



RESEARCH ARTICLE

Protective effects of *Khaya senegalensis* stem bark extracts against acetaminophen-induced oxidative damage, dyslipidaemia, and hepatotoxicity in rats

[version 1; peer review: awaiting peer review]

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Abstract

Background

Free radical attacks have been implicated in the aetiology of many diseases and several plants are used traditionally for the management of many oxidative-stress related diseases. *Khaya senegalensis* is used traditionally for the management diseases such as diabetes and for the treatment of infections. However, mechanisms underlying actions of *K. senegalensis* are poorly understood.

Purpose

This study aimed at the preliminary determination of the phytochemical constituents and investigation of the antioxidative and hepatoprotective actions of *K. senegalensis* in acetaminophen-treated rats.

Method

Aqueous extracts of *K. senegalensis* were screened for the presence of key phytochemicals. Total flavonoid and phenolic contents were quantified. Wistar albino rats were pre-treated with saline (control) or graded concentrations of *K. senegalensis* (50 – 200mg/kgbw) for 10

days prior to acetaminophen (2g/kg body weight) administration. Serum levels of vitamin C, thiobarbituric reactive substances, catalase activities, enzyme markers of liver function were assessed. Cholesterol-phospholipid ratio in treated-rats were determined.

Results

K. senegalensis extract showed the presence of saponins, tannins, cardiac glycosides, alkaloids, flavonoids and phenolic compounds. Total phenolic and total flavonoid contents were determined as $57.14 \pm 0.85 \text{ mgQE/g}$ and $51.72 \pm 0.77 \text{ mgGE/g}$. Acetaminophen (2g/kg bw) raised serum TBARS (4.7-fold, $P < 0.001$), H_2O_2 levels (2.3-fold, $P < 0.001$), AST (5.9-fold, $P < 0.001$), ALT (6.6-fold, $P < 0.001$) and ALP (4.2-fold, $P < 0.001$) and reduced serum levels of vitamin C (54%, $P < 0.001$) and catalase activity (74.6%, $P < 0.001$). Treatment of *K. senegalensis* extracts inhibited effects of acetaminophen on TBARS (18.2% - 46.4%, $P < 0.05 - 0.001$), vitamin C (1.4 - 1.8-fold, $P < 0.001 - 0.05$), H_2O_2 levels (19.1 - 50.1%, $P < 0.001 - 0.05$), catalase activities (1.4 - 3.1-fold, $P < 0.001 - 0.05$), AST (27.7 - 62.8%, $P < 0.001 - 0.05$), ALT (35.6 - 57.5%, $P < 0.001 - 0.05$) and ALP (15.9 - 46.2%, $P < 0.01 - 0.05$). The extract reduced cholesterol-phospholipid ratio (21 - 31%, $P < 0.05$).

Conclusion

These results motivate further development of the therapeutic potential of *K. senegalensis*

Keywords

Acetaminophen, oxidative stress, hepatotoxicity, lipid peroxidation, *Khaya senegalensis*, liver function

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Introduction

The generation of reactive oxygen species is often associated with normal physiological processes such as mitochondrial oxidative metabolism, which is a critical part of cellular respiration.^{1,2} Free radicals produced in healthy state play significant roles in the maintenance of cellular homeostasis, gene expression and receptor activation, and are often produced at a level that the body's antioxidant system can neutralise.^{3,4} However, during cellular injury or exposure to environmental pollutants and toxic materials, excessive production of reactive oxygen species (oxidative stress) occurs at a level that is beyond the body's antioxidant capacity.⁵ Similarly, reactive nitrogen species are produced when cells are exposed to hypoxia, leading to further generation of reactive compounds, such as malondialdehyde and 4-hydroxynonenal.⁶

The accumulation of free radicals, such as Reactive Oxygen Species (ROS) or Reactive Nitrogen Species (RNS), could lead to dire consequences for the cell, including the attack of proteins, lipids, and nucleic acids.⁷ Changes in the structure and functions of these molecules (caused by free radical attacks) have been implicated in the development of various diseases, including cancer,⁸ diabetes,⁹ and cardiovascular diseases.¹⁰ The association between oxidative stress, inflammation and the development of chronic inflammatory diseases have also been reported.¹¹ Increased levels of free radicals have also been associated with damage to body organs such as the brain and the liver.¹²

