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Evaluation of anti-diabetic potential and pancreatic beta cell regeneration activity of *Cornus officinalis* in streptozotocin induced diabetic Wistar rats.

Sakshi Kharat [1], Ms. Rutuja Mule [2], Mrs. Swapnali Girme [3], Dr. Swati Jogdand [4], Dr. Swati Deshmukh [5]
CAYMET's Siddhant college of Pharmacy, Sudumbare, Pune, Maharashtra, India.

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ABSTRACT:
Diabetes mellitus is a chronic metabolic disorder associated with persistent hyperglycemia, oxidative stress, metabolic disturbances, and pancreatic β-cell dysfunction. The present study evaluated the antidiabetic, antioxidant, and pancreatic β-cell regenerative potential of *Cornus officinalis* fruit extract in streptozotocin (STZ)-induced diabetic Wistar rats. Fruits of *Cornus officinalis* were successively extracted using solvents of increasing polarity, followed by phytochemical screening and evaluation of antioxidant activity using the DPPH assay and in vitro antidiabetic activity using α-amylase and α-glucosidase inhibition assays. The methanolic extract showed the highest extraction yield and contained abundant flavonoids, phenolics, tannins, glycosides, alkaloids, and saponins. It exhibited strong antioxidant activity with 84.83 ± 1.37% DPPH inhibition at 100 µg/mL, along with significant α-amylase and α-glucosidase inhibitory activities. In STZ-induced diabetic rats, oral administration of the extract for 28 days produced a dose-dependent reduction in fasting blood glucose, improvement in body weight, normalization of lipid profile, and improvement in liver and kidney function parameters. The extract also enhanced antioxidant defense by improving SOD, CAT, and GSH levels while reducing MDA levels. Histopathological examination demonstrated dose-dependent restoration of pancreatic architecture and marked β-cell regeneration, particularly at the 400 mg/kg dose, with effects approaching those observed with metformin. Overall, the findings indicate that *Cornus officinalis* methanolic fruit extract possesses promising antidiabetic, antioxidant, hepatoprotective, and pancreatic β-cell regenerative properties and may have potential as a natural therapeutic agent for the management of diabetes and its associated complications.

1. INTRODUCTION:

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. It has emerged as a major global health concern due to its rapidly increasing prevalence and associated complications affecting the kidneys, liver, nerves, eyes, and cardiovascular system. Chronic hyperglycemia induces disturbances in carbohydrate, lipid, and protein metabolism, leading to severe microvascular and macrovascular complications if left untreated [1,2].

Among the various forms of diabetes, Type 2 diabetes mellitus accounts for nearly 90–95% of all cases worldwide and is primarily associated with insulin resistance and progressive pancreatic β-cell dysfunction. Oxidative stress and chronic inflammation contribute to excessive ROS generation, lipid peroxidation, mitochondrial dysfunction, and apoptosis of pancreatic β-cells [3,4]. Persistent oxidative stress further impairs insulin secretion and glucose utilization, thereby aggravating hyperglycemia and diabetic complications [5].

Streptozotocin (STZ)-induced experimental diabetes is one of the most widely used animal models for evaluating antidiabetic agents because of its selective cytotoxic effect on pancreatic β-cells. STZ enters β-cells through GLUT-2 transporters and induces DNA alkylation, oxidative stress, and mitochondrial damage, ultimately leading to insulin deficiency and persistent hyperglycemia [6,7,21]. Histopathological alterations observed in STZ-induced diabetic animals closely resemble those seen in human diabetes, making this model highly suitable for investigating pancreatic protective and regenerative therapies [8].

Recent therapeutic strategies have focused not only on controlling blood glucose levels but also on preserving and regenerating pancreatic β-cells. Regeneration of β-cells through mechanisms such as β-cell replication, neogenesis, and protection against apoptosis may improve endogenous insulin secretion and long-term glycemic control [9,23]. Natural products and medicinal plants have attracted considerable attention due to their antioxidant, anti-inflammatory, and cytoprotective properties, which may support pancreatic regeneration and reduce diabetic complications [10].

Cornus officinalis, a medicinal plant widely used in traditional medicine, contains various bioactive phytoconstituents including flavonoids, phenolics, tannins, iridoids, and terpenoids with reported antioxidant and pharmacological activities. These phytochemicals may exert beneficial effects against oxidative stress-mediated pancreatic β-cell damage and metabolic dysfunction. Therefore, the present study was undertaken to evaluate the antidiabetic potential and pancreatic β-cell regeneration activity of Cornus officinalis extract in streptozotocin-induced diabetic Wistar rats.

