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Haematological and Biochemical Changes in Sorafenib-Induced Renal Toxicity

Adedoyin Omobolanle Adefisan-Adeoye[1,2], Mercy Oluwabukunmi Odewale[1], Oluwatosin Adekunle Adaramoye[1]*

[1]Drug Metabolism and Toxicology Research Laboratories Department of Biochemistry, College of Medicine, Faculty of Basic Medical Sciences, University of Ibadan, Ibadan, Nigeria
[2]Biochemistry Programme, Chemical Sciences Department, Faculty of Computing and Applied Sciences, Dominion University Ibadan, Ibadan Nigeria

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***Corresponding Author:** Oluwatosin Adekunle Adaramoye
Drug Metabolism and Toxicology Research Laboratories Department of Biochemistry, College of Medicine, Faculty of Basic Medical Sciences, University of Ibadan, Ibadan, Nigeria

Abstract

Sorafenib (SR), a liver cancer drug, is an antineoplastic agent that belongs to the group of drugs known as kinase inhibitors. It functions by preventing the aberrant protein that stimulates cancer cells to proliferate. In this study, we investigated the toxicological implications of SR on the kidneys in male *Wistar* rats. A total of 10 male rats were assigned equally into two groups. Group 1 served as control (received corn oil) while group 2 received SR (10 mg/kg). The SR was administered orally thrice a week for seven consecutive weeks. The blood and kidneys were processed for hematological, histological, and biochemical analyses. Results showed that the administration of SR decreased the body weight gained by 42% while the organo-somatic weight of the kidney increased by 13%, respectively. Administration of SR caused significant decreases in antioxidant activities of catalase and superoxide dismutase by 34% and 31%, respectively, when compared to controls. On the contrary, levels of lipid peroxidation significantly ($P<0.05$) increased by 53% while nitric oxide decreased by 54% in SR-administered rats. Furthermore, the levels of electrolyte concentration decreased in SR-administered rats. Precisely, sodium, potassium, and chloride ions decreased by 4%, 73%, and 17% respectively. Also, the white blood count drastically ($P<0.05$) decreased by 48.3% in SR-administered rats. Histology of kidney tissues revealed normal kidney cells and interstitial spaces with no inflammatory cells in both control and SR groups. In conclusion, the administration of Sorafenib induced oxidative stress with a concomitant decrease in the activities of first-line antioxidant enzymes.

Keywords: Sorafenib, Kidney, Oxidative stress, Antioxidant, Toxicology, Liver cancer.

INTRODUCTION

Sorafenib is a liver cancer drug that exerts its action in the body of the patients by the inhibition of several kinase proteins that are involved in both tumor cell proliferation and angiogenesis (Kashin *et al*, 2016). It is an orally administered drug that has been previously proven and used for the treatment of other solid tumors and was recently found to improve the chances of survival in patients with advanced stages of Hepatocellular Carcinoma (HCC), owing to its significant effects (Bahman *et al*, 2018). According to previous clinical trials, sorafenib exhibits significant importance in the treatment of advanced level of HCC patients through angiogenesis inhibition, cancer cell proliferation, and fibroblast growth factor receptor (Wan, 2012). Sorafenib exhibits major interpatient pharmacokinetic variability, and the research on whether the pharmacokinetic characteristics of sorafenib influence its toxicity or otherwise is still ongoing (Pascaline *et al*, 2012). Sorafenib, a molecular targeted medication for HCC, is recommended as a first-line treatment for patients suffering from primary HCC and, over the years has increased the survival rate of patients despite the inter-individual variability of pharmacokinetic parameters (Le Grazie *et al*, 2017).

Although sorafenib is useful in the treatment of HCC, it is best prescribed for patients with an advanced stage of HCC because patients with early stages of HCC can still have a good outcome if they opt for an organ transplant or surgery (Liu *et al,* 2023). However, sorafenib has a more significant role in the treatment of patients with advanced HCC that are no longer responsive to curative treatments such as surgery or organ transplant. This is because the advanced stage of

HCC has a very poor prognosis with minimal available options for treatment, and even systemic chemotherapy is not an option either. Therefore, sorafenib is being used as a standard systemic therapy in patients who have either advanced tumors or a well-preserved liver function (Martin, 2011).

