RESEARCH PAPER

Running title: Quercetin and APAP-Induced Toxicity

Quercetin Co-Administration Attenuates Paracetamol-Induced Hepato-Renal Toxicity and Modulates Pharmacokinetics in Wistar Rats

Sai Priyanka K[1], Dr. G. Srikar[1*]

[1] Department of Pharmaceutical Sciences, School of Biotechnology and Pharmaceutical Sciences, Vignan's Foundation for Science, Technology and Research (VFSTR), Vadlamudi, Guntur - 522213, Andhra Pradesh, India.

[*] Corresponding Author: Dr. G. Srikar, Professor, Department of Pharmaceutical Sciences, School of Biotechnology and Pharmaceutical Sciences, Vignan's Foundation for Science, Technology and Research (VFSTR), Vadlamudi, Guntur - 522213, Andhra Pradesh, India. Phone: 9491335467, Email: srikar.grandhi@gmail.com

ABSTRACT

Background: Paracetamol, in excessive doses (acetaminophen, APAP), continues to be a major contribution to drug-induced hepatic and renal damage. The main mechanisms of toxicity include oxidative stress, mitochondrial dysfunction, glutathione (GSH) depletion, and increased N-acetyl-p-benzoquinone imine (NAPQI) synthesis. A dietary flavonoid called quercetin has cytoprotective, anti-inflammatory, and antioxidant qualities. It may also affect the metabolism of xenobiotics.

Objectives: To investigate whether quercetin co-administration attenuates APAP-induced hepato-renal toxicity and alters APAP pharmacokinetics (PK) in Wistar rats.

Methods: Male Wistar rats were divided into four groups: quercetin + APAP, silymarin + APAP, control, and APAP toxic control. Renal (urea, creatinine, uric acid) and hepatic (ALT, AST, total and direct bilirubin) markers were assessed. The liver and kidney tissues were examined histopathologically using H&E staining. Serial blood samples were collected up to eighteen hours to enable non-compartmental PK study of APAP (Cmax, Tmax, AUC, t½, MRT, CL/F, Vz/F) and following one-way ANOVA, statistical significance was assessed using Tukey's test.

Results: Pharmacokinetic studies revealed a delayed elimination half-life, decreased apparent clearance, and a dose-dependent increase in paracetamol's Cmax and AUC when quercetin was co-administered.

Conclusion: Quercetin's efficacy as a pharmacotherapeutic adjunct is supported by its ability to protect against APAP-induced hepato-renal damage.

Keywords: acetaminophen; paracetamol; hepatotoxicity; pharmacokinetics; nephrotoxicity.