The need to prevent deleterious effects of free radical, particularly when the body's natural antioxidant system is overwhelmed is one of the reasons for the consumption of food sources or exogenous agents with antioxidative effects.¹³ Plants generally are rich in phytochemicals with significant antioxidant effects and the efficacy of many plant extracts in the treatment of many diseases has been linked with their antioxidative effects.¹⁴ *Khaya senegalensis* (Desr.) A. Juss (also known as mahogany) is an economic tree that is widely distributed across many parts of Africa.¹⁵ Extracts of *K. senegalensis* are reported used in traditional African medicinal practices for the treatment of diabetes, hypertension and infectious diseases such as malaria, diarrhoea and venereal diseases.¹⁶ Laboratory studies have also reported cardioprotective,¹⁷ antidiabetic,¹⁸ antinociceptive,¹⁹ antibacterial,²⁰ and anti-inflammatory²¹ effects of various extracts of *K. senegalensis*. While oxidative stress contributes significantly to the aetiology of the majority of these conditions, it is not yet clear if beneficial effects reported for *K. senegalensis* were mediated via its ability to protect against free radical attacks. Against this background, this study investigates protective effects of aqueous extracts of *K. senegalensis* in animals with acetaminophen-induced oxidative stress.

Methods

Plant materials

Fresh stem barks of *Khaya senegalensis* were collected in Sangere Village near Federal University of Technology (FUT), Yola. Botanical identification was conducted by an expert in the Department of Biological Sciences at the University prior to the deposition of voucher specimen (No: BR2017-20) in the herbarium of the Bioscience Research Education and Advisory Centre, Yola. Collected plant materials were dried under room temperature and were subsequently pulverized into fine powder. Plant powder (10 g) was soaked in distilled water (100 ml) for 12 hours and filtered using a Whatman's No. 1 filter paper. The filtrate was then concentrated using a vacuum concentrator. The resulting residue was weighed and re-suspended in water to produce a stock solution of 100 mg/ml. The stock solution was stored in a freezer (-20°C) until used for experiments.

Phytochemical screening and assessment of total phenolic and flavonoid contents

Aqueous stem bark extracts of *K. senegalensis* were screened for the presence of saponins, tannins, triterpines, alkaloids and flavonoids as previously described.²² The estimation of total phenolic was conducted using the Folin-Ciocalteu's method and by following the procedure described by Kim *et al.*²³ Total phenolic contents were expressed as gallic equivalent per gram of sample (GE/g). Similarly, total flavonoid contents were estimated as previously described by Park *et al.*²⁴ (2008) and expressed as quercetin equivalents per gram sample (QE/g).

In vivo experiments

Animals were male Wistar albino rats (average weight = 127 g), purchased from the animal house of University of Jos, Nigeria. Laboratory animals were maintained in an air-conditioned room (22±2°C) with regulated light:dark cycle. Animals were provided food and water provided *ad libitum* and all procedures were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986 and EU Directive 2010/63/EU for animal experiments. Animals (n = 6 per group) were treated with once daily oral administration of saline or aqueous *K. senegalensis* extract (100 mg/kg body weight). After treatment for 10, rats were administered a single oral overdose with acetaminophen (2 g/kg body weight). Rats in the control group were treated with saline for 10 days and administered with saline instead of acetaminophen. All animals were sacrificed within 12 hours of acetaminophen intoxication under mild anaesthesia. Serum was separated from terminal blood collected by heart puncture into heparinized bottles and stored at -20°C until used for biochemical analysis.

Assessment of effects of *K. senegalensis* stem bark extract on lipid peroxidation

In this study, the effect of pre-treatment of rats with extracts of *K. senegalensis* on acetaminophen-induced lipid peroxidation was assessed by measuring serum concentrations of thiobarbituric reactive substances (TBARS), erythrocyte lysate catalase activities (CAT), serum ascorbic acid level as well as serum cholesterol/phospholipids ratio.