Like other targeted drugs, sorafenib exhibits several limitations, such as its susceptibility to metabolic degradation within the body. Sorafenib has also been associated with some adverse side effects and depending on the toxicity level in the patients' system, the reduction of the drug dosage to 200 mg can lead to an amelioration of some of these side effects as well as a permanent discontinuation of the drug for all the patients who exhibit these side effects (Llovet *et al*, 2008). Some of the associated side effects include diarrhea, dermatological symptoms such as skin reactions, fatigue, hand-foot-and-mouth disease, asthenia, anorexia, weight loss, hypertension, and a drastic deterioration in the quality of patients' lives (Mousa, 2008). In 2020, it was documented that some patients developed acquired resistance to sorafenib despite it being a potent treatment for liver cancer for almost a decade (Gu and Tong, 2020).

Due to the effectiveness of sorafenib in treating liver cancer, much emphasis has been placed on its toxicological effect on the liver, neglecting other vital organs such as the kidney that plays regulatory functions and maintains homeostatic balance in the body (Ghelichi-Ghojogh *et al*, 2022). According to the research we conducted to study the toxicological effect of sorafenib on the kidney, evidence of oxidative stress by antioxidant markers and signs of inflammation by hematological profiles was detected in the kidney using male Wistar rats as the model. Despite the significant role sorafenib has on the liver of a patient suffering from advanced HCC, efforts at assessing its toxicological effects on the kidney have not been well researched in depth. Thus, this present study aimed to evaluate the toxicity of Sorafenib on the kidneys of male *Wistar* rats. This was achieved by measuring electrolyte concentration, biochemical parameters, hematological protocol, kidney enzyme markers, and histopathological analyses of the kidneys of experimental animals.

MATERIALS AND METHODS

Chemicals

Disodium hydrogen phosphate (Na_2HPO_4), disodium dihydrogen phosphate ($Na_2H_2PO_4$), dithionitrobenzoic acid (DTNB), reduced glutathione (GSH), Griess reagent, hydrogen peroxide (H_2O_2), hypochlorous acid (HOCL), O-dianisidine, N-naphthyl-ethylenediamine (NED), Tris-KCl, and 2-thiobarbituric acid (TBA) were acquired from AK Scientific. All the other chemicals used during this study were of analytical grade.

Animal model

10 male albino Wistar rats (5 weeks old) weighing 80-100g were purchased and housed in the animal house of the Biochemistry department, University of Ibadan. The rats were housed and acclimatized for two weeks after their procurement in the animal house to attain the desired weight, 150g. The rats were housed under standard laboratory conditions in well-aerated rat houses and kept at 25°C, fed with Happy Grower Chicken feed and water *ad libitum* and received humane treatment. The care for the animals and experimental protocols were conducted in line with the standard guidelines set by the University of Ibadan Ethical Committee (UI-ACUREC/057-0623/27). According to the Guide for the care and use of laboratory animals as prepared by (NAS) National Academy of Science and published by the National Institute of Health**.**

Experimental Protocol

The experimental rats were assigned randomly to two groups, each with five rats, and were observed for 49 consecutive days. Group I served as a control and was given corn oil, and Group 2 received sorafenib only (10 mg/kg). The rats administered a 10 mg/kg dose of Sorafenib, thrice per week, which was obtained from Kunle Ara Pharmacy, UCH, Ibadan. The Sorafenib was dissolved in corn oil for easy absorption and administered orally. Twenty-four hours after the last exposure, the final weights of the rats were taken, blood collected from ocular puncture using capillary tubes into lithium heparin tubes and centrifuged at 3000g for 10 minutes. The kidneys were removed from each of the animals after dissection. The sample organs collected were immediately washed in cold rinsing buffer, blotted with filter paper, and then weighed on a weighing balance, recorded, and thereafter processed for biochemical estimations and histopathological analyses. The samples were later diced into smaller pieces and homogenized into 32 volumes of the homogenizing buffer (pH 7.4) by using a Teflon homogenizer. The resulting homogenates were centrifuged at 15 000 rpm for 10 minutes at 4°C to get the post-mitochondrial fraction (PMF). The supernatants were thereafter taken and stored at 4°C and then used for biochemical analysis. A portion of the kidney samples was kept in Bouin's solution for pathological and histological examination.

