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Research Article

Prolonged Exposure to Quinolones and Antifolate Antimalarial Drugs Alter Renal Indices and Biochemical Parameters in Male Wistar Rats

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ABSTRACT

Background: Malaria remains a major public health challenge globally. Most antimalarial drugs have been reported to cause side effects on various body organs, especially with abuse and indiscriminate use. This study evaluates the impact of prolonged exposure to quinolones and antifolates on renal indices in male Wistar rats.

Methods: 35 male Wistar rats were split into five groups of seven rats each. Group 1 served as control and received 2ml/kg body weight of normal saline, Group 2 rats were given 30 mg/kg of Chloroquine, Group 3 rats took 30 mg/kg of Quinine, Group 4 was given 2.9 mg/kg of Proguanil and Group 5 was given 15 mg/kg of Pyrimethamine. Treatments were administered orally for six weeks, after which blood and tissue samples were collected under ketamine anesthesia (80mg/kgBW) for the assessment of kidney indices, antioxidant and histological parameters.

Results: Serum urea was significantly elevated in the chloroquine and quinine groups compared to control. ($P < 0.0001$ and $P = 0.0004$ respectively). Serum creatinine was also significantly elevated in the quinine group in comparison to control ($P = 0.0134$). There was significant increase in serum potassium and sodium levels in the chloroquine ($P = 0.0287$ and $P = 0.326$ respectively) and quinine groups ($P = 0.0113$ and $P = 0.0474$ respectively) versus control. Oxidative stress markers revealed elevated renal malondialdehyde levels in the chloroquine ($P = 0.0471$) and quinine groups ($P = 0.0470$) compared to the control. Glutathione peroxidase and superoxide dismutase activities were significantly reduced in the quinine ($P = 0.0081$ and $P = 0.0474$) group versus control. Histological analysis revealed glomerular shrinkage, tubular degeneration, and necrosis, more severe in quinolone-treated rats compared to antifolate-treated groups.

Conclusion: Prolonged exposure to quinolones and antifolate antimalarial drugs may lead to renal toxicity, characterized by oxidative stress, electrolyte imbalances, and histopathological alteration.

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1. Introduction

Malaria remains one of the most significant public health challenges globally, particularly in tropical and subtropical regions. It is a parasite-caused disease (Plasmodium) that is spread through the bite of female Anopheles mosquitoes (Longley *et al*., 2024). Malaria is an endemic disease transmitted by four species of Plasmodium. Parasites: *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae,* and *Plasmodium vivax* (Fletcher and Beeching, 2013). Malaria can lead to severe complications, such as cerebral malaria, severe anemia, coma, or death (Buck and Finnigan, 2023), with acidemia, hemolytic anemia, destruction of infected red blood cells in the blood vessels of many organs and others are contributing factors to the severity of its development (Vathi *et al.*, 2025). The choice of treatment and preventive measures depends on the specific malaria species, the region, the parasite's resistance to drugs, and the patient's characteristics.

Antimalarial drugs like quinolones and antifolates target the *Plasmodium* parasite through the inhibition of folate metabolism or disruption of heme detoxification (Bray *et al.,* 2005). Quinolones (including quinine, chloroquine, (a drug that was once discredited due to resistance, particularly against *Plasmodium falciparum* but now showing potential for reintroduction in certain regions (Adamu and Tukur, 2024) and mefloquine) and Antifolates (proguanil, pyrimethamine, cycloguanil, and trimethoprim) have been widely used primarily as antimalarial agents for decades. These drug compounds function by preventing the parasite from detoxifying heme, which eventually causes it to die. (Foley and Tilley, 1998). However, Plasmodium's emergence and spread of *falciparum* strains resistant to antifolates and quinolones have compromised their effectiveness in some regions (Enato *et al*., 2022). This has resulted in a higher propensity for indiscriminate and repeated use of the drugs in malaria management, particularly in places where the illness is endemic.

