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Research Article

Effect of ethanolic stem-bark extract of *Blighia unijugata* on body and organ weight, biochemistry, and hematology in Sprague-Dawley rats

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Abstract

Introduction: While the efficacy of *Blighia unijugata* against various conditions has been scientifically validated, very little is known of its safety in normal rats. This study aimed to assess the toxic effects of the ethanolic stem bark extract of *Blighia unijugata (EBU)* on body and organ weight, biochemistry, and hematology of Sprague Dawley rats following repeated oral administration.

Method: Twenty (20) male Sprague-Dawley rats were randomly selected into four groups (n = 5) and administered distilled water or EBU at doses of 50, 100, or 200 mg/kg respectively for 28 days. For each group, percentage changes in body and organ weight, serum lipid profile, fasting blood glucose levels, liver, and kidney functions, and the various hematological variables were determined.

Results: EBU treatment (50-200 mg/kg body weight) caused no significant changes ($p>0.05$) in the body weight and the relative organ weight of the heart, kidney, and spleen. Similarly, no significant changes ($p>0.05$) were observed in the lipid profile (Total Cholesterol, Triglycerides, High-Density Lipoproteins, Low-Density Lipoproteins, and Very Low-Density Lipoproteins), fasting blood glucose, serum urea, creatinine, albumin, globulin, total protein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and the hematological measures, except for a significant reduction ($p \leq 0.05$) in Alkaline Phosphatase after treatment with 200 mg/kg EBU.

Conclusion: Overall, this investigation underscores that EBU administration did not cause significant effects on the evaluated parameters, suggesting relative safety within the experimental conditions. However, for potential clinical trials and human use, additional studies such as chronic toxicity assessments across diverse animal models and dosage ranges are recommended.

Keywords: *Blighia unijugata*; biochemistry, hematology, body weight, organ weight

INTRODUCTION

Worldwide, about 80% of the population in developing countries rely on traditional medicine for their primary healthcare needs, with herbal remedies standing out as the most extensively employed option [1, 2]. This prevalence can be attributed to the substantial presence of phytochemicals in plants, which offer promising pharmacological properties against a range of diseases. As a result, the use of herbal remedies for addressing various ailments is gaining increasing traction in numerous communities. This surge in popularity can be attributed to factors such as accessibility, affordability, perceived efficacy, and safety. Medicinal plants are becoming a promising source to investigate in order to find alternatives to address the challenges with orthodox medications such as low efficacy and adverse effects, and to find novel drugs for conditions of global concern [3-5].

The toxicity associated with herbal remedies continues to present a significant hurdle, imposing constraints on their utilization despite the prevailing public perception of their safety and lack of potential harm. Among the prevalent toxicities are hepatotoxicity, nephrotoxicity, neurotoxicity, pulmonary toxicity, cardiac toxicity, adult respiratory distress syndrome, and seizures, among others [6, 7]. Consequently, the World Health Organization (WHO) advocates for the thorough scientific evaluation of herbal remedies, encompassing both effectiveness and safety assessments. This proactive approach is crucial to safeguarding the public from potential exposure to harmful plant-derived compounds [2, 6]

Blighia unijugata Baker is a shade-producing tree commonly found in tropical Africa [8, 9]. It is used indigenously to treat boils, vertigo, and post-partum hemorrhage, and also as a purgative, sedative, anti-emetic, and anthelminthic remedy [10, 11]. Several scientific studies have explored or validated its antimicrobial [12-15], molluscicidal [16, 17], antioxidant [15, 18, 19], hypotensive [20, 21], anti-inflammatory, antidepressant [22], and hematological [11] activities among others, in various models. Our lab has worked on ethanolic stem bark extract of *Blighia unijugata* over the years, particularly on its anti-fibroid [23], anti-hyperlipidemic, and anti-diabetic activities. We have also previously carried out acute toxicity studies and observed delayed toxicity for 14 days using its ethanolic stem bark extract [23].

While there are several studies on its efficacy, there remains a lack of substantial scientific support for the safety of using this plant in herbal medicines. Given the prevalent utilization of the

plant's stem bark in preparations, it becomes imperative to assess the potential toxicity stemming from prolonged and repetitive administration. This study was conducted to assess the impact of the ethanolic stem bark extract on body and organ weight, as well as biochemical and hematological parameters in Sprague Dawley rats. These assessments followed daily oral administration of the extracts over a span of 28 days.

