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Original Article

Hepatoprotective Effects of Methanolic *Salvia officinalis* Leaf Extract against Potassium Cyanide-Induced Hepatotoxicity in Male Wistar Rats

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Abstract

Background: Cyanide poisoning is a major cause of oxidative stress and hepatotoxicity in humans and animals, while effective and affordable therapeutic options remain limited. *Salvia officinalis* (common sage) is a medicinal plant rich in antioxidant phytochemicals with reported hepatoprotective properties. This study evaluated the hepatoprotective and antioxidant effects of methanolic *Salvia officinalis* leaf extract against potassium cyanide-induced hepatotoxicity in male Wistar rats, using sodium thiosulphate as the reference antidote.

Methods: Thirty male Wistar rats were randomly assigned to five groups (n = 6): control, potassium cyanide (7 mg/kg), *S. officinalis* extract (500 mg/kg), extract plus potassium cyanide, and sodium thiosulphate (600 mg/kg) plus potassium cyanide. Treatments were administered orally for 14 days. Serum liver function biomarkers (AST, ALT, GGT, ALP, total protein, and total bilirubin) and hepatic oxidative stress markers (malondialdehyde, reduced glutathione, glutathione S-transferase, superoxide dismutase, and catalase) were determined using standard spectrophotometric methods. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test.

Results: Potassium cyanide significantly ($p < 0.05$) elevated serum AST, ALT, GGT, ALP, total bilirubin, and hepatic malondialdehyde while significantly reducing total protein, reduced glutathione, glutathione S-transferase, superoxide dismutase, and catalase activities. Co-administration of *S. officinalis* extract significantly ameliorated these alterations, restoring liver function and antioxidant status toward normal values. The protective effects were comparable to those of sodium thiosulphate.

Conclusion: Methanolic *Salvia officinalis* leaf extract exhibited significant hepatoprotective and antioxidant activities against potassium cyanide-induced hepatotoxicity in male Wistar rats, suggesting its potential as an affordable natural therapeutic agent. Further studies should investigate its histopathological effects, molecular mechanisms, and long-term safety.

Keywords: *Salvia officinalis leaf, Sodium thiosulphate, Cyanide, Oxidative stress, Hepatotoxicity*

1. Introduction

Cyanide poisoning is a major global public health concern affecting both humans and animals due to its rapid and potentially fatal toxic effects [1]. Cyanides, which include the cyanide ion (CN^-) and its compounds such as potassium cyanide, sodium cyanide, hydrogen cyanide, and cyanogenic glycosides found in plants, are widely distributed in the environment [2,3]. Their toxicity primarily results from inhibition of mitochondrial cyto-

-chrome *c* oxidase, which blocks cellular respiration and oxidative phosphorylation, leading to impaired adenosine triphosphate (ATP) synthesis despite adequate oxygen availability. This process induces cytotoxic hypoxia, excessive production of reactive oxygen species (ROS), depletion of endogenous antioxidant defenses, and ultimately oxidative damage to cellular components [4–6].

Acute and chronic cyanide exposure can impair the function of multiple organs, producing clinical manifestations ranging from dizziness, seizures, cardiac arrhythmias, and loss of consciousness to respiratory failure and death [4–6]. Human exposure occurs through occupational activities such as mining, electroplating, metal processing, and chemical manufacturing, inhalation of smoke from burning plastics or tobacco, and ingestion of cyanogenic foods, particularly inadequately processed cassava [7–9]. Chronic cyanide intoxication has also been associated with neurological disorders and progressive organ dysfunction. In animals, cyanide poisoning commonly occurs through consumption of cyanogenic plants during grazing and is frequently accompanied by hepatic injury due to the central role of the liver in cyanide metabolism [10–14].

The liver detoxifies cyanide primarily through the mitochondrial enzyme rhodanese, which converts cyanide into the less toxic thiocyanate using sulphur donors such as sodium thiosulphate [15–17]. Consequently, sodium thiosulphate is widely used as a standard antidote for cyanide poisoning. Nevertheless, there is increasing interest in identifying naturally occurring compounds with antioxidant properties that may complement or enhance conventional therapy by limiting oxidative tissue injury. For example, quercetin, a naturally occurring flavonoid, has been reported to attenuate cyanide-induced hepatic oxidative stress in experimental animals [15].