- (a) *Measurement of TBARS*: Concentrations of thiobarbituric reactive substances (TBARS) in the serum of treated and untreated rats were measured as previously described by Ladeji *et al.*²² Serum samples (0.8ml) were mixed with TBA-reagent (1.2 ml, final concentration of 0.02% w/v, Merck UK, Cat. No T5500). Reaction tubes were heated in a boiling water bath for 10 min, allowed to cool down and were centrifuged at 300 rpm after the addition of 0.2N NaOH (2ml, Merck UK, Cat. No 221465). Absorbance of the pink coloured adduct formed was measured at 535nm and results were expressed as mmol/ml.
- (b) *Assessment of catalase activities (CAT)*: CAT activity in the erythrocyte lysates (10 µl) of treated and untreated animals was measured as described by Sinha.²⁵ Hydrogen peroxide (0.2 M, 50 µl, Merck UK, Cat. No 1072090250) was used as a substrate and decrease in the concentration of H₂O₂ at 22°C in phosphate buffer (0.05 M, pH 7.0, 100 µl, Merck UK, Cat. No P3813-1PK) was assessed by measuring absorbance at 240nm.
- (c) *Measurement of serum ascorbic acid levels*: Serum ascorbic acid levels were measured by monitoring the oxidation of ascorbic acid to diketogluconic acid in the presence of 2,4-dinitrophenylhydrazine (DNPH).²² The diphenylhydrazone formed was dissolved in HCl (1M, 200 µl, Merck UK, Cat. No. H1758) to form orange-red coloured complex and absorbance was measured at 520 nm.
- (d) *Serum cholesterol/phospholipids Index*: Serum cholesterol and phospholipids levels were measured as previously described by Searcy *et al.*²⁶ and Kobayashi *et al.*²⁷ respectively. Serum cholesterol/phospholipids index was calculated using the relationship:

$$\text{Cholesterol : Phospholipid Index} = \frac{\text{Concentration of Cholesterol}}{\text{Concentration of phospholipids}} \times 100$$

Assessment of effects of *K. senegalensis* stem bark extract on hepatotoxicity

Serum levels of alanine transaminase (ALT), aspartic transaminase (AST) and alkaline phosphatase (ALP) were estimated to assess the effect of the plant extract on liver function in treated rats. Commercially available kits from Randox Laboratories (Antrim, UK) for each of these parameters were used following the manufacturer's recommended protocol.

Statistical analysis

Results are expressed as mean ± S.E.M. Values were compared using one-way ANOVA followed by Student-Newman-Keuls *post hoc* test. P < 0.05 was considered statistically significant.

Results

Phytochemical analysis of *K. senegalensis* extracts

The screening of *K. senegalensis* extracts for key phytochemicals revealed the abundance of saponins, tannins, cardiac glycosides, alkaloids, flavonoids and phenolic compounds. Moreover, total phenolic and total flavonoid contents of the extracts were determined as 57.14±0.85 mgQE/g and 51.72±0.77 mgGE/g in that order. These values were interpolated from respective standard curves constructed for flavonoid (R² = 0.978) and phenolic (R² = 0.957) compounds.

Actions of *K. senegalensis* extracts on lipid peroxidation and plasma vitamin C level in acetaminophen-treated rats

Plasma malondialdehyde levels in control (saline treated) rats was observed as 10.3±1.8 nmol/l. However, plasma levels of malondialdehyde increased by 4.7-fold (P<0.001) in rats administered with acetaminophen (2 g/kg body weight) alone (Figure 1A). Extracts of *K. senegalensis* significantly inhibited acetaminophen-induced increase in plasma malondialdehyde levels in a concentration-dependent manner. Specifically, the elevation of plasma malondialdehyde levels was inhibited by 18.2% (P<0.05), 39.4% (P<0.01) and 46.4% (P<0.01) in rats treated with *K. senegalensis* at 50, 100 and 200 mg/kg body weight, respectively. Acetaminophen (2 g/kg bw) decreased plasma level of vitamin C by 54.0% (P<0.001) compared to the level observed in saline treated rats (Figure 1B). However, in the presence of *K. senegalensis* extracts, plasma vitamin C concentration increased by 1.4-fold (P<0.05), 1.6-fold (P<0.001) and 1.8-fold (P<0.001) at extract concentrations of 50, 100 and 200 mg/kg body weight respectively compared to rats treated with acetaminophen alone (Figure 1B).