2. MATERIALS AND METHODS:

Plant Material and Extraction

Fruits of *Cornus officinalis* were collected, authenticated, shade dried, and coarsely powdered. The powdered material was subjected to successive Soxhlet extraction using different solvents based on increasing polarity. The obtained extracts were concentrated using a rotary evaporator and stored in airtight containers for further studies [11,12].

Phytochemical Screening

Preliminary phytochemical screening of the extracts was carried out using standard qualitative methods to identify the presence of flavonoids, phenolic compounds, tannins, alkaloids, glycosides, saponins, and terpenoids [13,19,20].

In Vitro Antioxidant Activity

DPPH Free Radical Scavenging Assay

The antioxidant activity of *Cornus officinalis* extract was evaluated by DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay. Different concentrations of the extract (20–100 µg/mL) were prepared using methanol. A freshly prepared DPPH solution (0.1 mM) in methanol was used for the assay.

Briefly, 1 mL of DPPH solution was mixed with 1 mL of extract solution at different concentrations. The reaction mixture was shaken vigorously and incubated in dark conditions at room temperature for 30 min. Ascorbic acid was used as the standard antioxidant. After incubation, the absorbance was measured at 517 nm using a UV-visible spectrophotometer against methanol blank.
The percentage of DPPH radical scavenging activity was calculated using the following equation:

$$\text{DPPH inhibiton}\,(\%) = \left(1 - \frac{A - A_0}{A_1}\right) \times 100\%$$

Where:
(A) = Absorbance of control
(A_0) = Absorbance of sample
The antioxidant activity was expressed as percentage inhibition of DPPH radicals [14,18].

In Vitro Antidiabetic Activity

α-Amylase Inhibitory Assay

The α-amylase inhibitory activity of *Cornus officinalis* extract was evaluated using the standard starch-iodine method. Different concentrations of the extract (100–500 µg/mL) were prepared in phosphate buffer (0.02 M, pH 6.9) [24,25].
To 500 µL of extract solution, 500 µL of α-amylase enzyme solution (0.5 mg/mL) was added and incubated at 37°C for 10 min. Subsequently, 500 µL of 1% starch solution prepared in phosphate buffer was added to initiate the reaction. The reaction mixture was further incubated at 37°C for 15 min. The reaction was terminated by adding 1 mL of DNSA reagent and heating the mixture in a boiling water bath for 5 min.

After cooling, the absorbance was measured at 540 nm using a UV-visible spectrophotometer. Acarbose was used as the standard drug. The percentage inhibition of α-amylase activity was calculated using the following formula:
% Inhibition = [(Ac – As) / Ac] × 100
Where:
(Ac) = Absorbance of control
(As) = Absorbance of sample

α-Glucosidase Inhibitory Assay

The α-glucosidase inhibitory activity of *Cornus officinalis* extract was determined using standard spectrophotometric method [15,26]. Different concentrations of the extract (100–500 µg/mL) were prepared in phosphate buffer.

Briefly, 50 µL of extract solution was mixed with 100 µL of α-glucosidase enzyme solution and incubated at 37°C for 10 min. After incubation, 50 µL of p-nitrophenyl-α-D-glucopyranoside substrate solution was added to initiate the reaction. The reaction mixture was further incubated at 37°C for 20 min.

The reaction was terminated by addition of sodium carbonate solution, and the absorbance was measured at 405 nm using a UV-visible spectrophotometer. Acarbose was used as the standard reference drug. The percentage inhibition of α-glucosidase activity was calculated using the following equation:
% Inhibition = [(Ac – As) / Ac] × 100
Where:
(Ac) = Absorbance of control
(As) = Absorbance of sample

Experimental Animals

Healthy adult Wistar rats weighing approximately 150–200 g were used for the study. Animals were housed under standard laboratory conditions with controlled temperature, humidity, and a 12 h light/dark cycle. Standard pellet diet and water were provided ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) (Approval No. SCOP/IAEC/2025/11/3759).

Induction of Experimental Diabetes

Experimental diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ). Blood glucose levels were measured after 72 h, and animals showing significant hyperglycemia were considered diabetic and selected for the study [11,16,22].

