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HEPATOPROTECTIVE POTENTIAL OF EUGENIA UNIFLORA L AGAINST GENTAMYCIN- INDUCED HEPATOXICITY

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ABSTRACT

Hepatotoxicity is a common drug adverse effect and gentamycin has been linked to hepatotoxic adverse reactions. Folklore and ethnobotanical studies indicate *Eugenia uniflora L* is used in the treatment of gastrointestinal ailments and has exhibited diverse biological activities. We investigated the hepatoprotective potential of this plant in treating gentamycin-induced hepatoxicity and compared the effect with Celebrex a COX2 selective inhibitor. Twenty-eight male adult Wistar rats average of 225g were used for the study and randomised into groups as described: normal control(normal saline), negative control: Gentamycin (40mg/kg. i.p), positive control; Gentamycin (40mg/kg. i.p) +5mg/kg Celebrex. Extract low dose: Gentamycin (40mg/kg i.p)+(50mg/kg) Eugenia uniflora L. leaves, intermediate-dose: Gentamycin (40mg/kg i.p) +100mg/kg *Eugenia uniflora L* leaves, high dose : Gentamycin (40mg/kg, i.p)+ (200mg/kg,) of *Eugenia uniflora L* leaves. Our findings indicate that the body weight was unaffected throughout the experiment, as clearly demonstrated by the lack of significant variability ($p<0.05$). Hepatotoxicity was confirmed by dose-dependent alteration in Liver marker enzymes, including AST, ALT, and ALP. *Eugenia uniflora L* leaves were able to ameliorate the levels of these liver enzymes to a normal level. Liver tissue revealed a dose-dependent curative effect with *Eugenia uniflora L* compared to the COX2 inhibitor (Celebrex) treatment. Consequently, we hereby report, for the first time, that an aqueous extract of *Eugenia uniflora L* leaves confers hepatoprotection against gentamycin-induced hepatoxicity in Wistar rats.

KEYWORDS: Hepatoxicity, Inflammation, Liver Enzymes, Eugenia uniflora L, COX 2 inhibitor.

INTRODUCTION

The liver is an organ involved in a vast array of metabolic functions such as glycolysis, gluconeogenesis, glycogen storage, urea cycle, fatty acid metabolism, and even xenobiotic metabolism (1-2). The involvement of the liver drug (xenobiotic) metabolism predisposes the liver to injury(s) that could disrupt its functions and structure (3). Hepatotoxicity is one of the most common adverse effects of drugs and a leading cause of drug withdrawal in clinical practices (4). For instance, Gentamycin is an aminoglycoside antibiotic derived from micomonospora purpura and a well-documented hepatotoxic drug (2, 5-11). Although, it is an effective treatment in cases of gram-negative bacterial infections (6). Despite its wide clinical use, the drug is associated with the generation of reactive oxygen species (ROS), which affects membrane lipids' integrity and deteriorates cellular protein and nucleic acids, leading to hepatotoxicity (7).

Natural products have been used to ameliorate toxicities due to the adverse effects of drugs owing to the presence of natural compounds with broad therapeutic potentials (8). The phytochemical constituents such as flavonoids, terpenoids, and steroids influence the plants with diverse pharmacological properties, including hepatoprotective activity and antioxidant activities, antiparasitic activity, and attenuation of tumor development and treatment of inflammatory disease (12-14).

Eugenia uniflora L is also known as Surinam cherry, it is a perennial plant from the Myrtaceae family which became part of empirical medicine in the fifteenth century (15-16). The plant is a 4 to 10meters tall semi-deciduous tree or bush with a smooth light brown trunk and is widely distributed in South America,

Central America, the Caribbean, tropical areas of the United States, Southeast Asia, South Africa, Israel, and some parts of eastern Nigeria (17-18). The leaves, either fresh or dried, have been used empirically as medicine since the 15th century for treating inflammation and rheumatism, fever, hypertension, bronchitis influenza, and as a diuretic (19). The presence of many secondary metabolites in the leaves of this plant which includes volatile terpenoids oil, flavonoid and condensed and hydrolyzable tannins, leucoanthocyanidin, steroids, and triterpenoid, could be responsible for ethnomedicinal applications of *Eugenia uniflora L* (20).

