RESEARCH PAPER

Hepatoprotective Effect of Vernonia Amygdalina and Ademitionine Ethanolic Leaf Extract in Ccl4 Induced Hepatotoxicity in Wistar Rat

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ABSTRACT

Background: Carbon tetrachloride (CCl_4) is commonly used to induce experimental liver injury through the formation of reactive metabolites, oxidative stress, and lipid peroxidation. Vernonia amygdalina is a medicinal plant reported to contain antioxidant-associated phytochemical groups, while ademetionine (S-adenosyl-L-methionine; SAMe) participates in hepatic methylation and glutathione metabolism. This study evaluated the effects of V. amygdalina ethanolic leaf extract, ademetionine, and their combination in CCl_4-induced hepatotoxicity in Wistar rats.

Methods: Male Wistar rats were allocated to six groups: normal control, CCl_4 disease control, V. amygdalina plus CCl_4, ademetionine plus CCl_4, combination treatment plus CCl_4, and silymarin plus CCl_4. According to the thesis, CCl_4 was administered as a single intraperitoneal dose of 3 mL/kg on Day 1, followed by 14 days of treatment. V. amygdalina extract and silymarin were administered at 100 mg/kg, while the thesis lists ademetionine at 1 g/kg. Serum ALT, AST, ALP, total bilirubin, and total protein, oxidative-stress-related parameters (TBARS, GSH, CAT, and SOD), and liver histopathology were assessed.

Results: The thesis-reported mean values showed higher ALT, AST, ALP, total bilirubin, and TBARS in the disease-control group than in the normal-control group, alongside lower total protein, GSH, CAT, and SOD. In the combination group, ALT was 53.7 ± 3.1 U/L, AST 81.4 ± 4.2 U/L, ALP 103.2 ± 4.6 U/L, total bilirubin 0.79 ± 0.06 mg/dL, and total protein 6.57 ± 0.15 g/dL. The combination group also showed TBARS of 2.76 ± 0.15, GSH of 7.06 ± 0.29, CAT of 48.72 ± 2.01, and SOD of 7.84 ± 0.30 in the units reported in the thesis.

Conclusion: The thesis-reported results suggest that V. amygdalina extract and ademetionine were associated with improvement in biochemical, oxidative-stress-related, and histopathological measures in this model. The combination group showed a favourable descriptive profile.

Keywords: Vernonia amygdalina; ademetionine; S-adenosyl-L-methionine; carbon tetrachloride; hepatotoxicity; oxidative stress; hepatoprotection

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1. INTRODUCTION

The liver is one of the largest and most important organs of the human body [1]. It performs many important functions that help to maintain normal health. It helps in metabolism of carbohydrates, proteins, and fats. The liver also stores vitamins and minerals, produces bile for digestion, and removes harmful substances from the blood. In addition, it plays an important role in detoxification of drugs, chemicals, and other toxic compounds. Because of these important functions, any damage to the liver can affect the normal functioning of the entire body [2, 3].

Liver diseases are a major public health problem throughout the world. They may develop due to viral infections, alcohol consumption, environmental toxins, chemicals, or prolonged use of certain medicines. Continuous liver injury may lead to inflammation, fibrosis, cirrhosis, liver failure, and even liver cancer. Therefore, prevention and treatment of liver damage remain an important area of medical research [4, 5].

Carbon tetrachloride (CCl_4) is one of the most commonly used chemicals for producing experimental liver damage in laboratory animals [6]. After entering the body, CCl_4 is metabolized by cytochrome P450 enzymes into highly reactive free radicals **[7]**. These free radicals initiate lipid peroxidation, damage cell membranes, reduce antioxidant defense, and finally lead to liver cell necrosis. Because its mechanism is well understood, CCl_4-induced hepatotoxicity is widely used for evaluating the hepatoprotective activity of drugs and medicinal plants **[8]**.

