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CYMBOPOGON CITRATUS: A MODULATOR OF TNF-A AND IL-10 IN NSAID-INDUCED HEPATORENAL TOXICITY IN ADULT WISTAR RATS

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Pharmaceuticals typically induce toxicity in the liver and kidney, which are primary control mechanisms for maintaining bodily homeostasis and are more vulnerable to xenobiotics. Cymbopogon citratus (West Indian lemon grass) is used in traditional medicine globally for a variety of medicinal purposes. This study aimed to determine the therapeutic effectiveness of a methanolic leaf extract of C. citratus against NSAID-induced hepatorenal toxicity in adult Wistar rats (Rattus norvegicus domestica). Twenty rats weighing 180–220g were randomly assigned to four groups of five rats each. The unexposed control rats (Group 1) were administered distilled water, while the NSAID-exposed rats (Group 2-4) received Diclofenac at 5mg/kg/BW. While rats in Group 2 were untreated, rats in Groups 3 and 4 were treated with methanolic leaf extracts of C. citratus at 100mg/kg/BW and 200mg/kg/BW, respectively. Treatment with the methanolic extract of C. citratus modulates TNF-α and IL-10 expression ($P<0.05$) and ameliorates cellular alterations in the kidneys and liver of treated rats compared to the untreated group. This study established the efficacy of Cymbopogon citratus as a hepatorenal protector by considerably ameliorating the adverse effects of diclofenac-induced hepatorenal toxicity

***Keywords**: Cytokines, Health, Phytochemicals, Rats, Toxicity*

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are chemicals other than steroids that inhibit a component of the inflammatory cascade. These commonly used drugs include Acetaminophen (Paracetamol), Diclofenac, Ibuprofen, Indomethacin, Celecoxib, Mefenamic acid, Etoricoxib, Naproxen, sodium hyaluronate, polysulfated glycosaminoglycans, and aspirin-like compounds[1,2]. These drugs are administered orally, parenterally, percutaneously, or as a suppository, and the duration of administration ranges from a single dose to long-term treatment [3]. NSAIDs exert their analgesic, anti-inflammatory, and antipyretic actions by blocking the enzymes cyclo-oxygenase-1 and 2 (COX-1) and (COX-2) that are involved in prostaglandin synthesis[3,4].

Diclofenac (2-[(2,6-chlorophenyl) amino] phenylacetate) is a widely used nonsteroidal

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anti-inflammatory medication (NSAID) for the treatment of osteoarthritis, rheumatoid arthritis, and muscular pain. Diclofenac sodium's mechanism of action is the same as other NSAIDs; it acts through the inhibition of cyclooxygenase (COX)[5]. The physiological impact of this medication is a reduction in prostaglandin synthesis[6,7]. As an NSAID, diclofenac binds to both forms of COX (COX-1 and COX-2), therefore limiting the conversion of arachidonic acid to pro-inflammatory prostaglandins by chelation. It is also able to suppress tumour angiogenesis, in which COX-2 is implicated[8]. Diclofenac, are assumed to be safe; however, they have lately received attention due to the likelihood of renal injury[9]. Furthermore, NSAIDs are one of the leading causes of acute hepatic damage, although, the level of severe instances found is very rare; nonetheless, acute liver injuries are typically linked with idiosyncratic patterns, the mechanism partially understood, except for aspirin[10,2]. Diclofenac lowers prostaglandin production which can lead to impaired renal function, and reduced glomerular hydraulic pressure which can further contribute to acute kidney injury (AKI)[11,9]. Furthermore, because the kidneys are the primary organ for drug excretion, the renal arterioles and glomerular capillaries are particularly susceptible to drug effects[6]. NSAIDs limit prostaglandin production by inhibiting the enzyme responsible for converting arachidonate to prostaglandin H_2 via a two-step cyclo-oxygenation and peroxidation process. This reduces inflammation but has negative effects on the gastrointestinal system, kidney, and platelets[11,12].

