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ASSESSMENT OF LIPID-LOWERING POTENTIAL OF *COMBRETUM COMOSUM* EXTRACT IN HYPERLIPIDEMIC RATS

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ABSTRACT

Aim: The present study aimed to investigate the phytochemical profile, antioxidant potential, safety, and antihyperlipidemic activity of the ethanolic extract of *Combretum comosum* leaves using *in vitro* and *in vivo* experimental models. **Materials and Methods:** Leaves of *Combretum comosum* were collected, dried, and subjected to Soxhlet extraction using ethanol. The extract was evaluated for preliminary phytochemical constituents and quantitatively analyzed for total phenolic content (TPC) and total flavonoid content (TFC). Antioxidant activity was assessed using the DPPH radical scavenging assay. Acute oral toxicity was performed in Wistar rats. Antihyperlipidemic activity was evaluated using a high-fat diet-induced model, with animals divided into control, negative control, standard (simvastatin-treated), and extract-treated groups (200 mg/kg and 400 mg/kg). Serum lipid profile and liver function parameters were analyzed using standard biochemical methods. **Results:** Phytochemical screening confirmed the presence of flavonoids, phenolics, alkaloids, glycosides, tannins, terpenoids, and steroids. The extract exhibited significant TPC (49.11 mg GAE/g) and TFC (30.4 mg RE/g). In the DPPH assay, the extract showed notable antioxidant activity with an IC_{50} value of 48.68 µg/mL. Acute toxicity studies indicated no mortality or severe toxic effects up to 2000 mg/kg. In vivo studies demonstrated a significant, dose-dependent reduction in total cholesterol, LDL, triglycerides, and VLDL levels, along with improvement in HDL levels. Additionally, liver enzyme markers (ALT, AST, ALP) and bilirubin levels were significantly normalized in treated groups and improving liver structure as indicated by histopathological analysis. Higher doses resulted in better restoration of liver architecture and reduced fatty changes. **Conclusion:** The ethanolic extract of *Combretum comosum* exhibits significant antioxidant, antihyperlipidemic, supporting its potential as a natural therapeutic agent for the management of hyperlipidemia and associated liver disorders.

KEYWORDS: *Combretum comosum*, Antihyperlipidemic, Acute toxicity, Total flavonoid content and Antioxidant.

1. INTRODUCTION

Plants that have medicinal properties are said to be rich in phytochemical compounds such as saponin, alkaloid, tannins, phenolic compounds and antioxidants **(Kpemissi *et al.*, 2019).** Medicinal plants have historically been utilized to treat conditions such as diabetes, hypertension, and inflammation, owing to their rich phytochemical content, including saponins and antioxidants. Despite advancements in synthetic chemistry, natural products remain vital for developing new medicines **(Batista *et al.*, 2012).** The use of herbal remedies presents opportunities to manage nephropathies and mitigate nephrotoxicity due to the efficacy of compounds like phenolics. Researchers increasingly favor natural antioxidants for their safety and effectiveness in promoting health and preventing complications from various diseases **(Maroyi *et al.*, 2025).** Hyperlipidaemia is a disorder of lipid metabolism, leading to elevated plasma lipid levels and often associated with cardiovascular diseases, fatty liver disease, and cancer. Its incidence has risen in recent decades **(Baldissera *et al.*, 2016).** The main

manifestations of this disorder include increased plasma concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and low concentrations of high-density lipoprotein cholesterol (HDL-C) **(Russo *et al.*, 2020).** In contrast, certain plant-derived phytochemicals, especially flavonoids, may provide high physiological activity with minimal toxicity and help prevent diseases **(Chen *et al.*, 2014).** To develop a Hyperlipidaemia phytomedicine, *Combretum comosum* possesses significant therapeutic potential as a natural agent for the management of hyperlipidemia and associated liver disorders is studies, although further studies are required to elucidate its mechanisms and validate its clinical applicability.

2. MATERIALS AND METHODS

2.1 Plant collection

Approximately 250 grams of *Combretum comosum* (leaves**)** a fern known for its medicinal properties, were harvested for this study.