MATERIALS AND METHOD

Plant collection

In August 2016, fresh stem bark of *Blighia unijugata* was collected from Kwahu Asakraka, located in the Eastern Region of Ghana. The plant specimen was authenticated by a Botanist affiliated with the Department of Herbal Medicine at the Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana. To preserve the specimen, a sample with the voucher number KNUST/HM1/2016/SB 17, was generated which was stored in the department's herbarium.

Preparation of *Blighia unijugata* stem bark extract

The collected stem bark was air-dried and pulverized using a hammer mill (Liming®, China). Subsequently, an 800 g sample was measured and subjected to cold maceration in 70% (v/v) ethanol for three days. The macerated mixture was then concentrated using a rotary evaporator (Rotavapor R-210, Buchi, Switzerland) at 60 °C, then oven-dried at 50 °C (Gallenkamp®, UK) until it reached a consistent weight. The resulting product was a 31.3 g black slurry residue collected and stored until reconstituted into a solution for administration. This extract was labeled EBU and stored at 4°C for use in this investigation.

Experimental animals and Experimental protocol

The experimental procedures strictly adhered to the guidelines set forth by the National Institute of Health for the Care and Use of Laboratory Animals (NIH, Department of Health Services Publication). Approval for the research work and its procedures was obtained from the Department of Pharmacology at KNUST, Ghana, with an assigned ethical approval number (FPPS/PCOL/0043/2015).

Male Sprague-Dawley (SD) rats weighing between 140-180 g were procured from the Centre for Plant Medicine Research in Mampong, Ghana. Before commencing the study, the rats were acclimatized for one week. During the study, the rats were housed in groups of five (5) under carefully controlled colony conditions, and they were provided with unlimited access to food (ad libitum).

Twenty (20) male Sprague-Dawley rats were randomly selected into four groups: Normal control, EBU-50, EBU-100, and EBU-200 with 5 rats in each group. Rats in the NC group received distilled water, while those of EBU-50, EBU-100, and EBU-200 were treated with 50, 100, or 200 mg/kg of EBU respectively. The treatment period lasted for 28 days.

Collection of blood, serum preparation, biochemical and hematological determinations

Following the completion of the treatment phase, the rats in each group were weighed. Blood samples were collected from the various treatment groups through the severed jugular vein into serum-separating gel tubes (BD Vacutainer® blood collection Tube Product, USA) and EDTA tubes (Mediplus vacutainer K3, Sunphoria Co. Ltd., Taiwan) for serum preparation and hematological studies, respectively. Subsequently, the liver, spleen, heart, and kidney were promptly removed from the sacrificed animals to determine their relative organ weights.

An automated clinical chemistry analyzer (ABX Pentra C200, Horiba Medical, USA) was used to determine the serum lipid profile (Total Cholesterol (TC), triglycerides (TG), very-low-density lipoprotein (VLDL), Low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood glucose, liver function tests (ALT, AST, ALP, T-BIL, TP, and ALB), as well as kidney function tests (urea and creatinine). Additionally, an automated hematology analyzer (Sysmex XP-300 TM Automated Analyzer, USA) was employed to measure the hematological variables.

Statistical analysis

The data obtained were analyzed using GraphPad Prism (version 6), and the results were expressed as mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was performed, followed by appropriate post hoc tests. Statistical significance was considered at $p \leq 0.05$.

RESULT

Effect of EBU on body and organ weight

EBU treatment of normal rats did not cause any significant changes in body weight. The recorded percentage changes in body weight showed no statistical significance ($p>0.05$) (Figure 1.1a). The calculated relative organ weight of the heart, kidney, and spleen also remained unaffected by EBU treatment, showing non-significant changes ($p>0.05$) (Figure 1.1b-e).

Effect of EBU on lipid profile

There were no significant changes in lipid parameters (TC, TG, HDL, LDL, VLDL) between the EBU-treated group and the normal controls ($p>0.05$) (Figure 1.2).

Effect of EBU on serum liver enzymes

EBU administration did not lead to a significant elevation of liver enzymes ALT and AST compared to the normal control ($p>0.05$). However, treatment with 200 mg/kg EBU resulted in a significant reduction of serum levels of ALP ($p \leq 0.05$)(Table 1-1).

