Toxicology Reports 13 (2024) 101734

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Protective effect of *Ficus capensis* lyophilized extract against carboplatin-induced liver injury via inhibition of oxidative stress and inflammation in rats

Josiah Aja Nwadibia [a], Ilemobayo Victor Fasogbon [b], Angela Mumbua Musyoka [b], Ezebuilo Ugbala Ekpono [a], Udu Ama Ibiam [a], Obasi Uche Orji [a], Ejike Daniel Eze [c], Olufunke Onaadepo [e], Peter Chinedu Agu [d], Patrick Maduabuchi Aja [a,b,*]

[a] Biochemistry Department, Faculty of Science, Ebonyi State University, Abakaliki, Nigeria
[b] Biochemistry Department, Faculty of Biomedical Sciences, Kampala International University, Uganda
[c] Department of Physiology, School of Medicine, Kabale University, Kabale, Uganda
[d] Department of Biochemistry, Faculty of Science, Evangel University, Akaeze, Nigeria
[e] Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Abuja, Nigeria

ARTICLE INFO

Handling Editor: Prof. L.H. Lash

Keywords:
Ficus capensis
Oxidative stress
Inflammatory markers
Liver injury

ABSTRACT

Patients who are receiving carboplatin therapy for cancer often experience toxic side effects. This study examined the effects of lyophilized aqueous leaf extracts of F. capensis (LALEFC) on oxidative stress and inflammatory markers in albino rats with carboplatin-damaged livers. We randomly assigned 35 rats to five experimental groups. Groups 2–5 underwent liver injury induction using carboplatin, while groups 1 and 2 served as the normal and carboplatin control groups, respectively. Groups 3–5 were the treatment groups. Treatments were performed for 17 days. We analyzed the quantitative phytochemical constituents of LALEFC using standard procedures and analyzed the liver oxidative stress and inflammatory markers using liver homogenate. The phytochemical constituents of LALEFC (mg/100 g) occur in the following order: The most abundant compounds were phenols (1577.72 ± 0.008), flavonoids (1253.13 ± 0.007), tannins (878.97 ± 0.007), alkaloids (652.66 ± 0.007), glycosides (314.39 ± 0.011), and terpenoids (261.18 ± 0.154), while steroids (0.573 ± 0.062), saponins (0.370 ± 0.003), and HCN (0.254.00 ± 0.006) were found in trace amount. The study of oxidative stress and inflammatory markers showed that giving carboplatin to rats greatly increased the levels of interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), nuclear factor-kappa B (NF-α), malondialdehyde (MDA), reactive oxygen species (ROS), and caspase-3 activity. It also decreased the levels of reduced glutathione (GSH) and the activities of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). D). However, coadministration of LALEFC significantly restored the altered oxidative and inflammatory responses. This finding suggested that carboplatin induced liver injury through redox imbalance, which elevated the expression of inflammatory markers. LALEFC's restoration of altered markers could be relevant in the treatment of carboplatin-induced liver injury.

1. Introduction

Carboplatin is a platinum-based chemotherapy drug widely used in cancer treatment, particularly for ovarian, lung, and testicular cancers [11]. Its significance lies in its ability to interfere with DNA replication in cancer cells, leading to cell death. However, carboplatin is not without complications. One significant concern is its potential toxicity to liver tissue. Hepatotoxicity can manifest in the form of elevated liver enzymes, jaundice, and, in severe cases, liver failure [10]. This toxicity limits the drug's dosage and long-term use, necessitating careful monitoring of liver function during treatment. Understanding and managing these complications is crucial to optimising the therapeutic benefits of carboplatin while minimising harm to the patient. Hence, *F. carpensis* lyophilised extract could help minimise the harmful effects of carboplatin on the hepatic tissues.

Nature has offered medical therapies for a long time, and 80 % of

* Correspondence to: Biochemistry Department, Faculty of Biomedical Sciences, Kampala International University, Western Campus, Ishaka, Uganda.
E-mail address: aja.patrick@kiu.ac.ug (P.M. Aja).

https://doi.org/10.1016/j.toxrep.2024.101734
Received 25 July 2024; Received in revised form 10 September 2024; Accepted 12 September 2024
Available online 13 September 2024

developing nations rely on plant-based primary healthcare [23]. Scientists are interested in using native plant products for nutritional and ethnomedicinal objectives to find bioactive components that benefit humans [7,6,4]. Natural plant products and their uses have gained popularity, even in regions with conventional pharmaceuticals [30]. Minerals and phytochemicals in medicinal plants affect human physiology. These natural remedies address several diseases [35,42]. Most people in poor countries still use herbal medicines to treat their health [42], especially in rural regions where traditional medicine is part of the community's sociocultural and religious fabric. Rural Africans employ several affordable therapeutic plants compared to standard medications. Some Nigerian medicinal plants and vegetable leaves are the cheapest and most accessible sources of proteins, vitamins, and minerals; therefore, their therapeutic properties may benefit the public [1].

Capensis, a member of the Moraceae family, is popularly known as the "bush fig tree" [49]. People have long used *F. capensis* as a wound treatment and a medicine for dysentery [17]. *F. capensis* also treats leprosy, epilepsy, rickets, oedema, gonorrhea, circumcision wounds, respiratory problems, and miscarriage [36,40]. Blood-boosting [38,31], anti-sickling [29,47], antibacterial [41], anti-abortifacient [40], immune-stimulatory [12], antidiarrhea [39], antioxidant [43], and pro-fertility effects [7] are some more traditional uses. The aqueous extract of *F. capensis* leaves contained a variety of phytochemicals, including flavonoids, alkaloids, saponins, steroids, glycosides, terpenoids, tannins, and vitamins such as phylloquinone, calciferol, tocopherol, retinol, cobalamin, folic acid, biotin, pyridoxine, niacin, riboflavin, and thiamine [49]. This explains why it helps treat respiratory conditions, high blood pressure, diarrhea, and abortion [36,40].

The liver is an essential organ in the body, bio-transforming and detoxifying all exogenous and endogenous substances, including the neutralisation of reactive oxygen and nitrogen-free (RONS) radicals [8]. However, when RONS-induced oxidative stress increases beyond the body's capacity to neutralise it, liver damage mostly results. Oxidative stress causes the release of inflammatory mediators like IL-1β, IL-6, and TNF-α, as well as oxidation-related markers like SOD, CAT, GSH, GPx, and MDA. These mediators make liver damage worse through a feedback loop [46,27]. The phytochemical components of *F. capensis* leaves make it extremely promising to use natural antioxidants to counteract this damage [49,36].

