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# Medicinal Promise of a Zinc–Quercetin Complex: Antioxidant Activity and PharmADMEtox Profiling of a Metal–Flavonoid Hybrid

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***Abstract*—** *This study investigated the potential of a zinc–quercetin complex to scavenge reactive oxygen species (ROS) and assessed its predicted pharmacokinetic and toxicity profiles. A calcein AM-based assay was performed to evaluate cell viability. Antioxidant capacity was assessed using DPPH and nitric oxide (NO) radical scavenging assays, testing both the complex and free quercetin at concentrations of 10 µM and 1 µM. To anticipate the pharmacokinetics and toxicity of both substances, the SwissADME and ProTox computational models were utilized. Results from the antioxidant assays showed that the zinc–quercetin complex exhibited greater radical scavenging activity compared to free quercetin. Both the complex and quercetin maintained cell viability, with 1 µM ZQC showing a significant proliferative effect on C2C12 cells. ADME predictions indicated reduced oral bioavailability of the complex, likely due to its larger molecular size, increased polarity, and higher saturation. In terms of toxicity, complexation with zinc appeared to reduce quercetin's toxicity, with ZQC classified as toxicity class V ($LD_{50}$ = 3200 mg/kg), while quercetin was classified as class III ($LD_{50}$ = 159 mg/kg). These findings suggest that zinc complexation enhances the antioxidant activity and safety profile of quercetin, supporting its potential as a therapeutic agent against oxidative stress. Nonetheless, further research is required to fully characterize and optimize its pharmacological applications.*

**Keywords—** antioxidant: flavonoid: ProTox: SwissADME: zinc-quercetin complex

## I. Introduction

Reactive oxygen species (ROS) are highly reactive oxygen-containing molecules such as superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), and hydroxyl radicals (•OH). These molecules are routinely generated as natural byproducts of mitochondrial respiration, particularly during oxidative phosphorylation. [1] Though commonly linked to cellular damage, ROS at moderate, regulated levels serve important roles in physiological signaling—a phenomenon referred to as "oxidative eustress". [2]

Under normal conditions, ROS help modulate signaling networks that govern cellular activities like growth, differentiation, and immune responses. [3] For instance, hydrogen peroxide can function as a signaling molecule by influencing the activity of enzymes and transcription factors, including NF-κB and MAPKs. [4]

Conversely, when ROS are produced in excess and overwhelm antioxidant defenses, oxidative stress arises. This imbalance results in damage to cellular lipids, proteins, and DNA. [5] Such oxidative damage has been linked to the development of various chronic conditions, including cardiovascular disorders, neurodegeneration, diabetes, and cancer. [6-8]

Quercetin is a bioactive flavonoid commonly present in a variety of plant-based foods such as fruits, vegetables, and tea, and is well-known for its strong antioxidant capabilities. Its antioxidant action involves neutralizing reactive oxygen species (ROS), binding with metal ions that promote oxidative reactions, and enhancing the body's natural defense systems like glutathione and superoxide dismutase. [9,10] This function is largely due to its polyphenolic makeup, especially the hydroxyl groups that effectively donate electrons to stabilize free radicals. [11] In addition, quercetin influences key molecular pathways involved in oxidative stress regulation, including nuclear factor kappa B (NF-κB) and nuclear factor erythroid 2–related factor 2 (Nrf2), providing protective effects in various disease models. [12]

This research seeks to investigate and evaluate the biological activity of a zinc-quercetin complex in comparison to unbound (free) quercetin, with particular focus on their capacities to neutralize and scavenge reactive oxygen species (ROS). The study aims to determine whether complexation with zinc enhances quercetin's inherent antioxidant properties by improving its stability, reactivity, or interaction with cellular oxidative pathways. Through a series of in vitro antioxidant assays and computational predictions, the study will assess the efficiency and potential therapeutic relevance of both the zinc-complexed and free forms of quercetin in combating oxidative stress, which is implicated in the progression of various chronic and degenerative diseases.

