



HEPATOPROTECTIVE EFFECTS OF AQUEOUS EXTRACT OF *SYZYGIUM GUINEENSE* LEAVES ON POTASSIUM BROMATE INDUCED LIVER TOXICITY IN WISTAR RATS

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ABSTRACT

Hepatotoxicity remains a major global health concern linked to xenobiotics that disrupt hepatic oxidative balance. Potassium bromates, a potent oxidizing agent and possible human carcinogen, induces hepatic injury through reactive oxygen species generation. This study investigated the hepatoprotective potential of aqueous *Syzygium guineense* leaf extract against potassium bromate-induced liver toxicity in Wistar rats. Twelve Wistar rats were used for acute toxicity testing following Lorke's method. For the hepatoprotective study, twenty Wistar rats were divided into five groups (n=4): Group I (normal control) received distilled water (1 mL/kg); Group II (negative control) received KBrO₃ (100 mg/kg); Groups III-V received KBrO₃ (100 mg/kg) plus *Syzygium guineense* extract at 250, 500, and 1000 mg/kg respectively. All treatments were administered orally for 28 days. Liver function markers (ALT, AST, ALP) were assessed and histopathological examination was performed. The LD₅₀ of *Syzygium guineense* extract was >5000 mg/kg. Phytochemical screening revealed the presence of flavonoids, tannins, saponins, and other bioactive compounds. KBrO₃ significantly elevated ALT levels (10.25 ± 1.18 IU/L) compared to normal control (3.00 ± 0.91 IU/L). Treatment with *Syzygium guineense* extract significantly (p<0.05) reduced ALT levels at all doses tested. Histopathological examination revealed severe hepatic damage in the KBrO₃-only group, while groups treated with 500 and 1000 mg/kg of extract showed marked preservation of hepatic architecture. Aqueous extract of *Syzygium guineense* leaves demonstrated significant hepatoprotective activity against potassium bromate-induced liver damage, supporting its traditional medicinal use.

Keywords: Enzyme, Hepatoprotective activity, Histology, Potassium bromate, *Syzygium guineense*

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INTRODUCTION

Hepatotoxicity is among the most severe outcomes of drug and chemical-induced organ damage, contributing significantly to acute liver failure cases worldwide. As the central organ for xenobiotic metabolism and detoxification, the liver is highly vulnerable to injury from various chemical agents [1]. Drug-induced liver injury (DILI) affects approximately 14–19 individuals per 100,000 annually in developed countries, with potentially higher rates in developing nations like Nigeria due to unregulated exposure to chemicals, traditional remedies, and food additives [2].

The underlying mechanisms of chemical-induced hepatotoxicity are multifaceted, with oxidative stress playing a dominant role. Toxic xenobiotics trigger excessive production of reactive oxygen species (ROS), overwhelming endogenous antioxidant defences such as catalase, superoxide dismutase, and glutathione peroxidase. This imbalance leads to lipid peroxidation, protein denaturation, DNA damage, and ultimately

hepatocyte necrosis or apoptosis [3]. Clinically, this manifests as elevated serum aminotransferases, impaired liver function, and histopathological changes including cellular infiltration, steatosis, and fibrosis.

Potassium bromate (KBrO₃), an oxidizing agent commonly used in the baking industry to improve dough strength and bread texture, has been identified as a potent hepatotoxicant and a possible human carcinogen (Group 2B) by the International Agency for Research on Cancer [4]. It induces oxidative stress via free radical generation, resulting in hepatocellular damage marked by elevated liver enzymes, inflammation, and architectural distortion of hepatic tissue [5]. Despite bans in many countries, potassium bromate remains widely used in Nigerian bakeries due to its affordability and effectiveness [6].

The pursuit of effective hepatoprotective agents has spurred interest in medicinal plants with antioxidant properties. Natural products rich in polyphenols have shown promise in mitigating liver damage by scavenging free radicals, chelating metal ions, and enhancing antioxidant enzyme activity [7]. In Africa, where traditional medicine serves as the

primary healthcare source for nearly 80% of the population, numerous plants are employed to treat liver disorders [8].

