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The hepatorenal protective potential of Chromolaena odorata (Awolowo) leaf extract on diclofenac-induced liver and kidney damage in Wistar rats.

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ABSTRACT
Administration of diclofenac has been linked to several health issues in humans, such as gastrointestinal complications, renal toxicity, and liver damage, among others. Various indigenous medicinal plants are used locally to cure a variety of ailments. This study aims to investigate the hepatorenal protective effects of Chromolaena odorata (Awolowo) leaf extract on diclofenac-induced liver and kidney damage in Wistar rats. A total of twenty (20) healthy adult Wistar rats, with weights ranging from 110g to 200g, The rats were randomised to four groups in a random manner, with each group having five rats each. Group 1 served as the control group and was given distilled water and food. Group 2 received a dosage of 10 mg/kg body weight of diclofenac only. Group 3 received a dosage of 10 mg/kg body weight of diclofenac only, followed by a post-treatment of 200 mg/kg body weight of ethanolic leaf extract of Chromolaenaodorata. Group 4 received a dosage of 200 mg/kg body weight of ethanolic leaf extract of Chromolaena odorata. The diclofenac and Chromolaena odorata extracts were orally administered for a duration of fourteen (14) days. After the treatment was finished, the rats were euthanized, and blood samples were obtained by puncturing the heart to measure liver and kidney parameters. It was found that rats given diclofenac had higher levels of ALT, ALP, creatinine, and MDA, as well as lower levels of SOD, CAT, and GSH enzyme activities. This was statistically significant ($p<0.05$). In addition, administering Chromolaena odorata leaf extract to rats previously treated with diclofenac resulted in a significant and considerable reduction ($p<0.05$) in the levels of ALT, ALP, creatinine, and MDA. Additionally, it resulted in a significant increase in the levels of SOD, CAT, and GSH enzymes. Ultimately, the study determined that the leaf extract of Chromolaena odorata possesses the capacity to mitigate the liver and renal damage caused by diclofenac..

Keyword: Chromolaena odorata, Diclofenac, Liver, Kidney

I. INTRODUCTION

The therapeutic properties of plants are attributed to their bioactive components, including alkaloids, flavonoids, tannins, and phenolic compounds, which have unique physiological effects on the human body [16]. The growing utilisation of plant extracts in the food, cosmetic, and pharmaceutical sectors underscores the significance of conducting a systematic investigation of medicinal plants to extract their active components [1]. Plants serve as a significant reservoir of herbal medicines, as they contain secondary metabolites that are of interest for many therapeutic purposes [14]. Medicinal herbs have been utilised in many forms throughout indigenous systems of medicine such as Ayurveda, Siddha, and Unani. Several bioactive compounds have been extracted from plants, and many of them have a significant impact on contemporary medical treatment. Currently, around 30% or more of contemporary pharmacological medications are directly or indirectly derived from plants. These

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plants and their extracts play a significant role in homoeopathic or ayurvedic treatments [7]. Chromolaena odorata, commonly referred to as Awolowo Leaves, is a blossoming shrub that falls within the Asteraceae family. This plant species is distributed over tropical regions of Africa, North America, as well as South and Southeast Asia. The plant is referred to by multiple common names including Siam weed, Christmas bush, common floss flower, Armstrong's weed, baby tea, bitter bush, butterfly weed, devil weed, eupatorium, Jack in the bush, king weed, paraffin bush, paraffin weed, Siam weed, turpentine weed, and triffid weed. [16] [3]. The traditional medical uses encompass anti-diarrheal, astringent, antispasmodic, antihypertensive, anti-inflammatory, diuretic tonic, antipyretic, heart tonic, anti-helminthic, and analgesic properties.