2.2 Extraction process

The leaves of *Combretum comosum* were washed, dried at 35º-40º C, and pulverized to create an extractable powder. This powder underwent Soxhlet extraction using ethanol, with the solvent removed using a rotary evaporator, yielding a viscous substance that was stored in a refrigerator. Extraction concluded when the siphon tube showed no color change, indicating depletion of phytoconstituents, confirmed by evaporating a solvent aliquot. Concentration of the extracts was achieved under reduced pressure at 40 °C, resulting in semi-solid crude extracts. The percentage yield will be determined by comparing the weight of the dried extract with the initial plant powder **(Bennour *et al.*, 2020).**

2.3 Phytochemical investigation

The presence or absence of several bioactive components in the plant extract was assessed using a thorough qualitative phytochemical screening. Alkaloids, flavonoids, phenolic compounds, tannins, saponins, glycosides, terpenoids, and steroids are among the main types of phytochemicals that were examined **(Nurhadi *et al.*, 2020).**

2.4 Quantitative Phytochemical Estimation

2.4.1 Determination of Total Phenolic Content (TPC)

The Folin–Ciocaltleu reagent method was used to measure the amount of phenolics in *Combretum comosum*. Using a spectrophotometer and a blank as a reference, the absorbance was determined at 760 nm following incubation. Gallic acid standard solutions at concentrations of 20, 40, 60, 80, and 100µg/m were used to create a calibration curve **(Abu *et al.*, 2020).**

2.4.2 Determination of Total Flavonoid Content (TFC)

The tannin and flavonoid content of the leaves was assessed using the aluminum chloride colorimetric assay method. A spectrophotometer was used to test the reaction mixture's absorbance at 510 nm. The total flavonoid concentration was then determined using the calibration curve, and the results were reported as milligrams of Rutin equivalent per gram of dry extract weight **(Shraim *et al.*, 2021).**

2.5 DPPH Radical Scavenging Assay

The *Combretum comosum* extract's antioxidant capacity was assessed using the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay. A UV-Vis spectrophotometer was then used to measure the absorbance at 517 nm in comparison to a methanol blank **(Baliyan *et al.*, 2022).**

2.6 Acute Oral Toxicity Evaluation (Animal Model)

Healthy male Wistar rats were used for an acute oral toxicity study following OECD guidelines. Animals were fasted overnight, weighed, and administered fixed doses of an extract (5, 50, 300, or 2000 mg/kg). Behavioral, neurological, and physical changes were monitored for toxicity or mortality over 14 days, with close observation for the first 24 hours post-dosing **(Zainul *et al.*, 2020).**

2.7 Pharmacological Investigations

Induction of Hyperlipidemia via High-Fat Diet

Hyperlipidemia was induced in rats using a specially formulated high-fat diet (HFD) comprising 400 g normal chow, 320 g lard, 220 g casein, 15 g cholesterol, 50 g of a vitamin and mineral mixture, 0.5 g DL-methionine, 0.2 g yeast powder, and 0.2 g sodium chloride (NaCl). This diet was designed to elevate serum lipid levels in the experimental animals **(Munshi *et al.*, 2014).**

Experimental Design

The anti-ulcer activity was evaluated using an indomethacin-induced gastric ulcer model. Animals.

Experimental design

The hyperlipidemic activity of *Combretum comosum m*ethanolic extract was evaluated using a cholesterol-fed diet model in rats. Animals were randomly divided into five groups, with six rats in each group (n = 6), and treated as follows:

Group I (Normal Control): Normal rats received standard rat pellet diet and water ad libitum for 30 days and served as the control group.

Group II (Negative Control): Rats were fed a high-fat diet (HFD) to induce hyperlipidemia but did not receive any drug or extract.

Group III (Standard Treatment): Hyperlipidemic rats received simvastatin (4 mg/kg, p.o.) along with the HFD.

Group IV (Lower Concentration): Hyperlipidemic rats were administered the ethanolic extract of *Combretum comosum*at a dose of 200 mg/kg/day orally, along with HFD.