Effect of EBU on serum albumin, globulin, total bilirubin, and total protein,

Treatment with EBU did not result in significant changes in serum albumin, globulin, total protein, and total bilirubin levels ($p>0.05$)(Table 1-2).

Effect of EBU on serum urea and creatinine

The administration of EBU to rats led to a non-significant reduction in serum urea and creatinine levels ($p>0.05$) (Figure 1.3).

Effect of EBU on hematology

EBU treatment did not cause significant changes in various measured hematological parameters ($p>0.05$)(Table 1-3).

Effect of EBU on fasting blood glucose

EBU treatment of rats did not result in a significant change in fasting blood glucose levels ($p>0.05$)(Table 1-4).

Table 1-1: Effect of ethanolic extract of *Blighia unijugata* (EBU) on serum liver enzymes

Group	ALT (U/L)	AST (U/L)	ALP (U/L)
Normal Control (NC)	0.8000 ± 0.4000	0.0 ± 0.0	14.27 ± 3.867
EBU 50 mg/kg	11.33 ± 2.517	5.050 ± 5.050	5.050 ± 5.050
EBU 100 mg/kg	28.67 ± 22.93	3.600 ± 3.600	3.233 ± 1.795
EBU 200 mg/kg	13.80 ± 8.485	0.9750 ± 0.5633	0.9750 ± 0.5633 *

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase. Data presented as means ± SEM (n=5). *$P \leq 0.05$: significant difference between EBU-treated group compared to normal control group (NC) (one-way ANOVA, then Dunnett's multiple comparisons test).

Table 1-2: Effect of the oral administration of the ethanolic extract of *Blighia unijugata* (EBU) on albumin, globulin, total protein, and total bilirubin.

Group	ALB (g/dl)	GLOB (g/dl)	TP (g/dl)	T-BIL (mg/dl)
NC	38.3 ± 0.07	54.75 ± 0.05	93.05 ± 0.65	2.75 ± 0.15
50 mg/kg EBU	35.4 ± 0.10	53.90 ± 5.70	89.3 ± 5.60	3.45 ± 1.15
100 mg/kg EBU	38.3 ± 1.32	57.35 ± 4.28	93.65 ± 2.72	3.633 ± 0.88
200 mg/kg EBU	37.6 ± 1.51	60.75 ± 3.86	96.25 ± 3.75	4.075 ± 0.86

NC: Normal control, ALB: albumin, GLOB: globulin, T-BIL: Total Bilirubin. Data expressed as means ± SEM (n = 5), No changes ($p > 0.05$) was recorded when EBU treated group was compared to the normal control group using one-way ANOVA followed by Tukey's multiple comparisons test.

Table 1-3: Effect of EBU on the hematology of normal rats

PARAMETER	EBU TREATMENT [(mg/kg)]			
	0	50	100	200
WBC (×10^3/µl)	5.750 ± 3.25	9.250± 0.65	5.425 ± 1.71	8.125 ± 0.59
NEU (%)	13.85 ± 1.93	2.200 ± 0.10	5.600 ± 1.30	2.725 ± 0.66
NEUT NO. (×10^3/µl)	0.9000 ± 0.35	0.1500 ± 0.05	0.2500 ± 0.06	0.2000 ± 0.04
LYM (%)	71.40 ± 5.000	87.20 ± 0.6000	81.68 ± 1.996	87.98 ± 1.36
LYM NO. (×10^3/µl)	3.950 ± 1.18	8.100 ± 0.50	4.450 ± 1.38	7.175 ± 0.56
RBC (×10^6/µl)	6.220 ± 0.19	7.890 ± 0.14	6.790 ± 0.38	6.843 ± 0.20
HGB (g/dl)	10.50 ± 0.87	13.30 ± 0.50	12.25 ± 0.52	12.95 ± 0.21
HCT (%)	43.10 ± 1.10	49.35 ± 0.35	43.93 ± 2.04	47.53 ± 1.18
MCV (fl)	69.35 ± 0.35	62.55 ± 0.65	64.83 ± 1.35	69.50 ± 1.28
MCH (pg)	16.80 ± 1.90	16.85 ± 0.3500	18.08 ± 0.33	18.98 ± 0.47
MCHC (g/dl)	24.25 ± 1.65	26.95 ± 0.85	27.90 ± 0.53	27.28 ± 0.33
RDW-CV (%)	18.40 ± 1.39	14.75 ± 0.05	14.23 ± 0.14	17.60 ± 1.71
RDW-SD (fl)	48.45 ± 2.80	36.25 ± 0.55	36.48 ± 0.96	44.53 ± 2.68
MXD (%)	14.75 ± 0.95	10.60 ± 0.50	12.73 ± 1.27	9.300 ± 0.90
MXD NO. (×10^3/µl)	0.9000 ± 0.35	1.000 ± 0.10	0.7250 ± 0.29	0.7500 ±0.08
PLT (×10^3/µl)	438.5 ± 96.13	542.3 ± 106.00	491.3 ± 110.60	568.7 ± 90.91
MPV (µm^3)	5.600 ± 0.06	5.650 ± 0.35	5.700 ± 0.13	6.075 ± 0.09
PDW (µm^3)	6.700 ± 0.06	6.650 ± 0.55	6.800 ± 0.19	7.150 ± 0.21
PLCR (%)	2.650 ± 0.78	2.200 ± 1.30	2.250 ± 0.77	4.625 ± 0.70

