining importance in the field of medicine, from the antimicrobial organoarsenics that have been prominently used throughout history to the ferrocene-containing compounds that have been investigated for various diseases such as malaria or cancer. In the last three decades, inorganic medicinal chemistry has become relevant in the development of possible metal-based drugs for the treatment of various diseases [11]. Since the inclusion of cisplatin in cancer therapy, the design of new metal complexes with pharmacological effects has become an important approach for the treatment of these and other pathologies, such as parasitic diseases, bacterial diseases, and Alzheimer's disease [12].

The inclusion of a metal center in the structure of an organic molecule (bioactive ligand) can lead to improved pharmacological properties. The bioactive metal-ligand interaction would increase the bioavailability of the organic molecule by modifying the solubility, lipophilicity, and stability in biological systems, allowing therapeutic targets to be achieved more efficiently. Thus, index therapy can be improved by increasing biological activity, decreasing toxicity, or both. Furthermore, the coordination of a bioactive ligand network can achieve metal-drug synergism through dual or multiple mechanisms of action [13].

The aim of this work is to obtain novel organometallic complexes, resulting from structural modifications of the bioflavonoid quercetin with metals (Cu^{2+} , Co^{2+} , Zn^{2+} , Sn^{2+} , Al^{3+} , Cd^{2+} and Mg^{2+}), through chemically sustainable synthetic routes, and to evaluate their antioxidant and antimicrobial potentials. This study is relevant due to the innovative potential of the synthesized compounds, which can be used in various pharmaceutical practices. They can contribute to permeability and absorption studies (*in vitro*, *in vivo*, and

ex vivo), dissolution assays, drug delivery systems, and bioequivalence studies of quercetin and its derivatives by evaluating potential increases in bioavailability. The compounds can also serve as a basis for in silico studies of potential drug candidates with antimicrobial and anti-inflammatory properties.

2. Materials and Methods

2.1. Reagents and Materials

The reagents were purchased from commercial sources (Sigma Aldrich[®], St. Louis, MO, USA; Neon[®], São Paulo, Brazil; and Êxodo Científica[®]), Sumaré, São Paulo, Brazil) and were used without further purification: Quercetin $\geq 95\%$ (117-39-5), 2,2-bipyridine (366-18-7), triethylamine (121-44-8), methanol 99.8% (67-56-1) (MeOH), ethanol 99% (64-17-5) (EtOH), dimethylacetamide 99% (127-19-5) (DMA), dimethyl sulfoxide 99% (67-68-5) (DMSO), and diethyl ether 99% (60-29-7). Cobalt(II) chloride 99% (7791-13-1) ($\text{Cl}_2\text{Co} \cdot 6\text{H}_2\text{O}$), Copper(II) nitrate trihydrate 99% [$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$] (10031-43-3), Magnesium(II) chloride hexahydrate 99.0% ($\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$) (7791-18-6), Zinc(II) chloride 97% P.A. (ZnCl_2) (7646-85-7), Cadmium(II) iodide 99% (CdI_2) (7790-80-9), Aluminum(III) chloride 99% (7446-70-0) (AlCl_3), and Tin(II)chloride dihydrate 99% ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$) (10025-69-1).

2.2. Synthesis of the Metal-Quercetin Complexes

In this study, a series of organometallic compounds were synthesized through complexation with the metal salts Cu^{2+} , Co^{2+} , Zn^{2+} , Sn^{2+} , Al^{3+} , Cd^{2+} , and Mg^{2+} , resulting in seven metal complexes. The quercetin-metal complexes were synthesized using methods described in previous literature [14–18]. In a 50 cm^{-3} two-necked round-bottomed flask provide with electromagnetic stirrer, thermometer. Added quercetin $\bullet 2\text{H}_2\text{O}$ (0.17 g; 0.01 mol) in MeOH (20 mL) stirred until solid quercetin was completely dissolved within 15 min the color of the solution was light yellow then quickly added solid 0.02 mol of metal ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, $\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$, ZnCl_2 , $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, AlCl_3 , CdI_2 and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$) in the reaction mixture, the time varied according to the metallic salt used, for $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, $\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$, AlCl_3 and CdI_2 it was 1.5 h; for $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ it was 6 h; and for CoCl_2 and ZnCl_2 it was 3 h. After stirring the reaction mixture was filtered, and the filtrate was slowly evaporated at room temperature for 10 days. There was no further purification, the complexes and the complexes analyzed by FTIR that did not demonstrate modification were discarded.

2.3. Characterization of the Metal-Quercetin Complexes

2.3.1. Fourier Transform Infrared Spectroscopy (FTIR) Analysis

The absorption spectra in the infrared range, from 4000 to 650 cm^{-1} , were obtained with an FTIR spectrophotometer Cary 630 FTIR Spectrometer, brand Agilent Technologies[®] (Santa Clara, CA, USA), with 4 scans, resolution of 4 cm^{-1} , the crystal used was Diamond ATR (Attenuated Total Reflectance). The software used to produce the graphs was Origin Pro 8.

2.3.2. Nuclear Magnetic Resonance (NMR) Analysis

The NMR experiments were carried out on a Bruker (TX, USA) Avance III 500 spectrometer (11.75 T), operating at a frequency of 500.13 MHz for the hydrogen nucleus; equipped with a three-channel inverse detection probe 1H , ^{13}C and XBB, Broad Band Inverse Detection (BBI) for the analysis of liquid samples in 5 mm diameter tubes. The experiments were performed at $25\text{ }^\circ\text{C}$ (298 K), using dimethyl sulfoxide (DMSO) as solvent. Topspin 3.5 software (Bruker BioSpin) was used to operate and process the experiments. Amix Viewer software, version 3.9.15, was used for chemometric analyses.

2.3.3. UV/Visible Spectroscopy Analysis

UV-Vis analysis was performed on a Cary UV-Vis 60 from Agilent Technologies® (Santa Clara, CA, USA) in the range of 190 to 1000 nm. To solve the complexes, 5 mg of the synthesized complexes were dissolved in 100 mL of methanol in quartz cuvettes containing 3 mL of the solution.

2.4. Antioxidant Potentials

2.4.1. 2,2-Diphenyl-1-Picrylhydrazyl (DPPH•) Radical Scavenging Method

DPPH assays were conducted as proposed by Brand-Williams; Cuvelier and Berset [19]. It was necessary to prepare a solution containing 2.4 mg of DPPH radical, weighed in 100 mL of methanol. However, due to the sensitivity of the analytical balance, it was necessary to weigh 24 mg (0.024 g) in 100 mL of methanol and dilute it 10 times to obtain a concentration of 60 mM. From the synthesized product, dilutions with concentrations of 1000, 500, 250, 100, 50, and 25 $\mu\text{g mL}^{-1}$ were prepared, with 3 sample dilutions in each dilution: 0.1 mL of the extract + 3.9 mL of the 60 micromolar stock of DPPH. Then, after homogenization, the reading was carried out on the spectrophotometer, in three cuvettes, in the dark, and after 30 min, at 517 nm, after observing the stabilization of the absorbance, and the values obtained were noted. The procedure was also carried out in triplicate with a negative standard, i.e., the DPPH solution with methanol only, respecting the same quantity, noting the final absorbance and the absorbance after waiting 30 min. The absorbance of the blank (methanol only) was also measured without waiting 30 min.

2.4.2. Antioxidant 2,2'-Azinobis(3-Ethylbenzothiazoline-6-Sulfonic Acid) (ABTS•⁺) Radical Activity

ABTS assays were conducted as proposed by Re et al. [20]. A mass of 192 mg (0.192 g) of ABTS was dissolved in 50 mL of distilled water in a volumetric flask, followed by homogenization and transfer to a labeled amber glass bottle. The solution was stored under refrigeration for up to one month. Then, 189.2 mg (0.1892 g) of potassium persulfate was dissolved in distilled water and made up to 5 mL in a volumetric flask. The solution was then homogenized and transferred to an amber glass bottle. To perform the test, dilutions of the products obtained at concentrations of 1000, 500, 250, 100, 50, and 25 $\mu\text{g mL}^{-1}$ were prepared in triplicate. To perform the assay, 30 μL of each extract was transferred to 3.0 mL of ABTS•⁺ radical. Vortexing of the tubes in the presence of ABTS and products was necessary for better homogenization. After stirring, it was necessary to wait 6 min for the reaction between the radical and the product obtained to occur. The reading was made on a Femto (São Paulo, Brazil), model 700 Plus spectrophotometer, at a wavelength of 734 nm, in the dark, according to the equation:

$\text{ABTS}^{\bullet+} \text{ Absorbance (\%)} = (1 - A_0/A_1) \times 100$; where A_0 is the absorbance of the control and A_1 is the absorbance of the sample or standard. All assays were performed in triplicate. IC₅₀ values were calculated and expressed as the mean $\pm$ SD, in μM .

2.4.3. Ferric Reducing Antioxidant Power (FRAP) Assay

FRAP assays were conducted as proposed by Benzie and Strain [21]. The FRAP reagent was prepared by combining 25 mL of 0.3 M acetate buffer, 2.5 mL of 10 mM TPTZ solution and 2.5 mL of 20 mM ferric chloride aqueous solution and used immediately after preparation. For the test, dilutions of the products obtained at concentrations of 1000, 500, 250, 100, 50, and 25 $\mu\text{g mL}^{-1}$ were prepared in triplicate. In a dark environment, a 90 μL aliquot of each dilution of the extract was transferred to test tubes, to which 270 μL of distilled water was added, mixed with 2.7 mL of FRAP reagent, homogenized in a tube

shaker and kept in a water bath at 37 °C. After 30 min, the prepared mixture was read (595 nm) and the FRAP reagent was used as a blank to calibrate the spectrophotometer.