Protein determination level-

The Lowry *et al*., (1951) technique was used to measure protein levels in serum and kidney tissue.

Assessment of biomarkers of renal oxidative stress:

The Moron *et al*., (1979) technique was used to measure the activity of reduced glutathione (GSH) at 412 nm. The McCord and Fridovich technique (1969) were adopted for measuring superoxide dismutase (SOD) activity. Following Aebi's (1974) approach, Catalase (CAT) activity was evaluated using hydrogen peroxide as a substrate. With CNDB as a substrate, Glutathione-s-

transferase (GST) activity was measured following the procedures published by Habig *et al*. (1974). The Rotruck *et al*. (1973) method was adopted to measure the activity of glutathione peroxidase (GPx). Lipid peroxidation was measured as MDA following the procedure given by Buege and Aust (1978). According to the publication by Palmer *et al*. (1978), the kidney nitrite (NO) concentration was measured using a sodium nitrite curve and expressed as µM of nitrites/mg protein. Following the Trush *et al.,* (1994) method, myeloperoxidase (MPO) activity in kidney tissues was evaluated. Total sulphydryl (TSH) levels in kidney tissue were evaluated using Ellman's (1979) method and minor variations by Adefisan *et al.* (2019).

Histology:

Kidney tissue sections dropped in 10 % formalin were dehydrated in 95 % ethanol, then cleansed in xylene before being immersed in paraffin oil. Micro sections (3 µm) of kidney tissue were produced, stained with haematoxylin and eosin (H&E), and carefully inspected under a light microscope by a histopathologist oblivious of treatment groups.

Statistical analysis:

All the results were expressed as mean ± standard deviation (SD) of ten rats per group. The data were analyzed using the One-way analysis of variance (ANOVA), and statistical significance was determined at $p<0.05$.

RESULTS

Body weight gain and organo-somatic indices of the kidney of rats

The body weight gained and organo-somatic indices (OSI) of the kidneys for the control and sorafenib groups are presented in Table 1. After the exposure period, some effects of sorafenib were observed in the rats. The drug administration decreased the body weight gained of the rats by 42 % and increased the organo-somatic weight by 13 % when compared to the control group.

Table 1: Effect of Sorafenib on body weight and organosomatic weight of kidney in male *Wistar* rats

Groups (g)	(g)	Initial wt. (g)	Final wt. (g)	Weight diff. somatic wt (% bwt)	Kidney wt.
Control		144.20±1.48	192.80±12.64	48.60±12.20	1.10±0.13
SR (10mg/kg)	174.29±3.27	202.20±8.47	28.00±11.34	1.27±0.10	0.63±1.18

Values are expressed as mean ± S.D of 10 animals.
*Significantly different from control
Wt = weight, bwt- body weight, Diff = Difference, SR = Sorafenib.

Sorafenib decreased the electrolyte concentrations and biochemical parameters in the kidneys of exposed rats

There was a significant ($P<0.05$) decrease in the electrolyte concentrations of animals treated with sorafenib, as depicted in Table 2. Precisely, the levels of potassium, chlorine, and sodium ions decreased by 73 %, 17 % and, 4 %, respectively. However, there was a significant increase in the levels of hydrogen carbonate by 46 % in the kidneys of animals given sorafenib. Furthermore, the administration of sorafenib caused a significant decrease in renal biochemical parameters as displayed in Table 3. Specifically, the activities of urea and albumin decreased by 6 % and, 21 % respectively. However, there was a slight increase in creatinine levels of 8 % in the kidneys of Sorafenib-administered rats compared to the control group.

Table 2: Effect of Sorafenib on electrolyte concentration on the kidney of male Wistar rats.

Treatment	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	$HCO3^-$ (mmol/L)
Control	156.67±2.52	20.73±17.068	152±22.65	7.33±3.05
SR (10mg/kg)	150.33±2.31	5.7±2.6*	126.67±4.16	10.67±0.58*

Values are expressed as Mean ± SD of 10 animals.
* Significantly different from control ($p<0.05$). Na^+- Sodium ion, K^+- potassium ion, Cl^-- chloride ion, $HCO3^-$- bicarbonate ion

Table 3: Effect of Sorafenib on biochemical parameters on the kidney of male Wistar rats.

