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Renal impact of desloratadine/dihydroartemisinin /piperaquine on healthy and parasitized mice

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ABSTRACT

Desloratadine/dihydroartemisinin/piperaquine (DL/D/P) showed promising therapeutic activity on *Plasmodium berghei*. This study evaluated its renal impact on healthy and *Plasmodium berghei*-infected mice. Fifty-four adult Swiss albino mice used were randomized into 9 groups. Thirty mice (n=6/group) were inoculated with *Plasmodium berghei* (1 X 10^7) and treated with normal saline (0.2ml) (Parasitized control), DL, D/P and DL/D/P daily for 4 days, respectively. The non-parasitized control was treated with normal saline (0.2ml) daily for 4 days. In the sub-acute toxicity study, twenty four healthy mice (n=6/group) were treated with normal saline (0.2ml) (Control), DL, D/P and DL/D/P daily for 28 days, respectively. After treatment, the mice were weighed and anesthetized. Blood samples were collected and evaluate for renal biochemical markers. Kidney samples were weighed and analysed for markers of oxidative stress and histology. DL, D/P and DL/D/P did not produce significant ($p>0.05$) effects on renal function markers in parasitized mice when compared to control. DL, D/P and DL/D/P significantly decreased body weight and significantly increased kidney weight in healthy mice at $p<0.05$, $p<0.05$ and $p<0.01$, respectively when compared to control. Serum creatinine, urea, uric acid and kidney malondialdehyde levels were increased significantly in DL ($p<0.05$), D/P ($p<0.05$) and DL/D/P ($p<0.01$) treated healthy mice when compared to control. Significantly decreased kidney glutathione peroxidase, superoxide dismutase, glutathione, and catalase levels were observed in healthy mice treated with DL ($p<0.05$), D/P ($p<0.01$) and DL/D/P ($p<0.001$) when compared to control. DL/D/P produced tubular necrosis, vacuolated glomerular mesangial cells and increased Bowman's space in healthy mice. The prolonged use of DL/D/P may cause renal dysfunction.

Keywords: Dihydroartemisinin/piperaquine, Desloratadine, *Plasmodium*, Mice, Renal, Toxicity

1. INTRODUCTION

The kidney is essential for the disposal of waste products, regulation of extracellular fluid volume, electrolyte concentrations, and serum osmolality

(Bhatt and Jialal, 2020). Allopathic medicine has subjected patients to taking a variety of drugs for diagnostic and therapeutic reasons (Pazhayattil and Shirali, 2014). The kidneys provide the ultimate solution for the excretion and elimination of many drugs and metabolites, which often subject them to elevated levels of potentially toxic substances. As a result, kidney tubular cells and papillae are exposed to direct toxic damage causing nephrotoxicity (Mahmoudi et al., 2021). Drugs can cause nephrotoxic complications such as interstitial nephritis, nephrotic syndrome, impaired intraglomerular hemodynamics, tubulointerstitial disease, and renal scarring resulting in acute or chronic kidney injury (Sari, 2019). Nephrotoxic complications associated with drugs can by heralded by alterations in indices such glomerular filtration rate, blood urea nitrogen, serum creatinine, or urine output; however, some indices may remain unperturbed (Lillie and Cummings, 2018).

Nephrotoxicity associated with antimalarial drugs may be rare, but there are growing concerns based on reported observations (Wiwanitkit, 2015). Chloroquine may alter kidney structure and also impair kidney function causing inappropriate retention of sodium and chloride in renal tubules and alterations in renally active hormones (Musabayane et al., 2000). Quinine can precipitate acute kidney injury through immune-mediated reactions, especially thrombotic microangiopathy (Al-nouri et al., 2015; Liles et al., 2015). Artesunate may cause nephrotoxicity marked by diminished glomerular filtration capacity, increased kidney blood flow and urinary excretion of electrolytes (Campos et al., 2001) which may be reversible as reported in animal studies (Li et al., 2007).

