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Hepatoprotective Effects of *Phyllanthus Amarus* Ethanolic Extract On CCL_4-Induced Hepatotoxicity in Wistar Rats

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ABSTRACT

The hepatoprotective effect of ethanolic leaf extracts from *Phyllanthus amarus* was studied in relation to CCl4-induced hepatotoxicity in wistar rats. As controls, animals from Group 1 were used. 3mL/kg body weight (bw) of 30% CCl_4 in olive oil was administered once per week for two weeks to Group 2 animals to harm their livers. Animals in Groups 3 and 4 were treated with *Phyllanthus amarus* ethanol leaf extracts (50 mg/kg and 70 mg/kg, respectively) following CCl_4 induction.. The 14-day trial was conducted. The results of this study indicate that, when compared to those who received CCl_4, those who received ethanol leaf extracts of *phyllanthus amarus* showed a comparatively considerable liver protection against CCl_4-induced damage. A significant increase ($p<0.05$) in the levels of biochemical parameters: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) of rats administered with CCl_4 only was also observed. The *phyllanthus amarus* extract's activity at 70mg/kg bw (higher dose) give a reasonable decrease in the amount of these liver enzymes. Deducing from study results, it indicates that *Phyllanthus amarus* leaf extracts could be an effective hepatoprotective agent in CCl_4 mediated liver toxicity in adult wistar rats and drug development.

Keywords: Alanine aminotransferase (ALT**),** Alkaline phosphatase (ALP)**,** Aspartate aminotransferase, hepatoprotective **,** Phyllanthus amarus.

1 INTRODUCTION

The liver, the largest organ in the body, is crucial to the met abolism of harmful chemicals and, as a result, to the eliminati on of those compounds from the body. A disruption in liver f unction will have a significant impact on various homeostatic mechanisms and may have serious consequences [1]. The liver is often responsible for the body's metabolism, secretion , storage, and detoxification processes; any modest changes t o these processes frequently result in hepatotoxicity. Acute li ver illness and failure are linked to medications and other sub stances in about half of cases [2].

Useful bioactive substances are found in plants that are medinal in nature, that protect human from various biochemical complications. The fact that the liver is an important organ that is actively involved in several metabolic processes, that makes it a soft target to toxicants. Liver conditions are thought to be deadly and life-threatening. These are brought on by infections or liver exposure to poisonous chemicals like alcohol or narcotics. The pathobiochemistry method emphasizes in particular the induction of hepatocellular enlargement in human pathology as a result of liver cell necrosis caused by substances, foods, or pathogenic hepatotoxins. Acetaminophen, ethanol, and carbon tetrachloride (CCl4) are hepatotoxins that cause liver damage linked to varied degrees of hepatocyte degeneration and cell death. [3]. As a xenobiotic, CCl4 causes hepatotoxicity in both humans and a number of laboratory animals. The covalent attachment of CCl4, trichloromethyl free radicals to cell

proteins is the initial step in the series of reaction events that eventually led to membrane lipid peroxidation, necrosis of the cells, and ultimately cell death [4]. The industrially produced medications used to treat liver illness are still insufficient and, in some circumstances, have serious adverse effects, which are a global health concern [5]. Ayurvedic herbal preparations have been suggested for the treatment of liver malfunctions due to the lack of effective liver protecting drugs in modern medicine. These preparations are often safe because they come from natural sources.

Acute or chronic hepatitis, non-inflammatory diseases (hepatosis), and degenerative disorders leading to liver fibrosis (cirrhosis) are all categories for liver disease [6]. Its etiology is primarily caused by drinking too much alcohol, infections, autoimmune diseases, and a variety of medications and chemicals, such as antibiotics, chemotherapy, aflatoxin, peroxidized oil, carbon tetrachloride, chlorinated hydrocarbons, and others. Therapeutic substances known as "hepatoprotectives" can either protect the liver or, on the other side, encourage the creation of new liver cells [7]. Some plants have the ability to treat or prevent liver disorders through therapeutic use. Medicinal plants, which are a key source of these compounds, contain the majority of the hepatoprotective substances [8]. It has been demonstrated that about 170 phytoconstituents obtained from 110 plants belonging to 55 groups have hepatoprotective effects Cellular necrosis, an increase in tissue lipid peroxidation, and a decrease in tissue glutathione (GSH) levels are typical indicators of liver injury [9]. Triglycerides, cholesterol, bilirubin, glutamate oxalo-transaminase (SGOT), glutamate pyruvate transaminase (SGPT), and alkaline phosphatase all increase in serum levels (ALP). Trichloromethyl and trichloromethylperoxy radicals are produced as a result of CCl_4's liver toxicity; they start lipid peroxidation, which leads to fibrosis and cell necrosis [10].