The actions of the substance include reducing inflammation, lowering fever, preventing muscle spasms, fighting against bacterial infections, killing insects, protecting against oxidative damage, treating gonorrhoea, eliminating fungi, promoting urine production, aiding in blood clotting, and inhibiting the growth of microorganisms. [11] [9] [3] Traditional medicine practitioners have used fresh leaves of C. odorata or its decoction to treat several diseases, including human burns, soft tissue wounds, ulcerated wounds, blisters, postnatal wounds, leech stings, nausea and vomiting, and skin infection. [10]. The plant contains phytochemical components, specifically alkaloids, tannins, flavonoids, and other phenolic compounds, which possess medicinal properties. Plant secondary metabolites often exert their antimicrobial effects by affecting the function and structure of cell membranes, inhibiting the production of DNA and RNA, interfering with intermediate metabolism, promoting the coagulation of cytoplasmic components, and disturbing normal cell communication [13]. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) classified as a phenylacetic acid derivative. NSAIDs suppress the activity of cyclooxygenase (COX)-1 and 2, the enzymes involved in the synthesis of prostaglandins (PGs). Prostaglandins (PGs) are involved in the process of inflammation and the transmission of pain signals. Diclofenac, similar to other nonsteroidal anti-inflammatory drugs (NSAIDs), is frequently used as the initial treatment option for both acute and chronic pain and inflammation resulting from various causes [4]. Diclofenac is a commonly prescribed nonsteroidal anti-inflammatory drug (NSAID) known for its pain-relieving, anti-inflammatory, and fever-reducing properties [4]. Diclofenac induces liver damage. The aetiology of hepatotoxicity caused by diclofenac in humans is idiosyncratic. The liver breaks down diclofenac using different cytochrome P-450 enzymes. This creates drug-protein adducts, conjugates with glutathione (GSH), and lowers the function of mitochondria, which damages organs [17]. Nevertheless, it has been recorded that diclofenac, not its metabolite, is accountable for its toxicity [17]. Diclofenac also impacts the kidney,

contributes to inflammation of the kidneys (nephritis) and toxicity to the kidneys (nephrotoxicity) [12]. Additionally, the use of diclofenac leads to gastrointestinal complications, including gastric mucosa haemorrhage, reduced gastric blood flow, and apoptosis [6]. The liver and kidney play a crucial role in various biochemical processes, such as drug and hormone metabolism, toxin elimination, and cellular homeostasis maintenance [16]. The liver, regarded as the primary metabolic organ, serves as an effective defence mechanism against both environmental and metabolic toxins [17]. On the other hand, the kidneys primarily participate in the elimination of waste products through urine and in maintaining the balance of water and solutes in the body. The biological functions of these organs render them susceptible to oxidative assault from xenobiotics. Various synthetic medicines have been employed in the treatment of liver and kidney disorders. While their effectiveness is undeniable, these products are frequently prohibitively expensive, making them inaccessible to a significant portion of the population in underdeveloped countries. Furthermore, these interventions have been proposed to partially mitigate the metabolic abnormalities observed in illnesses, but they do not always rectify the underlying biochemical defects [17]. The majority of medicinal herbs now utilised by local herbalists lack substantial scientific information and evaluation on their impact on crucial organs such as the liver, kidney, and heart. Hence, it is crucial to obtain and record the ethno-medicinal assertions associated with these botanical remedies. Scientific research is necessary to determine the effectiveness of Chromolaena odorata in treating and managing various diseases, given its numerous traditional medicinal uses. The objective of this study was to investigate the impact of the aqueous leaf extract of Chromolaena odorata on the hepato-renal damage produced by diclofenac in Wistar albino rats. The aim of this study is to

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look at how well an aqueous extract from Chromolaena odorata leaves protects the liver and kidneys of albino rats that have had liver and kidney damage.

II. AIM OF THE STUDY

The study is aimed at investigating the hepato-renal protective potential of aqueous extract of Chromolaena odorata leaf in liver and kidney toxicity induced albino rats.

III. OBJECTIVE OF THE STUDY

1. To determine the serum concentration of liver markers (AST, ALT, and ALP) in Diclofenac treated albino rat.
2. To determine the serum concentration of renal function markers (urea and creatinine) in Diclofenac treated albino rats.
3. To determine the ameliorative effect of different concentrations of aqueous extract of Chromolaena odorata leaf in Diclofenacinduced liver and kidney injuries in albino rats.

IV. MATERIALS AND METHODS

CHEMICALS/REAGENTS

Diclofenac sodium (DIC) was purchased from Danson Pharmaceutical Company, OpoloYenagoa Bayelsa State, Nigeria. Chloroform, and Formal Saline was purchased from Angel Medical Store, Onopa, Yenagoa, Bayelsa State.