Dihydroartemisinin-piperaquine (D/P) is recommended by the World Health Organization (WHO) for the treatment of *Plasmodium falciparum* (*P.falciparum*) associated malaria (WHO, 2015). The complementary mechanisms of action of the combined drugs increase the effectiveness of treatment and prevent or delay the emergence of resistance (Reuter at al., 2015). D/P has demonstrated 100% clinical efficacy for the treatment of uncomplicated *P. falciparum* malaria with a day-3 parasitemia-positive rate of 6.2% (Sun et al., 2011). Nevertheless, the development of *Plasmodium* parasite resistance was observed in malaria endemic regions (Georgewill et al., 2021) and the possible occurrence of nephrotoxicity (Alabi et al., 2018). Desloratadine (DL) is a second-generation non-sedating antihistamine with long-acting activity used for the treatment of seasonal allergic rhinitis and idiopathic urticarial (Kazmi et al., 2015). In addition to its anti-histamine activity, it has shown promising antimalarial activity (Aneesa, 2011). DL has been shown to increase the antiplasmodial activity of D/P, which suggests possible clinical use as an antimalarial drug (Georgewill et al., 2021). However, there is lack of scientific safety data on DL and D/P combination. The current study deemed it imperative to assess the safety of DL/D/P by tacking into cognisance effect on the kidneys of healthy and *P. berghei*-infected mice.

2. MATERIALS AND METHODS

2.1. Drugs, Animals, and Malaria Parasite

Fifty-four adult Swiss mice (22-25g) were procured from the animal unit of the Department of Pharmacology, Faculty of Basic Cinical Sciences, University of Port Harcourt, Rivers State, Nigeria. The mice were grouped (n=6/group) and acclimated for 2 weeks before the study commenced. The mice were kept under natural conditions and had access to food and water freely. Desloratadine (DL) (Merck & Co), and Dihydroartemisinin/piperaquine (D/P) (Bliss GVS Pharma Ltd India) were used. The doses of (D/P) (1.71/13.7 mg/kg), and DL (5 mg/kg) used were derived from previous antiplasmodial studies (Georgewill et al., 2021).

2.2. Parasite inoculation of mice and treatment

Mice infected with chloroquine-sensitive *P. berghei* (NK65) supplied by the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos, Nigeria, were used as the donor. Thirty mice were randomised into 5 groups of n=6/group. Groups II-V were inoculated intraperitoneally (i.p) with *P. berghei* containing 1×10^7parasitized erythrocytes. After 3 days, treatment commenced orally as follows: Group 1(Normal control) and group II (parasitized control): normal saline (0.2 ml), groups III-V: (D/P) (1.71/13.7 mg/kg), DL (5 mg/kg) and DL/D/P daily for 4 days, respectively.

2.3. Treatment of healthy mice

Twenty-four adult Swiss albino mice were grouped into 4 of n=6/group. Group I (Control) daily received normal saline (0.2mL) orally for 28 days. Groups II-IV orally received (D/P) (1.71/13.7 mg/kg), DL (5 mg/kg) and DL/D/P daily for 28 days, respectively.

2.4. Animal sacrifice

After treatment, the mice were fasted overnight, weighed and anesthetized (diethylether), and blood samples were obtained by cardiac puncture. Blood samples were centrifuged (1200 rpm for 20 minutes) and sera separated and evaluated for renal biochemical markers. The mice were sacrificed, kidneys were harvested, rinsed in saline and homogenized in 0.1 M Tris-HCl

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solution buffered (pH 7.4). The homogenates were centrifuged (2000 rmp for 20 minutes) and the supernatants decanted and evaluated for oxidative stress markers.

2.5. Serum biochemical markers assessments

Sera were evaluated for creatinine, urea, uric acid, and electrolytes (sodium, potassium, chloride, and bicarbonate ions) using an auto analyser.

2.6. Oxidative stress marker assay

Kidney glutathione (GSH) was assessed as described by Sedlak and Lindsay (1968). Catalase (CAT) was assessed as explained by Aebi, (1984). Glutathione peroxidase (GPx) was evaluated according to the protocol reported by Rotruck *et al*. (1973). Superoxide dismutase (SOD) was determined as described by Sun and Zigman (1978). Malondialdehyde (MDA) was measured using the protocol explained by Buege and Aust (1978).