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Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are commonly used indicators of hepatocellular injury. Alkaline phosphatase (ALP), bilirubin, and total protein provide complementary information on hepatobiliary function and hepatic synthetic status. Oxidative stress is an important component of CCl_4 toxicity; measurements of thiobarbituric-acid-reactive substances (TBARS), reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) can help characterize lipid peroxidation and antioxidant defences [9,10].

Natural products have gained considerable attention because many medicinal plants possess antioxidant and anti-inflammatory properties. Plant-derived compounds are considered safer and may provide effective protection against liver injury. India, more than 300 herbal medicines are used to treat liver dysfunctions such as jaundice, fatty liver, etc around 600 herbal product are available worldwide that claim to protect the liver [11].

Vernonia amygdalina (bitter leaf) has attracted significant interest. It is widely distributed in tropical Africa and has been traditionally used for the treatment of malaria, diabetes, gastrointestinal disorders, fever, and liver diseases. The leaves contain several bioactive compounds such as flavonoids, sesquiterpene lactones, saponins, alkaloids, tannins, and phenolic compounds that exhibit antioxidant and hepatoprotective activities [12].

Ademetionine, also known as S-adenosyl-L-methionine (SAMe), is a naturally occurring compound present in almost all body tissues. It participates in methylation reactions, synthesis of glutathione, and maintenance of normal liver function. Reduced glutathione levels are commonly observed during liver injury. Administration of ademetionine helps restore glutathione concentration, reduces oxidative stress, improves hepatocyte function, and supports liver regeneration. Therefore, ademetionine has been used clinically in several liver disorders [13, 14].

The present study evaluated the effects of ethanolic *V. amygdalina* leaf extract, ademetionine, and their combination on serum biochemical parameters, oxidative-stress-related markers, and liver histopathology in Wistar rats subjected to CCl_4-induced hepatotoxicity, with silymarin included as a standard treatment.

2. MATERIALS AND METHODS

2.1 Plant material and authentication

V. amygdalina leaves were collected in January, cleaned, washed, shade-dried, and mechanically powdered. The specimen was authenticated at the Botanical Garden of India Republic (BGIR), Noida, by a taxonomist and authentication certificate were obtained.

2.2 Extraction Preparation

The collected leaves were washed twice with tap water and shade-dried for 7–10 days. The dried leaves were ground into a coarse powder and stored in a cool, dry place. About 100 g of leaf powder was extracted with 1000 mL of 60% ethanol using a Soxhlet apparatus for 24 hours. The extract was concentrated using a rotary evaporator at 35°C and stored in an airtight container [15].

2.3 Preliminary phytochemical screening

Qualitative phytochemical screening was performed using standard colour- and precipitation-based tests. The thesis reports positive reactions for alkaloids (Mayer's, Dragendorff's, and Hager's tests), saponins (foam and lead acetate tests), flavonoids (alkaline reagent, lead acetate, and Shinoda's tests), and phenolic compounds (ferric chloride and lead acetate tests). This test was carried out followed the procedure described by Bargah [16]. These results indicate the reported presence of broad phytochemical classes.

2.4 Experimental animals and ethical approval

Wistar rats weighing between 180-200g were purchased from Biotenic Pharma Private Limited Dadri, G. Noida after receiving the clearance of the IAEC of college (Approval no.:2026/HIMT/IAEC/FB/11). The animals were kept at Animal House Facility (AHF), HIMT, G. Noida. Rats were quarantined for 10 days under controlled environmental conditions: Temp was maintained at 26 ± 2^{o} C, relative humidity at around 100%, and a 12-hour light/dark cycle was followed. The rats had free access to standard pellet feed and water throughout the study. Prior to the initiation of the experiment, all animals were examined for any visible signs of illness or injury to ensure their health status.

2.5 Experimental design and treatment groups

The thesis describes six groups and a 14-day treatment period. CCl_4 was reportedly administered intraperitoneally at 3 mL/kg body weight as a single dose on Day 1, followed by treatment for 14 days. The group sizes and routes below reproduce the thesis tables; the actual animal log and dosing sheets should be checked because the route for ademetionine and the combination treatment is not consistently described across the thesis.

Table 1. Shows Treatment Protocol.