EXPERIMENTAL DESIGN

The rats were divided into four (4) groups with each group consisting of 5 rats each.

Group 1 (Negative control): Received distilled water and pellet feed for 14days.

Group 2 (Test group): Received 10mg/kg per body weight of diclofenac daily by oral route for 14 days.

Group 3 (Test group): Received 10mg/kg per body weight of diclofenac daily by oral route for 14 days and post treated with 200mg/kg body weight of leaves of Chromolaena odorata orally for 14 days.

Group 4: Received 200mg/kg body weight of leaves of Chromolaena odorata only orally for 14 days.

V. RESULTS

Table 1: Effect of Diclofenac and Chromolaena odorata on Liver Function and Renal Parameters in Adult Albino Rats Exposed to Diclofenac

Enzyme Parameters	ALT(U/L)	ALP(U/L)	CREA (U/L)
NORMAL CONTROL	49.81 ± 4.14^{a}	83.70 ± 7.94^{a}	0.55 ± 0.03^{a}
DICLOFENAC	137.73 ± 19.64^{b}	149.60 ± 49.00^{b}	0.97 ± 0.25^{b}
DICLO + AWOLOWO	79.65 ± 7.44^{ab}	98.72 ± 33.32^{ab}	0.61 ± 0.10^{ab}
AWOLOWO	50.32 ± 4.72^{c}	79.02 ± 23.92^{c}	0.54 ± 0.55^{c}

Values with superscript alphabet is considered significant ($p<0.05$). ANOVA was used to compare the different groups. All post hoc testing were done using Bonferroni multiple comparison.

The result revealed a statistically significant ($p<0.05$) increase in serum ALT (137.73±19.64), ALP (149.60±49.00) and creatinine (0.97±0.25) in the diclofenac alone treated group (group 2) when compared with the group 1 (control group) (49.81±4.14; 83.70±7.94 and 0.55±0.03) respectively. However, post treatment with 200mg/kg body weight of Chromolaena odorataleaf extract (group 3) causes drastic reduction in the serum ALT (79.65±7.44), ALP (98.72±33.32) and creatinine (0.61±0.10) levels when compared with the control (group 1). There was no significant difference observed in the serum ALT (50.32±4.72), ALP (79.02±23.92) and creatinine (0.54±0.55) levels of Chromolaena odorata alone treated rats (group 4) when compared with the group 1 (49.81±4.14; 83.70±7.94 and 0.55±0.03) respectively.

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Table 2: Effect of Diclofenac and Chromolaena odorata on Oxidative Stress Biomarkers in Adult Albino Rats Exposed to Diclofenac

Antioxidant Parameters	SOD (mg/kg protein)	CAT(mg/kg protein)	GSH(mg/kg protein)	MDA(mg/kg protein)
NORMAL CONTROL	6.67±2.31[a]	4.98±1.95[a]	6.08±2.7[a]	2.18±1.04[a]
DICLOFENAC	2.65±1.00[b]	2.76±0.92[b]	3.08±1.70[b]	4.65±2.70[b]
DICLO + AWOLOWO	5.43±2.11[ab]	4.53±2.00[ab]	5.52±2.09[ab]	2.66±0.73[ab]
AWOLOWO	6.64±4.21[c]	4.69±4.21[c]	6.18±4.21[c]	2.17±10.30[c]

Values with superscript alphabet is considered significant ($p<0.05$). ANOVA was used to compare the different groups. All post hoc testing were done using Bonferroni multiple comparison.

The result revealed that there is statistically significant ($p<0.05$) reduction in serum SOD (2.65±1.00), CAT (2.76±0.92) and GSH (3.08±1.70) in the diclofenac alone treated group (group 2) when compared with the group 1 (control group) (6.67±2.31; 4.98±1.95 and 6.08±2.7) respectively. While malondialdehyde(4.65±2.70) levels was significantly ($p<0.05$) higher in the diclofenac alone treated group (group 2) when compared with the group 1(2.18±1.04). However, post treatment with 200mg/kg body weight of Chromolaena odorata leaf extract (group 3) causes near to normal significant elevation in the serum SOD (5.43±2.11), CAT (4.53±2.00) and GSH (5.52±2.09) levels when compared with the control (group). While malondialdehyde (2.66±0.73) levels causes a drastic reduction of malondialdehyde levels compared with the control (2.18±0.14). There was no significant difference observed in the serum SOD (6.64±4.21), CAT (4.69±4.21), GSH (6.18±4.21) and MDA (2.17±10.30) levels of Chromolaena odorata alone treated rats (group 4) when compared with the group 1 (6.67±2.31; 4.98±1.95; 6.08±2.7 and 2.18±1.04) respectively.