2.6. Histology of the kidney

Harvested kidney tissues were cut and immersed in Bouin's solution for 24hr. The tissues were dehydrated in alcohol-graded series, processed and fixed in paraffin wax. Sections (3 μm) were cut and stained (Haematoxylin and Eosin) on slides. The slides were examined under light microscope and appropriate sections photographed using a digital camera.

2.7. Statistical analysis

Data are presented as mean ± standard error of mean (SEM). Differences between groups were assessed using one-way analysis of variance (ANOVA) followed by Tukey's multiple range test (Graph Pad Prism 5 Software, San Diego, CA USA). *P* values less than 0.05, 0.01 and 0.001 were considered statistically significant.

3. RESULTS

3.1. Effects of desloratadine/dihydroartemisinin/piperaquine on body, kidney weights and serum biochemical markers of parasitized mice

Parasitized mice treated with DL, D/P and DL/D/P for 4 days showed no evident (P > 0.05) changes in body and kidney weights when compared to control (Table 1). Treatment of parasitized mice with DL, D/P and DL/D/P for 4 days had no significant (P > 0.05) effects on serum urea, uric acid, creatinine and serum electrolytes when compared to control (Tables 2 and 3).

3.2. Effects of desloratadine/dihydroartemisinin/piperaquine on body, kidney weights and serum biomarker of healthy mice

Healthy mice treated with DL, D/P and DL/D/P for 28 days showed significantly reduced body weight at P < 0.05, P < 0.05 and P < 0.01, respectively when compared to control (Table 1). Treatment of health mice with DL, D/P and DL/D/P significant increased kidney weight at P < 0.05, P < 0.05 and P < 0.01, respectively when compared to control (Table 1). Serum creatinine, urea, and uric acid levels were elevated significantly in healthy mice treated with DL (P < 0.05), D/P (P < 0.05) and DL/D/P (P < 0.01) when compared to control (Table 2). The effects of DL, D/P and DL/D/P on serum electrolytes levels in healthy mice were not significantly (P > 0.05) different from the control (Table 3).

Table 1: Effects of desloratadine/dihydroartemisinin/piperaquine on body and kidney weights of healthy and parasitized mice

Treatment	Final body weight (g)		Absolute kidney weight (g)		Relative kidney weight (%)	
	Healthy mice	Parasitized mice	Healthy mice	Parasitized mice	Healthy mice	Parasitized mice
Control	30.10±2.18	29.60±3.01	0.58± 0.04	0.46±0.05	1.92±0.03	1.55±0.03
DL	24.20±2.72*	29.20±2.14	0.74±0.03*	0.43±0.03	3.05±0.05*	1.47±0.07
D/P	23.70±2.23*	27.40±2.28	0.80±0.05*	0.44±0.07	3.37±0.03*	1.61±0.05
DL/ D/ P	20.20±3.47$^{\pi}$	26.80±2.15	0.99±0.02$^{\pi}$	0.42±0.04	4.90±0.04$^{\pi}$	1.57±0.04

Data as mean ± SEM, SEM: Standard error of mean. n=6, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, * p<0.05, $^{\pi}$ p<0.01 Differ significantly when compared to control (Healthy mice) (ANOVA).

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Table 2: Effect of desloratadine/dihydroartemisinin/piperaquine on serum renal function markers of healthy and parasitized mice

Treatment	Healthy mice			Parasitized mice		
	Creatinine (mg/dL)	Urea(mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)
Control	0.72±0.05	9.35±0.07	3.84±0.20	0.78±0.04	9.77±0.03	1.58±0.34
DL	1.38±0.03*	12.50±1.15*	2.96±0.11*	0.73±0.06	9.86±0.06	1.64±0.28
D/P	1.51±0.07*	14.20±0.22*	3.57±0.09*	0.76±0.09	9.97±0.09	1.57±0.51
DL/ D/ P	2.58±0.02π	21.50±1.75π	5.12±0.67π	0.78±0.05	9.99±0.05	1.53±0.69

Data as mean ± SEM, SEM: Standard error of mean. n=6, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, * p<0.05, π p<0.01 Differ significantly when compared to control (Healthy mice) (ANOVA).