Treatment	Urea(mg/dL)	Creatinine(mg/dL)	Albumin(g/dL)	Total protein(g/dL)
Control	48±1	0.53±0.05	12.3±2.56	5.3±0.75
Sorafenib (10mg/kg)	45±7.9	0.57±0.06	9.73±0.85	4.57±0.21

Values are expressed as Mean ± SD of 10 animals. Changes in kidney function parameters in sorafenib-administered rats.

Sorafenib increased hematological indices in the kidneys of exposed rats

The influence of sorafenib administration on the hematological indices in the kidneys of the rats is presented in Table 4. There was an increase in the levels of hematological indices in rats administered with sorafenib. Precisely, the levels of EO increased by 66 %, PLAT increased by 21%, the total PCV increased by 5 %, LYMPH increased by 4 %, RBC increased by 3 % while HB increased by 2 % respectively. On the other

hand, the levels of WBC and NEUT decreased by 48.3 % and 14.3 % respectively.

Table 4: Effect of Sorafenib on hematological protocol in male Wistar rats.

Grouping	Control	Test
PCV	56.00±2.71	58.75±2.75
HB	18.48±0.29	18.83±0.29
RBC	9.02±0.52	9.3±0.56
WBC	2225±278.39	1150±177.95*
PLAT	40250±9912.11	48750±11672.62
LYMPH	78.50±5.80	81.50±5.51
NEUT.	19.25±6.02	16.50±6.03
MON.	1.50±0.58	1.50±0.58
EO	1.50±0.96	2.50±1.00*

PCV = Part cell volume, HB = Hemoglobin, RBC = Red blood cells, WBC = White blood cells, PLAT. = Platelet, LYMPH = Lymphocytes, NEUT. = Neutrophils, MON. = Monocytes, EO = Eosinophil.
Values are expressed as Mean ± SD of 10 animals.

- Significantly different from control ($p<0.05$).

Sorafenib induced oxidative damage and inflammation in the kidneys of exposed rats

The indices of oxidative stress in the kidneys of control rats and those administered with Sorafenib are depicted in Figures 1-4. There was an increase in oxidative stress indices and a decrease in antioxidant status in rats given sorafenib compared with the control group. A significant ($p<0.05$) increase in lipid peroxidation (LPO) levels of 53 % relative to the control was observed. Additionally, Sorafenib administration significantly decreased the activity of antioxidant enzymes. Specifically, there was a significant decrease in superoxide dismutase (SOD) activities by 31% and catalase (CAT) activities decreased by 34.2% when compared to controls. However, there was a slight increase in reduced glutathione levels of 4 % but not significantly expressed. In addition, the influence of sorafenib administration on the inflammatory biomarkers in the kidneys of exposed rats is presented in Figures 1-4**.** Administration of sorafenib slightly increased the MPO activities by 2.1% but not significantly expressed when compared with the control. However, the activity of NO significantly decreased by 54 % in sorafenib-administered rats relative to controls.