Syzygium guineense (Wild.) DC., known as water berry or woodland waterberry, is a medicinal plant from the Myrtaceae family, widely distributed across tropical Africa. Traditional healers have used various parts of this plant to treat ailments such as liver disorders, diabetes, diarrhoea, and inflammation [9]. Phytochemical studies have identified bioactive compounds in *S. guineense*, including flavonoids, tannins, triterpenes, and phenolic acids recognized for their antioxidant and anti-inflammatory effects [10]. Its extracts have demonstrated strong antioxidant activity, including DPPH radical scavenging and inhibition of lipid peroxidation [11].

Despite its traditional use and promising phytochemical profile, scientific validation of *S. guineense*'s hepatoprotective efficacy against chemically induced liver damage remains limited. This study therefore investigates the hepatoprotective effects of aqueous extract of *S. guineense* leaves against potassium bromate-induced hepatotoxicity in Wistar rats, using both biochemical and histopathological assessments.

MATERIALS AND METHODS

Plant collection and authentication

Fresh leaves of *Syzygium guineense* were collected in March 2023 from Duwo village, located in Darazo Local Government Area, Bauchi State, Nigeria. The plant was identified and authenticated by Mr. Namadi Sanusi at the Herbarium, Department of Biological Sciences, Ahmadu Bello University, Zaria. A voucher specimen (V/N: 053) was deposited at the herbarium for future reference.

Preparation of plant extract

The collected *Syzygium guineense* leaves were thoroughly washed with distilled water to eliminate surface debris and then air-dried under shade for two weeks at ambient temperature (25–30°C). Once dried, the leaves were pulverized using an electric grinder to produce a coarse powder.

Aqueous extraction was carried out using the cold maceration technique as described by Sofowora [12]. Specifically, 120 g of the powdered material was soaked in 1200 mL of distilled water in a conical flask. The mixture was continuously agitated on an orbital shaker for 72 hours at room temperature. After maceration, the extract was filtered initially through muslin cloth and subsequently through Whatman No. 1 filter paper.

The resulting filtrate was concentrated using a rotary evaporator at 40°C and further dried in an oven at the same temperature to yield a semi-solid extract. The percentage yield was calculated to be 54.2% (w/w). The final extract was stored in an

airtight container at 4°C until required for experimental use.

Phytochemical screening

Qualitative phytochemical screening of the aqueous extract was performed to identify the presence of various secondary metabolites using standard procedures described by Evans [13]. The extract was tested for alkaloids (Dragendorff's test), anthraquinones (Borntrager's test), carbohydrates (Molisch's test), cardiac glycosides (Keller-Killiani test), flavonoids (Shinoda test), saponins (Frothing test), steroids (Salkowski test), tannins (Ferric chloride test), and triterpenes (Liebermann-Burchard test)

Experimental animals

Thirty-two (32) healthy adults male Wistar rats, weighing between 140–200 g, were obtained from the National Veterinary Research Institute, Vom, Jos, Nigeria. The animals were housed in well-ventilated polypropylene cages (four rats per cage) under standard laboratory conditions: temperature (25 ± 2°C), relative humidity (50 ± 5%), and a 12-hour light/dark cycle. They were fed standard rat pellets (Grand Cereals Ltd., Jos, Nigeria) and given water *ad libitum*. All rats were acclimatized to laboratory conditions for two weeks prior to the start of the experiment.

Ethical considerations

This study adhered to the ethical standards set forth by Bauchi State University to ensure the protection of animal's right and welfare. (Reference: BASUG/FBMS/REC/ VOL. 08/01033)

Acute toxicity study

Acute toxicity was assessed using Lorke's method [14], which was conducted in two phases.

Phase I: Nine male Wistar rats were divided into three groups (n=3) and administered single oral doses of 10, 100, and 1000 mg/kg of the extract. Animals were observed for clinical signs and mortality over 24 hours, then monitored daily for 14 days.