The liver is the largest and most vital internal organ that functions as a gateway of entry and metabolises all chemicals that enter the body through the gastrointestinal system[13,14,15]

Diclofenac has been associated with hepatotoxicity, and the hepatotoxicity caused by diclofenac is mainly due to its metabolites, but genetic factors can also increase the level of susceptibility to synthesize and accumulate the reactive acylglucuronide metabolite, which triggers an immune response and liver injury[4].

According to Sies[16], oxidative stress is an imbalance between the production and accumulation of ROS in cells and tissues and the biological system's ability to detoxify these reactive products. Oxidative stress has an impact on a variety of renal-related diseases. Glomerular and tubulointerstitial nephritis, renal failure, proteinuria, and uremia studies show that NSAIDs in relation to nicotinamide adenine dinucleotide (NADPH) oxidases, nitric oxide synthase, lipoxygenase, cytochrome P450s, xanthine oxidoreductase, and cyclooxygenases produce ROS in biological systems, potentially leading to liver and other organs damage[17,18].

Cymbopogon citratus, often known as lemongrass, is also known as "Ewe tea", "Lemuntsamiciyawa", and "Lemon ahihia" in Yoruba, Hausa, and Igbo. Specific components of *C. citratus* have been discovered to display pharmacological actions that include free radical scavengers, antioxidants, anti-inflammatory characteristics, and antimutagenic activity[19].

C. citratus belongs to the Gramineae family, which has around 660 genera and 9000 species. *C. citratus*, a fragrant perennial plant of the Poaceae family, with long, thin green leaves is widely utilised and supplied globally[20,21]. The leaves contain phenolic compounds, hydroxycinnamic acids, flavones, condensed-type tannin, triterpenes, electrolytes, and minerals. Citral, the main component of *C. citratus*, has been shown to have anti-inflammatory, antioxidant, and antiradical properties, with studies also demonstrating that *C. citratus* treatment effectively reduces the increase in hepatic enzyme activity and attenuates pathological changes caused by oxidative stress [22,21]. Using murine models, this study evaluated *Cymbopogon citratus'* immunomodulatory potential in $NSAID_S$-induced hepatorenal toxicity.

MATERIALS AND METHODS

Drugs and reagents

TRIZOL reagent (InvitrogenTM, Denmark), ProtoScript II First Strand cDNA Synthesis kit (Biolabs, New England), Luna Mastermix kit (Biolabs, New England), Taqman kit probes (TibM01bi; Berlin, Germany), Primers to cDNA; Inqaba biotech (Hatfield, South Africa), Diclofenac Potassium Tablets 50 mg by Wintech Pharmaceuticals Limited (Mumbai, India).

Plant collection

Fresh leaves of *Cymbopogon citratus* were collected at a farm in Laje village, Ondo town, Ondo State, Nigeria, and identified by a botanist at the Department of Biological Sciences, University of Medical Sciences, Ondo, with herbarium number 033 assigned to the identified plant. The leaves were washed with tap water, sterilised with 70% ethyl alcohol to remove contaminants, and then carefully rinsed in sterile distilled water before being dried at room temperature and stored in a sealed plastic bag at ambient temperature and protected from light[23].

Preparation of the plant extract

A total of 150g of the dried leaves were blended to powder and dissolved in 2000 mL of 80% methanol, which was left to stand for 24 hours while being shaken intermittently. The mixture was initially filtered using cheesecloth, then the filtrate was filtered again with Whatman filter paper No. 1. After filtering, the methanolic filtrate was freeze-dried, yielding an extract-like solid residue[24]. The concentrations of 100mg/kg and 200mg/kg were constituted with distilled water and administered to the experimental animals across the respective groups.

Experimental Design

Twenty adult male Wistar rats weighing between 180–220g were obtained from the animal house of the University of Medical Sciences in Ondo and acclimatised for two weeks before commencing the experiment. The rats had unrestricted access to water and normal rat pellets from New Hope pellet feed, produced by New Hope Agriculture and Technology, Nigeria and obtained from the Jopoka feed depot in Ondo town, Ondo state. They were maintained in a clean plastic cage in the animal house with appropriate ventilation. The rats were randomly and evenly distributed among four groups of five rats each. The first group (negative control group) received just distilled water, while the remaining test groups (2-4) received diclofenac orally at a standard dosage of 5mg/kg/BW. While rats in group 2 were left untreated after being exposed to diclofenac, rats in groups 3 and 4 were orally administered with *Cymbopogon citratus* extracts at dosages of 100mg/kg/BW and 200mg/kg/BW respectively.

