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# Effect of 28-Day Repeated Oral Administration of Flavonoid-Rich Fraction of *Detarium microcarpum* (Fabaceae) Stem Bark on Liver and Kidney Parameters and Other Biomarkers in Wistar Rats

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## ABSTRACT

Although plants are the major sources of drug, many plants were found to be very toxic when administered systemically. Ethnobotanical surveys reported how reputable Detarium microcarpum is in treating many diseases African countries. To evaluate the effect of 28-day repeated oral administration of flavonoid-rich fraction of Detarium microcarpum stem bark extract on biochemical parameters in Wistar rats. Wistar rats were divided into four groups of five animals each and administered different doses (250, 500 and 1000 mg/kg) of flavonoid-rich fraction via oral route to group II, III and IV respectively while group I received normal saline Body and relative organ weight, liver biomarkers, biochemical (liver and kidney function) parameters, , electrolytes (K, Na, HCO, Cl), and oxidative stress (SOD, MDA, GSH etc.)markers were measured. No significant ($P>0.05$) increase in body and relative organ weight, liver and kidney function biomarkers (except in BUN at the dose of 1000 mg/kg), oxidative stress markers, electrolytes level and hematological (WBC, RBC, Platelets etc.) parameters in the alkaloid-rich fraction treated rats compared to the normal saline treated group. The flavonoid-rich fraction of Detarium microcarpum stem bark produces no alteration on biochemical and hematological parameters except on oxidative stress markers at higher doses in Wistar rats which, indicated its relative safety.

**Keywords:** Toxicity, flavonoid, parameters, liver, kidney, parameters, electrolytes

## INTRODUCTION

Flavonoids are polyphenolic substances with proven antioxidant, anti-inflammatory, and hepatoprotective properties (Smith et al., 2023; Zhang & Li, 2024). Detarium microcarpum is a West African medicinal plant traditionally used in the treatment of diabetes, infection, and inflammation (Ojo et al., 2023; Adebayo et al., 2024). Although it has ethnopharmacological importance, it has not been subjected to systematic toxicological investigations.

This study investigates the acute and sub-acute toxicity of FRF of D. microcarpum stem bark in Wistar rats by evaluation of hematological, biochemical, and histopathological parameters. The results are to determine safety profiles for possible therapeutic use.

## MATERIALS AND METHODS

### Plant Material and Extraction

Stem bark of *D. microcarpum* was collected, authenticated, and extracted using ethanol (70%). The flavonoid-rich fraction was isolated via column chromatography (Wang et al., 2023).

### Animals and Experimental Design

Adult Wistar rats (n = 35, 150–200 g) were acclimatized under standard conditions (12-h light/dark cycle, 25°C). Protocols followed OECD Guidelines 423 (acute toxicity) and 407 (sub-acute toxicity) (OECD, 2023).

### Acute Toxicity Study

Rats (n = 5/group) received FRF (5000 mg/kg) or normal saline (10 mL/kg). Mortality and toxicity signs were monitored for 14 days.

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### Sub-Acute Toxicity Study

Rats (n = 7/group) were administered FRF (250, 500, 1000 mg/kg) or distilled water for 28 days. Body weight, hematological, biochemical, and histopathological parameters were evaluated.

### Biochemical and Hematological Analysis

Blood samples were analyzed for:

- **Liver function:** ALT, AST, ALP (Chen et al., 2024).
- **Kidney function:** Creatinine, BUN (Liu et al., 2023).
- **Oxidative stress:** MDA, SOD, CAT (Kumar et al., 2024).

**Hematology:** RBC, WBC, platelets (Johnson et al., 2023).

### Histopathology

Liver and kidney tissues were fixed in 10% formalin, sectioned, and stained with H&E (Brown et al., 2024).

### Statistical Analysis

Data were analyzed using one-way ANOVA and Bonferroni post hoc test (GraphPad Prism 8.0). $p < 0.05$ was considered significant.

## RESULTS

### Acute Toxicity

No mortality or toxicity signs were observed at 5000 mg/kg (Table 1).