2.5. Antimicrobial Potentials

Minimum inhibitory concentrations (MICs) were determined for quercetin and metal complexes using the 96-well plate microdilution method (SPL Life Sciences®, Gyeonggi-do, Korea). The studies were performed according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Briefly, 100 µL of Mueller-Hinton broth (Merck®, Darmstadt, Germany) was added to each well and serial dilutions of each substance were performed to obtain concentrations in the range of 1–1000 µg mL^{−1}.

The bacterial cell suspension was adjusted to the turbidity of the McFarland 0.5 standard (108 cells/mL), and for *Candida*, 5×10^3 cells/mL was confirmed by hemocytometric counting [22,23]. The MICs, minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) of each compound were determined by the microdilution method using 96-well plates. The wells without substances were used as positive controls, while the controls with substances were used as negative controls. An inoculum of each microbial cell suspension was added to the wells and the plates were incubated at 35 °C for 24 h. At the end of this incubation, the colony counts on the blood agar medium were used to determine Minimum inhibitory concentrations (MIC), Minimum bactericidal concentration (MBC), and Minimum fungicidal concentration (MFC). Analyses were repeated three times.

3. Results and Discussion

3.1. Synthesis of Metal Complexes

The complexation of quercetin with Cu²⁺, Co²⁺, Zn²⁺, Sn²⁺, Al³⁺, Cd²⁺, and Mg²⁺ ions produced seven metal-quercetin complexes. These complexes' structures can be explained based on spectroscopic evidence and established coordination chemistry principles. While the lack of single-crystal X-ray diffraction (XRD) data prevents definitive structural determination, the proposed coordination modes are supported by Fourier-transform infrared (FTIR), ultraviolet–visible (UV–Vis), and nuclear magnetic resonance (NMR) analyses. There is also strong consistency with previously reported quercetin–metal systems. Therefore, the structures discussed herein should be regarded as hypothetical yet chemically plausible models [24–26].

Flavonoids such as quercetin preferentially coordinate metal ions through the 4-oxo and 5-hydroxyl groups, forming stable chelate rings that significantly alter their physicochemical and biological properties [27]. Quercetin contains multiple oxygen donor sites that can coordinate metal ions. These sites include the 3-hydroxyl/4-carbonyl (O3/O4), 5-hydroxyl/4-carbonyl (O5/O4), and catechol moiety at the B ring (O3'/O4'). The chelation site involving the C4 carbonyl group and the C5 hydroxyl group is widely recognized as thermodynamically favorable due to the formation of stable five-membered chelate rings [28,29]. Spectroscopic data from this study suggest that complexation primarily occurs at this pharmacologically relevant site, leading to substantial electronic redistribution within the flavonoid framework.

Coordination involving the hydroxyl groups at the 3' and 4' positions of the B ring was also inferred, particularly for metal ions with high affinity for catechol-type ligands. Although this site is generally considered of lower pharmacological importance compared to the C-ring chelation site, its participation in metal binding has been extensively reported [13,15,30]. Indeed, depending on the nature of the metal ion and experimental

conditions, quercetin–metal complexation has been described at the O3/O4, O4/O5, and O3'/O4' positions [14,18,31].

The propensity of specific hydroxyl groups to participate in metal coordination is closely related to their acidity, since binding typically occurs through deprotonated hydroxyl oxygens. Structural considerations suggest that the hydroxyl group at position 3 is more acidic than that at position 5 due to its proximity to the carbonyl group and the heterocyclic character of ring C [32,33]. These features enhance electron delocalization and facilitate deprotonation, favoring coordination at the O3/O4 site. Nevertheless, several experimental studies have demonstrated that coordination at the O5/O4 site is also highly favorable, particularly for divalent and trivalent metal ions [32,34,35].

Literature data further corroborate these coordination preferences. Ren et al. demonstrated that iron–quercetin complexes preferentially form via the 3-OH/4-C=O site, with binding strength following the order 3–4 > 4–5 > 3'–4' [30]. Similar trends have been reported for nickel, magnesium, calcium, and zinc complexes, supporting the idea that quercetin can adopt different coordination modes depending on the metal ion and stoichiometry [14,36–38]. In complexes containing one metal ion per quercetin molecule, chelation through the O3/O4 site generally predominates. However, higher metal-to-ligand ratios may promote additional coordination involving the B-ring hydroxyl groups.

The synthetic routes employed in this study (Figure 1) were selected or adapted to favor complexation at established coordination sites. Although literature-based methods have been successfully applied to various complexes, modifications to reaction times were necessary for the Cu(II), Al(III), and Zn(II) systems to effectively chelate. These adaptations are consistent with previous reports emphasizing quercetin's sensitivity to solvent polarity, temperature, and metal salt reactivity [13,39,40]. It should be noted that the synthesis route for the Al(III)–quercetin complex was not described by the aforementioned authors and was tested for the first time in this study.

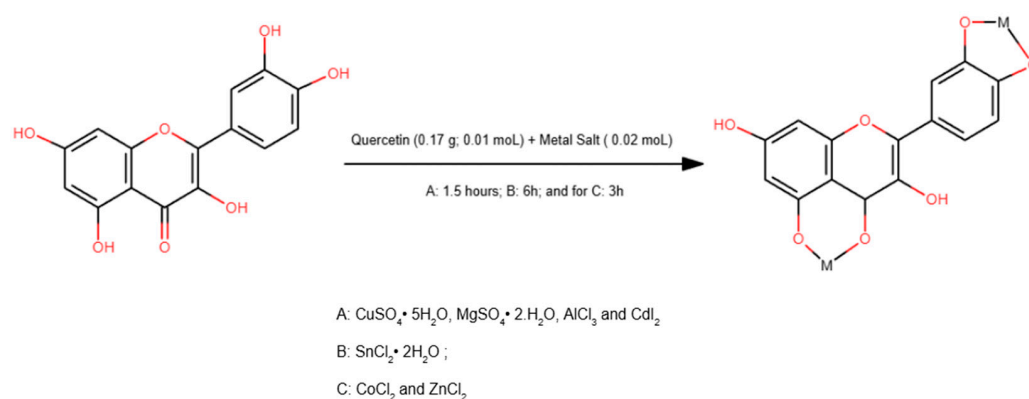


Figure 1. Hypothetical structural formulas of the synthesized complexes.

Overall, inserting metal ions into the quercetin structure induces significant changes to its electronic and coordination environment, primarily through chelation of carbonyl and phenolic oxygen atoms. While definitive structural elucidation awaits XRD analysis, the proposed structures are strongly supported by spectroscopic evidence and extensive precedent in the literature [39,40]. These hypothetical structural models provide a sound basis for interpreting the physicochemical and biological properties of the synthesized metal–quercetin complexes.

3.2. FTIR Characterization of Metal Complexes

The FTIR spectrum of free quercetin shows well-defined absorption bands that are characteristic of flavonoids. A broad $\nu(\text{O–H})$ stretching band is observed in the $3400\text{--}3200\text{ cm}^{-1}$

region, which arises from phenolic hydroxyl groups involved in intra- and intermolecular hydrogen bonding. The strong absorption near 1660 cm^{-1} is attributed to the $\nu(\text{C}=\text{O})$ stretching vibration of the γ -pyrone ring, while bands in the $1600\text{--}1500\text{ cm}^{-1}$ region correspond to aromatic $\nu(\text{C}=\text{C})$ stretching modes. Additional absorptions in the $1300\text{--}1000\text{ cm}^{-1}$ range are attributed to $\nu(\text{C}-\text{O})$ stretching vibrations of phenolic and ether groups. These functional groups are well known to influence both metal coordination and antioxidant activity in quercetin-based systems [33,41,42].

Upon complexation with metal ions, systematic and metal-dependent spectral changes are observed, confirming coordination through oxygen donor atoms. In the Al(III) –quercetin complex, the $\nu(\text{O}-\text{H})$ stretching band decreases in intensity and shifts slightly toward lower wavenumbers. This indicates the involvement of phenolic hydroxyl groups in metal binding. Concurrently, the $\nu(\text{C}=\text{O})$ stretching band shifts downwards more clearly than in free quercetin, confirming the participation of the carbonyl oxygen in coordination. These features are consistent with the formation of a bidentate chelate involving the 3-OH and 4-C=O sites, as has been widely reported for Al(III) –quercetin complexes [42–44].

The FTIR spectrum of the Cd(II) –quercetin complex exhibits more pronounced modifications. Significant broadening and attenuation of the $\nu(\text{O}-\text{H})$ band are observed, together with a marked shift in the $\nu(\text{C}=\text{O})$ band to lower wavenumbers. Noticeable changes in the $1300\text{--}1000\text{ cm}^{-1}$ region, associated with $\nu(\text{C}-\text{O})$ vibrations, further support coordination via phenolic and carbonyl oxygen atoms. These spectral features suggest strong metal–ligand interactions and reduced availability of free hydroxyl groups, consistent with prior research on Cd(II) –quercetin complexes [17,45,46].

