Galore International Journal of Health Sciences and Research
Vol. 7; Issue: 2; April-June 2022
Website: www.gijhsr.com
Original Research Article *P-ISSN: 2456-9321*

Hepato-Ameliorative Effect of Aqueous Extract of *Moringa oleifera* Stem Bark on Paracetamol-Induced Liver Injury in Wistar Rats

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DOI: https://doi.org/10.52403/gijhsr.20220407

ABSTRACT

Aim: The effect of aqueous extract of *Moringa oleifera* stems bark on paracetamol-induced liver injury in wistar rats was investigated.
Method: 25 male Wistar rats were used for this study. They were randomly divided into five groups: Positive control, Paracetamol control, paracetamol+1000mg/kg, paracetamol+ 1500mg/kg and paracetamol+2000mg/kg *Moringa* stem bark and 600mg/kg body weight per oral of Paracetamol was administered once daily with respective treatment. Weights of the rats were measured and liver biochemical markers (AST, ALT, ALP, Bilirubin, Total Protein, Albumin and Globulin) were determined using enzymatic kits. Histological assessment was also carried out on the liver tissues using H&E and viewed under light microscope. The experiment lasted for 10 days.
Results: There was a significant ($p<0.05$) decrease in the weight of the liver in the groups treated with different doses of *M. oleifera*. There was a slight increase in weight of liver, although not significant, when compared with positive control. *M. oleifera* significantly ($p<0.05$) reduced the blood levels of AST, ALT, ALP and bilirubin when compared with the paracetamol control. The results indicated a dose dependent increase in serum albumin and globulin levels which was significant when compared with paracetamol control group but not significant when compared to the control group. Histological assessment of the liver of the Wistar revealed that aqueous extract of *Moringa oleifera* stem bark have hepato-protective ability revealed by regenerating hepatocytes.
Conclusion: *Moringa oleifera* stem bark has hepato-protective potentials as reveal from the biochemical and histological outcome of this study. Hence, *Moringa oleifera* stem bark can be used to ameliorate or manage paracetamol induced hepatotoxicity.

Key words: *Moringa oleifera* stem bark, Paracetamol, Liver Injury, Biochemical parameters

INTRODUCTION

Liver is an organ in the upper abdomen that regulates homeostasis. It is involved with biochemical pathways related to growth, fight against disease, nutrient supply, and energy provision [1]. Besides performing physiological functions, it aids in digestion and removes waste products and worn-out cells from the blood. It is a vital organ present in vertebrate and some other animals, which has a wide range of functions including detoxification and protein synthesis. The liver is our greatest chemical factory, it builds complex molecules from simple substances absorbed from the digestive tract, it neutralizes toxins, it manufactures bile which aids fat digestion and removes toxins through the bowels [2]. But the ability of the liver to perform these functions is often compromised by

numerous substances we are exposed to on a daily basis; these substances include certain medicinal agents which when taken in over doses and sometimes when introduced within therapeutic ranges injures the organ [3]. Liver disease is a worldwide problem. Conventional, drugs used in the treatment of liver diseases are sometimes inadequate and can have serious adverse effects. Therefore, it is necessary to search for alternative drugs for the treatment of liver disease in order to replace currently used drugs of doubtful efficacy and safety [4]. In the absence of reliable liver protective drugs in allopathic medical practices, herbs play a role in the management of various liver disorders. However, we do not have satisfactory remedy for serious liver disease; most of the herbal drugs speed up the natural healing process of liver, so the search for effective hepato-protective drug continues.