Experimental Design

Animals were divided into different groups including normal control, diabetic control, standard drug-treated

group, and extract-treated groups receiving different doses of *Cornus officinalis* extract. Treatment was continued for 28 days.

Table 1: Experimental Design

Group Name	Dose	Route of Administration	No. of Animals
Group I	Control Group	Per Oral	6
Group II	STZ (55 mg/kg)	Intraperitoneal	6
Group III	Metformin (100 mg/kg)	Per Oral	6
Group IV	*Cornus officinalis* Extract (200 mg/kg)	Per Oral	6
Group V	*Cornus officinalis* Extract (300 mg/kg)	Per Oral	6
Group VI	*Cornus officinalis* Extract (400 mg/kg)	Per Oral	6
Total animals required			**36**

Evaluation of Antidiabetic Activity
Fasting blood glucose levels and body weight were recorded at regular intervals during the treatment period. At the end of the study, blood samples were collected for biochemical analysis.[27]

Biochemical Analysis
Serum samples were analyzed for lipid profile parameters including total cholesterol, triglycerides, HDL, LDL, and VLDL. Liver function parameters such as SGOT, SGPT, and ALP, along with kidney function markers including serum creatinine and urea, were also evaluated using standard diagnostic kits.

Table 2: Biochemical Parameters Evaluated

Parameters	Biomarkers
Lipid Profile	Total cholesterol, triglycerides, HDL, LDL, VLDL
Liver Function Test	SGOT, SGPT, ALP
Kidney Function Test	Serum creatinine, urea
Oxidative Stress Markers	SOD, CAT, GSH, MDA

Antioxidant Parameters
Antioxidant enzyme levels including superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and malondialdehyde (MDA) were estimated using standard biochemical methods [28,29,30,31].

Histopathological Study
Pancreatic tissues were isolated and fixed in formalin solution. Tissue samples were processed, embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin. Histopathological examination was carried out under a microscope to evaluate pancreatic architecture and β-cell regeneration activity [32].

Statistical Analysis
All experimental data were expressed as mean ± SEM. Statistical analysis was performed using GraphPad Prism software. Differences among groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. A value of $p < 0.05$ was considered statistically significant.

3. RESULTS:
Table 3: Percentage Yield of Different Solvent Extracts of *Cornus officinalis* Fruits

Extract	Weight of Dried Extract (g)	Percentage Yield (% w/w)
n-Hexane Extract	8.25	1.65
Chloroform Extract	12.40	2.48
Ethyl Acetate Extract	18.65	3.73
Acetone Extract	24.85	4.97
Methanol Extract	42.70	8.54

The methanolic extract showed the highest percentage yield (8.54%) followed by acetone (4.97%), ethyl acetate (3.73%), chloroform (2.48%), and n-hexane extracts (1.65%), indicating the efficient extraction of polar phytoconstituents by methanol from *Cornus officinalis* fruits.

Table 4: Preliminary Phytochemical Screening of Different Extracts of *Cornus officinalis* Fruits

Phytoconstituents	n-Hexane	Chloroform	Ethyl Acetate	Acetone	Methanol

Alkaloids	−	+	++	++	+++
Flavonoids	−	+	++	++	+++
Tannins	−	−	+	++	+++
Phenolic Compounds	−	+	++	++	+++
Glycosides	−	+	++	++	+++
Saponins	−	−	+	++	+++
Carbohydrates	−	+	+	++	+++
Proteins	−	−	+	+	++
Terpenoids	++	+++	++	+	+

Key: (−) Absent, (+) Present, (++) Moderately Present, (+++) Abundantly Present.
Preliminary phytochemical screening revealed the presence of various secondary metabolites in different extracts of *Cornus officinalis* fruits. The methanolic extract showed abundant amounts of alkaloids, flavonoids, tannins, phenolics, glycosides, saponins, and carbohydrates, whereas terpenoids were predominantly observed in chloroform and n-hexane extracts, indicating methanol as the most effective solvent for extraction of bioactive phytoconstituents.