Moderate but distinct spectral changes are detected for the Co(II) –quercetin complex. The $\nu(\text{O}-\text{H})$ band shows reduced intensity, while the $\nu(\text{C}=\text{O})$ stretching vibration undergoes a slight downshift, indicating coordination through the carbonyl group and at least one hydroxyl function. In contrast, the aromatic $\nu(\text{C}=\text{C})$ bands remain largely unchanged, suggesting preservation of the flavonoid π -electron system. Similar FTIR behavior has been reported for Co(II) –quercetin complexes and is associated with the partial retention of redox-active sites [16,29,47].

More pronounced spectral alterations are observed in the Cu(II) –quercetin complex. A substantial decrease in the intensity of the $\nu(\text{O}-\text{H})$ stretching band, together with a clear shift in the $\nu(\text{C}=\text{O})$ band to lower wavenumbers, indicates strong coordination involving both the phenolic and carbonyl oxygen atoms. Additional changes in the $1200\text{--}1000\text{ cm}^{-1}$ region further confirm chelation. These findings are consistent with the strong affinity of Cu(II) for oxygen donor ligands and with literature reports describing significant electronic reorganization in Cu(II) –quercetin complexes, often correlated with altered antioxidant behavior [18,44,48].

In contrast, the Mg(II) –quercetin complex exhibits comparatively subtle spectral changes. The $\nu(\text{O}-\text{H})$ band remains visible, although slightly shifted and less intense than in free quercetin, while only a minor displacement of the $\nu(\text{C}=\text{O})$ band is observed. Overall, the FTIR profile of MgQ closely resembles that of the free ligand, suggesting weaker and more ionic metal–ligand interactions. This behavior is characteristic of Mg(II) –flavonoid complexes and has been associated with the preservation or enhancement of antioxidant activity due to the retention of free phenolic hydroxyl groups [15,49].

Significant spectral changes are also observed upon coordination with Sn(II) . The $\nu(\text{O}-\text{H})$ band becomes broader and shifts toward lower wavenumbers, indicating the strong involvement of phenolic hydroxyl groups and suggesting partial or complete deprotonation. The $\nu(\text{C}=\text{O})$ stretching band shows a noticeable downshift compared to free quercetin, which provides strong evidence for coordination through the carbonyl oxygen. Alterations in the $1200\text{--}1000\text{ cm}^{-1}$ region, attributed to $\nu(\text{C}-\text{O})$ vibrations, further support chelation

via oxygen donor atoms. According to Dehghan and Khoshkam [17], the strong interaction between Sn(II) and phenolic groups results in stable complexes, though it reduces antioxidant activity by occupying redox-active hydroxyl sites [17,49].

In comparison, the Zn(II)–quercetin complex exhibits more subtle spectral modifications. The $\nu(\text{O-H})$ band remains broad with slightly reduced intensity, indicating the partial involvement of hydroxyl groups without extensive deprotonation, a behavior typical of Zn(II) as a moderate Lewis acid forming relatively labile metal–oxygen bonds [14]. A slight shift in the $\nu(\text{C=O})$ stretching frequency suggests the carbonyl group participates in chelation, likely through bidentate coordination involving the 3-OH/4-C=O or 5-OH/4-C=O sites, as is commonly observed in Zn(II)–flavonoid complexes [49]. Changes in the $1300\text{--}1100\text{ cm}^{-1}$ region associated with $\nu(\text{C-O})$ vibrations further confirm complex formation. Importantly, Zn(II)'s relatively mild coordination preserves some of the free phenolic hydroxyl groups. This explains why antioxidant activity is maintained or enhanced in DPPH and ABTS assays for ZnQ, as documented extensively in the literature [14].

Overall, the FTIR results unequivocally confirm the formation of quercetin–metal complexes and demonstrate that coordination predominantly occurs through phenolic hydroxyl and carbonyl groups. The extent of spectral perturbation depends heavily on the nature of the metal ion. Cu(II), Cd(II), and Sn(II) induce more pronounced modifications, while Mg(II) and Zn(II) produce milder effects. These observations are consistent with the reported structure–coordination relationships in quercetin–metal systems (Figure 2) and provide a robust spectroscopic framework for interpreting differences in antioxidant behavior.

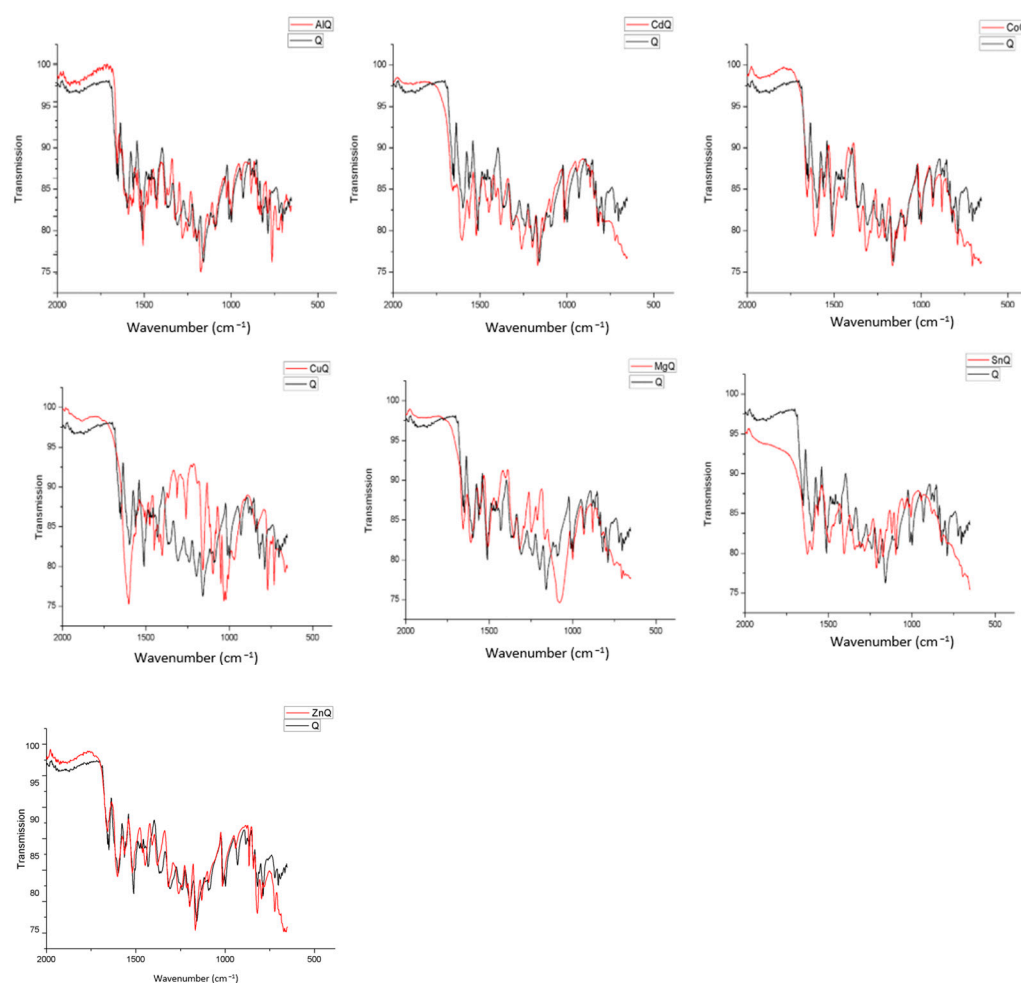


Figure 2. FTIR spectra of synthesized all synthesized complexes.

3.3. NMR Analysis of Metal Complexes

In the ^1H NMR spectra, free quercetin exhibited signals in the 6–9 ppm range (Figure 3). These signals were attributed to the aromatic protons of the hydroxylated flavonoid structure of quercetin, which is consistent with classical spectral assignments for flavonoids [50,51]. These signals were absent in the metal–quercetin complexes, indicating coordination through phenolic hydroxyl groups and leading to deprotonation and metal insertion. All complexes exhibited significant spectral changes compared to free quercetin, confirming coordination. SnQ and CoQ displayed singlets around 4 ppm, which were assigned to protons involved in metal–oxygen interactions. This evidence suggests the direct participation of hydroxyl groups in complex formation. In contrast, signals near 3 ppm were preserved in the other complexes and were attributed to non-coordinating hydroxyl groups at C-3 and C-7. This finding is consistent with previous reports on flavonoid systems, in which these positions do not participate in chelation [50]. The singlet observed at approximately 12 ppm in free quercetin and in the complexes CoQ, CdQ, and ZnQ was assigned to a proton engaged in strong intramolecular hydrogen bonding with the 4-oxo group. This demonstrates the preservation of the carbonyl functionality in complexes where this moiety is not involved in metal coordination [52,53].