At the end of the 28-day experiment, the rats were euthanised by cervical dislocation, and the kidneys and livers were extracted and immediately transferred into 10% neutral buffered formalin for histological studies. Samples for mRNA expression of TNF-α and IL-10 were washed in TRIZOL and processed according to the manufacturer's procedures[25, 26].

Histopathological Studies

Following the completion of the experiment, the kidneys and livers were processed for histopathological examination as described by Moronkeji et al.[23]. The tissues were dehydrated in ascending grades of alcohol (50%, 60%, 70%, 90%, 100%) before clearing with two changes of xylene, infiltrated with two changes of wax bath, and finally embedded in paraffin wax. Tissue sections were then hydrated and stained with Harris Haematoxylin for five minutes before being rinsed in water and differentiated with 1% acid alcohol for one minute, blued in tap water for ten minutes, counterstained with 1% aqueous eosin, and dehydrated in ascending alcohol grades. The dehydrated sections were cleared in two changes of xylene, mounted with dibutyl phthalate propylene xylene (DPX), and examined under a light microscope to assess any pathological alterations microscopically using x10 and x40 objectives[27, 28, 29.]

mRNA expression studies

The RNA was harvested from the tissue and the expression level was determined by PCR as described by Barajas et al.[26]. Briefly, RNA was purified from 200mg from the tissues using TRIZOL reagent (Inqaba Biotech West Africa Ltd) as described by the manufacturer (InvitrogenTM, Denmark). Extracted RNA (2µl) was used for the reverse transcription reaction to synthesize complementary DNA (cDNA) using ProtoScript II First Strand cDNA Synthesis kit (Biolabs, New England) in a 3-step reaction condition: 65ºC for 5 minutes, 42ºC for 1 hour and 80ºC for 5 minutes. Polymerase chain reaction (PCR) and amplification for gene expression were done using the Luna Mastermix kit (Biolabs, New England) and Taqman kit probes from TibM01bi (Berlin, Germany) in a

thermocycler. Gel imaging was performed on an electrophoresis gel imager, using β-actin as the reference gene. Primers to cDNA were purchased from Inqaba Biotech (Hatfield, South Africa). The specific primers employed for PCR are as follows:-

- TNF-α; forward (5'-CCAGACCCTCACACTCAGATCA-3')
- Reverse (5'-TCCGCTTGGTGGTGGTTTGCTA-3')
- IL-10; forward (5'-TTGAACCACCCGGCATCTAC-3)
- Reverse (5'-CCAAGGAGTTGCTCCCGTTA-3′)
- β-actin: forward (5'-CCCGCGAGTACAACCTTCT-3′)
- Reverse (5'-CGTCATCCATGGCGAACT-3′).

Statistical analysis

The data gathered was presented as mean ± SD. The data was analysed using one-way ANOVA, then Duncan's multiple tests for post-hoc analysis (DMRT). Statistical analysis was performed using SPSS version 17.0 for Windows, with a 95% confidence interval ($p < 0.05$).

RESULT AND DISCUSSION

Result

Histopathological Findings

Histopathological studies demonstrated that *C. citratus* mitigate NSAID-induced hepatorenal toxicity. As shown in **Fig. 1a**, the unexposed rats had normal kidney histoarchitecture typified by a normal glomerulus and renal tubules, as well as an interstitial space devoid of inflammation and congestion. The untreated NSAID-exposed rats had periglomerular inflammation, dilated renal tubules, and congested interstitial space (**Fig. 1b**) while the NSAID-exposed rats treated with methanolic extracts of *C. citratus* at 100mg/kg/BW and 200mg/kg/BW showed normal glomeruli and renal tubules (**Fig. 1c and Fig. 1d**).