HISTOLOGY OF THE LIVER

Control

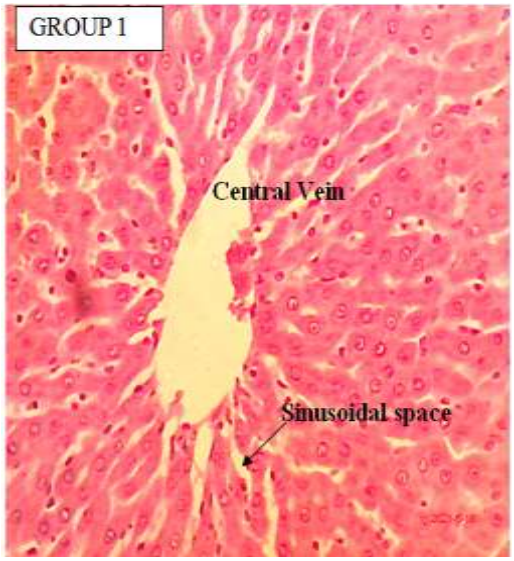

PLATE 1: Displays the anatomical structure of a typical rat under normal conditions. The slide displays the typical structure of the liver, including the central vein (CV) and intact hepatocytes (H) with a sinusoidal space (S). (X10)H&E

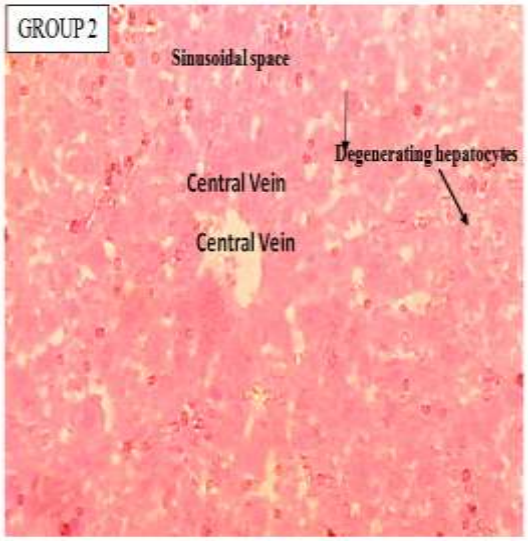

PLATE 2: Displays the structural characteristics of the liver following the introduction of Diclofenac at a dosage of 10 mg/kg for a duration of 14 days. The slide reveals the presence of congestion in the central vein (CV), together with balloon degeneration of hepatocytes (arrow) and sinusoidal space (S) containing Kupffer cells (K) at a magnification of 10X using H&E staining. This demonstrates the toxic effects of a chemical given to the liver.

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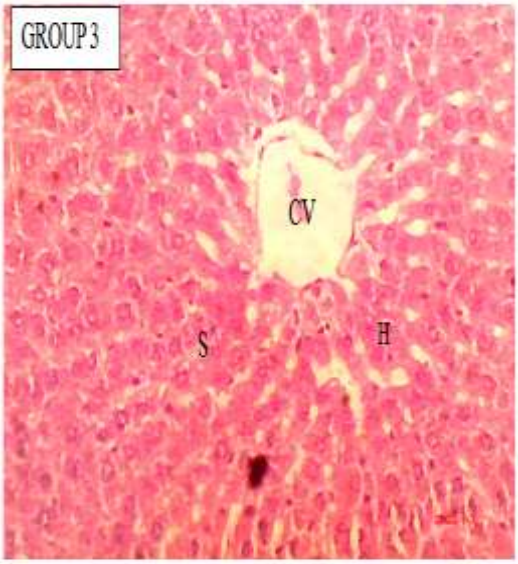