The kidneys are essential organs involved in regulating and maintaining homeostasis within the human body. They play a key role in filtration, electrolyte balance, and the maintenance of acid

base equilibrium (Luyendyk *et al*., 2014; Molitoris *et al.*, 2016). Additionally, the kidneys are responsible for removing waste products and excess fluids from the bloodstream, which helps prevent the buildup of toxins (Bonventre and Weinberg, 2013). They also produce hormones that influence blood pressure and red blood cell production, further contributing to overall physiological stability. Proper kidney function is crucial for ensuring the body's internal environment remains balanced and health is maintained (Rosner and Bolton, 2006). Renal indices are a set of parameters used to assess the functioning level of the kidneys (Chauhan *et al*., 2016). These parameters are significant in scaling the toxicity of drugs and other substances and they provide valuable information for diagnosis, treatment, and disease management. The body's antioxidant mechanisms and the handling of reactive oxygen species are commonly impacted by prolonged intake of medications, which in turn may culminate in the dysfunction of major organs (kidneys) involved in drug metabolism (Freedman, 2008). This study aims to provide insight into the possible alterations in kidney function that may result directly or indirectly from prolonged exposure to quinolones and antifolate antimalarial drugs.

2. Materials and Methods

2.1 Animal Model

Thirty-five male Wistar rats of about 120 – 200 grams were obtained from an accredited animal facility and housed in standard conditions (temperature, 25±2°C, 12 hours light and 12 hours dark cycle), having unrestricted access to water and food. Rats were kept in the animal house of the Department of Physiology, School of Basic Medical Sciences, in The Federal University of Technology, Akure (FUTA), Ondo State, Nigeria. The acclimatization process took two weeks before the commencement of treatments. All rats were weighed before commencement of the experiment and weighed weekly during the period of the experiment using a sensitive weighing balance, and the weight was recorded in grams (g).

2.2 Ethical Approval

Institutional ethical approval was obtained from the Centre for Research and Development (CERAD), Federal University of Technology Akure, with reference number: FUTA/ETH/25/233. Handling of the animals in this study was in accordance with the research guidelines for animal experimentation as prescribed in the ethical principles in the Helsinki Declaration, and Guidelines for animal care and use (Arokoyo *et al*., 2025).

2.3 Experimental Design

Thirty-five male Wistar rats were divided into five groups of seven at random. Group 1 (CNTRL) was the control group and received 2ml/kg body weight of normal saline while rats in Group 2 (CQ) were given 30 mg/kg of Chloroquine, Group 3 (QUN) were given 30 mg/kg of Quinine, Group 4 (PRNL) were given 2.9 mg/kg of Proguanil and Group 5 (PYRM) rats were

given 15 mg/kg of Pyrimethamine. The normal saline and drugs were administered orally and directly throughout the experiment, using an oropharyngeal cannula for 6 weeks.

2.4 Preparation and Dosages for Antimalarial Drugs

The dosage of Chloroquine used was 30 mg/kg of body weight (Iwalokun, 2008). 300 mg of Chloroquine was dissolved in 20 ml of normal saline to get the stock solution of 15 mg/ml. The dosage of Quinine used was 30mg/kg of body weight (Gbotolorun *et al*., 2018). 300mg of Quinine was dissolved in 20ml of normal saline to get the stock solution of 15mg/ml. The dosage of Proguanil used was 2.9mg/kg of body weight (Kumar *et al*., 2013). 100mg of Proguanil was dissolved in 68.97ml of distilled water to get the stock solution of 1.45mg/ml.The dosage of Pyrimethamine used was 15mg/kg of body weight (Kumar *et al*., 2013). 50mg of Pyrimethamine was dissolved in 6.66ml of distilled water to get the stock solution of 7.5mg/ml.

2.5 Sample Collection

Animals were weighed using a sensitive weighing balance 24 hours after the last administration. The blood sample was collected via cardiac puncture into the sample bottles, animals were euthanized via exsanguination under ketamine injection of 80mg/kgBW, and tissue samples were collected from the rats for the assessment of kidney indices, antioxidant parameters, and histological analysis. The blood sample was centrifuged at 3000rpm for 15mins (SH-80-3) and separated through decantation to collect the serum into a fresh sample bottle. The animals were opened up from the abdominal region down to the pelvic region, and the kidneys were harvested and weighed on a digital weighing scale.

2.6 Biochemical Analysis

2.6.1 Urea Determination

Urea concentration in serum samples was assessed using a UV spectrophotometer by measuring absorbance changes at 340 nm using the Urease-glutamate dehydrogenase (GLDH) enzymatic method (AGAPE kit with Lot Number 32412488). (Fawcett *et al*,.1960).

2.6.2 Creatinine Determination

Serum samples were reacted with picric acid; color intensity at 520 nm indicates creatinine concentration using the Jaffe reaction method. This absorbance of the color intensity change was assessed by a UV spectrophotometer (AGAPE kit with Lot Number 32501456).