2. Materials and methods

2.1. Plant material gathering and preparation

Dr. Onyebuchi Ephraim Nwankwo, a plant taxonomist from the Department of Applied Biology at Ebonyi State University, Abakaliki, Nigeria, classified the wild, free-growing *F. capensis* leaves we collected in Abakaliki, Ebonyi State, in April 2022. The plant was given the voucher number EBSU-I-112, and a portion of it was placed in the herbarium of the biology department at Ebonyi State University in Nigeria. We collected two (2) kilogrammes of fresh *F. capensis* leaves, washed, air-dried, and ground them to a fine powder using an electrical grinder. We soaked approximately 800 g of the powder in 8 litres of distilled water for 24 hours at room temperature, occasionally stirring. We dried the resulting filtrate in an oven at 55 °C for 48 hours and then lyophilised it in a freeze dryer for 72 hours to obtain a brown crude extract, known as LALEFC.

We used the phytochemical analytical guide by Balamurugan et al. [9] to determine the alkaloids, flavonoids, phenols, terpenoids, steroids, tannins, saponins, glycosides, and HCN.

2.2. Acute toxicity of LALEFC

We used two (2)-month-old male albino Wistar rats. We administered 4000 mg/kg LALEFC orally to a male rat after seven days of acclimatization, following an overnight fast. We meticulously examined the animals for the first half an hour after LALEFC administration for changes in behavioural or physical patterns. We observed the samples for the next 24 hours and then every day for the next 14 days. Following their survival, we fasted the other four rats for 4 hours, administered the same LALEFC dose, and monitored them for the next 14 days for any signs of toxicity. Overall, at the limit test dose of 4000 mg/kg, the animals did not exhibit any gross behavioural or physical alterations, such as a decrease in feeding, motor activities, or hair erection. This led to the selection of OECD guideline no. 425 is 10 % of the maximum dose (4000 mg/kg) as the middle dose. We took half of it (200 mg) at the low dose and twice it (800 mg) at the higher dose [37,13].

2.3. Experimental animals and design

The Ebonyi State University's Research, Innovation, and Institutional Ethics Committee (EBSU/BCH/ET/22/018) oversaw and authorised this work. We adhered to the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, updated in 1996) for all animal study protocols, as reported by Kalariya et al. [20] and Tusubra et al. [44]. We procured thirty-five male Wistar rats (2–3 months old) from the Animal Unit of the Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Nigeria, and acclimatised them for two weeks. We then randomly assigned the rats to 5 groups, each consisting of 7 rats. On day 14, rats in Group 2 (the carboplatin control) were given 60 mg/kg of body weight (bw) and intraperitoneal (ip) carboplatin to hurt their livers. We administered 200 (low dose (LD)), 400 (intermediate dose (ID)), and 800 (high dose (HD)) mg/kg b.w. of LALEFC to Groups 3–5 rats for 17 days and added 60 mg/kg b.w. of carboplatin on day 14 only. We referred to the LALEFC dosages administered to groups 3, 4, and 5 as low, medium, and high, respectively.

2.4. Tissue sample collection

After 17 days of the study, we starved the rats overnight and euthanised them with a carbon dioxide overdose. Following a laparotomy, we cleansed and dried the liver and kidneys in cold, normal saline. Homogenise the liver or kidneys in 0.1 M phosphate-buffered saline (1:5 w/v, pH 6.4) and centrifuge for 20 min at 4000 ×g. We measured antioxidant enzyme activities, GSH, ROS, malondialdehyde, and pro-inflammatory markers in the supernatants.

2.5. Determination of oxidative stress markers

We measured the oxidative stress markers using standard procedures. We determined the activity of CAT using Aebi's methods [3]. We assayed SOD using the methods of Marklund and Marklund [28]. We estimated GPx activity using the method of Flohe and Gunzler [16]. The method of Jollow et al. [19] determined the GSH levels, while Ohkawa et al. [34] measured the thiobarbituric acid reactive substances (TBARS) to estimate MDA.

2.6. Determination of inflammatory markers and caspase-3 activity

We used rat's enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's protocols, to determine the levels of IL-1, IL-6, TNF-U, and NF-B. We also measured Caspase-3 activity in cell lysates spectrophotometrically using rat assay kits, adhering to the manufacturer's recommendations.

2.6.1. Histological examination of the liver

The prior study's instructions guided the preparation of tissue for histological investigations [48,51]. We preserved the liver tissues in 10 % formaldehyde for three days after their removal. We used an automated tissue processor and a rotary microtome to trim the fixed tissues for processing and sectioning, respectively. Fischer et al. [15]

used haematoxylin and eosin (H and E) to stain the tissue slices of the liver and kidney. We captured the photomicrographs using a light microscope (Olympus BH2) equipped with a Nikon Digital Sight DS-L1 (Nikon Corporation, Japan).

2.6.2. Statistical analysis

All data were analysed using GraphPad Prism 5, version 8. The mean and standard deviation were used. The data means were compared using a post-hoc one-way ANOVA at $p<0.05$. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at $p<0.05$.

3. Results

Phytochemical Constituents of Lyophilized Aqueous Leaf-extract of *F. capensis*

The following phytochemical components were found in the lyophilised aqueous leaf extract of F. capensis, in order of their concentration in mg/100 g: The phytochemical ingredients occur in the following order: There were a lot of phenols (1577.72 ± 0.008), flavonoids (1253.13 ± 0.007), tannins (878.97 ± 0.007), alkaloids (652.66 ± 0.007), glycosides (314.39 ± 0.011), and terpenoids (261.18 ± 0.154). But there were also very small amounts of steroids (0.573 ± 0.062), saponins (0.370 ± 0.003), and HCN (0.254.00 ± 0.006), as shown in Fig. 1.

3.1. Effects of lyophilized aqueous leaf-extract of F. capensis on oxidative stress and inflammatory markers

When the study animals were given carboplatin, the level of GSH and the activities of CAT, SOD, and GPx dropped by a large amount (Figs. 2–5). It also increased the levels of ROS and MDA when compared to the animals in the normal control group (Figs. 6 and 7). However, the combination of LALEC and carboplatin markedly elevated the levels of GSH and the activities of CAT, SOD, and GPx, while the levels of ROS and MDA decreased compared to the carboplatin group (Figs. 2–7).

