Evaluation of the Antidiabetic Activity of Methanolic Extract of Coptis in Streptozotocin-Induced Diabetes Rats

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***Abstract*—The present study aimed to evaluate the antidiabetic, hypolipidemic, and antioxidant activities of the methanolic extract of Coptis in a Streptozotocin induced hypertensive rat model. Rats were divided into five groups: normal control, Streptozotocin control, standard drug (hydrochlorothiazide), and two doses of Coptis extract (200 mg/kg and 500 mg/kg). Treatment was administered orally, and parameters including fasting blood glucose, serum insulin, lipid profile, liver glycogen content, antioxidant enzyme levels (GST, GSH, SOD), and body weight changes were measured.**

Streptozotocin treatment induced significant hyperglycemia, dyslipidemia, oxidative stress, and weight loss. Administration of Coptis extract significantly reduced fasting blood glucose and improved glucose tolerance, serum insulin levels, and liver glycogen content in a dose-dependent manner. Additionally, the extract normalized serum lipid profiles by lowering total cholesterol, triglycerides, LDL-C, and VLDL-C, while increasing HDL-C. Antioxidant enzyme activities and total protein content were markedly restored by Coptis treatment, indicating a potent antioxidative effect.

The Coptis methanolic extract exerts multi-faceted protective effects against metabolic disturbances associated with Streptozotocin induced hypertension. This supports its potential therapeutic application as a natural agent for managing diabetes and cardiovascular complications.

***Index Terms*—Coptis, hypertension, hypertension, LDL-C, cholesterols**

I. INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both, altered metabolism of lipids, carbohydrates, and proteins, and an increased risk of complications of vascular diseases[1]. It is the most common endocrine disorder and can be associated with serious complications and premature death.

II. HISTORY [2, 3]

Knowledge of diabetes mellitus dates back to many centuries. Eber's Egyptian Papyrus (1500 BC) described it as an illness associated with the passage of much urine. A renowned Greek physician Arataeus of Cappodica coined the name diabetes (a siphon which described it as melting down of flesh and limbs into urine.

Scholars in China, Japan, and India during the 3rd and 6th centuries AD wrote of a condition with polyurea in which urine was 'sweet and sticky'. Although it has been for centuries, it was until 1674, that Willis added the observation 'as it imbued with honey and sugar'. The name diabetes mellitus (mellitus- honey) was thus established. A century after Willis, Dobson demonstrated that the sweetness was due to sugar. From the earliest recorded history of diabetes, progress in understanding came slowly until the middle of the 19th century. An association was established with a disturbance in the beta cells, clustered as tiny islets of tissue in the exocrine pancreas.

Brockman first noticed the presence of these islets in fish during the 19th century. Soon after, the German scientists, Mering and Minkowski, found that surgical removal of the pancreas produced diabetes in dogs. The breakthrough of the discovery of insulin was by Fredrick Banting and Charles Best in 1921.

By 1952, various purified modified versions of insulin were available and by 1982, recombinant DNA insulin

became available. Thus diabetes, which was synonymous with an inevitably fatal disease, became a more benign controllable disease [4-8].

III. MATERIALS AND METHODS

Collection and Authentication of plant material:
The plant Macroptilium Atropurpureum was collected from natural habitat of Ranga Reddy District, Telangana, India. The taxonomic identification of the plant was confirmed by Department of Botany, Government Degree College, Kukatpally, Medchal District, Telangana State. The Macroptilium Atropurpureum were cleaned and drying under sunlight. The dried plant was grind with mortar pestle and passed through sieve no. 14. The powdered plant was kept in airtight container for extraction.

Extraction
The fresh leaves of Coptis are collected and shade dried for one week, the dried leaves are pulverized by a mechanical grinder reduced to coarse powder and around 60g of powder material was subjected to successively hot continuous extraction .a weight quantity of each of the plant powdered material was extracted by Soxhlet with methanol of 300ml for 24hrs with intermediate heating at 40 ^{0} c after that the residues were extracted the extract was filtered using Whatmann filter paper and then the extract was evaporated in a rota evaporator and further dried under vacuum.