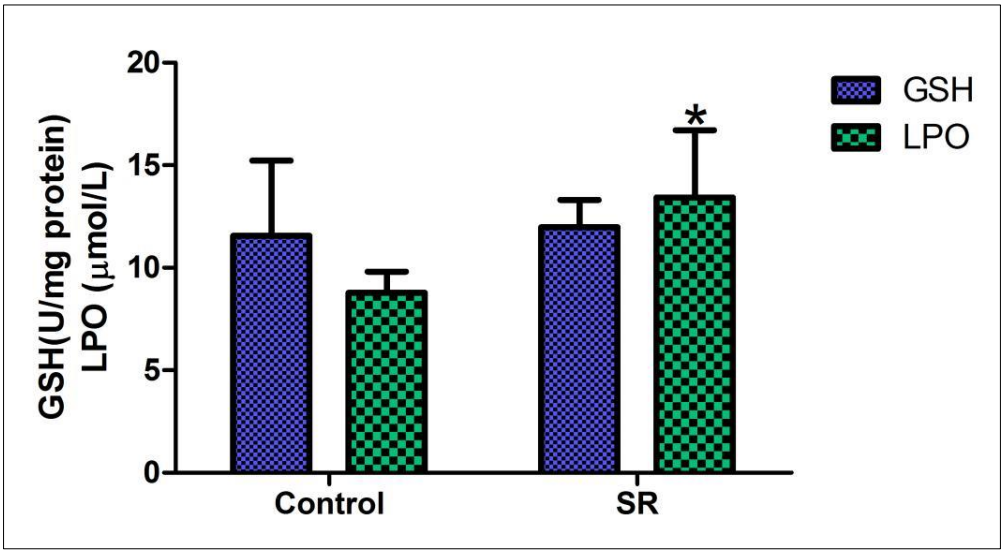


Figure 1: Effects of Sorafenib on renal reduced glutathione levels in male Wistar rats
Values are expressed as mean ± SD of 8 animals.
*Significantly different from control ($p<0.05$)
SR= Sorafenib, GSH= reduced Glutathione, LPO= Lipid peroxidation.

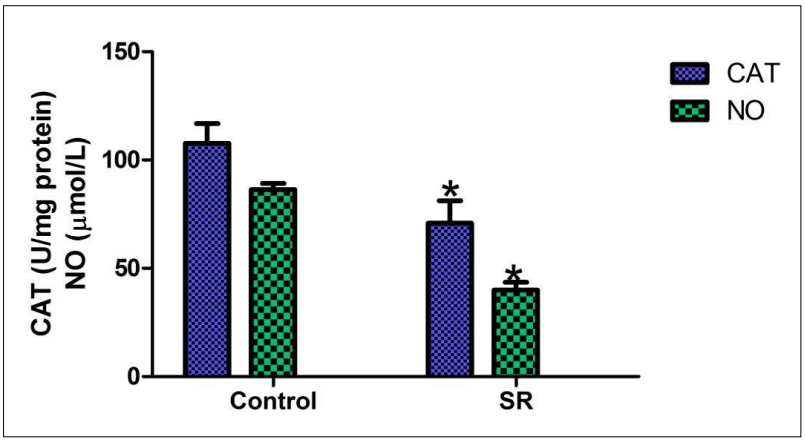


Figure 2: Effects of Sorafenib on renal catalase activities in male Wistar rats
Values are expressed as mean ± SD of 8 animals
*Significantly different from control ($p<0.05$)
SR= Sorafenib, CAT=Catalase, NO= Nitric oxide

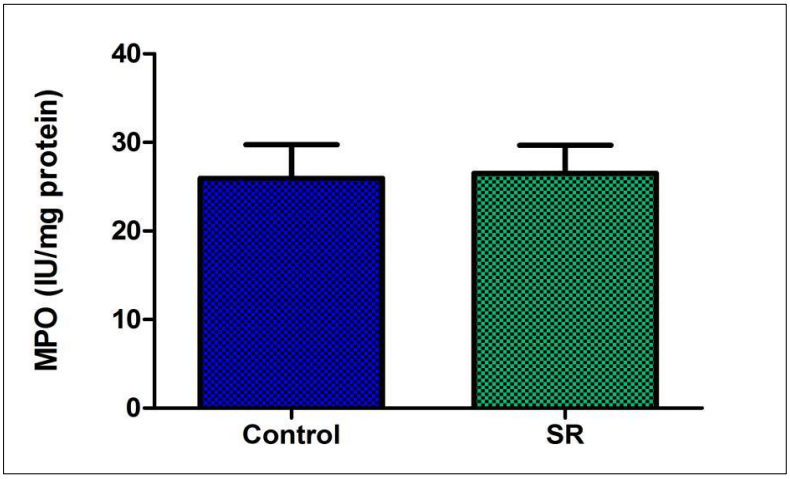


Figure 3: Effects of Sorafenib on renal myeloperoxidase activities in male Wistar rats
Values are expressed as mean ± SD of 8 animals
SR= Sorafenib, MPO=Myeloperoxidase