Moringa oleifera belongs to the Moringaceae family of perennial angiosperm plants. It is a fast growing tree that can attain a height of about 10-12m with a diameter of about 45cm [5,6]. Although native to the Sub-Himalayan tracts of India, Pakistan, Bangladesh and Afghanistan, it is now cultivated throughout the tropical and sub-tropical regions of the world because of its numerous benefits[7,8,9]. In Nigeria, *Moringa oleifera* is planted in all parts of the country and is identified by a variety of local names including, 'Zogale' (Hausa); 'ewe igbale' (Yoruba) and 'ikwa oyibo' (Ibo) [10].The leaves, fruit, flowers and immature pods of *Moringa oleifera* are highly nutritious and have also been utilized in ethnomedicine for the treatment of various human ailments [11,12]. Specifically, the leaves are reported to be rich in proteins, mineral elements, vitamins A, C, E, β-carotene, various polyphenolic compounds and natural antioxidants [13,14]. *Moringa* leaves had been reported to contain 7 times the vitamin C of oranges, 4 times the calcium of milk, 4 times the vitamin A of carrot. Moreover, a variety of pharmacological activities have been attributed to the extract of *Moringa* including anticancer, anti-inflammatory, bactericidal, hypocholesterolemic, anti-atherosclerotic, antioxidant, neuro and hepatoprotective [15,16,17,18,19]. In many cases, published *in-vitro* (cultured cells) and *in-vivo* (animal) trials do provide a degree of mechanistic support for some of the claims that have sprung from the traditional medicine lore. Numerous studies now point to the elevation of a variety of detoxication and antioxidant enzymes and biomarkers as a result of treatment with *Moringa* or with phytochemicals isolated from *Moringa* [20,21,22]. This study was designed to investigate the hepatoprotective effect of the ethanolic stem bark extract of *Moringa oleifera* on the biochemical and histology of paracetamol induced liver damage.

METHODOLOGY

Ethical Clearance

All procedures carried out during this research were done in accordance with the guiding principles of research involving animals as recommended by the Research Ethics Committee of the University of Port Harcourt. Animals were kept in standard metal cages and at normal room temperature.

Procurement of Animal

Twenty-five male albino rats weighting 150 to 210g were used for this study and were obtained from Animal House of Department of Pharmacology, University of Port Harcourt, River State, Nigeria and acclimatized for 2 weeks. The animals were maintained before and throughout the experiment period in standard cages with access to clean water and food (pellets) *ad libitum* under standard environmental conditions (temperature: 27.0±1.0°, relative humidity: 55-65% and 12 h light/12 h dark cycle). At the start of the experiment, the animals were randomly distributed into 5 groups of 5 animals each.

Preparation of Plant Materials

Fresh *Moringa* stem barks were collected from Choba in Obio/Akpor Local

Government Area of Rivers State and identified in the herbarium of the Department of Plant Science and Biotechnology in the University of Port Harcourt. The leaves were washed and air dried at room temperature and then grounded into fine powder after drying properly. 20g of grounded *Moringa* stem bark was dissolved in 200ml of distilled water and shaken vigorously for five minutes and allowed to stand for ten (10) minutes, then shaken again for five minutes and allowed to stand for twenty four (24) hours at room temperature. The mixture was filtered after 24hours, first with a piece of white cloth, six times and then with Whatman No.1 filters paper. The filtrate served as stock solution from which dilutions of 100mg/kg and 200mg/kg were prepared for each sample and refrigerated at 4^0C for the duration of administration.

Toxicity studies

Toxicity studies of the extracts were carried out in Wistar rats of either sex weighing between150 to 210g. The extract was found to be safe till 6000mg/kg p.o. Therefore, doses were selected as 1000mg/kg, 1500mg/kg and 2000mg/kg body weight [23].

Drug Purchase and Preparation

Paracetamol manufactured by Emzor Pharmaceutical Industries Limited purchased from Greenhouse Pharmacy located inside the University of Port Harcourt. Its chemical name is N-(4-hydroxyphenyl) acetamide or N-(4-hydroxyphenyl)ethanamide. The LD50 of paracetamol for rats adopted was 1944mg/kg [24].