Percentage of yield

$$\text{Percentage of yield} = \frac{\text{Weight of crude extract}}{\text{Weight of dried material}} \times 100$$

$$\text{Percentage of yield} = \frac{26g}{200g} \times 100 = 13\%$$

200gms of drug dissolved in 800ml of solvent in 1:4 Ratio

Experimental grouping
I Group Normal Control Vehicle only
II Group Streptozotocin Control Streptozotocin + Saline (no treatment)
III Group Standard Drug Hydrochlorothiazide (10 mg/kg orally)
IV Group Coptis extract 200 mg/kg orally)
V Group Coptis extract (500 mg/kg orally)

IV. PARAMETERS FOR EVALUATION

Fasting Blood Sugar (FBS):
Fasting blood sugar level was determined by using glucose oxidase peroxidase reactive strips. Lipid Profile:
The lipid profiles viz Serum cholesterol, Serum triglycerides, and HDL Cholesterol were estimated by using an auto analyser. On the 15th day, animals were sacrificed by cervical dislocation, and the following parameters were monitored.

Liver Glycogen Content:
Estimation of liver glycogen:
Each liver tissue was minced and placed in an efficient blender containing an approximate volume (about 5ml) of 5% Trichloroacetic acid and homogenized for 3 minutes. The homogenate was centrifuged at 3000 rpm for 5 minutes. The supernatant was decanted upon an acid-washed filter paper (glass wool was used) in a funnel, draining into a graduated cylinder. The residue was then transferred into the blender with an appropriate volume of TCA (5 ml) and homogenized again for 1 minute. The homogenate was centrifuged and the supernatant was poured through the same filter. This was repeated two more times. The total volume of filtrate collected in the graduated cylinder was noted. 10µl of this filtrate was pipetted into 15-ml Pyrex centrifuge tubes. To each tube, 5 ml of 95% methanol was added and the tubes were allowed to stand overnight at room temperature. After completion of the precipitation of glycogen, the tubes were centrifuged at 3000 rpm for 15 minutes. The clear liquid was gently decanted out from the packed glycogen and the tubes were kept in an inverted position for 10 minutes to make the packed glycogen free from alcohol. The glycogen was dissolved in 2 ml of distilled water.
Calculation:

$$\text{mg of glycogen/gm of liver} \frac{\text{DU}}{\text{DS}} \times 0.05 \times \frac{\text{Total volume of extract (ml)}}{\text{Weight of tissue (g)}} \times \frac{0.9}{0.01}$$

Where,
DU = Optical density of unknown

DS = Optical density of standard
0.05 = mg of glucose in 2 ml of standard solution
0.9 = Conversion factor.

Changes in Body Weight
The changes in the body weight were calculated by checking the weights of individual animals on the 0th, 5th,10th, and 15th day.
Serum Insulin Estimation

V. IN-VIVO ANTIOXIDANT STUDIES

Estimation of Total Proteins[9]
Estimation of Superoxide Dismutase (SOD)[10]
Procedure: 1.2ml sodium pyrophosphate buffer, 0.1ml of Phenazine metho sulfate, and 0.3ml of NBT were added to the test tube. 1.2ml homogenate was added to the test tube. The reaction was started by the addition of 0.2 ml of NADH. After incubation at 30°C for 90 sec, the reaction was stopped by the addition of 1ml glacial acetic acid. The reaction mixture was stirred vigorously and shaken with 4ml butanol. The mixture was allowed to stand for 10 minutes, centrifuged and the butanol layer was taken out. The color intensity of the chromogen in the butanol was measured at 560 nm.
Calculation: The Superoxide dismutase activity was determined in the tissue and the results were expressed in U/gm.

Estimation of Glutathione Synthetase (GSH)[11]
Estimation of Glutathione Synthetase (GSH)
Procedure: 0.2 ml of homogenate was added to the test tube and dissolved in 1.8 ml water. The solution was mixed thoroughly. 3 ml of precipitating solution was added promptly and mixed.

Allowed to stand for 5 minutes at room temperature and filtered through coarse filter paper.

Reagent (ml)	Blank (ml)	Sample (ml)
Filtrate		2
Precipitating solution	1.2	
Water	0.8	
Na2HPO4 solution	8	8
DTNB solution	1	1

Then, the absorbance was measured at 412 nm.

Procedure: 1 ml of CDNB solution was added to 0.6 ml of supernatant of kidney homogenate. 2.2 ml of phosphate buffer pH 6.5 was added to it. This was then incubated at 37 °C for 5 minutes. 0.1 ml of 30 mM GSH solution was added. The absorbance was read at 340 nm at intervals of 1, 2, 3, 4, and 5 minutes. The blank reading was carried out in the same manner without the homogenate.