Table 3: Effect of desloratadine/dihydroartemisinin/piperaquine serum electrolytes of healthy and parasitized mice

Treatment	Healthy mice				Parasitized mice			
	K (mmol/L)	Na (mmol/L)	C1 (mmol/L)	HCO_3 (mmol/L)	K (mmol/L)	Na (mmol/L)	Cl (mmol/L)	HCO_3 (mmol/L)
Control	5.84±0.72	121.76±13.2	135.25±14.1	14.25±1.86	5.57±0.39	107.96±12.9	123.87±14.0	15.27±1.80
DL	5.81±0.66	118.53±11.5	132.93±12.2	14.11±1.57	5.60±0.24	109.85±12.4	125.95±13.3	15.58±1.29
D/P	5.78±0.46	117.15±14.8	130.87±12.0	13.88±1.78	5.63±0.16	112.68±13.6	128.06±12.1	15.73±1.85
DL/ D/ P	5.76±0..41	115.43±11.6	127.74±13.4	13.65±1.39	5.67±0.21	114.66±12.1	130.80±10.7	15.86±1.55

Data as mean ± SEM, SEM: Standard error of mean. n=6, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine (ANOVA)

Table 4: Effect of desloratadine/dihydroartemisinin/piperaquine on kidney oxidative stress markers of parasitized mice

Treatment	MDA nmole/mg protein	GSH µmole/mg protein	CAT U/mg protein	SOD U/mg protein	GPx U/mg protein
Control	0.22±0.05	12.00±1.00	23.47±1.44	15.00±2.00	16.71±1.00
PC	0.21±0.07	11.98±1.34	23.40±2.21	14.98±1.63	16.69±1.00
DL	0.23±0.01	11.95±1.21	23.31±2.32	14.96±1.52	16.65±1.26
D/P	0.25±0.04	12.21±1.31	23.29±3.20	15.00±1.27	16.70±1.34
DL/ D/ P	0.27±0.06	11.97±0.67	23.26±3.41	14.89±1.33	16.57±1.33π

Data as mean ± SEM, n=6, SEM: Standard error of mean, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, MDA: Malondialdehyde, GSH: Glutathione, CAT: Catalase, SOD: Superoxide dismutase, GPx: Glutathione peroxidase.

Table 5: Effect of desloratadine/dihydroartemisinin/piperaquine on kidney oxidative stress markers of healthy mice

Treatment	MDA nmole/mg protein	GSH µmole/mg protein	CAT U/mg protein	SOD U/mg protein	GPx U/mg protein
Control	0.29±0.03	10.05±0.81	27.4±1.89	12.34±3.86	17.65±0.21
DL	0.49±0.06*	7.00±0.98*	21.3±2.15*	9.65±3.41*	13.20±0.27*
D/P	0.72±0.09**	5.12±0.53**	17.40±1.26**	7.73±1.57**	10.70±0.61**
DL/ D/ P	1.47±0.02π	4.23±0.39π	12.90±0.83π	4.63±3.01π	7.52±0.25π

Data as mean ± SEM, n=6, SEM: Standard error of mean, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, MDA: Malondialdehyde, GSH: Glutathione, CAT: Catalase, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, * p<0.05, **p<0.01, π p<0.001 Differ significantly when compared to control.

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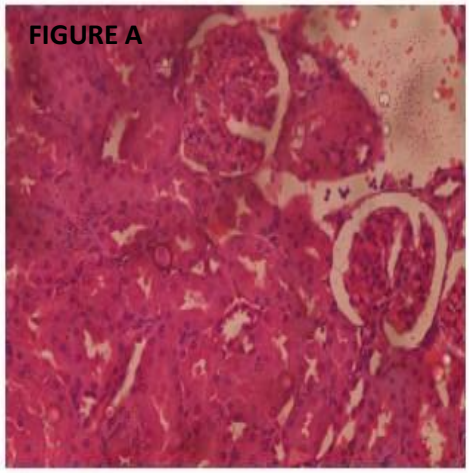
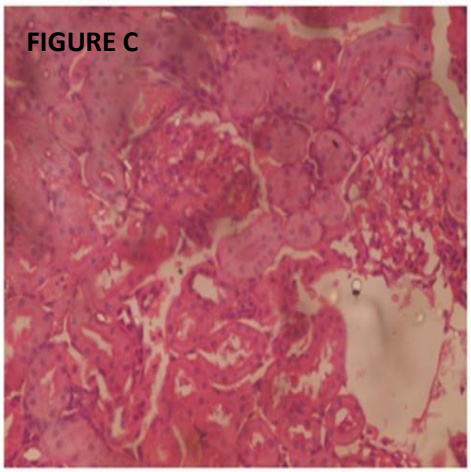
3.3. Effects of desloratadine/dihydroartemisinin/piperaquine on kidney oxidative stress markers of healthy and parasitized mice