## II. Method

### *A. Materials*

#### *2.1.1 Reagents*

All chemicals and reagents were purchased from commercial sources and were used without further purification.

### *B. Experimental Procedure*

#### *2.2.1 Cell Culture Work*

Mouse C2C12 skeletal myoblasts were maintained in high glucose-Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 20% fetal bovine serum (FBS) and 1%

penicillin-streptomycin in a humidified atmosphere with 5% $CO_2$ at 37°C. When the cells reached the desired confluency, the medium was switched to DMEM supplemented with heat-inactivated horse serum for 5–7 days to facilitate myocytic differentiation. The media for the control or normal condition ("healthy") consisted of DMEM (11 mM glucose) with 2% heat-inactivated horse serum. Each prepared healthy control medium was sterilely filtered using a 0.20 µm syringe filter. To mimic glucolipotoxic-driven oxidative stress conditions or GLT (high glucose and high fatty acids) in vitro, cells were incubated for 5 days in media similar to the healthy condition, except the glucose concentration was increased to 28 mM and supplemented with 200 µM palmitic acid and 200 µM oleic acid. The same GLT media preparation was also used for the MGO-treated condition, with the additional inclusion of 500 µM methylglyoxal (MGO) solution.

*2.2.2 Cell Counting, Recovery, and Plate Seeding*

Briefly, cells were washed three times with pre-warmed sterile phosphate-buffered saline (PBS), trypsinized to detach the adherent cells, and neutralized with an appropriate amount of complete growth media by incubating in 4 mL of Trypsin-Ethylenediaminetetraacetic acid (EDTA). Trypsin was then neutralized with an equal volume of complete growth media. A 10-µL cell suspension was collected to count the cells using an automated cell counter. Harvested cells were resuspended in a 1-mL cryovial using a 7:2:1 cryopreservation medium [DMEM:Dimethylsulfoxide (DMSO)] and stored in a -80°C freezer. Cells recovered from long-term storage were defrosted and gently mixed with 3–5 mL of complete growth media before centrifugation to collect the pellets. Thereafter, cell pellets were resuspended in 3–5 mL of growth media, seeded appropriately in a culture flask, and incubated at 37°C in a 5% $CO_2$ atmosphere.

2.2.3 *Cell Viability Using Calcein AM Assay*

To monitor cell viability, a calcein AM-based assay was employed based on the protocol developed by Riss et al., with modifications. Briefly, C2C12 muscle cells were cultured in healthy control, GLT-, and MGO-treated media for 24 hours. Zinc-quercetin complex (ZQC) and quercetin (10 µM and 1 µM) were then added and incubated for 1 hour in both GLT-treated conditions. Cells were subsequently washed three times with Dulbecco's Phosphate Buffered Saline, and 200 µL of filter-sterilized calcein solution (0.15 mg/mL) in growth media was added to each well and incubated for 1 hour. Cell viability was then measured via fluorescence, using excitation and emission wavelengths of 560 nm and 590 nm, respectively, and expressed as a percentage change relative to the control.

*2.2.4. DPPH Antioxidant Assay*

The free RSA of ZQC and quercetin was assessed using 2,2-diphenyl-1-picrylhydrazyl (DPPH). Briefly, a volume of 500 µL of ZQC and quercetin at concentrations of 10 µM and 1 µM was added to 1 mL of a 0.1 mM DPPH solution in methanol. The resulting solution was mixed thoroughly and allowed to react at room temperature in the dark for 30 minutes. The absorbance of the solution was then measured at 517 nm. Vitamin C was used as the positive control, whereas methanol was used as the blank. A control solution containing only a methanolic solution of DPPH, without test compounds, was prepared. The percentage of antioxidant activity (RSA) was calculated using the following formula:

$$\% \, Activity = (Abs.\, control - Abs.\, sample)/Abs.\, control \; x \; 100$$

*2.2.5 Nitric Oxide (NO) Radical Scavenging Assay*

1mL of 10mM sodium nitroprusside, 0.25mL phosphate buffer (pH 7.4), and 0.5mL of zinc-quercetin complex and quercetin (10 and 1uM) were added to test tubes and incubated at 25ºC for 2h. Following incubation, 0.5 mL of the reaction mixture was poured into a fresh test tube, and 1 mL of sulfanilic acid reagent (0.33% in 20% glacial acetic acid) was added. To finish diazotization, the new mixture was then vortexed and left to sit for 5 minutes. Lastly, 1mL of naphthylethylene diamine dihydrochloride (0.1%) was added, mixed and left to stand for 30 minutes. The absorbance was measured at 540 nm against their corresponding blank solutions (all reagents were added except for the samples). Ascorbic acid served as the positive control.

*2.2.6 Pharmacokinetics Prediction (ADME)*

The pharmacokinetic properties of quercetin and the zinc-quercetin complex (ZQC) were evaluated using SwissADME, an online computational tool for predicting absorption, distribution, metabolism, and excretion (ADME) parameters. The molecular structures of quercetin and ZQC were first drawn and optimized using Avogadros software. The optimized structures were then submitted to the SwissADME web server (http://www.swissadme.ch/) for analysis. The tool generated predictions based on molecular descriptors and physiochemical properties, providing insights into the potential pharmacokinetics of both compounds. The results obtained from SwissADME were recorded and later analyzed to compare the effects of zinc complexation on quercetin's ADME profile.

*2.2.7 Toxicity Prediction (ProTox)*

The toxicity profiles of Quercetin and the Zinc-Quercetin Complex (ZQC) were predicted using the Protox server (https://tox.charite.de/protox3/index.php?site=compound_input). The SMILES codes of the optimized structures of Quercetin and ZQC, obtained from Avogadro, were inputted into the Protox platform for analysis. The server was used to predict the potential toxicity of both compounds based on their chemical structures. The predicted results, including their toxicity classes and associated risks, were obtained and analyzed to assess the safety profiles of the ligands for potential therapeutic applications.

*2.2.8 Statistical Analysis*

The experiments and assays will be performed in triplicates, and the results will be presented as the mean of the replicates ± standard error of the mean (mean ± SD). The data will be statistically analyzed using GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, California USA, www.graphpad.com), and will be subjected to single-factor ANOVA. If the data are found to be significant ($p<0.05$), appropriate post hoc tests (Dunnett's and Tukey's) will be employed.

## III. Results and Discussion

*3.1 Cell Viability*

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The Calcein AM assay is a fluorescence-based method for assessing cell viability by detecting intracellular esterase activity. Calcein AM is a non-fluorescent, cell-permeable dye that is converted by live-cell esterases into Calcein, a fluorescent compound that accumulates in the cytoplasm. This conversion produces a bright green signal (excitation ~495 nm, emission ~515 nm), proportional to the number of viable cells. Dead or damaged cells lack esterase activity and show little to no fluorescence, making the assay a sensitive and reliable tool for evaluating viability and cytotoxicity. [13]
All treatment groups showed high cell viability relative to the healthy control, indicating minimal cytotoxic effects. Among them, 10 µM quercetin showed the lowest viability (96%), while 1 µM zinc-quercetin complex (ZQC) demonstrated the highest (118%), suggesting enhanced viability at lower ZQC concentrations. Glucolipotoxic (GLT)-treated cells exhibited 100.38% viability, nearly equal to the control, implying preserved metabolic activity despite stress exposure. However, cellular pathways may still have been affected even without an immediate drop in viability. Since only a one-day incubation was used, potential long-term damage from GLT stress may not have been evident yet. Prolonged exposure could reveal progressive cytotoxic effects or metabolic dysfunction. The short incubation was intentional to assess the immediate cellular response to ZQC and quercetin. Statistical analysis via one-way ANOVA showed a significant difference among treatments ($p = 0.0246$). A post- hoc Dunnett's test identified 1 µM ZQC as significantly different from the control. This underscores the biological effect of ZQC at this concentration. Overall, the results suggest that ZQC may improve cell viability at lower doses. Further research is needed to investigate its mechanism of action and potential therapeutic applications under oxidative stress conditions.