Staining process
The histopathological examination included Haematoxylin and Eosin staining of the tissues to observe any morphological changes in the cells present. The same tissue blocks were used for triple staining to differentiate between alpha, beta, and delta cells.

a) Haematoxylin and Eosin staining Preparation of Haematoxylin solution:
Haematoxylin (2 g) was dissolved in absolute alcohol followed by the addition of glycerol (100 ml), distilled water (100 ml), glacial acetic acid (100 ml), and potash alum in excess. The solution was allowed to stand for a few days. Preparation of Eosin solution: A 5% eosin solution in distilled water was made with eosin G.

b) Triple staining [12-15]
The following reagents were prepared for the procedure. 0.03 % of silver nitrate solution by dissolving 30 mg of silver nitrate in distilled water. This solution was prepared freshly. Reducing solution: This was prepared freshly by dissolving 1g of hydroquinone and 5 g of sodium sulfite in 100 ml of distilled water. Aldehyde Fuchsin solution: This was prepared three days before the experiment. 0.5% of basic fuchsin in 60% alcohol was prepared (500mg in 100 ml of 60% alcohol). To this solution, 1.5 ml of concentrated hydrochloric acid and 1 ml of paraldehyde solution were added. This was then stored in the refrigerator for three days to make ready when the color changed to gentian violet. Lead Haematoxylin: 50 ml 5% lead nitrate solution was mixed with the same volume of saturated ammonium acetate solution. This was filtered and 2 ml of 37% formaldehyde solution was added to it. 0.2 g of haematoxylin was dissolved in 1.5 ml of 95% alcohol 10 ml of the above solution and 10 ml of distilled water was added to it. This was filtered and the volume was made up to 75 ml. The tissue was washed, dehydrated

with alcohol, cleared with xylene, and paraffin blocks were made. Serial sections of 5-micron thickness were cut using a rotary microtome. The sections were then deparaffinized with xylene and hydrated in descending grades of alcohol. The slides were then placed in 0.03% of solution silver nitrate overnight at 37 °C. They were then transferred to freshly prepared reducing solution followed by rinsing in aldehyde fuchsin solution for 30 seconds and rinsing in three changes of distilled water. The tissues were then rinsed in lead hematoxylin solution and finally rinsed in three changes of water. The sections were then dehydrated in ascending grades of alcohol (50, 70, 90 %, and ending in absolute alcohol for 2 minutes each) and then cleared in xylene and mounted using DPX mounting.

Observation

Slides were observed under the light microscope. The various histopathological changes studied included :

Changes in the liver like loss of cellular architecture, inflammation of cells, central vein dilatation, piknosis, congestion of cells, dilated sinusoids, and ruptured vessels.

Changes in the kidney like glomerular basement membrane thickening and vacuolation of cells.

Changes in the pancreas like reduction of the islet cells.

VI. STATISTICAL ANALYSIS

The results of biochemical estimations were reported as mean ± S.E.M The total variation present in the data was analyzed by one-way analysis of variance (ANOVA). Differences among the means were analysed by Dunnett's test. For this, a window-based PRISM computer package was used.

VII. RESULT AND DISCUSSION

SUCCESSIVE SOLVENT EXTRACTIVE VALUES

Table: Successive extractive values of the powdered of Coptis

Sl. No.	Extract	Yield (% w/w)
1	Methanol Extract	2.91

Phytoconstituents	Methanol extract
Carbohydrate	+
Flavonoids	+
Terpenoids	+
Tannins	-+
Alkaloids	+
Protein and amino acid	+
Steroids	-
Phenols	+

VIII. PHYTOCHEMICAL SCREENING

Table Result of preliminary phytochemical screening of the powdered flower Coptis +Ve = absences, -Ve = Presents

Oral glucose tolerance test

Time (min)	Group I Normal Control	Group II Streptozotocin Control	Group III Hydrochlorothiazide	Group IV Coptis 200 mg/kg	Group V Coptis 500 mg/kg
0 (Fasting)	88.5 ± 4.2	110.3 ± 5.8	98.2 ± 4.9	96.4 ± 4.7	92.1 ± 3.9
15	135.6 ± 6.1	181.4 ± 8.2	152.3 ± 6.7	145.2 ± 5.4	132.5 ± 5.0
30	150.2 ± 5.4	210.7 ± 9.1	170.5 ± 7.3	160.8 ± 6.0	145.1 ± 6.2
60	122.8 ± 4.6	188.9 ± 8.0	140.9 ± 6.1	132.2 ± 5.7	120.6 ± 5.3
90	101.5 ± 4.2	162.4 ± 7.2	120.3 ± 5.8	110.9 ± 4.9	98.3 ± 4.5
120	91.7 ± 3.8	148.6 ± 6.9	105.6 ± 4.9	98.1 ± 4.3	89.4 ± 4.1