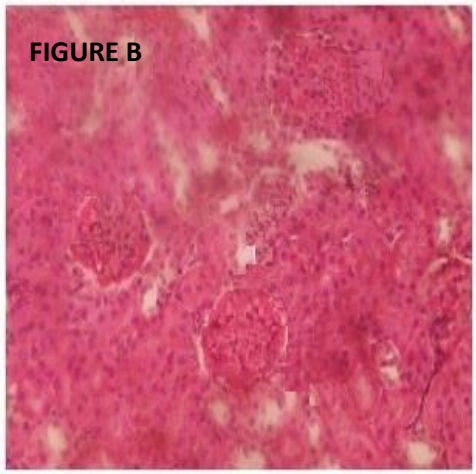
Kidney antioxidants (SOD, GPx, GSH and CAT) were unchanged ($P > 0.05$) in parasitized mice treated with DL, D/P and DL/D/P for 4 days when compared to control (Table 4). But kidney antioxidants were significantly reduced in healthy mice treated with DL ($P < 0.05$), D/P ($P < 0.01$) and DL/D/P ($P < 0.001$) for 28 days when compared to control (Table 5). MDA levels were unchanged ($P > 0.05$) in parasitized mice treated with DL, D/P and DL/D/P for 4 days (Table 4). In contrast, MDA levels were elevated in healthy mice treated with DL ($P < 0.05$), D/P ($P < 0.01$) and DL/D/P ($P < 0.001$) for 28 days when compared to control (Table 5).

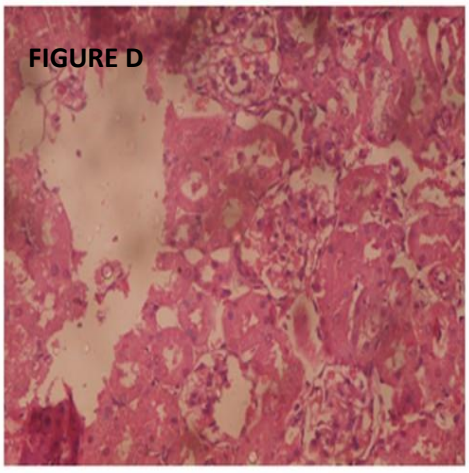
3.4. Effect of desloratadine/dihydroartemisinin/piperaquine on kidney histology of healthy mice

The kidney of the control mice showed normal glomerulus and renal tubules (Fig A) while the kidney of DL (Fig B) and D/P (Fig C) treated health mice showed normal renal tubules and vacuolated glomerular mesangial cells. Kidney of DL/D/P treated healthy mice showed tubular necrosis, vacuolated glomerular mesangial cells and widened Bowman's space (Fig D).









The kidney of control mice showed normal glomerulus and renal tubules (Figure A). Kidney of DL (Figure B) and D/P (Figure C) treated health mice showed normal renal tubules and vacuolated glomerular mesangial cells. Kidney of DL/D/P treated healthy mice showed tubular necrosis, vacuolated glomerular mesangial cells and widened Bowman's space (Fig D). H and EX 400