2.6.3 Electrolyte Analysis

Sodium and Potassium Ions in serum samples were measured using flame photometry with specific emission wavelengths (589 nm for Na^+ and 766 nm for K^+) with Fortress kit.

2.6.4 Antioxidant Assays

Kidney tissues were homogenized, centrifuged, and analyzed to assess the antioxidant parameters.

Malondialdehyde (MDA) Assay: Assesses lipid peroxidation using the TBARS method, with absorbance read at 532 nm using a UV spectrophotometer.

2.6.5 Catalase Activity

Monitored via hydrogen peroxide decomposition, measured at 240 nm. Superoxide Dismutase (SOD) Activity: Evaluated using the NBT reduction method, with absorbance at 560 nm using a UV spectrophotometer.

2.6.6 Glutathione Peroxidase (GPx) Activity

Measured by NADPH oxidation rate, monitored at 340 nm using a UV spectrophotometer.

2.6.7 Reduced Glutathione (GSH) Assay

Estimated using Ellman's reagent method, with absorbance at 412 nm using a UV spectrophotometer.

2.6.8 Total Protein Determination

Protein content was quantified by measuring the violet color formed at 540 nm after mixing with Biuret reagent using the Biuret method using a UV spectrophotometer.

2.7 Histological Analysis

Right kidney from each animal was fixed in 10% neutral buffered formalin for 48 hours, dehydrated through ascending grades of alcohol (70%, 80%, 90% &100%). This was infiltrated and embedded in paraffin wax. The tissues were sectioned at 5µm thickness and Hematoxylin and Eosin-stained (H&E). Chemical attraction between tissue and dye is the principle involved in the Hematoxylin and eosin stain and this principle was employed (Feldman and Wolfe, 2014).

Hematoxylin, a basic dye imparts blue-purple contrast on basophilic structures, basically those containing nucleic acid moieties such as chromatin, ribosomes and cytoplasmic regions with plenty RNAs while an acidic eosin counterstained the primary elements such as red blood cells, cytoplasm, muscle and collagen in different degrees of pink, orange and red (Feldman and Wolfe, 2014).

All micrographs were taken with a light microscope and a Moticam DCM400 digital eyepiece mounted to the microscope (Leica, Germany). The photos were then sent to a computer to be captured by the eyepiece.

2.8 Data Analysis

All data were expressed as mean ± standard error of mean (S.E.M). The data was analyzed using a one-way analysis of variance (ANOVA). All statistics were determined by using GraphPad Prism version 10.0 (GraphPad Software Inc., San Diego, CA, USA). Followed by the post hoc Turkey's test where P-value < 0.05 was considered significant.

3. Results

3.1 Effect of Prolonged Exposure to Quinolones and Antifolates on Biochemical Parameters

As shown in Figure 1a, serum creatinine concentration was significantly elevated (P = 0.0134) in the quinine-treated group when compared to the control. Furthermore, when the pyrimethamine group was compared to the quinine group, a significant difference was also observed (P = 0.0148).

For urea concentration (Fig. 1b), the chloroquine and quinine groups demonstrated highly significant increases (P < 0.0001 and P = 0.0004, respectively) compared to the control. Notably, the proguanil group showed a statistically significant reduction in urea levels relative to both the chloroquine (P < 0.0001) and quinine (P = 0.0002) groups. A similar trend was observed in the pyrimethamine group when compared to the chloroquine group (P = 0.0015).

Analysis of renal electrolyte concentrations revealed that sodium (Na^+) levels (Fig. 1c) were significantly elevated only in the quinine group (P = 0.0326) relative to the control group. For potassium (K^+) levels (Fig. 1d), statistically significant elevations were detected in both the chloroquine (P = 0.0287) and quinine (P = 0.0113) groups when compared to the control.

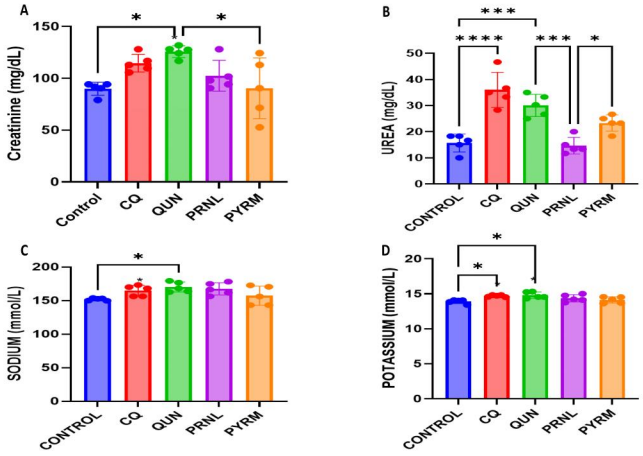

Figure 1: Serum electrolytes, urea and creatinine of control and drug-treated groups. (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001) [CQ=Chloroquine; QUN=Quinine; PRNL=Proguanil; PYRM=Pyrimethamine]

