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RESEARCH ARTICLE

Evaluation of Anti-Diabetic and Hepatoprotective Activity of Methanolic Bark Extract of *Symplocos racemosa* Roxb Bark Extract in Alloxan Induced Diabetic Rats

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Abstract: *Symplocos racemosa* is a plant known to possess anti-oxidant, analgesic, anti-inflammatory and other pharmacological activities. This research work aims to assess the anti-diabetic potential of *Symplocos racemosa* Roxb bark extract in Alloxan-induced experimental diabetes in rats. Oral administration of methanolic extract of *Symplocos racemosa* (200 and 400 mg/kg/body weight/rat/day) for 30 days significantly reduced elevated blood glucose levels in diabetic rats. Electron microscopic studies revealed noteworthy morphological changes in the mitochondria and endoplasmic reticulum of β cells in Alloxan-induced diabetic rats. Additionally, a decrease in the number of secretory granules of beta cells was observed. The extract demonstrated a significant ($P<0.05$) glucose uptake, though less effective than the reference drug, Metformin. Pathological abnormalities were normalized post-treatment with *Symplocos racemosa* extract, showcasing comparable efficacy to Metformin, a well-known hypoglycemic drug. This suggests that the methanolic extract of *Symplocos racemosa* may be an effective anti-diabetic agent. Simultaneously, this study also aimed to evaluate the hepatoprotective activity of methanolic extract of *Symplocos racemosa* (MESR) bark extract at doses of 200 and 400 mg/kg/body weight/rat/day in paracetamol-induced hepatic damage in rats over 7 days. Hepatoprotection was assessed through serum transaminases (AST and ALT), alkaline phosphatase (ALP) on the 8th day, and histopathological observations. The results from this work indicate that MESR bark is an effective hepatoprotective agent against paracetamol-induced hepatic damage, suggesting potential clinical applications in the treatment of liver diseases.

Keywords: *Symplocos racemosa*; Anti-diabetic Activity; Hepatoprotection; Alloxan; Paracetamol; Liver Enzymes

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels due to defects in insulin secretion or insulin action [1,2]. It has become one of the major threat to human health worldwide due to sedentary lifestyle and unhealthy diet. As per International Diabetes Federation (IDF), approximately 463 million adults (20-79 years) were living with diabetes in 2019 and the number is projected to rise to 700 million by 2045 [3]. Poor glycemic control leads to micro and macrovascular complications affecting eyes, kidneys, nerves and cardiovascular system. Currently available therapies are able to control symptoms but are not curative and have side effects. Therefore, there is growing interest in alternative treatment approaches including herbal medicines.

Liver is one of the prime organs involved in glucose and lipid homeostasis. Diabetes and obesity are a major risk factor for non-alcoholic fatty liver disease (NAFLD) which can further progress to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis [4]. NAFLD affects one-third of general population and almost 90% of diabetic and obese individuals globally [5]. It is a major cause of chronic liver disease worldwide due to lack of approved drugs.

Symplocos racemosa Roxb. (Symplocaceae) commonly known as Lodh tree, is a small evergreen tree widely distributed in the Indian subcontinent and Southeast Asian countries. Traditionally various parts of the plant are used in folk medicine for the treatment of diabetes, liver disorders, wounds, diarrhea, dysentery and skin diseases [6]. Previous studies have shown *S. racemosa* to possess antioxidant [7], anti-inflammatory [8], analgesic [9], anticancer [10], antimicrobial [11] and wound healing properties [12]. Phytochemical investigations have revealed the presence of bioactive constituents like flavonoids, phenolic compounds, triterpenoids and phytosterols [13].

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Despite its ethnomedicinal claims, the antidiabetic and hepatoprotective potential of *S. racemosa* have not been scientifically evaluated. Hence, the present study was carried out to investigate the antidiabetic and hepatoprotective activity of methanolic bark extract of *S. racemosa* in animal models of diabetes and paracetamol-induced liver toxicity

Figure 1. Leaves and fruits of *S. racemosa*

2. Materials and methods

2.1. Collection and Authentication of Plant Material

The bark of *Symplocos racemosa* was collected from Ayurvedic Store, Kakinada, India in July 2019. The plant material was authenticated by Dr. Srinivasa Rao, Department of Botany, PRG Govt Degree College, Kakinada, Andhra Pradesh, India. A voucher specimen (specimen no. SR/2019) has been deposited in the herbarium of the department for future reference.