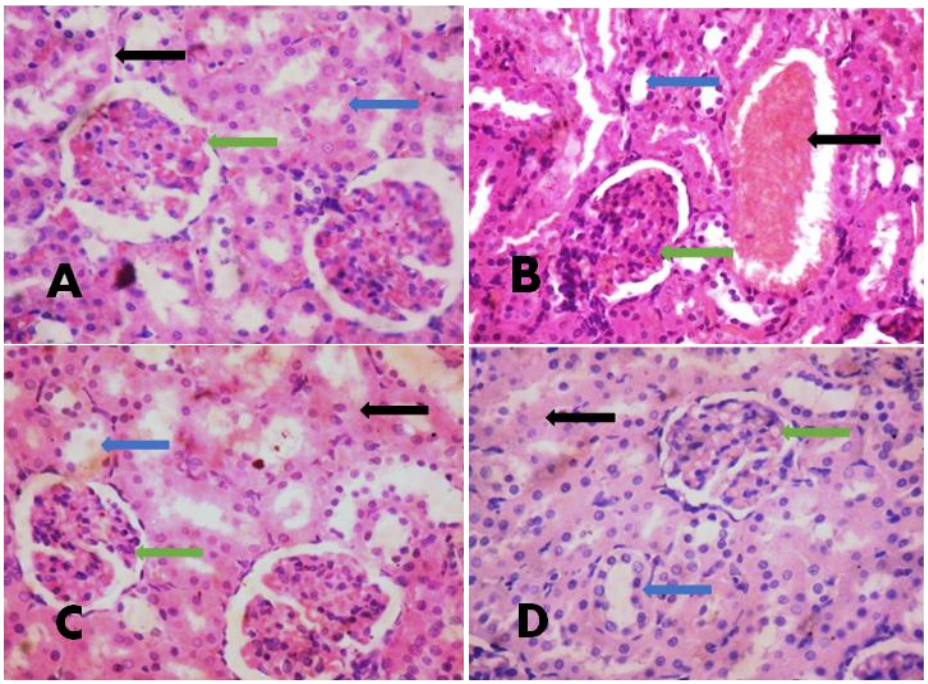

Fig. 1: H and E-stained kidney sections of rats. **A.** Control rat's glomeruli (green arrow), renal tubules (blue arrow) and interstitial space (black arrow) appear normal. **B.** Kidney of NSAID-exposed, untreated rats showing peri-glomerular inflammation (green arrow), dilated and congested interstitium (black arrow), renal tubules (blue arrow). **C.** NSAID-exposed rats administered with methanolic extracts of *C. citratus* at 100mg/kg/BW showed normal glomeruli (green arrow) and renal tubules (blue arrow) with non-congested interstitium (black arrow). **D.** NSAID-exposed rats administered with extracts of *C. citratus* at 200mg/kg/BW showed normal glomeruli (green arrow), renal tubules (blue arrow) and interstitium (black arrow) (Magnification x400).

The liver of the unexposed control rats showed no pathological abnormalities, with normal hepatocytes and sinusoidal spaces devoid of congestion and inflammation (**Fig. 2a**).

The liver section of NSAID-exposed untreated rats showed poor histoarchitecture evidenced by a congested central vein and hepatocytic vacuolation with the morphology of the hepatocytes indicating severe hepatic steatosis (**Fig. 2b**), whereas NSAID-exposed rats administered with extracts of *C. citratus* at 100mg/kg/BW had mild hepatic steatosis with non-congested sinusoidal spaces and a central vein devoid of congestion (**Fig. 2c**). The liver section of NSAID-exposed rats treated with methanolic extracts of *C. citratus* at 200mg/kg/BW revealed normal hepatocyte morphology, sinusoids devoid of congestion, and a non-congested central vein (**Fig. 2d**).