WBC: white blood cells, NEU: neutrophils, LYM: lymphocyte, RBC: red Blood cell, HGB: hemoglobin, MCV: mean corpuscular volume, HCT: hematocrit, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW-CV: red cell distribution width-coefficient of variation, RDW-SD: red cell distribution width-standard deviation, MXD: mixture of monocytes, basophils and eosinophils, PLT: Plateletcrit, MPV: mean platelet volume, PDW: platelet distribution width, PLCR: platelet-to-large-cell ratio. Values are expressed as mean ± SEM (n=5), no significant changes were recorded when EBU-treated groups were compared with the normal control using one-way ANOVA followed by Sidak multiple comparison test.

Table 1-4: Effect of ethanolic extract of *Blighia unijugata* (EBU) on blood glucose

Group	Fasting blood glucose (mmol/L)
Normal control (NC)	3.667 ± 0.13
EBU 50 mg/kg	4.467 ± 0.82
EBU 100 mg/kg	4.333 ± 0.72
EBU 200 mg/kg	4.400 ± 0.51

Data presented as means ± SEM (n=5), no significant changes was seen between the EBU-treated groups versus normal control group (NC) (one-way ANOVA followed by Dunnett's multiple comparisons test).

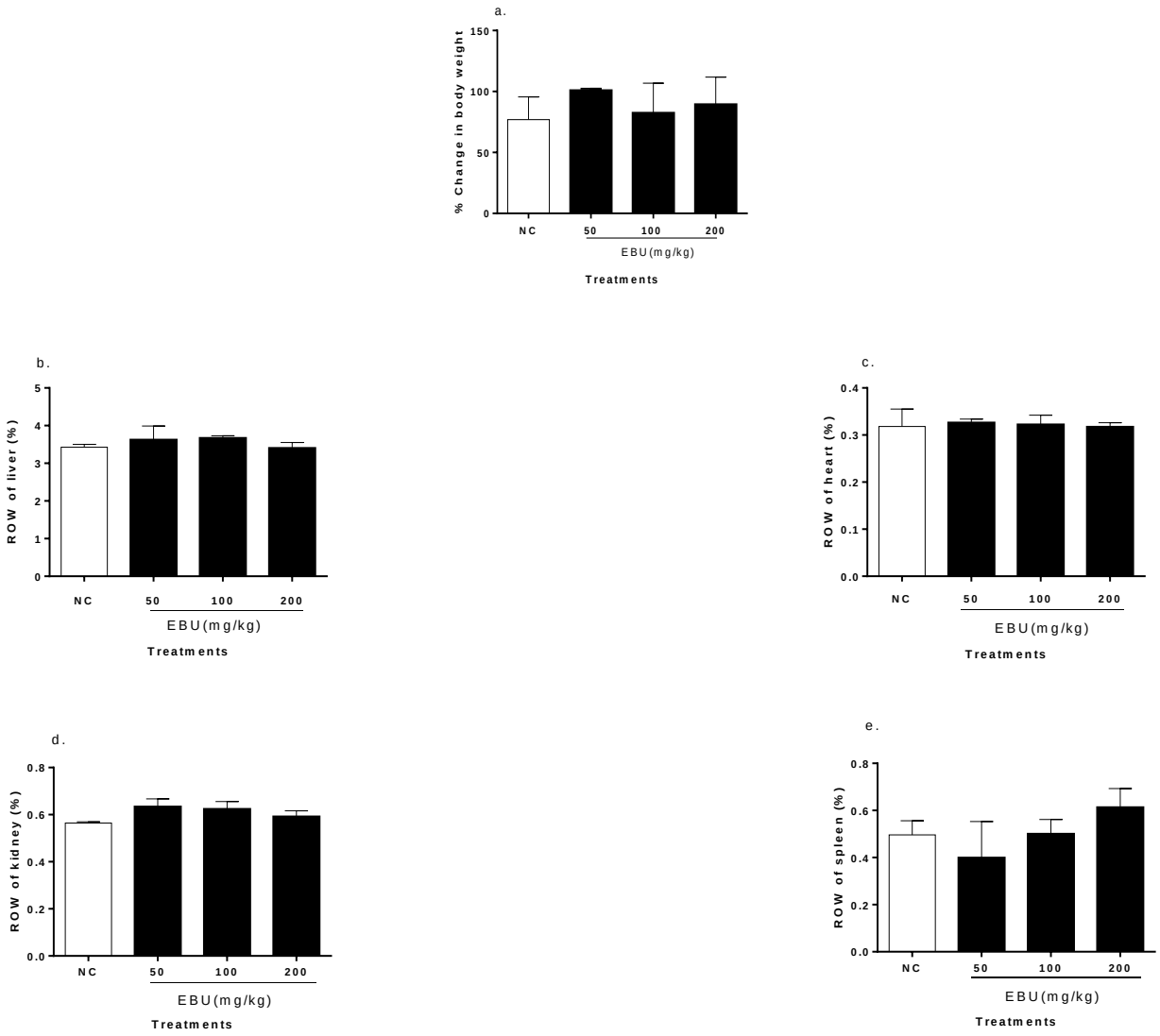

Figure 1.1: Effect of EBU (50,100,200 mg/kg) on (a) percentage changes in body weight and the relative organ weights (ROW) of the (b) liver, (c) heart, (d) kidney and (e) spleen of Sprague-Dawley rats. Data presented as means ± SEM. (n=5). No significant changes were seen between the EBU-treated groups versus normal control group (one-way ANOVA, then by Dunnett's multiple comparisons test).

