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Effect of ethanolic extracts of *Cymbopogon citratus* (Lemongrass), *Ocimum gratissimum*, and *Azadirachta indica* on the kidney function test, following Plasmodium berghei- induced malaria in mice

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Abstract

This study explored the effects of the antimalarial effects of *Cymbopogon citratus* (lemongrass), *Ocimum gratissimum*, and *Azadirachta indica* on the Kidney function test in wistar rats. Fifty male mice were purchased from a local market, animals were maintained with normal laboratory chow (Grower feed) and water ad libitium. The animals were acclimatized for two weeks before induction of the Plasmodium berghei and ethanolic leave extract of *Azadirachta indica*, *Cymbopogon citratus* and *Ocimum gratissimum*. Plasmodium berghei were inoculated intraperitoneally with 0.2ml blood suspension. Group A was the Negative control group, induced with Plasmodium berghei without any treatment. Group B was Positive control, received only food and water. Group C was induced with *P. berghei* and treated with (500 mg/kg) of *Azadirachta indica*. Group D was induced with *P. berghei* and treated with (100 mg/kg) ethanolic extract of *Cymbopogon citratus*. Group E was induced with *P. berghei* and treated with (500 mg/kg) ethanolic extract of *Cymbopogon citratus*. Group F was induced with *P. berghei* and treated with 100 mg/kg) ethanolic extract of *Ocimum gratissimum*. Group G was induced with *P. berghei* and treated with (500 mg/kg) ethanolic extract of *Ocimum gratissimum*. Group H was induced with *P. berghei* and treated with (100 mg/kg) ethanolic extract of *Azadirachta indica*. Group I was induced with *P. berghei* and treated with standard drug. Group J was induced with *P. berghei* and treated with (500 mg/kg) ethanolic extracts of the leaves (*Azadirachta indica*, *Cymbopogon citratus*, and *Ocimum gratissimum*). The Administration of the extract lasted for 7 days. This study demonstrated that infection with Plasmodium berghei significantly impairs kidney function, as evidenced by increased relative kidney weight, elevated levels of urea, uric acid, and creatinine, along with histological signs of renal damage. Treatment with ethanolic extracts of *Azadirachta indica, Cymbopogon citratus, and Ocimum gratissimum*—individually and in combination—significantly ameliorated these effects.

Keywords: Malaria; *Azadirachta indica; Cymbopogon citratus; Ocimum gratissimum*; Kidney Function

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1. Introduction

Malaria can cause life-threatening changes, as recurrent incidents can lead to life-threatening metabolic acidosis (Akinosoglou *et al.,* 2012; Al-Salahy *et al.,* 2016; White, 2018). The kidneys are important physiologic-anatomy organ with metabolic and excretory function, with the nephron been the functional units consisting of the glomerulus (Rayner *et al.,* 2016). The kidneys are important complex metabolic organ that play a role in homeostasis and involved deeply in the plasma osmolarity by modulating the amount of water, solutes, and electrolytes in the blood (Ogobuiro and Tuma, 2019). The kidneys are involved in the filtration process through a specialized capillary network through the glomerular barrier, which yields the filtrated substances into Bowman's capsule space, and then into the renal tubules (Rayner *et al.,* 2016). Creatinine is the breakdown product of creatine phosphate released from skeletal muscle at a steady state. It is filtered by the glomerulus and a small amount is also secreted into the glomerular filtrate by the proximal tubules (Kene *et al.,* 2021). Urea an organic compound is involved deeply in nitrogen metabolism as well as nitrogen-containing compounds; and a significant waste product from dietary protein, which is filtered freely into urine by the kidneys (Dorgalaleh *et al.,* 2013; Ossman *et al.,* 2014). Urea is the major nitrogenous end product of metabolic breakdown of protein in humans. It is dissolved in the blood and transported and excreted by the kidney as a component of urine (Higgins, 2016).

Azadirachta indica is called the “Divine tree” which is attributed to its diverse medicinal values to humanity because of its secondary metabolites (Islas *et al.,* 2020).

Cymbopogon citratus, Stapf (Lemongrass) is used in teas, soups, and curries, and is suitable for poultry, fish, and seafood. Cymbopogon originated from the Greek word "kymbe - pogon" meaning boat-beard (due to its flower spike configuration) and *citratus* (Latin) means lemon-scented leaves (Shah *et al.,* 2011).

Ocimum gratissimum (OG) is a medicinal plant widely grown in tropical and subtropical regions with the leaf decoction usually taken in folk medicine to enhance erectile performance in men although the probable mechanism of actions remains undetermined (Ojo *et al.,*2019).

2. Material and methods

2.1. Ethical Approval

Ethical approval was obtained from the Animal ethics committee, Abia State University, Uturu.

2.2. Plant Collection

Samples of *Azadirachta indica, Cymbopogon citratus* and *Ocimum gratissimum* were harvested from a farm at Okofia Community, Otolo in Nnewi, Anambra state. The botanical identification and authentication were confirmed in the herbarium of Department of Botany, Nnamdi Azikiwe University, Awka, Anambra State.