Quantitative determination of Total Phenolic Content (TPC)

The total phenolic content (TPC) of the methanolic fruit extract of Cornus officinalis was determined by the Folin–Ciocalteu colorimetric method using tannic acid as the reference standard. The calibration curve of tannic acid showed excellent linearity over the concentration range of 20–100 µg/mL, with the regression equation $y = 0.0079x - 0.0008$ and a correlation coefficient ($R^2 = 0.9982$). The methanolic fruit extract exhibited a mean absorbance of 0.683 ± 0.006, corresponding to a total phenolic content of 85.30 ± 0.75 mg TAE/g extract. The high phenolic content indicates that the extract is a rich source of phenolic compounds, which may contribute to its antioxidant and antidiabetic activities.

Table 4 : Total Phenolic Content (TPC) of Cornus officinalis Methanol Fruit Extract

Tannic acid (µg/mL)	Absorbance
20	0.165
40	0.319
60	0.481
80	0.642
100	0.798

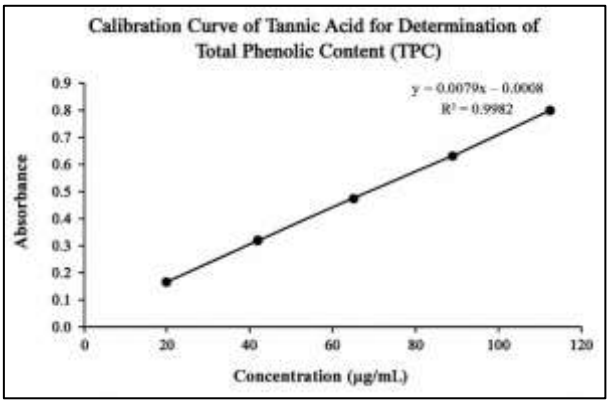

Figure 1: Calibration Curve of Tannic Acid for Determination of Total Phenolic Content (TPC)

Quantitative determination of Total Flavonoid Content (TFC)

The total flavonoid content (TFC) of the methanolic fruit extract of Cornus officinalis was determined by the aluminium chloride ($AlCl_3$) colorimetric method using quercetin as the reference standard. The calibration curve of quercetin exhibited good linearity within the concentration range of 20–100 µg/mL, with the regression equation $y = 0.0064x - 0.0272$ and a correlation coefficient ($R^2 = 0.996$). The methanolic fruit extract showed a mean absorbance of 0.432 ± 0.006, corresponding to a total flavonoid content of 71.57 ± 0.97 mg QE/g extract. The appreciable flavonoid content indicates the presence of bioactive flavonoids that may be responsible for the antioxidant and antidiabetic potential of the extract.

Table 5: Total Flavonoid Content (TFC) of Cornus officinalis Methanol Fruit Extract

Quercetin (µg/mL)	Absorbance
20	0.112
40	0.236
60	0.361
80	0.486
100	0.608

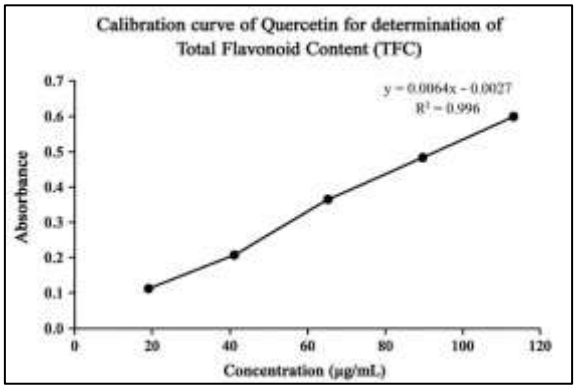

Figure 2: Calibration curve of Quercetin for determination of Total Flavonoid Content (TFC)

Table 6: Quantitative Estimation of Total Phenolic and Total Flavonoid Contents of the Methanolic Fruit Extract of Cornus officinalis

Parameter	Value (Mean ± SD)
Mean TPC absorbance	0.683 ± 0.006
TPC (mg TAE/g extract)	85.30 ± 0.75
Mean TFC absorbance	0.432 ± 0.006
TFC (mg QE/g extract)	71.57 ± 0.97

Values are expressed as Mean ± SEM (n = 3).