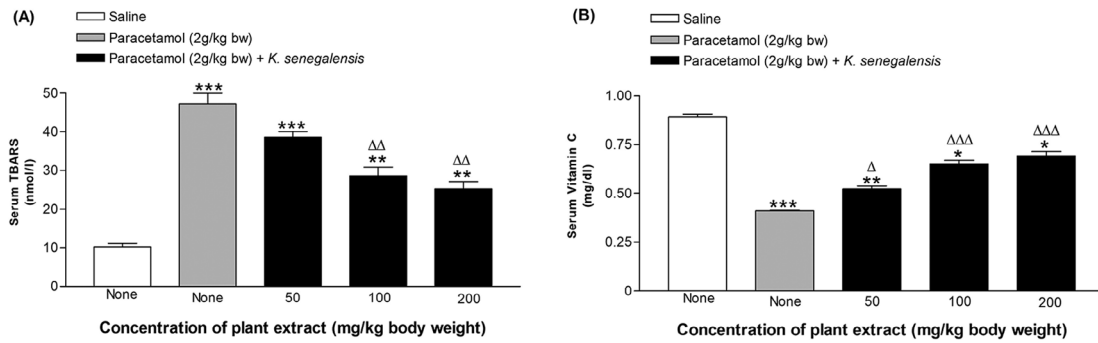


Figure 1. Effects of *Khaya senegalensis* on levels of thiobarbituric reactive substances (A) and vitamin C (B). Values are mean $\pm$ standard error of the mean with $n = 6$. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared with saline treated (control) rats. $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$, and $^{\Delta\Delta\Delta}P < 0.001$ compared with acetaminophen-treated rats in the absence of the plant extract.

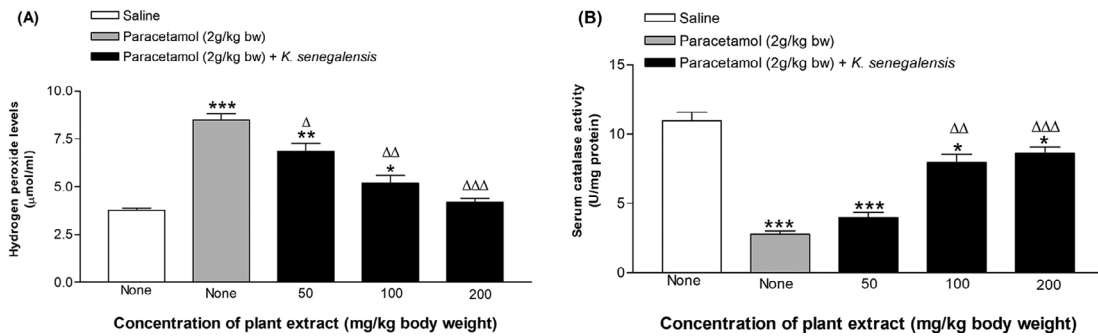


Figure 2. Effects of *Khaya senegalensis* on levels of hydrogen peroxide (A) and catalase activities (B). Values are mean $\pm$ standard error of the mean with $n = 6$. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared with saline treated (control) rats. $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$, and $^{\Delta\Delta\Delta}P < 0.001$ compared with acetaminophen-treated rats in the absence of the plant extract.