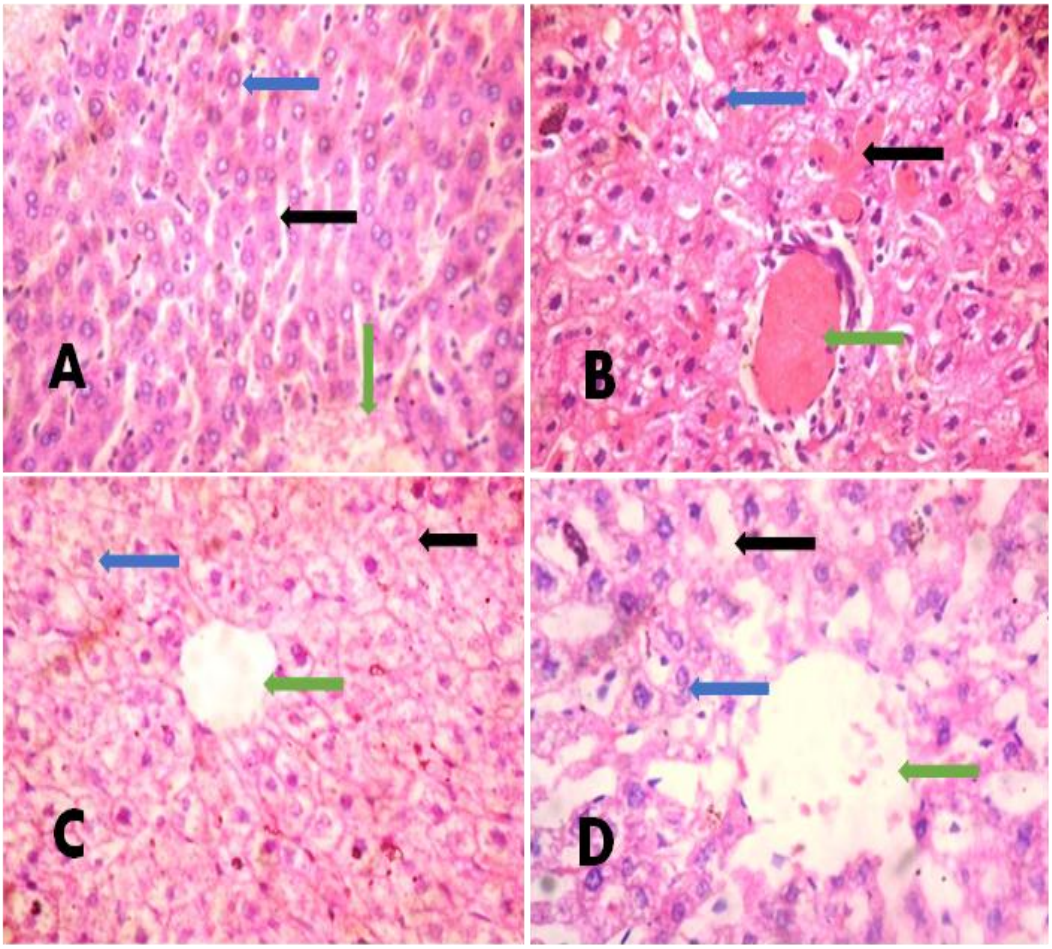

Fig. 2: H and E-stained liver sections of rats. **A.** Liver of the control rat showing normal Hepatocytes (blue arrow), sinusoidal spaces (green arrow) and central vein (green arrow). **B.** NSAID-exposed untreated rats showing a congested central vein (green arrow), severe hepatic steatosis (blue arrow) and dilated and congested sinusoids (black arrow) **C.** NSAID-exposed rats administered with extracts of *C. citratus* at 100mg/kg/BW showed mild hepatic steatosis (blue arrow), non-congested sinusoidal spaces (blue arrow), and non-congested central veins (green arrow). **D.** NSAID-exposed rats administered with methanolic extracts of *C. citratus* at 200mg/kg/BW showed a normal hepatocyte (black arrow), non-congested sinusoids (blue arrow) and central vein (green arrow) (Magnification x400).

mRNA expression studies of TNF-α and IL-10

The administration of NSAID at a standard dosage of 5mg/kg/BW elevated TNF-α levels while downregulating IL-10 expression in untreated rats, and the exposed rats treated with *C. citratus* at 100mg/kg/bw and 200mg/kg/bw showed significantly lower TNF-α expression compared to the untreated rats (P<0.05). The methanolic extracts of *C. citratus* at doses of 100mg/kg/bw and 200mg/kg/bw showed a significant reduction in TNF-α levels and oxidative damage when compared to untreated rats exposed to NSAID (**Fig. 3**). The immunomodulatory effect of *C. citratus* in NSAID-induced oxidative damage on IL-10 expression levels across the various groups shows that Diclofenac downregulated the expression of IL-10 when compared to the unexposed control rats, while a significantly expressed value was observed in rats treated with the plant extracts at 100 mg/kg/bw (P<0.05). However, no significant difference in IL-10 expression was observed in rats treated with *C. citratus* extracts at a dose of 200mg/kg/bw compared to the Diclofenac-exposed untreated group (P>0.05) (**Fig. 4**).