Also, it was discovered that giving rats carboplatin greatly raised the amounts of IL-1β, IL-6β, TNF-α, NF-κB, and caspase-3 compared to the healthy control group. When rats were given LALEFC along with carboplatin, however, the amounts of IL-1β, IL-6β, TNF-α, NF-κB, and caspase-3 activity were much lower than when rats were only given

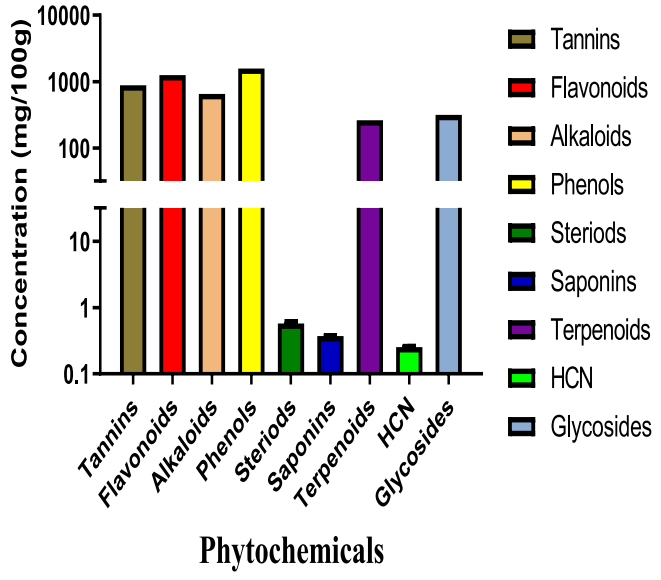

Fig. 1. Phytochemical composition of lyophilized aqueous leaf extract of *Ficus capensis*. Data are shown as mean ± S.D (n=3).

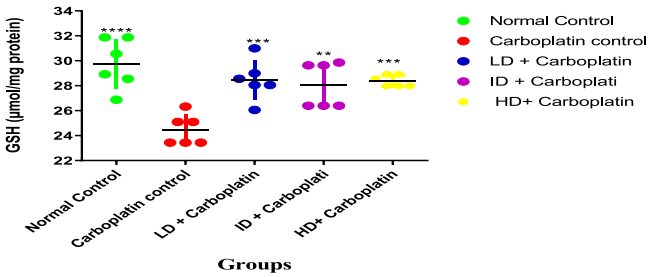

Fig. 2. Effects of LALEFC on Liver GSH Level in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

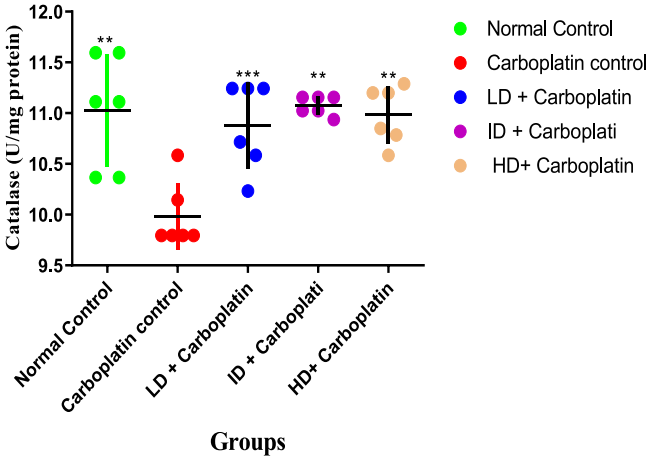

Fig. 3. Effect of LALEFC on Liver CAT Activity in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

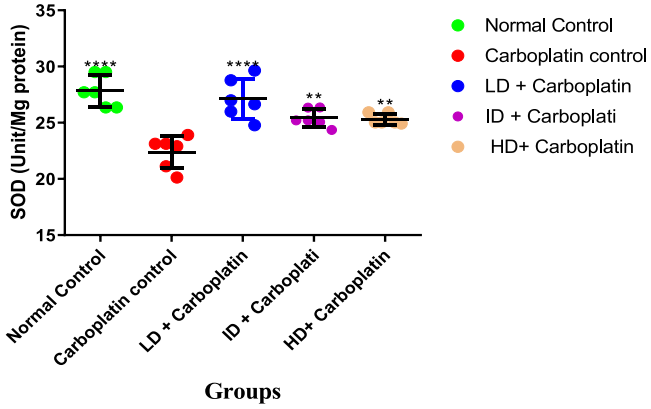

Fig. 4. Effect of LALEFC on Liver SOD Activity in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

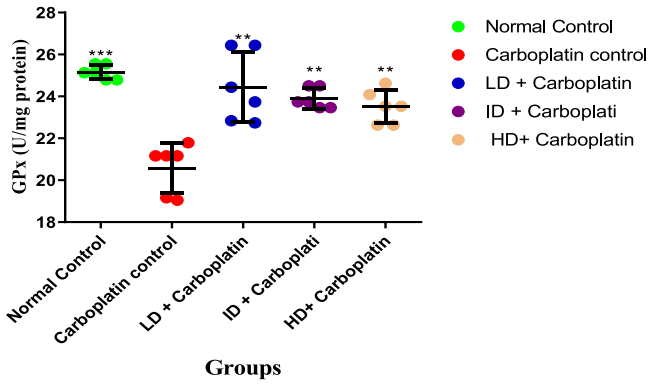

Fig. 5. Effect of LALEFC on Liver GPx Activity in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

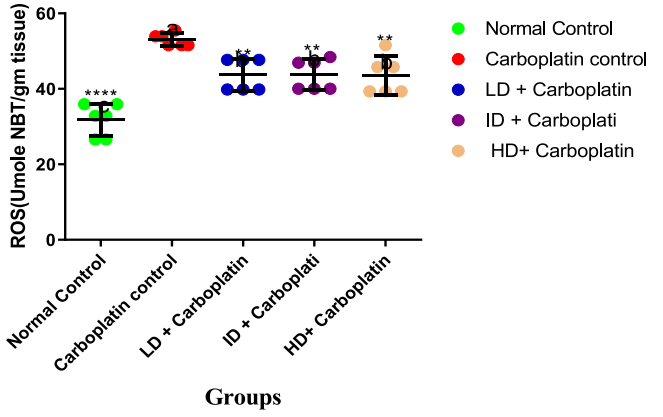

Fig. 6. Effect of LALEFC on Liver ROS Level in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

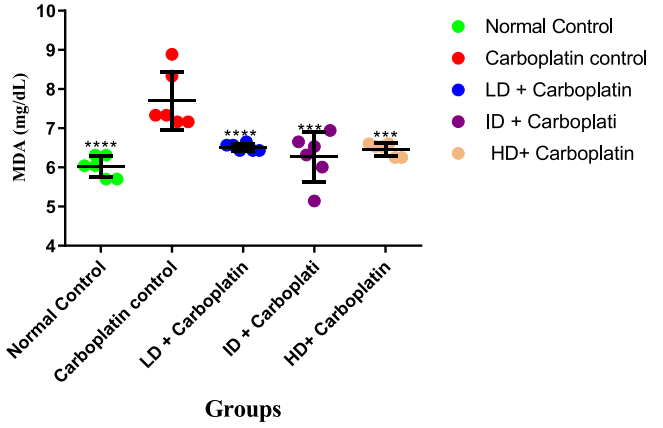

Fig. 7. Effect of LALEFC on Liver MDA Level in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