Medicinal plants remain an important source of bioactive compounds with diverse pharmacological properties [18]. *Salvia officinalis* L. (common sage), a member of the Lamiaceae family, is widely used as a culinary herb and in traditional medicine for the management of various diseases [19]. Phytochemical studies have shown that *S. officinalis* is rich in flavonoids, phenolic acids, and other antioxidant constituents that exhibit anti-inflammatory, antimicrobial, antihyperglycaemic, antihypertensive, antiproliferative, and hepatoprotective activities [20–26]. These bioactive compounds possess potent free radical-scavenging properties and may therefore protect tissues against oxidative damage induced by toxic agents.

Based on these documented antioxidant properties, we hypothesized that methanolic leaf extract of *Salvia officinalis* would protect against potassium cyanide-induced hepatotoxicity by attenuating oxidative stress and preserving hepatic antioxidant defense mechanisms. Therefore, this study evaluated the hepatoprotective and antioxidant effects of methanolic *Salvia officinalis* leaf extract in male Wistar rats exposed to potassium cyanide. Specifically, the study assessed changes in liver function biomarkers and oxidative stress indices, compared the efficacy of the extract with that of sodium thiosulphate, and investigated its potential as an affordable natural therapeutic agent for the management of cyanide-induced liver injury.

2. Materials and Methods

2.1. Plant Collection, Authentication, and Extraction

Fresh leaves of *Salvia officinalis* were collected from Vom-Jos, Plateau State, Nigeria, and authenticated by a botanist. A voucher specimen (FS/20/21/00121) was deposited for future reference. The plant was subsequently propagated and maintained in a botanical garden in Asaba, Delta State, Nigeria. The leaves were washed, cut into small pieces, and air-dried at 30–40°C for 21 days before being pulverized into a fine powder. Fifty grams (50 g) of the powdered leaves were macerated in 400 mL of absolute methanol with intermittent agitation for 72 h. The mixture was filtered through muslin cloth, and the filtrate was further concentrated using a Soxhlet extraction system. The resulting extract was stored in an airtight container at 4°C until use. The extraction yield was 14.6% (w/w).

2.2. Preparation of the Extract

The methanolic extract of *Salvia officinalis* leaves was freshly suspended in normal saline immediately before administration at a dose of 500 mg/kg body weight.

2.3. Chemicals and Reagents

All chemicals and reagents used were of analytical grade. Potassium cyanide (KCN, ≥97% purity; CAS No. 151-50-8), sodium thiosulphate ($Na_2S_2O_3$, ≥99% purity; CAS No. 7772-98-7), and commercial assay kits for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total protein, and total bilirubin were obtained from Mindray (Shenzhen, China). Thiobarbituric acid (TBA), 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), glutathione standards, and other analytical reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). All reagents were prepared according to the manufacturers' instructions.

2.4. Experimental Animals

Healthy adult male Wistar rats weighing 150–250 g were used for the study. Animals were housed under standard laboratory conditions (12-h light/12-h dark cycle, temperature 25 ± 2°C, relative humidity 55 ± 10%) with free access to commercial growers' mash and clean drinking water *ad libitum*. The animals were acclimatized for one week before commencement of the experiment.

2.5. Acute Oral Toxicity Study

Acute oral toxicity of the methanolic extract was evaluated according to the Organisation for Economic Co-operation and Development (OECD) Guideline 423 [27]. Healthy adult female albino mice (20–24 g; n = 6 per group) were administered single oral doses of 2,000 or 5,000 mg/kg body weight of the extract. Animals were monitored continuously during the first 24 h and thereafter for 72 h for signs of toxicity, behavioural changes, and mortality.

2.6. Experimental Design

Thirty male Wistar rats were randomly allocated into five groups (n = 6 per group):

Group A (Control): Received 0.4 mL corn oil orally for 14 days.