S. No.	Group	Treatment	Dose and schedule	Animal
I.	Normal control	Normal saline	10 mL/kg, oral, 14 days	5
II.	Disease control	CCl_4	3 mL/kg, single intraperitoneal dose on Day 1	5
III.	Test group 1	CCl_4 + V. amygdalina extract	CCl_4 3 mL/kg once; extract 100	5

			mg/kg for 14 days, oral	
IV.	Test group 2	CCl_4 + ademetionine	CCl_4 3 mL/kg once; ademetionine 1 g/kg for 14 days	5
V.	Test group 3	CCl_4 + V. amygdalina + ademetionine	CCl_4 3 mL/kg once; extract 100 mg/kg + ademetionine 1 g/kg for 14 days	5
VI.	Standard control	CCl_4 + silymarin	CCl_4 3 mL/kg once; silymarin 100 mg/kg, oral, 14 days	5

2.6 Sample collection and biochemical analysis

On day 15th, the rats were anesthetized by ketamine (60 mg/kg, Ip) then blood was obtained from all the experimental animals by cardiac puncture followed euthanasia by CO_2 inhalation. To separate the serum, the obtained blood was placed into centrifugation. The serum was then used to estimate various biochemical parameters such ALP, AST, and ALT. In addition to the blood analysis, liver tissues were harvested from all the animals and preserved for histopathological examination

2.7 Estimation of Evaluation Parameters

The following evaluation parameters were assessed:

A. Oxidative stress markers:

- TBARS **[90]**
- Catalase (CAT) **[91]**
- Superoxide Dismutase (SOD) **[92]**
- Reduced Glutathione (GSH) **[93]**

B. Biochemical Parameters:

- Serum Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST).
- Total Bilirubin
- Total Protein

C. Histopathological Examination:

- Liver tissue was preserved in 10% formalin and stained with haematoxylin and eosin for microscopic evaluation & observed for necrosis, inflammation, fatty degeneration, cellular damage

D. Statistical Analysis:

- One-way analysis variance (ANOVA) was performed using Graph Pad Prism statistical software. Tukey t-test is used for multiple comparisons. The values are considered significantly different at $p < 0.05$.

3. RESULTS

3.1 Preliminary Phytochemical Screening

Preliminary phytochemical screening was performed to determine the major classes of secondary metabolites present in the ethanolic extract of *Vernonia amygdalina* leaves. The results demonstrated positive reactions for alkaloids, saponins, flavonoids, and phenolic compounds. The presence of these phytochemical groups was indicated by the characteristic colour changes or precipitate formation obtained with the respective qualitative chemical tests. The findings provide preliminary evidence that the prepared extract contains several classes of biologically active secondary metabolites.

Table 2: Results of preliminary phytochemical screening of *Vernonia amygdalina* leaf extract

Phytochemical constituent	Test performed	Observation	Result
Alkaloids	Mayer's test	Cream-coloured precipitate	Present (+)
Alkaloids	Dragendroff's test	Reddish-brown/orange precipitate	Present (+)
Alkaloids	Hager's test	Yellow precipitate	Present (+)
Saponins	Foam test	Persistent/stable foam	Present (+)
Saponins	Lead acetate test	White/yellowish residue	Present (+)
Flavonoids	Alkaline reagent test	Yellow colour which disappeared/decreased after HCl	Present (+)
Flavonoids	Lead acetate test	Yellow precipitate	Present (+)
Phenols	Ferric chloride test	Green colour	Present (+)
Phenols	Lead acetate test	White precipitate	Present (+)

3.2 Serum biochemical parameters

Serum ALT, AST, ALP, total bilirubin, and total protein were measured to assess liver damage and the protective effects of the treatments. CCl_4 administration increased ALT (42.3 ± 2.1 to 128.4 ± 6.7 U/L), AST (68.5 ± 3.4 to 211.6 ± 9.5 U/L), ALP (92.6 ± 4.2 to 191.8 ± 7.8 U/L), and total bilirubin (0.68 ± 0.05 to 1.82 ± 0.11 mg/dL) compared with the normal-control group. Total protein decreased from 6.82 ± 0.18 to 4.91 ± 0.16 g/dL, indicating liver damage and reduced protein synthesis.