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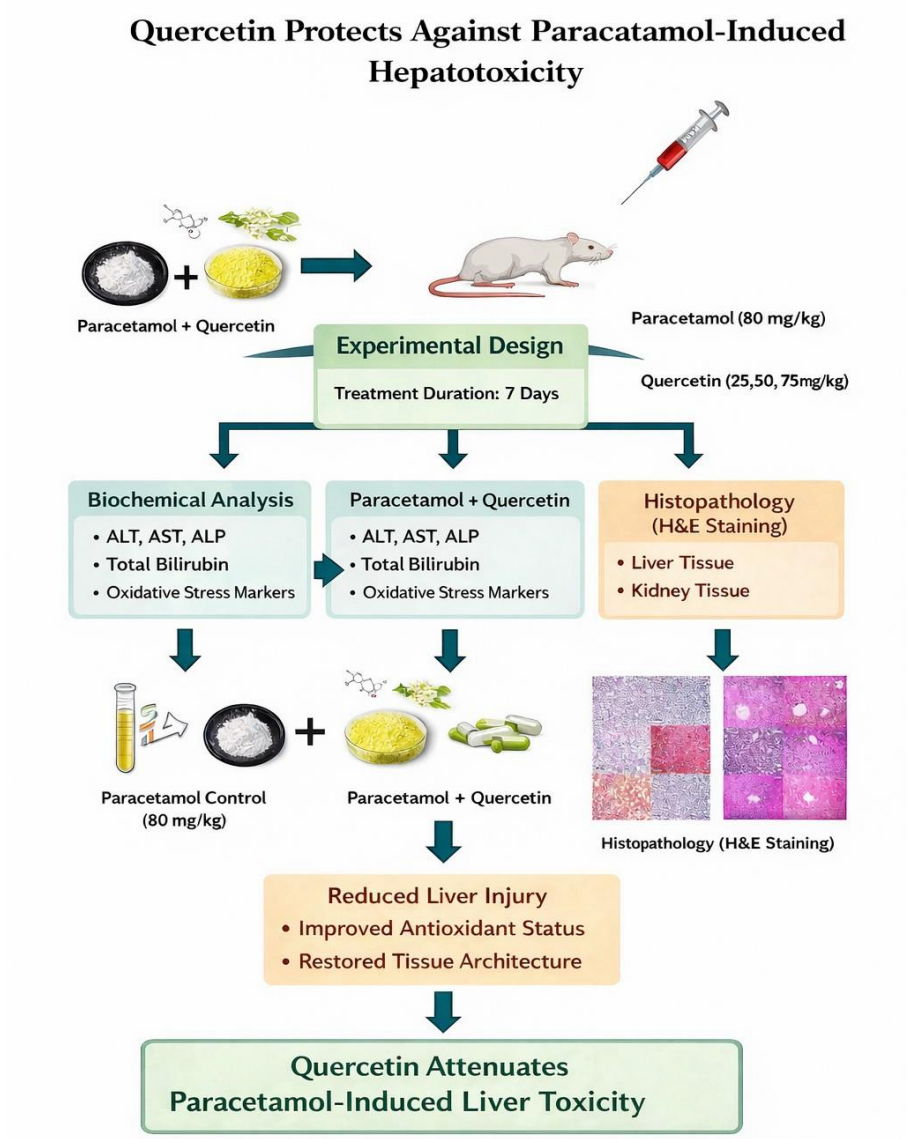
Quercetin co-administration attenuates paracetamol-induced hepato-renal toxicity and modulates pharmacokinetics in Wistar rats



Graphical Abstract: A schematic illustration summarizing the experimental design, paracetamol-induced toxicity, quercetin treatment groups, biochemical evaluation, pharmacokinetic assessment, and histopathological examination

Male Wistar rats were randomly assigned to experimental groups and pretreated orally with quercetin (25, 50, and 75 mg/kg) or silymarin for 21 days before receiving a single oral dose of paracetamol (APAP, 80 mg/kg) to produce hepato-renal damage. Blood samples were drawn at predetermined intervals for biochemical and pharmacokinetic studies of paracetamol. Histopathological evaluation of liver and kidney tissues was performed using hematoxylin and eosin (H&E) staining. The schematic summarizestreatment allocation, dose schedule, sample collection, biochemical evaluation, pharmacokinetic assessment, and histological analysis.

1. Introduction

Paracetamol (acetaminophen, APAP) is often used as an analgesic and antipyretic. Overdosing causes dose-dependent hepatocellular and renal damage [1-3]. The primary mechanism involved in hepatotoxicity is the biotransformation of paracetamol by cytochrome P450 into N-acetyl-p-benzoquinone imine (NAPQI), a reactive metabolite.

This is followed by oxidative stress, mitochondrial impairment, rapid intracellular glutathione (GSH) depletion, and cellular necrosis. In addition to hepatic damage, APAP exposure can impair renal proximal tubular function, which can lead to an increase in renal biomarkers and deterioration in histopathological features [1,3]. molecular processes underlying paracetamol-induced hepatotoxicity, such as oxidative stress, glutathione depletion, and cytochrome P450-mediated NAPQI production are illustrated in figure 1.

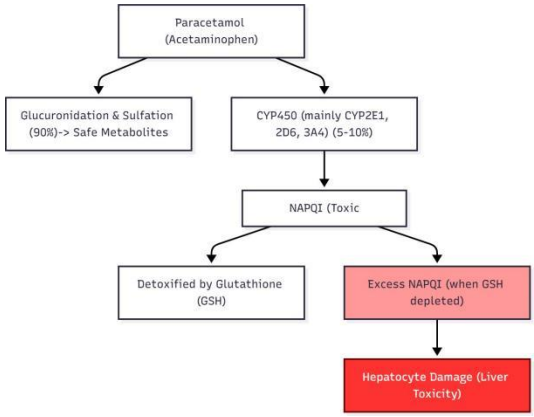


Figure 1. Mechanism of paracetamol-induced hepatotoxicity.