Experimental Design

The method described by Tella and Ojo[25] and Buraimoh *et al.*[15] with slight modification were used. 25 adult male Wistar rats weighing between 150 and 210g were grouped as below:

- Group I: Administered 10mL/kg per oral (p.o) of water once daily for 10 days, and served as normal control
- Group II: Served as the negative control (paracetamol control) group and were administered 10mL/kg p.o of water for 10 days.
- Group III: Was administered 1000mg/kg body weight of the aqueous extract of *Moringa oleifera* stem bark on a daily basis for 10 days.
- Group IV: Was administered 1500mg/kg body weight of the aqueous extract of *Moringa oleifera* stem bark on a daily basis for 10 days.
- Group V: Was administered 2000mg/kg body weight of the aqueous extract of *Moringa oleifera* stem bark on a daily basis for 10 days

Paracetamol 600mg/kg b.w p.o was administered once daily with respective treatment according to Tabassum and Agrawal (2004) to rats in group II, III, IV and V. Oral route of administration was used and the administration lasted for 10 days.

Determination of Weight

The initial and final body weight of Wistar rats and the liver weight were determined using Cammry Electronic Weighing balance calibrated in gram and kilogram.

Biochemical Analysis

After the ten days of treatment, blood samples were collected by direct cardiac puncture from the of rats in each cage and put into lithium heparin bottles, the serum was used for the assay of biochemical markers such as Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Total Protein (TP), Albumin (ALB) and Globulin (GLB). They were determined using enzymatic kits (CYPRESS® Diagnostics, Langdorp, Belgium) according to the manufacturer's instructions.

Histological Evaluation of Liver

The liver tissues of the experimental rats were harvested by making a median incision through the abdominal; cavity, the harvested liver tissues were fixed in 10% buffered formalin solution for tissue processing and staining (H & E).

Method of Data Analysis

Data were analyzed using SPSS version 23.0. All data obtained were expressed as Mean ± SEM. One-way analysis of variance (ANOVA) was used to compare the means between and within the groups and a *p*-value <0.05 was considered significant. A Tuckey's post-hoc test was also applied to assess significant differences between groups.

RESULTS

Table 1: Effect of *Moringa oleifera* stem bark on the Body Weight and Liver Weight in Paracetamol-induced injury in Wistar rats

Group	Body Weight (Mean±SEM)		Weight of Liver (Mean±SEM)
	Initial Day (Day 1)	Initial Day (Day 10)	
Positive Control	168±0.54	188±1.62	5.73±0.32
Paracetamol Control	167±1.07	146±1.43*	7.02±0.21*
Para + 1000mg/kg MOE	168±1.98	171±0.88*#	5.80±0.43#
Para + 1500mg/kg MOE	166±2.04	173±1.40*#	6.04±0.13#
Para + 2000mg/kg MOE	167±1.32	176±2.21*#	5.96±0.16#

Each value represents mean±SEM, Values marked with (*) differ significantly from Positive control value (*p<0.05) while those marked with (#) differ significantly from Paracetamol control group (#p<0.05). Para = Paracetamol, MOE = *Moringa oleifera* Extract

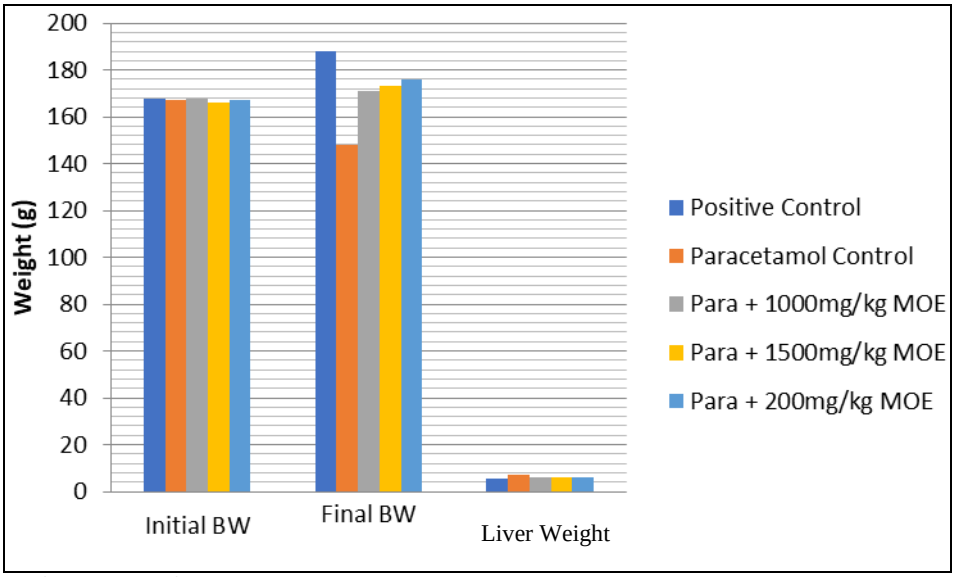

Figure 1: Effect of *Moringa oleifera* stem bark on the body weight and liver weight in Paracetamol-induced liver injury in Wistar rats