2.2. Experimental animals

Male Wistar rats, weighing 150-200g were procured from Ghosh Enterprises, Kolkata and housed at standard laboratory conditions (temperature 25±2°C) with free access to food and water ad libitum. The study was approved by the Institutional Animal Ethics Committee.

2.3. Preparation of plant extract

The collected bark was dried in shade, coarsely powdered using a mechanical grinder and passed through a 40-mesh sieve. About 500g of dried powdered bark was extracted with 80% v/v methanol using maceration process for 7 days with occasional shaking and stirring. The extract was filtered and solvent was removed using a rotary vacuum evaporator (Superfit, India) at reduced temperature and pressure [14,15]. The concentrated extract was stored in an airtight container in a refrigerator at 4°C until further use.

2.4. Preliminary phytochemical screening

The methanolic extract of *Symplocos racemosa* leaves were screened by for its active constituents phytochemical analysis [16,17]. The following tests were conducted:

2.4.1. Tests for Carbohydrates

The filtrate was subjected to Molisch's test to detect carbohydrates.

2.4.2. Tests for Glycosides

The hydrolyzed portion of the extract was treated with Legal's and Borntrager's tests for glycosides.

2.4.3. Tests for Alkaloids

Filtrate stirred with dil. HCl and tested with Mayer's, Dragandroff's, Hager's, and Wagner's reagents for alkaloid presence.

2.4.4. Test for Phytosterol

Refluxed extract with alcoholic potassium hydroxide, followed by Liebermann Burchard test for phytosterol presence.

2.4.5. Tests for Fixed Oils

Spot test for appearance of oil stain. Mixture heated with 0.5N alcoholic potassium hydroxide, indicating fixed oils and fats.

2.4.6. Tests for Saponins

Extract diluted and agitated; formation of foam layer indicates saponin presence.

2.4.7. Tests for Proteins and Free Amino Acids

Extract treated with Million's reagent, Ninhydrin reagent, and Biuret test for protein and amino acid presence.

2.4.8. Tests for Phenolic Compounds and Tannins

Extract tested with dilute ferric chloride solution, 1% gelatin solution containing 10% sodium chloride, and 10% lead acetate solution for phenolic compounds and tannins.

2.4.9. Tests for Flavonoids

Aqueous sodium hydroxide and concentrated sulphuric acid used to identify flavonoids. Shinoda's test conducted to confirm the presence of flavonoids.

2.5. Acute oral toxicity study

The acute oral toxicity of the extract is assessed in accordance with the guidelines outlined by the Organisation for Economic Co-operation and Development (OECD) guideline 423 [18]. The purpose of this study was to evaluate the potential adverse effects and determine the lethal dose of the test substance when administered orally, providing crucial insights into its safety profile. The OECD guideline 423 is a standardized protocol widely recognized for its systematic approach in determining acute toxicity, ensuring consistency and comparability across studies. The study design and methodology adhered to the specified OECD guidelines to facilitate reliable and relevant findings regarding the substance's oral toxicity.

2.6. Evaluation of anti-diabetic activity

2.6.1. Induction of diabetes

Diabetes was induced in overnight fasted rats by a single intraperitoneal injection of 150mg/kg body weight of alloxan monohydrate in citrate buffer, pH 4.5 [19].

2.6.2. Experimental design

Rats were divided into 5 groups of 6 animals each.

- Group 1: Normal control, received vehicle (5% Tween-80 in water)
- Group 2: Diabetic control
- Group 3: Diabetic + Standard (Metformin 100mg/kg)
- Group 4: Diabetic + Methanolic Extract 200mg/kg
- Group 5: Diabetic + Methanolic Extract 400mg/kg

Blood glucose levels and body weights were measured initially and weekly for 21 days.