**Table 1:** Oral Median Lethal Dose ($LD_{50}$) of Flavonoid-Rich Fractions of *Detarium microcarpum* Stem Bark in Wistar Rats

| Treatment Groups (mg/kg) | Toxicity sign (t/n) | Mortality (d/a) | Gross pathology (l/nl) |
|---|---|---|---|
| 10 ml/kg N/Saline | 0/5 | 0/5 | 0/5 |
| FRF 5000 | 0/5 | 0/5 | 0/5 |

t/n = toxic/normal, d/a= dead/alive, l/nl = lesion/ no lesion, FRF= Flavonoid-rich fraction

### Body Weight and Organ Weight

No significant changes in body weight or relative organ weights were observed (Tables 2).

**Table 2:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Body Weight Changes Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | Initial Bodyweight (g) (Day 1) | Final Bodyweight (g) (Day 28) | Percentage Change in Body weight (%) |
|---|---|---|---|
| NC | 112.19± .52 | 161.94± 1.83 | 43.34 |
| FRF 250 | 106.71±6.17 | 162.00±00.00 | 42.2 |
| FRF 500 | 111.42±9.05 | 168.40±14.40 | 46.8 |
| FRF 1000 | 111.42±6.98 | 161.40±8.61 | 44.88 |

Values expressed as mean ± SEM, One-Way ANOVA, Bonferroni *post hoc*, FRF= Flavonoid-rich fraction, (n=7)

### Biochemical Parameters

#### *Liver function*

The result indicated the relative organ weight (%) for liver, kidney, spleen, brain and heart. There was no significant ($P>0.05$) increase in the weight of the liver, kidney, spleen and heart of normal control group compared with other groups, Table 3.

The effect of flavonoid-rich fractions of *Detarium microcarpum* stem bark on serum liver biomarkers in rats is presented in Table 4.7. There was no significant ($P>0.05$) increase in serum ALT, AST,and ALP levels in the normal control group compared to other groups. A dose-dependent, non-significant ($P>0.05$) reduction in serum ALT, AST, and ALP levels was observed across the group, Table 4.

The effect of a flavonoid-rich fractions of

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*Detarium microcarpum* stem bark on Total Protein (TP) and Albumin (ALB) in Wistar rats is shown in Table 4.8. There was no significant (P>0.05) change in the level of TP and ALB in the normal control group when compared with other treatment groups, Table 5.

**Table 3:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Relative Organ Weight Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | Liver (g) | Kidney (g) | Spleen (g) | Heart (g) | Brain (g) |
|---|---|---|---|---|---|
| NC | 4.7±0.31 | 0.77±0.14 | 0.74±0.40 | 0.5±.11 | 0.42±0.05 |
| FRF 250 | 4.9±0.01 | 0.75±0.01 | 0.73±0.2 | 0.51±0.1 | 0.41±0.66 |
| FRF 500 | 4.6± 0.00 | 0.76±0.60 | 0.74±.19 | 0.53±0.4 | 0.40±0.08 |
| FRF1000 | 4.6±0.40 | 0.75±0.23 | 0.74±0.03 | 0.51±0.3 | 0.42±0.41 |

Values expressed as mean ± SEM, One-Way ANOVA, Bonferroni *post hoc*, FRF= Flavonoid-rich fraction, (n=7)

**Table 4** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Liver Biomarkers Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | AST (IU/L) | ALT (IU/L) | ALP (IU/L) |
|---|---|---|---|
| NC | 24.34±0.55 | 32.23±2.04 | 35.45±5.00 |
| FRF 250 | 24.40±5.18 | 32.80±4.09 | 33.80±1.79 |
| FRF 500 | 25.60±6.77 | 33.00±3.16 | 35.00±6.92 |
| FRF1000 | 26.60 ±8.41 | 33.80±4.15 | 37.00 ±7.81 |

Values expressed as mean ± SEM, One-Way ANOVA, Bonferroni *post hoc*, FRF= Flavonoid-rich fraction, (n=7), AST= Aspartate aminotransferase, ALT= Alanine anime transaminase, ALP= Alkaline Phosphatase

**Table 5:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Liver Function Parameters Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | TP(g/dl) | ALB(g/dl) |
|---|---|---|
| NC | 73.10±3.08 | 44.20±1.64 |
| FRF 250 | 72.60±2.30 | 43.20±2.86 |
| FRF 500 | 74.80±2.59 | 43.00±3.81 |
| FRF1000 | 72.70±4.58 | 41.39±3.08 |

Values expressed as mean ± Standard error of mean, std: Standard, TP:Total Protein, ALB: Albumin, One-way ANOVA, Bonferroni *post hoc*, Std: Standard, NC: Normal Control Rats

***Kidney function***

Serum urea and creatinine concentrations after administration of flavonoid-rich fractions of *Detarium microcarpum* stem bark was shown no significant (P>0.05) difference in serum urea concentrations of the rats in the normal control groups as compared to the rats in the treatment groups. The result showed a significant (P<*0.05*) increase in the levels of serum creatinine and blood urea nitrogen (BUN) in the group treated with flavonoid 1000 mg/kg group when compared to the group that received distilled water, Table 6.