Treatment with *V. amygdalina* (VA) extract and ademetionine improved these biochemical changes. The combined treatment showed greater improvement,

reducing ALT, AST, and ALP to 53.7 ± 3.1, 81.4 ± 4.2, and 103.2 ± 4.6 U/L, respectively, and total bilirubin to 0.79 ± 0.06 mg/dL. Total protein increased to 6.57 ± 0.15 g/dL. Ademetionine and silymarin also improved the liver parameters. Overall, the combined VA and ademetionine treatment showed stronger hepatoprotective effects than the individual treatments in this illustrative dataset. Results should be reported as Mean ± SEM, with statistical significance determined using ANOVA followed by Tukey's post-hoc test.

Table 3: Effect of treatments on serum biochemical parameters

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Total protein (g/dL)
Normal control	42.3 ± 2.1	68.5 ± 3.4	92.6 ± 4.2	0.68 ± 0.05	6.82 ± 0.18
Disease control	128.4 ± 6.7	211.6 ± 9.5	191.8 ± 7.8	1.82 ± 0.11	4.91 ± 0.16
V. amygdalina 100 mg/kg	87.6 ± 4.8	137.2 ± 6.4	143.5 ± 6.1	1.24 ± 0.08	5.76 ± 0.14
Ademetionine 1 g/kg	76.8 ± 4.2	119.5 ± 5.7	127.4 ± 5.3	1.08 ± 0.07	6.02 ± 0.17
Combination	53.7 ± 3.1	81.4 ± 4.2	103.2 ± 4.6	0.79 ± 0.06	6.57 ± 0.15
Silymarin 100 mg/kg	48.9 ± 2.8	74.6 ± 3.8	98.7 ± 4.1	0.74 ± 0.05	6.65 ± 0.16