Group V (Higher Concentration): Hyperlipidemic rats were administered the ethanolic extract of *Combretum comosum*at a dose of 400 mg/kg/day orally, along with HFD.

control. Test formulations were administered orally after ulcer induction **(Nam *et al.*, 2018).**

2.8 Estimation of serum lipid profile

The study evaluated serum lipid profiles at three intervals—baseline, after 30 days on a high-fat diet, and after 15 and 30 days of treatment with either a standard drug or methanolic extract of Combretum comosum. Blood samples from overnight-fasted animals were analyzed for total cholesterol, HDL-C, LDL-C, and triglycerides using enzymatic assay kits, with VLDL-C calculated via the Friedewald equation **(Fujii *et al.*, 2020; Mohammadshahi *et al.*, 2023).**

2.9 Collection of blood samples and measurement of biochemical parameters

The experimental period, animals from all groups were euthanized under mild anesthesia, and blood samples were collected for biochemical analysis of lipid parameters, including total cholesterol, triglycerides, and high-density lipoprotein cholesterol **(Abalymov *et al.*, 2020; Singh *et al.*, 2022).**

2.10 Serum biochemical parameters

Alkaline phosphatase (ALP)

Alkaline phosphatase (ALP) catalyzes the conversion of p-nitrophenyl phosphate (pNPP) into phosphate and p-nitrophenol, resulting in a yellow color at pH 10.3. The enzyme activity is measured by the increase in absorbance at 405 nm.

Aspartate Transaminase AST

Aspartate Transaminase (AST), or SGOT, facilitates the conversion of L-aspartate and α-ketoglutarate into L-glutamate and oxaloacetate, which is further reduced to malate by malate dehydrogenase (MDH).

Alanine transaminase (ALT)

Alanine transaminase (ALT), or SGPT, converts L-alanine and α-ketoglutarate into pyruvate and L-glutamate.

ALT activity is calculated using the formula:

ALT activity (IU/L) = Δ A/minute × 1768.

Total Bilirubin

The Jendrassik and Grof method determines total bilirubin levels in blood or plasma by reacting diazotized sulfanilic acid with bilirubin in the presence of solubilizing agents like caffeine, sodium benzoate, and sodium acetate.

3. RESULTS AND DISCUSSION

3.1 Percentage Yield

Table 1: Percentage yield.

S. No	Plant name	Solvent	Theoretical weight	Yield(gm)	% yield		
1.	*Combretum comosum*	Ethanol	250	8.96	3.58%	24.28	6.07

3.2 Preliminary Phytochemical study

Table 2: Phytochemical testing of the extract of methanol.

Sr.no	Experiment	Presence or absence ofphytochemical test
Ethanolic Extract		
1.	**Alkaloids**	Present
2.	**Glycoside**	Present
3.	**Carbohydrates**	Present
4.	**Proteins and Amino Acids**	Absent
5.	**Flavonoids**	Present
6.	**Tannin and Phenolic Compounds**	Present
7.	**Saponin**	Absent
8.	**Test for Triterpenoids and Steroids**	Present

3.3 Total Phenolic content (TPC) estimation

Table 3: Standard table for Gallic acid.

S. No.	Concentration (µg/ml)	Absorbance
1.	20	0.115
2.	40	0.148
3.	60	0.218
4.	80	0.218
5.	100	0.257

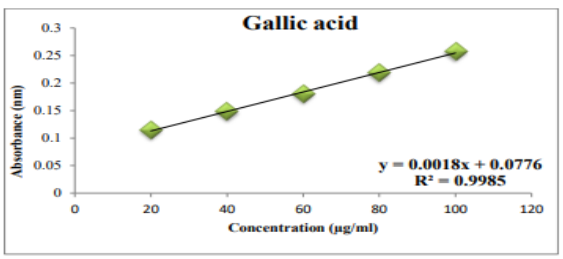


Table 5: Total Phenolic Content in *Combretum comosum* extract.

S. No	Absorbance	TPC in mg/gm equivalent of Gallic Acid
Combretum comosum	0.156	49.11mg/gm
	0.166	
	0.176	

3.4 Total Flavonoids content (TFC) estimation.

Table 6: Standard table for Rutin.

S.No.	Concentration (µg/ml)	Absorbance
1.	20	0.135
2.	40	0.159
3.	60	0.178
4.	80	0.189
5.	100	0.219

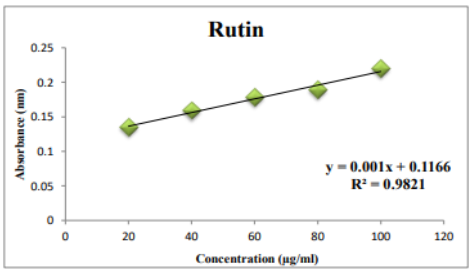


Table 8: Total Flavonoid Content in *Combretum comosum* extract.