Phase II: Based on Phase I outcomes, three rats received higher doses of 1600, 2900, and 5000 mg/kg. Observations followed the same protocol. The LD₅₀ was calculated as the geometric mean of the lowest lethal dose and the highest non-lethal dose

Experimental design for hepatoprotective study

Twenty adults male Wistar rats were randomly assigned into five groups (n=4 per group):

Group I (Normal control): Received distilled water (1 mL/kg) orally

Group II (Negative control): Received potassium bromate (KBrO₃, 100 mg/kg) orally

Group III: Received KBrO₃ (100 mg/kg) + *S. guineense* extract (250 mg/kg) orally

Group IV: Received KBrO₃ (100 mg/kg) + *S. guineense* extract (500 mg/kg) orally

Group V: Received KBrO₃ (100 mg/kg) + *S. guineense* extract (1000 mg/kg) orally

All treatments were administered once daily for 28 consecutive days. The dose of potassium bromate and duration of exposure were selected based on previous studies [15, 16].

Blood sample collection and biochemical analysis

On day 29, following an overnight fast, rats were anesthetized with ketamine hydrochloride (10 mg/kg, i.p.). Blood samples (3–5 mL) were collected via cardiac puncture into plain tubes. After clotting at room temperature for 30 minutes, samples were centrifuged at 3000 rpm for 15 minutes to separate serum, which was stored at –20°C until analysis.

Serum levels of liver function markers were determined using commercial diagnostic kits. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using Randox kits (Randox Laboratories Ltd., Crumlin, UK), while alkaline phosphatase (ALP) was assessed using Agape Diagnostics kits (Agape Diagnostics, Switzerland). All assays were performed using a UV-Vis spectrophotometer (Jenway 6305, UK) according to manufacturers' protocols.

Histopathological examination

Following blood collection, rats were euthanized by cervical dislocation. The liver was excised, rinsed in ice-cold normal saline, and blotted dry. A section from the left lobe was fixed in 10% neutral buffered formalin for 48 hours. Tissues were dehydrated through graded alcohols (70%, 90%, and 100%), cleared in xylene, and embedded in paraffin wax. Sections (5 µm thick) were cut using a rotary microtome (Leica RM2125, Germany) and stained with hematoxylin and eosin (H&E) following the method of Bancroft and Gamble [17].

Slides were examined under a light microscope (Olympus BX51, Japan) at ×400 magnification, and photomicrographs were captured using a digital camera.

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). Statistical comparisons were made using one-way analysis of variance (ANOVA), followed by Dunnett's post-hoc test to compare treatment groups with the negative control. All analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Acute toxicity study

The acute toxicity assessment of the aqueous extract of *Syzygium guineense* leaves showed no mortality or observable signs of toxicity at doses up to 5000 mg/kg body weight (Table 1). Throughout the 14-day observation period, all animals maintained normal behaviour, physical activity, feeding patterns, and body weight. Based on these findings, the LD₅₀ was estimated to be greater than 5000 mg/kg, indicating a high margin of safety for oral administration.

Table 1: Acute toxicity study of aqueous extract of *Syzygium guineense* leaves

Phase	Dose (mg/kg)	Number of animals	Mortality	Signs of toxicity
I	10	3	0/3	None
I	100	3	0/3	None
I	1000	3	0/3	None
II	1600	1	0/1	None
II	2900	1	0/1	None
II	5000	1	0/1	None

LD₅₀ > 5000 mg/kg body weight

Phytochemical screening

Qualitative analysis of the aqueous extract confirmed the presence of several bioactive compounds (Table 2). Carbohydrates, cardiac glycosides, flavonoids, saponins, steroids, tannins, and triterpenes were detected, while alkaloids and anthraquinones were absent.