2.6.3. Oral glucose tolerance test (OGTT)

OGTT was performed in overnight fasted normal and diabetic rats. Blood glucose levels were measured at 0, 30, 60, 90 and 120min [20,21] after oral administration of glucose (2g/kg).

2.7. Evaluation of hepatoprotective activity

2.7.1. Paracetamol-induced hepatic damage

Hepatotoxicity was induced in overnight fasted rats by oral administration of paracetamol (500mg/kg) suspended in 1% CMC for 7 consecutive days [22].

2.7.2. Experimental Design

Animal Grouping: Rats were systematically divided into five groups, with each group comprising six animals [23].

- Group 1 (Control): Received 5% methylcellulose.
- Group 2 (Toxicant Control): Administered Paracetamol at a dosage of 500 mg/kg/body weight orally, daily for 7 days.
- Group 3 (Treatment Group): Received Methanol extract of *Symplocos racemosa* bark at a dose of 200 mg/kg/body weight orally, and concurrently administered Paracetamol (500 mg/kg/body weight, p.o.) daily for 7 days.
- Group 4 (Treatment Group): Received Methanol extract of *Symplocos racemosa* bark at a dose of 400 mg/kg/body weight orally, and concurrently administered Paracetamol (500 mg/kg/body weight, p.o.) daily for 7 days.
- Group 5 (Positive Control): Administered Silymarin at a dose of 25 mg/kg/body weight orally, and simultaneously administered Paracetamol (500 mg/kg/body weight, p.o.) daily for 7 days.

At the end of the experimental period, all animals were euthanized under diethyl ether anesthesia. Blood samples were collected, allowed to clot, and serum was separated by centrifugation at 3000 rpm for 10 minutes [24,25]. The obtained serum samples were subsequently analyzed for various biochemical parameters and histopathological studies are conducted on the liver cells obtained from the rats.

3. Results and discussion

3.1. Phytochemical screening

The preliminary phytochemical screening of the methanolic bark extract revealed the presence of various phytoconstituents like carbohydrates, alkaloids, flavonoids, tannins, sterols, saponins etc.

3.2. Acute oral toxicity study

No mortality or any clinical signs of toxicity were observed up to 2000mg/kg dose of the extract. The median lethal dose (LD50) was found to be greater than 2000mg/kg.

3.3. Anti-diabetic activity

3.3.1. Effect on blood glucose levels

Table 1 presents the outcomes of the antidiabetic activity evaluation, showcasing the blood glucose levels (mg/dL) at various time intervals for different experimental groups. The normal group exhibited a baseline blood glucose level of 89.16±3.11 mg/dL. After 30 minutes, there was a significant increase to 206.16±3.7 mg/dL ($p<0.001$), which continued to rise at subsequent intervals. The highest blood glucose level was observed at 60 minutes (234.7±6.2 mg/dL), followed by a gradual decline over the subsequent time points.

The standard group treated with Metformin (MET) showed a steady reduction in blood glucose levels over the 180-minute period. Significant reductions were noted at all time intervals compared to the baseline, with the lowest level recorded at 180 minutes (68.5±3.64 mg/dL. The group administered with Methanolic extract of *Symplocos racemosa* (MESR) at 200 mg/kg demonstrated a noticeable decrease in blood glucose levels.

Significant reductions were observed from 30 minutes (167.8±3.4 mg/dL, $p<0.01$) to the final time point (76.5±2.01 mg/dL, $p<0.001$). The MESR group at 400 mg/kg exhibited a distinct pattern of blood glucose reduction. Substantial decreases were noted at various intervals, with the most pronounced reduction observed at 180 minutes (88.33±4.1 mg/dL, $p<0.001$). The results of blood glucose levels are shown in Table 1.