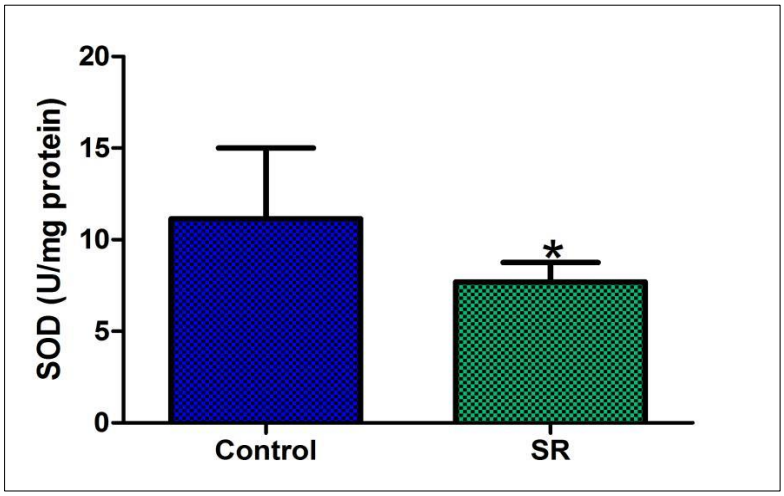
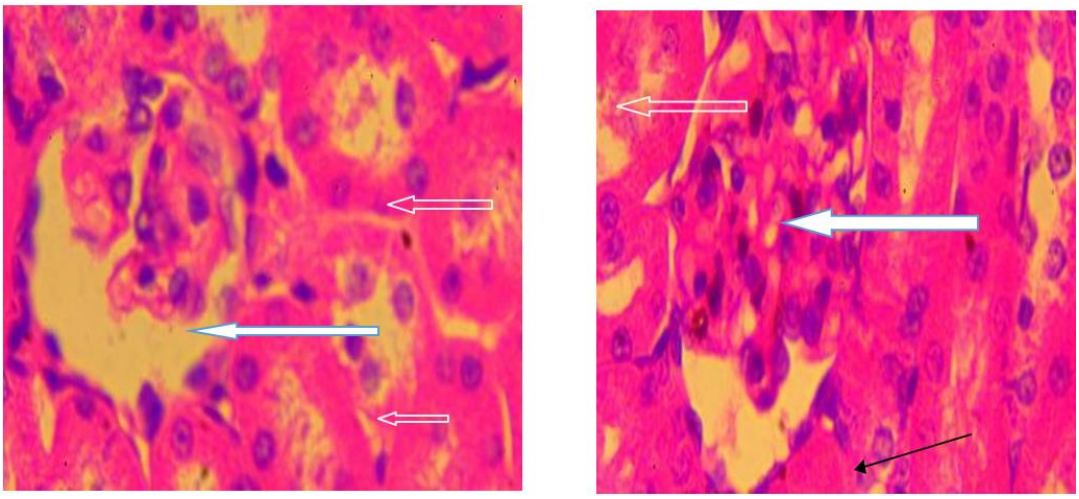


Figure 4: Effects of Sorafenib on renal superoxide dismutase activities in male Wistar rats
Values are expressed as mean ± SD of 8 animals
*Significantly different from control ($p<0.05$)
SR= Sorafenib, SOD= Superoxide dismutase.

Sorafenib retains the histology of the kidney of exposed rats

Figure 5 depicts the representative photomicrographs of the kidney from the control and sorafenib groups**.** Microscopic examination revealed normal architecture, the renal cortex shows normal glomeruli with normal mesangial cells and capsular spaces. The renal tubules and the interstitial spaces appear normal for both the Sorafenib and control groups. Therefore, the kidneys of the rats in both groups had a normal histological appearance, indicating no signs of toxicity.



Control **Sorafenib**

Figure 5: Photomicrograph showing the effect of Sorafenib on kidney integrity in male Wistar rats
White arrow: capsular spaces, blue arrow: renal tubules, slender arrow: interstitial spaces.