Table 2: Phytochemical constituents of aqueous extract of *Syzygium guineense* leaves

Phytochemical Constituent	Inference
Alkaloids	-
Anthraquinones	-
Carbohydrates	+
Cardiac glycosides	+
Flavonoids	+
Saponins	+
Steroids	+
Tannins	+
Triterpenes	+

= Present; - = Absent

Effect on liver function markers

The impact of *S. guineense* extract on serum liver enzymes in potassium bromate-intoxicated rats is summarized in Table 3. Rats treated with KBrO₃ alone (Group II) exhibited a significant (p<0.05) increase in ALT levels (10.25 ± 1.18 IU/L) compared to the normal control (3.00 ± 0.91 IU/L), indicating hepatocellular injury.

Co-treatment with *S. guineense* extracts at all doses significantly (p<0.05) reduced ALT levels, with the 500 mg/kg dose showing the most pronounced effect (1.38 ± 0.55 IU/L). Although changes in AST and ALP were not statistically significant, a dose-

dependent trend toward normalization was observed, particularly at 500 mg/kg.

Table 3: Effect of aqueous extract of *Syzygium guineense* on liver function markers in potassium bromate-intoxicated rats

Group	Treatment	ALT (IU/L)	AST (IU/L)	ALP (IU/L)
I	Normal control (Distilled water)	3.00 ± 0.91	8.75 ± 2.36	19.73 ± 1.15
II	KBrO ₃ (100 mg/kg)	10.25 ± 1.18#	6.88 ± 2.55	25.16 ± 3.03
III	KBrO ₃ + SG (250 mg/kg)	4.50 ± 0.96*	11.75 ± 3.82	30.08 ± 3.40
IV	KBrO ₃ + SG (500 mg/kg)	1.38 ± 0.55*	4.95 ± 2.15	13.35 ± 1.58
V	KBrO ₃ + SG (1000 mg/kg)	2.13 ± 1.01*	9.50 ± 7.28	22.38 ± 7.56

Values are expressed as mean ± SEM (n=4). #p<0.05 vs. normal control; *p<0.05 vs. negative control (KBrO₃ alone) ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; SG: *Syzygium guineense*

Histopathological findings

Microscopic examination of liver tissues revealed distinct histological differences across groups (Figure 1). The normal control group (Group I) displayed intact hepatic architecture with orderly hepatocyte arrangement, clear sinusoidal spaces, and no pathological changes. Group II (KBrO₃ alone) showed extensive hepatic damage, including congested central veins, ballooning degeneration, vacuolization, sinusoidal dilation, and focal necrosis with inflammatory infiltration. Group III (250 mg/kg extract) exhibited moderate protection, with reduced congestion but persistent hepatocyte degeneration. Groups IV and V (500 and 1000 mg/kg extract) showed marked hepatoprotection, characterized by near-normal architecture, minimal congestion, and preserved hepatocyte integrity.