The Euphorbiaceae family of plants includes the worldwide herb *P. amarus Schum* and Thonn, also known as stone breaker, hurricane weed, shatterstone, dukunanak (Malay), chanca-piedra (Spanish), quebra-pedra (Brazil), and carry-me-seed. *Phyllanthus amarus* and *Phyllanthu sniruri L.* are synonymous, and they are frequently confused for one another [11]. The Phyllanthus genus has been reorganized, and *P. amarus* has been designated as a variety of P. niruri. Hepatoprotective, antiviral, antibacterial, antioxidant, anti-inflammatory, anticancer, hypolipidemic, antidiabetic, antispasmodic, nephroprotective, and diuretic qualities are only a few of the pharmacological effects of *Phyllanthus amarus* [6;12]. Its extensive use in research is made possible by *Phyllanthus amarus'* unique antiviral activity against the hepatitis B virus and for its many other biological functions. The presence of various beneficial phytochemicals, including lignans, flavonoids, hydrolyzable tannins (ellagitannins), triterpenes, alkaloids, sterols, and volatile oil, has been found in *Phyllanthus amarus* after phytochemical screening. A review by Samy *et al*. (2008)[13] reveals that *Phyllanthus amarus* has a variety of active metabolites. Comparatively to other Phyllanthus species, the phytochemistry of *P. amarus* has generally been investigated more thoroughly, and phyllanthin is the main compound responsible for a number of biological effects. The hepatoprotective properties of *Phyllanthus amarus* are discussed in this study.

It has been stated that chemotherapy has shown to have severe side effects over time and that liver disorders have been a major hazard and cause of many deaths [14]. Thus, it is necessary to assess more cell-friendly medicinal molecules from plants, such *Phyallantus amarus. Phyallanthus amarus* has, nevertheless, been documented as having a history of use in traditional medicine. However, sufficient information regarding its impact on hepatoprotective cells is absent. As a result, the information gained from this research is adequate to understand the *Phyallanthus amarus* effect. This research sought to ascertain the hepatoprotective effects of *Phyallantus amarus* fractions against CCL_4-induced liver damage in wistar rats as well as the impact of *Phyallantus amarus* ethanolic extract on the liver function indices of wistar rats exposed to CCL_4.

2. Methods

2.1 Plant Material Collection and Extraction

Mature and fresh leaves *Phyallantus amarus* were collected within Federal University Wukari premises, washed and air dried for one week and pulverized using mortar and pestle. Precisely 100 g of pulverized sample of *Phyallanthus amarus* was weighed and soaked in 400 ml of ethanol for 48 hours at room temperature and the extract was filtered first using a clean sieving mesh and then with whatman's No 1 filter paper. Dried ethanol extract was obtained after removing the solvent by evaporation under exposure to air. The extract was placed in air tight vessel and was kept at 4^oC in a refrigerator.

2.2 Animal management

Wistar rats weighing between 150 and 200g were obtained from the stock on hand. Standard laboratory settings (temperature (272 oC), natural light-dark cycle (photoperiod of 12 h light and 12 h dark), and humidity 55–60%) were used to maintain the animals. The rats were kept on a regular pellet diet and had unlimited access to water. The animal ethical committee provided its ethical approvals.

2.3 Experimental Design

Sixteen (16) rats were used for evaluation of the hepatoprotective activity of *Phyllanthus amarus* leaves extract on liver alterations (medicinal property). The wistar rats were divided into four groups of four rats in each group for the study of hepatoprotective activity of *Phyllanthus amarus*.