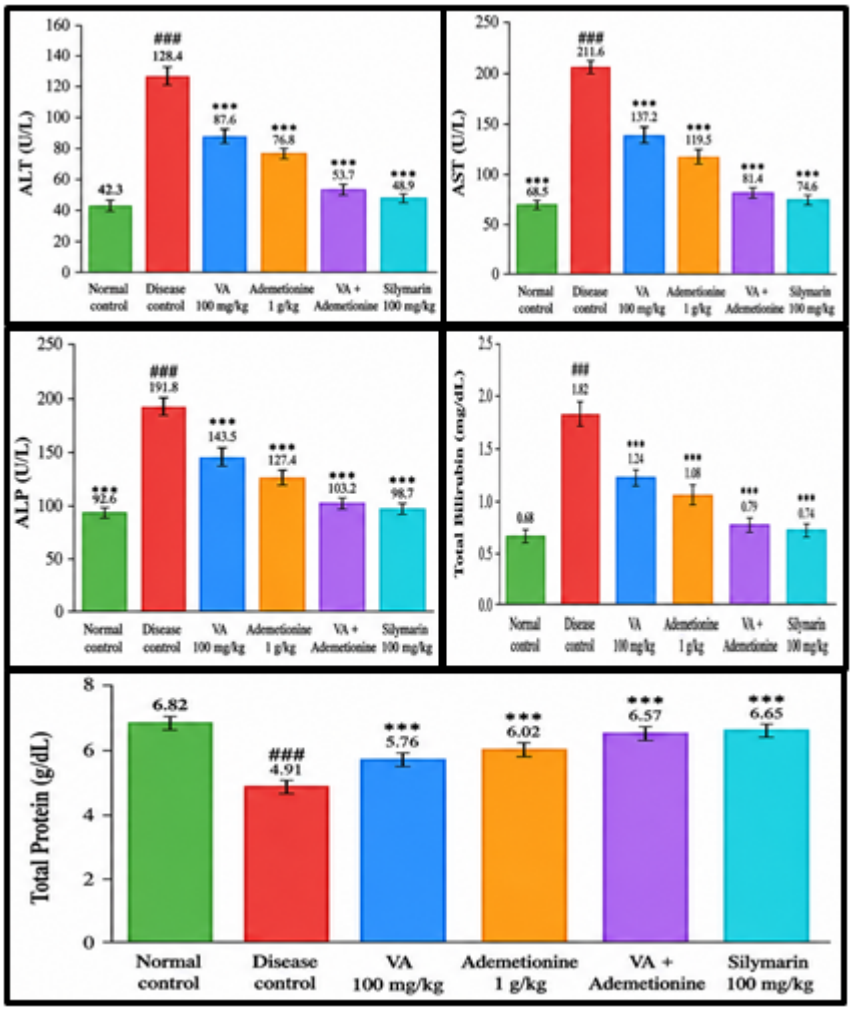


Figure: 1. Effect of treatments on serum ALT, AST, ALP, total bilirubin and total protein levels

3.3 Oxidative-stress-related parameters

CCl_4-induced liver damage and the effects of *Vernonia amygdalina* (VA), ademetionine, their combination, and silymarin were assessed using oxidative-stress markers, including TBARS/MDA, GSH, CAT, and SOD. The disease-control group showed increased TBARS/MDA levels compared with the normal-control group, indicating increased lipid peroxidation and oxidative damage to liver cells.

CCl_4 also reduced GSH levels and CAT and SOD activities, indicating weakened antioxidant defenses. Treatment with *VA* and ademetionine improved these parameters, while their combination showed greater improvement than the individual treatments. Silymarin

also reduced lipid peroxidation and improved antioxidant defenses. Overall, the combined VA and ademetionine treatment showed promising hepatoprotective and antioxidant effects. Statistical significance should be reported according to the actual experimental results.

Table 4: Effect of treatments on hepatic oxidative-stress markers

Group	TBARS (nmol MDA/mg protein)	GSH (µg/mg protein)	CAT (U/mg protein)	SOD (U/mg protein)
Normal control	2.10 ± 0.12	7.82 ± 0.31	52.40 ± 2.18	8.52 ± 0.34
Disease control	5.84 ± 0.26	3.12 ± 0.18	27.35 ± 1.64	4.18 ± 0.22
V. amygdalina 100 mg/kg	4.05 ± 0.21	5.18 ± 0.24	39.26 ± 1.72	6.18 ± 0.28
Ademetionine 1 g/kg	3.68 ± 0.19	5.72 ± 0.27	42.15 ± 1.85	6.65 ± 0.31
Combination	2.76 ± 0.15	7.06 ± 0.29	48.72 ± 2.01	7.84 ± 0.30
Silymarin 100 mg/kg	2.58 ± 0.14	7.31 ± 0.32	49.65 ± 1.94	8.05 ± 0.27