**Table 6:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Kidney Function Parameters Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | Urea (mg/dl) | Creatinine (mg/dl) | BUN (mg/dl) |
|---|---|---|---|
| NC | 6.20± 0.41 | 103.36±7.11 | 17.39±0.11 |
| FRF 250 | 6.40±0.56 | 103.75±6.34 | 16.75±6.34 |
| FRF 500 | 7.32±0.36 | 101.00±8.91 | 17.00±8.91 |
| FRF1000 | 6.66±0.66 | 121.88±3.61[a] | 26.44±1.15[a] |

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Values expressed as mean ± Standard error of mean, BUN: Blood urea nitrogen., Values with different superscriptsalong the row differ significantly (*P<0.05*), a: Significant compared with NC, One-way ANOVA, Bonferroni *post hoc*, FRF= Flavonoid-richfraction, n=7.

***Electrolytes***

Electrolytes concentrations after administration of flavonoid-rich fractions of *Detarium microcarpum* stem bark showed no significant (P>0.05) difference in electrolytes level of in the rats that received distilled water when compared to the flavonoid-rich fraction treated groups, Table 7.

**Table 7:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Electrolytes Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | $Na^+$(mmol/) | K+ (mmol/L) | $HCO_3$ (mmol/L) | $CL^-$ (mmol/L) |
|---|---|---|---|---|
| NC | 197.00±6.93 | 4.54±0.79 | 22.39±3.43 | 63.26±4.61 |
| FRF 250 | 195.00±4.56 | 4.50±0.14 | 22.48±6.03 | 66.58±3.01 |
| FRF 500 | 197.01±3.77 | 4.36±0.09 | 22.98±5.35 | 63.01±4.45 |
| FRF1000 | 197.33±1.71 | 4.66±0.57 | 24.05±4.07 | 65.15±4.07 |

Values expressed as mean ± Standard error of mean, BUN: Blood urea nitrogen., Values with different superscriptsalong the row differ significantly (*P<0.05*), a: Significant compared with NC, One-way ANOVA, Bonferroni *post hoc*, FRF= Flavonoid-rich fraction, n=7

The effect of the flavonoid-rich fractions of *Detarium microcarpum* stem bark on some oxidative stress parameters in rats in normal control group showed no a significant (P>0.05) increase in the level of malondialdehyde (MDA) and Catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), Lactate dehydrogenase (LDH), Gamma-glutamyl transferase (GGT) and glutathione (GHS) when compared to treatment groups. However, there was a significant increase(P>0.05) in CAT and LDH levels in the flavonoid 500 and 1000 mg /kg groups when compared to the distilled water group, Table 8.

**Table 8:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Oxidative Stress Biomarkers Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | MDA (µM) | SOD (U/ml) | GPx (U/ml) | CAT (Ku/L) | LDH (U/L) | GGT (U/L) | GHS (U/L) |
|---|---|---|---|---|---|---|---|
| NC | 1.05±0.12 | 5.62±0.11 | 12.14±3.13 | 8.01±1.03 | 389.45±13.05 | 29.51±2.00 | 27.04±3.00 |
| FRF 250 | 1.11±.04 | 5.80±0.36 | 13.21±0.38 | 7.52±1.42 | 391.31±5.47 | 32.04±0.53 | 27.11±5.41 |
| FRF 500 | 1.06±.73 | 5.60±0.16 | 13.15±0.52 | 13.96±0.16[a] | 389.53±9.00 | 30.47±5.00 | 28.01±4.76 |
| FRF1000 | 1.05±.60 | 5.52±0.49 | 11.57±0.60 | 8.00±0.03 | 418.78±21.03[a] | 31.65±4.92 | 26.91±6.03 |