2.3. Plant Extraction

Azadirachta indica, Cymbopogon citratus and *Ocimum gratissimum* leaves were washed in running tap water to remove dirt and air-dried under ambient temperature. The dried leaves were milled into a coarsely powdered form using a local blender. Two hundred and fifty grams of the dried leaves of *Azadirachta indica, Cymbopogon citratus* and *Ocimum gratissimum* were macerated in 1000 ml of 95 % Absolute Ethanol(BDH England) for 48 hours. It was filtered using a porcelain cloth and was further filtered using Whatman No 1 filter paper into a clean glass beaker. The filtrate was concentrated using a Rotatory Evaporator (TT-55 Techmel&Techmel, USA) and dried further using a Thermostat Oven (DHG 9021A PEC Medicals, USA) at 45 ^{0}C into a gel-like form. The extracts were preserved in airtight container and kept in a refrigerator for further usage. The extraction method was done with modifications as described according to the method employed by Al-Attar and Abu-Zeid, (2013).

2.4. Experimental design

Fifty male mice weighing 21-35g were obtained from the Animal House, Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Abia State University, Uturu. Animals were kept in standard cages at a room temperature of 27±2 °C. The animals were maintained with normal laboratory chow (Grower feed) and water ad libitium. The animals were acclimatized for two weeks before induction of the Plasmodium berghei and ethanolic leave extract of *Azadirachta indica, Cymbopogon citratus* and *Ocimum gratissimum*. The animals were kept on 12hours light and dark cycles.

Plasmodium berghei ANKA strain parasitized erythrocytes was obtained from donor mice (Department of Zoology, University of Nigeria, Nsukka). Blood was collected via ocular puncture and diluted in 1:20 of 0.9% normal saline. The mice were inoculated intraperitoneally with 0.2ml blood suspension (Basir *et al.,* 2012a). The animals were observed for four days without treatment, after which parasite level was estimated quantitatively as described by the method of Fidock *et al.,* (2004). The tail of the mice was punctured to collect small drops of blood, which was used to make a thin smear on a slide. The smears were allowed to dry and fixed with methanol and stained with 10 % Leishman stain on the side containing the smear for a period of 5-10 minutes after which it was rinsed with distilled water and allow to air dry. Immersion oil was dropped on the slide to increase its refractive index, and the slide were viewed under a microscope with a ×100 magnification field *(Fidock et al.,* 2004; Okokon *et al.,* 2022).

- Group A was the Negative control group, induced with Plasmodium berghei without any treatment.
- Group B was Positive control, received only food and water
- Group C was induced with *P. berghei* and treated with (500 mg/kg) of *Azadirachta indica.*
- Group D was induced with *P. berghei* and treated with (100 mg/kg) ethanolic extract of *Cymbopogon citratus*.
- Group E was induced with *P. berghei* and treated with (500mg/kg) ethanolic extract of *Cymbopogon citratus*
- Group F was induced with *P. berghei* and treated with 100mg/kg) ethanolic extract of *Ocimum gratissimum*
- Group G was induced with *P. berghei* and treated with (500mng/kg) ethanolic extract of *Ocimum gratissimum*.
- Group H was induced with *P. berghei* and treated with (100mg/kg) ethanolic extract of *Azadirachta indica*.
- Group I was induced with *P. berghei* and treated with standard drug.
- Group J was induced with *P. berghei* and treated with (500mg/kg) ethanolic extracts of the leaves (*Azadirachta indica, Cymbopogon citratus,* and *Ocimum gratissimum*).

The Administration of the extract lasted for 7 days. Blood samples were collected via ocular puncture and sample sent to the lab for Kidney Function test. Kidney tissues were sent to the lab for histology. Data was analyzed using SPSS version 25.

3. Results

Table 1 Effect of ethanolic extract of *Cymbopogon citratus*, *Occimum Gratissimum*, And *Azadirachta indica* on relative kidney and liver weight following Plasmodium berghei induced toxicity

	Relative kidney weight (g)
	MEAN±SEM
Group A (Malaria only)	0.72±0.14
Group B (Normal control)	0.53±0.03[a]
Group C (Malaria + 500mg/kg EAI)	0.40±0.05 [a]
Group D (Malaria + 100mg/kg ECC)	0.79±0.00 [b]
Group E (Malaria + 500mg/kg ECC)	0.54±0.00 [a]
Group F (malaria + 100mg/kg EOG)	0.48±0.03 [a]
Group G (malaria + 500mg/kg EOG)	0.49±0.08 [a]
Group H (Malaria + 100mg/kg EAI)	0.49±0.04 [a]
Group I (Malaria + Standard drug)	0.61±0.00 [b]
Group J (Malaria + 500mg/kg EOG + EAI + ECC)	0.57±0.05 [b]
F-value	3.75

Data was analyzed using ANOVA, and values considered significant at $p<0.05$. SEM: Standard error of mean. EOG: ethanolic leaf extract of *Ocimum gratissimum*, EAI: ethanolic leaf extract of *Azadirachta indica*, ECC: ethanolic leaf extract of *Cymbopogon citratus* ([a]= significant, [b]= not significant)

Table 1 result revealed a significant increase in the relative kidney weight in-group A compared to B (*p=0.03*). Groups C, E, F, G, and H had a significant decrease (*p=0.01, p=0.04, p=0.01, p=0.01, p=0.01*), group D had an insignificant increase (*p=0.45*), in contrast groups I and J had an insignificant decrease (*p=0.18, p=0.09*) compared to group A.