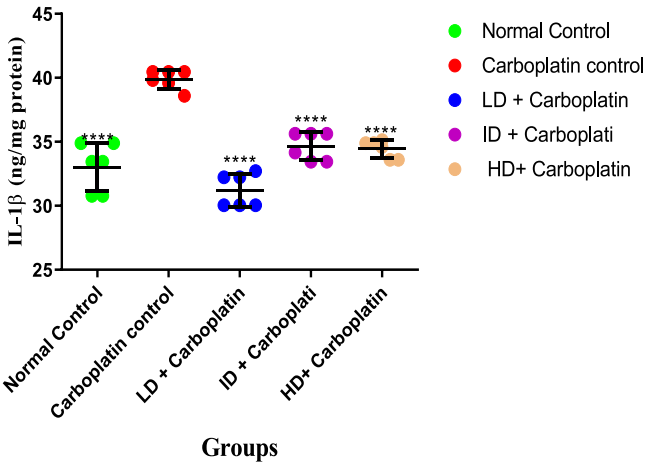

Fig. 8. Effect of LALEFC on Liver Interleukin-1β Level in carboplatin-induced liver injury Wistar in albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

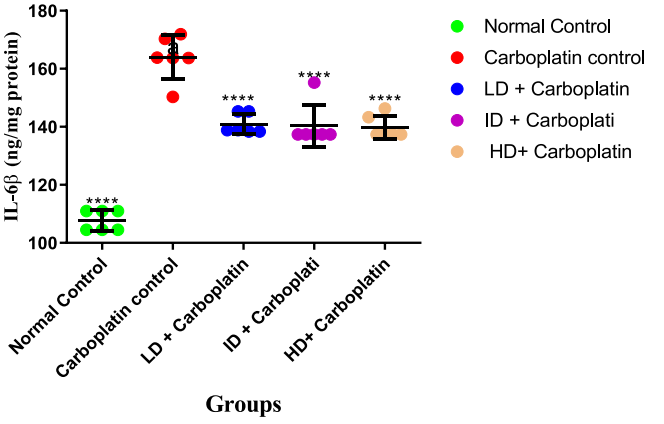

Fig. 9. Effect of LALEFC on Liver Interleukin-6β Level in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

carboplatin (Figs. 8–12).

3.2. Effects of lyophilized aqueous leaf-extract of F. capensis on histology of the liver

As illustrated in Fig. 13, the liver section from group 1 (normal control) has a central vein and hepatocytes (H) that are well-perfused and normal. The carboplatin-treated group only had severe damage and long-lasting groups of an inflammatory cell (IHAIC) inside the liver. The overall appearance is consistent with chronic hepatitis. The rats that received a small amount of LALEFC and carboplatin showed some mild healing in their livers. There was also a moderate portal aggregate of inflammatory cells (PAIC) and congestion of the portal vein (CPV). On the other hand, rats treated with carboplatin and a medium or high dose of LALEFC healed more slowly due to poor blood flow, clogged central veins, and mild fatty changes (FC) in their liver cells.

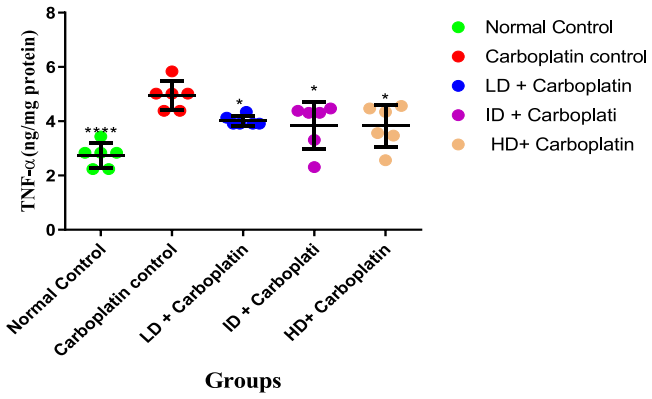

Fig. 10. Effect of LALEFC on Liver Tumor Necrosis Factor-Alpha Level in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p< 0.0001, ***p< 0.0006, **p< 0.003, **p< 0.0045. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

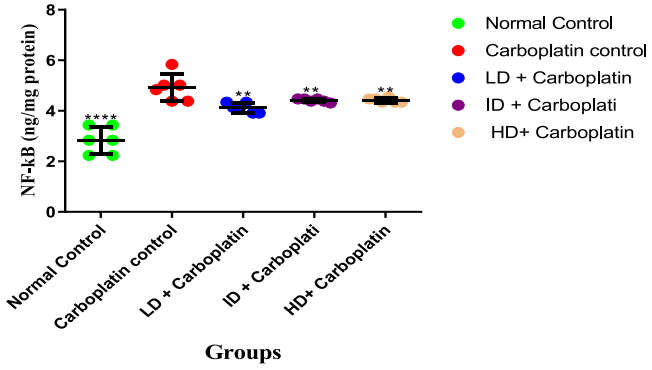

Fig. 11. Effects of LALEFC on Liver Nuclear Factor Kappa B Level in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

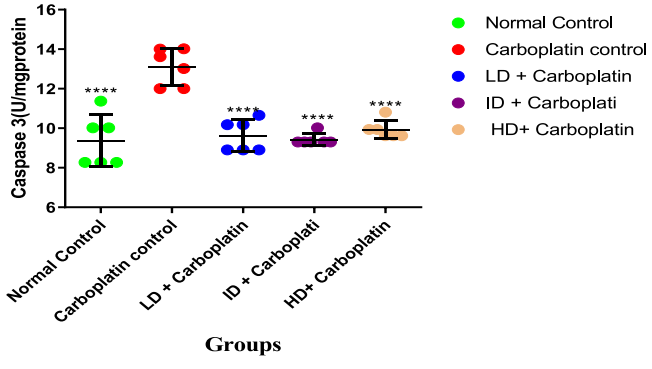

Fig. 12. Effects of LALEFC on Liver Caspase-3 Activity in carboplatin-induced liver injury in Wistar albino rats. The mean(n=6) values with asterisk ****p<0.0001, ***p<0.0006, **p<0.003. Groups' mean values were compared to group B (carboplatin only) using Dunnett's multiple comparisons test, revealing significant differences at p<0.05. LD (low dose), ID (intermediate dose), and HD (High dose).