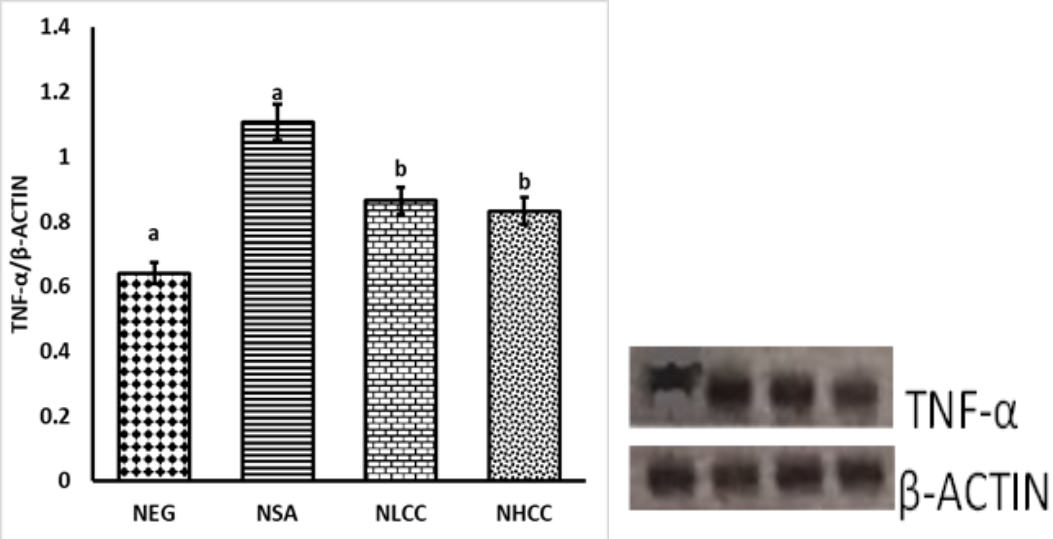

Fig. 3: Shows the relative TNF-α expression across various groups.

Keys: "NEG" for the unexposed control group, **"NSA"** for the NSAIDs exposed, untreated group, **"NLCC"** for the exposed group administered with a low dose of the methanolic extract of *C. citratus*at 100mg/kg/bw, **"NHCC"** for the exposed group administered with a high dose of methanolic extract of *C. citratus* at 200mg/kg/bw.