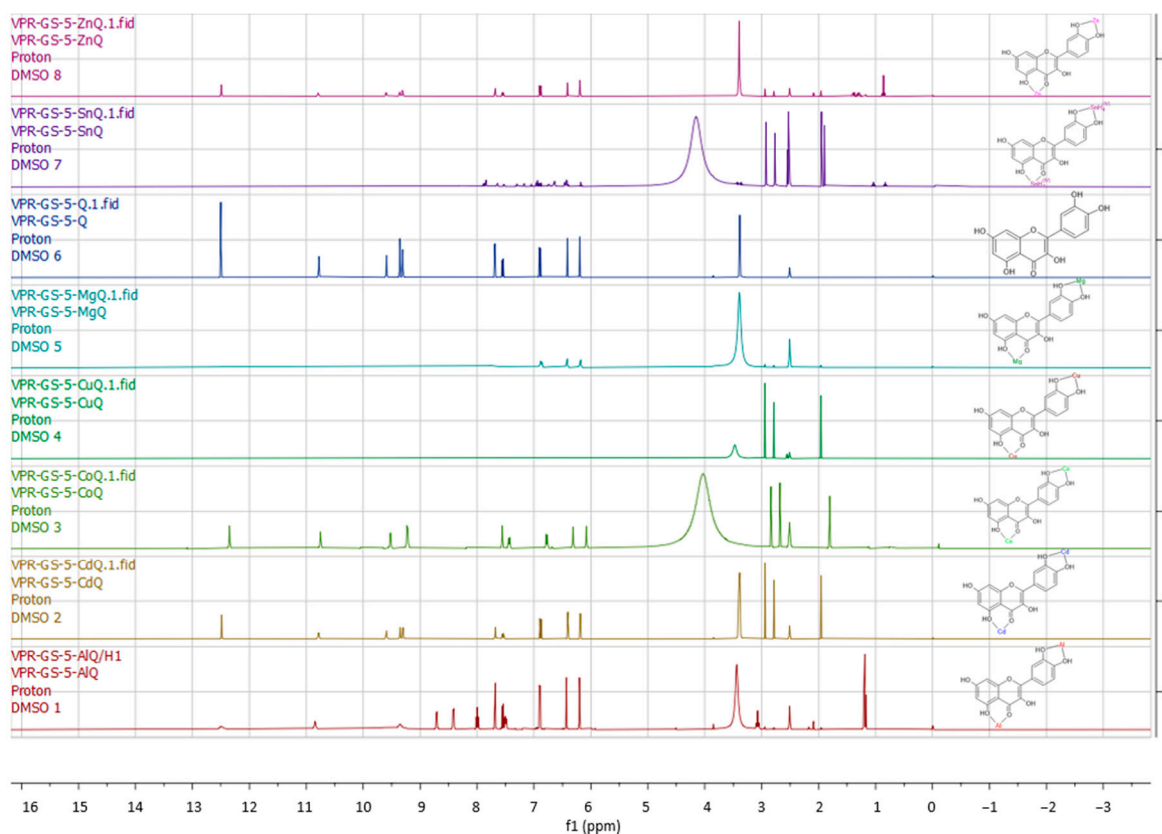


Figure 3. NMR spectra of synthesized complexes with quercetin.

These observations are consistent with the findings of Ghosh et al. [15], who reported the disappearance of the 3-OH signal and chemical shift perturbations in the Mg–quercetin complex due to deprotonation and increased electronic conjugation upon formation of the complex. Similarly, Halevas et al. [14] demonstrated that the protons of ring A in the Zn–quercetin complex remained largely unaffected, while significant changes occurred in the B-ring proton signals. This confirms preferential coordination through the 3',4'-dihydroxy system. From a broader perspective, systematic NMR studies of flavonoid–metal complexes indicate that, depending on the nature of the metal ion and the coordination environment,

quercetin preferentially coordinates metal ions via the phenolic hydroxyls of ring B and/or the 5-OH/4-oxo chelation site. This leads to hydroxyl signal suppression, chemical shift perturbations, and electronic reorganization of the flavonoid framework, as established in foundational works and coordination chemistry studies [52,53]. The signals obtained by NMR were:

Q ^1H NMR (400 MHz, DMSO) δ 12.50, 10.78, 9.59, 9.36, 9.31, 7.69, 7.69, 7.56, 7.56, 7.54, 7.54, 6.90, 6.88, 6.42, 6.41, 6.20, 6.19, 3.85, 3.39, 2.52, 2.51, 2.51, 2.50, 2.50, 1.20.

AlQ RMN H' ^1H NMR (400 MHz, DMSO) δ 12.49, 10.85, 9.63, 9.35, 8.72, 8.71, 8.70, 8.43, 8.41, 8.02, 8.01, 8.00, 7.99, 7.98, 7.97, 7.68, 7.68, 7.57, 7.56, 7.56, 7.54, 7.53, 7.51, 7.51, 7.50, 7.50, 7.50, 7.49, 7.48, 7.48, 7.20, 6.94, 6.91, 6.89, 6.49, 6.43, 6.43, 6.20, 6.20, 6.00, 5.99, 5.99, 3.85, 3.44, 3.11, 3.09, 3.09, 3.08, 3.07, 3.06, 3.05, 3.04, 2.94, 2.78, 2.52, 2.51, 2.51, 2.50, 2.50, 2.17, 2.09, 1.96, 1.21, 1.19, 1.17, -0.01 .

CdQ ^1H NMR (400 MHz, DMSO) δ 12.48, 10.78, 9.59, 9.59, 9.35, 9.30, 7.68, 7.68, 7.56, 7.55, 7.54, 7.53, 6.90, 6.87, 6.41, 6.40, 6.19, 6.18, 3.85, 3.41, 3.40, 3.40, 3.39, 3.39, 3.38, 2.94, 2.78, 2.52, 2.51, 2.51, 2.50, 2.50, 1.96, 1.21, -0.01 .

CoQ ^1H NMR (400 MHz, DMSO) δ 12.35, 10.75, 9.52, 9.23, 9.22, 7.56, 7.55, 7.45, 7.44, 7.43, 7.42, 6.79, 6.77, 6.32, 6.31, 6.08, 6.08, 4.03, 2.84, 2.68, 2.51, 1.81, 1.12, -0.11 .

CuQ ^1H NMR (400 MHz, DMSO) δ 7.92, 7.91, 7.90, 7.89, 7.86, 7.86, 7.84, 7.68, 7.67, 7.56, 7.55, 7.54, 7.53, 7.53, 7.50, 7.43, 7.41, 7.40, 7.40, 7.23, 7.10, 6.97, 6.94, 6.90, 6.89, 6.88, 6.87, 6.78, 6.75, 6.73, 6.68, 6.67, 6.66, 6.66, 6.64, 6.63, 6.62, 6.48, 6.47, 6.47, 6.46, 6.45, 6.44, 6.44, 6.43, 6.43, 6.42, 6.42, 6.41, 6.19, 6.19, 6.18, 6.17, 6.16, 6.16, 3.85, 3.48, 2.95, 2.79, 2.61, 2.57, 2.55, 2.54, 2.52, 2.51, 2.51, 2.50, 2.50, 1.96, 1.91, 1.23, 0.00.

MgQ ^1H NMR (400 MHz, DMSO) δ 10.83, 9.23, 7.91, 7.77, 7.76, 6.88, 6.86, 6.42, 6.18, 3.39, 2.95, 2.79, 2.51, 1.96, 1.23, 0.88, 0.87, 0.85, 0.00.

SnQ ^1H NMR (400 MHz, DMSO) δ 8.26, 7.85, 7.84, 7.81, 7.17, 7.04, 6.96, 6.94, 6.66, 6.65, 6.64, 6.64, 6.63, 6.63, 6.46, 6.44, 6.43, 6.42, 6.42, 4.15, 2.93, 2.77, 2.55, 2.53, 2.52, 2.51, 2.51, 2.50, 1.95, 1.90.

ZnQ ^1H NMR (400 MHz, DMSO) δ 12.49, 10.79, 9.60, 9.36, 9.31, 7.68, 7.68, 7.66, 7.56, 7.55, 7.54, 7.53, 6.90, 6.88, 6.42, 6.41, 6.19, 6.19, 4.33, 3.85, 3.40, 3.10, 3.08, 3.07, 2.94, 2.78, 2.52, 2.51, 2.51, 2.50, 2.50, 2.09, 1.96, 1.43, 1.42, 1.41, 1.41, 1.40, 1.39, 1.39, 1.39, 1.37, 1.37, 1.36, 1.36, 1.35, 1.34, 1.34, 1.33, 1.32, 1.31, 1.30, 1.30, 1.29, 1.29, 1.28, 1.27, 1.27, 1.26, 1.25, 1.22, 1.19, 1.17, 1.15, 0.88, 0.86, 0.84, -0.01 .

3.4. UV-Vis Characterization of Metal Complexes

Flavonoids exhibit absorption bands in the ultraviolet (UV) and visible (Vis) regions that arise from electronic $\pi\text{--}\pi^*$ transitions [54]. The UV-Vis spectrum of quercetin in ethanol exhibits two characteristic absorption bands at 256 and 374 nm. These bands are attributed to the benzoyl (rings A/B) and cinnamoyl (rings B/C) systems, respectively. The spectra of the synthesized complexes (Figure 4) showed significant shifts in the 375 nm band for complexes A, B, C, E, F, and G. However, complex D retained both quercetin bands, which shifted bathochromically to 270 and 410 nm.

Flavonoids typically exhibit two absorption bands in the UV-Vis region: Band I (320–385 nm) is associated with the cinnamoyl system of ring B. Band II (240–280 nm) is related to the benzoyl system of ring A. Both bands originate from $\pi \rightarrow \pi^*$ electronic transitions. Upon metal coordination, these bands undergo bathochromic shifts, indicating modifications in electronic structure and conjugation [52]. Metal binding to quercetin preferentially involves the 3-OH and 4-oxo groups because of the higher acidity and chelating ability of the 3-hydroxyl proton. The 3',4'-dihydroxy groups may coordinate a second metal ion. The 5-OH group generally does not participate because of its lower

acidity and steric hindrance after initial complexation [47]. Comparative UV–Vis studies with related flavonoids support this coordination pattern [30].