Natural bioactive components with cytoprotective and antioxidant properties are gaining considerable research attention as supplemental treatment alternatives for drug-induced organ damage [3]. Quercetin, a dietary flavonoid possesses strong anti-inflammatory, antioxidant, scavenging of free radicals, and membrane-stabilizing ability compared to the other flavonoids [4-6]. Previous works on quercetin demonstrated that it possesses nephroprotective and hepatoprotective capabilities against xenobiotic-induced damage [7, 8]. Quercetin's capacity to modify drug metabolic pathways may change pharmacokinetic activity [9,10]. Quercetin's therapeutic potential against APAP-induced hepato-renal damage and its effect on APAP pharmacokinetics have not been fully investigated, despite the data that is currently available. When evaluating substances that may alter metabolic or transporter-mediated drug disposition, integrated pharmacokinetic-toxicological profiling offers insightful mechanistic information. The proposed mechanistic pathway through which quercetin counteracts paracetamol-induced hepatotoxicity is summarized in **Figure 2**

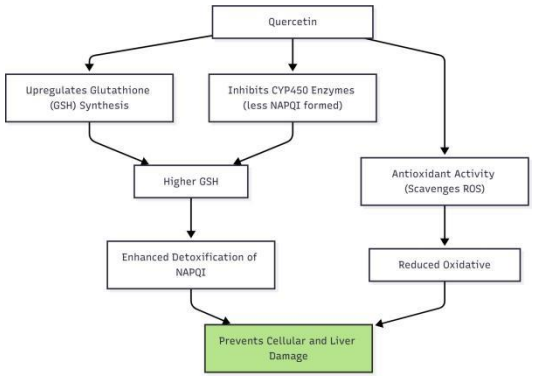


Figure 2. Proposed mechanistic pathway of quercetin against the paracetamol-induced hepatotoxicity

2. Materials and Methods

Ethical Approval

Each procedure was approved by the Institutional Animal Ethics Committee (IAEC) in accordance with CPCSEA/ARRIVE standards. The approval date and reference number are VFSTR 2046/1AEC/V/2023-5. Unless otherwise stated, there were no unexpected deaths or exclusions, and animals were monitored at least twice a day with defined humane objectives.

Animal Welfare Compliance [11,12]

Every experimental procedure adhered to the CPCSEA guidelines and the ARRIVE 2.0 reporting criteria for animal research. The Institutional Animal Ethics Committee approved research study protocol (VFSTR 2046/1AEC/V/2023-5). There were no unexpected fatalities during the trial, and humane goals were developed to reduce animal suffering. The rats' behaviour, food and water consumption, and clinical signs were all observed twice a day.

Experimental Animals and Housing [13]

Male Wistar rats were obtained from CPCSEA-licensed breeding facility (body weight range: 200-250 g). Before the trial, the animals were allowed initially seven days to adjust to the lab setting. Rats were housed in polypropylene cages with sterile bedding and kept in regulated settings (22 ± 2 °C, 50-60% humidity, 12-hour light/dark cycle). They had full availability of filtered water and a normal

pellet meal. There was environmental enrichment (tunnels and nesting materials).

Study Design and Randomization [14]

A computer-generated randomization list was utilized to randomly assign animals to experimental groups. A sample size of four rats per group was chosen based on previous investigations on APAP-induced hepatotoxicity models, in which comparable group sizes demonstrated adequate sensitivity to detect biochemical and histological changes. The study consisted of the following groups (n=4 each): 1. Normal control 2. Toxic control of paracetamol (APAP) 3. APAP with Silymarin (positive control) 4. Low-dose quercetin with APAP 5. Medium-dose quercetin with APAP 6. High-dose quercetin with APAP. In order to attain scientific validity, the CPCSEA criteria also advise using as few animals as feasible. In controlled toxicological research, this small sample size offers enough statistical power to identify meaningful treatment-related effects. Blinded assessment was used for both biochemical tests and histological investigation. There were no exclusions; all animals completed the study.