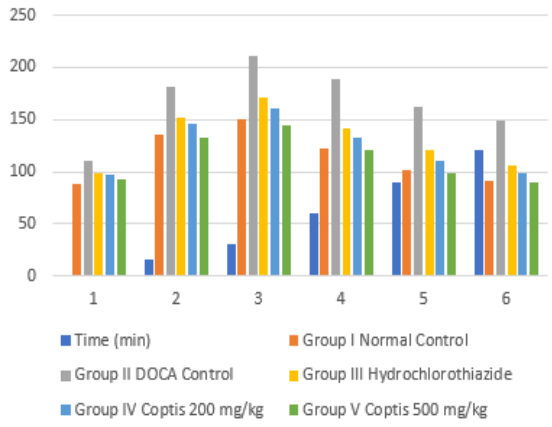
The Streptozotocin Control group showed significantly higher glucose levels at all time points, indicating impaired glucose tolerance.

The Hydrochlorothiazide group showed partial improvement in glucose tolerance.

Both Coptis extract-treated groups (200 & 500 mg/kg) showed marked improvement, especially the 500

mg/kg dose, which almost normalized glucose levels close to the normal control group.

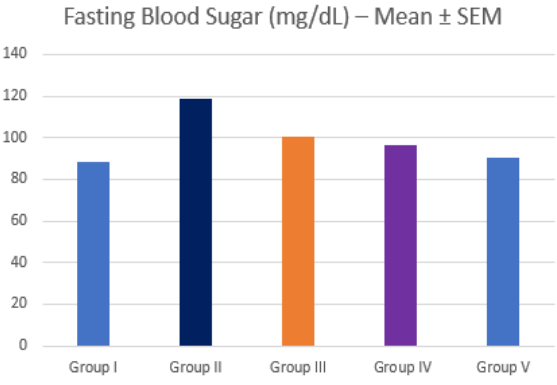
The AUC analysis supports this trend - Coptis 500 mg/kg has the lowest AUC among treated groups, suggesting enhanced glucose tolerance.



Fasting Blood Sugar Level

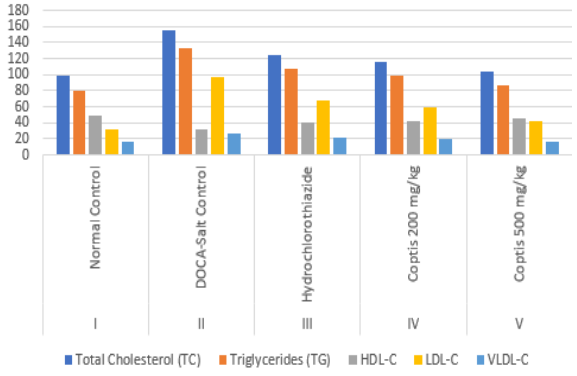
Effect of extracts of the Coptis on fasting blood glucose levels in rats.

Group No.	Group Name	Fasting Blood Sugar (mg/dL) – Mean ± SEM
Group I	Normal Control	88.5 ± 4.2
Group II	Streptozotocin Control	118.9 ± 5.7
Group III	Hydrochlorothiazide (10 mg/kg)	100.3 ± 4.8
Group IV	Coptis Extract 200 mg/kg	96.8 ± 4.5
Group V	Coptis Extract 500 mg/kg	90.6 ± 4.1