Table 2 Effect of ethanolic extract of *Cymbopogon citratus*, *Ocimum gratissimum*, and *Azadirachta indica* on urea, uric acid, and creatinine level following Plasmodium berghei induced nephrotoxicity

	Urea level (mg/dl)	**Uric acid level (mg/dl)**	**Creatinine level (mg/dl)**
	MEAN±SEM	**MEAN±SEM**	**MEAN±SEM**
Group A (Malaria only)	90.33±2.91	5.03±0.19	4.82±0.04
Group B (Normal control)	60.76±0.03[a]	3.28±0.00 [a]	3.01±0.01 [a]
Group C (Malaria + 500mg/kg EAI)	68.28±4.05 [a]	3.55±0.13 [a]	3.07±0.02 [a]
Group D (Malaria + 100mg/kg ECC)	76.27±0.24 [a]	3.92±0.02 [a]	3.90±0.16 [a]
Group E (Malaria + 500mg/kg ECC)	74.64±0.24 [a]	3.89±0.01 [a]	3.03±0.01 [a]
Group F (malaria + 100mg/kg EOG)	73.68±0.59 [a]	3.66±0.05 [a]	3.93±0.02 [a]
Group G (malaria + 500mg/kg EOG)	72.19±0.24 [a]	3.57±0.00 [a]	3.86±0.38 [a]
Group H (Malaria + 100mg/kg EAI)	73.41±0.47 [a]	3.56±0.06 [a]	2.78±0.06 [a]
Group I (Malaria + Standard drug)	71.17±0.12 [a]	3.35±0.00 [a]	1.65±0.00 [a]
Group J (Malaria + 500mg/kg EOG + EAI + ECC)	72.80±0.12 [a]	3.54±0.05 [a]	1.70±0.01 [a]
F-value	21.24	41.24	55.29

Data was analyzed using ANOVA, and values considered significant at *p<0.05*. SEM: Standard error of mean. EOG: ethanolic leaf extract of *Ocimum gratissimum*, EAI: ethanolic leaf extract of *Azadirachta indica*, ECC: ethanolic leaf extract of *Cymbopogon citratus* ([a]= significant, [b]= not significant)

Table 2 result revealed a significant increase in the urea level in-group A compared to B (*p=0.02*). Groups C, D, E, F, G, H, I, and J had a significant decrease (*p=0.01, p=0.03, p=0.00, p=0.01, p=0.04, p=0.00, p=0.01*) compared to group A. The uric acid level showed a significant increase in the urea level in-group A compared to B (*p=0.00*). Groups C, D, E, F, G, H, I, and J had a significant decrease (*p=0.00, p=0.04, p=0.02, p=0.02, p=0.01, p=0.00, p=0.03*) compared to group A. The creatinine level showed a significant increase in the urea level in-group A compared to B (*p=0.04*). Groups C, D, E, F, G, H, I, and J had a significant decrease (*p=0.00, p=0.02, p=0.01, p=0.02, p=0.05, p=0.00, p=0.02*) compared to group A.

3.1 histopathological report

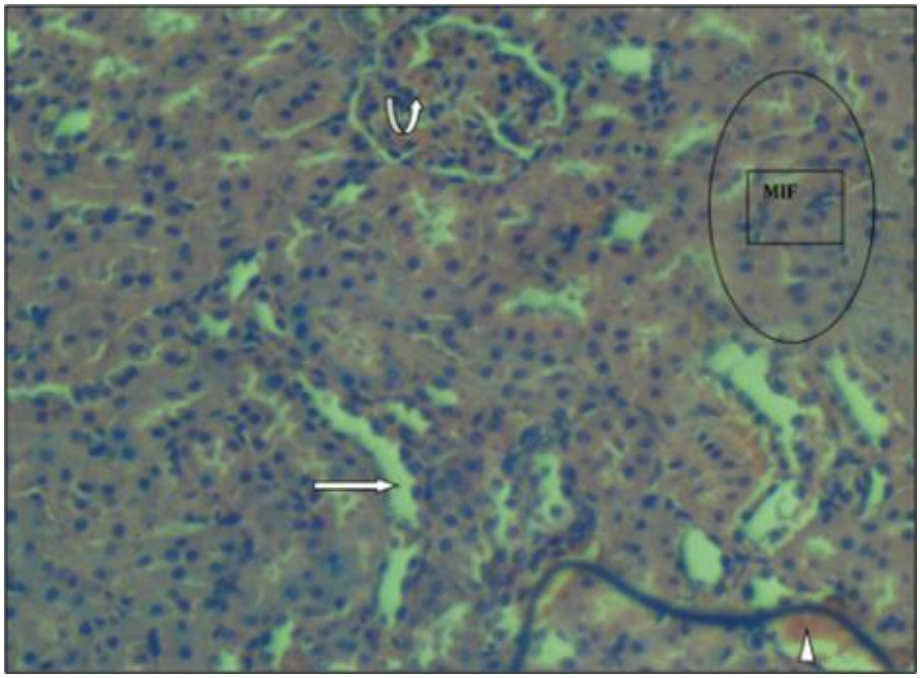

Figure 1 Group A received 0.2ml of *P. berghei* only. Photomicrograph section of the kidney shows mild inflammation (MIF) background, dilation of the renal tubules (arrow), mild shrunken glomerulus (curved arrow) and mild hemorrhage (arrow head). Stained with H and E (x 400)