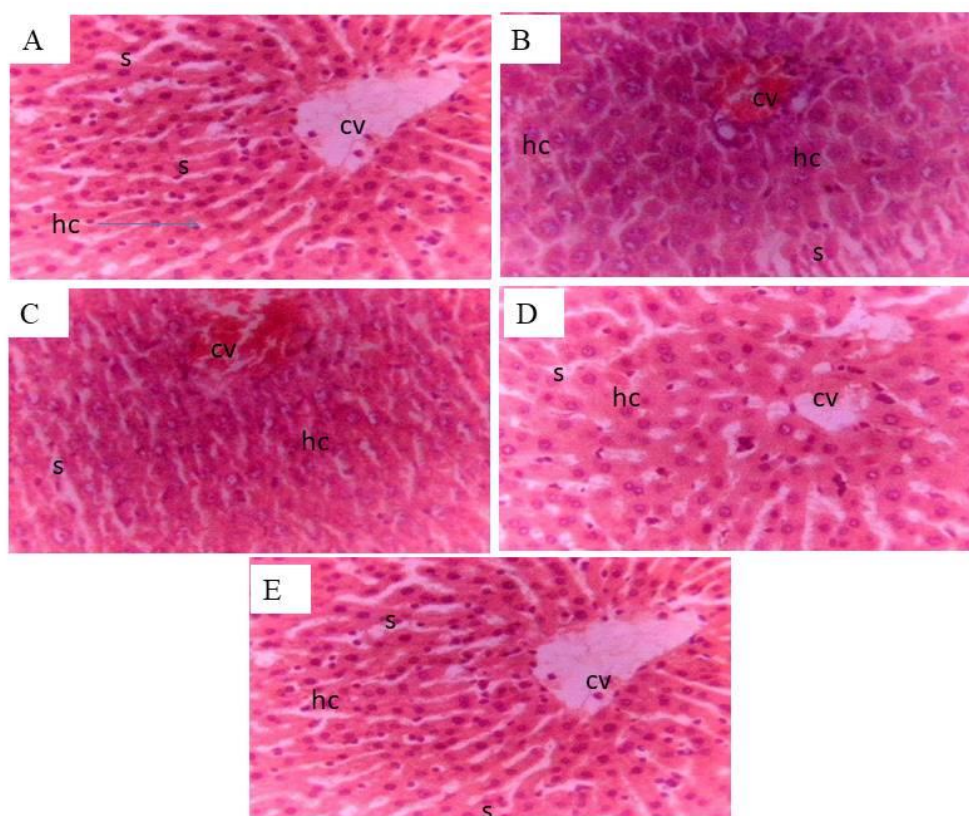


Figure 1: Photomicrographs of liver sections (H&E, ×400).

(A) Normal control: intact architecture, (B) KBrO₃ control: severe damage with congested central vein (cv), ballooning hepatocytes (hc), and dilated sinusoids (s), (C) KBrO₃ + SG 250 mg/kg: moderate

protection, (D) KBrO₃ + SG 500 mg/kg: marked protection and (E) KBrO₃ + SG 1000 mg/kg: significant hepatoprotection with near-normal architecture

DISCUSSION

This study examined the hepatoprotective efficacy of aqueous extract of *Syzygium guineense* leaves against potassium bromate-induced liver injury in Wistar rats. The results, supported by both biochemical and histopathological evidence, affirm the traditional use of *S. guineense* in managing liver disorders and provide a scientific foundation for its therapeutic potential.

The acute toxicity assessment revealed that the extract is remarkably safe, with no mortality or adverse effects observed at doses up to 5000 mg/kg. According to the Globally Harmonized System of Classification and Labelling of Chemicals, substances with oral LD₅₀ values exceeding 5000 mg/kg are considered practically non-toxic [18]. This aligns with findings by Idu *et al.* [19] and Pieme *et al.* [11], who similarly reported no toxicity at high doses. Such a wide safety margin underscores the potential of *S. guineense* as a candidate for therapeutic development, although comprehensive chronic toxicity studies are essential to confirm long-term safety.

Phytochemical screening revealed the presence of flavonoids, tannins, saponins, and other polyphenolic compounds well known for their antioxidant and hepatoprotective properties. Flavonoids, in particular, have been extensively documented for their ability to neutralize reactive oxygen species (ROS), chelate transition metals, and modulate antioxidant enzyme activity [20]. These compounds likely contribute to the observed protective effects. Interestingly, the absence of alkaloids in the aqueous extract contrasts with reports using organic solvents, suggesting that solvent polarity significantly influences phytochemical yield and profile [21].

Potassium bromate administration resulted in a marked elevation of serum ALT levels, confirming its hepatotoxic nature. ALT is a sensitive biomarker of hepatocellular injury, and its release into circulation reflects compromised membrane integrity and cellular damage [22]. The 3.4-fold increase in ALT observed here is consistent with previous studies on KBrO₃-induced liver toxicity [15, 16]. Mechanistically, KBrO₃ exerts its toxic effects via oxidative stress, generating ROS that overwhelm endogenous defences and initiate lipid peroxidation, protein oxidation, and DNA fragmentation [23].