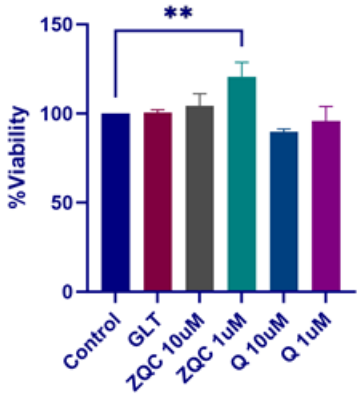


Figure 1. Cell viability of different treatments. (*p<0.05, sig. difference; Dunnet's post hoc test wrt to control group).

### *3.2 Antioxidant Ability of Zinc-Quercetin Complex*

The antioxidant potential of ZQC was evaluated using DPPH (2,2-diphenyl-1-picrylhydrazyl) and NO (nitrogen oxide) scavenging assay. 10 and 1uM of the complex was used to evaluate the extent of its antioxidant activity.

Based on Fig. 2, the 10 µM concentration of ZQC exhibited the highest DPPH radical scavenging activity, achieving an impressive inhibition rate of 75.55 ± 0.68%. In comparison, quercetin at the same concentration demonstrated a lower activity of 62.90 ± 0.13%, highlighting a significant enhancement in antioxidant potential upon complexation with zinc. At the lower concentration of 1 µM, both ZQC and free quercetin exhibited similar levels of activity, ranging between 52% and 55%, indicating a less pronounced effect at minimal doses.

When benchmarked against the positive control, vitamin C, the 10 µM treatment of ascorbic acid showed a scavenging activity of 71.54 ± 5.89%, slightly lower than that of ZQC but still within a comparable range. Likewise, at 1 µM, vitamin C exhibited activity levels similar to those of ZQC and quercetin, suggesting uniform antioxidant performance at this concentration.

Statistical analysis using Tukey's post hoc test revealed no significant difference between the activities of 10 µM ZQC and vitamin C, indicating comparable efficacy. However, the test confirmed a statistically significant difference between 10 µM ZQC and both concentrations of free quercetin. These findings suggest that the complexation of quercetin with zinc not only enhances its free radical scavenging capacity but also elevates its functional performance to a level comparable with established antioxidants like vitamin C.

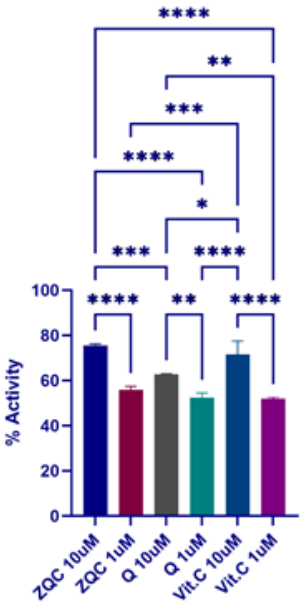


Figure 2. Percentage antioxidant activity of the different treatments in the DPPH assay. (p<0.05, sig. difference; Tukey's post hoc test).

The nitric oxide (NO) scavenging percentages for all treatments is shown in Fig. 3. Among the tested samples, ZQC at 10 µM exhibited the highest NO scavenging activity, achieving 47.55 ± 5.69%. In comparison, free quercetin at the same concentration demonstrated a significantly lower activity of 31.03 ± 3.68%. At 1 µM, ZQC and quercetin exhibited NO scavenging activities of 38.40 ± 3.48% and 34.84 ± 1.78%, respectively. These results indicate that complexation with zinc notably enhances the NO scavenging potential of quercetin.