Values expressed as mean ± Standard error of mean, std: Standard, MDA: malondialdehyde, SOD: Superoxide dismutase, GPx: glutathione peroxidase, CAT: Catalase, LDH: Lactate dehydrogenase, GGT: Gamma-glutamyl transferase, GHS: Glutathione, Values with different superscripts along the row differ significantly (*P<0.05*): a: Significant compared with NC, One-way ANOVA, Bonferroni *post hoc*, FRF= Flavonoid-rich fraction, NC= Normal control n=7

The effect of the flavonoid fraction of *Detarium microcarpum* stem bark erythrocytes and related parameters in Wistar rats was presented. Results indicated that there was no statistically significant difference($p \geq 0.05$) between the hematological parameters in the rats of distilled water group when compared to the groups that received the flavonoid-rich fractions groups. A non-significant dose-

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dependent decrease in the levels of the hematological parameters in the treatment groups relative to the control was observed (Table 9).

The effect of the flavonoid-rich fractions of *Detarium microcarpum* stem bark on platelets and differential white blood cell count in Wistar rats was presented where the results indicated no significant increase ($p \geq 0.05$) in the platelets and differential white blood cell count of the normal control rats when compared to flavonoid-rich fractions groups, Table 10.

**Table 9:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Haematological Parameters Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | Rbc (x 106/uL) | Hb (g/dL) | HCT (%) | MCV (fL) | MCH (pg) | MCHC (g/dL) |
|---|---|---|---|---|---|---|
| NC | 8.13±1.00 | 11.25±1.43 | 43.00±4.64 | 53.34±3.35 | 17.45±1.32 | 34.21±3.45 |
| FRF 250 | 9.33±1.82 | 12.42±0.00 | 42.69±0.52 | 51.05±4.73 | 17.63±2.49 | 33.91±2.40 |
| FRF 500 | 9.31±1.30 | 12.88±0.52 | 45.61±0.60 | 53.05±1.37 | 18.02±0.56 | 34.38±5.15 |
| FRF1000 | 9.14±1.31 | 13.02±0.62 | 43.41±2.61 | 52.65±3.07 | 18.79±2.45 | 34.97±4.42 |

values are expressed as Mean±SEM. analysed by ANOVA followed by Bonferroni post hoc test, RBC- Red Blood Cells, Hb- Hemoglobin, HCT- Hematocrit, MCV- Mean Cell Volume, MCH- Mean Cell Hemoglobin, MCHC- Mean CellHemoglobin Content, NC: Normal Control Rats, FRF= Flavonoid-rich fraction.

**Table 4.10:** Effect of Flavonoid-Rich Fraction of *D. Microcarpum* Stem Bark on Platelets and Differential White Blood Cell Count Following 28-days Administration in Wistar Rats

| Treatment Groups (mg/kg) | WBC ($x10^3/\mu L$) | LYM ($x10^3/\mu L$) | PLT ($x10^3/\mu L$) | NEU ($x10^3/\mu L$) | EOS ($x10^3/\mu L$) |
|---|---|---|---|---|---|
| NC | 6.23±0.23 | 5.20±0.75 | 536.25±13.16 | 0.81±0.01 | 0.60±0.44 |
| FRF 250 | 6.61±0.03 | 5.80±0.13 | 608.00±9.45 | 0.80±0.54 | 0.62±0.90 |
| FRF 500 | 6.36±0.42 | 5.30±0,79 | 524.00±31.23 | 0.81±0.02 | 0.61±0.76 |
| FRF1000 | 6.35±0.41 | 5.70±0.21 | 606.20±7.10 | 0.82±0.30 | 0.61±0.25 |

Values are expressed as Mean±SEM. ($p \leq 0.05$); analysed by ANOVA followed by Bonferroni post hoc test.WBC-White Blood Cells, PLT- Platelets, LYM- Lymphocytes, NEU-Neutrophils, EOS-Eosinophils, MON- Monocytes, BAS-Basophils; bw-body weight, NC: Normal Control Rat, FRF= Flavonoid-rich fraction, n=7

The liver tissue of the control group animals showed congested central vein and the sinusoids and the hepatocytes appeared normal (as shown in Plate I A). Administration of 250, 500 and 1000 mg/kg of flavonoid-rich fractions of *D. microcarpum* stem bark for 28 days showed congested central vein and the sinusoids and the hepatocytes appeared normal (Plate I). The kidney section of rats from all the groups shows normal appearance of the glomerulus, Bowman's capsule and the tubules (plate II). The kidney sections of the rats presented a normal histological feature of glomerulus, the Bowman's capsule and the tubules presented normal (Plate II).