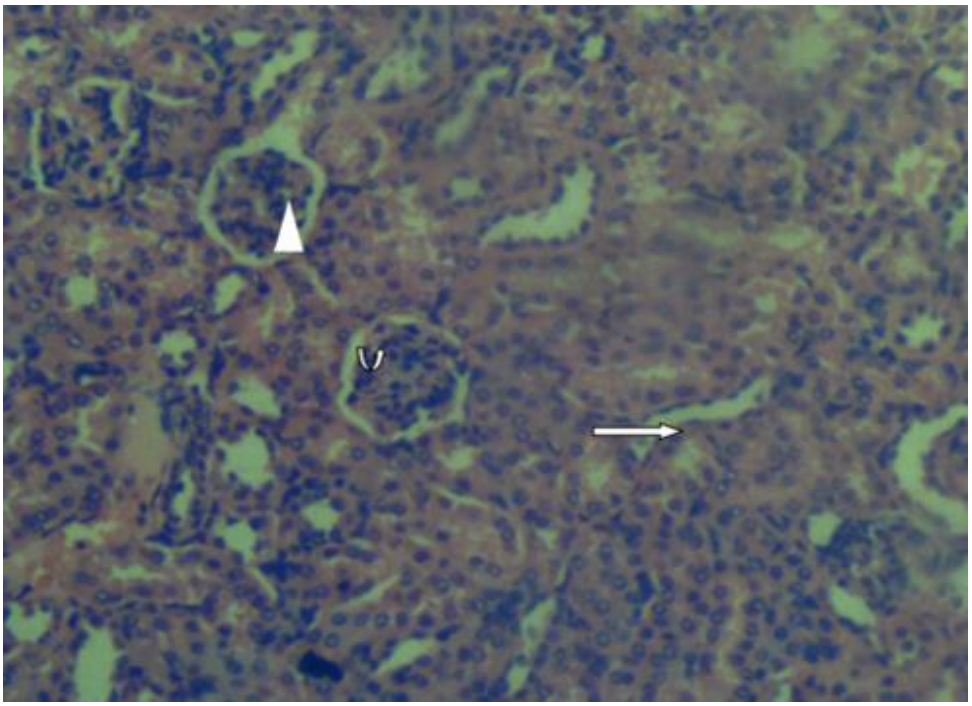

Figure 2 Group B received feed and water *ad libitum*. A photomicrographed section of the kidney shows normal glomeruli (arrowhead), renal tubule (arrow), and bowman's capsule (curved arrow) appear normal. Stained by H and E (X 400)

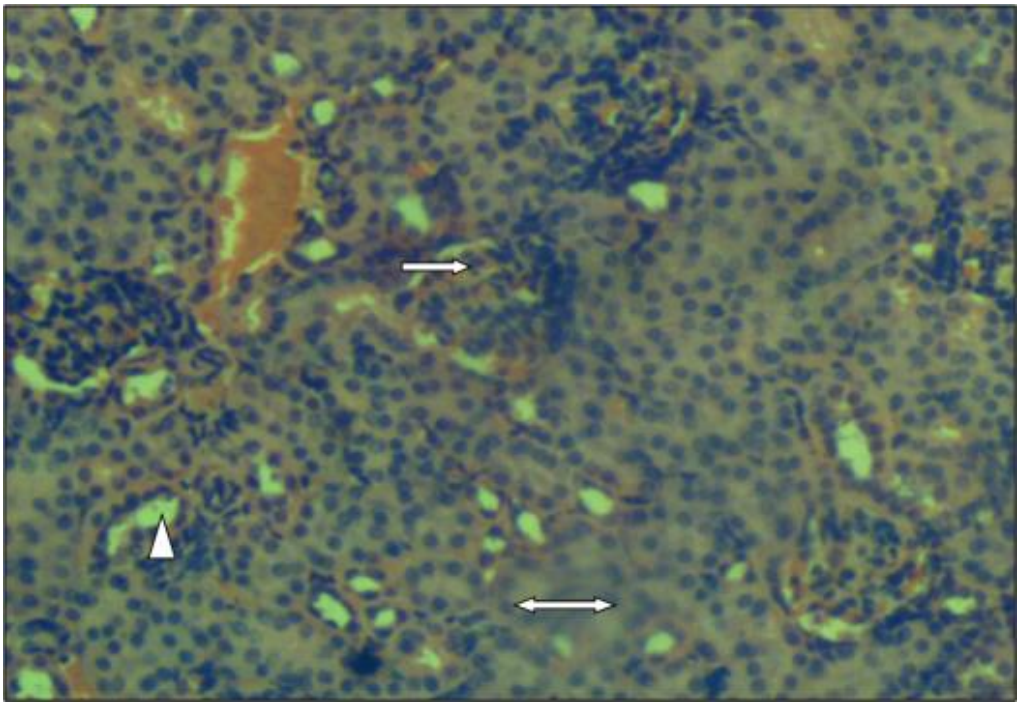

Figure 3 Group C (Malaria + 500mg/kg EAI). Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology but with moderate diffuse inflammatory background (double head arrow). The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (Stained by H and E, x 400)