Table 2: Effect of Aqueous extract of *Moringa oleifera* stem bark on AST, ALT and ALP Parameters of paracetamol-induced Liver injury in Wistar rats

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Positive Control	58.3±1.13	52.2±1.62	138.1±2.55
Paracetamol Control	105.8±2.04*	93.2±2.12*	260.6±2.64*
Para+1000mg/kg MOE	90.2±1.65*#	76.9±2.41*#	232.5±5.68*#
Para+1500mg/kg MOE	78.4±2.14*#	72.8±1.38*#	192.7±6.10*#
Para+2000mg/kg MOE	64.5±1.84*#	63.5±1.64*#	165.8±3.45*#

Each value represents mean±SEM, Values marked with (*) differ significantly from positive control (1ml of Water) value (*p<0.05) while those marked with (#) differ significantly from negative control (1mg/kg Paracetamol) group (#p<0.05). Para = Paracetamol, MOE = *Moringa oleifera* Extract

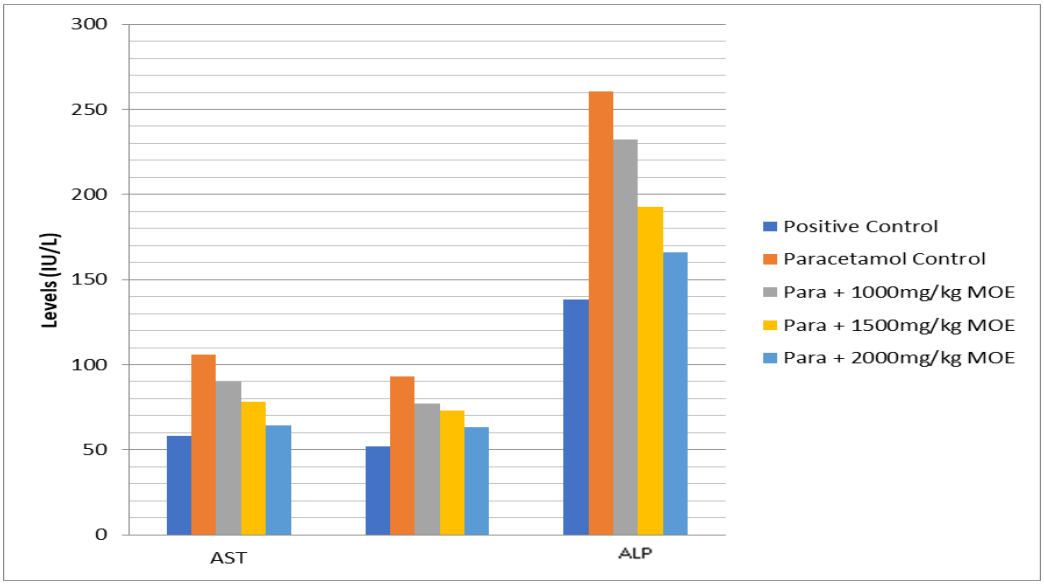

Figure 2: Effect of *Moringa oleifera* stem bark on AST, ALT and ALP levels in paracetamol-induced liver injury in Wistar rats

Table 3: Effect of Aqueous extract of *Moringa oleifera* stem bark on Total Protein, Albumin and Globulin Parameters of paracetamol-induced Liver injury in Wistar rats