S. No	Absorbance	TFC in mg/gm equivalent of Rutin
1	0. 136	**30.4 mg/gm**
2	0. 147	
3	0. 158	

3.5 DPPH 1, 1- diphenyl-2-picryl hydrazyl Assay

Table 9: DPPH radical scavenging activity of Std. Ascorbic acid.

Concentration (µg/ml)	Absorbance	% Inhibition
20	0.513	48.390
40	0.459	53.822
60	0.378	61.971
80	0.297	70.120
100	0.161	83.802
Control 0.994		**IC50 28.77**

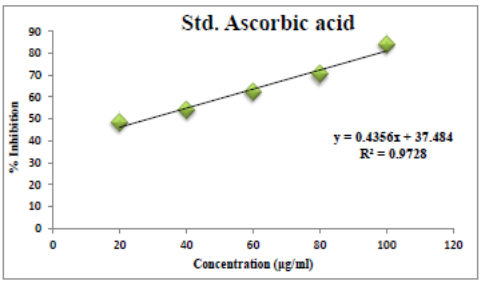
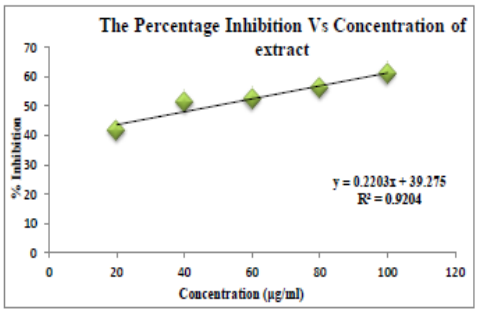


Table 10: DPPH radical scavenging activity of Ethanol extract of *Combretum comosum*.

Concentration (µg/ml)	Absorbance	% Inhibition
20	0.532	41.448
40	0.482	51.409
60	0.473	52.414
80	0.437	56.036
100	0.369	61.167
Control 0.944		**IC50 48.68**



Graph 1: Represents the Percentage Inhibition Vs Concentration of extract.

3.6 *In vivo* acute oral toxicity (OECD 423)

Table 12: Parameter of acute oral toxicity, extract dose 2000 mg/kg per body weight.

Extract Dose 2000 mg/kg							
Parameter	**1 DAY**	**3 DAY**	**5 DAY**	**7 DAY**	**9 DAY**	**11 DAY**	**14 DAY**
Body weight	180 gm	184 gm	189 gm	194 gm	197 gm	199gm	204 gm
Skin & fur	Normal	Red color	Red color	Acute redness	Acute redness	Normal	Normal
Eye	Normal	Normal	redness	redness	Normal	Normal	Normal
Mucous membrane	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Salivation	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Stool	Normal	Hard	Hard	Hard	Hard	Hard	Hard
Urination	Normal	Normal	yellowish	Colour change	yellowish	Normal	Normal

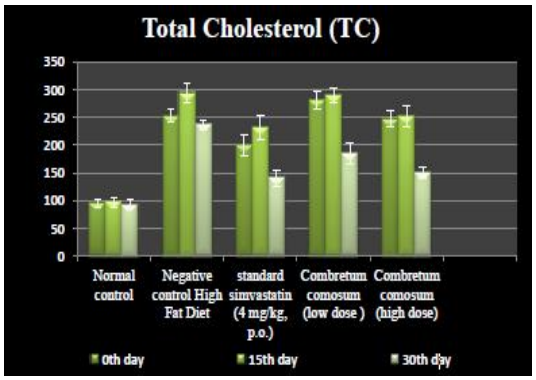
Sleep	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Behaviour	Normal	Normal	aggressive	aggressive	aggressive	Normal	Normal
Somatomotor activity	Normal	Normal	Photo phobia	Photo phobia	Photo phobia	Normal	Normal
Mortality	Normal	Normal	Normal	Normal	Normal	Normal	Normal

3.7 Estimation of serum lipid profile

3.7.1 Estimation of Total Cholesterol

Table 13: serum lipid profile of Total Cholesterol (TC).