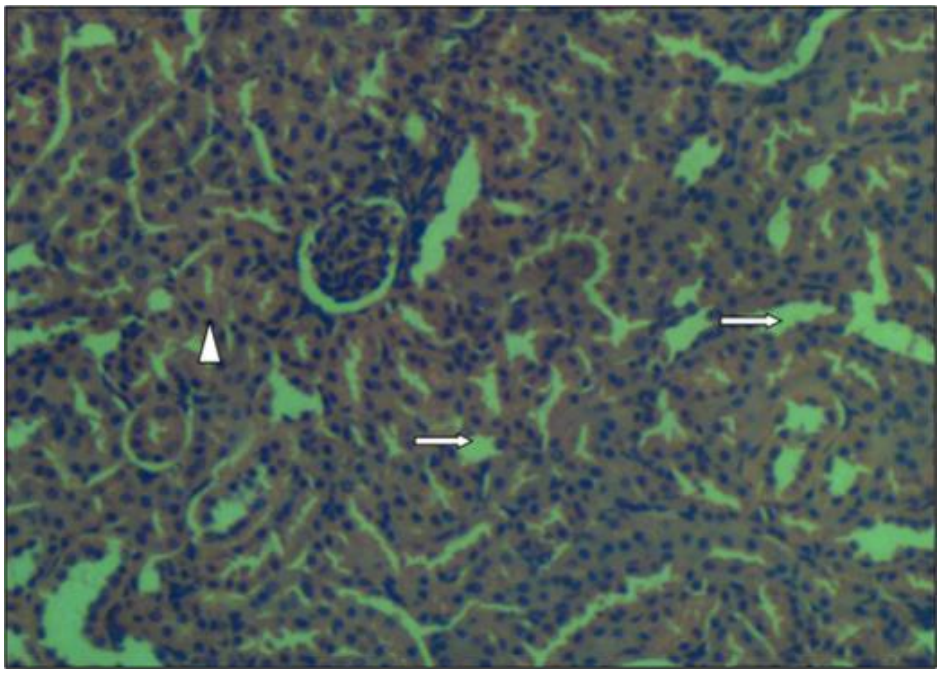

Figure 4 Group D: (Malaria + 100mg/kg ECC). Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury. Stained by H and E (x 400)

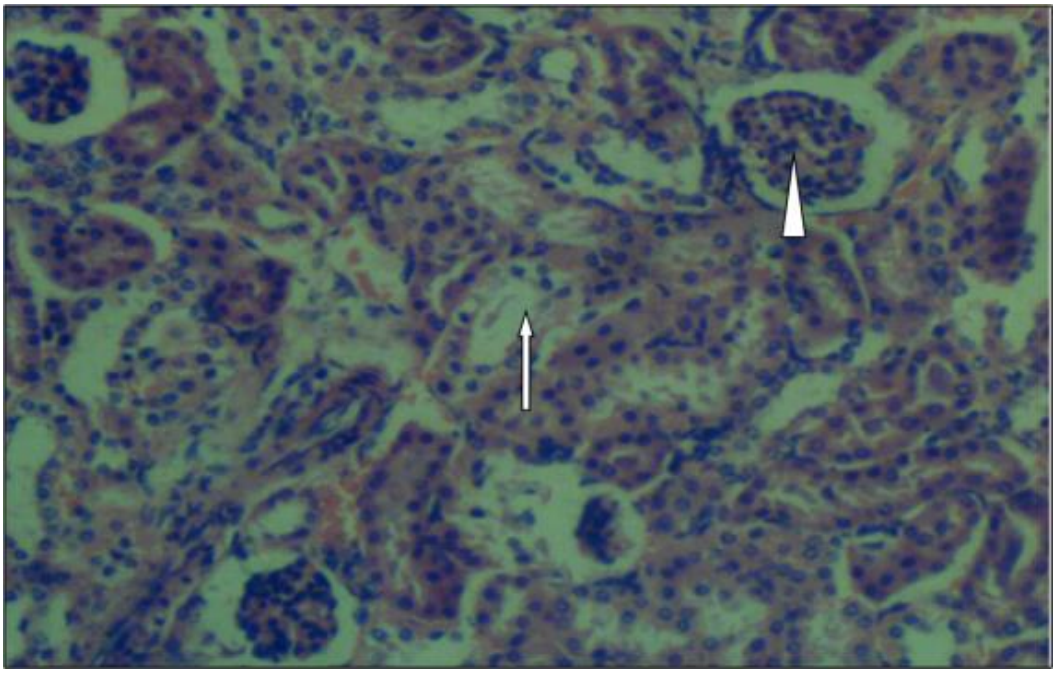

Figure 5 Group E: Malaria + 500mg/kg ECC. Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (HandE X400)