4. Discussion

There was a total of 1577.72 ± 0.008 phenols in 100 g of the lyophilised aqueous leaf extract of *Ficus capensis*. These were followed by flavonoids (1253.13 ± 0.007), tannins (878.97 ± 0.00), alkaloids (652.66 ± 0.007), glycosides (314.39 ± 0.011), and terpenoids (261.18 ± 0.154). Steroids (0.573 ± 0.062), saponins (0.370 ± 0.003), and HCN (0.254.00 ± 0.006) were also present in small amounts (Fig. 1). These findings are consistent with those of Aja et al. [5], who reported high amounts of flavonoids, alkaloids, saponins, and tannins in *D. rotundifolia* root and leaf. This study also backs up what Ugwu et al. [45] reported about the flavonoids, steroids, terpenoids, tannins, and alkaloids found in the ethanol root extract and fractions of *S. jollyanum*. Since *F. carpensis* is rich in phenols and flavonoids that possess antioxidant capacity, it may prevent several diseases, including oxidative stress and inflammatory-related disorders. The presence of alkaloids may explain this plant's pharmacology, such as CNS stimulants, topical anaesthetics, strong painkillers, and anti-puretics.

In this study, administering carboplatin to rats significantly reduced GSH levels, activities of SOD, CAT, and GPx, and increased ROS and MDA levels in the rats. But when LALEFC and carboplatin were mixed, the levels of GSH and the activities of CAT, SOD, and GPx went up a lot compared to the carboplatin group. On the other hand, ROS and MDA levels went down. Obiajulu et al. [33] also observed an increase in SOD, GPx, and CAT activity in the livers of animals given 200 mg/kg (b.w.) of *F. capensis* and 400 mg/kg (b.w.) of *C. aconitifolius*. Additionally, Obiajulu et al. [33] observed that in experimental rats, liver toxicity stimulation led to a significant (p<0.05) increase in the MDA level. Still, the MDA level went down significantly (p<0.05) when the extracts from *F. capensis* and *C. aconitifolius* were given together. Other earlier studies [6,4,46,27] are in support of these present results.

The liver cells encourage these endogenous antioxidants—GSH, SOD, CAT, and GPx—to combat abnormal oxidative stress [27]. The extract appears to have the potential to treat liver damage resulting from carboplatin, as it reversed the drug-induced decline in GSH levels and activity of SOD, CAT, and GPx while also reducing ROS levels. Lipid peroxidation produces MDA, which is a sign of the majority of oxidative stress in the body. When compared to the normal control group, the liver MDA level in the carboplatin group increased considerably. It's intriguing to note that the groups that received LLEFCs and omega-3 fatty acids showed a significant decrease in MDA levels. López-Mejía et al. [27] found the same thing that we did: lipid peroxidation products increase redox imbalance, lower GSH levels, and then lower GPx activity after carboplatin is given. However, LALEFC, or omega-3 fatty acids, was able to restore this impact. The administration of carboplatin to the groups may have resulted in increased lipid peroxidation in their livers, as the drug generates free radicals that reduce the body's antioxidant levels. The liver of the LALEFC-carboplatin group had higher levels of GSH and antioxidant enzymes and lower levels of MDA, which was different. This suggests that this plant could potentially counteract the hepatotoxicity of carboplatin by enhancing the liver's antioxidant enzyme levels.

Thus, research has connected an increase in oxidative stress to inflammation, a physiological reaction to cell damage [6]. Carboplatin greatly raised the levels of TNF-α, NF-κB, IL-1β, and IL-6 in Wistar albino rats compared to the normal control group. It also increased the activity of caspase-3. In contrast to the carboplatin group, the levels of NF-κB, TNF-α, IL-1β, and IL-6β, as well as caspase-3 activity, went down a lot when LALEFC was mixed with carboplatin. This is consistent with previous research demonstrating the interaction between oxidative stress, inflammation, and apoptosis [14,18,32]. All cells can normally turn on or off NF-B, a redox-sensitive nuclear transcription factor that regulates numerous genes implicated in inflammation [24]. Carboplatin can cause oxidative stress, which can lead to the production of an inhibitor of kappa B kinase (IKK). IKK then breaks down the inhibitor of kappa B (IB) and makes it easier for NF-kB to bind to DNA. This is because many