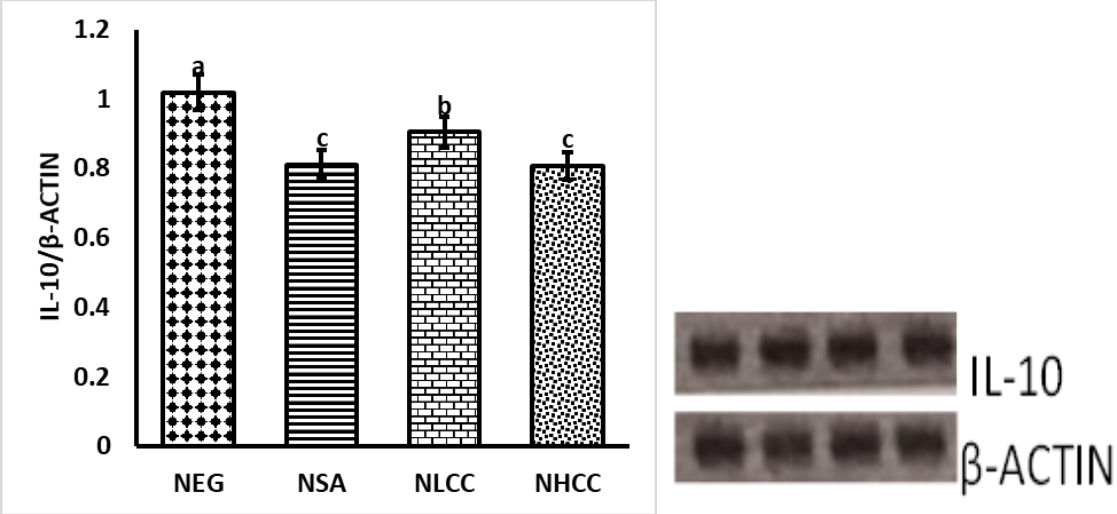

Fig. 4: Shows the IL-10 expression across the various groups.

Keys: "NEG" for the unexposed control group, **"NSA"** for the NSAIDs exposed, untreated group, **"NLCC"** for the exposed group administered with a low dose of methanolic extract of *C. citratus* at 100mg/kg/bw, **"NHCC"** for the exposed group administered with a high dose of methanolic extract of *C. citratus* at 200mg/kg/bw.

Discussion

Despite its effectiveness, diclofenac is one of the drugs known to induce kidney and liver cell injury. The adverse effects of diclofenac and its derivative, 4, 5-hydroxydiclofenac, have been related to immune-mediated defence system deterioration and mitochondrial damage[30]. Studies have demonstrated the toxicity of diclofenac, with evidence demonstrating that diclofenac induces cell necrosis in kidney and liver cells, which is associated with the generation of ROS and the loss of both enzymatic and non-enzymatic antioxidant activity[31,32]. Research has suggested that certain medicinal plants with antioxidant activity may reduce the cellular damage caused by ROS and can be upgraded to a medicated attitude[33,23].

The histopathological findings in this study demonstrated that the methanolic extracts of *Cymbopogon citratus* improved diclofenac-induced renal interstitial congestion, increased glomeruli cellularity, and hepatic steatosis, most likely by inhibiting lipid peroxidation and reactive oxygen species as evidenced by the suppression of the TNF-α and up-regulation of IL-10. TNF-α is a cytokine produced by activated macrophages that plays a role in immune regulation. It has pro-inflammatory properties and is necessary for both innate and adaptive immunity and also induces the expression of endothelial adhesion molecules and chemokines which attract inflammatory leukocytes to sites of tissue injury[34,35,36]. Studies by Alabi and Akomolafe [37] reported that oral diclofenac therapy had a nephrotoxic effect and resulted in a significant decline in the body weight of the experimental animals. The abrupt change was accompanied by increased aggressiveness, loss of appetite, and diarrhoea in the diclofenac-exposed untreated rats, with a few fatalities reported over time, which is consistent with the study's findings.

Interleukin-10 (IL-10) is also recognized to be a pleiotropic and powerful anti-inflammatory and immunosuppressive cytokine generated by both innate and adaptive immune cells, including dendritic cells, and macrophages[38]. IL-10 is a key natural counter-regulator of cytokine-mediated inflammation which causes the production and function of key pro-inflammations like IL-1β, IL-6 and TNF-α to be inhibited[39]. The mRNA expression studies align with the anti-inflammatory and antioxidant properties of *C. citratus* as treatment with the extracts modulating the expression of the studied markers. In this study, the administration of diclofenac at a dose of 5 mg/kg/day for 28 consecutive days induced a marked impairment in the kidney and altered liver functions and histoarchitecture. This was evidenced by an elevation in the expression of

the proinflammatory TNF-α and repression of the anti-inflammatory IL-10 in the studied organs of the diclofenac-exposed untreated rats while the control group showed no signs of oxidative distress or reactivity throughout the study, and the histoarchitecture of the kidneys and liver appeared normal. TNF-α levels were lower and IL-10 levels were upregulated in rats treated with *C. citratus* extracts compared to untreated rats exposed to diclofenac. The diclofenac-exposed untreated rats showed the most oxidative distress, which is consistent with the findings of Bromley et al.[14]. Hassan et al.[40] also documented the cytopathic effect of NSAIDs on the liver, with hepatocytes exhibiting severe hepatic steatosis and vascular congestion which agrees with the findings in this study.