Group B (Cyanide): Received potassium cyanide (7 mg/kg body weight/day) orally for 14 days.

Group C (Extract): Received methanolic *Salvia officinalis* extract (500 mg/kg body weight/day) orally for 14 days.

Group D (Extract + Cyanide): Received methanolic *Salvia officinalis* extract (500 mg/kg body weight/day) together with potassium cyanide (7 mg/kg body weight/day) orally for 14 days.

Group E (Sodium Thiosulphate + Cyanide): Received sodium thiosulphate (600 mg/kg body weight/day) together with potassium cyanide (7 mg/kg body weight/day) orally for 14 days.

Treatment doses were selected based on previous studies demonstrating their efficacy and safety [15,20,22]. Animals were monitored daily for clinical signs of toxicity, and body weights were recorded every two days throughout the experimental period.

2.7. Sample Collection and Tissue Preparation

Twenty-four hours after the final treatment, blood samples were collected from the retro-orbital plexus into plain sample tubes. After clotting, samples were centrifuged at 3,000 rpm for 10 min at 4°C to obtain serum, which was stored at −20°C until biochemical analysis. Animals were then euthanized by cervical dislocation under deep anaesthesia. The liver, kidneys, and heart were excised, rinsed in ice-cold physiological saline, blotted dry, weighed, and stored appropriately. Liver tissues were homogenized in ice-cold phosphate buffer (0.1 M, pH 7.4) and centrifuged at 10,000 × g for 10 min at 4°C. The post-mitochondrial supernatant was collected for estimation of oxidative stress biomarkers.

2.8. Liver Function Assays

Serum AST and ALT activities were determined using the Reitman and Frankel method [28]. ALP activity was assayed according to the method of Binkley [29], while GGT activity was measured using the method of Gjerde [30]. Total protein and total bilirubin concentrations were determined using the methods of Reinhold [31] and Malloy and Evelyn [32], respectively. Analyses were performed using Mindray commercial reagent kits with an automated chemistry analyser (BA-88A, E. LabBST, China).

2.9. Determination of Oxidative Stress Biomarkers

Lipid peroxidation was assessed by estimating malondialdehyde (MDA) as thiobarbituric acid-reactive substances (TBARS) using the method of Buege and Aust [33]. Catalase activity was determined according to the method of Sinha [34], while superoxide dismutase (SOD) activity was measured using the method of Misra and Fridovich [35]. Glutathione-S-transferase (GST) activity was estimated following the method of Habig *et al.* [36], and reduced glutathione (GSH) concentration was determined using Ellman's reagent according to Beutler *et al.* [37]. Tissue protein concentration was measured using the Lowry method [38] with bovine serum albumin as the standard.

2.10. Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA, USA). Differences among groups were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison post hoc test. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Acute Toxicity

There was no mortality and signs of toxicity at doses of 2,000 and 5,000 mg/kg b.wt. of *Salvia officinalis* leaf extract, indicating an $LD_{50} > 5{,}000$ mg/kg.

3.2. Body Weight Changes

The body weights of rats in all treatment groups had no significant difference ($p > 0.05$) between initial and final weight, and among groups (Table 1).Values are Mean ± SEM (n=6). Values sharing the same superscript in a row did not differ significantly ($p > 0.05$). The initial body weights of the rats were comparable across all treatment groups, with no significant differences observed ($p > 0.05$), indicating similar baseline characteristics before treatment. Although body weight increased in all groups by the end of the study, these within-group changes were not statistically significant ($p > 0.05$). However, rats treated with the extract alone and those receiving the extract plus cyanide had significantly higher final body weights than the control, cyanide-only, and sodium thiosulfate plus cyanide groups ($p < 0.05$), suggesting that the extract may have promoted greater weight gain.