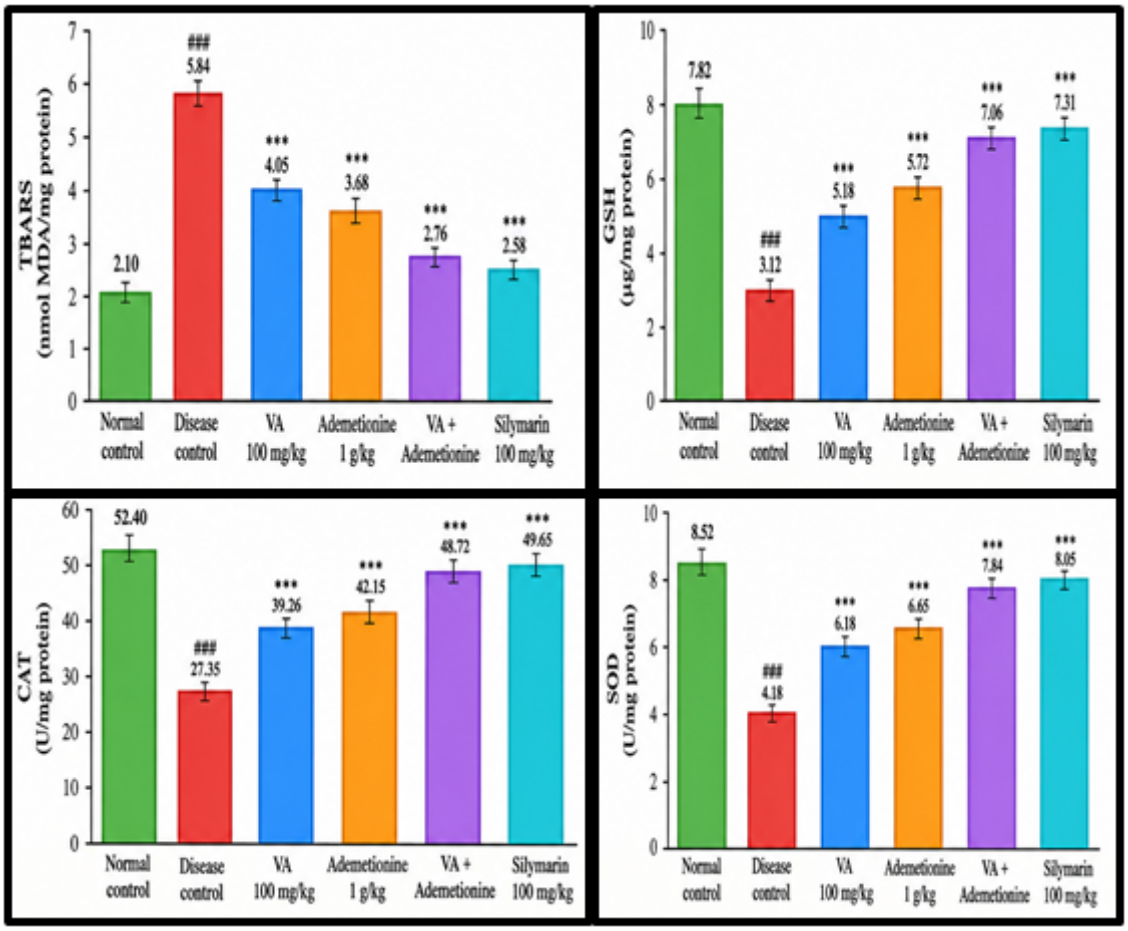


Figure: 2. Effect of treatments on oxidative markers TBARS, GSH, CAT, and SOD Levels

3.4 Histopathological Evaluation of Liver

Histopathological examination was performed to assess liver damage caused by CCl_4 and the protective effects of the treatments. The normal-control group showed normal liver structure, while the disease-control group exhibited hepatocyte degeneration, inflammation, fatty changes, sinusoidal alterations, and necrosis.

Treatment with V. amygdalina (VA) extract and ademetionine improved liver structure and reduced cellular damage and inflammation. The combined VA plus ademetionine treatment showed better preservation of hepatic architecture, with fewer degenerative and necrotic changes. The silymarin-treated group also showed relatively normal liver structure.

These findings support the biochemical results and suggest that the combined treatment may provide greater hepatoprotection against CCl_4-induced liver damage than either treatment alone.