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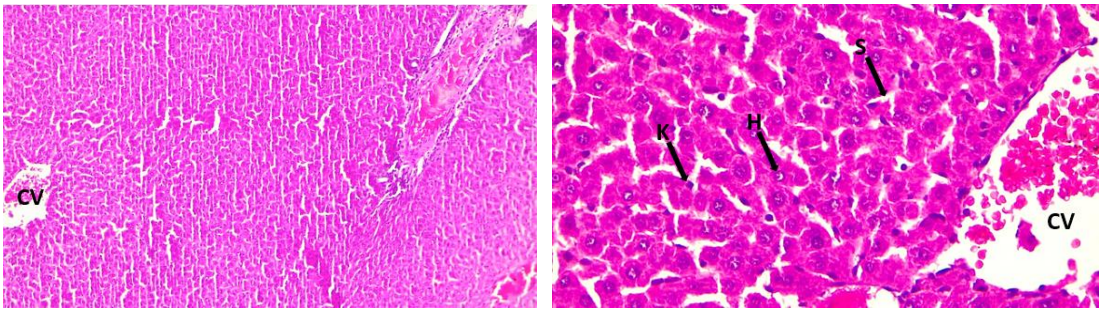
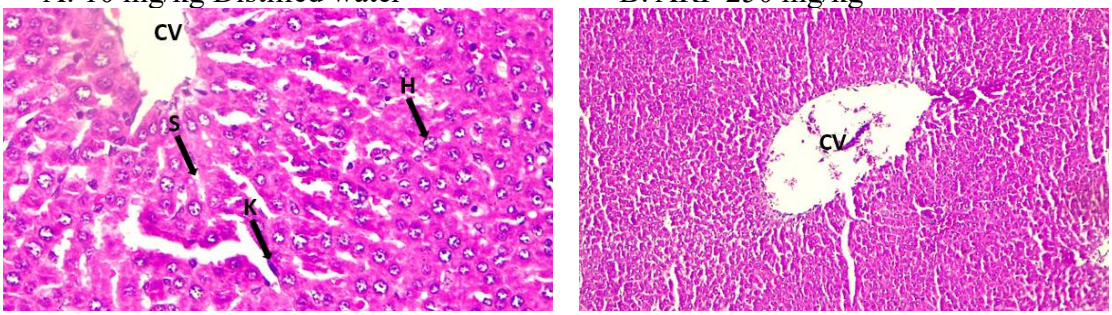