Pharmacological studies on *Eugenia uniflora L* have unraveled a number of therapeutic effects of these plants. These include antinociceptive, hypothermic, anti-inflammatory, antioxidant, antihypertensive, antitumor, and diuretic (15). In addition, *Eugenia uniflora L* has also been reported to exhibit antibacterial, antiviral, antifungal, and antiprotozoal activities (21). The diverse pharmacological properties of *Eugenia uniflora L* prompted us to investigate the potential of this plant in treating gentamycin-induced hepatoxicity.

MATERIALS AND METHODS

Plant Collection and Extraction

The fresh leaves of *Eugenia uniflora L* were collected from River Lane GRA, Enugu, Nigeria, and identified by a curator in the Department of Plant Science and Biotechnology of the University of Nigeria, Nsukka. The plant names were verified by http://www.theplantlist.org.

Aqueous extract of *Eugenia uniflora L* leaves was extracted according to Okon et al., (22) with minor modifications. Briefly, the leaves were washed, air-dried, and grounded in a blade mill. About 2785.49g of *Eugenia uniflora L* leaves were soaked for 24hrs in 10Ltrs of distilled water, followed by filtration and concentration of filtrate at 90^{o}C using a water bath. The filtrate was stored at 4^{o}C until further use.

Reagents

Gentamycin and Celebrex drugs were purchased from a registered pharmaceutical store in Enugu, Nigeria. All other chemicals and reagents were of analytical grade.

Ethical Approval and Animal Handling

Ethical approval for the use of animals for this study was obtained from Departmental Ethics and Research Committee (DREC/2019/002). Twenty-eight male adult Wistar rats average of 225g were purchased from an animal farm of the Department of Anatomy EBSU Abakaliki in Ebonyi State. The Animals were kept in iron cages with wood shavings as beddings in the animal house of the Department of Anatomy, Enugu State University of Science and Technology. They were allowed to acclimatize for two weeks. They were provided with free access to a standard diet and water ad libitum throughout the experiment.

Experimental Design

Experimental animals were clustered into six groups of 4 animals each and were treated as follows adapting the method of Falcão et al.(16) with modifications in treatments.

Group 1 (NC); serves as the normal control and was only treated with normal saline

Group 2 (GIC); received an intraperitoneal injection of Gentamycin (40mg/kg) for one week and was left untreated, serving as the negative control.

Group 3 (GCT); received an intraperitoneal injection of Gentamycin (40mg/kg) for one week followed by oral administration of 15mg/kg Celebrex, serving as the positive control.

Group 4 (GLE); received an intraperitoneal injection of Gentamycin (40mg/kg) for one week followed by a low dose (50mg/kg) oral administration of Aqueous extract of *Eugenia uniflora L* leaves

Group 5 (GIE); received an intraperitoneal injection of Gentamycin (40mg/kg) for one week followed by an intermediate dose (100mg/kg) oral administration of Aqueous extract of *Eugenia uniflora L* leaves

Group 6 (GHE); received an intraperitoneal injection of Gentamycin (40mg/kg) for one week followed by a high dose (200mg/kg) of oral administration of aqueous extract of *Eugenia uniflora L* leaves.

Body weight

The weight of animals in all groups was measured daily using spring balance for the total duration of the experiment.

Biochemical Analysis

Animals were sacrificed on day 15, and blood was collected transcardially after ketamine anesthesia. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were assayed and measured using an autoanalyzer (Bio-Tech. India).

Histological Study

The liver was harvested from the sacrificed animals for histological analysis. Tissues were fixed with 10% neutral-buffered formalin and manually processed for paraffin embedding, sectioned at 5um thickness for hematoxylin, and eosin staining. Photomicrographs were captured using Amscope 3.0.

Statistical Analysis

Data were analyzed using GraphPad prism 9. One-way ANOVA was performed, and results were reported in bar charts as mean ± standard deviation.

RESULTS

Animal Body weights

The body weight of experimental animals was observed to be unaffected throughout the experiment, as clearly demonstrated by the lack of significant variability ($p<0.05$) of body weight within groups after days 8 and 15 (Figure 4). This indicates that gentamycin toxicity does not have an apparent effect on the body weight of the experimental animals.