DISCUSSION

Hepatocellular carcinoma is one of the deadliest and most common type of liver cancer in the world (Massarweh *et al,* 2017). However, technological advancements have made liver cancer treatments much easier with hepatectomy and drugs, such as Sorafenib (Lee *et al*, 2017). While hepatectomy is an effective method for liver cancer treatment, some studies have revealed that sorafenib is a much more effective treatment method, such that it prevents the recurrence of liver tumors in hepatocellular carcinoma (Labeur e*t al*, 2020). Sorafenib characteristic effects on the system, such as apoptosis and anti-angiogenesis, make it a better drug option for liver cancer patients who have had hepatectomy (Feng *et al*, 2014). In recent times, sorafenib has been prescribed for the treatment of different cancer diseases aside from HCC, such as renal cell carcinoma, breast cancer, colon cancer, and prostate cancer (Gauthier *et al*, 2013). Like any other drug, studies have revealed that sorafenib has an acceptable level of toxicity in the system of patients with advanced HCC (Cheng *et a*l, 2009). While many studies have been conducted to determine the toxicological and adverse effects of sorafenib on the liver, not much is known about its effect on the kidney (Hootegem *et al*, 2010). For liver cancer patients, it was observed that sorafenib induced treatment-related toxicities, including diarrhoea, hypertension, and fatigue (Li *et al*, 2015). This current investigation, however, showed the toxicological effects of sorafenib in the kidneys of the rat by evaluating parameters such as hematological parameters, body weight loss, organo-somatic weight, among others. Aside from the organo-somatic effects, biochemical parameters, inflammatory markers, and histological analyses were also assessed to evaluate the toxicology profile of sorafenib on the kidneys of the rats. From our findings, sorafenib triggers renal toxicities and induces oxidative stress in the kidneys of the experimental rats.

Biochemical parameters have a significant role in evaluating toxicological profiles because changes in the biochemical levels are considered one of the best general indicators of toxicity level in the system (Singla *et al,* 2019). This study indicated via biochemical and hematological parameters that sorafenib incited oxidative and inflammatory responses in the kidneys of rats that were administered sorafenib. Kidney function tests can provide adequate information on the prognosis of several kidney diseases, which is why these tests were conducted to determine sorafenib renal toxicity (Lopez-Giacoman *et al*, 2015). Creatinine, urea, and electrolytes are three important biochemical markers required for the proper function of the kidney. This study revealed that there was an increase in creatinine levels, which indicates a reduction in the renal function of the kidneys in the rat models (Pandya *et al*, 2016). The decreased urea, albumin, and total protein levels indicate potential kidney damage (Martin, 2011). This implies that the kidney integrity was slightly compromised following the administration of sorafenib to the rats for the exposure duration. However, in a study conducted by Demirtas and colleagues (2023), their findings revealed that sorafenib exacerbated liver damage in both cisplatin-treated and healthy mice and when delivered to healthy rats, sorafenib had no significant effect on the kidneys; however, it did have a healing effect on the kidneys after

cisplatin induced stress. These findings may be attributable to the sorafenib exposure time of 7 days (Demirtas *et al,* 2023), implying that a longer sorafenib treatment of the rats might result in potential kidney damage. Specifically, the toxicity of sorafenib to a healthy kidney wasn't confirmed by Demirtas and colleague's (2023) study. According to the parameters they studied, they administered sorafenib (20 mg/kg) to the rats for only 7 days. The short period of exposure might be insufficient to show renal toxicity, even though liver toxicity was confirmed. However, in our study, Sorafenib (10 mg/kg) was administered for 49 days, a higher cumulative exposure, enough to show slight toxicity of sorafenib to a healthy kidney. Therefore, alterations in the biochemical activities of these kidney markers are an indication of impaired kidney function (Kalra *et al*, 2010).

In addition, inflammation of the kidney was induced by Sorafenib, indicating that this drug can cause the activation of the signaling process that activates essential processes, leading to kidney inflammation (Martens *et al*, 2017). Several pro-inflammatory proteins also cause neutrophils, a WBC component, to generate MPO and reactive oxygen species during an infection (Wright *et al*, 2010). In this experiment, Sorafenib affected inflammatory biomarkers by slightly increasing MPO activities and drastically decreasing NO levels. The implication of an increase in MPO activity is a result of kidney inflammation, and MPO is an enzyme that uses hydrogen peroxide to generate reactive oxygen species (ROS) that exacerbate kidney oxidative injuries (Correa *et al*, 2020). Decreased NO production is also detrimental to kidney health as it indicates a problem with blood flow regulation within the kidney (Ahmad *et al*, 2018).