Actions of *K. senegalensis* extracts on hydrogen peroxide levels and catalase activities in acetaminophen-treated rats

Elevated serum hydrogen peroxide levels (2.3-fold, $P < 0.001$) were observed in rats treated with acetaminophen (2 g/kg bw) compared to saline treated rats (Figure 2A). However, this elevation of hydrogen peroxide levels was inhibited by the administration of *K. senegalensis* extracts. Specifically, hydrogen peroxide levels reduced by 19.1% ($P < 0.05$) at 50 mg/kg bw, 38.7% ($P < 0.01$) at 100 mg/kg bw and 50.1% ($P < 0.001$) at 200 mg/kg bw compared to rats treated with acetaminophen alone (Figure 2A). For catalase activity, a reduction of 74.6% ($P < 0.001$, Figure 2B) was observed in acetaminophen-treated rats compared to rats treated with saline. A dose-dependent inhibition of the effect of acetaminophen on catalase activities was observed in rats treated with *K. senegalensis*. Catalase activities increased by 1.4- ($P < 0.05$), 2.9-fold ($P < 0.001$) and 3.1-fold ($P < 0.001$) at 50 mg/kg bw, 100 mg/kg bw and 200 mg/kg bw extract concentrations respectively (Figure 2B).

Actions of *K. senegalensis* extracts on plasma cholesterol and phospholipid concentrations in acetaminophen-treated rats

Similar cholesterol levels were observed in rats treated with saline alone or acetaminophen in the presence or absence of *K. senegalensis* extracts (Figure 3A). However, plasma phospholipid concentration reduced by 39.4% ($P < 0.001$) in rats treated with acetaminophen (2 g/kg body weight). Pre-treatment of rats with *K. senegalensis* at 50 mg/kg bw did not produce a significant inhibition of the effect of acetaminophen on phospholipid levels. However, in rats treated with higher concentrations of the plant extracts, improved phospholipid levels were observed (1.3-fold, $P < 0.05$ at 100 mg/kg bw and 1.5-fold, $P < 0.01$ at 200 mg/kg bw). The reduction in plasma levels of phospholipids translated to increased cholesterol-phospholipid ratio for rats treated with acetaminophen alone (1.6-fold, $P < 0.01$) compared with saline treated rats. No significant effect was observed in the presence of *K. senegalensis* extracts at 50 mg/kg bw. However, the ratio reduced by 21% ($P < 0.05$) and 31% ($P < 0.05$) at extract concentrations of 100 and 200 mg/kg bw, respectively.