3.2 Renal Antioxidant Biomarkers

The antioxidant profile in renal tissues is detailed in Table 1. Protein concentration in the Proguanil group showed statistically significant decrease when compared to the Chloroquine group (P = 0.0088) and the Quinine group (P = 0.0129) respectively. The concentration of protein in the Pyrimethamine group showed statistically significant decrease when compared to the Chloroquine group (P = 0.0088) and the Quinine group (P = 0.0129) respectively. Proguanil and Pyrimethamine showed significant decrease (P = 0.001) compared with the control and Chloroquine and Quinine showed significant increase (P = 0.005) when compared with control.

Malondialdehyde (MDA) levels were significantly increased (P = 0.0471 for Chloroquine, P = 0.0470 for Quinine and P = 0.0142 for proguanil) across all drug-treated groups when compared to the control but there were no significant differences within the treated groups.

Catalase activity was significantly suppressed in the chloroquine group (P = 0.0410), whereas the proguanil and pyrimethamine groups demonstrated elevated catalase activity compared to the control group (P = 0.0045 and P = 0.0046 respectively). Catalase concentration in the Proguanil group showed significant increase when compared to the Chloroquine

group (P = 0.0045) and the Quinine group (P = 0.0115) respectively. The concentration of Catalase in the Pyrimethamine group demonstrated statistical significance increase when compared to the Chloroquine group (P = 0.0046) and the Quinine group (P = 0.0118) respectively.

Superoxide dismutase (SOD) activity decreased significantly in the quinine group relative to the control (P = 0.0474). However, the proguanil group showed significant (P = 0.0468) SOD elevation compared to the control group. SOD concentration in Proguanil group showed significant increase when compared to the Chloroquine group (P = 0.0231) and the Quinine group (P = 0.0046) respectively.

Glutathione peroxidase (GPx) activity was significantly reduced in the chloroquine group compared to the control (P = 0.0410). Proguanil and pyrimethamine-treated rats exhibited a marked increase in GPx activity when compared to the control (P = 0.0404 and 0.0410 respectively). GPX activity in the Proguanil and Pyrimethamine group showed significant increase when compared to the Chloroquine group (P = 0.0007 and P = 0.0008 respectively) and the Quinine group (P = 0.0110 and P = 0.0128 respectively).

Reduced glutathione (GSH) levels were significantly higher in the proguanil group when compared to both the control (P < 0.05) and chloroquine groups (P = 0.0351). However, there was no statistically significant difference when the chloroquine group was compared to the control.

Table 1: Level of Antioxidant Biomarkers in Kidney Homogenates of all Groups

		QUINOLINES		ANTIFOLATE	
Groups	CNTRL	CQ	QUN	PRNL	PYRM
PROTEIN	0.52±0.01	0.59±0.02[a]	0.59±0.03[a]	0.50±0.02[a]	0.50±0.01
MDA	2.83±0.30	5.88±0.24	5.88±0.60	6.45±1.03	5.52±0.99
CATALASE	730 ± 16.9	633 ± 18.1[a]	646±25.8[a]	762±29.8	762± 18.4
SOD	356± 8.88	309 ± 10.3	294±14.0	378±13.3	353± 22.4
GPX	451 ± 4.98	374± 17.6[aa]	398± 14.9	470±15.3	469± 12.7
GSH	60.0 ± 1.95	47.5 ± 1.84	59.7± 4.64	66.2 ± 6.77[aa]	58.5± 3.64

Key: [ap<0.05; aap<0.001; aaap<0.0001; n=7; CNTRL=Control; CQ=Chloroquine; QUN=Quinine; PRNL=Proguanil; PYRM=Pyrimethamine]

3.3 Renal Histology

Histological analysis of the renal tissues revealed drug-specific structural distortions, as illustrated in Figure 2. The control group exhibited normal renal architecture characterized by intact glomeruli and tubular arrangement. However, tissue sections from the quinine and chloroquine groups revealed evident tubular degeneration, glomerular shrinkage, and the presence of inflammatory cells. The proguanil and pyrimethamine groups displayed moderate pathological changes, including focal tubular necrosis and mild interstitial inflammation, albeit less severe when compared to those treated with quinolones.