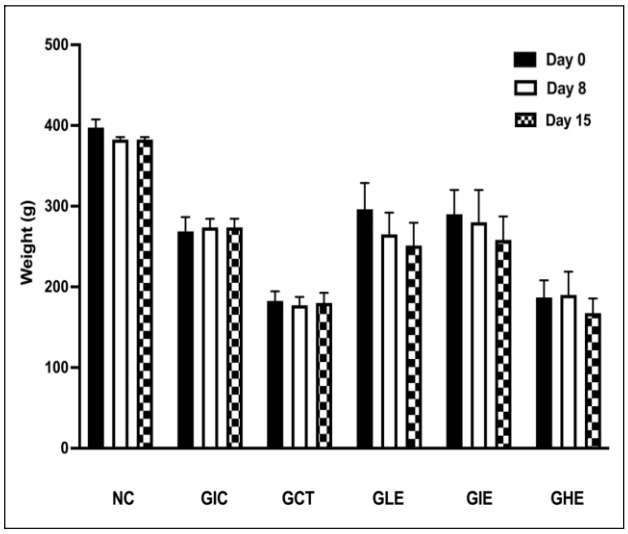


Fig. 1: Effect of Eugenia Uniflora Leaves Aqueous Extract on Body Weights of Experimental Animals. NC Normal Control, GIC Gentamycin-induced Untreated, GCT Gentamycin-induced Treated with Celebrex, GLE Gentamycin-induced Treated with Low Dose Extract, GIE Gentamycin-induced Treated with Intermediate-dose Extract, GHE Gentamycin-induced Treated with High Dose Extract

Biochemical Analysis

The ALP level was found to increase significantly ($p<0.05$) in the induced untreated group (GIC) compared with the normal control group (NC) (Figure 1). The standard drug Celebrex was able to lower this altered serum ALP in the positive control group (GCT), but the level is still significantly ($p<0.05$) higher than in the NC group. However, the ALP level in both groups treated with low dose (GLE) and intermediate-dose (GIE) of *Eugenia uniflora L* leaves extract was lowered to the same level as the NC group, with no statistical difference ($p<0.05$). On the other hand, the ALP level in the group treated with the high-dosage extract (GHE) was significantly higher than the GIC group, suggesting the toxicity of this regimen at a high dose. ALT level was significantly decreased in the induced untreated group (GIC) relative to the normal control group (Figure 2). Neither standard drug nor low or intermediate doses of *Eugenia uniflora L* leaves extract were able to improve the ALT level of the experimental animals. High-dose *Eugenia uniflora L* leaves extract, however, was able to increase the ALT level to the same level ($p<0.05$) as the normal control group. Similarly, the AST level in the induced untreated group (GIC) was lower than normal (NC) due to gentamycin toxicity (Figure 3). Here, both standard drugs, low and intermediate doses of *Eugenia uniflora L* leaves extract, were able to reverse the AST level comparable to the level in the normal control group, as shown in GCT, GLE, and GIE (figure 3). A high dose of this extract raises the AST level (GHE) significantly ($p<0.05$) higher than the level in the normal control group, which may be undesirable.

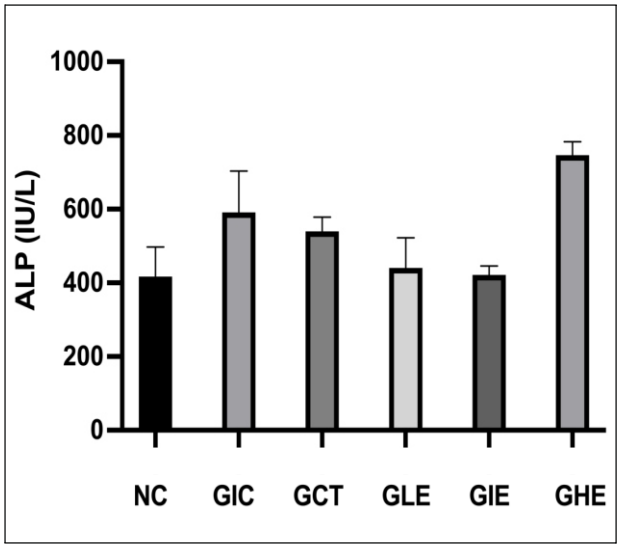


Fig. 2: Effect of Eugenia Uniflora Leaves Aqueous Extract on Body Weights of Experimental Animals. NC Normal Control, GIC Gentamycin-induced Untreated, GCT Gentamycin-induced Treated with Celebrex, GLE Gentamycin-induced Treated with Low Dose Extract, GIE Gentamycin-induced Treated with Intermediate-dose Extract, GHE Gentamycin-induced Treated with High Dose Extract