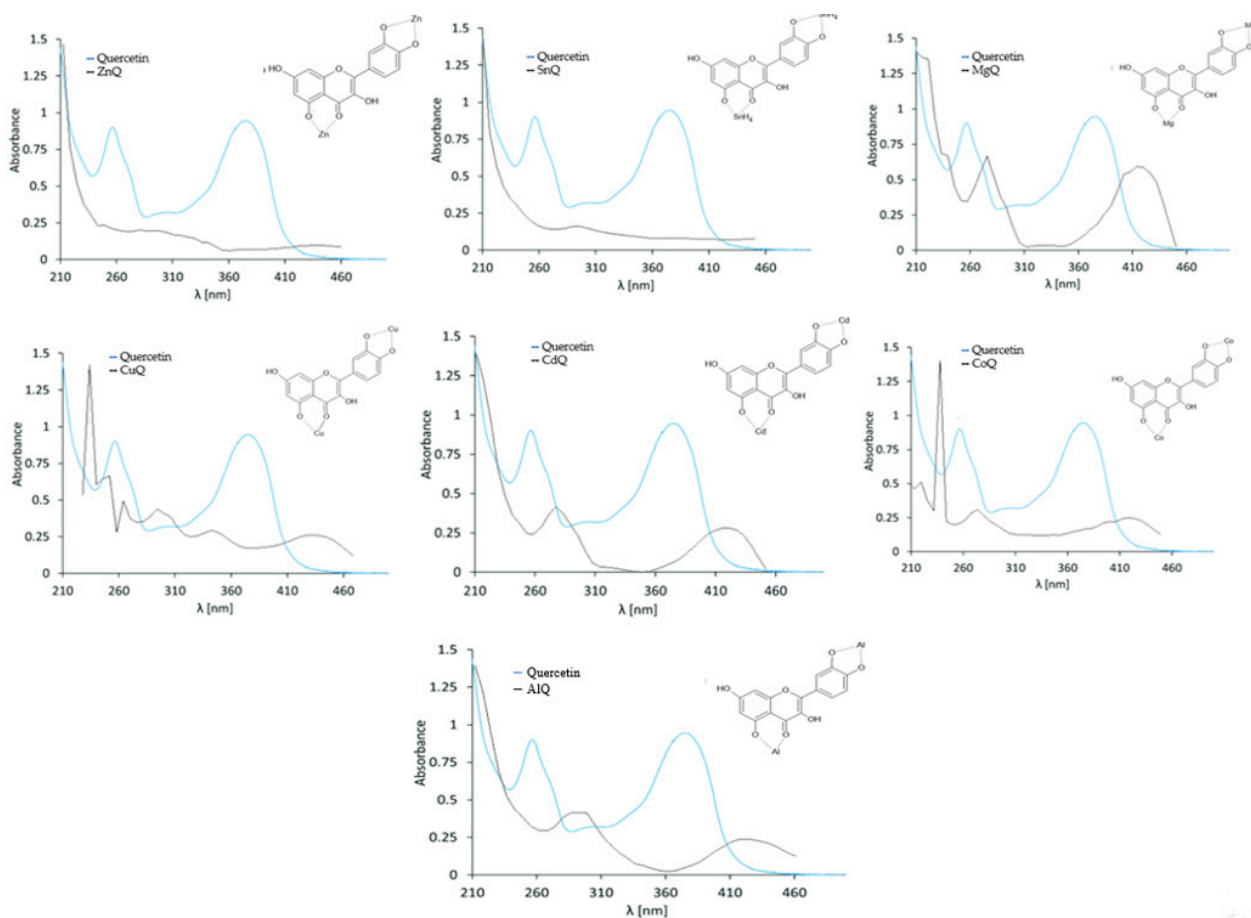


Figure 4. UV-Vis spectra of synthesized complexes with quercetin.

Several metal–quercetin complexes have been reported to exhibit consistent bathochromic and hypo- or hyperchromic effects. Zn^{2+} coordination induces a significant red shift in Band I to approximately 428 nm, which is attributed to increased conjugation via chelation through the 3-OH/4-oxo moiety [13,14]. Similarly, Sn^{2+} complexation produces a gradual red shift in Band I and the appearance of a new absorption band near 443 nm, which confirms coordination at the 3-hydroxyl and 4-carbonyl groups [16].

Similar spectral behavior has been observed in other flavonoid–metal systems. For example, Halevas et al. [14] reported bathochromic and hyperchromic shifts in curcumin–metal complexes, which are indicative of extended π -electron delocalization upon coordination [43]. Bukhari et al. [16] observed a red shift in the absorption maximum from ~407 to ~427 nm in Co^{2+} –quercetin complexes, accompanied by a visible color change. This further supports conjugation extension induced by metal binding.

Overall, the consistent bathochromic shifts observed across different metal–quercetin complexes provide strong spectroscopic evidence of coordination-driven electronic reorganization. The 3-OH/4-oxo chelation site plays a dominant role in modulating quercetin's optical and physicochemical properties.

3.5. Antioxidant Potential Assessment

Quercetin has significant antioxidant potential due to its ability to neutralize free radicals due to the presence of multiple phenolic hydroxyls [33]. We sought to evaluate the antioxidant potential of compounds synthesized between quercetin and metals (Cu^{2+} ,

Co^{2+} , Zn^{2+} , Sn^{2+} , Al^{3+} , Cd^{2+} and Mg^{2+}). The 3' and 4' ortho-dihydroxyl groups are the major contributors to the antioxidant activity of flavonoids. These catechol moieties form ortho-semiquinone radicals which 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 aids in the delocalization of the π -electrons in the B ring. This in turn influences the dissociation of the phenolic hydroxyl groups as well as the stability of the phenoxy radicals formed on the B ring [55]. The meta-hydroxyl groups present in the A ring are less important than the dihydroxy groups on the B ring, which are more readily oxidized [44]. Thus, the most important 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 have the 3'-OH and 4'-OH groups in their structure and that the coordination is preferably at the 5-OH, 4-C-OH and/or 3-OH groups.

In classic antioxidant assays (DPPH, ABTS, and FRAP), the analytical response reflects specific reaction mechanisms, such as hydrogen donation, electron transfer, or reducing power. The presence of metals and alcoholic/phenolic groups alters these mechanisms, yet does not invalidate the assay. It is important to note that these tests do not measure "absolute antioxidant activity," but rather the ability to interact with a specific chemical reagent. Therefore, when a metal complex exhibits lower activity than free quercetin, it does not indicate a failure of the method. Rather, it suggests that coordination has reduced the availability of hydrogen donor sites or altered the kinetics of electron transfer [19–21,48]. The use of IC_{50} in antioxidant assays is preferred because these methods evaluate functional responses that are dependent on both dose and time, and involve multiple, non-stoichiometric mechanisms. Thus, IC_{50} provides a robust, reproducible, and widely accepted comparative measure of antioxidant efficiency [38,56].

3.5.1. DPPH• Radical Scavenging Method

As shown in Figure 5, the results confirm the high antioxidant capacity of standard quercetin. At the highest evaluated concentration, quercetin inhibited 92.88% of the DPPH• radical, which is consistent with its well-established radical scavenging properties. This strong activity is associated with quercetin's molecular structure, particularly the presence of 3',4'-dihydroxyl groups on the B ring. These groups play a central role in hydrogen atom transfer reactions with the DPPH• radical and electron donation processes [57,58]. As expected, the radical scavenging efficiency of free quercetin increased in a dose- and time-dependent manner, reflecting its high intrinsic antioxidant potential.

Metal complexation significantly altered this behavior and enhanced the antioxidant activity of the complexes relative to free quercetin in several cases. The CdQ, MgQ, and ZnQ complexes exhibited antioxidant activities comparable to or greater than quercetin's, with inhibition values of 96.0%, 94.3%, and 95.2%, respectively. Similarly, the AlQ and ZnQ complexes demonstrated high antioxidant activity with inhibition values of 86.02% and 95.2%, respectively, at 1000 μM . These results suggest that coordination with specific metal ions may favor hydrogen atom or electron transfer processes through electronic redistribution or stabilization of radical intermediates, thereby enhancing DPPH• scavenging efficiency. Similar enhancements have been reported for Co(II), Fe(II), and Cu(II) quercetin complexes, which displayed lower IC_{50} values and higher scavenging efficiencies than free quercetin in DPPH assays [15–17]. Notably, Co(II)-quercetin exhibited an IC_{50} value of $2.01 \pm 0.25 \mu\text{M}$, which is significantly lower than the value for quercetin ($3.88 \pm 0.06 \mu\text{M}$). This confirms that, under certain conditions, metal coordination can enhance antiradical activity.