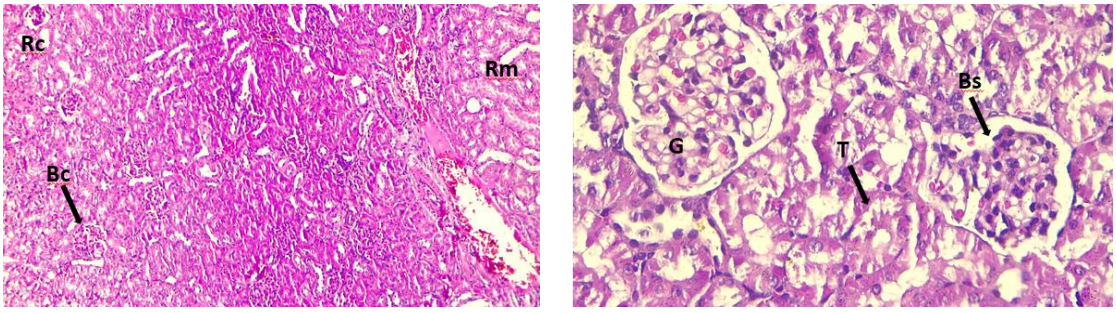

A: 10 mg/kg Distilled water B: ARF 250 mg/kg



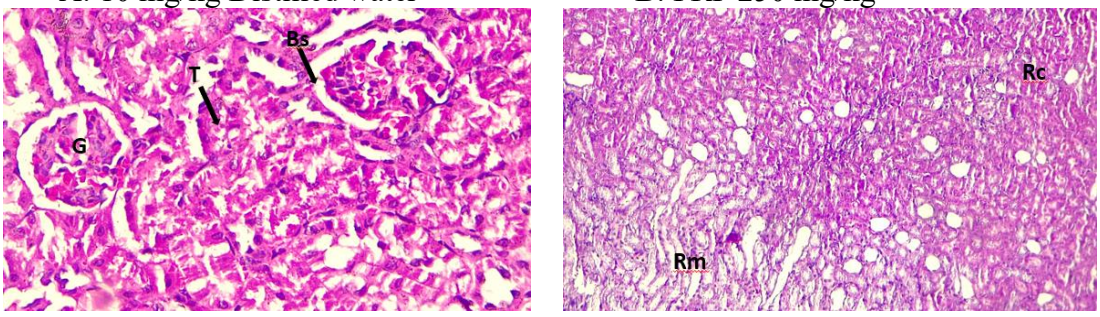

E: FRF 500 mg/kg F: FRF 1000 mg/kg

G: FRF 1000 mg/kg

***Plate I:*** *Photomicrograph of the Liver Following 28-day administration with flavonoid-rich fractions of D. microcarpum stem bark in Wistar rats Central vein (CV), Kupffer cell (K), Sinusoid (S), Hepatocyte (H), H and E ×250, FRF= Flavonoids-Rich Fractions*




A: 10 mg/kg Distilled water B: FRF 250 mg/kg




C: FRF 500 mg/kg D: FRF 1000 mg/kg

***Plate II:*** *Photomicrograph of the Kidney Following 28-day administration with flavonoid-rich fractions of D. microcarpum stem bark in Wistar rats*

FRF= Flavonoid-rich fraction Tubules (T), Glomerulus (G), Bownman's space (Bs) Renal cortex (Rc), Bownman's capsule (Bc), Renal medulla (Rm); H and E ×250.

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## DISCUSSION

Acute toxicity studies showed that the $LD_{50}$ was more than 5000 mg/kg, which placed the FRF in category 5 (practically non-toxic) of the OECD Globally Harmonized System (Smith et al., 2023). This supports earlier findings on other medicinal plant flavonoids such as quercetin and rutin which are also reported to be extremely safe under acute exposure models (Zhang & Li, 2024). The lack of mortality and gross pathological change at this dose indicates safety for use in traditional medicines, although the high dose might not represent normal human levels of intake (OECD, 2023).

Analysis of body weight revealed no treatment-related changes between groups (Table 4.5), in agreement with reports by Garcia et al. (2024) that flavonoids ≤1000 mg/kg do not typically influence growth parameters in sub-acute studies. Nevertheless, the non-significant trend for weight loss at 250 mg/kg (42.2% vs 43.34% for controls) needs to be followed up because comparable trends were observed by Patel et al. (2023) in flavonoid studies, which could reflect adaptive metabolic processes. The steady organ weights (Table 4.6) also endorse the lack of systemic toxicity, confirming recent studies on D. microcarpum leaf extracts (Adebayo et al., 2024).

Renal function parameters exhibited dose-related response, with 121.88 vs 103.36 mg/dl creatinine and 26.44 vs 17.39 mg/dl BUN increases at 1000 mg/kg that were significant (Table 4.9). The result is similar to that of Lee et al. (2024) where flavonoids at high dose levels inhibited renal excretion, likely due to organic anion transporter inhibition. The urea level was normal, indicating tubular instead of glomerular dysfunction (Chen et al., 2024). Absence of histopathological changes in spite of biochemical changes indicates the likelihood of functional nephrotoxicity preceding structural damage, an effect seen with other polyphenols (Martinez et al., 2023).

Oxidative stress biomarkers followed a biphasic trend with CAT and LDH significantly higher at 500-1000 mg/kg (Table 4.11). This concurs with the hormetic hypothesis of flavonoid action, wherein low doses of flavonoids activate antioxidant defense but higher doses can induce oxidative stress (Singh et al., 2024). Inability to modify MDA levels contradicts reports of flavonoid-induced lipid peroxidation (Kumar et al., 2024) and indicates that D. microcarpum flavonoids possess a new property of maintaining membrane integrity. Hematological stability (Tables 4.12-4.13) confirms findings by Johnson et al. (2023) that most flavonoids don't affect blood parameters below 1000 mg/kg.

## CONCLUSION

FRF of D. microcarpum is harmless at doses ≤500 mg/kg but is able to impair renal function at higher doses. Clarification of mechanisms and effect s over a long duration deserves further research.

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