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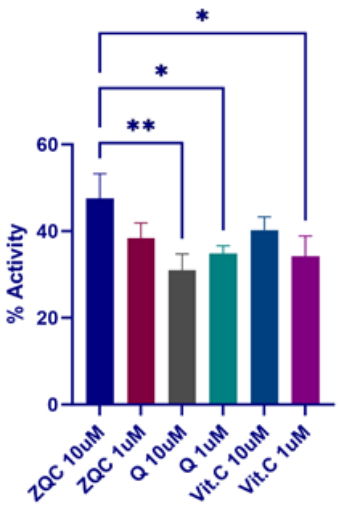


Figure 3. NO radical scavenging activities of the different treatment in the NO scavenging assay. ($p<0.05$, sig. difference; Tukey's post hoc test).

Vitamin C, used as a positive control, showed moderate scavenging capabilities at both tested concentrations, with 40.29 ± 3.00% at 10 µM and 34.16 ± 4.71% at 1 µM. Notably, ZQC at both concentrations outperformed vitamin C in terms of NO scavenging efficiency. Statistical analysis using Tukey's post hoc test revealed no significant difference between the activities of ZQC at 1 µM and 10 µM, nor between the activities of vitamin C at 10 µM. However, a significant difference was observed between 10 µM ZQC and both concentrations of free quercetin, as well as 1 µM vitamin C. These findings reinforce the conclusion that zinc complexation substantially enhances the antioxidant efficacy of quercetin, highlighting ZQC as a more potent NO scavenger than the unmodified flavonoid.

The antioxidant property of ZQC lies on the unique molecular structure of quercetin (Fig. 4). Quercetin contains multiple hydroxyl groups that could donate electron or proton stabilizing the free radical or reactive species. The key moiety of the structure is the catechol group containing the 3' and 4'OH in ring. The stability of the radical generated from catechol moiety relies on the hydrogen bond (HB) formed between the hydroxyl and oxygen possessing unpaired electron, reaction 1. The delocalization of an unpaired electron is also greatly influenced by the existence of a C=C double bond in ring C that is linked to a 4-oxo group. [14,15]

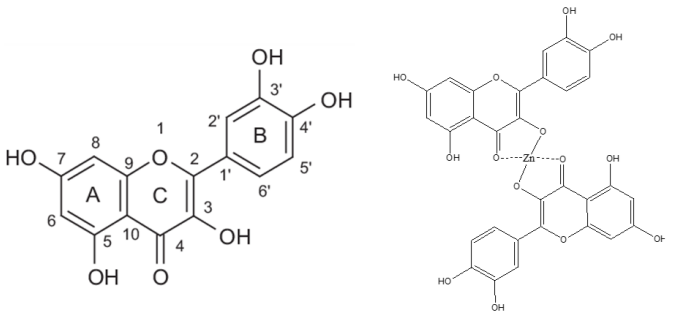


Figure 4. Molecular structure of quercetin (left) and zinc-quercetin complex (ZQC).

Given that ZQC consists of two quercetin moieties coordinated to a central zinc ion, and considering that the catechol groups on both quercetin units remain uncoordinated and thus chemically accessible, the complex likely exhibits an enhanced capacity for free radical scavenging (Fig. 4). The presence of two such functional moieties in close proximity, supported structurally by zinc coordination, may result in a synergistic effect, thereby allowing ZQC to neutralize reactive oxygen and nitrogen species more effectively than the uncomplexed quercetin molecule alone.

### *3.3 Pharmacokinetics Prediction*

To theoretically predict the pharmacokinetics and drug-likeness of the zinc-quercetin complex and free quercetin, SwissADME was used. This computational tool provides key insights into the absorption, distribution, metabolism, and excretion (ADME) properties of a compound, which are essential for assessing its potential as a bioactive agent. Additionally, SwissADME evaluates drug-likeness based on various criteria, including Lipinski's rule of five, water solubility, gastrointestinal (GI) absorption, and blood-brain barrier (BBB) permeability. Other important parameters such as cytochrome P450 enzyme interactions, P-glycoprotein substrate affinity, and skin permeability can also be analyzed to predict metabolic stability and transport properties. [16]

The SwissADME results, illustrated in Fig. 5, present the BOILED-Egg plot and bioavailability radar charts for both the zinc-quercetin complex (ZQC) and free quercetin. The BOILED-Egg plot reveals that quercetin falls outside the optimal bioavailability region, signifying its poor passive gastrointestinal (GI) absorption and minimal brain permeability. This suggests that quercetin may have difficulty crossing biological membranes, which could limit its systemic bioavailability.