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4. DISCUSSION

Studies showed promising antimalarial activity of DL/D/P (Georgewill et al., 2021), but without scientific literature on its toxicity profile. This study evaluated the toxicity profile of DL/D/P by assessing impact on kidney function and structure of healthy and *P. berghei*-infected mice. The kidney been a major organ for the excretion of drugs increases its vulnerability to toxicity (Craig et al., 2014). The assessments of organ and body weights are essential aspects in the toxicity studies of chemical substances (Sellers et al., 2007). In this study, DL/D/P had no deleterious impacts on the body and kidney weights of parasitized mice. However, DL/D/P increased kidney weight and decreased body weight in healthy mice after 28days of treatment. The decreased body weight and increased kidney weight may be due to appetite suppression and inflammation caused by DL/D/P, respectively. Renal biomarkers are used to envisage the extent of kidney injury. Clinically, renal biomarkers give essential information on renal status during therapeutic interventions using pharmacologic agents (Gowda et al., 2010). In this study, serum electrolytes, creatinine, uric acid and urea were assessed (Adikwu et al., 2019a) to ascertain the impact of DL/D/P on renal function of treated mice. Treatment with DL/D/P had no detrimental effects on serum creatinine, urea and uric acid levels of parasitized mice. In contrast, DL/D/P treatment for 28 days in healthy mice, increased serum creatinine, urea and uric acid levels. The observations in healthy mice are signs of nephrotoxicity (Adikwu et al., 2019b). Electrolytes such as sodium, potassium, bicarbonate and chloride are vital for basic functions including the generation and conduction of action potentials in nerves and muscles (Shrimanker and Bhattarai, 2021). Serum electrolyte test is used to examine acid-base imbalance, which is important in clinical conditions associated with renal, endocrine and other systems (Gowda et al., 2010). In this study, DL/D/P had no detriment impact on serum electrolytes of healthy and parasitized mice. Reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide and hydroxyl radicals are produced by mitochondria in both physiological and pathological state as metabolic by-products (Pizzino et al., 2017). When ROS increases beyond regulation, it becomes harmful to important cellular structures (proteins, lipids, and nucleic acids) (Wu et al., 2013). Cells utilize antioxidant defensive mechanism like GSH, SOD, CAT, and GPx, to prevent damage due to ROS-induced oxidative stress. Oxidative stress establishes itself when there is excess production and accumulation of ROS in cells which overwhelms antioxidant capacity (Pizzino et al., 2017). In this present study, there were no alterations in kidney antioxidants of parasitized mice treated with DL/D/P for 4 days. However, decreased kidney antioxidants were noted in healthy mice treated with DL/D/P for 28 days. The observation in healthy mice is a pointer to oxidative stress (Adikwu et al., 2021). Lipid peroxidation is a free-radical-mediated chain of reactions that once initiated, results in an oxidative deterioration of polyunsaturated lipids. MDA is a low-molecular weight aldehyde that is produced during lipid peroxidation (Grotto et al., 2009). The determination of MDA has attracted interest, because it offers a facile means of assessing lipid peroxidation in biological systems. The current study observed normal Kidney MDA levels in parasitized mice treated with DL/D/P for 4 days. But kidney MDA levels were elevated in mice treated with DL/D/P for 28 days. The observation connotes that DL/D/P might have induced kidney lipid peroxidation through the degeneration of poly unsaturated fatty acids due to ROS generation in healthy mice. Histology, an imperative tool in toxicity studies is a descriptive and interpretive science that examines the structural manifestations of disease at the light-microscopic level (Crissman et al., 2004). In this study, the histologic examination of the kidneys of DL/D/P treated healthy mice showed tubular necrosis, enlarged bowman's space and vacuolated mesangial cells in the glomerulus. This may be due to oxidative stress induced by DL/D/P causing damage to cellular components (protein, lipids and DNA) in the kidney. In this study, altered serum renal biochemical markers and kidney histology in D/P treated healthy mice support previous studies (Olayinka and Ore, 2013). Despite the fact that DL seems safe (Monroe et al., 2003), this study observed renal damage marked by elevated serum creatinine, urea, uric acid and vacuolated mesangial cells in the glomerulus of treated healthy mice.

5. CONCLUSION

This study suggests that the use of DL/D/P as an antimalarial drug may not perturb the kidney, but prolonged use may cause nephrotoxicity.

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Conflict of Interest:

The authors declare that there are no conflicts of interests.

Ethical approval

The Animal ethical guidelines are followed in the study for experimentation.

Data and materials availability:

All data associated with this study are present in the paper.

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