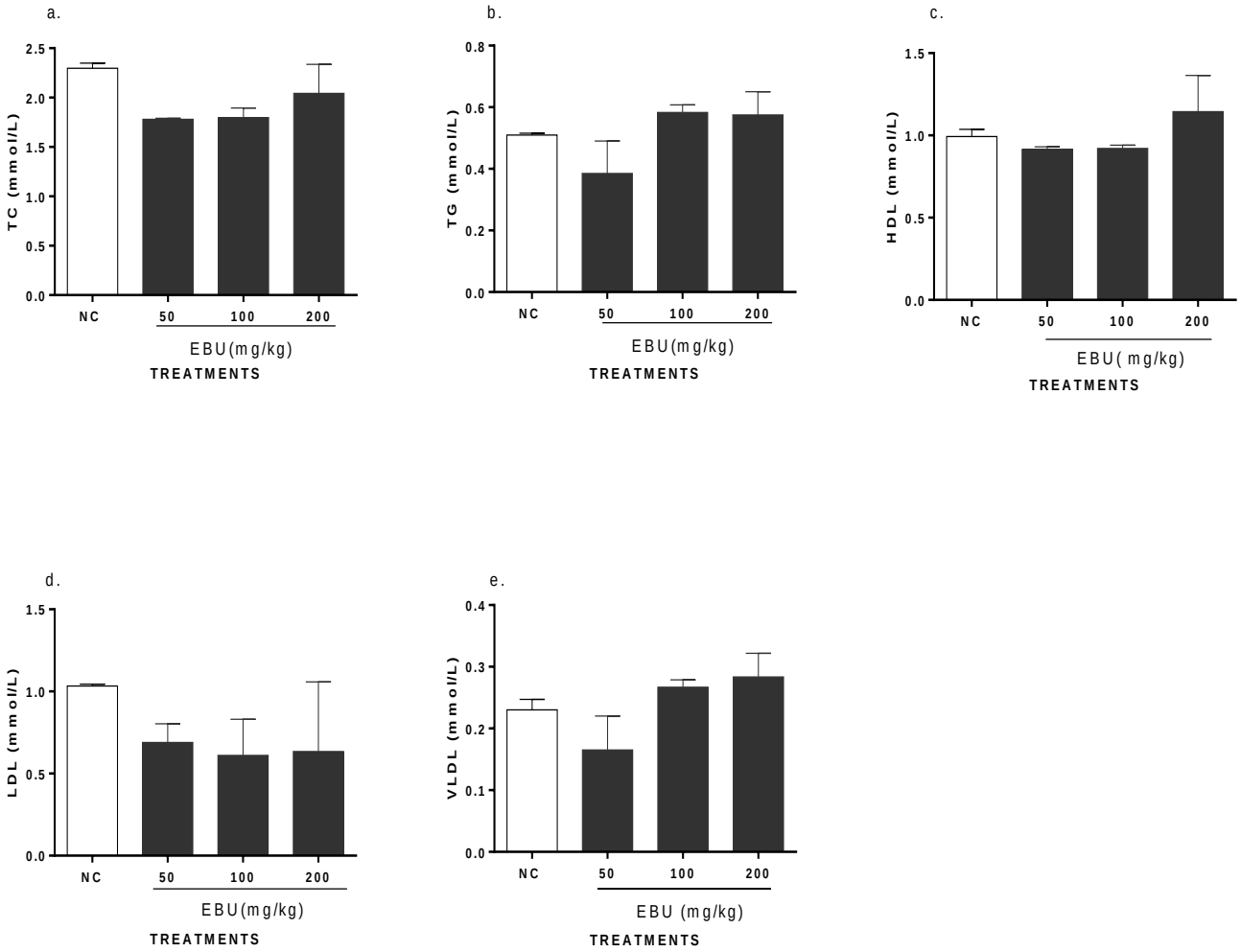

Figure 1.2: Effect of EBU (50,100,200 mg/kg) on (a) Total Cholesterol (TC), (b) Triglycerides (TG), (c) High Density Lipoprotein (HDL-c), (d) Low Density Lipoprotein (LDL-c), (e) Very Low Density Lipoprotein (VLDL-c) of Sprague-Dawley rats. Data obtained are presented as means ± SEM (n = 5). There was no significant difference when EBU-treated groups were compared to the normal control using one-way ANOVA followed by Dunnett's multiple comparisons test.