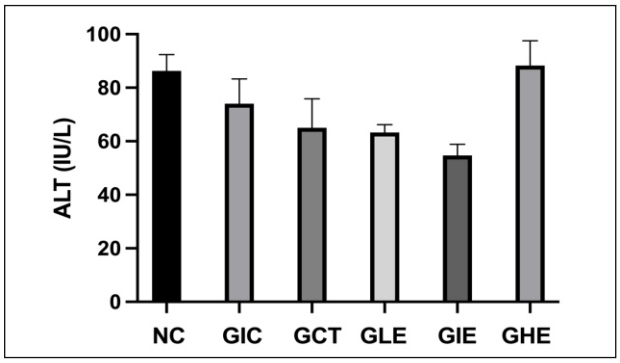


Fig. 3: Effect of Eugenia Uniflora L Leaves Aqueous Extract on Serum Alanine Aminotransferase Level of Experimental Animals. NC Normal Control, GIC Gentamycin-induced Untreated, GCT Gentamycin-induced Treated with Celebrex, GLE Gentamycin-induced Treated with Low Dose Extract, GIE Gentamycin-induced Treated with Intermediate-dose Extract, GHE Gentamycin-induced Treated with High Dose Extract

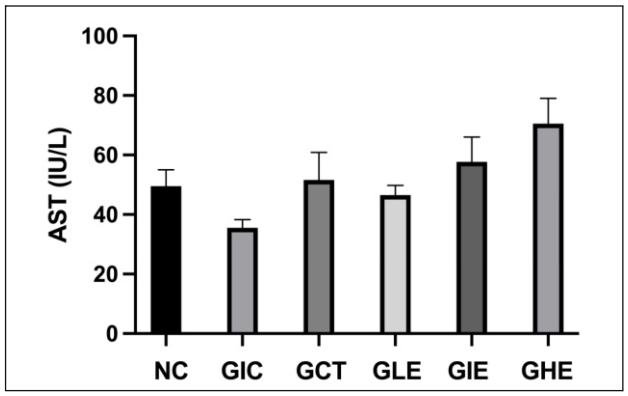
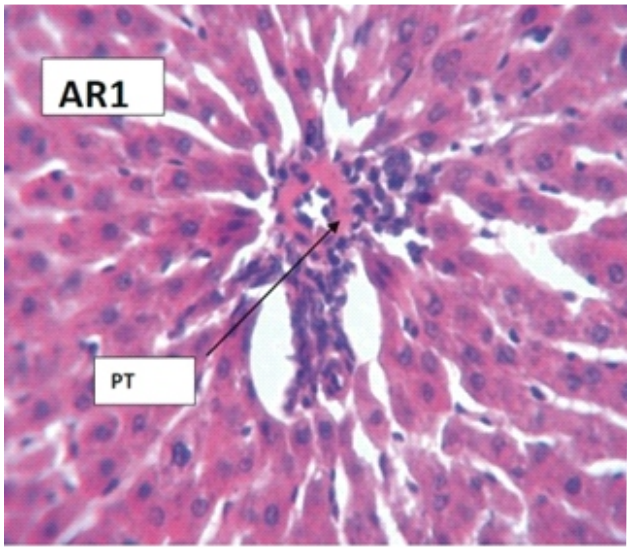


Fig. 4: Effect of Eugenia Uniflora L Leaves Aqueous Extract on Serum Aspartate Aminotransferase Level of Experimental Animals. NC Normal Control, GIC Gentamycin-induced Untreated, GCT Gentamycin-induced Treated with Celebrex, GLE Gentamycin-induced Treated with Low Dose Extract, GIE Gentamycin-induced Treated with Intermediate-dose Extract, GHE Gentamycin-Induced Treated with High Dose Extract

Histological Studies

Photomicrograph of liver tissue reveals that the normal control group has a normal hepatic architecture with well-perfused cytoplasm, hepatocyte, portal triad, and central vein (AR1 and AR2, Plate 1). Gentamycin was toxic to the liver as shown by severe portal aggregate inflammation, a focal aggregate of intrahepatic inflammation, and a focal area of intrahepatic hemorrhage in the negative control group (BR1 and BR2, Plate 2). Conversely, the standard drug, Celebrex, shows a mild focal area of cytoplasmic ground glass appearance and mild portal aggregate inflammation, indicating moderate healing (CR1 and CR2, Plate 3). Similarly, all doses of *Eugenia uniflora L* leaves extract confers mild healing, showing either moderate fatty change and moderate portal aggregate inflammation (GLE, plate 4), or moderate fatty change, moderate portal aggregate inflammation, Vacuolation of the hepatic cells (GIE, Plate 5) or severe fatty change, moderate portal aggregate inflammation cytoplasmic ground glass appearance, focal area intrahepatic hemorrhage (GHE, plate 6). However, the low and intermediate-doses treatment groups (Plate 4 & 5) showed better healing which is even comparable to the standard drug treatment group (Plate 3).