Table 1: Body weights of rats in different treatment groups

Group	Initial Weight (g)	Final Weight (g)
A (Control)	194.00 ± 5.45[a]	203.63 ± 16.25[a]
B (Cyanide only)	196.33 ± 6.11[a]	201.93 ± 4.65[a]
C (Extract only)	195.67 ± 20.50[a]	215.43 ± 12.47[c]
D (Extract + Cyanide)	193.00 ± 16.64[a]	217.43 ± 13.28[c]
E ($Na_2S_2O_3$ + Cyanide)	193.33 ± 4.16[a]	204.83 ± 17.18[a]

3.3. Liver function parameters

Potassium cyanide administration markedly impaired liver function, as evidenced by a significant increase ($p < 0.001$) in serum AST, ALT, GGT, ALP, and total bilirubin (TB), alongside a significant reduction in total protein (TP) compared with the control group. Co-administration of *Salvia officinalis* leaf extract (Group D) or sodium thiosulphate (Group E) significantly attenuated these alterations, with values shifting toward those of the control group, although complete normalization was not achieved for all parameters. Rats treated with the extract alone (Group C) showed liver function indices comparable to the control, indicating that the extract did not adversely affect hepatic function. Furthermore, the greater elevation of ALT relative to AST in the cyanide-only group resulted in an AST/ALT ratio of approximately 0.65, compared with approximately 1.0 in the control group, suggesting predominant hepatocellular injury following cyanide exposure. Overall, these findings indicate that *Salvia officinalis* leaf extract exerted a hepatoprotective effect against cyanide-induced liver damage, comparable to that of sodium thiosulphate.

Table 2: Effect of treatments on serum liver function parameters

Group	TP (g/L)	GGT (U/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	TB (µmol/L)
A (Control)	88.00 ± 1.20	27.27 ± 2.19	30.00 ± 6.85	30.10 ± 1.20	40.27 ± 6.17	14.18 ± 2.75
B (Cyanide only)	46.10 ± 3.60***	60.17 ± 3.18***	110.10 ± 10.18**	168.40 ± 3.60***	156.90 ± 8.66***	68.43 ± 4.96***
C (Extract only)	92.50 ± 2.48*	29.00 ± 3.12*	44.60 ± 3.82*	43.48 ± 2.47*	53.21 ± 10.31*	12.10 ± 3.37*
D (Extract + Cyanide)	82.40 ± 2.30*	36.10 ± 10.80*	60.10 ± 8.51*	58.60 ± 2.63*	98.67 ± 12.49**	48.64 ± 3.19**
E ($Na_2S_2O_3$ + Cyanide)	87.04 ± 3.20	30.00 ± 8.16*	70.16 ± 6.18**	60.12 ± 3.18**	90.35 ± 12.12**	50.06 ± 3.18**

**Values are Mean ± SEM (n=6). ***p < 0.001 vs. control; *p < 0.05,* *p < 0.01 vs. cyanide-only group

Table 3: Hepatic oxidative stress and antioxidant markers

Group	MDA (µg/g tissue)	GSH (µg/g tissue)	GST (nmol/mg protein)	SOD (U/mg protein)	Catalase (Kat)
A (Control)	0.598 ± 0.102	6.60 ± 0.346	0.465 ± 0.056	3.464 ± 0.326	0.2008 ± 0.006
B (Cyanide only)	2.801 ± 0.38***	3.94 ± 0.100*	0.165 ± 0.050*	2.000 ± 0.098*	0.0680 ± 0.006*
C (Extract only)	0.630 ± 0.038	7.60 ± 0.520	0.484 ± 0.044	3.43 ± 0.304	0.198 ± 0.006
D (Extract + Cyanide)	1.142 ± 0.116*	6.10 ± 0.460	0.406 ± 0.025	3.501 ± 0.156*	0.146 ± 0.006#*
E ($Na_2S_2O_3$ + Cyanide)	1.110 ± 0.113*	7.90 ± 0.40*	0.600 ± 0.026*	2.60 ± 0.345	0.156 ± 0.008*