Drugs and Reagents

This investigation used analytical-grade silymarin (HPLC grade), quercetin (>98% purity), and paracetamol (acetaminophen) procured from Merck (Mumbai, India). Every chemical and reagent employed met acceptable laboratory purity requirements for use in animal research. Quercetin and silymarin were suspended in 0.5% carboxymethylcellulose (CMC) as a carrier, whereas paracetamol was freshly prepared in distilled water. Additional in vivo reagents include Phosphate-buffered solution (PBS) saline for tissue washing and formalin for sample fixation. The remaining chemicals and solvents were procured from licensed laboratory suppliers and were analytical grade.

Drug Administration and Dosing Protocol [15]

A single hepatotoxic dose of paracetamol was administered orally at 80 mg/kg. For 21 days prior to administering APAP, quercetin and silymarin were administered orally once a day. APAP was administered on day 21 following pre-treatment. The usual dose volume was 10 mL/kg. The control animals were given an identical amount of vehicle.

Sample Collection and Biochemical Analysis [16]

Blood samples were collected via the retro-orbital plexus under mild anesthesia and serum was collected for biochemical analysis. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, urea, creatinine, and uric acid were done using commercially available diagnostic kits as according to the manufacturer's directions after blood was separated by centrifugation.

Pharmacokinetic Study and Analysis

To assess pharmacokinetics, serial blood samples were collected at regular time intervals of 0, 0.5, 1, 2, 4, 6, 8, 12, and 18 hours to enable non-compartmental pharmacokinetic analysis. The levels of plasma APAP were measured using spectrophotometric technique using a validated UV-spectrophotometric method as reported previously. The analytical method used for plasma APAP estimation was validated for selectivity, linearity, accuracy, precision, and stability. Non-compartmental PK parameters Cmax, t_{max}, AUC0, AUC0-∞, t1/2, were calculated using the linear-up log-down trapezoidal technique.

Histopathological Examination

Tissues from the liver and kidneys were extracted, washed with saline sectioned at 4-5 µm slices and stained in Hematoxylin and eosin (H&E). A blinded histopathologist examined liver cell necrosis, inflammatory infiltration, hepatic cord disruption, tubular epithelial degeneration, and interstitial inflammation. A semi-quantitative grading scale (0-3) was utilized.

Statistical Analysis

The results are shown as mean ± SD (n=4). Statistical comparisons were performed using one-way ANOVA and Tukey's post-hoc test. The Shapiro-Wilk test was used to ensure that the data were normally distributed. A significance criterion of $p < 0.05$ was set.

3. Results

Effects on Hepatic Biomarkers [17,18] [19]

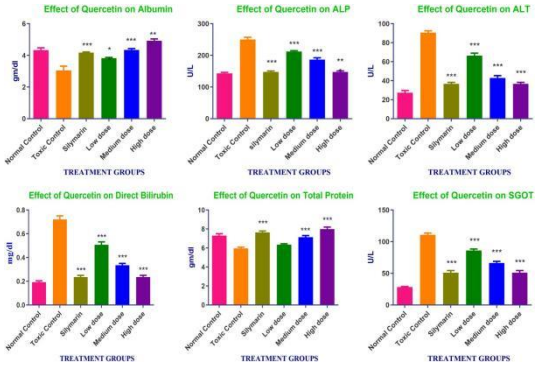


Figure 3. Effect of paracetamol and quercetin on liver biochemical parameters

Serum levels of ALT, AST, ALP, bilirubin, and total protein across experimental groups. Data are presented as "mean ±SD (n=4)"

Effects on Renal Biomarkers [20,21]

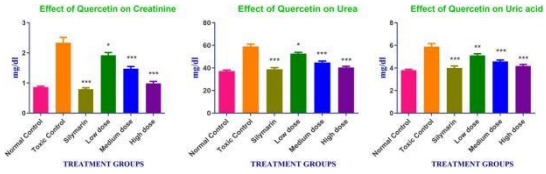


Figure 4. Effect of paracetamol and quercetin on kidney biochemical parameters

Serum concentrations of urea, creatinine, uric acid, and BUN in all treatment groups. Data are presented as mean ±SD (n=4)

Abbreviations

ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
ALP – Alkaline phosphatase
TB – Total Bilirubin
DB – Direct Bilirubin
TP – Total Protein
Alb – Albumin
UA – Uric Acid
Cr – Creatinine
Urea – Blood urea nitrogen (renal marker)

Pharmacokinetic Findings [22,23]