Table 1. Results of antidiabetic activity (blood glucose levels)

GROUPS	Blood Glucose levels (mg/dL) at various time intervals (mins)						
	0	**30 Min**	**60 Min**	**90 Min**	**120 Min**	**150 Min**	**180Min**
Normal	89.16±3.11	206.16±3.7***	234.7±6.2***	202.66±6.6***	180.83±5.2***	153±4.0***	132.16±2.9***
Standard (MET)	89.5±3.36	130.5±3.8	176±4.2	140.3±3.48	104.6±4.5	80.16±3.7	68.5±3.64
MESR (200 mg/kg)	89±2.47	167.8±3.4**	219±4.1**	176.16±3.51*	151±1.8**	125.6±2.7**	76.5±2.01***
MESR (400 mg/kg)	198.6±8.3	190.16±13.1**	178.83±15.1**	142.6±9.02*	118.5±3.5***	88.33±4.1***	64.33±3.5***

MESR : Methanolic extract of *Symplocos racemosa* R. In mg/kg. MET:Metformin in mg/kg. Data represented as mean ± S.E.M values of 6 animals each. *p<0.05, **p<0.01, ***p <0.001 (Dunnett t-test) by using Graph Pad Prism, Version 5. Comparision: Standard Group Compared with Tests and Normal

3.3.2. Effect on body weight

The effect of Methanolic Extract of *Symplocos racemosa* (MESR) on the body weights of Alloxan-induced diabetic rats were studied over a 21-day period. The normal group exhibited a gradual increase in body weight from the baseline (160.83±1.85 g) to the 21st day (180.16±1.13 g). Alloxan-induced diabetic rats in the control group experienced a decline in body weight over the experimental period. The reduction was significant at the 7th day (167.6±1.83 g, p<0.01) and the 21st day (156±1.48 g, p<0.01). The standard group, treated with the reference drug, displayed an increasing trend in body weight. A significant increase was observed at the 14th day (177.33±1.85 g, p<0.01) and maintained at the 21st day (180.66±1.99 g, p<0.01). Rats administered with MESR at 200 mg/kg exhibited a slight increase in body weight over the experimental duration. The differences reached significance at the 14th day (167±1.52 g, p<0.05) and continued to the 21st day (172.66±1.64 g, p<0.05). The group receiving MESR at 400 mg/kg demonstrated a notable increase in body weight. Significant differences were observed at the 14th day (173.66±1.8 g, p<0.01) and sustained through the 21st day (177.88±2.0 g, p<0.01). These findings indicate that MESR, particularly at the higher dose (400 mg/kg), contributes to the amelioration of body weight loss in Alloxan-induced diabetic rats, suggesting a potential positive effect on overall health. Statistical significance was determined using Dunnett t-test, with comparisons made against the diabetic control group.

Table 2. Effect of MESR on Body weights of Alloxan-induced Diabetic rats.

Groups	Body weight (in g)			
	0th day	**7th day**	**14th day**	**21st day**
Normal	160.83±1.85	165.66±1.45	173.33±2.1	180.16±1.13
Diabetic control	174.3±1.45	167.6±1.83**	160.5±2.04	156±1.48**
Standard	161.66±1.97	168.83±1.55	177.33±1.85**	180.66±1.99**
MESR (200mg/kg)	159.16±1.68	162.16±0.61*	167±1.52	172.66±1.64*
MESR (400mg/kg)	159.5±1.76	167±1.59	173.66±1.8**	177.88±2.0**

MESR : Methanolic extract of *Symplocos racemosa R.* In mg/kg. MET: Metformin in mg/kg. Data represented as mean ± S.E.M values of 6 animals each. P<0.05, P<0.01 (Dunnett t-test) by using Graph Pad Prism,Version 5. Comparision: Standard Compared with Tests.

3.3.3. Oral Glucose Tolerance Test (OGTT)

The extract 200 and 400mg/kg pre-treated groups showed significant reduction in rise in blood glucose levels at different time intervals during OGTT compared to diabetic control, indicating improvement in glucose tolerance.