PLATE 3.3: Shows the morphology of the liver after the administration of Diclofenac 10mg/kg and Chromolaena odorata 200mg/kg after 14 days. Slide shows the central vein (CV),occluded sinusoidal space (S) with mild balloon degeneration of hepatocytes (H) (X40)H&E not as bad as that given Diclofenac alone

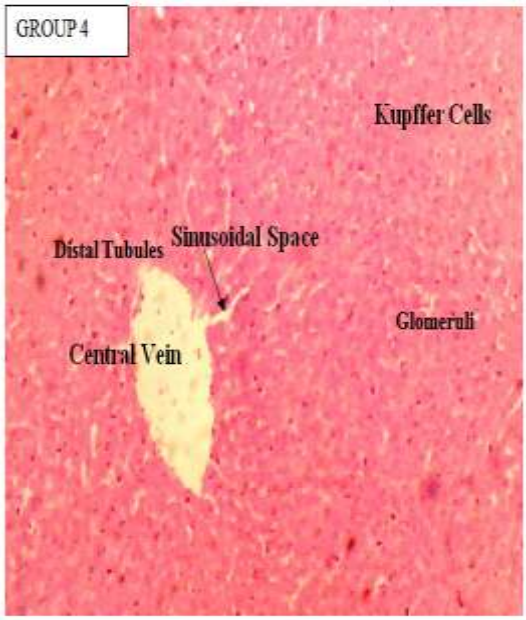

PLATE 4: Displays the structural characteristics of the liver following the introduction of Chromolaena odorata at a dosage of 200mg/kg during a period of 14 days.The slide exhibits the typical structure of the liver, including the central vein (CV), hepatocytes (H) with intact sinusoidal space (S), and just a few Kupffer cells (K) (X10)H&E

HISTOLOGY OF THE KIDNEY

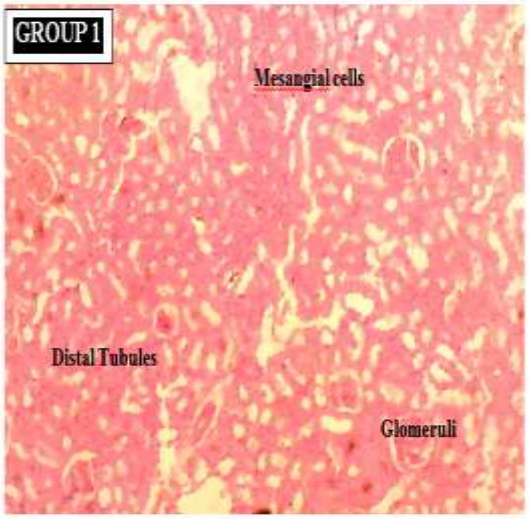

PLATE 1: Displays the anatomical structure of the kidney in the rat under normal conditions. The slide displays typical glomeruli (G), distal tubules (DT), and the presence of mesangial cells (MS)..(X40) H&E

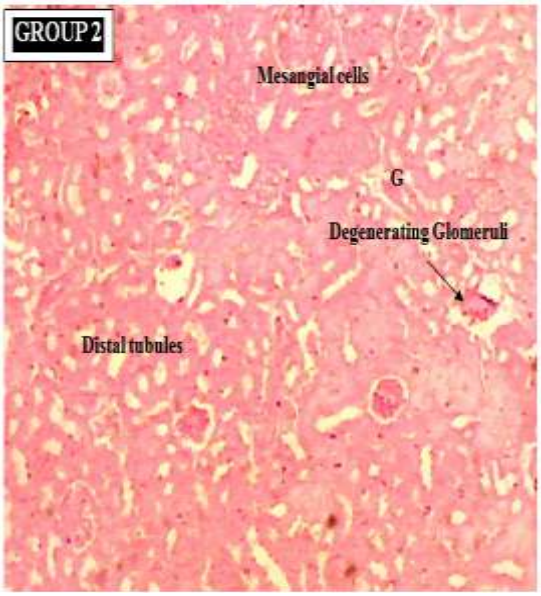

PLATE 2: Displays the structural characteristics of the kidney following the administration of diclofenac at a dosage of 10mg/kg. The slide exhibits the degeneration of glomeruli (G), distal tubules (DT), and a significant abundance of mesangial cells (MS)..(X10) H&E