S.No	Groups	Serum Lipid Levels (Mg/Dl) On Day(S)		
		0th day	15th day	30th day
1	Normal control	95.06 ± 8.66	97.02 ±8.71	93.03 ±8.75
2	Negative control High Fat Diet	252.71 ± 11.37	293.87 ± 17.49	236.39 ± 9.49
3	standard simvastatin (4 mg/kg, p.o.)	199.40 ± 18.35	231.26 ± 22.61	141.16 ± 14.46
4	*Combretum comosum* (low dose)	280.49 ± 15.22	289.68± 13.74	184.51 ± 18.31
5	*Combretum comosum*(high dose)	247.35 ± 13.40	252.15 ± 19.43	149.63 ± 10.41

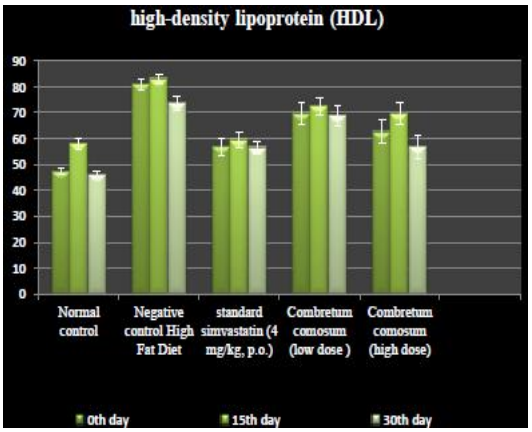


Graph 2: Bar graph of HDL.

3.7.2 Estimation of high-density lipoprotein

Table 15: Serum Lipid Profile of High-Density Lipoprotein (HDL).

S. No	Groups	Serum Lipid Levels (Mg/Dl) On Day(S)		
		0th day	**15th day**	**30th day**
1	Normal control	47.35±1.03	57.92±2.32	45.90 ± 1.25
2	Negative control High Fat Diet	80.91 ± 2.02	82.93 ± 1.65	73.52± 2.53
3	Standard simvastatin (4 mg/kg, p.o.)	56.65 ± 3.26	59.46 ± 3.13	56.41± 2.65
4	*Combretum comosum* (low dose)	69.66± 4.02	72.46 ± 3.49	68.81± 3.96
5	*Combretum comosum* (high dose)	62.65 ± 4.39	69.53± 4.28	56.68± 4.29

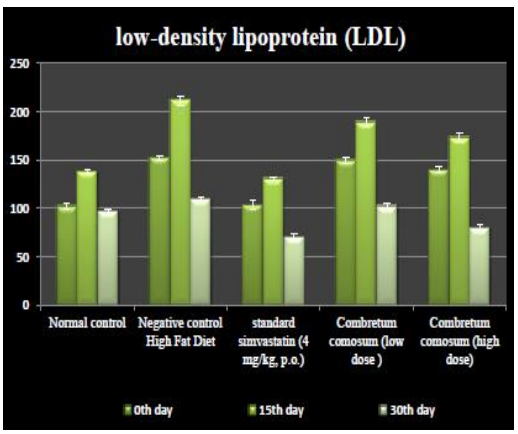


Graph 3: Bar graph of HDL.

3.7.3 Estimation of low-density lipoprotein

Table 15: serum lipid profile of low-density lipoprotein (LDL).

S. No	Groups	Serum Lipid Levels (Mg/Dl) On Day(S)		
			15th day	30th day
1	Normal control	102.01 ± 3.66	138.09 ±2.36	96.32 ±2.31
2	Negative control High Fat Diet	151.80 ± 2.86	211.33 ± 4.36	109.08 ± 2.56
3	Standard simvastatin (4 mg/kg, p.o.)	103.23 ± 4.93	130.68± 2.10	69.88 ± 3.94
4	*Combretum comosum*(low dose)	149.42 ± 3.06	188.57 ± 5.02	102.10 ± 2.34
5	*Combretum comosum*(high dose)	139.63 ± 2.85	173.14 ± 5.35	79.57 ± 4.11

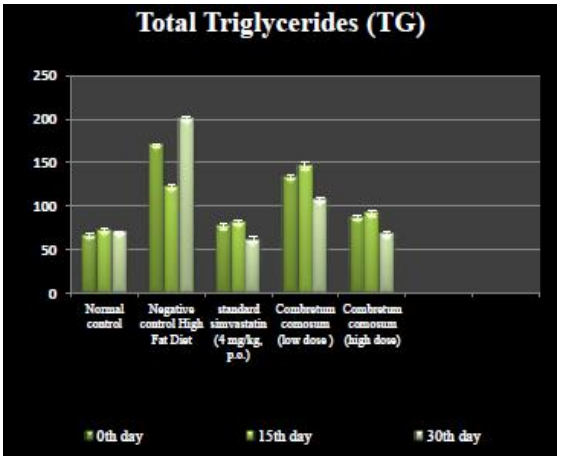


Graph 4: Bar graph of VLDL.