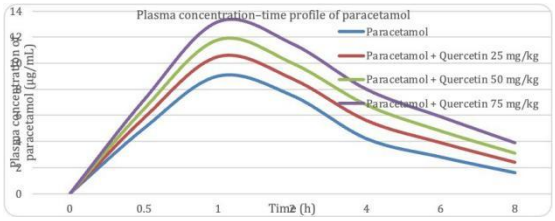


Figure 5 Plasma concentration–time profile of paracetamol following oral administration of paracetamol alone and in combination with quercetin (25, 50, and 75 mg/kg) in rats. The figure illustrates the dose-dependent trend in plasma exposure of paracetamol over time. Values represent mean plasma concentrations (n = 4).

Pharmacokinetic Parameters of Paracetamol

Table 1: Pharmacokinetic Parameters of Paracetamol (Mean± SD)

Q5, Q10, and Q15 represent quercetin doses of 25, 50, and 75 mg/kg, respectively.

Units: Cmax (µg/mL); AUC (µg·h/mL); tmax (h); t½ (h); MRT (h); CL/F (mL/h/kg); Vz/F and Vss/F (mL/kg)

Parameter	APAP	APAP + Silymarin	APAP + Q5	APAP + Q10	APAP + Q15
Cmax (µg/mL)	8.012 ± 0.234	11.212 ± 0.322	12.012 ± 0.001	12.012 ± 0.223	14.912 ± 0.322
AUC0–12 (µg·h/mL)	51.431 ± 0.344	62.571 ± 0.813	51.431 ± 0.945	64.431 ± 0.234	68.910 ± 0.430
AUC0–∞ (µg·h/mL)	44.021 ± 0.980 *	56.016 ± 2.761	64.021 ± 0.654	78.021 ± 1.345	89.021 ± 1.000
Tmax (h)	1.321 ± 0.123	1.112 ± 1.234 †	1.038 ± 0.974 †	3 ± 0.452 †	1 ± 0.004
t½ (h)	1.923 ± 0.098	2.219 ± 0.743	3.923 ± 1.832 †	3.923 ± 0.004	6.923 ± 1.234
MRT (h)	6.313 ± 0.341	6.931 ± 0.533	6.313 ± 0.532	6.313 ± 1.757	6.313 ± 0.943
CL/F (mL/h/kg)	0.292 ± 1.324 †	0.112 ± 0.115	0.281 ± 1.945 †	0.212 ± 0.013	0.145 ± 0.211

Vz/F (mL/kg)	2.193 ± 0.375	1.476 ± 0.440	1.943 ± 0.750	1.635 ± 1.335 †	1.145 ± 0.843
Vss/F (mL/kg)	2.653 ± 1.384 †	1.673 ± 0.067	1.983 ± 0.678	1.876 ± 0.194	1.233 ± 0.255

Extrapolation was used to determine the $AUC_{0-\infty}$ values, which may vary from AUC_{0-12} because of elimination phase variability.

The semi-quantitative scoring of hepatic histopathological features across different treatment groups is summarized in Table 2

Table 2: Histopathology Semi-Quantitative Score Table

Feature	Normal	APAP Toxic	Silymarin	Q-Low	Q-Medium	Q-High
Inflammation	0	+++	+	++	+	0
Necrosis	0	+++	+	++	+	+
Vacuolization	0	+++	+	++	+	0

**Scoring legend: ** 0 = none, + mild, ++ moderate, +++ severe

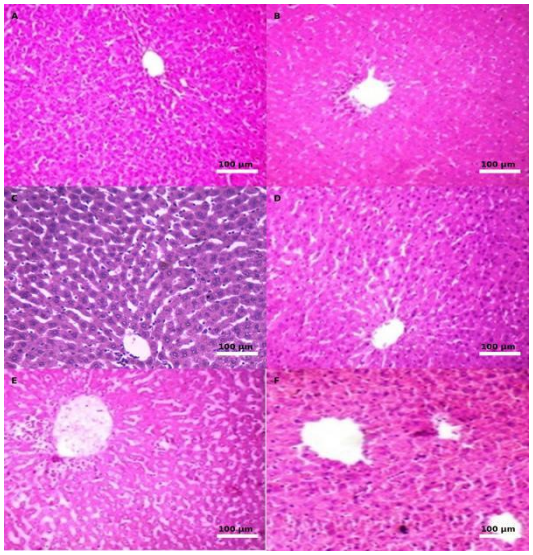


Figure 6. Liver histopathology of experimental groups (H&E)

A: Normal control; B: Toxic control; C: Silymarin-treated; D: Quercetin low dose; E: Quercetin medium dose; F: Quercetin high dose. All sections stained with H&E; scale bar=100 µm**.** Representative kidney sections showing the protective role of quercetin against paracetamol-induced nephrotoxicity.