Effect of extracts of Coptis on serum lipid profile in rats

Group	Group Name	Total Cholesterol (TC)	Triglycerides (TG)	HDL-C	LDL-C	VLDL-C
I	Normal Control	98.2 ± 4.3	80.6 ± 3.9	48.5 ± 2.1	32.4 ± 1.8	16.1 ± 0.9
II	Streptozotocin Control	155.7 ± 5.8	132.4 ± 5.2	32.8 ± 1.9	96.3 ± 4.3	26.5 ± 1.1
III	Hydrochlorothiazide	124.3 ± 4.7	108.1 ± 4.6	40.2 ± 2.0	68.2 ± 3.2	21.6 ± 1.0
IV	Coptis 200 mg/kg	116.5 ± 4.1	98.9 ± 4.3	42.7 ± 2.3	60.1 ± 2.9	19.7 ± 0.9
V	Coptis 500 mg/kg	104.8 ± 3.8	86.4 ± 3.6	46.2 ± 2.0	42.5 ± 2.1	17.3 ± 0.8

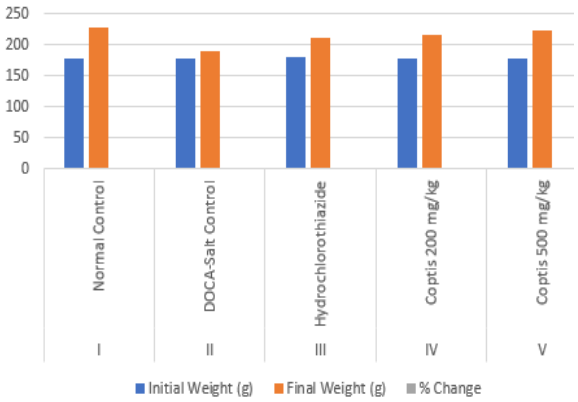


Body weight changes

Group	Group Name	Initial Weight (g)	Final Weight (g)	% Change
I	Normal Control	178.4 ± 4.2	228.6 ± 5.3	28.10 %
II	Streptozotocin Control	176.9 ± 4.8	190.2 ± 5.1	7.50%

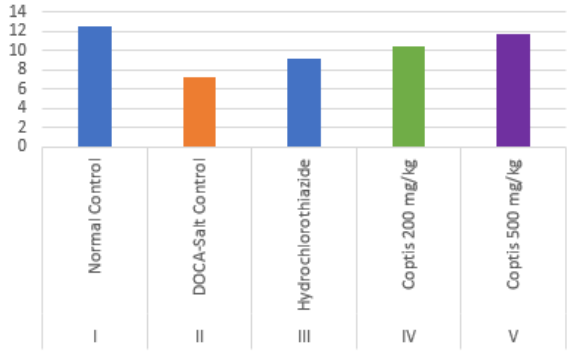
III	Hydrochlorothiazide	179.5 ± 4.3	210.8 ± 5.0	17.50 %
IV	Coptis 200 mg/kg	177.2 ± 4.6	215.1 ± 5.2	21.40 %
V	Coptis 500 mg/kg	178.7 ± 4.1	223.4 ± 5.5	25.00 %

Values expressed as mean ± S. E. M.; n = no. of animals in each group. * p < 0.05 significant Vs diabetic control. One-way ANOVA followed by the Dunnett test



Serum Insulin and Liver Glycogen

Group	Group Name	Serum Insulin (µIU/mL)
I	Normal Control	12.5 ± 0.8
II	Streptozotocin Control	7.2 ± 0.6
III	Hydrochlorothiazide	9.1 ± 0.7
IV	Coptis 200 mg/kg	10.4 ± 0.7
V	Coptis 500 mg/kg	11.7 ± 0.6



In vivo antioxidant activity

Effect of extracts of Coptis on tissue GST, GSH, SOD, and Protein levels in rats

Group	Group Name	GST (µmol/min/mg protein)	GSH (µmol/mg protein)	SOD (U/mg protein)	Total Protein (mg/g tissue)
I	Normal Control	12.5 ± 0.7	8.9 ± 0.4	7.6 ± 0.3	5.2 ± 0.2
II	Streptozotocin Control	6.8 ± 0.5	4.3 ± 0.3	3.9 ± 0.4	3.1 ± 0.3
III	Hydrochlorothiazide	9.7 ± 0.6	6.7 ± 0.3	6.0 ± 0.3	4.3 ± 0.2
IV	Coptis 200 mg/kg	10.8 ± 0.5	7.5 ± 0.3	6.8 ± 0.2	4.7 ± 0.2
V	Coptis 500 mg/kg	12.0 ± 0.6	8.5 ± 0.4	7.4 ± 0.3	5.0 ± 0.2

IX. DISCUSSION

The present study evaluated the antidiabetic, antihypertensive, and antioxidant potential of the methanolic extract of Coptis in a Streptozotocin induced hypertensive rat model. The findings demonstrated that Coptis extract significantly improved glucose tolerance, normalized fasting blood sugar, enhanced serum insulin levels, improved lipid profiles, restored body weight, and alleviated oxidative stress in a dose-dependent manner.