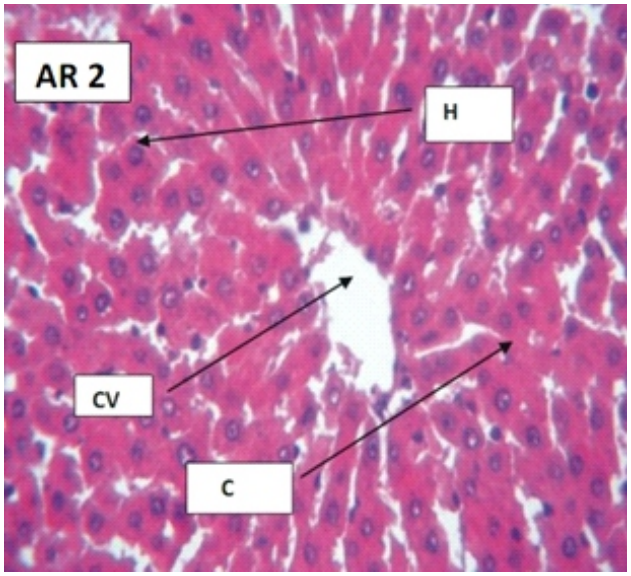


Plate 1: Photomicrograph Section of the Liver of Animals From Normal Control (NC) Group. C Cytoplasm, H Hepatocyte, PT Portal Triad, CV Central Vain

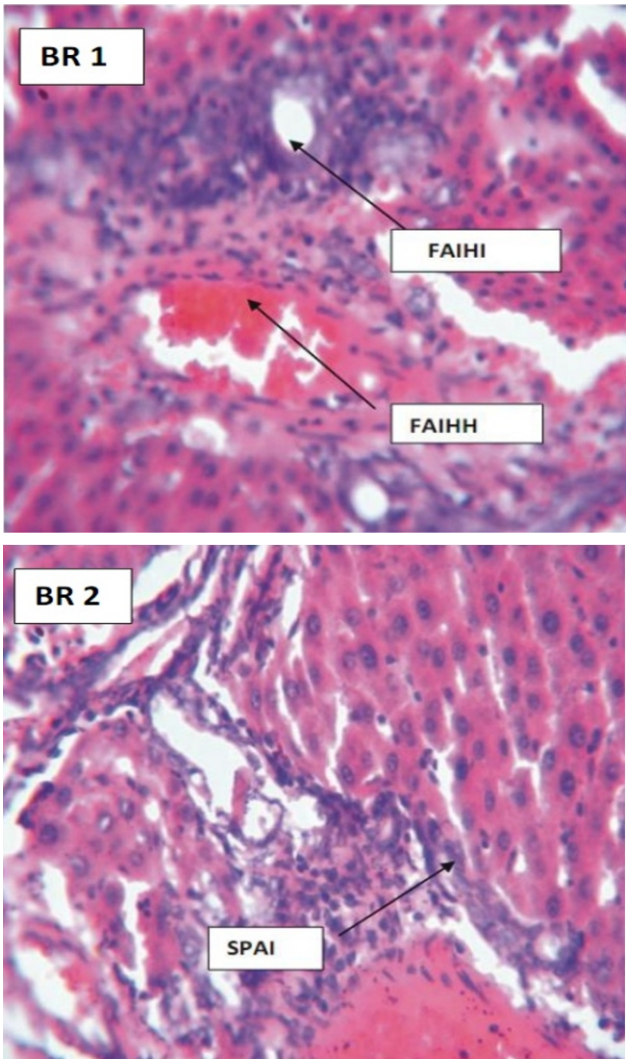
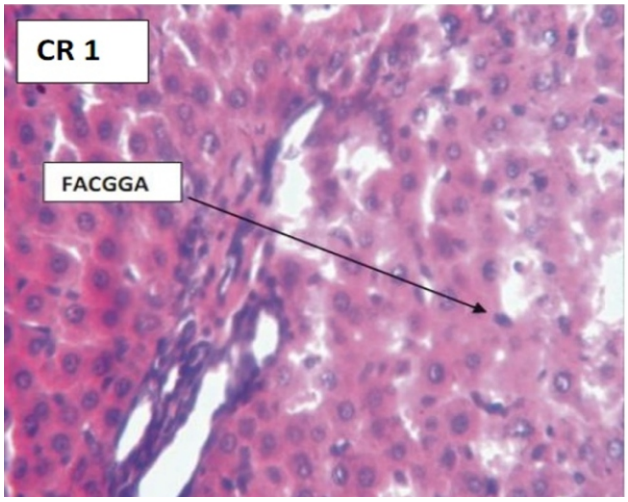