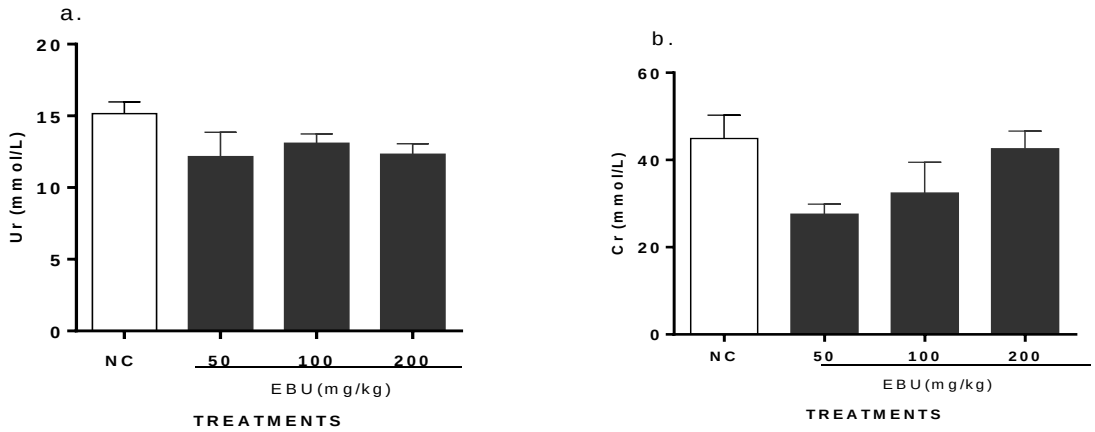

Figure 1.3: Effect of the oral administration of the ethanolic extract of the stem bark of Blighia unijugata EBU (50,100,200 mg/kg) on serum kidney function parameters: (a) Urea (Ur) and (b) Creatinine (Cr) of Sprague- Dawley rats. Data presented as means± SEM (n=5), no significant changes was seen between the EBU-treated groups compared with normal control group (NC: no STZ, distilled water) (one-way ANOVA, then Dunnett's multiple comparisons test).

DISCUSSION

This study aimed to evaluate the effects of ethanolic stem-bark extract of *Blighia unijugata* (EBU) on a range of key physiological parameters in normal rats. The focus was on investigating its potential impact on lipid profile and blood glucose levels, as well as exploring its influence on other critical factors such as changes in body and organ weights, and liver and kidney functions. Particularly, it was to determine whether EBU could induce any undesired below-normal values of glucose levels and lipid profile. Previous investigations in our lab had studied the remarkable anti-hyperglycemic and anti-hyperlipidemic activities of EBU. However, this particular study sought to determine whether EBU could also exhibit hypolipidemic and hypoglycemic properties when administered to normal rats. This is crucial because an agent that induces hypolipidemia or hypoglycemia in normal animals may be deemed undesirable, since it is the reported adverse effect of certain class of orthodox medicines. Therefore, the expectation was that EBU, when administered to normal rats, will not alter the parameters under study below or above levels closely resembling normal physiological values.

The lipid profile carried out assessed Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and Very-Low-Density Lipoprotein (VLDL). It reflects the metabolism of lipids in the body and is closely linked to cardiovascular health. Changes in lipid levels may indicate the potential effects of the medicinal plant on lipid metabolism, which is important in assessing its implications for cardiovascular diseases. Also, because of our previous studies on the anti-hyperlipidemic activity of EBU, this work was carried out to assess if the extract will cause a hypolipidemic effect in normal rats. The lipid profile analysis demonstrated that EBU treatment did not cause any substantial alterations in these parameters. The absence of significant differences between the EBU-treated group and the normal control group suggests that EBU did not impact the lipid profile of the experimental rats at the doses studied.