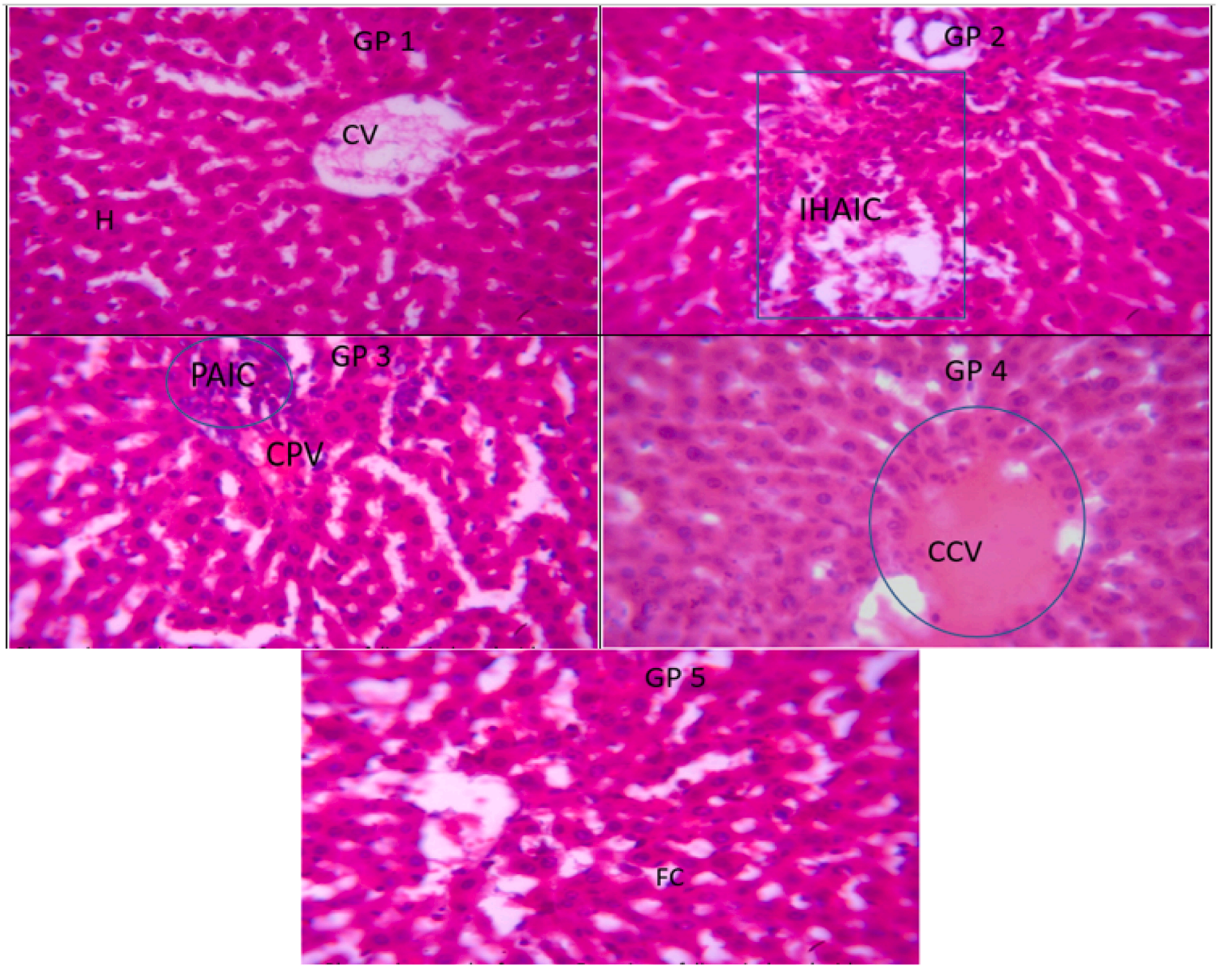

Fig. 13. Effects of Lyophilized Aqueous Leaf-extract of F. capensis or carboplatin on the histology of the liver(x400).

target genes, such as those that produce TNF-α, IL-2β, and IL-6β, are controlled by activated NF-κB, which travels from the cytoplasm to the nucleus. However, activating the NF-B signalling pathway significantly impacts cellular toxicity [50]. Blocking the NF-B signalling pathway has been shown to stop the production of too much IL-6, TNF-β, IL-1, and NO [21,25,2].

Caspases, which are essential, mediate apoptosis, or programmed cell death. Regular triggers trigger Caspase-3, a death protease that cleaves a variety of important cellular proteins. As part of this study, giving rats carboplatin increased caspase-3 activity significantly. However, giving rats carboplatin and LALEFC together decreased caspase-3 expression significantly. Carboplatin turned on Caspase-3 by causing a redox imbalance and the production of more cytokines (IL-6β, TNF-α, and IL-1β). Administering LALEFC and carboplatin together prevented oxidative stress and NF-B activation. This lowered the expression of proinflammatory cytokines, which in turn decreased the amount of caspase-3 in Sertoli and Leydig cells. The results back up earlier research that found that carboplatin raises Caspase-3, which kills cells in mice [22,26] and goat testis Sertoli cells [52]. Because it has a lot of healthy nutrients, LALEFC can lower NF-κB, IL-2β, IL-6β, TNF-α, and Caspase-3 in albino rats whose livers have been damaged by carboplatin. This means that it can help with antioxidant, inflammatory, and apoptotic processes. The effects of carboplatin or LALEFC on antioxidants and inflammatory markers were consistent with the liver histology results.

5. Conclusion

The study finds that lyophilised aqueous leaf extract from *F. capensis*, which is high in phenols and other phytochemicals, effectively reduces liver damage caused by carboplatin by blocking redox imbalance and the NF-Kb/IL-β1 and 6/TNF-α/Caspas-3 signalling pathways. This restores normal liver architecture in rats. This suggests *F. capensis* has significant therapeutic potential for protecting against chemotherapy-induced liver toxicity.

Funding

No funding was received for this study.

CRediT authorship contribution statement

Patrick Maduabuchi Aja: Writing – review & editing, Supervision, Software, Project administration, Methodology, Formal analysis. **Olufunke Onaadepo:** Writing – review & editing, Visualization, Validation, Supervision, Resources. **Peter Chinedu Agu:** Writing – original draft, Validation, Project administration, Data curation. **Angela Mumbua Musyoka:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Data curation. **Ilemobayo Victor Fasogbon:** Software, Resources, Investigation, Formal analysis, Data curation. **Josiah Aja Nwadibia:** Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Udu Ama Ibiam:** Software, Resources, Methodology, Investigation, Data curation. **Ezebuilo Ugbala Ekpono:** Visualization, Validation, Methodology, Investigation, Data curation. **Ejike Daniel Eze:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis. **Obasi Uche Orji:** Visualization,

Validation, Project administration, Formal analysis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Aja, Patrick Maduabuchi Aja reports equipment, drugs, or supplies was provided by Ebonyi State University Faculty of Biological Sciences. Aja, Patrick Maduabuchi reports a relationship with Kampala International University - Western Campus that includes: employment. Patrick Maduabuchi Aja has patent pending to Aja, Patrick Maduabuchi. There is no other information on conflict of interest. Thank you If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgements

The authors thank the Almighty God, the source of knowledge; Mr. Charles, the animal house officer; and Mr. O. Ugwu, the technician, for their cooperation.

References

[1] N.K. Achi, C. Onyeabo, C.A. Ekeleme-Egedigwe, J.C. Onyeanula, Phytochemical, proximate analysis, vitamin and mineral composition of aqueous extract of Ficus capensis leaves in South Eastern Nigeria, J. Appl. Pharm. Sci. 7 (3) (2017) 117–122.

[2] S.A. Adelakun, O.W. Akintunde, S.O. Jeje, O.A. Alao, Ameliorating and protective potential of 1-isothiocyanato-4-methyl sulfonyl butane on cisplatin induced oligozoospermia and testicular dysfunction via redox-inflammatory pathway: histomorphometric and immunohistochemical evaluation using proliferating cell nuclear antigen, Phytomedicine 2 (2) (2022) 100268.

[3] H.E. Aebi, in: H.U. Bergmeyer (Ed.), CAT. In: Methods of Enzymatic Analysis, 3rd ed., Deerfield Beach, Weinhein, 1983, pp. 273–285.

[4] P.C. Agu, P.M. Aja, E. Ekpono Ugbala, H.A. Ogwoni, E.M. Ezeh, P.C. Oscar-Amobi, A. Asuk Atamgba, O.G. Ani, J.N. Awoke, F.E. Nwite, et al., Cucumeropsis mannii seed oil (CMSO) attenuates alterations in testicular biochemistry and histology against Bisphenol a-induced toxicity in male Wister albino rats, Heliyon 8 (3) (2022) e09162.

[5] P.M. Aja, E.U. Alum, N.N. Ezeani, U.A. Ibiam, C. Egwu, Comparative phytochemical evaluation of Dissotis rotundifolia root and leaf. Global, Veterinaria 14 (3) (2015) 418–424.

[6] P.M. Aja, F.I. Izekwe, A.C. Famurewa, E.U. Ekpono, F.E. Nwite, I.O. Igwenyi, J. N. Awoke, O.G. Ani, C. Aloke, N.A. Obasi, et al., Hesperidin protects against cadmium-induced pancreatitis by modulating insulin secretion, redox imbalance and iNOS/NF-κB signaling in rats, Life Sci. 259 (2020) 118268.