Group	Bilirubin (g/dL)	TP (g/dL)	Albumin (g/dL)	Globulin (g/dL)
Positive Control	0.8±0.70	6.1±0.16	3.1±0.43	2.7±0.15
Paracetamol Control	3.1±0.11*	4.8±0.84*	1.7±0.74*	3.1±0.41*
Para+1000mg/kg MOE	1.4±0.13*#	6.6±0.12#	4.2±0.11*#	2.9±0.09#
Para+1500mg/kg MOE	1.1±0.20#	6.2±0.04#	3.5±0.86#	2.7±0.20#
Para+2000mg/kg MOE	0.9±0.10#	5.8±0.09#	3.2±0.62#	2.4±0.18#

Each value represents mean±SEM, Values marked with (*) differ significantly from positive control (1ml of Water) value (*p<0.05) while those marked with (#) differ significantly from negative control (1mg/kg Paracetamol) group (#p<0.05). Para = Paracetamol, MOE = *Moringa oleifera* Extract

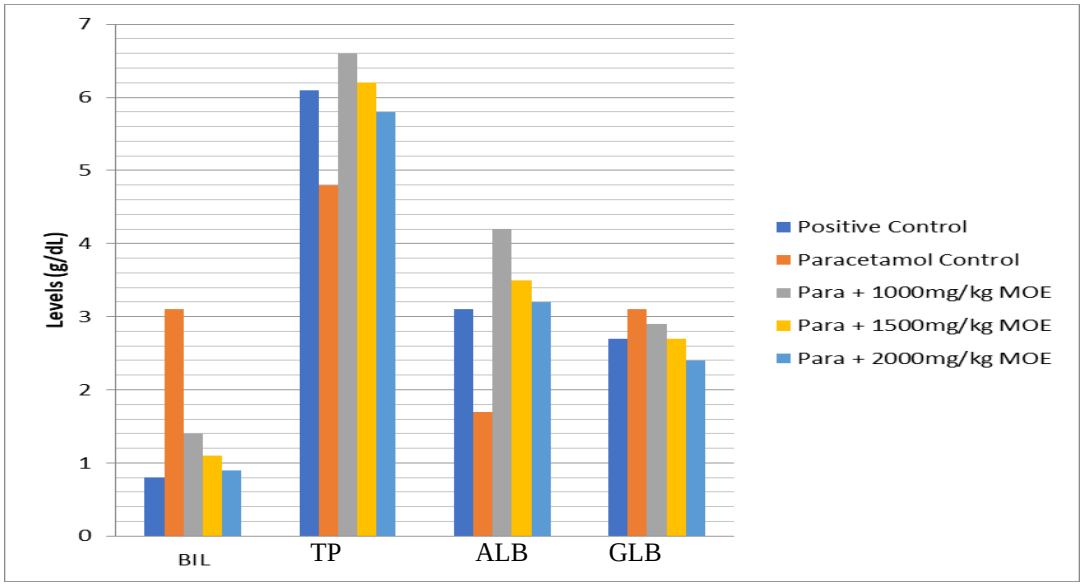

Figure 3: Effect of *Moringa oleifera* stem bark on Bilirubin (BIL), Total Protein (TP), Albumin (ALB) and Globulin (GLB) levels in paracetamol-induced liver injury in Wistar rats