The Kidney is one of the organs in the body that plays several major roles, including xenobiotics (detoxification of foreign substances such as chemicals, drugs, and toxins inside the body), and the excretion of waste products of such metabolism from the body (Ghelichi-Ghojogh *et al*, 2022). Therefore, the kidney can be a prime target for first-line targeted drugs such as Sorafenib. Thus, investigating the integrity of the kidney following its exposure to sorafenib is essential in determining if it is unaffected. In this study, an investigation on ROS production in the kidney was conducted to investigate if administering sorafenib to animals induced oxidative damage. Catalase and SOD are two important forefront antioxidant enzymes against reactive oxygen species (Saxena *et al*, 2022). SOD is considered the only antioxidant enzyme connected with the foraging of radical superoxide by changing it to oxygen and hydrogen peroxide, thus obviating more oxidative damage (Lobo *et al,* 2010). The hydrogen peroxide formed can therefore be changed to oxygen and water by catalase. From the research we conducted, we observed that the administration of Sorafenib drastically decreased activities of superoxide dismutase and catalase, with a slight increase in reduced glutathione levels in the kidney. Reduced glutathione is a reducing agent that plays a major role in the continuance of antioxidant enzymes' functions and detoxification of xenobiotics in the aqueous state of cellular systems (Rana *et al,* 2002). In renal cell carcinoma, the proposed reason for the increased reduced glutathione levels is the counteracting of damaging ROS to sustain the viability and growth of malignancy (*Xiao et al*, 2019). Therefore, a slight increase in reduced glutathione levels indicates an increase in enzymatic activity, which generally increases antioxidant capacity and resistance to oxidative stress, as observed in cancer cells (Ahmad *et al*, 2010). An imbalance in redox homeostasis through elevated levels of reactive oxygen species and decreased activities of antioxidant enzymes has been linked to apoptosis via oxidative damage to DNA and intracellular proteins (Belozerskaia and Gessler, 2007). The histopathological examinations showed no changes in the renal cells, both in the control and sorafenib groups. Our findings show that even in the absence of obvious histological abnormalities, prolonged exposure to sorafenib causes notable changes in serum biochemical markers and hematological indices suggestive of kidney damage. For long-term sorafenib therapy in clinical settings, these findings underscore the possibility of functional renal impairment occurring before morphological harm.

CONCLUSION

According to the data obtained from this study, it was observed that the administration of sorafenib triggered renal toxicities through an imbalance in antioxidant levels, and the kidneys showed changes in some of the parameters studied. It was observed that oxidative stress was induced with a concomitant decrease in the activities of first-line antioxidant enzymes, resulting in alterations in kidney indices. This study has been able to show that exposure to sorafenib for a lengthy period induces oxidative stress responses, which have a detrimental effect on the kidneys in experimental male Wistar rats. Considering that there is insufficient information on sorafenib, we concluded that our findings will immensely contribute to the currently available literature.

Statements and Declarations

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Competing Interest

The authors do not have any relevant financial or non-financial interests to disclose.

Data Availability

All data are presented in the manuscript. Other data information is available on request to the corresponding author.

Authors Contributions

Ouwatosin Adekunle Adaramoye conceived and designed the study. Material preparation, data collection and analysis were performed by Mercy Oluwabukunmi Odewale and Adedoyin Omobolanle Adefisan-Adeoye. The first draft of the manuscript was written by Mercy Oluwabukunmi Odewale and Adedoyin Omobolanle Adefisan-Adeoye. All authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

Ethics Approval

The care for the animals and experimental protocols were conducted in line with the standard guidelines set by the University of Ibadan Ethical Committee (UI-ACUREC/057-0623/27). According to the Guide for the care and use of laboratory animals as prepared by (NAS) National Academy of Science and published by the National Institute of Health**.**

Consent to Participate: Not applicable

Consent for Publication: Not Applicable

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