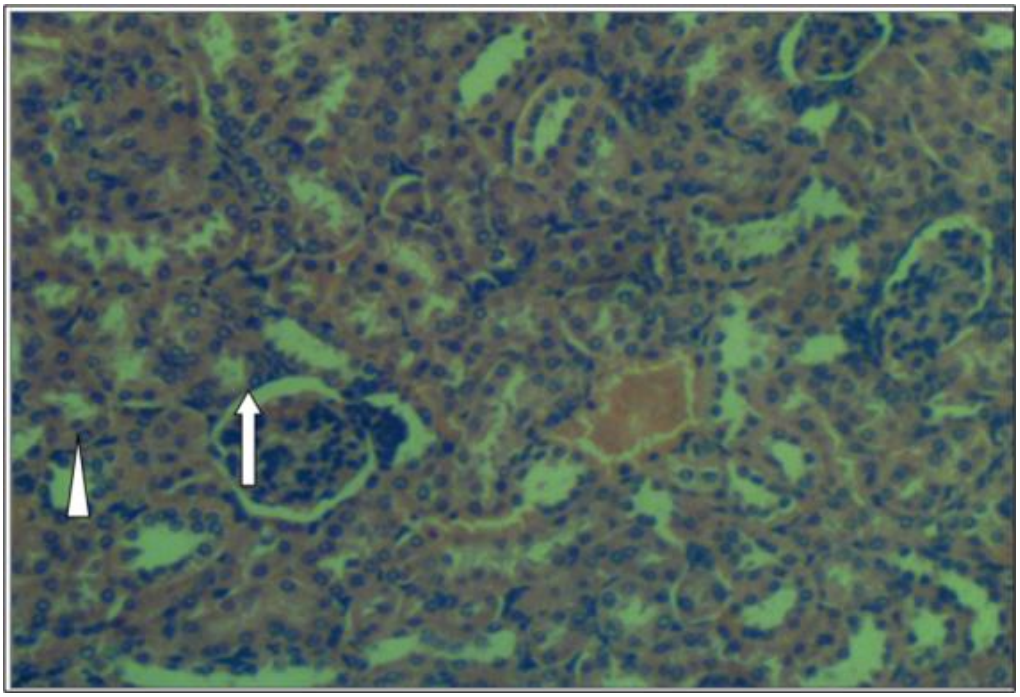

Figure 6 Group F (malaria + 100mg/kg EOG): Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (HandE)

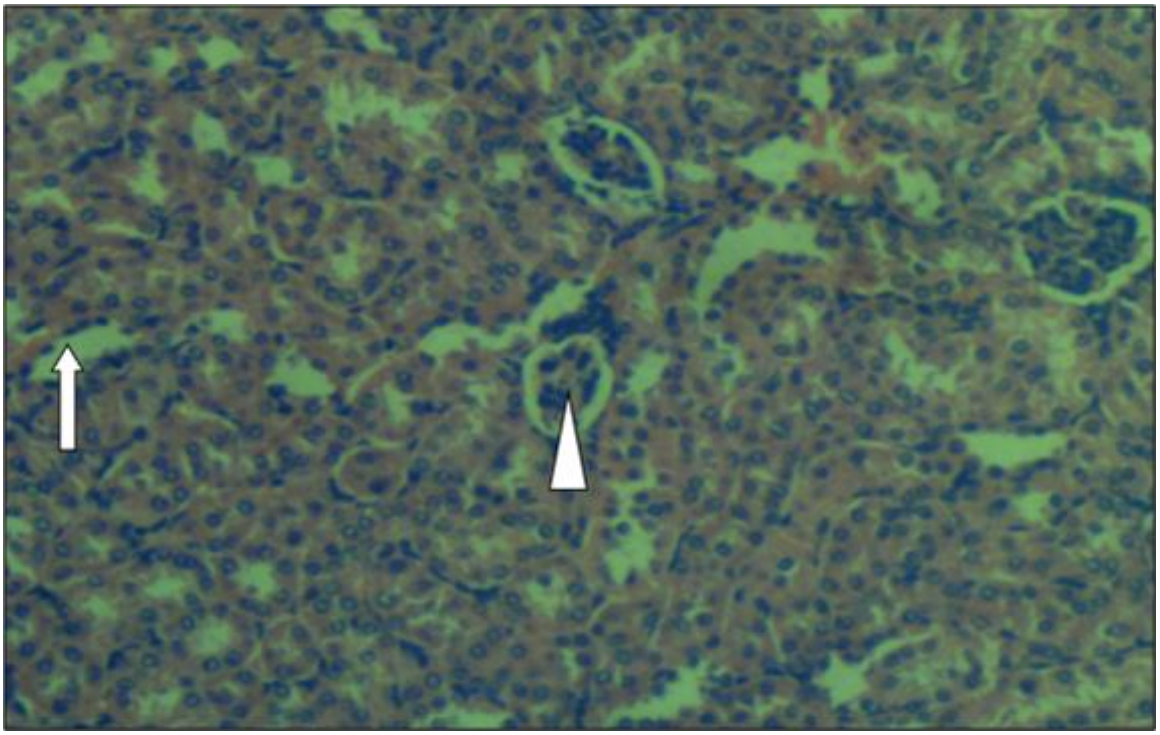

Figure 7 Group G(malaria + 500mg/kg EOG): Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (HandE X 400)