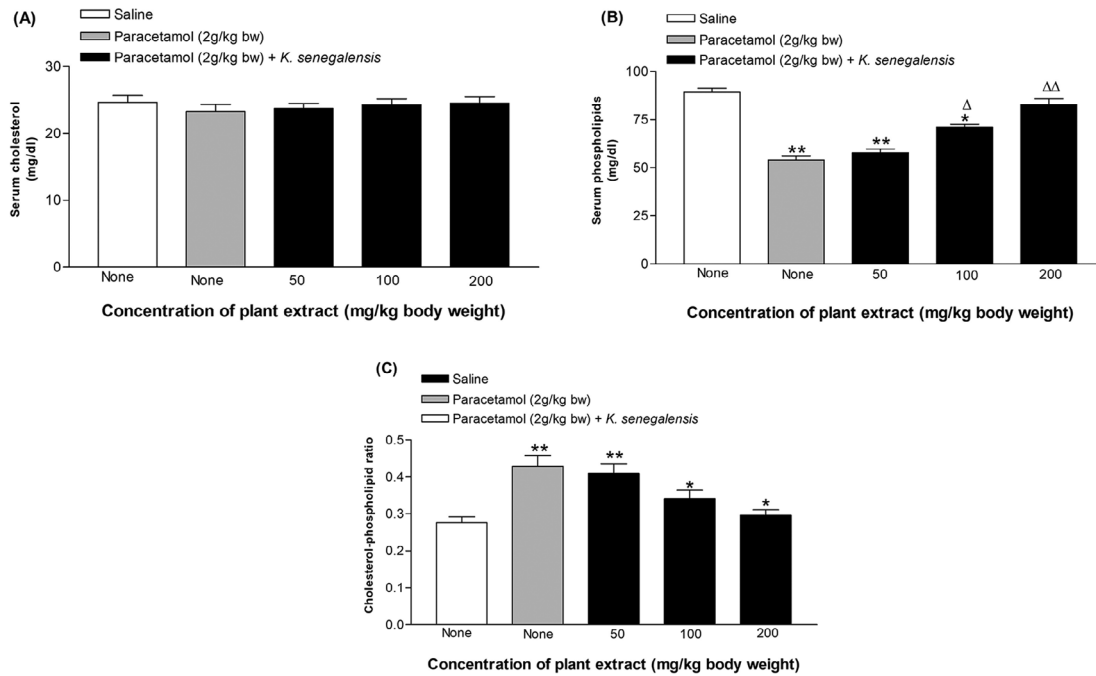


Figure 3. Effects of *Khaya senegalensis* on levels of cholesterol (A), phospholipids (B) and cholesterol-phospholipids ratio (C). Values are mean $\pm$ standard error of mean with $n = 6$. * $P < 0.05$, and ** $P < 0.01$ compared with saline treated rats. $^{\Delta}P < 0.05$ and $^{\Delta\Delta}P < 0.01$ compared with acetaminophen-treated rats in the absence of the plant extract.

Actions of *K. senegalensis* extracts on liver function in acetaminophen-treated rats

Impaired liver function, exemplified by elevated plasma levels of AST (5.9-fold, $P < 0.001$), ALT (6.6-fold, $P < 0.001$) and ALP (4.2-fold, $P < 0.001$) was observed in rats administered acetaminophen (Figure 4). However, the administration of

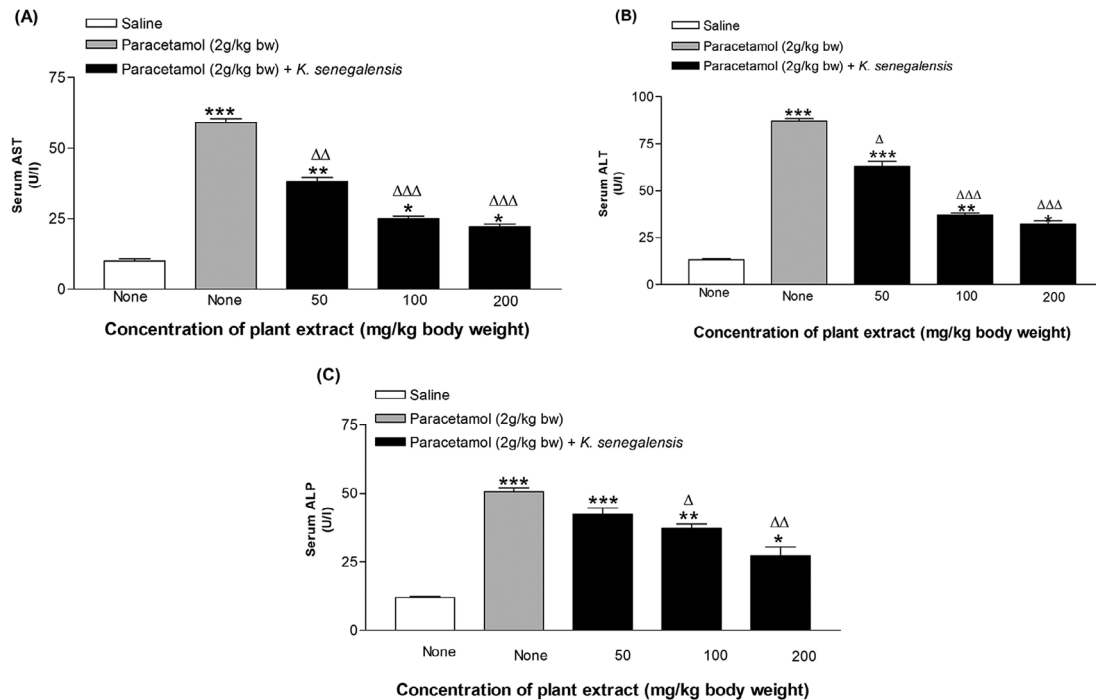


Figure 4. Effects of *Khaya senegalensis* on levels of aspartic transaminase (A), alanine transaminase (B) and alkaline phosphatase (C). Values are mean $\pm$ standard error of the mean with $n = 6$. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared with saline treated (control) rats. $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$, and $^{\Delta\Delta\Delta}P < 0.001$ compared with acetaminophen-treated rats in the absence of the plant extract.