Antidiabetic Activity

Streptozotocin hypertensive rats exhibited impaired glucose tolerance, elevated fasting blood glucose, and reduced serum insulin levels compared to normal controls, indicating an induced state of metabolic dysregulation consistent with hypertension-related insulin resistance. Treatment with Coptis extract significantly lowered fasting blood glucose and improved glucose tolerance as seen in the OGTT results. The increase in serum insulin levels further suggests improved pancreatic β-cell function or enhanced insulin secretion. These findings align with previous reports where Coptis species have demonstrated hypoglycemic effects potentially mediated through bioactive alkaloids like berberine,

known to enhance insulin sensitivity and glucose uptake.

Lipid Profile and Body Weight

Streptozotocin control rats showed dyslipidemia characterized by increased total cholesterol, triglycerides, LDL-C, and VLDL-C along with decreased HDL-C levels. Such lipid abnormalities are common in hypertensive and metabolic syndrome models and contribute to cardiovascular risk. Coptis extract administration reversed these alterations, reducing atherogenic lipids and elevating protective HDL-C, indicating a hypolipidemic effect. Moreover, Coptis treatment significantly improved body weight gain compared to Streptozotocin controls, suggesting restoration of normal metabolic function and reduced disease-associated wasting.

Antioxidant Effects

Oxidative stress plays a pivotal role in the pathogenesis of hypertension and diabetes. The marked decrease in antioxidant enzymes (GST, GSH, SOD) and total protein content observed in Streptozotocin control rats indicates enhanced oxidative damage and compromised cellular defense. Coptis extract treatment restored these antioxidants markers close to normal levels, suggesting strong free radical scavenging and cytoprotective properties. The antioxidant activity likely contributes to the amelioration of metabolic disturbances and organ protection observed.

Liver Glycogen Content

Reduced liver glycogen content in Streptozotocin control rats reflects impaired glucose storage, consistent with insulin resistance and disrupted carbohydrate metabolism. The restoration of glycogen levels in Coptis-treated groups further supports its beneficial effect on glucose homeostasis, potentially through enhancing glycogen synthesis pathways.

Mechanistic Insights and Clinical Relevance

The multifaceted benefits of Coptis extract can be attributed to its rich phytochemical composition, especially isoquinoline alkaloids like berberine, which have been shown to modulate key metabolic pathways, reduce oxidative stress, and improve endothelial function. By addressing hyperglycemia, dyslipidemia, and oxidative damage concurrently, Coptis may offer a promising complementary therapy for managing hypertension complicated by metabolic syndrome and diabetes.

X. CONCLUSION

The present study demonstrated that the methanolic extract of Coptis exhibits significant antidiabetic effects in Streptozotocin induced hypertensive rats. Treatment with the extract improved glucose tolerance, lowered fasting blood sugar levels, and enhanced serum insulin secretion, indicating a restoration of pancreatic function and improved glucose metabolism. These findings suggest that Coptis possesses potent hypoglycemic activity, which may be beneficial in managing diabetes associated with hypertension.

In addition to its antidiabetic properties, Coptis extract effectively normalized serum lipid profiles by reducing total cholesterol, triglycerides, LDL-C, and VLDL-C levels while elevating HDL-C. This improvement in lipid metabolism, along with the observed recovery in body weight, highlights the extract's potential to mitigate cardiovascular risk factors commonly associated with metabolic syndrome and hypertension.

Furthermore, the extract exhibited strong antioxidant activity by restoring the levels of critical antioxidant enzymes such as GST, GSH, and SOD, as well as total protein content in liver tissues. The reduction in oxidative stress likely contributes to the overall protective effects of Coptis against metabolic and vascular damage induced by Streptozotocin hypertension. Enhanced liver glycogen content in treated animals further supports its role in improving carbohydrate metabolism and energy storage.

Overall, Coptis methanolic extract shows promising multi-target therapeutic potential by ameliorating hyperglycemia, dyslipidemia, oxidative stress, and metabolic disturbances in hypertensive diabetic conditions. These findings provide a scientific basis for its traditional use and warrant further research into its active components and clinical applicability.

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