Table 3. Oral Glucose Tolerance Test in Diabetic rats

GROUPS	Blood Glucose levels (mg/dl) at various time intervals						
	0 Min	30 Min	60 Min	90 Min	120 Min	150 Min	180 Min
Normal	89.16±8.1**	206.16±3.7**	234.7±6.2*	202.6±6.6**	180.83±5.2***	153±4.0***	132.16±2.9***
Diabetic Control	282.5±6.7	277.6±12.9	253.5±12.47	259.3±7.5	239.16±14.3	261.5±11***	242.6±7.4
Standard (MET)	221.8±11.2**	234.1±13.0	209.6±7.7**	201.83±10.9	198.33±8.1***	178.16±6.0**	151.16±7.8
MESR (200mg/kg)	244.6±6.76*	268.5±17.5	246.6±19.29*	228.16±13.5**	207.6±14.8**	196.83±8.5***	181.16±8.5***
MESR (400mg/kg)	244.5±11.8*	245±14.8	205±16.8**	195.6±19.4**	170.33±13.5***	158.16±14.5***	149.5±14.8***

MESR : Methanolic extract of *Symplocos racemosa R.* In mg/kg. MET:Metformin in mg/kg. Data represented as mean ± S.E.M values of 6 animals each. *p<0.05, **p<0.01, ***p<0.001 (Dunnett t-test) by using Graph Pad Prism, Version 5. Comparision: Diabetic Compared with Standard and Normal, Tests compared with Standard.

The impact of the methanolic bark extract of *Symplocos racemosa* on blood glucose levels in Alloxan-induced diabetic rats was also evaluated over a 21-day period. The normal control group maintained a consistent baseline blood glucose level, while the diabetic control group exhibited a significant elevation throughout the study. Administration of the standard drug (Metformin) and the methanolic extracts at 200 mg/kg and 400 mg/kg body weight demonstrated substantial antidiabetic effects. Noteworthy reductions in blood glucose levels were observed in both extract-treated groups compared to the diabetic control, with the higher dose (400 mg/kg) displaying greater efficacy. Statistical analysis using the Dunnett t-test revealed significant differences at various time points, emphasizing the potential of the methanolic extract of *Symplocos racemosa* in ameliorating hyperglycemia in diabetic rats. The results are shown in Table 4.

Table 4. Effect of methanolic bark extract of plant *Symplocos racemosa* on alloxan induced diabetic rats on blood glucose levels

Day	Normal Control	Diabetic Control	Standard	Extract Test 1 (200mg/kg Body weight)	Extract Test 2 (400 mg/kg body weight)
0	78.16±3.92	367±28.67	195.83±21.00***	275.33±19.63**	267.83±17.40*
1	82.66±2.30	391.5±6.88	258.5±1.11***	354.33±16.13*	344.16±12.84**
7	73±1.93	303.5±5.11	180.83±1.24***	187.83±1.16***	158.5±1.11***
14	69.83±1.07	230.16±2.91	171.5±1.25***	179.66±1.68***	150.5±1.47***
21	79.83±1.07	233.5±2.34	127±1.36***	131.83±1.30***	128.33±1.05***

MESR : Methanolic extract of *Symplocos racemosa R.* In mg/kg. MET:Metformin in mg/kg. Data represented as mean ± S.E.M values of 6 animals each. *P<0.05, **P<0.01, ***P<0.001 (Dunnett t-test; Individual drug treated group (standard) compared with diabetic group,Extracts(MESR-200mg/kg and 400mg/kg) compared with standard (MET)

3.4. Hepatoprotective activity

3.4.1. Effect on Liver Enzymes

The assessment of biochemical parameters in the experimental groups reveals significant variations in SGOT, SGPT, and ALP levels, providing insights into the hepatoprotective effects of different treatments. The normal control group (Group I) displayed baseline levels of SGOT (26.33 ± 3.28 U/L), SGPT (19.66 ± 1.38 U/L), and ALP (72.5 ± 3.47 U/L). The acetaminophen-induced hepatotoxicity group (Group II) exhibited marked elevations in all three parameters, indicating liver damage. In contrast, groups treated with Methanolic Extract of *Symplocos racemosa* (MESR) at 200 mg/kg (Group III) and 400 mg/kg (Group IV) demonstrated significant reductions in SGOT, SGPT, and ALP levels, suggesting hepatoprotective effects. Notably, the silymarin-treated group (Group V) also exhibited lowered enzyme levels, further supporting its hepatoprotective potential. Statistical analysis using Dunnett t-test confirmed the significance of these observations, underscoring the potential of MESR as a hepatoprotective agent against acetaminophen-induced liver damage. The results are shown in Table 5.