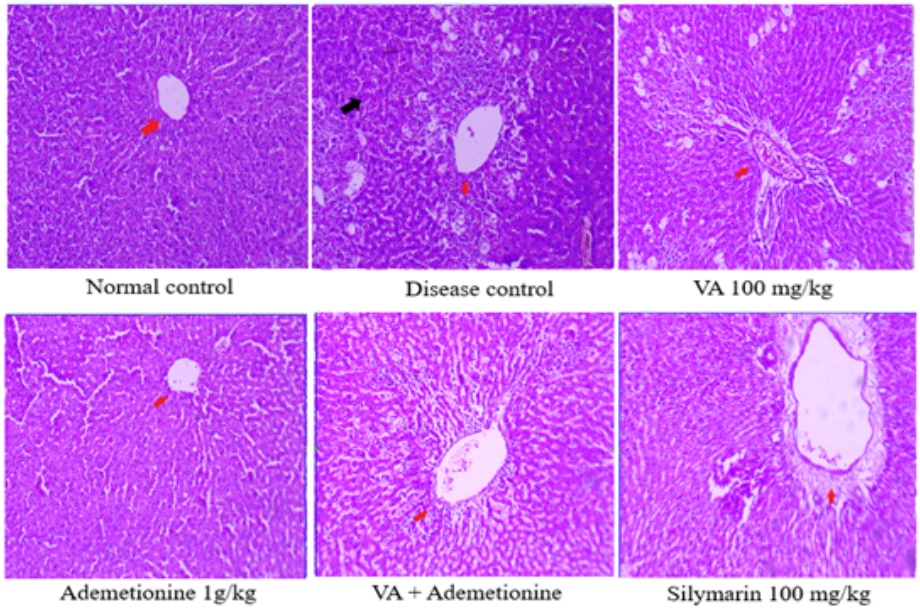


Figure: 3. Histopathological representation of liver tissues

- **Red arrows** → central vein / vascular structure
- **Yellow arrows** → hepatocellular degeneration / vacuolar change
- **Black arrows** → inflammatory cellular infiltration

5.3. Statistical Analysis and Overall Findings

All data were expressed as Mean ± SEM and analyzed using one-way ANOVA followed by Tukey's multiple-comparison test. A p value below 0.05 was considered statistically significant. GraphPad Prism version 5.06 was used for analysis. Actual experimental values were used to compare each biochemical and oxidative-stress parameter with the normal-control and disease-control groups. Significant differences were indicated in tables and graphs.

Overall, CCl_4 administration caused liver damage, increased oxidative stress and serum liver enzymes, altered bilirubin and total protein levels, and damaged hepatic tissue. Treatment with Vernonia amygdalina (VA) extract improved these changes, while ademetionine also showed protective effects. The combined VA and ademetionine treatment appeared to provide greater protection against liver injury, as supported by biochemical, antioxidant, and histopathological findings.

The hepatoprotective effects of VA may be partly related to reduce oxidative stress and improved antioxidant defenses. Phytochemicals such as flavonoids, phenolic compounds, saponins, and alkaloids may contribute to these effects. Further studies are needed to identify the active compounds and clarify the mechanisms responsible for its hepatoprotective activity.

4. DISCUSSION

The increase in serum ALT, AST, ALP, and bilirubin, along with the decrease in total protein in the disease-control group, indicates CCl_4-induced liver damage. CCl_4 toxicity involves the formation of reactive metabolites through cytochrome P450 enzymes, leading to lipid peroxidation and damage to cell membranes [9, 10]. Increased TBARS and decreased GSH, CAT, and SOD levels also indicate oxidative stress and reduced antioxidant defenses.

Treatment with V. amygdalina extract improved the biochemical and oxidative-stress parameters. These findings agree with previous studies showing that VA leaf extract can reduce biochemical changes and lipid peroxidation in CCl_4-treated rats [17, 18]. However, differences in extract preparation, solvents, doses, and animal models may affect the results. The presence of flavonoids and phenolic compounds may explain its antioxidant potential [19].

Ademetionine treatment also showed improvement in the measured parameters. S-adenosylmethionine (SAMe) is involved in hepatic methylation and other metabolic processes and may contribute to liver protection [20].

The combination of VA and ademetionine showed a favorable improvement in biochemical and oxidative-stress parameters, along with better liver structure in histopathological observations.

5. CONCLUSION

The present study evaluated the hepatoprotective effects of Vernonia amygdalina (VA), ademetionine, their combination, and silymarin against CCl_4-induced liver damage. Phytochemical screening revealed alkaloids, saponins, flavonoids, and phenolic compounds in the VA extract.

CCl_4 increased liver enzymes and oxidative stress while reducing total protein and antioxidant defenses. VA and ademetionine improved these changes, with the combination showing greater improvement in biochemical parameters and liver structure. These findings suggest that

VA has promising hepatoprotective and antioxidant potential. However, further studies are needed to confirm its mechanisms, safety, and clinical effectiveness.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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