TNF-α expression and IL-10 suppression were increased in the exposed-untreated group due to oxidative stress generated by NSAIDs, indicating cytotoxicity in the hepato-renal system. Treatment with *C. citratus* at dosages of 100mg/kg/BW and 200mg/kg/BW resulted in significant repair due to *C. citratus'* therapeutic and antioxidant properties. A near-normal renal morphology was restored, which is consistent with the reports of Ahmed et al.[41] and Saenthaweesuk et al.[19]. The study observed that administering *C. citratus* at doses of 100mg/kg/bw and 200mg/kg/bw effectively alleviated the acute renal and liver toxicity caused by diclofenac, confirming *C. citratus'* anti-inflammatory and anti-oxidant potential in diclofenac-induced hepatorenal toxicity by improving the antioxidant defence system due to the presence of phytoconstituents in the plants.

The information and findings from this study go a long way towards highlighting the effects of the oxidative stress response on the kidney and liver, as well as the therapeutic effects of *C. citratus* in improving the antioxidant defence system due to the presence of radical scavengers as phytoconstituents in the studied plants.

Conclusion

Oxidative stress is a primary cause of organ damage, and extended use of NSAIDs such as diclofenac has been linked to the generation of ROS, which can induce hepatorenal damage. This study observed that methanolic extracts of *Cymbopogon citratus* at doses of 100mg/kg/bw and 200mg/kg/bw ameliorate diclofenac-induced hepatorenal toxicity and restored basal levels of TNF-α and IL-10 in the experimental animals, indicating therapeutic potential.

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سيمبوبوجون ستراتس: منظم لمستويات TNF-α و IL-10 في الجرذان البالغة من نوع ويستار في التسمم الكبدي الكلوي الناتج عن مضادات الالتهاب غير الستيرويدية

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تؤدي الأدوية عادة إلى التسمم في الكبد والكلى، وهما الجهازان الرئيسيان المسؤولان عن الحفاظ على التوازن الداخلي للجسم وهما أكثر عرضة للمواد السامة. سيمبوبوجون ستراتس (عشب الليمون الهندي الغربي) يُستخدم في الطب التقليدي عالميًا لأغراض علاجية متنوعة. هدفت هذه الدراسة إلى تحديد فعالية المستخلص الميثانولي لأوراق سيمبوبوجون ستراتس ضد التسمم الكبدي الكلوي الناتج عن مضادات الالتهاب غير الستيرويدية في الجرذان البالغة من نوع ويستار (راتس نورفيجس دومستيكا). تم توزيع عشرون جرذًا، وزنهم بين ١٨٠ و٢٢٠ جرامًا، عشوائيًا إلى أربع مجموعات من خمسة جرذان لكل مجموعة. تم إعطاء الجرذان غير المعرضة للمادة (المجموعة ١) ماءً مقطرًا، بينما تم إعطاء الجرذان المعرضة للمضادات الالتهابية غير الستيرويدية (المجموعة ٢–٤) دواء ديكلوفيناك بجرعة ٥ ملج/كجم من وزن الجسم. بينما لم يتم علاج الجرذان في المجموعة ٢، تم علاج الجرذان في المجموعات ٣ و ٤ بمستخلص ميثانولي من أوراق سيمبوبوجون ستراتس بجرعات ١٠٠ ملج/كجم من وزن الجسم و ٢٠٠ ملج/كجم من وزن الجسم على التوالي. أظهر العلاج بمستخلص سيمبوبوجون ستراتس الميثانولي تأثيرًا منظمًا على مستوى TNF-α و IL-10 ($P<0.05$)، كما ساعد في تحسين التغيرات الخلوية في الكلى والكبد مقارنة بالمجموعة غير المعالجة. خلصت الدراسة إلى فعالية سيمبوبوجون ستراتس كحامٍ للكبد والكلى من خلال التخفيف الكبير من الآثار الضارة للتسمم الكبدي الكلوي الناتج عن ديكلوفيناك.