Rats of group I were treated with 1 ml/kg body weight of normal saline (0.85% NaCl) intra-gastrically twice a week for two weeks.

Rats of group II, was treated with CCl_4 (30% in olive oil) at a dose of 3 ml/kg bw intra-peritoneally twice a week for two weeks.

Rats of group III received 50mg/kg dose of the extract in addition to CCl_4 treatment daily for two weeks.

Rats of group IV also received 70 mg/kg dose of the extract in addition to CCl_4 treatment daily for two weeks.

The already dried extract was reconstituted and the volume to be administered was determined based on the weight of the rats and required dose to be administered to the experimental rats after 3hours of induction using the following relation.

$$\text{Volume (mL)} = \frac{\text{Weight of rat (g)} \times \text{Dosage (mg/kg)}}{\text{Concentration of the extract (mg/mL)}}$$

2.4 Induction of kidney damage

Three mL/kg body weight of carbon tetrachloride was used to induce liver damage to the albino rats according to Adeneye *et al.,* (2008)[15]. The dose of CCl_4 administered was determined by the weight of the rat in accordance with the mathematical expression below:

$$\text{Volume} = \frac{3\ \text{mL} \times \text{Weight of rat (g)}}{1000\ \text{g}}$$

2.5 Assay of Marker Enzymes of Liver Damage

After receiving medication for 14 days, the wistar rats were put to sleep with chloroform, and blood was drawn for serum biochemical analysis by cardiac puncture into plain tubes. The blood samples were maintained at room temperature for one hour, and then the sera were extracted using a bench top centrifuge by centrifuging the blood samples at 3000 rpm for 30 minutes. As a result, the Aggape Diagnostic kit was used to assess the serum levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

2.6 Serum Determination of Aspartate Aminotransferase (AST)

In order to create glutamate and oxaloacetate, aspartate aminotransferase (AST) or (serum) glutamic oxaloacetic transaminase (SGOT) catalyzes the transamination of aspartate to alpha-ketoglutarate. It then interacts with 2,4-dinitro-phenylhydrazine to create hydrazone derivative of oxaloacetate [16].

L-malate + alpha ketoglutarate $\xrightarrow{\text{AST}}$ L- Glutamate + L-Oxaloacetate

Oxaloacetate + NADH + H^+ $\xrightarrow{\text{MDH}}$ L- malate + NAD^+

Aggape kit was used for the determination of Aspartate aminotransaminase (AST).

Laboratory procedure for semi auto analyser	
Working reagent	1000 µL
Sample	100 µL

Mix and incubate at 37ºC for 1 minute. Read the Absorbance change per 20secs in the 1minute

2.7 Serum Determination of Alanine Transaminase (ALT)

Alanine transaminase is the name of a transaminase enzyme (ALT). Alanine aminotransferase (ALAT), formerly known as serum glutamate-pyruvate transaminase (SGPT) or serum glutamic-pyruvic transaminase, is the enzyme's current name (SGPT). To create glutamate and pyruvic acid, alanine aminotransferase (ALT) catalyzes the transamination of alanine to alpha-ketoglutarate. Following interactions with 2,4-dinitro-phenylhydrazine, pyruvic acid creates a vibrant complex that can be seen at 546 nm. [16;17].

L-alanine + á-ketoglutarate $\xrightarrow{\text{ALT}}$ pyruvate+ L-glutamate

ALT levels in the blood are commonly used as a way of screening for liver problems. ALT levels were determined using Aggape kit.

Laboratory procedure for semi auto analyser	
Working reagent	1000 µL
Sample	20 µL

Mix and incubate at 37ºC for 1minute. The change in Absorbance per minute during 3minutes was measured.

2.8 Determination of Alkaline Phosphatase (ALP)

Serum alkaline phosphatase (ALP) was measured in accordance with Klein et alinstructions .'s from 1960[18]. Serum alkaline phosphatase catalyzed the hydrolysis of a colorless substrate of phenolphthalein monophosphate to produce phosphoric acid and phenolphthalein, which, at alkaline pH, transform into a pink color that can be measured photometrically at 550 nm [19]. ALP was determined using Aggape kit.