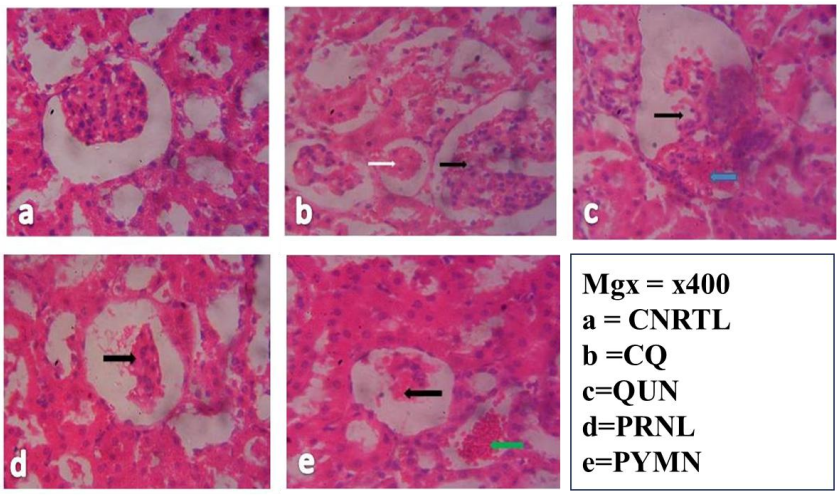

Figure 2: Photomicrograph of renal tissue sections showing: (a) Slides from Control rats with normal histoarchitecture. (b) Slides from Chloroquine treated rats with tubular degeneration, tubular necrosis (c). Slides from Quinine treated rats with degenerated glomerulus with edema (black arrow). (d) Slides from Proguanil treated rats with degeneration in the glomerulus with inflammation. (e) Slides from Pyrimethamine treated rats with a degeneration in the glomerulus (black arrow).

4. Discussion

The findings obtained from biochemical, antioxidant, and histological analysis in the study indicate that these classes of drugs have differential effects on kidney function, especially through oxidative stress, changes in enzyme activity, and histo-architectural disruptions.

Creatinine and urea clearance are primary indicators of the kidneys' excretory function, and high serum levels of these substances are usually an indication of impaired glomerular filtration. The alterations observed in these renal indices and electrolytes in drug-treated groups indicated possible nephrotoxicity with prolonged exposure to these drugs. The quinolones, especially quinine, appear to be more nephrotoxic, with higher elevations in serum creatinine and urea relative to those observed with antifolates, suggesting a more pronounced nephrotoxic effect. This finding is consistent with earlier studies that have linked quinine with acute renal impairment and tubular dysfunction (Adebayo *et al*., 2017; Ekanem *et al*., 2015). The animals exposed to prolonged treatment with proguanil and pyrimethamine equally exhibited signs of nephrotoxicity, albeit less pronounced, with milder elevations in the renal parameters. (Madu *et al.,* 2014)

Similarly, serum sodium (Na^+) levels were significantly altered in the quinine-treated group, which may indicate a dysfunction in tubular reabsorption and/or a deregulation of aldosterone-mediated sodium handling (Palmer and Clegg, 2019; Mohammed et al., 2020). In both the chloroquine and quinine groups, potassium (K^+) levels were significantly elevated, a common manifestation of renal tubular injury that may arise from direct nephron damage or interference with Na^+/K^+-ATPase activity (Chandra *et al*., 1992). Hyperkalemia can result from decreased activity of Na+/K+-ATPase in the basolateral membrane of the renal tubular epithelial cells, which can affect renal sodium reabsorption and interfere with the process of potassium excretion (Basile *et al*., 2012; Chandra *et al*., 1992).

Oxidative stress is a central phenomenon of nephrotoxicity, which is frequently estimated by the evaluation of the antioxidant enzymes and lipid peroxidation products measurement. In this study, markers of lipid peroxidation, as measured by malondialdehyde (MDA) levels, were markedly increased in treated groups, indicating lipid peroxidation in tubular and glomerular membranes. This suggests that nephron segments, particularly proximal tubules, were vulnerable to oxidative damage due to the accumulation of drug metabolites and high oxygen demand. Elevated MDA has been associated with renal tubular necrosis and interstitial damage in drug toxicity models (Osonuga *et al*., 2017).