Plate 2: Photomicrograph of a Liver Section of Animals from Gentamycin Induced Untreated Group (GIC). SPAI Severe Portal Aggregate Inflammation, FAIHI Focal Aggregate of Intrahepatic Inflammation, FAIHH Focal Area of Intrahepatic Hemorrhage



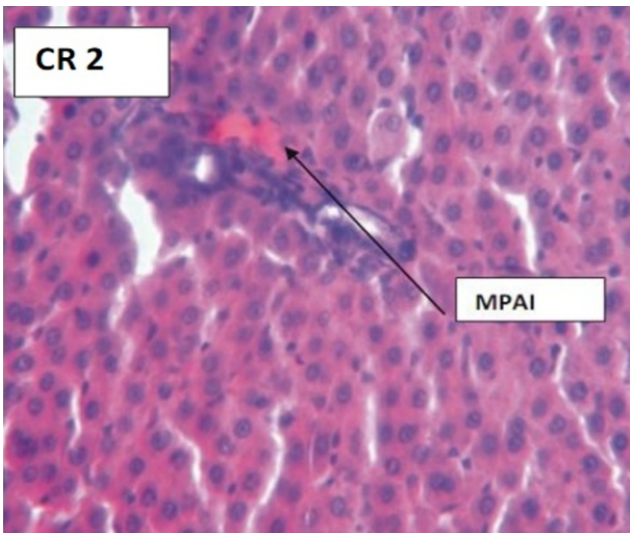


Plate 3: Photomicrograph of Liver Tissue Section of Animals Treated with Standard Drug (GCT). FACGGA Focal Area of Cytoplasmic Ground Glass Appearance, MPAI Mild Portal Aggregate Inflammation

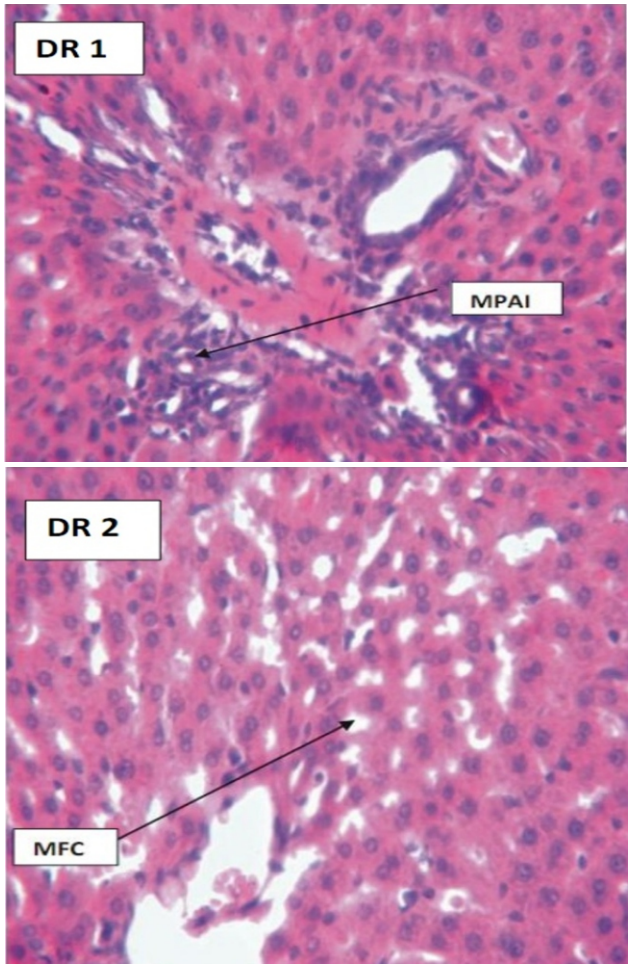


Plate 4: Photomicrograph of Liver Tissue Section of Animals Treated with Low Dose (GLE) Extract of Eugenia Uniflora L Leaves. MFC Moderate Fatty Change, MPAI Moderate Portal Aggregate Inflammation