Principle: Kinetic determination of ALP according to the following reactions

Para-nitrophenylphosphate+H_2O $\xrightarrow{\text{ALP}}$ P-Nitrophenol + Inorganic phosphate.

Laboratory procedure for semi auto analyser	
Working reagent	1000 µL
Sample	20 µL

Incubate at 37ºC for 1minute after mix. Change in Absorbance per minute during 3minutes was measured.

2.9 Statistical analysis

The values are all expressed in means±SD. The results obtained were evaluated by one-way ANOVA and Tukey's multiple comparison tests. Statistically significant differences between groups were defined as $P > 0.05$.

3 Results

3.1 Effects of extract on alkaline phosphatase

The mean plot below represents the result of the effect of extract on the treatment groups. From the plot, it can be deduced, group 2 has the highest ALP activity. Although, group 1, 3 and 4 shown no significant difference (P>0.05). The effect of the extract on group 3 with the lower dose brought ALP levels almost near to normal while its levels in group 4 which received the highest dose was brought even below the normal level.

3.2 Effect of extracts on Alanine transaminase

The effect of the extract on the treatment groups is depicted in the mean plot below. It is obvious from the plot that group 2 exhibits ALT activity. Although group 1, which received the favorable therapy, shows no significant change in its individual result values at 0.05 significant levels, neither group 3 nor group 4 do. As previously mentioned, there was a large change in the levels of ALT in this group; however as can be seen from the plot below, this group differs somewhat from the other groups. Group 3 received a dose of 50 mg/kg, which drove the enzyme levels down to almost normal levels, while group 4 received a greater dose of 70 mg/kg, which caused the ALT levels to drop even lower.

3.3 Effect of extract on Aspartate transaminase

The mean plot below represents the result of the effect of extract on the treatment groups. From the plot, it can be deduced, group 2 has the ALP activity. Though for group 1, 3, and 4, there is no significant differences among the groups at 0.05 significant levels.