K. senegalensis extract significantly inhibited effects of acetaminophen on these liver enzymes. Plasma levels of AST reduced by 27.7 – 62.8% ($P < 0.001 - 0.05$) in the presence of the plant extract (Figure 4A). Similarly, ALT and ALP levels reduced by 35.6 – 57.5% ($P < 0.001 - 0.05$) and 15.9 – 46.2% ($P < 0.01 - 0.05$) respectively in the presence of the plant extract compared to rats treated with acetaminophen alone (Figure 4B and 4C).

Discussion

Results obtained in this study largely indicate significantly impaired antioxidant status, lipid metabolism and liver function in animals administered high doses of acetaminophen. Effects observed for acetaminophen in this study are consistent with effects observed in previous studies in our laboratory²² as well as effects widely reported previously for acetaminophen at high concentrations.²⁸ Though acetaminophen is safe at low doses and it is often used as analgesic and antipyretic, these studies have consistently indicated the toxicity of acetaminophen at high concentrations.

Consistent with findings of this study, damage to the liver (such as hepatic centrilobular necrosis) and significant formation of lipid peroxidation products have been reported in animals administered high doses of acetaminophen.²⁹ In addition, Ladeji *et al.*²² previously reported that acetaminophen, at the concentration used in this study, produced reduced catalase activity, reduced vitamin C levels, and higher cholesterol-phospholipids ratio in Wistar albino rats. Similar results were obtained in this study. Studies investigating acetaminophen toxicity have suggested that its deleterious effects are caused by the accumulation of the metabolite, N-acetyl-P benzoquinone imine.²⁹ Gorrochategui *et al.*³⁰ particularly highlighted that N-acetyl-P benzoquinone imine interacts with sulphhydryl groups in proteins and lipids to produce organ-level damage observed in acetaminophen-treated animals.^{31,32} In this study, elevated serum levels of enzyme markers of liver function (AST, ALT and ALP) were also observed in this study. This is consistent with liver damage that has been widely reported in animals administered high doses of acetaminophen. As liver cells are destroyed, these enzymes leak into the blood serum.³³

These deleterious effects of acetaminophen were significantly inhibited in animals pre-treated with extracts of *K. senegalensis* extracts in a dose-dependent manner in this study. Specifically, significant reduction in the levels of thiobarbituric reactive substances (TBARS) was observed in animals treated with the plant extract. Also, increased catalase activity and elevated vitamin C levels were observed in extract treated animals. Several mechanisms may be involved in these beneficial actions of *K. senegalensis* extracts. In the first instance, it is possible that phytochemicals in the plant extract interact with N-acetyl-P benzoquinone imine to prevent the metabolite from causing damage to cellular proteins and lipids. On the other hand, it has been reported that the accumulation of N-acetyl-P benzoquinone imine (NAPQI) could lead to the depletion of glutathione stores in the liver, leading to oxidative stress.³⁴ However, it is possible that increased catalase activities associated with the administration of the plant extract may have enhanced antioxidant status in treated animals, thereby preventing oxidative stress caused by NAPQI.

Consistent with these suggestions, studies have reported significant antioxidant effects of various extracts of *K. senegalensis*. For instance, in a study which conducted phytochemical screening of different parts of *K. senegalensis* and assessed antioxidant effects of these extracts, Marius *et al.*³⁵ reported the presence of phytochemicals also identified in this study (including tannin, flavonoids, saponins, flavonoids and cardiac glycosides) and concluded that antioxidative effects observed for these extracts may be linked to their phytochemical constituents. Similarly, Atawodi *et al.*³⁶ reported antioxidant potentials and free radical scavenging effects of leaf, stem and bark extracts of *K. senegalensis*. The study particularly pinpointed that these activities may be due to the preponderance of procyanidin in these extracts.