[7] S.F. Akomolafe, G. Oboh, S.I. Oyeleye, A.A. Boligon, Aqueous extract from Ficus capensis leaves inhibits key enzymes linked to erectile dysfunction and prevent oxidative stress in rats' penile tissue, NFS journal. 2016 Oct 1;4:15-21, J. Nutr. Food Sci. 4 (2016) 15–21.

[8] M.N. Al-Seeni, H.A. El-Rabey, M.A. Zamzami, A.M. Alnefayee, The hepatoprotective activity of olive oil and Nigella sativa oil against CCl4 induced hepatotoxicity in male rats, BMC Complement. Altern. Med. 16 (2016) 1–14.

[9] V. Balamurugan, S. Fatima, S. Velurajan, A guide to phytochemical analysis, Int. J. Adv. Res. Innov. Ideas Educ. 5 (1) (2019) 236–245.

[10] H.K. Björnsson, E.S. Björnsson, Drug-induced liver injury: pathogenesis, epidemiology, clinical features, and practical management, Eur. J. Intern. Med. *97* (2022) 26–31.

[11] G. Ciarimboli, Anticancer platinum drugs update, Biomolecules 11 (11) (2021) 1637.

[12] O.A. Daikwo, J.A. Tende, S.M. Okey, E.D. Eze, A.S. Isa, The effect of aqueous extract of leaf of Ficus capensis on invivo leukocyte mobilization in Wistar rats, Br. J. Pharmacol. Toxicol. 3 (3) (2012) 110–114.

[13] C. Eleazu, I. Ezekwibe, M. Egbe, S. Saidu, K. Eleazu, C. Egedigwe, Dietary intake of boiled breadfruit (Treculia africana) seeds did not improve hyperglycemia in streptozotocin induced diabetic rats: effect on the oral glucose tolerance of normoglycemic rats, Acta Sci. Pol. Technol. Aliment 16 (2017) 93–99.

[14] A.C. Famurewa, N.T. Asogwa, P.M. Aja, G.G. Akunna, J.N. Awoke, C.A. Ekeleme-Egedigwe, E.K. Maduagwuna, A.M. Folawiyo, E.E. Besong, E.U. Ekpono, P. A. Nwoha, Moringa oleifera seed oil modulates redox imbalance and iNOS/NF-κB/caspase-3 signaling pathway to exert antioxidant, anti-inflammatory and antiapoptotic mechanisms against anticancer drug 5-fluorouracil-induced nephrotoxicity in rats, South Afr. J. Bot. 127 (2019) 96–103.

[15] A.H. Fischer, K.A. Jacobson, J. Rose, R. Zeller, Hematoxylin and eosin staining of tissue and cell sections, Cold Spring Harb. Protoc. 3 (5) (2008), https://doi.org/10.1101/PDB.PROT4986.

[16] L. Flohe, W.A. Gunzler, Analysis of glutathione peroxidase, Method Enzymol. 105 (1984) 114–121.

[17] J.O. Igoli, O.G. Ogaji, A. Tor-Aryiin, N.P. Igoli, Traditional medicinal practices amongst the Igede people of Nigeria, Part 2. African, J. Tradit. Complement 2 (2) (2005) 134–152.

[18] D. Jiao, Q. Jiang, Y. Liu, L. Ji, Nephroprotective effect of wogonin against cadmium-induced nephrotoxicity via inhibition of oxidative stress–induced MAPK and NF-kB pathway in Sprague Dawley rats, Hum. Exp. Toxicol. 38 (9) (2019) 1082–1091.

[19] D.J. Jollow, J.R. Michell, N. Zampaglione, J. Gillete, Bromobenzene-induced liver necrosis: Protective role of glutathione and evidence for 3,4-bromobenzene oxide as the hepatotoxic metabolite, Pharmacology 11 (1974) 151–169.

[20] M. Kalariya, R. Prajapati, S.K. Parmar, N. Sheth, Effect of hydroalcoholic extract of leaves of Colocasia esculenta on marble-burying behavior in mice: implications for obsessive–compulsive disorder, Pharm. Biol. 53 (8) (2015) 1239–1242.

[21] F.M. Kandemir, S. Yıldırım, S. Kucukler, C. Caglayan, E. Darendelioğlu, M. B. Dortbudak, Protective effects of morin against acrylamide-induced hepatotoxicity and nephrotoxicity: a multi-biomarker approach, Food Chem. Toxicol. 138 (2020) 111190.

[22] S. Kaur, S. Sadwal, Studies on the phytomodulatory potential of fenugreek (Trigonella foenum-graecum) on bisphenol-A induced testicular damage in mice, Andrologia 52 (2) (2020) e13492.

[23] M.S.A. Khan, I. Ahmad, Herbal medicine: current trends and future prospects. New Look to Phytomedicine, Academic Press, 2019, pp. 3–13.

[24] I.G. Ko, J.J. Jin, L. Hwang, S.H. Kim, C.J. Kim, J.H. Han, S. Lee, H.I. Kim, H.P. Shin, J.W. Jeon, Polydeoxyribonucleotide exerts protective effect against CCl4-induced acute liver injury through inactivation of NF-κB/MAPK signaling pathway in mice, Int. J. Mol. Sci. 21 (21) (2020) 7894.

[25] S. Küçükler, F.M. Kandemir, S. Özdemir, S. Çomaklı, C. Caglayan, Protective effects of rutin against deltamethrin-induced hepatotoxicity and nephrotoxicity in rats via regulation of oxidative stress, inflammation, and apoptosis, Environ. Sci. Pollut. Res. 28 (2021) 62975–62990.

[26] X. Li, Z. Lv, J. Chen, E. Nepovimova, M. Long, W. Wu, K. Kuca, Bacillus amyloliquefaciens B10 can alleviate liver apoptosis and oxidative stress induced by aflatoxin B1, Food Chem. Toxicol. 151 (2021) 112124.

[27] A. López-Mejía, L.G. Ortega-Pérez, O.R. Magana-Rodriguez, L.A. Ayala-Ruiz, J. S. Pinón-Simental, D.G. Hernández, P. Rios-Chavez, Protective effect of Callistemon citrinus on oxidative stress in rats with 1, 2-dimethylhydrazine-induced colon cancer, Biomed. Pharmacother. 142 (2021) 112070.

[28] S. Marklund, G. Marklund, Involvement of the superoxide anion radical in the auto oxidation of pyrogallol and a convenient assay for superoxide dismutase, Eur. J. Biochem. 47 (1974) 469–474.

[29] P.T. Mpiana, V. Mudogo, D.S. Tshibangu, E.K. Kitwa, A.B. Kanangila, J.B. Lumbu, K.N. Ngbolua, E.K. Atibu, M.K. Kakule, Antisickling activity of anthocyanins from Bombax pentadrum, Ficus capensis and Ziziphus mucronata: photodegradation effect, J. Ethnopharmacol. 120 (2008) 413–418.