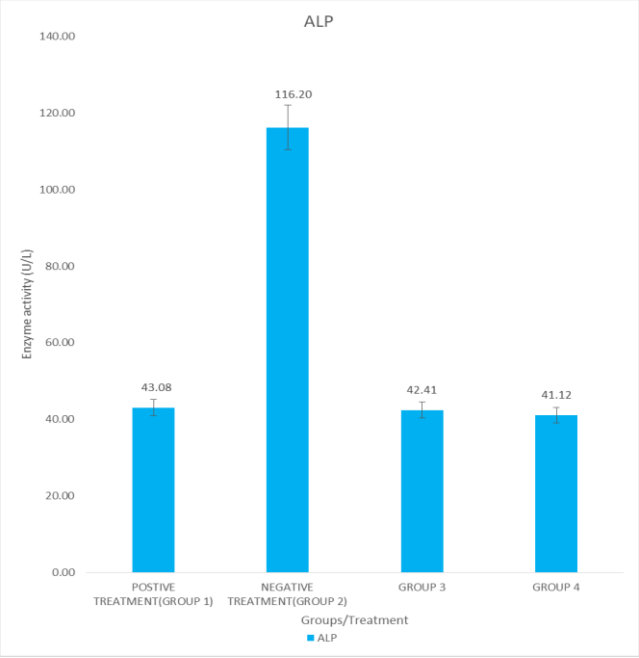

Figure 1: Mean plot for ALP

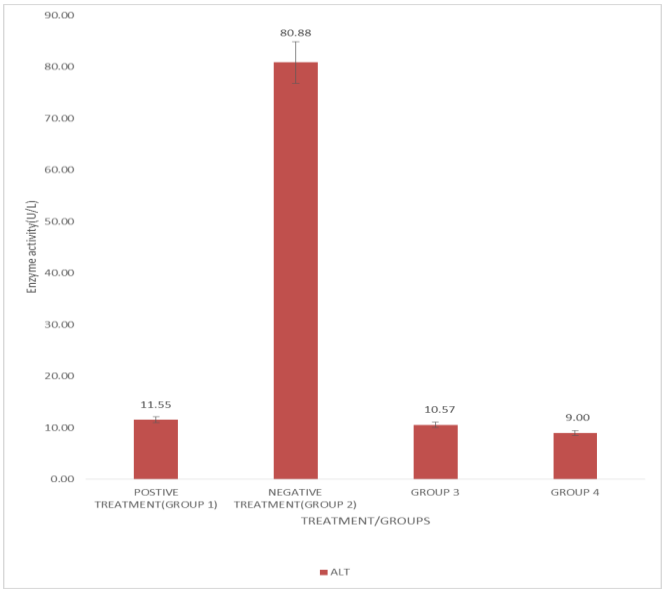

Figure 2: Mean plot for ALT

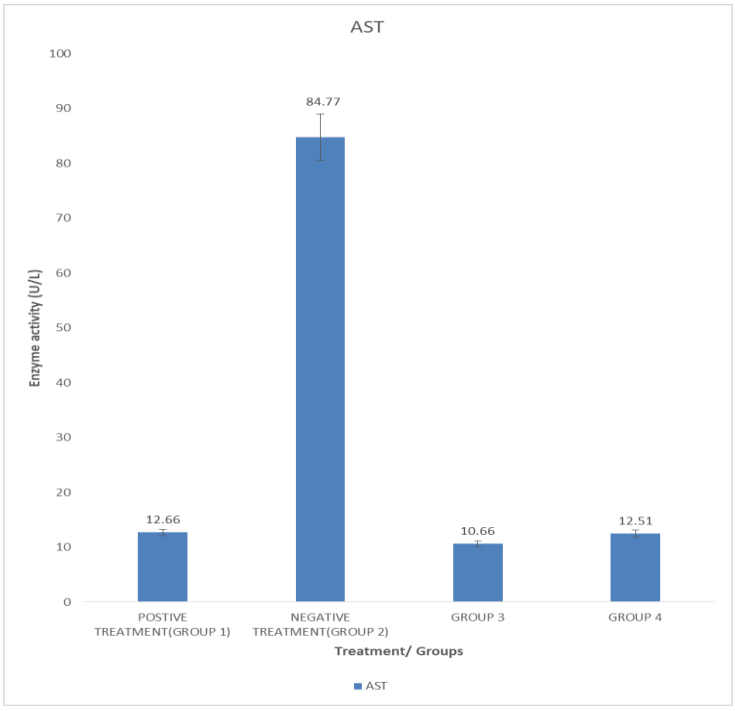

Figure 3: Mean plot for AST

4 Discussion

The aim of this research was to examine the hepatoprotective efficacy of ethanolic leaf extracts from *Phyllanthus amarus* in liver damage or destruction brought on by carbon tetrachloride (CCl_4). When CCl_4 is administered to healthy rats, the serum levels of ALT, AST, and ALP rise. According to research by Yan *et al.*, (2004), Vagvala and O'Connor (2018) [20;21] and others, the liver enzymes ALT, AST, and ALP are often low under normal control.

The leaking of enzymes into the bloodstream and the

resulting damage to the liver cells constitutes an inflammation of the hepatic cells. Small changes in the permeability and transport capacity of the hepatocytes' lipid membrane brought on by oxidation make it easier for enzymes to leave the cells [22]. The release of these enzymes and their increased activity in experimental animals exposed to carbon tetrachloride may be due to liver cell death and a change in membrane permeability [23]. The *Phyllanthus amarus* extracts' ability to stabilize membranes and so limit intracellular enzyme leakage may be responsible for the reversed elevation of serum enzymes seen in carbon tetrachloride-induced liver cell injury. This study's finding that *Phyllanthus amarus* extract has a protective effect supports earlier findings from Seyd, (2012) and Abu *et al*. (2022)[24; 25], which also noted that kidney and liver diseases can be treated and managed with *Phyllanthus amarus* as a traditional herb without causing any appreciable organ damage. It is important to note that any hepatoprotective medication's effectiveness depends on its capacity to either reduce the negative impact or restore the normal physiology of the liver after a recognized hepatotoxin has distorted or altered it [26].