The bioavailability radar further supports this observation, as it highlights quercetin's high polarity, with a topological polar surface area (TPSA) close to 140 Å². While this level of through lipid-rich cell membranes, leading to reduced absorption and distribution within the body. Additionally, polarity may contribute to good solubility in aqueous environments, it simultaneously hinders its ability to pass quercetin exhibits moderate molecular size and low lipophilicity, factors that further restrict its membrane permeability.

On the other hand, the ZQC radar plot demonstrates that the complex has an even larger molecular size, significantly higher polarity, and reduced lipophilicity compared to quercetin. These characteristics indicate that ZQC is even less suited for passive absorption, as its molecular bulk and high TPSA further impede its ability to permeate biological barriers. Furthermore, both compounds exhibit a high degree of unsaturation, which may influence their solubility and stability in physiological conditions.

Taken together, these findings strongly suggest that neither quercetin nor ZQC are optimal candidates for oral drug administration due to their poor membrane permeability and low passive absorption potential. To overcome these limitations, alternative drug delivery strategies should be considered, such as encapsulation in nanoparticles, liposomal

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formulations, or prodrug approaches to enhance bioavailability and therapeutic efficacy.

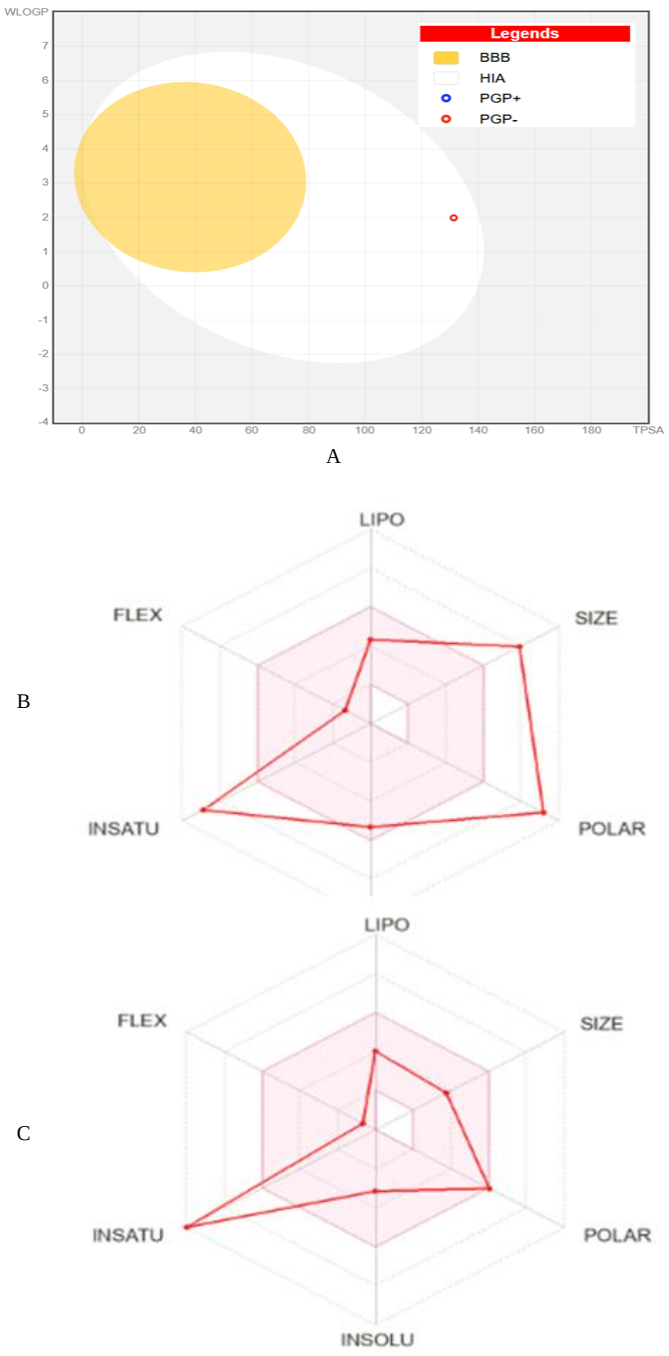


Figure 5. (A) Boiled egg plot and bioavailability radar of (B) ZQC and (C) Quercetin.

### *3.4 Toxicity Prediction*

To predict the toxicological profile of the synthesized zinc–quercetin complex (ZQC), in silico analysis was performed using the ProTox-3.0 platform. This tool utilizes machine learning models trained on experimental data to estimate various toxicity endpoints, including organ toxicity, systemic toxicity, nuclear receptor activity, stress response pathways, and metabolic interactions. [17-19] The objective of this screening was to identify any potential toxic liabilities of ZQC prior to further biological testing and application.

TABLE 1. Oral toxicity prediction results for ZQC and Quercetin

| | ZQC | Quercetin |
|---|---|---|
| **Predicted LD50** | 3200mg/kg | 159mg/kg |
| **Predicted Toxicity Class** | 5 | 3 |
| **Average Similarity** | 42.38% | 100% |
| **Prediction Accuracy** | 54.26% | 100% |