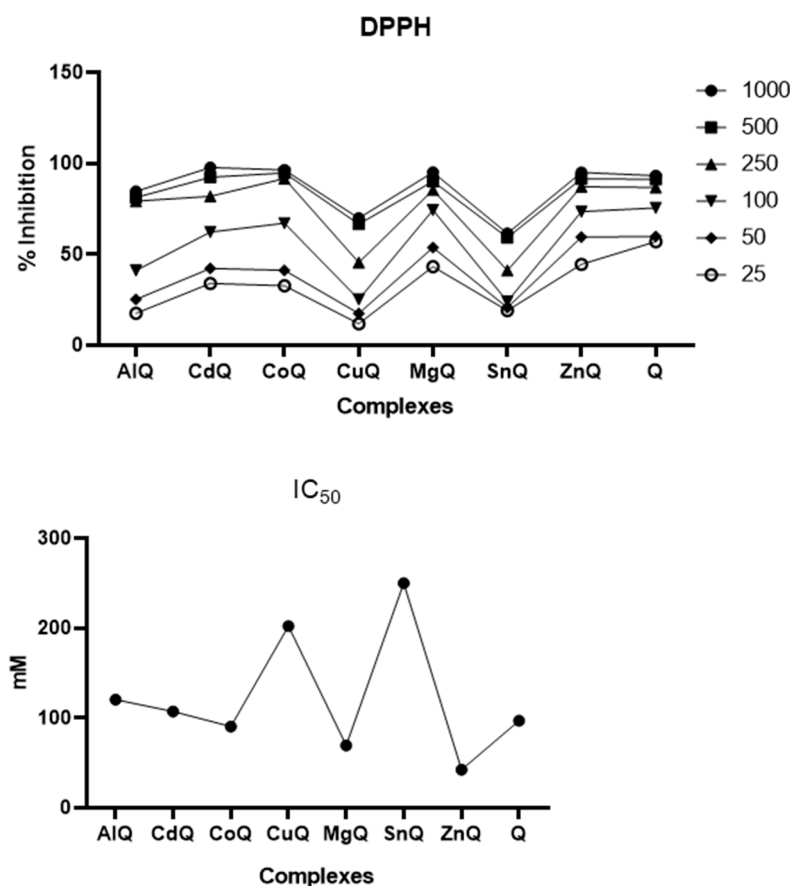


Figure 5. Inhibition of DPPH by metal complexes and IC₅₀ values.

In contrast, the SnQ and CuQ complexes exhibited significantly reduced antioxidant activity compared to the positive control, underscoring the pivotal role of the coordinated metal ion in shaping the overall antioxidant behavior. This reduction is consistent with previous reports indicating that quercetin–Sn(II) and quercetin–Tb(III) complexes exhibit weaker DPPH• scavenging activity than free quercetin due to the suppression of hydrogen-donating sites during coordination [17,57]. Spectrophotometric analyses after the DPPH• reaction corroborate these observations because metal coordination mainly occurs through phenolic hydroxyl and carbonyl groups. These groups are directly responsible for quercetin’s antioxidant activity. Depending on the metal, such coordination can stabilize radical intermediates or reduce the availability of free hydroxyl groups, thereby diminishing antioxidant efficiency.

The present results are largely consistent with previously reported data. Dehghan and Khoshkam [17] reported that the SnQ complex inhibited approximately 40% of DPPH•, which is consistent with the low activity observed here. Bukhari et al. [16] showed that the CoQ complex achieved around 80% inhibition at 700 μM, while free quercetin inhibited approximately 90% of the radical. These values are comparable to those obtained in this study. Ghosh et al. [15] reported 55% inhibition for the MgQ complex after 30 min at 700 μM. Notably, the MgQ complex synthesized in this study exhibited superior performance (approximately 85% inhibition). This suggests that the synthetic route and coordination environment can substantially influence antioxidant outcomes. However, the lower activity observed here (86.34% at 700 μM) further emphasizes the sensitivity of DPPH• scavenging to synthesis conditions and metal–ligand interactions when compared to the results of Halevas et al. [18], who reported approximately 95% inhibition for the CuQ complex.

IC₅₀ values further support these trends. The ZnQ complex exhibited the lowest IC₅₀ value (42.36 ± 7.98 μM), which is even lower than the value for the standard compound

quercetin ($96.81 \pm 8.11 \mu\text{M}$). This finding confirms the ZnQ complex's superior antioxidant efficiency. Conversely, SnQ and CuQ displayed the highest IC_{50} values ($249.9 \pm 8.33 \mu\text{M}$ and $202.2 \pm 10.66 \mu\text{M}$, respectively), indicating reduced radical scavenging capacity. These results show that metal complexation can enhance or reduce quercetin's antioxidant activity depending on the metal ion's nature.

As reported by De Giovani et al. 2004 [27], metal coordination modifies the redox behavior of flavonoids, which may enhance radical scavenging activity by stabilizing the oxidized flavonoid species. From a mechanistic perspective, quercetin's antioxidant activity is primarily associated with the 3'-OH and 4'-OH groups of ring B. These groups are directly involved in hydrogen atom transfer reactions with $\text{DPPH}^\bullet$. Additionally, intramolecular hydrogen bonding involving the 3-OH group promotes coplanarity of the flavonoid rings, favoring electron delocalization and stabilization of radical species [58–60]. However, metal coordination can modify this electronic distribution by engaging hydroxyl groups or altering redox properties. This can either enhance radical stabilization or limit hydrogen donation, as observed for Cd(II), Co(II), Fe(II), Tb(III), and Sn(II) complexes [16,61]. Overall, these results reinforce the concept that metal ions can positively or negatively modulate quercetin's physicochemical and antioxidant properties, depending on their coordination behavior and redox characteristics.

3.5.2. Antioxidant 2,2'-Azinobis(3-Ethylbenzothiazoline-6-Sulfonic Acid) ($\text{ABTS}^{\bullet+}$) Radical Activity

The $\text{ABTS}^{\bullet+}$ radical scavenging assay revealed that most of the synthesized quercetin-metal complexes had high antioxidant capacity, especially at higher concentrations (Figure 6). The CdQ complex exhibited complete $\text{ABTS}^{\bullet+}$ inhibition, achieving 100% scavenging; meanwhile, free quercetin (Q) demonstrated nearly identical inhibition at 99.7%. Similarly, AlQ (99.86%), CoQ (99.85%), MgQ (98.52%), and ZnQ (99.5%) exhibited antioxidant activity comparable to quercetin's at the commonly used concentration of $1000 \mu\text{g mL}^{-1}$, suggesting that coordination with these metals largely preserves the flavonoid's intrinsic radical scavenging properties. However, the CuQ and SnQ complexes exhibited reduced antioxidant activity, with inhibition values of 49.86% and 28.3%, respectively. This suggests that complexation with these metals negatively affects quercetin's antioxidant performance. concentration-dependent analysis further supported these observations.

A concentration-dependent analysis further supported these observations. All complexes exhibited strong $\text{ABTS}^{\bullet+}$ scavenging activity at the highest tested concentrations (1000 and $500 \mu\text{g mL}^{-1}$), whereas free quercetin demonstrated the most potent inhibition across the entire evaluated concentration range (1000 – $25 \mu\text{g mL}^{-1}$). This behavior underscores the potent antioxidant capacity of quercetin at the molecular level and suggests that metal coordination exerts a more significant impact on radical scavenging efficiency at lower concentrations.

These findings are consistent with previous studies on quercetin-metal complexes evaluated using the ABTS assay. For example, studies on the quercetin-Tb(III) complex revealed a concentration-dependent decrease in $\text{ABTS}^{\bullet+}$ absorbance at 734 nm for free quercetin and the complex, indicating effective antiradical activity. However, free quercetin consistently exhibited superior scavenging efficiency compared to the quercetin-Tb(III) complex. This indicates that metal coordination reduces, but does not eliminate, the $\text{ABTS}^{\bullet+}$ radical scavenging capacity of quercetin [61]. A similar trend was reported for the quercetin-cadmium complex: the percentage of $\text{ABTS}^{\bullet+}$ scavenging efficiency was consistently lower than that of free quercetin across the studied concentration range. This reduced activity has been attributed to the quercetin-Cd(II) complex's higher oxidation potential relative to

free quercetin, which limits its ability to donate electrons or hydrogen atoms to the ABTS radical [62].

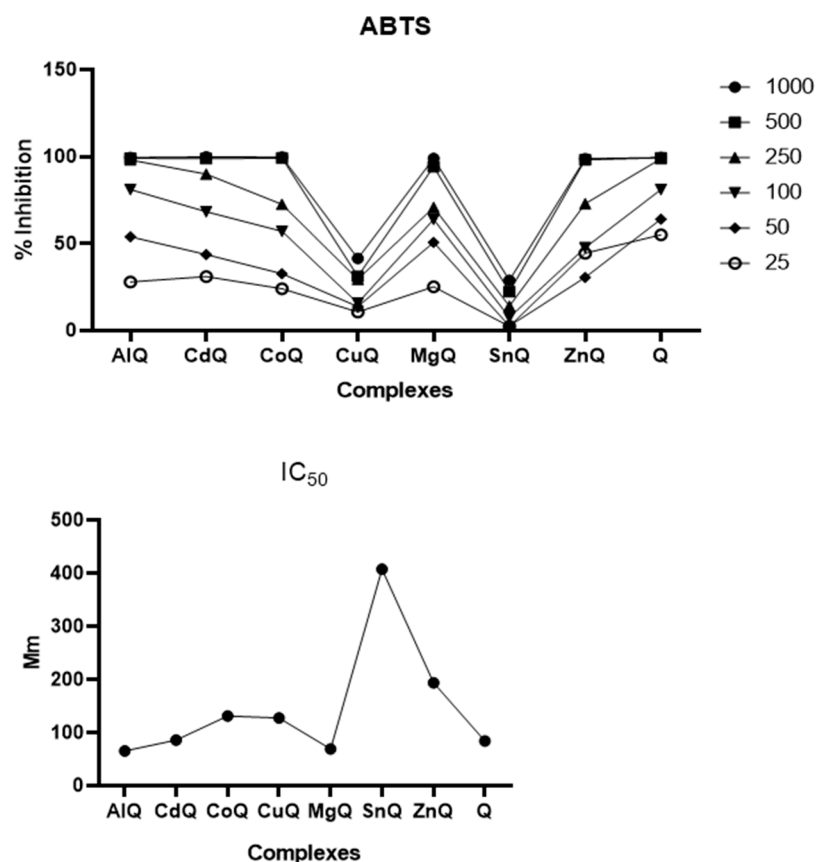


Figure 6. Inhibition and IC₅₀ of antioxidant activity by the ABTS^{•+} test.