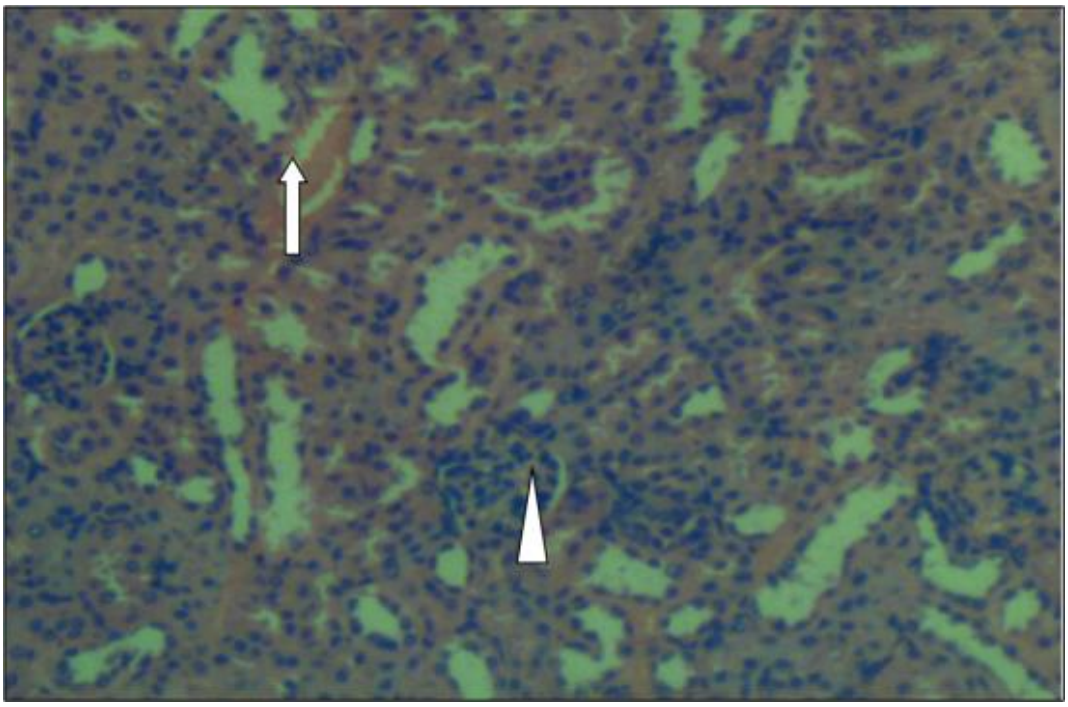

Figure 8 Group H (Malaria + 100mg/kg EAI): Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (HandE X 400)

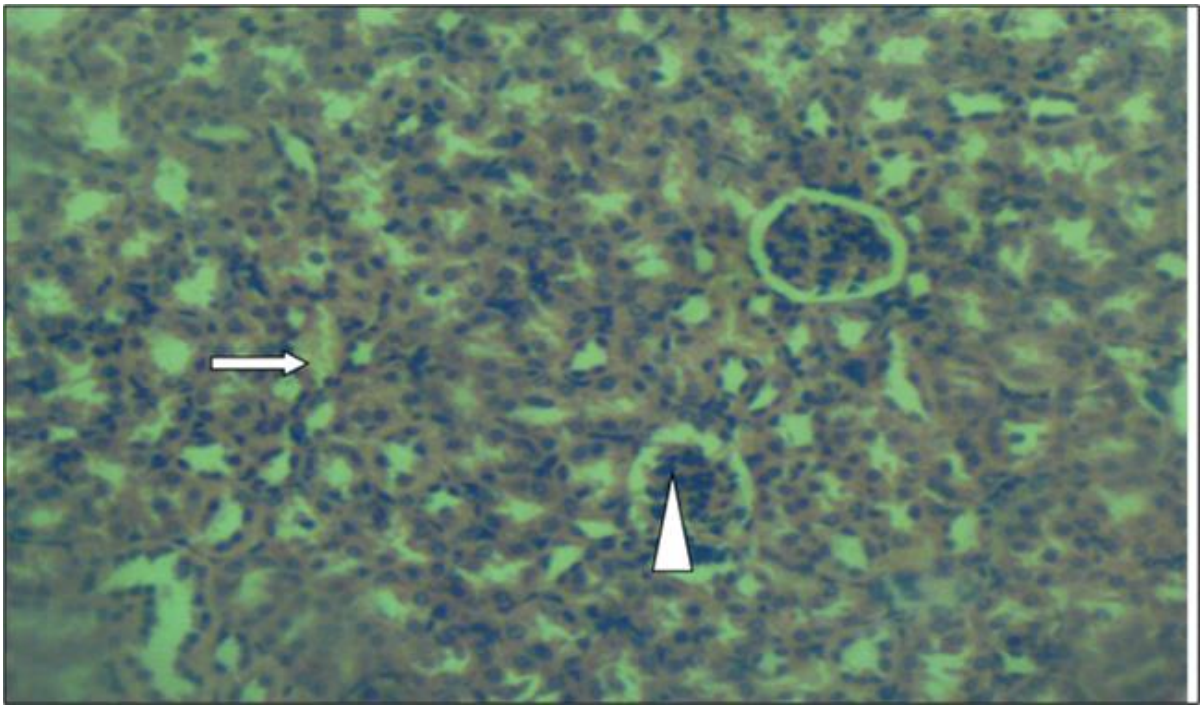

Figure 9 Group I (Malaria + Standard drug): Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (HandE X 400)