Concurrently, SOD and CAT activities were significantly reduced in renal tissues, reflecting impaired enzymatic defense against ROS. This decline suggests that the ROS generated during drug metabolism exceeded the antioxidant buffering capacity of renal cells, leading to oxidative injury. Moreover, GSH depletion was observed in the kidneys across all drug-treated groups, suggesting either increased consumption for detoxification or impaired

regeneration. Antifolate-treated rats, particularly those receiving pyrimethamine, showed more pronounced depletion, which may be linked to the inhibition of folate-dependent glutathione biosynthesis pathways (Akanmu *et al*., 2016; Oladiji *et al*., 2020). Since renal GSH is critical for protection against nephrotoxic agents, its depletion likely contributed to the histological findings of tubular necrosis, interstitial edema, and glomerular shrinkage observed in this study. The parallel oxidative stress responses in both hepatic and renal tissues suggest a systemic redox imbalance induced by prolonged quinolone and antifolate exposure. Mechanistically, the increased ROS burden may arise from mitochondrial dysfunction, drug–heme interactions, and disruption of electron transport chains, particularly in quinolone-treated groups (Kaur *et al*., 2023). In antifolate groups, impairment of folate metabolism further exacerbates oxidative stress by limiting nucleotide synthesis and glutathione regeneration (Umumararungu *et al*., 2023). The combined effect of elevated MDA and reduced antioxidant enzymes is consistent with the oxidative stress hypothesis of drug toxicity, which posits that an imbalance between ROS production and antioxidant defenses culminates in biomolecular damage, cellular death, and ultimately organ dysfunction (Osonuga *et al*., 2017; Oladiji *et al*., 2020). These findings corroborate earlier reports that prolonged antimalarial therapy predisposes to hepato-renal injury via oxidative stress pathways. Importantly, the concurrent oxidative stress in both organs may act synergistically to worsen systemic toxicity, since impaired renal clearance increases liver metabolic burden, while compromised liver detoxification leads to higher renal exposure to reactive metabolites. This interplay underscores the importance of monitoring oxidative stress markers in patients undergoing prolonged or repeated antimalarial therapy.

Microscopic observation of kidney tissue supported evidence of structural derangements in keeping with the biochemical findings. Tubular necrosis, inflammatory infiltration, and glomerular atrophy were observed in kidney sections obtained from quinine and chloroquine groups. Such structural modifications complement the functional and oxidative disturbances witnessed and explain that exposure to such antimalarials over a period of time may damage organ architecture.

The mechanisms seem to imply oxidative stress, mitochondrial disruption, lipid peroxidase – enzyme leakage, and tissue degeneration (Franco and Cidlowski, 2019; Gbotosho *et al*., 2009). Antifolates had a relatively less toxic profile, probably because of better redox homeostasis and the lack of considerable interference with the processes taking place in the mitochondria.

Findings are in agreement with the reported risk of renal injury from chronic exposure to antimalarial drugs reported by Freedman (2008), Litescu *et al* (2010), and Mehra *et al* (2017). This study also broadens the understanding of the particular antioxidant perturbations related to every drug, which may be useful for stratifying their long-term use risks.

5. Conclusion

This study shows that prolonged exposure to quinolones and antifolate antimalarial drugs in male Wistar rats leads to substantial changes in the renal indices. The quinolones (quinine and chloroquine) appear to have more deleterious effects on biochemical markers, antioxidant enzyme activity, as well as on tissue histology, suggesting higher levels of toxicity than the Antifolate agents (proguanil and pyrimethamine), which exhibited less toxicity.

These effects were mediated mainly through oxidative stress, based on the changes in the levels of oxidative stress markers within the kidney tissue. The study confirms the need for caution in the usage of antimalarial agents with regard to the class of drug, dosing, and duration of treatment.

6. Conflict of Interest Declaration

All authors declare that there is no conflict of interest with regards to any part of this manuscript

7. References

Adamu Ahmed Adamu and Umar Muhammad Tukur. (2024). Revisiting Chloroquine In Malaria Treatment: A Pharmacological Perspective. *IOSR Journal of Dental and Medical Sciences*; 23(10): 48-54. https://doi.org.10.9790/0853-2310064854

Adebayo, J. O., Balogun, E. A. and Malomo, S. O. (2017). Antimalarial drugs-induced oxidative stress and organ damage: Implications for therapy. *Current Topics in Medicinal Chemistry; 17*(10): 1157–1170.