Table 5. Effect of methanolic bark extract of *Symplocos racemosa* in acetaminophen induced hepatotoxic rats.

Groups	Biochemical parameters		
	SGOT (U/L)	**SGPT (U/L)**	**ALP (U/L)**
Group I (Normal Control)	26.33 ± 3.28	19.66 ± 1.38	72.5 ± 3.47
Group II (ACET:500mg/kg)	63 ± 4.66	45.33 ± 5.28	135.66 ± 3.47
Group III (MESR:200mg/kg)	29.66 ± 2.13	28.16 ± 1.16	108.5 ± 6.93
Group IV (MESR:400mg/kg)	26.83 ± 2.07	21.83 ± 1.16	114.66 ± 5.80
Group V (Silymarin:25mg/kg)	28.66 ± 2.98	23 ± 1.77	112.5 ± 3.36

MESR : Methanolic extract of *Symplocos racemosa* R. In mg/kg. ACET: Acetaminophen in mg/kg. Data represented as mean ± S.E.M values of 6 animals each. $P<0.05$, $P<0.01$,$P<0.001$ (Dunnett t-test) by using Graph Pad Prism, Version 5

3.4.2. Histopathological studies

Liver sections of paracetamol control showed extensive centrilobular necrosis with inflammatory cell infiltrations. Treatment with extract protected the liver as evident from the normal hepatic cells with mild congestion [26].