**Values are Mean ± SEM (n=6). p< 0.05 vs. control; #p < 0.05 vs. cyanide-only group.*

3.4. Oxidative Stress Parameters

Potassium cyanide administration (Group B) significantly ($p < 0.05$) increased hepatic malondialdehyde (MDA) levels while significantly reducing glutathione (GSH), glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase activities compared with the control group, indicating pronounced oxidative stress and impairment of the hepatic antioxidant defense system. Co-administration of *Salvia officinalis* leaf extract (Group D) or sodium thiosulphate (Group E) significantly ($p < 0.05$) reduced MDA levels and restored antioxidant enzyme activities toward normal values. Rats treated with the extract alone (Group C) exhibited oxidative stress and antioxidant indices comparable to the control group,

suggesting that the extract did not induce oxidative damage. Although both treatments ameliorated cyanide-induced oxidative stress, the *Salvia officinalis* extract produced a higher SOD activity than sodium thiosulphate, whereas sodium thiosulphate resulted in greater restoration of GSH and GST activities. These findings demonstrate that *Salvia officinalis* leaf extract possesses potent antioxidant activity capable of mitigating cyanide-induced hepatic oxidative damage.

3.5. Organ Weights and Liver Protein

Potassium cyanide administration (Group B) significantly ($p < 0.01$) increased the weights of the heart, kidneys, and liver while significantly reducing liver protein content compared with the control group, indicating cyanide-induced organ enlargement and impaired hepatic protein synthesis. Co-administration of *Salvia officinalis* leaf extract (Group D) or sodium thiosulphate (Group E) significantly ($p < 0.05$) attenuated these changes, reducing organ weights toward control values and restoring liver protein content. Rats treated with the extract alone (Group C) showed liver protein levels comparable to the control group, with only slight increases in organ weights that remained markedly lower than those observed in the cyanide-only group. Overall, these findings suggest that *Salvia officinalis* leaf extract effectively protects against cyanide-induced organ toxicity and preserves hepatic protein synthesis, with effects comparable to those of sodium thiosulphate.

Table 4: Organ weights and liver protein content

Group	Liver Protein (mg/g tissue)	Heart Weight (g)	Kidney Weight (g)	Liver Weight (g)
A (Control)	268.312 ± 13.10	0.32 ± 0.07	0.31 ± 0.06	3.40 ± 0.16
B (Cyanide only)	235.132 ± 22.2*	0.84 ± 0.18**	0.64 ± 0.16**	6.10 ± 0.28**
C (Extract only)	278.234 ± 18.60	0.48 ± 0.28*	0.43 ± 0.16*	4.80 ± 0.38*
D (Extract + Cyanide)	296.213 ± 17.67	0.38 ± 0.15*	0.34 ± 0.21*	3.80 ± 0.16*
E ($Na_2S_2O_3$ + Cyanide)	293.703 ± 19.72	0.42 ± 0.08*	0.48 ± 0.38*	4.00 ± 0.42*

**Values are Mean ± SEM (n=6). **p < 0.01 vs. control; p< 0.05 vs. cyanide-only group.*

4. Discussion

Cyanide poisoning exerts its toxic effects by inhibiting mitochondrial cytochrome *c* oxidase, thereby blocking cellular respiration and oxidative phosphorylation, resulting in impaired ATP production despite adequate oxygen availability. This cytotoxic hypoxia shifts cellular metabolism towards anaerobic glycolysis, leading to lactic acidosis and excessive generation of reactive oxygen species (ROS), which promote lipid peroxidation and oxidative tissue damage [1,4,5,7,15,39–42]. The present study demonstrated that potassium cyanide significantly increased hepatic malondialdehyde (MDA) levels while reducing glutathione (GSH), glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase activities, confirming the induction of oxidative stress. These findings are consistent with previous reports by Kadiri and Asagba [43], who observed depletion of antioxidant enzymes following cyanide exposure. Similar studies have shown that cyanide-induced toxicity is characterized by excessive ROS generation, depletion of endogenous antioxidants, and disruption of cellular redox balance, ultimately resulting in membrane lipid peroxidation and tissue injury [1,10,44].