Akanmu, A. S., Olowookere, S. A. and Osunkalu, V. O. (2016). Toxicological implications of chronic use of antimalarial drugs. *African Journal of Medicine and Medical Sciences; 45*(1): 33–41.

Arokoyo D.S, Fagbangbe P.I., Oladimeji O.C., Olaoye A.O., Oyediran A.E., Adegboye M.B. (2025). Duration of cuteneous analgesia induced by bupivacaine and ketamine in female Wistar rats;

role of epinephrine. *Scientific African*; 28: e02660. https://doi.org/10.1016/j.sciaf.2025.e02660.

Bonventre, J. V., and Weinberg, J. M. (2013). Recent advances in the pathophysiology of ischemic acute kidney injury. *Journal of Clinical Investigation*; 123(9): 3283–3290. https://doi.org.10.1097/01.asn.0000079785.13922.f6

Bray, P. G., Ward, S. A. and O'Neill, P. M. (2005). Quinoline antimalarials: mechanisms of action and resistance. *Journal of Pharmacy and Pharmacology*; 57(9): 1163-1174.

Buck, E., and Finnigan, N. A. (2023). Malaria. Malaria: Epidemiology and treatment. *Global Health Journal*; 9(2): 45-56. PMID: 31869175

Chandra M., Riley M.G., Johnson D.E. (1992). Spontaneous neoplasms in aged Sprague-Dawley rats. *Arch Toxicol*; 66(7): 496-502. https://doi.org.10.1007/BF01970675.

Chauhan, A., Sultan, L. R., Furth, E. E., Jones, L. P., Khungar, V., and Sehgal, C. M. (2016). Diagnostic accuracy of hepatorenal index in the detection and grading of hepatic steatosis. *Journal of Clinical Ultrasound*; 44(9): 580586. https://doi.org/10.1002/jcu.22382

Ekanem, J. T., Yusuf, O. K., and Oyewole, O. I. (2015). Nephrotoxic effects of quinine in experimental models. *Journal of Applied Pharmaceutical Science; 5*(7): 124–129.

Elliott, P., Cotton, R. G., and Orme, N. (2017). Kidney toxicity and oxidative stress: mechanisms and prevention. *Toxicological Sciences*; 155(2): 393–405.

Enato, I. G., Sadoh, A. E., Ibadin, O. M., Odunvbun, M. E., and Osaigbovo, II. (2022). Distinct pattern and prevalence of Plasmodium falciparum dihydropteroate synthase gene mutations in children with sickle cell anaemia and haemoglobin AA in Benin City, Nigeria: the impact of HbAA. *Pan Afr Med J*.; 43: 80.

Fawcett, J. K., and Scott, J. E. (1960). A rapid and precise method for the determination of urea. *Journal of Clinical Pathology*; 13(2): 156–159.

Feldman AT and Wolfe D. (2014). Tissue processing and hematoxylin and eosin staining. *Methods Mol Biol*.; 1180: 31-43. https://doi.org/10.1007/978-1-4939-1050-2_3.

Fletcher, T. E., and Beeching, N. J. (2013). Malaria. *Journal of the Royal Army Medical Corps*; 159(3): 158–166. https://doi:10.1136/jramc-2013-000112

Foley, M., and Tilley, L. (1997). Quinoline antimalarials: mechanisms of action and resistance. *International journal for parasitology*; 27(2): 231–240. dx. https://doi.org/10.1016/S0020-7519(96)00152-X

Franco, R. and Cidlowski, J. A. (2019). Cell death mechanisms in human diseases: The role of oxidative stress and antioxidant defenses. *International Journal of Molecular Sciences*; 20(7): 1744.

Freedman DO. (2008) Clinical practice. Malaria prevention in short-term travelers. *N Engl J Med*; 359(6): 603-12. https://doi.org.10.1056/NEJMcp0803572.

Furst, D. E. (2016). Pharmacology and toxicology of antimalarial drugs. *Expert Opinion on Drug Safety*; 15(10): 1271-1283.