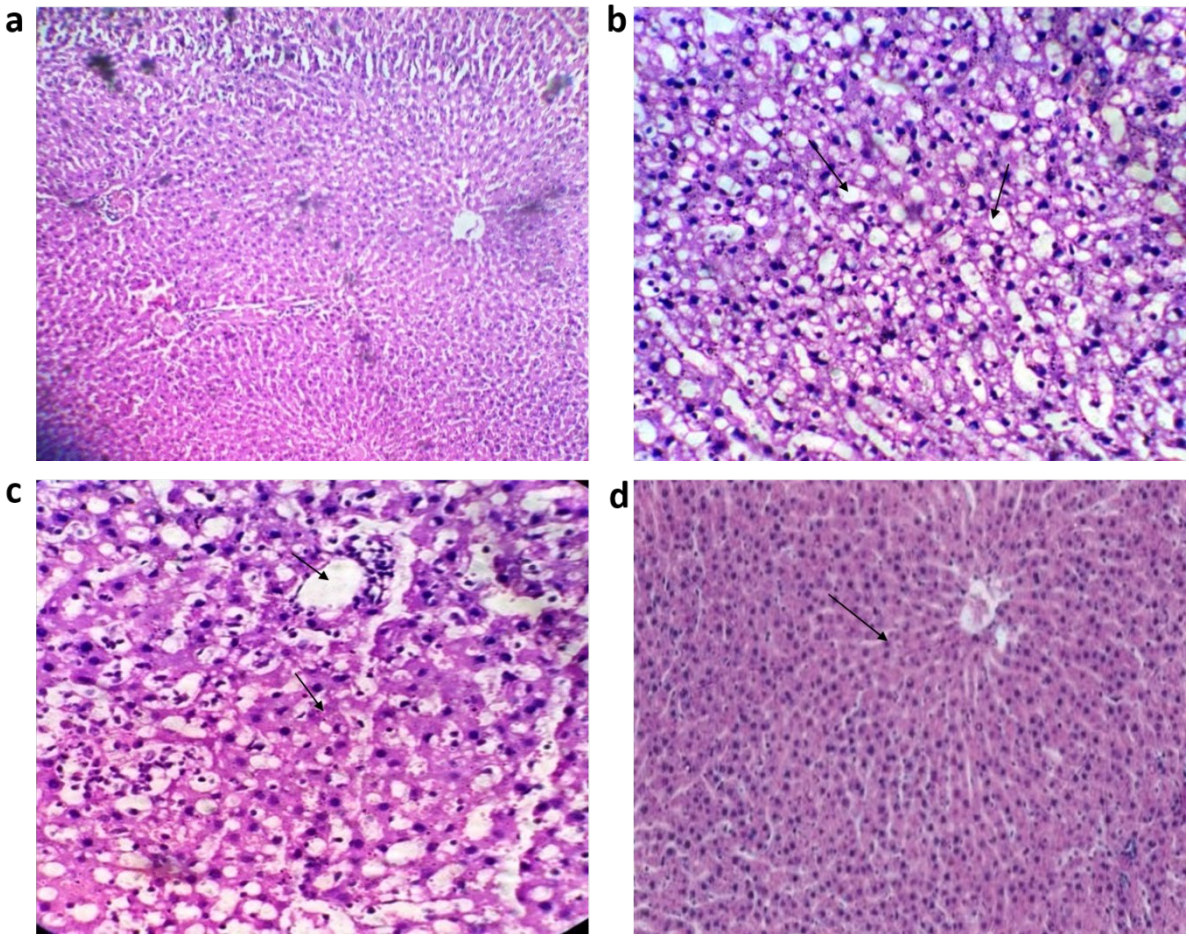

Figure 1: Histopathology studies of the liver cells a. Normal section showing intact parenchyma b. Acetaminophen treated liver cells showing effaced architecture, apoptotic hepatocytes, mild peri portal lymphocytic collections, cytoplasmic vacuolations c. Treatment with methanolic extract 200 mg/kg d. Treatment with methanolic extract with 400 mg/kg showing few regenerative hepatocytes, scattered mononuclear inflammatory cells

4. Discussion

The present study was carried out to determine the anti-diabetic and hepatoprotective potential of *Symplocos racemosa* bark extract. Alloxan is widely used to induce experimental diabetes in animals. It selectively destroys the insulin-producing pancreatic β-cells, thereby causing a reduction in endogenous insulin release and increased blood glucose levels [19,21]. OGTT is an important test to evaluate glucose tolerance in the body. The ability of the extract to significantly suppress the rise in blood glucose levels during OGTT suggests its antidiabetic potential by improving glucose tolerance, possibly by potentiating the insulin effect of plasma by regeneration of β-cells or increased insulin secretion [14].

Paracetamol hepatotoxicity is a commonly used model to evaluate hepatoprotective potential of drugs. Paracetamol is metabolized in the liver by cytochrome P450 to form a highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which causes depletion of glutathione and covalently binds to cellular proteins leading to centrilobular necrosis [15,16]. Reduction in elevated liver enzymes in the treatment groups indicates the ability of the extract to minimize the paracetamol induced hepatic damage. This could be attributed to the antioxidant and free radical scavenging activities of the bioactive phytoconstituents present. [18]

Histopathological examination further proved the hepatoprotective potential of the extract as evident from the regeneration of normal liver architecture. The results corroborate with the ethnobotanical claim and scientifically validate the anti-hyperglycemic and hepatoprotective effects of *S. racemosa* bark extract, which could be due to the synergistic actions of various bioactive compounds like flavonoids, alkaloids, tannins etc. However, further studies are required to isolate the active principles responsible for these effects.

5. Conclusion

The present study provides strong evidence that the methanolic bark extract of *Symplocos racemosa* possess significant anti-diabetic and hepatoprotective properties. The anti-hyperglycemic effect was evident from its ability to reduce elevated blood glucose levels and improve glucose tolerance in alloxan induced diabetic rats. Moreover, it protected against paracetamol induced hepatic damage by lowering elevated liver enzymes and preserving the normal hepatic architecture. The results scientifically validate the ethnomedical claims and support further investigations to isolate active principles responsible for potent anti-diabetic and hepatoprotective effects from this plant.

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