Evaluation of fasting blood glucose levels indicated that EBU treatment did not induce a significant change in glucose levels compared to the control group. This is noteworthy since hypoglycemia has historically been linked to early-generation Sulphonylureas and hypolipidemia to conditions like chronic liver disorders and malabsorption [24]. The preservation of near-normal blood lipid and glucose levels implies that EBU. This suggests that EBU did not disrupt the equilibrium of body and serum lipids and glucose at the administered doses.

The seed oils from the kernel, aril, Kernel/aril mixture of *Blighia unijugata* elevated TC, LDL, HDL but did not affect TG levels [25]. Frederic et al[26] also reported reduction in glucose, total cholesterol, HDL, LDL when butanol fraction of the leaves were administered. The plant parts used, and the doses administered could account for these varied findings.

The liver enzymes Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) are markers of liver function. Assessing liver enzymes helps in determining the impact of the medicinal plant on liver health and potential hepatotoxicity. Elevated levels of these enzymes may indicate liver damage or dysfunction. Elevated ALT and AST levels typically signify liver injury, with ALT being liver-specific, while AST and ALP originate from hepatic and non-hepatic sources. Elevated enzyme levels indicate leakage due to infection, toxin-induced inflammation, or the action of hypolipidemic drugs like statins [27]. Raised ALP levels are associated with bile duct obstruction, cholestasis, and other disorders. The study revealed that the administration of EBU did not cause a significant increase in the levels of liver enzymes ALT and AST when compared to the normal control group. However, it is noteworthy that the administration of 200 mg/kg EBU led to a significant decrease in serum ALP levels. The tests on albumin, globulin, total bilirubin, and total protein are part of liver function assessments and provide additional insights into liver health and protein metabolism. Changes in these parameters can indicate liver dysfunction and hepatic diseases. Assessment of these serum parameters revealed that EBU treatment did not result in significant changes in the studied parameters when compared to the control group. The lack of significant differences suggests that EBU did not have a considerable impact on these biochemical measures the doses administered.