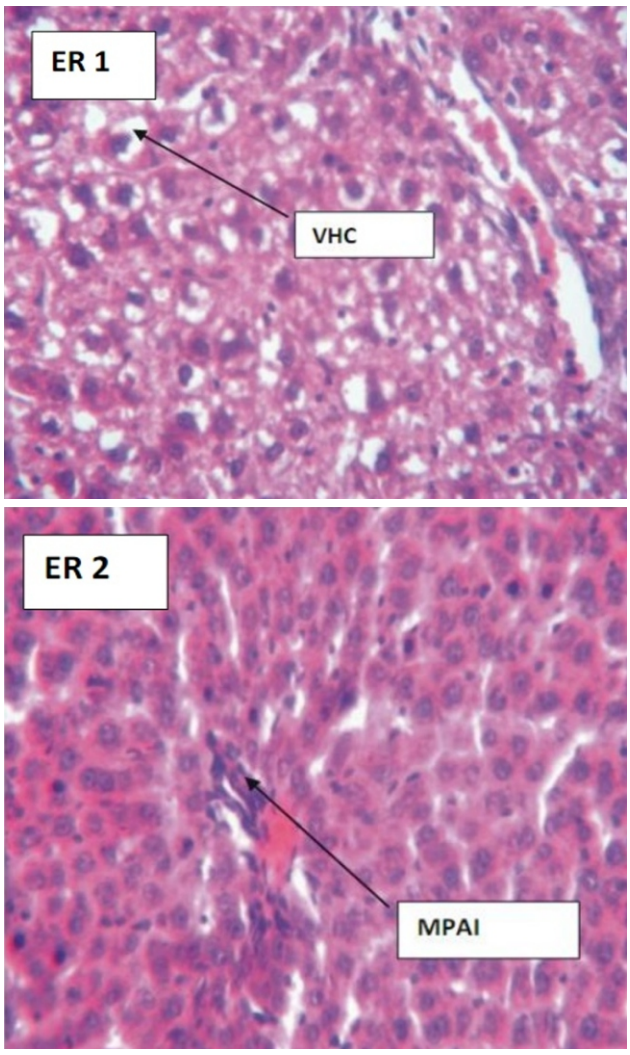
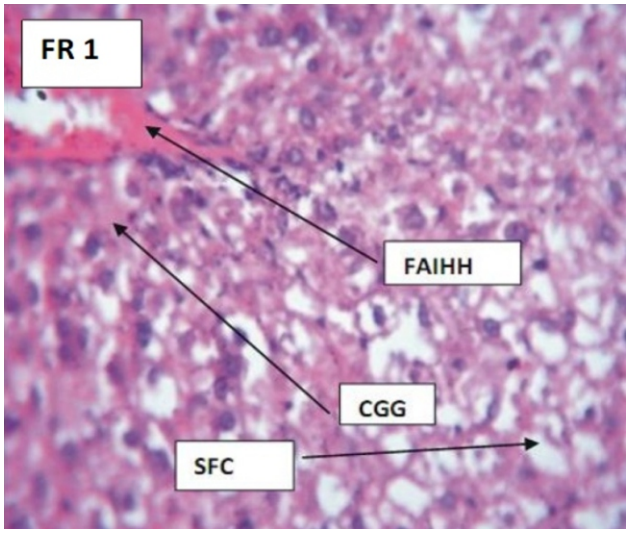


Plate 5: Photomicrograph of Liver Tissue Section of Animals Treated with Intermediate-dose (GIE) Extract of Eugenia Uniflora L Leaves. MFC Moderate Fatty Change, MPAI Moderate Portal Aggregate Inflammation, VHC Vacuolation of the Hepatic Cells