According to the findings, *Phyllanthus amarus* extracts taken at a dose of 70 mg/kg appear to be more efficient than those given at a dose of 50 mg/kg in preventing CCl_4-induced liver damage. Due to the potential antioxidant function of flavonoids, the ethanol extract of *Phyllanthus amarus* may have demonstrated considerable *Phyllanthus amarus* hetoprotective activity [27].

5 Conclusion

The results of the experiments clearly supported the idea that *Phyllanthus amarus* could be employed as a source for hepatoprotective substance. The fact that its phenolic compounds can operate as strong antioxidants and anti-inflammatory agents is what gives it its hepatoprotective properties. These encouraging results found in this paper suggest that the ethanolic extract of P*hyllanthus amarus* and its components show promising hepatoprotective properties. The study's findings suggest that *Phyllanthus amarus* may be a useful hepatoprotective agent in adult wistar rats with liver damage caused by CCl_4. More specifically, the possible health benefits of *phyllanthus amarus* can be used to advance the creation of contemporary medicines, namely contemporary hepatoprotective medicines.

References

[1]. Seki, E. and Schnabl, B. (2012). Role of innate immunity and the microbiota in liver fibrosis: crosstalk between the liver and gut. J Physiol.590:447–58.

[2]. Yakubu , O.E., Ojogbane , E., Nwaneri-Chidozie, V.O., Ibuzo, P.N., Ale, E. M. and Awudu, S.S. (2020). Ameliorative Effects of Ethanol Extract of Ficus sur on Diethylnitrosamine-induced Hepatotoxicity in Wistar Rats. American Journal of Biochemistry and Molecular Biology, 10: 6-11.

[3]. Meyer, S.A. and Kulkarni, A.P. (2001). Hepatotoxicity. In: Hodgson,E. and Smart, R.C., Eds., Introduction to Biochemical toxicology, 3rd Edition, John Wiley and sons, New York, 487.

[4]. Yachi, R., Igarashi, O. and Kiyose, C. (2010). Protective effects of vitamin E analogs against carbon tetrachloride-induced fatty liver in rats. J Clin Biochem Nutr, 47:148–154.

[5]. Tulio, P.R., Correa, J.A., Beatriz, J.V., Aarestrup, M.F., Orlando de Sousa, V. A., Ademar, Filho da Silva. (2014). Protective effects of Baccharis dracuncufolia leaves extract against carbon tetra choloride and Acetominophen –induced hepatotoxicity in experimental animals Molecules, 19:9257-9272.

[6]. Obianime, A.W. and Uche, F.I. (2008). The phytochemical screening and the effects of methanolic extract of Phyllanthusamarus leaf on the biochemical parameters of male guinea pigs. J. Applied Sci. Environ. Management. 12(4): 73-77.

[7]. Sangeeta, S., Neelu, S., Amita, J. (2014). Antioxidative, antiperioxidative and hepatoprotective potential of P. amarus against anti-TB drugs In: Pharmacology and nutritional intervention in the treatment of disease. Intech. 283-294.

[8]. Bapat, A., Mukundan, U., Mukhopadhyaya, P.N., Parekh, H., Nagee, A. and Kunjadia, P. (2013). Varying influence on different biomarkers related to hepato-recovery events in liver injured rats when treated with extracts of Andrographis paniculata, Phyllanthus amarus or their active principles individually and in combination. International Journal of Phytomedicine, 5(2): 178-190

[9]. Akhtar, M.S., Amin, M. and Maqsood, A. (2009). Hepatoprotective effect of Rheum emodi roots (Revandchini) and Akseer-e-Jigar against paracetamol-induced hepatotoxicity in rats. *Ethnobotanical Leaflets*, **2**: 3.

[10]. Patel, J.R., Tripathi, P., Sharma, V., Chauhan, N.S. and Dixit, V.K. (2011). P. amarus: ethnomedicinal uses, phytochemistry and pharmacology: a review. Journal of Ethnopharmacology. 138(2): 286-313.

[11]. Arun, K. and Balasubramanian, U. (2011). Comparative study on hepatoprotective activity of P. amarus and Ecliptaprostrata against alcohol-induced albino rats. *International Journal of Environmental Sciences.* **2**(1): 361-379.