3.7.4 Estimation of Total Triglycerides

Table 16: serum lipid profile of Total Triglycerides (TG).

S. No	Groups	Serum Lipid Levels (Mg/Dl) On Day(S)		
		0th day	15th day	30th day
1	Normal control	66.26 ± 2.06	72.02±3.02	69.32±1.76
2	Negative control High Fat Diet	169.39± 2.45	121.53 ± 3.09	199.36 ± 2.96
3	Standard simvastatin (4 mg/kg, p.o.)	76.69 ± 3.62	81.60 ± 2.65	60.82 ± 3.63
4	*Combretum comosum*(low dose)	133.36 ± 3.02	146.18 ± 3.84	106.58 ± 3.05
5	*Combretum comosum*(high dose)	86.53 ± 3.36	91.41 ± 4.03	67.81 ± 3.85

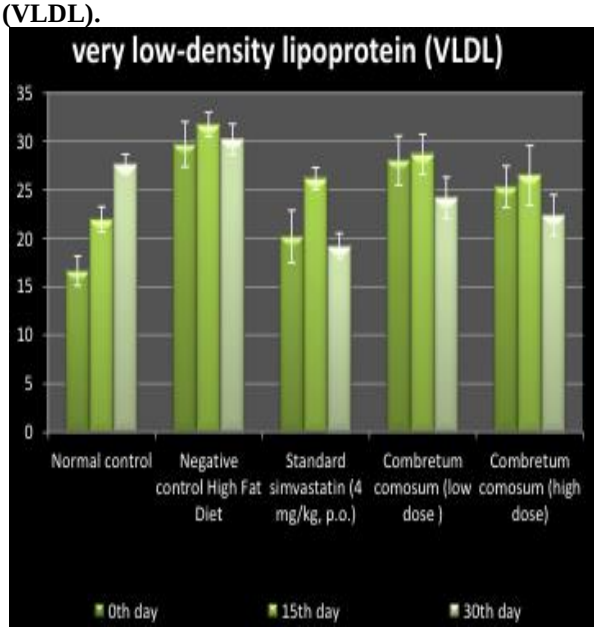


Graph 5: Bar graph of TG.

3.7.5 Estimation of very low-density lipoprotein

Table 17: serum lipid profile of very low-density lipoprotein (VLDL).

S. No	Groups	Serum Lipid Levels (Mg/Dl) On Day(S)		
		0th day	15th day	30th day
1	Normal control	16.67 ± 1.54	21.96±1.31	27.62±1.03
2	Negative control High Fat Diet	29.69 ± 2.29	31.74 ± 1.23	30.23 ± 1.52
3	Standard simvastatin (4 mg/kg, p.o.)	20.18 ± 2.69	26.16 ± 1.16	19.18 ± 1.36
4	*Combretum comosum*(low dose)	28.05- ± 2.53	28.68 ± 2.03	24.16 ± 2.15
5	*Combretum comosum*(high dose)	25.33 ± 2.11	26.51 ± 3.06	22.39± 2.09



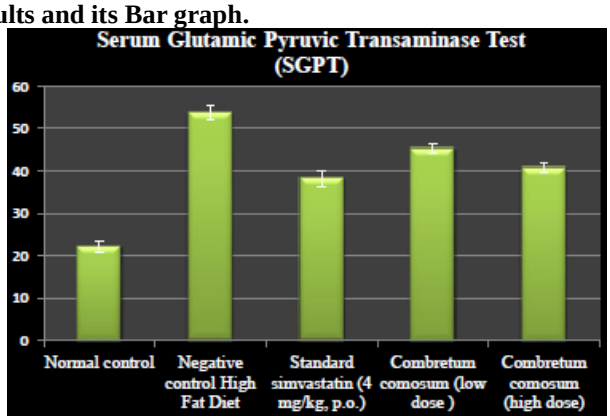
Graph 6: Bar graph of VLDL.

3.8 Serum biochemical parameters

3.8.1 Serum Glutamic Pyruvic Transaminase Test (SGPT)

Table 18: Serum Glutamic Pyruvic Transaminase Test results and its Bar graph.