Vitro Antioxidant Activity

Table 7: DPPH Free Radical Scavenging Activity of Methanolic Extract of *Cornus officinalis* Fruits

Concentration (µg/mL)	Ascorbic Acid (% Inhibition)	Methanolic Extract (% Inhibition)
20	31.84 ± 0.72	24.15 ± 0.61
40	46.27 ± 0.86	38.42 ± 0.74
60	61.58 ± 1.04	53.17 ± 0.92
80	78.33 ± 1.28	69.26 ± 1.13
100	91.42 ± 1.51	84.83 ± 1.37

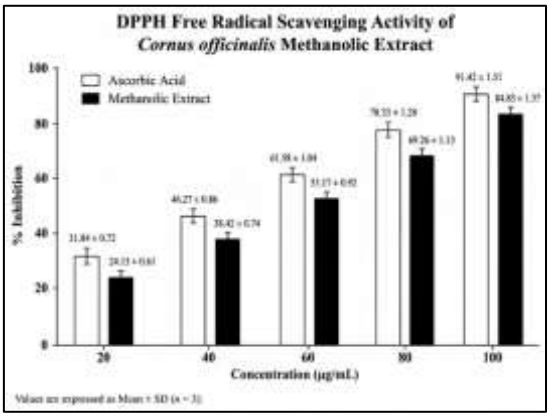

Figure 3: DPPH Free Radical Scavenging Activity of Methanolic Extract of Cornus officinalis Fruits

The methanolic extract of *Cornus officinalis* showed significant concentration-dependent DPPH free radical scavenging activity, with 84.83 ± 1.37% inhibition at 100 µg/mL, comparable to ascorbic acid (91.42 ± 1.51%). The antioxidant activity may be attributed to the presence of phenolics and flavonoids.

Table 8: IC_{50} Values of DPPH Free Radical Scavenging Activity

Sample	IC_{50} (µg/mL)
Ascorbic Acid	42.18 ± 1.26
Methanolic Extract of *Cornus officinalis*	54.72 ± 1.84

The IC_{50} value of the methanolic extract was found to be 54.72 ± 1.84 µg/mL, indicating strong antioxidant activity. Although the activity was slightly lower than that of the standard ascorbic acid, the extract demonstrated considerable free radical scavenging potential.

In Vitro α-Amylase Inhibition Assay

Table 9: α-Amylase Inhibitory Activity of *Cornus officinalis* Extract

Concentration (µg/mL)	% Inhibition (Extract)	% Inhibition (Acarbose)
100	28.16 ± 1.04	41.33 ± 1.18
200	39.50 ± 1.22	56.17 ± 1.34
300	51.83 ± 1.41	68.50 ± 1.52
400	63.17 ± 1.58	79.66 ± 1.71
50	74.50 ± 1.82	89.17 ± 1.94

Values are expressed as Mean ± SD (n = 3).

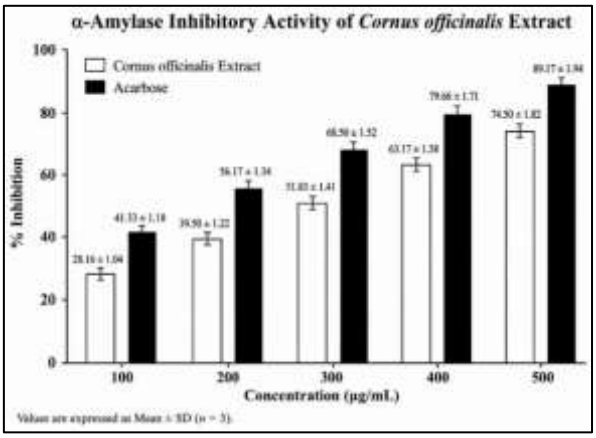

Figure 4: α-Amylase Inhibitory Activity of *Cornus officinalis* Extract

In Vitro α-Glucosidase Inhibition Assay

Table 9: α-Glucosidase Inhibitory Activity of *Cornus officinalis* Extract

Concentration (µg/mL)	% Inhibition (Extract)	% Inhibition (Acarbose)
100	31.33 ± 1.08	45.16 ± 1.24
200	44.50 ± 1.27	59.83 ± 1.43
300	57.66 ± 1.49	72.17 ± 1.66
400	69.17 ± 1.72	84.33 ± 1.84
500	81.50 ± 1.96	93.50 ± 2.08

Values are expressed as Mean ± SD (n = 3)