A review of the literature revealed limited reports employing the ABTS^{•+} assay for quercetin–metal complexes. Dehghan and Khoshkam [17] reported approximately 55% ABTS^{•+} inhibition for the SnQ complex at 700 μM . In the present study, however, SnQ exhibited significantly lower scavenging efficiency (approximately 24%) under comparable conditions. This finding confirms its consistently poor antioxidant performance and emphasizes the strong dependence of ABTS^{•+} scavenging activity on the nature of the coordinated metal ion and the resulting electronic structure of the complex.

Although CdQ achieved complete inhibition of ABTS^{•+} at the highest tested concentration, analysis of scavenging efficiency as a function of concentration revealed that its antioxidant activity was inferior to that of free quercetin. The superior performance of quercetin can be attributed to its multiple hydroxyl groups with low oxidation potential, which facilitate efficient hydrogen atom transfer and electron donation. In contrast, coordination with Cd(II) and other metal ions, such as Tb(III), can increase the flavonoid framework's oxidation potential and restrict the availability of hydroxyl groups, thereby reducing radical scavenging efficiency [61–63].

The IC₅₀ values obtained from the ABTS assay quantitatively support these trends. The SnQ complex exhibited the highest IC₅₀ value ($407.30 \pm 19.77 \mu\text{g mL}^{-1}$), confirming its weak radical scavenging capacity. Conversely, AlQ ($65.12 \pm 11.12 \mu\text{g mL}^{-1}$) and MgQ ($68.77 \pm 3.44 \mu\text{g mL}^{-1}$) exhibited the lowest IC₅₀ values among the synthesized complexes, which were approximately 20 $\mu\text{g mL}^{-1}$ lower than the value for free quercetin ($83.98 \pm 12.22 \mu\text{g mL}^{-1}$). This indicates enhanced antioxidant efficiency. CdQ ($85.79 \pm 9.32 \mu\text{g mL}^{-1}$) had an IC₅₀ value similar to quercetin's, consistent with previous

reports indicating that cadmium coordination partially suppresses ABTS^{•+} scavenging activity relative to the free ligand [62]. CoQ, CuQ, and ZnQ displayed intermediate IC₅₀ values, reflecting their moderate antioxidant performance.

Overall, these results demonstrate that metal complexation can modulate the ABTS^{•+} scavenging activity of quercetin in different ways. Coordination with certain metal ions, such as Al³⁺ and Mg²⁺, enhances antioxidant efficiency. However, coordination with other metal ions, particularly Sn²⁺, Cu²⁺, Cd²⁺, and Tb³⁺, tends to reduce radical scavenging capacity by increasing oxidation potential and limiting electron transfer. These findings align well with previously reported structure–activity relationships for quercetin–metal complexes, confirming that the observed antioxidant behavior in the ABTS assay depends heavily on metal identity and coordination-induced electronic effects.

3.5.3. Ferric Reducing Antioxidant Power (FRAP) Assay

We employed the ferric reducing antioxidant power (FRAP) assay to evaluate the antioxidant potential of quercetin (Q) and its metal complexes further, providing additional information on their electron-donating capacity. The FRAP assay is based on antioxidants' ability to reduce the Fe(III)-TPTZ complex to Fe(II)-TPTZ under acidic conditions. This reaction forms an intense blue complex with a maximum absorption wavelength of 593 nm. The amount of Fe(II) generated is directly proportional to antioxidant activity [57]. Consistent with previous reports on quercetin–Tb(III) complexes [61], which demonstrated that metal coordination can modulate, but not suppress, the reducing ability of quercetin, the present results suggest that FRAP activity depends strongly on concentration and metal identity.

At the highest tested concentration (1000 µg mL^{−1}), free quercetin exhibited an inhibition profile similar to those of the AlQ, CdQ, CoQ, MgQ, and ZnQ complexes. This indicates that complexation with these metals largely preserves quercetin's ferric reducing ability. A similar trend was previously observed for the quercetin–Tb(III) complex, which retained measurable reducing power but displayed lower activity than free quercetin [61]. This is consistent with the idea that electron transfer is partially attenuated upon chelation. In contrast, the CuQ and SnQ complexes exhibited the weakest antioxidant activity, suggesting that coordination with these metal ions interferes more strongly with electron donation.

At the lowest evaluated concentration, free quercetin inhibited approximately 48% of the FRAP complex, demonstrating the highest reducing capacity of all the tested compounds. This behavior is consistent with previous studies on flavonoids that demonstrated quercetin has the strongest ferric reducing ability and apigenin has the weakest [57]. Structural comparisons suggest that having a single hydroxyl group on the B ring, as with apigenin and chrysin, has a minimal impact on antioxidant activity because of its reduced electron-donating capability. In contrast, kaempferol's (Kae) higher ferric reducing ability relative to apigenin's (Api) has been attributed to the presence of the 3-OH group, which highlights the importance of hydroxyl substitution patterns [57]. MgQ exhibited the second-highest activity, with approximately 40% inhibition. The remaining complexes displayed negligible reducing ability at low concentrations, emphasizing the dominant contribution of free hydroxyl groups to electron donation.

At higher concentrations, all synthesized complexes except SnQ and CuQ exhibited inhibition values approaching 100%, which is comparable to the performance of free quercetin (Figure 7). These results are similar to those observed for quercetin–Tb(III) [61], where an increased effective concentration partially compensated for coordination-induced electronic effects, enabling the complex to approach the reducing performance of free quercetin. Overall, these results suggest that, when sufficient concentration is available to overcome chelation-related electronic constraints, metal complexation generally preserves and sometimes enhances the antioxidant potential of quercetin.

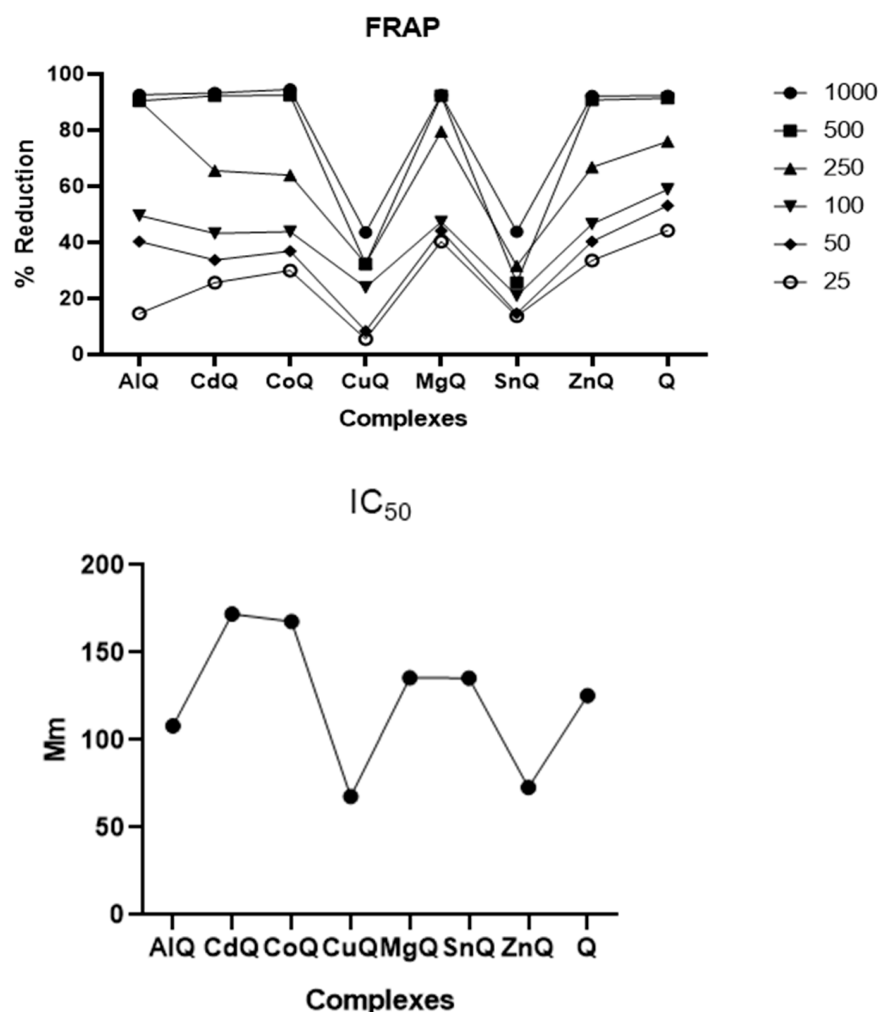


Figure 7. Inhibition and IC₅₀ of antioxidant activity by the FRAP test.