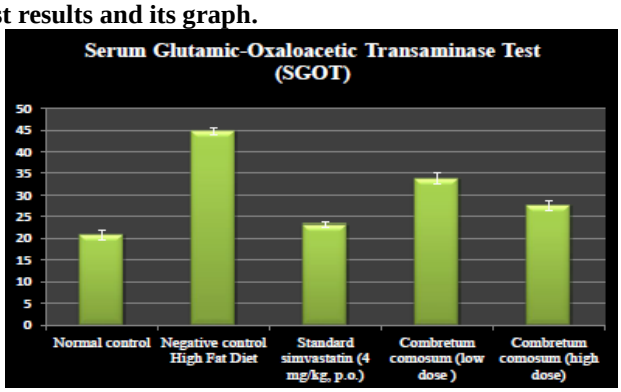
S. No	Treatment Group	Results (Mean±Sd)
1.	Normal control	22.25±1.25
2.	Negative control High Fat Diet	53.75±1.85
3.	Standard simvastatin (4 mg/kg, p.o.)	38.25±1.95
4.	*Combretum comosum*(low dose)	45.25±1.24
5.	*Combretum comosum*(high dose)	40.75±1.27



3.8.2 Serum Glutamic-Oxaloacetic Transaminase Test (SGOT)

Table 19: Serum Glutamic-Oxaloacetic Transaminase Test results and its graph.

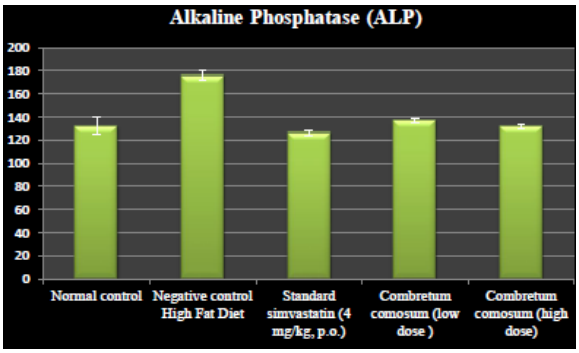
S. No	Treatment Group	Results (Mean±Sd)
1.	Normal control	20.75±1.109
2.	Negative control High Fat Diet	44.75±0.854
3.	Standard simvastatin (4 mg/kg, p.o.)	23.23 ±0.707
4.	*Combretum comosum* (low dose)	33.75±1.25
5.	*Combretum comosum* (high dose)	27.5±1.041



3.8.3 Alkaline Phosphatase (ALP) Test

Table 20: Alkaline Phosphatase (ALP) Test results and its Bar.

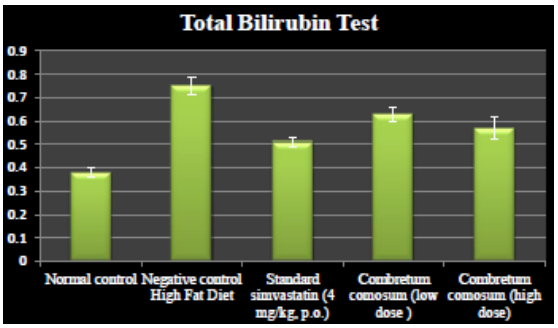
S. No	Treatment Group	Results (Mean±Sd)
1.	Normal control	132±7.52
2.	Negative control High Fat Diet	176±4.08
3.	Standard simvastatin (4 mg/kg, p.o.)	126±2.89
4.	*Combretum comosum* (low dose)	137±2.38
5.	*Combretum comosum* (high dose)	132±2.25



3.8.4 Total Bilirubin Test

Table 21: Total Bilirubin Test results.

S. No	Treatment Group	Results (Mean±Sd)
1.	Normal control	0.38±0.02
2.	Negative control High Fat Diet	0.75±0.04
3.	Standard simvastatin (4 mg/kg, p.o.)	0.51±0.02
4.	*Combretum comosum*(low dose)	0.63±0.03
5.	*Combretum comosum*(high dose)	0.57±0.05



Graph 9: Bar graph represents the Total bilirubin test results.