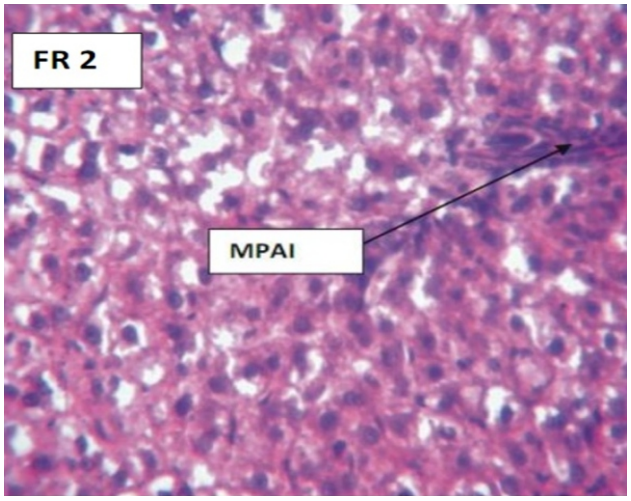


Plate 6: Photomicrograph of Liver Tissue Section of Animals Treated with High Dose (GHE) Extract of Eugenia Uniflora L Leaves. SFC Severe Fatty Change, MPAI Moderate Portal Aggregate Inflammation, CGGA Cytoplasmic Ground Glass Appearance, FAIHH Focal Area Intrahepatic Hemorrhage

DISCUSSION

Adverse drug reactions have been linked to drug-induced liver injury (DILI), a common phenomenon with most classes of drugs causing liver disease and toxicity (23-25). Thus, drug-induced hepatotoxicity is a frequent cause of acute liver failure due to the involvement of the liver in drug metabolism. Drugs are metabolized by the liver p450 system in phase I and phase II reactions. Liver damage and hepatic cell death by apoptosis or necrosis are mediated by toxic intermediates of the metabolism of drugs and even other agents (23-25). The binding of drugs to cellular membranes is known to elicit immunologic events that recruit the major histocompatibility complex (MHC) resulting in hepatic inflammation (25-26). The toxicity of the liver induced by gentamycin often precipitates the participation of toxic metabolites that elicits an immune response or direct effect on cell functions, such as mitochondrial dysfunction and liver enzymes (3, 27). On the other hand, gentamycin could generate reactive oxygen species linked to an increase in lipid peroxidation and a decrease in antioxidant enzyme activity in organs (28).

In the current studies, hepatotoxicity was induced in Wistar rats using Gentamycin, and the test animals were treated with an aqueous extract of Eugenia uniflora L leaves to cure the condition. Hepatotoxicity was confirmed by altered levels of Liver marker enzymes, including AST, ALT, and ALP, which are indicators of hepatic function and are used as a sensitive parameters in disease conditions (29-30). Our study agrees with the previous reports that gentamycin causes mild and asymptomatic elevations

in serum alkaline phosphatase levels (ALP) and the level of aminotransferase levels (30, 31, 32) For ALP and AST, the low and intermediate doses of the aqueous extract of Eugenia uniflora L leaves ameliorate the levels of these liver enzymes to a normal level. However, only the high dose of the extract was able to correct the level of AST. This might imply an additive effect of the gentamycin and high dose which equally revealed abnormal raise in the level of AST. Leaves from Eugenia uniflora, have a high content of flavonoids that possess several biological effects such as anti-inflammatory and antioxidant activities (16). Eugenia uniflora exerts a dose-dependent effect which was credited to its antioxidant and anti-inflammatory activities. The Celebrex exhibited a similar effect as the low dose of the extract on AST. It is a known fact COX 2 inhibitor exerts inflammatory activities by blocking COX 2 enzyme (32-33).

Evaluation of hepatic pathology in terms of the pattern of injury, its severity, appropriate timing, and cause of the injury underpinned the diagnosis. Drugs, herbal agents, and environmental exposure to toxicants have been widely reported causes of liver injury characterized by inflammation. In the present study, the histological features of the liver were also assessed to reveal the existence of structural changes. In agreement with the liver enzymes findings, sections of the processed liver tissue revealed a mild curative effect at the low and intermediate-dose extract of Eugenia uniflora L leaves. The effect was perhaps mild because of the short duration of treatment. However, severe inflammatory signs such as severe portal aggregate inflammation, the focal aggregate of intrahepatic inflammation, and hemorrhage observed due to the gentamycin toxicity were positively improved by the extract within the short duration of the administration. Thus, prolonged treatment could offer more beneficial outcomes and better tissue healing. A similar effect was observed (focal area of cytoplasmic vacuolations, and mild portal aggregate/inflammation in standard Celebrex but attenuated rapidly when gentamycin was stopped. This is also consistent with the postulation that withdrawal of the noxious substance prevented ongoing damage in tissues. The study also established the hepatoprotective activity of Eugenia .u. via its antioxidant and anti-inflammatory activities.

CONCLUSION

The present study proved that the aqueous extract of *Eugenia uniflora L* leaves exhibited hepatoprotective properties, an anti-inflammatory property against Gentamycin-induced inflammation in the experimental rats.

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