From a structure–activity perspective, quercetin’s strong ferric reducing ability has been attributed to its multiple hydroxyl groups, especially the 3-OH group, which plays a critical role in electron donation. Comparative FRAP analyses have shown that quercetin’s ferric reducing capacity exceeds that of apigenin (Api), chrysin (Chr), and kaempferol (Kae) by 1.06, 1.07, and 0.28 mmol Fe²⁺ L^{−1}, respectively. This confirms that hydroxyl substituents significantly enhance the FRAP response of flavonoid compounds [63]. However, coordination to metal ions, such as Tb(III), may partially limit the availability of these hydroxyl and carbonyl sites for redox reactions, thereby modulating FRAP activity [61].

Overall, the FRAP results corroborate the findings from the DPPH• and ABTS•⁺ assays and align with prior studies on quercetin–Tb(III) complexes [61], demonstrating that metal complexation can influence quercetin’s antioxidant behavior differently. Certain metal ions preserve or enhance quercetin’s ferric reducing capacity, while others significantly attenuate it. This underscores the critical roles of hydroxyl substitution patterns, metal identity, and coordination environment in determining antioxidant efficiency.

3.6. Antimicrobial Potential Assessment

This study revealed the antibacterial and antifungal properties of the tested metal and quercetin combination (Table 1). However, the activity of these compounds varied considerably. In general, these compounds exhibited greater activity against fungi than bacteria. The following trend was observed in microbial susceptibility to the compounds: *C. glabrata* > *S. aureus* > *B. cereus*.

Table 1. Antimicrobial activity ($\mu\text{g mL}^{-1}$) of the complexes against bacterial strains.

Complexes	Gram (–) <i>P. aeruginosa</i> ATCC 27583	Gram (–) <i>E. coli</i> ATCC 25922	Gram (+) <i>S. aureus</i> ATCC 12600	Gram (+) <i>B. cereus</i> ATCC 14579	<i>C. albicans</i> ATCC 10231	<i>C. glabrata</i> ATCC 2001
AlQ	>500	>500	>250	>500	>250	>500
CdQ	>500	>500	>250	>250	>500	>250
CoQ	>250	>500	>500	>500	>250	>75
CuQ	>500	>500	>500	>500	>500	>500
MgQ	>500	>500	>125	>500	>500	>500
SnQ	>500	>500	>500	>500	>500	>500
ZnQ	>500	>500	>500	>500	>500	>500
Q	>500	>500	>500	>500	>500	>500
Gentamicin/ Fluconazole	7.5	7.5	7.5	7.5	7.5	7.5
DMSO	>500	>500	>500	>500	>500	>500

The metal–quercetin complexes exhibited antibacterial and antifungal activity, demonstrating substantial variability among compounds and microorganisms (Table 1). Generally, the antifungal efficacy was higher than the antibacterial efficacy, and the order of microbial susceptibility was *C. glabrata* > *S. aureus* > *B. cereus*. CdQ and CoQ exhibited the most pronounced antibacterial effects, inhibiting *P. aeruginosa* and *E. coli* at minimum inhibitory concentrations (MIC) of $250 \mu\text{g mL}^{-1}$, while AlQ, CdQ, and MgQ were more active than free quercetin against *S. aureus* with MIC values of 250, 250, and $125 \mu\text{g mL}^{-1}$, respectively. Furthermore, CdQ exhibited bacteriostatic activity against *B. cereus* at concentrations above $250 \mu\text{g mL}^{-1}$.

Fungal strains showed greater sensitivity than bacterial strains, particularly *Candida* spp. and *C. glabrata*, which has been reported to be highly susceptible to metal-based antimicrobial agents due to its membrane composition and metal ion uptake mechanisms, showed the highest sensitivity. Of the complexes, CoQ exhibited the most promising antifungal profile, inhibiting *C. albicans* at concentrations above $75 \mu\text{g mL}^{-1}$ and *C. glabrata* at concentrations above $250 \mu\text{g mL}^{-1}$. AlQ and CdQ were active against *C. albicans* and *C. glabrata*, respectively, at concentrations above $250 \mu\text{g mL}^{-1}$. Although they outperformed free quercetin, none of the complexes matched the inhibitory potency of fluconazole.

The antimicrobial action of flavonoids is widely associated with their ability to interact with microbial cell envelopes. Scalbert [64] demonstrated that flavonoids and related polyphenols can bind to cell wall proteins and membrane-associated enzymes, which leads to structural destabilization and impaired cellular function. Cushnie and Lamb [65] further demonstrated that flavonoids disrupt cytoplasmic membranes by increasing their permeability, inducing the leakage of essential ions and promoting the aggregation of bacterial cells. This membrane damage results in depolarization and the collapse of cellular energy metabolism, which is consistent with observations of bacteriostatic and bactericidal effects [66]. Pawlikowska-Pawlega et al. [67] clarified that these effects require an initial interaction of flavonoids with the polar head groups of phospholipids, followed by penetration into hydrophobic membrane regions. This explains why fungi with sterol-rich membranes are more susceptible.

Metal complexation further amplifies these effects by altering the flavonoid's physico-chemical properties. According to Chohan and Supuran [68], chelation increases lipophilicity and facilitates transmembrane transport, enabling metal–flavonoid complexes to reach intracellular targets more efficiently. Singh et al. [69] demonstrated that metal–flavonoid complexes interfere with microbial respiration and inhibit protein and nucleic acid synthesis, leading to irreversible growth arrest. Additionally, Sumra and Chohan [70] and

Yasmeen et al. [71] showed that chelation reduces metal ion polarity through partial charge sharing with donor atoms and π -electron delocalization within the chelate ring. This enhances membrane permeability and biological activity. Consequently, metal complexes can function as both activated carriers of bioactive ligands and intrinsically cytotoxic species, which explains their consistently higher antimicrobial efficacy compared to free quercetin.

Investigating organometallic complexes with flavonoids, particularly quercetin–metal complexes, is more than just a chemical curiosity. Altering the geometry of the molecule can modify its physicochemical properties, such as increasing lipophilicity and consequently its ability to cross cell membranes. The goal of this study was to synthesize, characterize, and evaluate the antioxidant and antimicrobial potential of organometallic compounds derived from quercetin. Innovations in the pharmaceutical field are essential for developing metal-based drugs to treat cancer, infectious diseases, and other illnesses. In the cosmetics sector, organometallic complexes can be used as preservatives, pigments, and delivery agents for active ingredients, ensuring greater penetration of the skin in a controlled and effective manner. Thus, this work contributes to the fields of chemistry, pharmacy, cosmetics, and nutrition by exploring the potential of these metal–flavonoid complexes.

4. Conclusions

This study demonstrates that quercetin is a versatile ligand that can form stable coordination compounds with metal ions of different charges and electronic properties, including Cu(II), Co(II), Zn(II), Sn(II), Al(III), Cd(II), and Mg(II). Despite the need for adjustments in selected synthetic protocols, the successful synthesis of all seven complexes highlights the strong sensitivity of quercetin–metal complexation to reaction parameters such as solvent, stoichiometry, and metal salt reactivity.

FTIR, NMR, and UV–Vis analyses confirmed quercetin's coordination with metal ions. This was evidenced by shifts in the O–H, C=O, and C–O bands; changes in the NMR chemical environment; and bathochromic shifts in the UV–Vis spectra. Together, these results suggest the formation of metal–quercetin complexes.

The antioxidant evaluation revealed that metal coordination modulates the redox behavior of quercetin in a metal-dependent manner. Notably, the Zn(II)–, Mg(II)–, and Al(III)–quercetin complexes exhibited antioxidant activities equal to or greater than free quercetin. This indicates that coordination with redox-inactive or weakly interacting metal ions can preserve and enhance the flavonoid's radical-scavenging capacity. This enhancement is attributed to limited perturbation of phenolic hydroxyl groups and favorable electronic delocalization within the quercetin framework, as supported by spectroscopic analyses. These findings reinforce the potential of selected metal–quercetin complexes as improved antioxidant systems compared to the parent molecule.

The biological response depended heavily on the metal coordination, with certain complexes exhibiting notable antibacterial or antifungal effects, particularly against *Candida* species. These results suggest that metal coordination enhances quercetin's bioactivity by improving its interaction with microbial cells. However, its efficacy remains lower than that of standard antifungal drugs. This study proposes evaluating the synthesis, characterization, and preliminary testing of organometallic compounds derived from quercetin. However, based on the results obtained, we suggest expanding the bioassays to include cytotoxicity, antitumor, and acute and chronic toxicity tests as future prospects. Overall, this study clearly shows that coordination with metal ions significantly changes the electronic structure and functional properties of quercetin.

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Abbreviations

The following abbreviations are used in this manuscript:

ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
DPPH	1,1-diphenyl-2-picrylhydrazyl
FRAP	Ferric Reducing Antioxidant Power
FTIR	Fourier Transform Infrared Spectroscopy
MBC	Minimum bactericidal concentration
MFC	Minimum fungicidal concentration
MIC	Minimum inhibitory concentrations
NMR	Nuclear Magnetic Resonance
TPTZ	2,4,6-Tris(2-Pyridyl)-S-Triazine
UV-VIS	UV/visible spectroscopy

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