The reduction in hepatic GSH observed in the cyanide-treated rats may also be attributed to increased utilization of sulphur-containing amino acids during cyanide detoxification through rhodanese and mercaptopyruvate sulphurtransferase pathways, thereby reducing glutathione availability [1,4,15,45]. Oxidative damage arising from these mechanisms contributes to impairment of cellular integrity and organ dysfunction. Co-administration of *Salvia officinalis* leaf extract markedly reduced MDA levels and restored GSH, GST, SOD, and catalase activities toward normal values, demonstrating a strong antioxidant effect. These findings corroborate earlier reports by Ola-Mudathir and Jeje [15] and Bayliak et al. [46], who reported similar antioxidant properties of plant-derived phytochemicals. The protective effects of *S. officinalis* are likely attributable to its rich flavonoid and phenolic constituents, which possess potent free radical-scavenging and antioxidant activities [20,25,26]. Although both *S. officinalis* and sodium thiosulphate improved antioxidant status, sodium thiosulphate produced greater restoration of GSH and GST activities, probably because it provides sulphur required for cyanide detoxification.

Cyanide administration also produced significant increases in serum AST, ALT, ALP, GGT, and total bilirubin, accompanied by a reduction in total protein, indicating hepatocellular injury and impaired hepatic synthetic function. These biochemical alterations are well-established indicators of liver damage resulting from increased membrane permeability and leakage of intracellular enzymes into the circulation. Similar findings have been reported in experimental and occupational cyanide exposure studies [7,47–49]. The greater elevation of ALT relative to AST, reflected by an AST/ALT ratio of approximately 0.65, further suggests predominant

hepatocellular injury because ALT is more specific to hepatic tissue.

Treatment with *Salvia officinalis* leaf extract significantly attenuated these biochemical abnormalities, indicating hepatoprotective activity comparable to that of sodium thiosulphate. The reduction in liver enzyme activities and bilirubin, together with restoration of total protein, suggests preservation of hepatocyte membrane integrity and improved liver function. Furthermore, cyanide exposure significantly increased the weights of the liver, kidneys, and heart while reducing hepatic protein content. These changes may reflect tissue inflammation, oxidative injury, and cellular swelling associated with lipid peroxidation. Administration of *S. officinalis* extract or sodium thiosulphate reduced organ weights and restored liver protein levels toward normal values, further supporting their protective effects against cyanide-induced organ toxicity.

Overall, the findings indicate that *Salvia officinalis* leaf extract protects against cyanide-induced hepatotoxicity primarily through attenuation of oxidative stress and preservation of endogenous antioxidant defense mechanisms. This study has several limitations. First, histopathological examination of liver tissue was not performed to corroborate the biochemical findings. Second, only male Wistar rats were used, precluding assessment of possible sex-related differences in response to treatment. Third, the precise molecular mechanisms underlying the hepatoprotective effects of *Salvia officinalis* were not investigated. Future studies should include histopathological evaluation, dose-response experiments, chronic toxicity assessment, and mechanistic investigations involving antioxidant signaling pathways such as Nrf2 and enzymes involved in cyanide detoxification, including rhodanese.

5. Conclusion

Methanolic extract of *Salvia officinalis* leaves demonstrated significant hepatoprotective and antioxidant activities against potassium cyanide-induced hepatotoxicity in male Wistar rats. The extract effectively ameliorated alterations in liver function biomarkers, restored endogenous antioxidant defenses, reduced lipid peroxidation, and improved hepatic protein content, with protective effects comparable to those of sodium thiosulphate. These findings suggest that *S. officinalis* may serve as a promising natural therapeutic agent for mitigating cyanide-induced liver injury. Nevertheless, further studies involving histopathology, molecular mechanisms, dose optimization, chronic toxicity, and clinical evaluation are required before its therapeutic application can be recommended.

Declarations

Consent for publication: The author, declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by him.

Consent to Participate: Not applicable.

Data availability statement: All data generated and analyzed during the current study are available within the article.

Competing Interests: The author declares no conflict of interests.

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Ethics: The study protocol was approved by the Research Ethics Committee, Faculty of Science, Delta State University, Abraka, Nigeria (Approval No. REC/FS/23/019), and all procedures were conducted in accordance with internationally accepted guidelines for the care and use of laboratory animals.

Authors' Contributions: MAT Conceptualized, reviewed & edited and submitted the manuscript.

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