Histopathology

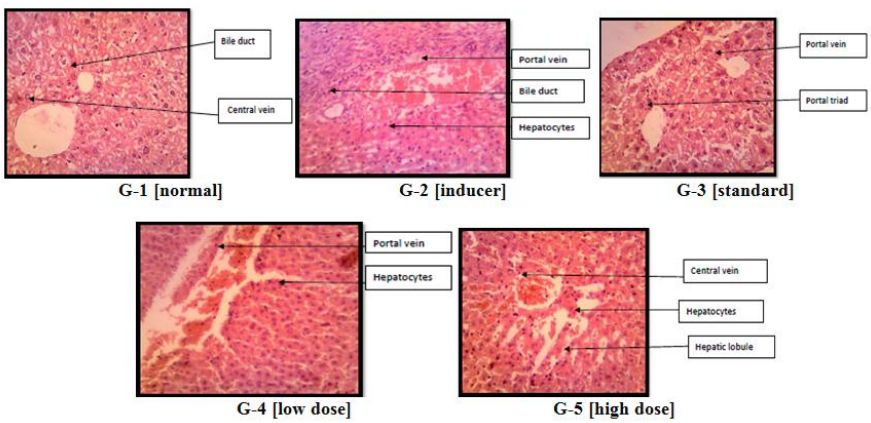


Figure 1: Histopathological examination.

4. DISCUSSION

The study examined the phytochemical composition, antioxidant potential, safety, and antihyperlipidemic effectiveness of the ethanolic extract of *Combretum comosum* leaves. Results indicate a significant biological activity attributed to its rich phytochemical profile, with a high yield of polar and semi-polar constituents. Major secondary metabolites identified include flavonoids, phenolic compounds, tannins, and alkaloids, known for their antioxidant and lipid-lowering effects. The extract contained 49.11 mg GAE/g of total phenolic content and 30.4 mg RE/g of total flavonoid content, indicating a strong source of polyphenolic compounds that scavenge free radicals and enhance antioxidant defenses. The DPPH assay showed concentration-dependent radical scavenging activity with an IC_{50} value of 48.68 µg/mL, highlighting its potential to reduce oxidative damage, albeit less potent than ascorbic acid.

The acute oral toxicity study indicated that the extract is safe up to a dose of 2000 mg/kg, with no mortality and only transient behavioral alterations. This finding highlights the relatively low toxicity and favorable safety profile of the extract, which is essential for its consideration as a therapeutic agent. Hyperlipidemia induced by a high-fat diet resulted in a significant elevation of serum lipid parameters, including total cholesterol, LDL, triglycerides, and VLDL, confirming the successful establishment of the disease model. Treatment with the ethanolic extract of *Combretum comosum* produced a dose-dependent reduction in these lipid parameters. Notably, the higher dose (400 mg/kg) demonstrated a pronounced effect, with lipid levels approaching those observed in the standard drug-treated group (simvastatin). This suggests that the extract may modulate lipid metabolism through mechanisms such as inhibition of cholesterol biosynthesis, enhancement of lipoprotein lipase activity, or increased clearance of circulating lipids. In addition to its antihyperlipidemic effect, the extract also exhibited a protective effect on liver function. Elevated levels of serum hepatic enzymes (ALT, AST, and ALP) and bilirubin in hyperlipidemic animals were significantly reduced following treatment, indicating improved hepatic integrity and function. Histopathological analysis of liver tissues indicated that the G-1 group had normal architecture, while the G-2 group showed fatty degeneration due to hyperlipidemia. The G-3 group displayed recovery with reduced fat deposition. The G-4 and G-5 groups, treated with *Combretum comosum* extract, demonstrated dose-dependent protective effects, with the high dose leading to better liver structure restoration and reduced fatty changes.

4. CONCLUSION

The present study concludes that the ethanolic extract of *Combretum comosum* leaves is a rich source of bioactive phytoconstituents, particularly phenolics and flavonoids, which contribute significantly to its biological activities. The extract exhibited notable antioxidant potential, indicating its ability to scavenge free radicals and reduce oxidative stress. In vivo findings confirmed that the extract is safe at higher doses (up to 2000 mg/kg) and produces no significant toxicity. Furthermore, it demonstrated a pronounced antihyperlipidemic effect by effectively reducing elevated levels of total cholesterol, LDL, triglycerides, and VLDL in high-fat diet-induced hyperlipidemic rats, while also showing improvement in HDL levels. In addition, the extract exerted hepatoprotective effects, as evidenced by the normalization of liver enzyme markers (ALT, AST, ALP) and bilirubin levels, suggesting restoration of hepatic function. Overall, the study indicates that *Combretum comosum* possesses significant therapeutic potential as a natural agent for the management of hyperlipidemia and associated liver disorders, although further studies are required to elucidate its mechanisms and validate its clinical applicability.

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