Histology

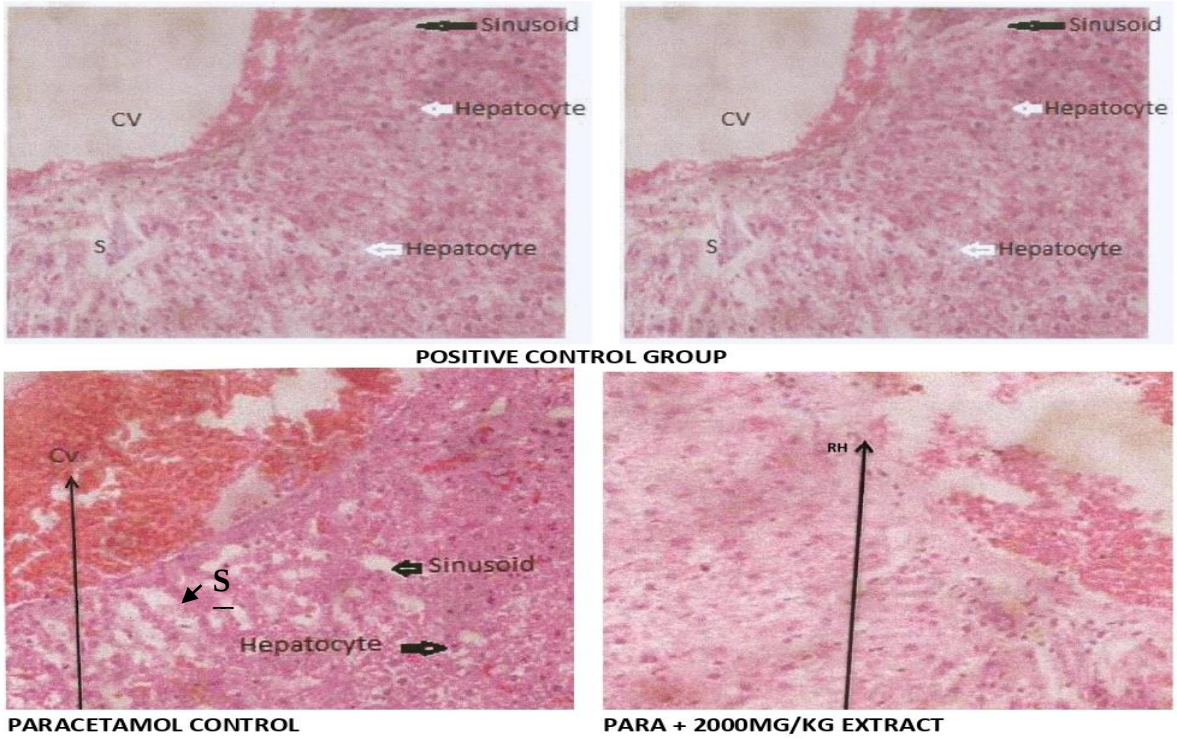

Figure 4: Photomicrograph of liver tissue exposed to 10ml of water after 10 days displaying histologically normal liver with intact hepatocytes (H), sinusoids (S) containing kupffer cells and central vein (CV) in positive control group; Photomicrograph of liver tissue exposed to 600mg/kg paracetamol after 10 days displaying histologically distorted liver with hepatocytes (H), different degrees of steatosis (ST) and congested central vein (CV). Photomicrograph of liver tissue exposed to 2000mg/kg paracetamol after 10 days displaying regenerating hepatocytes (RH). Magnification: x200

DISCUSSION

Paracetamol with IUPAC name; N-(4-hydroxyphenyl) ethanamide, is the most commonly used oral analgesics and antipyretic and pain reliever and since 1955 has been available over-the-counter as a single formulation or in combination with other substances [26]. As indicated by the World Health Organization, this drug can be used in all the three steps of pain intensity. Being the main drug prescribed for feeble pains, it can be used together with non-steroidal analgesic drugs also to treat pains of moderate intensity. The usual dosing of immediate-release oral preparations in adults is 325-650mg every 4-6 hours or 1g every 4-6 hours as necessary, without exceeding 4g per day [27]. Conversely, in children, the recommended dose is 10-15mg/kg every 4-6 hours up to a maximum daily dose of 50-75mg/kg [28]. Metabolism of paracetamol occurs primarily in the liver and adverse events typically associated with paracetamol intoxication are represented by acute liver failure (ALF), centrilobular hepatic necrosis, renal tubular necrosis and hypoglycaemic coma [28,29].

The present study was aimed at assessing the ameliorative effect of aqueous extract of *Moringa oleifera* stem bark in paracetamol-induced liver injury in Wistar rats. The result of body weight of rats was well as weight of liver as presented in Table 1 and Figure 1 indicated a significant ($p<0.05$) increase in the body weight of the experimental rats when compared to the paracetamol control group and a significant ($p<0.05$) decrease in body weight when compared to the positive control group. There was a significant ($p<0.05$) decrease in the weight of the liver in the groups treated with different doses of *M. oleifera* when compared to the paracetamol control. There was a slight increase in weight of liver, although not significant, when compared with positive control. This finding conforms to the study by [30].