The results indicated that the zinc–quercetin complex (ZQC) exhibits lower predicted toxicity compared to free quercetin, with ProTox classifying ZQC under Toxicity Class 5, while quercetin was classified as Class 3. This classification corresponds with the predicted $LD_{50}$ values, where ZQC had a significantly higher $LD_{50}$ of 3200 mg/kg, suggesting it would require a much larger dose to exert lethal effects. In contrast, free quercetin had an $LD_{50}$ of 159 mg/kg, indicating relatively higher acute toxicity.

The reduced toxicity of ZQC supports its improved safety profile, potentially due to the coordination of quercetin with zinc, which may alter its bioavailability and interaction with biological targets. However, it is important to consider the average similarity and prediction accuracy values reported by the ProTox model. ZQC displayed a lower average structural similarity (42.38%) and prediction accuracy (54.26%), indicating that the compound shares limited similarity with known toxicants in the ProTox training database. This structural novelty may result in reduced model confidence, and therefore, its toxicity prediction should be interpreted with caution.

In contrast, quercetin, a well-studied flavonoid, showed 100% prediction accuracy and structural similarity, reflecting high confidence in the reliability of its toxicity classification. The higher accuracy is due to the presence of numerous structurally similar compounds within the ProTox dataset, allowing for a more precise prediction based on established molecular patterns [172]. While ZQC demonstrates a safer toxicity profile compared to its parent ligand, the lower prediction confidence highlights the importance of experimental validation, especially for novel metal-organic complexes that are underrepresented in current predictive toxicity databases.

## IV. Conclusion

The findings of this study demonstrate that complexation of quercetin with zinc significantly enhances its antioxidant activity, as evidenced by the DPPH and nitric oxide radical scavenging assays. The Calcein AM cell viability assay further confirms that both zinc-quercetin complex (ZQC) and free quercetin maintain cell viability at levels comparable to untreated controls, indicating low cytotoxicity. In silico ADME predictions suggest that while ZQC may have limited oral bioavailability due to its size and polarity, ProTox toxicity analysis indicates that zinc complexation reduces quercetin's predicted toxicity. Overall, these results suggest that ZQC is a promising candidate for therapeutic applications targeting oxidative stress, warranting further investigation into its bioavailability and mechanistic pathways in vivo.

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