[30] A. Najmi, S.A. Javed, M. Al Bratty, H.A. Alhazmi, Modern approaches in the discovery and development of plant-based natural products and their analogues as potential therapeutic agents, Molecules 27 (2) (2022) 349.

[31] N.N. Njoku-Oji, C.V. Nwike, U. Dimkpa, N.O. Ifegwu, L.C. Anike, S.O. Maduka, O. A. Sobanke, R.C. Uchefuna, Hematological changes following oral administration of aqueous leaf extract of Ficus capensis in albino rats, Int. Blood Res. Rev. 5 (1) (2016) 1–7.

[32] V.U. Nna, G.A. Ujah, J.B. Suleiman, M. Mohamed, C. Nwokocha, T.J. Akpan, H. C. Ekuma, V.V. Fubara, C.B. Kekung-Asu, E.E. Osim, Tert-butylhydroquinone preserve testicular steroidogenesis and spermatogenesis in cisplatin-intoxicated rats by targeting oxidative stress, inflammation and apoptosis, Toxicology 441 (2020) 152528.

[33] E. Obiajulu Christian, E.F. Chukwuemeka, Antidiabetic and modulatory effect of ethanol extract of neem Leaf on Some essential biochemical parameters of streptozotocin-induced diabetic rats, Int. J. Biochem. Res. Rev. 28 (4) (2020) 1–11.

[34] H. Ohkawa, N. Ohishi, K. Yagi, Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction, Ann. Biochem. 95 (1979) 351–358.

[35] R.N. Okigbo, U.E. Eme, S. Ogbogu, Biodiversity and conservation of medicinal and aromatic plants in Africa, Biotechnol. Mol. Biol. Revis. 3 (6) (2008) 127–134.

[36] J.D. Olowokudejo, A.B. Kadiri, V.A. Travih, An ethnobotanical survey of herbal markets and medicinal plants in Lagos State of Nigeria, Ethnobot. Leafl. 12 (2008) 851–865.

[37] Organisation for Economic Co-operation and Development. 2008. Test No. 425: acute oral toxicity: up-and-down procedure. OECD publishing.

[38] G.T.O. Otitoju, J.U. Nwamarah, O. Otitoju, L.U. Iyeghe, Nutrient composition of some lesser known green leafy vegetables in Nsukka L.G.A of Enugu State, J. Biodivers. Environ. Sci. 4 (4) (2014) 233–239.

[39] O.J. Owolabi, Active ileum relaxant fractions from the leaves of Ficus capensis Thunb (Moraceae), Nigerian J. Pharm. Sci. 12 (1) (2013) 1–7.

[40] O.J. Owolabi, Z.A. Nworgu, A. Falodun, B.A. Ayinde, C.N. Nwako, Evaluation of tocolytic activity of ethanol extract of the stem bark of Ficus capensis Thunb. (Moraceae), Acta Pol. Pharm. Drug Res. 66 (3) (2009) 293–296.

[41] S.B. Oyeleke, B.E.N. Dauda, O.A. Boye, Antibacterial activity of Ficus capensis, Afr. J. Biotechnol. 7 (10) (2008) 1414–1417.

[42] E.O.J. Ozioma, O.A.N. Chinwe, Herbal medicines in African traditional medicine, Herb. Med. 10 (2019) 191–214.
[43] A. Ramde-Tiendrebeogo, A. Tibiri, A. Hilou, O.M. Lomp, H. Millogo-Kone, O. G. Nacoulma, P. Guissou, Antioxidative and antibacterial activities of phenolic compounds from Ficus sur Forssk and Ficus sycomorus. Potential for sickle cell disease treatment in Burkina Faso, Int. J. Biol. Chem. Sci. 6 (1) (2012) 328–336.
[44] D. Tusubira, P.M. Aja, J. Munezero, F. Ssedyabane, N. Namale, J.E. Ifie, P.C. Agu, C.O. Ajayi, J. Okoboi, Safety profile of colocasia esculenta tuber extracts in benign prostate hyperplasia, BMC Complement. Med. Ther. 23 (1) (2023) 187.
[45] O.P.C. Ugwu, E.U. Alum, M.B. Okon, P.M. Aja, E.I. Obeagu, E.C. Onyeneke, Anti-nutritional and gas chromatography-mass spectrometry (GC-MS) analysis of ethanol root extract and fractions of Sphenocentrum jollyanum, RPS Pharm. Pharmacol. Rep. 2 (2) (2023) rqad007.
[46] H. Ullah, A. Khan, M.W. Baig, N. Ullah, N. Ahmed, M.K. Tipu, H. Ali, S. Khan, Poncirin attenuates CCL4-induced liver injury through inhibition of oxidative stress and inflammatory cytokines in mice, BMC Complement. Med. Ther. 20 (1) (2020) 1–14.
[47] B.O. Umeokoli, F.A. Onyegbule, T.H. Gugu, S.O. Igboeme, Evaluation of the erythropoietic and anti-sickling properties of Ficus capensis leaf extract in the treatment of anaemia, Plant Med. 79 (2013) 99–102.
[48] I. Usman, A. Buraimoh, A. Ibegbu, Histological and biochemical studies of Tamarindus indica pulp extract on the cerebral cortex in prenatal ethanol exposure in Wistar rats, J. Exp. Clin. Anat. 15 (2) (2016) 96, https://doi.org/10.4103/1596-2393.200919.
[49] N.M. Uzoekwe, J.J. Mohammed, Phytochemical, proximate and mineral contents of leaves and bark of Ficus capensis, J. Appl. Sci. Environ. Manag. 8 (4) (2015) 125–129.
[50] M. Yan, L. Guo, Y. Yang, B. Zhang, Z. Hou, Y. Gao, H. Gu, H. Gong, Glycyrrhetinic acid protects α-naphthylisothiocyanate-induced cholestasis through regulating transporters, inflammation and apoptosis, Front. Pharmacol. 12 (2021) 701240.
[51] H.R. Yusuf, S.A. Musa, A.N. Agbon, E.D. Eze, A.A. Okesina, I. Onanuga, T. Pius, V. Archibong, M.E.F. Diaz, J.J. Ochieng, N. Kusiima, B.Y. Sunday, I.M. Usman, Hepatoprotective potential of Tamarindus indica following prenatal aluminum exposure in Wistar rat pups, Toxicol. Rep. 10 (2023) 376–381, https://doi.org/10.1016/J.TOXREP.2023.03.002.
[52] L. Zhang, X. Ji, F. Ding, X. Wu, N. Tang, Q. Wu, Apoptosis and blood-testis barrier disruption during male reproductive dysfunction induced by PAHs of different molecular weights, Environ. Pollut. 300 (2022) 118959 nflammatory cytokines in mice. BMC complementary medicine and therapies, 20(1), 1.