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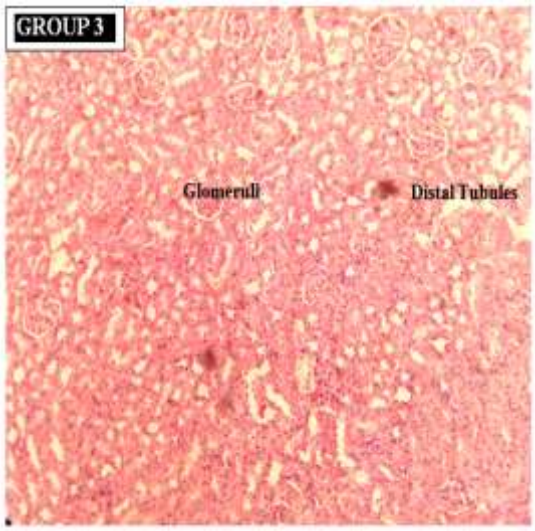

PLATE 3: Displays the structural characteristics of the kidney following the administration of diclofenac and Chromolena odorata The slide displays the typical structure of the kidney, including the glomeruli (G) and distal tubules (DT).(X10)

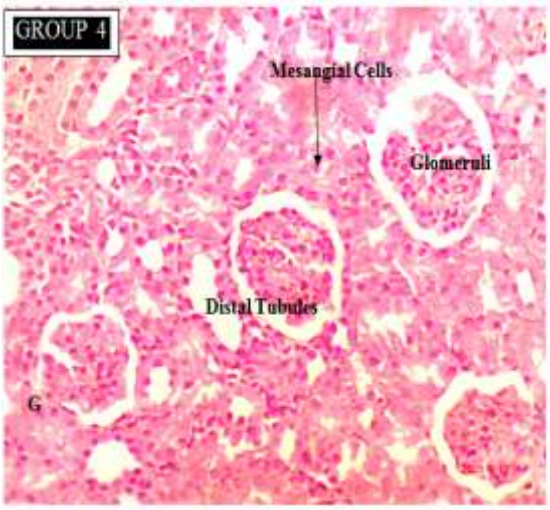

PLATE 4: Reveals the structural characteristics of the kidney following the administration of Chromolena odorata. The slide displays typical glomeruli (G), distal tubules (DT), and the presence of mesangial cells (MS).X40) H&E

VI. DISCUSSION

Medicinal plants include several phytochemical components, including flavonoids, saponins, protease inhibitors, glycosides, anthraquinones, terpenes, tannins, sterols, alkaloids, and allicin. These components are responsible for the biological activity of the plant [2]. Diclofenac is frequently given due to its pain-relieving and inflammation-reducing properties, as well as its ability to lower fever [4]. Although diclofenac is widely used, cases of hepato-renal and gastrointestinal problems have been described after its treatment [6].

Elevated levels of liver enzymes such as ALT, ALP, and AST, as well as renal indicators like urea and creatinine, are frequently observed in cases of liver and kidney damage [2]. The elevation of hepatic function enzymes indicates significant damage to liver cells, leading to the release of these enzymes from the cytoplasm into the bloodstream [2]. Table 1 shows that the levels of ALT (137.73±19.64) and ALP (149.60±49.00) in the blood were significantly higher ($p<0.05$) in the group that was only given diclofenac (group 2) compared to the control group (group 1). Nevertheless, the administration of Chromolaena odorata leaf extract at a dosage of 200 mg/kg body weight results in a significant decrease in serum ALT (79.65±7.44) and ALP (98.72±33.32) levels compared to the control group (49.81±4.14 and 83.70±7.94), respectively. This discovery suggests that the injection of diclofenac caused significant harm to the liver membrane. The elevation in ALT and ALP levels can be attributed to the underlying cause.

Diclofenac undergoes hepatic metabolism through various cytochrome P-450 enzymes, leading to the development of drug-protein adducts and glutathione (GSH) conjugation, as well as mitochondrial dysfunction and organ damage [2]. A decrease in the concentration of PGE-2, which in turn resulted from a decrease in the production of COX-2 protein, may have contributed to the hepatotoxicity that diclofenac caused [4]. This finding is consistent with the earlier studies conducted by [8] and [19], which documented increased levels of AST, ALT, and ALP in rats induced by diclofenac. The decrease in ALT and ALP levels seen in the rats treated with Chromolaena odorata leaf extract may be related to the antioxidant properties of the plants.