Evaluating serum urea and creatinine levels is crucial in assessing kidney function. Altered levels may indicate kidney impairment or renal dysfunction. Monitoring these parameters helps in identifying the potential nephrotoxic effects of the medicinal plant. The administration of EBU was associated with a non-significant reduction in serum urea and creatinine levels, indicating that EBU treatment did not induce any marked alterations in kidney function. This finding suggests that EBU may not have adverse effects on renal function.

In contrast to the above findings, Oderinde et al [25], reported that the seed oils elevated GGT, urea and cholesterol, while specifically the kernel oil decreased ALT and the aril oil decreased ALP. Frederic et al [26] also reported the butanol fraction of *Blighia unijugata* elevated AST, ALT, urea, and total protein but decreased in bilirubin levels.

Hematological tests provide information about the blood's ability to carry oxygen, immune response, and overall blood health. Changes in hematological parameters can help identify any adverse effects on blood composition and immune function. Assessing hematological parameters is a crucial tool for determining biological activity or toxic effects on the blood post-extract or drug administration [28]. The findings suggest that EBU did not exert substantial effects on the hematological profile of the rats under study. The absence of significant alterations in hematological parameters upon EBU treatment suggests that the extract did not significantly impact the blood's composition. The difference in findings from that of Agbafor et al [11], who reported an increased red blood cell count with the aqueous extract of its leaves, could be attributed to variations in plant parts, extraction solvents and the doses used. Frederic et al [29] reported that whiles all other hematological parameters remain unaltered, administering butanol fractions of *Blighia unijugata* leaves to wistar rats caused a significant drop in hematocrit and thrombocyte levels . The seed oil extracted from the kernel and kernel / aril mixture of *Blighia unijugata* caused elevated red blood cells and hemoglobin levels. Paradoxically, the kernel oil was reported to increase packed cell volume whiles aril oil showed decreased in packed cell volume [25]. Here again, the difference could be as a result of the different experimental conditions such as the plant parts, kind of extract used, and even the doses of the extracts used.

Monitoring body weight is essential as it provides valuable information about the overall health and well-being of the experimental subjects. Changes in body weight can indicate the presence of any adverse effects, toxicity, or alterations in metabolic processes caused by the medicinal plant or its compounds. Additionally, measuring organ weight helps identify any potential impact on specific organs, which may be indicative of toxicity or organ-specific effects. This approach is more comprehensive than simply comparing organ weights, as it factors in changes that might not be solely treatment-induced. Evidently, the organ-body weight ratio showed no significant changes post-EBU treatment, implying that the extract may not induce pronounced organ toxicity at the administered doses.

Further examination of the data showed no significant deviations in weight parameters—no excessive weight gain or loss—after EBU treatment. This outcome contrasts with the idea of toxic compounds repressing appetite and inducing rapid weight loss [30]. Additionally, toxic components can alter nutrient absorption, food utilization, and metabolism, impacting body weight [31]. The lack of significant changes in body weight and relative organ weight following EBU treatment suggests that the EBU did not cause any noticeable alterations in the overall health or growth of the experimental rats. This stability in body and organ weight could indicate that EBU did not exert any adverse effects on the animals' metabolic rate or organ function. Similarly, Frederic et al [29] reported that the body weight and the relative weight of heart, liver, spleen, and kidney were not significantly altered after administering butanol fractions of *Blighia unijugata* leaves to wistar rats for 28 days. In contrast, Oderinde et al [25] reported that the seed oils from *Blighia unijugata* caused weight gain and elevated liver weight in albino rats whiles the weight of the intestines, spleen, heart, kidney remained unaltered .

CONCLUSION

In conclusion, the study's findings present a comprehensive assessment of EBU's effects on a multitude of parameters in normal rats at the given doses. The extract's ability to maintain near-normal levels across various physiological markers, such as lipid profile, blood glucose, body and organ weights, hematological parameters, and serum biochemical markers, highlights its potential safety at the administered doses. The absence of significant alterations in these vital parameters suggests that EBU may not pose undesired hypo-effects in normal subjects. However, further exploration across diverse contexts and dosages is needed to confirm these findings and to ascertain the extract's broader safety profile.

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