Co-treatment with *S. guineense* extracts significantly mitigated the ALT elevation across all doses, with the 500 mg/kg dose producing the most substantial reduction (86.5% compared to the negative control). This dose-dependent response, followed by a slight decline in efficacy at 1000 mg/kg, suggests a non-linear relationship—possibly indicative of hormesis. Such biphasic effects have been reported with other polyphenol-rich extracts, where higher concentrations may exert pro-oxidant activity [24].

Although AST and ALP levels did not show statistically significant changes, their trend toward normalization supports the extract's hepatoprotective role. The differential response may be attributed to the distinct cellular localization and release kinetics of these enzymes. AST is present in both cytosolic and mitochondrial compartments, while ALP is membrane-bound, making their serum levels less sensitive to early hepatocellular injury compared to ALT [25].

Histopathological analysis provided compelling visual confirmation of the biochemical findings. The KBrO₃ only group exhibited severe hepatic damage, including central vein congestion, ballooning degeneration, vacuolization, and inflammatory infiltration—hallmarks of oxidative and inflammatory injury [19, 26]. These changes are consistent with activation of NF- κ B and pro-inflammatory cytokines, which mediate hepatocyte apoptosis and necrosis in response to oxidative stress [27].

Treatment with *S. guineense* extract, particularly at 500 and 1000 mg/kg, resulted in notable preservation of hepatic architecture. Reduced congestion, minimal inflammatory infiltration, and intact hepatocyte morphology suggest that the extract not only counteracts oxidative damage but also modulates inflammatory pathways. This dual mechanism aligns with the known pharmacological actions of flavonoids and tannins, which exhibit both antioxidant and anti-inflammatory effects [28].

The hepatoprotective action of *S. guineense* likely involves several interrelated mechanisms. First, its polyphenolic constituents directly scavenge ROS, thereby preventing oxidative damage. Previous studies have demonstrated strong DPPH radical scavenging and lipid peroxidation inhibition by *S. guineense* extracts [11]. Second, the extract may enhance endogenous antioxidant defences by upregulating enzymes such as catalase, superoxide dismutase, and glutathione peroxidase [29]. Third, its anti-inflammatory properties may suppress cytokine-mediated tissue injury, further contributing to hepatoprotection [30].

Notably, our findings differ from those of Isa *et al.* [31], who reported hepatotoxic effects at high doses of *S. guineense*. This discrepancy may stem from variations in extraction methods, plant parts used, or the presence of arabinogalactan polysaccharides, which can provoke inflammatory responses at elevated concentrations [32]. The aqueous extraction method employed in our study may have selectively excluded such compounds while retaining beneficial polyphenols.

Despite its strengths, this study has limitations. The absence of a positive control (e.g., silymarin) restricts comparative evaluation of efficacy. Additionally, we did not assess direct markers of oxidative stress or inflammation, such as malondialdehyde levels or cytokine profiles, which

would have provided mechanistic insights. The 28-day duration may also be insufficient to detect long-term or delayed effects. Future research should incorporate molecular analyses, longer treatment periods, and comparative controls to fully elucidate the therapeutic potential of *S. guineense*.

The clinical relevance of these findings is particularly significant in resource-limited settings, where potassium bromate remains in use and access to conventional hepatoprotective agents is constrained. The demonstrated safety and efficacy of *S. guineense* extract position it as a promising, low-cost alternative for managing chemically induced liver injury. However, clinical translation will require rigorous standardization, dose optimization, and human trials to confirm its therapeutic value.

CONCLUSION

This study demonstrated that the aqueous extract of *Syzygium guineense* leaves possesses significant hepatoprotective activity against potassium bromate-induced liver toxicity in Wistar rats, particularly at doses of 500 and 1000 mg/kg. The protection was evidenced by normalized ALT levels and preserved hepatic architecture. These findings provide scientific validation for the traditional use of *S. guineense* in treating liver ailments. Further studies are warranted to isolate active compounds and elucidate specific molecular mechanisms

CONFLICT OF INTERESTS

Authors have declared that no competing interests exist.

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