Increased levels of serum creatinine compared to the control group further supported the findings that the administration of diclofenac alone resulted in a significant decrease in renal function. Nevertheless, administering Chromolaena odorata leaf extract at a dosage of 200 mg/kg body weight significantly decreased serum creatine levels in comparison to the control group. The rise in creatinine levels can be linked to the failure to remove metabolised substances from the body, leading to significant impairment of renal tubular

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function. This finding aligns with the previous studies conducted by [12] and [5], which reported a notable decline in renal function in rats treated with diclofenac. The decrease in serum concentration in the Chromolaena odorata leaf extract-treated rats can be linked to the antioxidant properties of the plants.

Superoxide dismutase (SOD) and catalase (CAT) are the primary enzymes responsible for scavenging radicals. Superoxide dismutase serves as the primary enzymatic protection against the superoxide anion. Catalase is a heme protein that facilitates the reduction of hydrogen peroxide and safeguards tissues from hydroxyl radicals [15]. One group that was given diclofenac alone (group 2) had significantly lower levels of serum superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) compared to the control group (group 1). This was found to be significant ($p<0.05$). Nevertheless, administration of Chromolaena odorata leaf extract at a dosage of 200 mg/kg body weight (group 3) resulted in a substantial increase in serum SOD, CAT (4.53±2.00), and GSH levels, approaching normal values. This effect was observed when compared to the control group, as illustrated in table 2. The decline in the enzymatic activities of superoxide dismutase (SOD) and catalase (CAT), as well as the reduced levels of glutathione (GSH) in both the liver and kidney during the illness state, might be attributed to the excessive generation of reactive oxygen species in animals [15]. When there are too many free radicals, they damage the lipids and proteins in the cell membrane through oxidative stress. This lowers the levels of GSH and the activity of the enzyme that works with it.

The level of MDA can be used as an indicator to monitor lipid peroxidation. Therefore, MDA is regarded as a prominent indicator of the oxidative process in cellular structures [5]. In this study, MDA levels went up a lot in the rats that were given diclofenac (group 2) compared to the rats that were not given diclofenac (2.18±1.04). Even so, giving Chromolaena odorata leaf extract after treatment lowers serum malondialdehyde levels by a lot (2.66±0.73) compared to the control group (2.18±0.14). Furthermore, [15] observed a comparable outcome, indicating an elevation in lipid peroxidation within the testes of rats that were subjected to diclofenac.

Histological examinations of the liver and kidney tissues from Group II revealed the presence of hazardous chemicals. The presence of hepatic cellular infiltrations and degeneration of glomeruli (G) and distal tubules (DT) observed in Group II may be attributed to the inflammatory reaction. The observed enhancement in liver and kidney cells in Group III can be linked to the hepatorenal protective properties of the chromolaena odorata (awolowo) leaf extract. The histological examination of the liver and heart confirmed the biochemical data that showed pretreatment with chromolaena odorata (awolowo) leaf extract, particularly at higher doses, had hepatoprotective and renoprotective effects against CCl4-intoxicated rats [19].

VII. IX CONCLUSIONS

An animal model demonstrated that the Chromolaena odorata leaf extract reduced diclofenac-induced liver and kidney damage. Diclofenac-induced rats had elevated ALT, ALP, creatinine, and MDA levels and decreased SOD, CAT, and GSH. However, diclofenac-induced rats treated with Chromolaena odorata leaf extract have significantly lower ALT, ALP, creatinine, and MDA levels and higher SOD, CAT, and GSH activities.

Adherence to ethical standards

Expressions of gratitude
The authors express their gratitude to the Technical laboratory team of the Department of Biochemistry at Niger Delta University, Amassoma.

Declaration of a conflict of interest
The authors assert that there are no conflicts of interest.

Ethical approval statement
The study procedure received approval from the Ethical and Research Committee of Niger Delta University, located in Bayelsa State, Nigeria. The study strictly adhered to the ethical standards for medical research with animal subjects as defined in the Helsinki declaration in 1975 and its amendments.

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