A: Normal control – intact glomeruli and renal tubules.

B: Paracetamol toxic control – tubular epithelial degeneration, necrosis, and interstitial inflammation.

C: Silymarin + APAP – preserved renal tubular structure with minimal inflammation.

D: Quercetin low dose – mild improvement in tubular morphology.

E: Quercetin medium dose – partial restoration of tubular architecture.

F: Quercetin high dose – near-normal renal histology with markedly reduced damage. Black arrows indicate tubular degeneration, necrotic areas, inflammatory regions, and restored nephron segments.

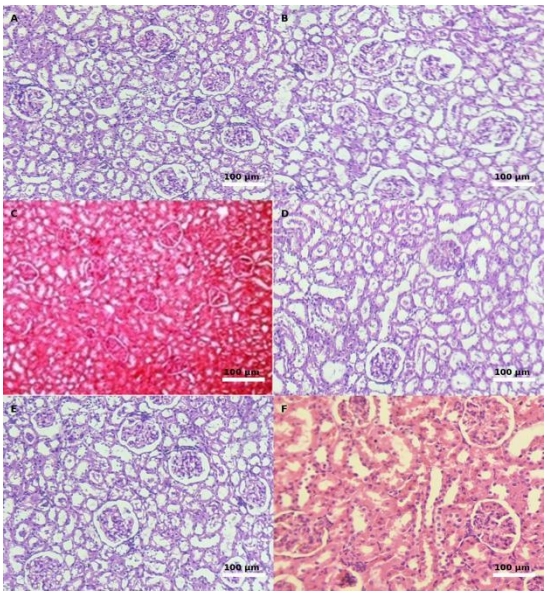


Figure 7. Kidney histopathology of experimental groups (H&E)

A: Normal control; B: Toxic control; C: Silymarin-treated; D: Quercetin low dose; E: Quercetin medium dose; F: Quercetin high dose. All sections stained with H&E; scale bar=100 µm

4. Discussion

Effects on Hepatic & Renal Biomarkers

Kidney biomarkers like urea, creatinine, and uric acid were greatly elevated by paracetamol toxicity; however, quercetin treatment had a dose-dependent nephroprotective effect, significantly lowering elevated kidney markers and restoring normal biochemical balance, comparable to the group receiving standard treatment. Following paracetamol (APAP) medication, serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly higher than in the normal control group, suggesting significant liver damage. Hepatoprotective effects were shown by quercetin pretreatment. Comparable protective benefits were indicated by the biomarker results of the silymarin-treated group and the group with the highest quercetin dose.

Rats treated with paracetamol and quercetin had a notable effect on liver indicators. ALT, AST, ALP (alkaline phosphatase), and bilirubin levels were significantly higher in the toxic control group, although albumin and protein levels were lower. Quercetin treatment showed hepatoprotective effects, particularly at medium and high doses, and was significantly better than paracetamol control, just as the traditional medication silymarin.

In the present study, co-administration of quercetin substantially lowered the hepato-renal toxicity brought on by paracetamol, as demonstrated by improved histological architecture, biochemical indicator normalization, and pharmacokinetic parameter modification. Significantly, the groups treated with quercetin had longer elimination half-lives and higher Cmax and AUC, indicating altered disposition of paracetamol. These findings suggest that pharmacokinetic and metabolic mechanisms influence a protective effect.