[12]. Yakubu, O.E., Bando, C.D., Moses, Z., Isaac, J. U., and Michael, S. A. (2022). Kidney function status of Wistar rat treated with ethanolic extract of Phyllanthus amarus leaves owing to diethylnitrosamine intoxication. Asian J Nat Prod Biochem.20(1): 6-9.

[13]. Samy, R.P., Pushparaj, P.N. and Gipalakrishnakone, P. (2008). A compilation of bioactive compounds from Ayurveda. Bioinformation. 3(3): 100-110.

[14]. Su, W., Mao, Z., Liu, Y., Zhang, X., Zhang, W., Gustafsson, J.A. and Guan, Y. (2019). Role of HSD17B13 in the liver physiology and pathophysiology. Mol Cell Endocrinol, 489:119- 125.

[15]. Adeneye A.A. and Agbaje E.O. (2008). Pharmacological Evaluation of Oral Hypoglycemic and Antidiabetic Effects of Fresh Leaves Ethanol Extract of Morinda Lucida Benth. in Normal and Alloxan- Induced Diabetic Rats. African Journal of Biomedical Research, Vol. 11: 65 – 71.
[16].Yakubu,E.O., Obot,A.C. and Dawoye, Y. (2016). Effects of ethanol extract of Hymenocardia Acida leaves on Aluminium chloride-induced toxicity in male Albino Rats. *J. Anal Pharm Res.* 3(2).
[17]. Adeva, M.M., Souto, G., Blanco, N., and Donapetry, C. (2012). Ammonium metabolism in humans. Metabolism 61: 1495–1511.
[18].Khlein, G. et al., (1960). Demonstration of resistance against methylcholanthrene-induced sarcomas in the primary autochthonous host. Cancer Res. 1960 Dec.
[19]. Hang, L., Jikun, Z., Shengnan, L., Yufei, Y., and Xinming, Li. (2020). Consecutive dephosphorylation by alkaline phosphatase-directed in situ formation of porous hydrogels of SF with nanocrystalline calcium phosphate ceramics for bone regeneration. Journal of Materials chemistry B, 39:111-112.
[20]. Yan, J. L., Jie-ping, Y., Zhao, H. S. and Wang, L.G. (2004). Extract reverses CCL4 – induced liver fibrosis in rats. World. J. Gastroenterol., 10, 1037 -1042.
[21]. Vagvala, S.H. and O'Connor, S.D. (2018). Imaging of abnormal liver function tests. Clin Liver Dis (Hoboken), 11(5):128-134.
[22]. Nsari, J. A. and Asif, R. (2012); Hepatoprotective effect of Tabernaemontana divaricate against acetaminophen-induced liver toxicity". Med. Chem. Drug. Disc. 3(2), 146-151.
[23]. Fakurazi, S., Hairuszah, I. and Nanthini, U. (2008). Moringaoleifera Lam prevents acetaminophen induced liver injury through restoration of glutathione level". Food.Chem.Toxicol. 46: 2611–2615.
[24]. Syed, A. B., Iqbal, M. M. Kiranmai, M. and Ibrahim, M. (2012). Hepatoprotective Activity of Phyllanthusamarus Seeds Extracts in CCl4 Treated Rats: In Vitro andIn Vivo. J. Med. Res. 12(6), 38-49.
[25]. Abu, M.S., Yakubu, O.E., Innocent, O.C. and Onuche, J.I. (2022). Biosafety evaluation of ethanolic extract of Phyllanthus amarus leaves on liver and kidney of wistar rats. Asian j. Nat. Prod. Biochem., 20(1):2580-2550.
[26]. Rajkapoor, B., Venugopal, Y., Anbu, J., Harikrishnan, N., Gobinath, M. and Ravichandran, V. (2008); Protective effect of Phyllanthuspolyphyllus on acetaminophen induced hepatotoxicity in rats". Pak. J. Pharm. Sci 21(1), 57-62.
[27]. Khan, J., Deb, P.K., Priya, S., Medina, K.D., Devi, R., Walode, S.G.and Rudrapal, M. (2021). Dietary Flavonoids: Cardioprotective Potential with Antioxidant Effects and Their Pharmacokinetic, Toxicological and Therapeutic Concerns. Molecules 26, 4021.

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