Gbotolorun, S. C., Inikori, O., Bamisi, O. D., Osinubi, A. A. A., and Okanlawon, A. O. (2018). Quinine inhibits ovulation and produces oxidative stress in the ovary of cyclic Sprague-Dawley rats. *African health sciences*; 18(2): 253–259. https://doi.org/10.4314/ahs.v18i2.8

Gbotosho, G. O., Folarin, O. A., Sowunmi, A., Happi, C. T., Oduola, A. M. J., and Falade, C. O. (2009). Caution in the use of artemisinin combination therapy: prescribing practices prior to introduction of ACT in Nigeria. *Malaria Journal; 8*: 313. https://doi.org/10.1186/1475-2875-8-313

Iwalokun B. A. (2008). Enhanced antimalarial effects of chloroquine by aqueous Vernonia amygdalina leaf extract in mice infected with chloroquine-resistant and sensitive Plasmodium berghei strains. *African health sciences*; 8(1): 25–35. https://doi.org/10.4314/ahs.v8i1.7043

Kumar, R., Gopalakrishnan, R., and Reddy, P. (2012). Nephrotoxicity of antimalarial drugs: a review. *Journal of Nephrology & Therapeutics*; 2(3): 123-129.

Luyendyk, J. P., Guo, L., and Anthony, R. M. (2014). The role of the complement system in acute kidney injury. *American Journal of Physiology-Renal Physiology*; 306(8): F799–F814.

Madu, A. J., Ugwu, S. N., and Onyemelukwe, G. C. (2014). Nephrotoxicity of antimalarial drugs: a review. *African Journal of Medicine and Medical Sciences*; 43(2): 135-141.

Mohammed, M. H. and Al-Furat Al-Awsat (2020). Effect of quinine on hepatotoxicity and kidney function in male rat. *Plant Archives; 20*(2): 6859-6862.

Molitoris, B. A., Dagher, P. C., and DeHaan, E. (2016). Kidney injury and repair: Focus on the roles of mitochondrial function. *Nature Reviews Nephrology*; 12(8): 514–530.

Okocha, R. C., Nnamani, C. V. and Orji, R. H. (2017). Oxidative stress and renal function impairment: a review of the impacts of antimalarial drugs. *African Journal of Medicine and Medical Sciences*; 46(4): 343-351.

Oladiji, A. T., Olayemi, F. O., and Adepoju, A. A. (2020). Nephroprotective potential of medicinal plants against drug-induced kidney toxicity: A review. *Clinical Phytoscience; 6*(1): 1–12.

Osonuga, O. A., Osonuga, I. O., & Osonuga, A. A. (2017). Antimalarial drugs and renal function: Current perspectives. *International Journal of Nephrology and Renovascular Disease;* 10: 93–100.

Palmer, B. F. and Clegg, D. J. (2019). Physiology and pathophysiology of sodium retention in heart failure, cirrhosis, and nephrotic syndrome. *Reviews in Endocrine and Metabolic Disorders;* 20(2): 157–167.

Rosner, M. H., and Bolton, W. K. (2006). Renal function testing. *American journal of kidney diseases: the official journal of the National Kidney Foundation*; 47(1): 174–183. https://doi:10.1053/j.ajkd.2005.08.038

Shu, P., Liang, H., Zhang, J., Lin, Y., Chen, W., and Zhang, D. (2023). Reactive oxygen species formation and its effect on $CD4^+$ T cell-mediated inflammation. *Frontiers in immunology*; 14: 1199233. https://doi.org/10.3389/fimmu.2023.1199233

Umumararungu, T., Nkuranga, J. B., Habarurema, G., Nyandwi, J. B., Mukazayire, M. J., Mukiza, J., Muganga, R., Hahirwa, I., Mpenda, M., Katembezi, A. N., Olawode, E. O., Kayitare, E., and Kayumba, P. C. (2023). Recent developments in antimalarial drug discovery. *Bioorganic & Medicinal Chemistry;* 88–89: 117339. https://doi.org/10.1016/j.bmc.2023.117339

Vaidya, V. S., Waikar, S. S., Ferguson, M. A., Collings, F. B., Sunderland, K., Gioules, C., Bradwin, G., Matsouaka, R., Betensky, R. A., Curhan, G. C. and Bonventre, J. V. (2008). Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. *Clinical and Translational Science;* 1(3), 200-20.

Vathi, S., Corriero, A., Rodríguez, E.E. Moreau A. Bogossian E.G. Baggiani M., Hites M., Sonneville, R., Taccone F.S., and Salvagno, M. (2025). Management and monitoring strategies for severe cerebral malaria: a guide for the intensivist. *Ann. Intensive Care*; **15**: 154. https://doi.org/10.1186/s13613-025-01584-3.