Also, the results obtained revealed as presented in Table 2, figure 2 and figure 3 that the *M. oleifera* extract significantly

($p<0.05$) reduced the blood levels of AST, ALT, ALP and bilirubin when compared with the paracetamol control. This decrease was dose dependent (Table 2 and figure 2). This reduction the levels of AST, ALT and ALP proved of the protective effect and restoration of the liver integrity which was affected by the lesion caused by paracetamol induction and this is due to the non-toxic nature and tissue protective nature against various toxic metabolites of *M oleifera*. The result of this study conforms to that of Islam *et al.* [30] that carried out a similar study and opined that "*M oleifera* extract seemed to offer protection and maintain the functional integrity of hepatic cells." Study by Fakurazi *et al.*[31] who carried out a study on *Moringa oleifera* hydroethanolic extracts effectively alleviate acetaminophen-induced hepatotoxicity in experimental rats through their antioxidant nature revealed that Administration of *Moringa oleifera* flowers and leaves extract significantly reduced the extent of liver damage following a high dose of acetaminophen. There was a significant decrease of serum ALT level in rats treated with flowers and leaves extract. This is in agreement with this study as well as studies by Omobowale *et al.* [32], Yang *et al.* [33] and Terneus *et al.* [34].

Plasma proteins (except immunoglobulins) are mainly produced by the liver. Plasma protein level is decreased by severe liver damage resulting in reduced serum levels of total protein, albumin and globulin [35,36]. Decreased protein production may result in prolonged prothrombin or activated partial thromboplastin times [37,38]. The results indicated a dose dependent increase in serum albumin and globulin levels which was significant when compared with paracetamol control group but not significant when compared to the control group as presented in Table 3 and figure 3. The result of the study agrees with the findings of Islam *et al.*[30] and Omobowale *et al.* [32].

Histological assessment of the liver of the Wistar as presented in figure 4 revealed that aqueous extract of *Moringa oleifera* stem bark have hepato-protective ability where there was fewer necrotic cells and wider sinusoidal spaces when compared with the paracetamol control group that showed distorted hepatic cords, necrotic cells and obliterated sinusoids. This shows the hepatotoxic nature of Paracetamol was used in this study [38]. *Moringa oleifera* stem bark was able to cause regeneration of hepatocytes and bring to normal the integrity of the liver. This finding agrees with the study by Buraimoh *et al.*[15] who carried out a study on the hepato-protective effect of ethanolic leave extract of *Moringa oleifera* on the histology of paracetamol induced liver damage in Wistar rats and posited that *M. oleifera* leave extract has hepato-protective effect. It is also in agreement with the study by Akpanyung *et al.*[39] who carried out a study on the evaluation of the protective effect of *Moringa oleifera* leaf extract against aluminium induced liver damage in male Albino Wistar rats and stated that the administration of ethanol leaf extract of *Moringa oleifera* moderated the deleterious effects of aluminium chloride.

CONCLUSION

The present investigation suggested that *Moringa oleifera* stem bark has a potential role in therapeutic action in ameliorating hepatic injury resulting from paracetamol toxicity; this due to the rich presence of phytochemicals and anti-oxidants in the *Moringa oleifera* plant parts. However, further investigations are essential to elucidate the precise molecular mechanism of specific bio-active agents from *Moringa oleifera* stem bark for protection/treatment against hepatotoxin induced hepatotoxicity and it has to be tested against various biologically important markers.

Acknowledgements: The authors wish to thank the Laboratory Assistants in the Department of Biochemistry for their input in ensuring this research is a success.

Conflict of Interest: None
Source of Funding: None
Ethical Approval: Approved

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How to cite this article: Omeodu S.I., Aleme, B.M, Akoko S. et.al. Hepato-ameliorative effect of aqueous extract of moringa oleifera stem bark on paracetamol-induced liver injury in wistar rats. *Gal Int J Health Sci Res*. 2022; 7(2): 46-54. *DOI: https://doi.org/10.52403/gijhsr.20220407*

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