In this study, *K. senegalensis* extracts were observed to exhibit significant hepatoprotective effects in acetaminophen-administered rats. The observed reduction in the levels of AST, ALT and ALP in extract-treated rats are indicative of reduced damage to hepatocytes and is consistent with observations previously reported for *K. senegalensis*. For instance, in a study which investigated protective effects of *K. senegalensis* extracts against CCl₄-induced liver injury in rats, Ali *et al.*³⁷ reported significantly reduced levels of enzyme markers of liver injury. Similar effects of *K. senegalensis* were reported by Muhammad *et al.*³⁸ These results notwithstanding, the exact mechanism through which *K. senegalensis* extract exhibit its hepatoprotective effects is not yet fully understood. Evidence from the present research strongly suggests that the antioxidative effect of *K. senegalensis*, culminating in its free radical scavenging actions, may play a significant role in its hepatoprotective effects. We hypothesise that reduced levels of free radicals in the presence of the extract will lead to reduced risk of free radical attack leading to liver damage. However, further studies to prove this hypothesis are needed.

In this study, extracts of *K. senegalensis* inhibited deleterious effects of acetaminophen on cholesterol-phospholipid ratio in the serum of treated rats. Cholesterol-phospholipid ratio is a known indicator of the risk of atherosclerosis as well as marker of plasma membrane integrity in human.³⁹ Under normal physiologic conditions, equimolar concentrations of

phospholipids and cholesterol in the plasma membrane is often observed. Therefore, any change in the ratio is an indication of defective lipid metabolism.³⁹ Therefore, actions observed for *K. senegalensis* is beneficial and is indicative of its ability to reduce risks of acetaminophen-induced atherosclerosis in human. Results obtained in this study are consistent with what have been reported for other plant materials. For example, Ladeji *et al.*²² reported a similar inhibition of the effect of acetaminophen on cholesterol-phospholipid ratio in rats treated with extracts of *Prosopis africana* while Trautwein *et al.*⁴⁰ further explained that sterols present in plant samples play significant roles in regulating the rate of cholesterol production in human. Moreover, it has been highlighted that the structural similarity between phytosterols and cholesterol may elicit a form of competition which limits cellular uptake and absorption of cholesterol.⁴¹ However, further investigations of how *K. senegalensis* extracts exhibit these roles are needed.

Conclusion

In conclusion, actions of *K. senegalensis* reported in this study strongly motivates further investigations of its potential utility as a therapeutic agent for oxidative-stress related diseases. The investigation of its efficacy in animal models of these diseases (such as diabetes, cardiovascular diseases and neurological diseases) is recommended. It is also recommended that these future studies should focus on the elucidation of mechanisms underlying actions that have been reported for *K. senegalensis* extracts.

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. Ethical approval for the study was obtained from the Life Sciences Ethical Committee prior to the commencement of the study (Approval date = 08/02/2023; Approval Number = LSEC/2022-23/OO/003). Authors confirm that confirm that all efforts were made to ameliorate suffering of animals. Specifically, animals were placed in air conditioned room with 12 h light:dark cycle. Animals have access to food and water *ad libitum*. The principle of reduction, refinement and replacement was adhered to by ensuring that minimal number of animals were used.

Data availability

Underlying data

Raw data is available via Open Science Framework (DOI [10.17605/OSF.IO/7BE6N](https://doi.org/10.17605/OSF.IO/7BE6N)).⁴²

The project contains the following data:

1. Figures
2. Raw data.xlsx

Extended data

Open Science Framework (OSF): Protective effects of Khaya senegalensis stem bark extracts against acetaminophen-induced oxidative damage, dyslipidaemia, and hepatotoxicity in rats (doi: <https://doi.org/10.17605/OSF.IO/7BE6N>).⁴²

The project contains the following extended data:

1. The ARRIVE guidelines 2 - completed

Data is available under the terms of the [CC0 1.0 Universal licence](https://creativecommons.org/licenses/by/4.0/).

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