Pharmacokinetic Findings

According to pharmacokinetic studies, as quercetin dosage increased, paracetamol's Cmax and AUC increased dose-dependently. This increase in exposure could be attributed to quercetin's inhibition of hepatic drug-metabolizing enzymes, which reduces paracetamol clearance. Importantly, the absence of equivalent biochemical or histological damage shows efficient hepatoprotection even with greater systemic exposure. At the highest dose of quercetin tested in this study, the elimination half-life of paracetamol rose substantially and dose-dependently, indicating prolonged systemic persistence. Longer half-lives are usually associated with increased systemic exposure and poor metabolic clearance. This action, which causes paracetamol to be eliminated more slowly, may be explained by quercetin-mediated modulation of hepatic drug-metabolizing enzymes. Crucially, the lack of associated hepatic or renal damage indicates that quercetin provides efficient protective mechanisms despite higher exposure.

Rats treated with paracetamol (APAP) had a significant rise in plasma concentration, followed by a biphasic clearance phase. The silymarin-treated group had a protective pharmacokinetic profile, similar to quercetin

Histological examinations of liver

In histological examinations of liver sections, rats given APAP displayed significant centrilobular necrosis, hepatocyte ballooning, sinusoidal congestion, and inflammatory cell infiltration. Kidney tissues exhibited glomerular abnormalities, inflammatory alterations, and tubular epithelial deterioration. In contrast, quercetin-treated groups demonstrated dose-dependent recovery, decreased necrotic foci, reduced inflammatory infiltration, and preserved hepatic lobular architecture. The renal tissues showed significant tubular epithelial preservation and less pathological abnormalities. Representative kidney histopathological sections demonstrating the dose-dependent nephroprotective effect of quercetin against paracetamol-induced damage are presented in **Figure 7**.

El-Shafey et al. (2017) reported that quercetin reduced ALT, AST, and bilirubin levels in APAP-treated rats. We also saw these changes in liver enzymes in our work, with higher doses most frequently lowering the levels (Figure 4). However, the renal outcomes and pharmacokinetic data go beyond the findings of their work, as illustrated (Figure 4 and Table 1&2).

In APAP models, Tzankova et al. (2017) found that quercetin encapsulated in nanoparticles reduced lipid peroxidation and restored GSH more effectively than free quercetin. Although our results differ in formulation—we employed free quercetin and still obtained significant biochemical and histological advantages at larger dosages (Figures 6 and 7)—they are compatible with their

antioxidant observations (we exhibit normalized GSH and decreased MDA; Fig. 1C/D). Our PK results (Table 1&2) demonstrate that quercetin modifies APAP exposure, suggesting that formulation strategies (as suggested by Tzankova) could further enhance the PK/PD benefits we found and lower the recommended dosage.

In APAP-induced renal impairment, Bayoumy et al., (2020) observed that quercetin reduced urea and creatinine. Our results show a similar reno protective trend, with strong histological preservation (Figure 5) and significant improvements in kidney markers (Figure 7). This study shows modified systemic exposure to paracetamol (AUC and Cmax), protective regulation of paracetamol-induced toxicity by quercetin co-administration is suggested by the lower toxicity shown despite greater systemic exposure.

Haidara et al. (2020) demonstrated that quercetin and resveratrol together reduced renal tubular ultrastructure damage caused by APAP. As demonstrated by the figures showing reduced tubular damage. Our findings support this protective tendency, as do the stable renal markers (Figure 7). Our results show that quercetin alone can offer comparable tissue protection, even though their study included a mixture of antioxidants. Additionally, the pharmacokinetic changes seen in our work offer a mechanistic insight not investigated in their ultrastructural analysis (Figure 7).

Conclusion

The current study demonstrates that quercetin's tissue-preserving and antioxidant activities provide significant hepatoprotective and nephroprotective effects against paracetamol-induced damage. These findings suggest the development of quercetin-based formulations or combination therapies to improve safety when administering high-risk drugs. To validate its therapeutic promise, more research into controlled clinical trials, dosage optimization, and molecular characterization is needed.

Author's Contributions

SPK designed the study, conducted the in vivo experiments, performed biochemical and histopathological analysis, and contributed to manuscript drafting. GSK supervised the overall research work, provided guidance for experimental design, validated the results, and critically reviewed and edited the final manuscript. Both authors read and approved the final version of the manuscript.

Data Availability statement

The manuscript contains all of the data generated or analysed during this investigation. On reasonable request, the corresponding author may offer additional raw data, histopathology photos, and laboratory records.

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Conflict of Interest:

Regarding this study, the authors declare that they have no conflicts of interest.

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