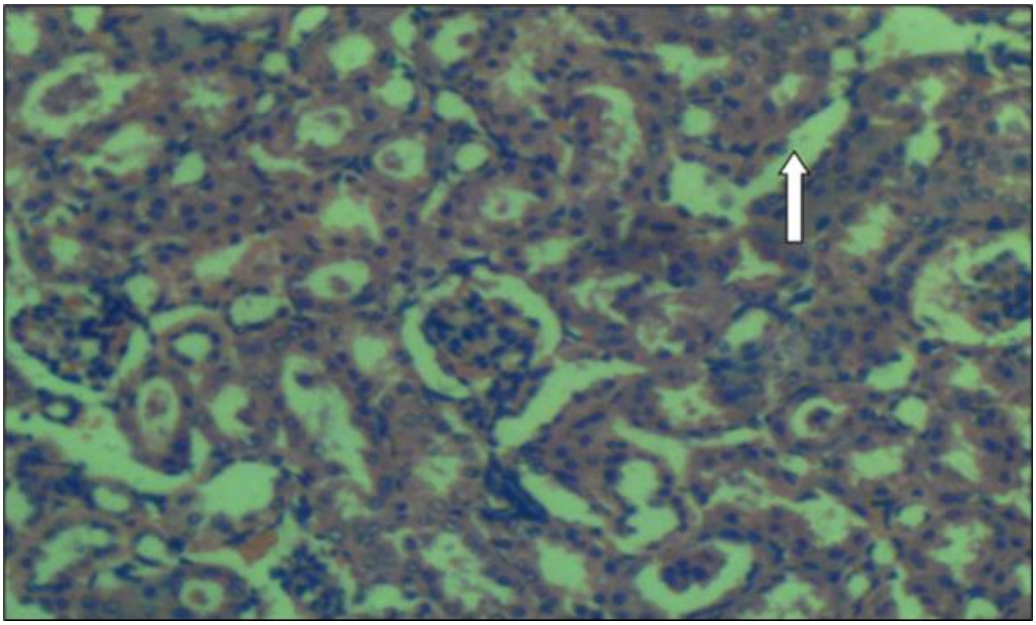

Figure 10 Group J (Malaria + 500mg/kg EOG + EAI + ECC): Photomicrographs show Kidney sections of Wistar rat with kidney histology consistent with normal morphology. The Renal capsules (arrowhead) and the tubules (arrow) are normal with no sign of injury (HandE X 400)

4. Discussion

Herbal remedies have increasingly gained prominence in the treatment and management of malaria caused by Plasmodium species (Mohammadi et al., 2020; Rudrapal and Chetia, 2021).

The present study demonstrated a significant increase in relative kidney weight in the malaria-infected group (Group A) compared to the normal control group (Group B). This increase may be attributed to renal stress and inflammation

induced by Plasmodium berghei infection. Conversely, treatment with ethanolic extracts of *Azadirachta indica*, *Cymbopogon citratus*, and *Ocimum gratissimum* at various doses (Groups C, E, F, G, and H) resulted in a significant reduction in relative kidney weight. This effect suggests a nephroprotective role of these plant extracts, potentially linked to their rich phytochemical composition, including alkaloids, tannins, flavonoids, terpenoids, and saponins.

Interestingly, Group D (low-dose C. citratus) exhibited a non-significant increase in kidney weight, while Groups I (standard drug) and J (combined extract treatment) also showed non-significant reductions, indicating that higher doses or specific plant combinations might be more effective.

The reduction In kidney weight following treatment may also reflect reduced oxidative stress and inflammation, as supported by histopathological observations showing normal renal morphology in treated groups.

Our findings align with those of Sharma et al. (2012), who also reported renal weight changes associated with *P. berghei* infection. The extracts' effectiveness in restoring renal function and morphology underscores their potential as complementary therapies in malaria management.

5. Conclusion

This study demonstrated that infection with Plasmodium berghei significantly impairs kidney function, as evidenced by increased relative kidney weight, elevated levels of urea, uric acid, and creatinine, along with histological signs of renal damage. Treatment with ethanolic extracts of *Azadirachta indica, Cymbopogon citratus, and Ocimum gratissimum*—individually and in combination—significantly ameliorated these effects. The improvement observed in biochemical and histological parameters suggests a nephroprotective potential of these plant extracts, likely due to their rich content of bioactive phytochemicals. These findings support the potential use of these medicinal plants as adjunct therapies in the management of malaria-induced nephrotoxicity.

Further studies, including clinical trials and mechanistic investigations, are recommended to validate these findings and to better understand the therapeutic pathways involved.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained from the Animal ethics committee, Abia State University, Uturu.

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