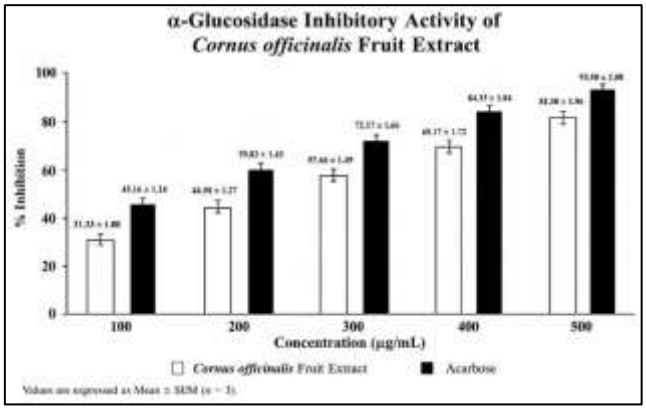

Figure 5: α-Glucosidase Inhibitory Activity of *Cornus officinalis* Extract

Fasting Blood Glucose Levels

Table 10: Effect of *Cornus officinalis* Fruit Extract on Fasting Blood Glucose Levels (mg/dL)

Groups	Day 0	Day 7	Day 14	Day 21	Day 28
Normal Control	92.83 ± 2.14	94.16 ± 1.87	93.66 ± 2.03	94.50 ± 1.96	95.33 ± 2.11
Diabetic Control	286.17 ± 5.42	298.66 ± 6.11$^{###}$	314.83 ± 7.26$^{###}$	329.50 ± 8.14$^{###}$	345.16 ± 8.52$^{###}$

Metformin (100 mg/kg)	284.50 ± 5.18	224.66 ± 4.92***	176.33 ± 4.28***	134.50 ± 3.16***	108.83 ± 2.75***
COE-LD (200 mg/kg)	285.33 ± 5.26	251.83 ± 5.02*	223.16 ± 4.77**	194.50 ± 4.32***	167.83 ± 3.94***
COE-MD (300 mg/kg)	286.00 ± 5.29	244.50 ± 4.95**	210.66 ± 4.51***	171.83 ± 3.88***	143.50 ± 3.26***
COE-HD (400 mg/kg)	286.66 ± 5.34	238.17 ± 4.88**	198.33 ± 4.26***	152.66 ± 3.51***	122.17 ± 2.83***

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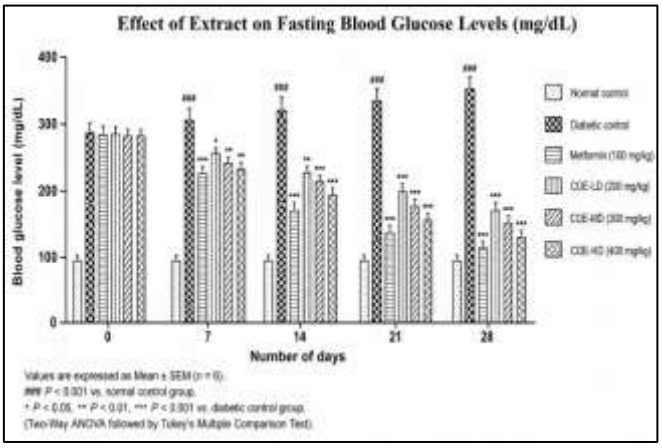

Figure 6: Effect of *Cornus officinalis* Fruit Extract on Fasting Blood Glucose Levels (mg/dL)

Body Weight

Table 11: Effect of *Cornus officinalis* Fruit Extract on Body Weight (g)

Groups	Day 0	Day 7	Day 14	Day 21	Day 28
Normal Control	184.33 ± 3.24	188.66 ± 3.18	192.17 ± 3.02	196.50 ± 2.84	201.16 ± 2.91
Diabetic Control	185.66 ± 3.45	178.83 ± 3.17###	171.50 ± 2.92###	163.33 ± 2.66###	156.50 ± 2.51###
Metformin (100 mg/kg)	184.83 ± 3.18	186.66 ± 2.97	191.33 ± 2.88***	197.16 ± 2.75***	203.50 ± 2.61***
COE-LD (200 mg/kg)	185.17 ± 3.27	182.50 ± 3.11	185.33 ± 2.94*	188.66 ± 2.87**	193.83 ± 2.73***
COE-MD (300 mg/kg)	185.33 ± 3.22	183.66 ± 3.08	187.16 ± 2.91**	191.83 ± 2.81***	196.50 ± 2.66***
COE-HD (400 mg/kg)	185.50 ± 3.19	184.83 ± 3.04	188.66 ± 2.89**	193.50 ± 2.76***	198.33 ± 2.58***

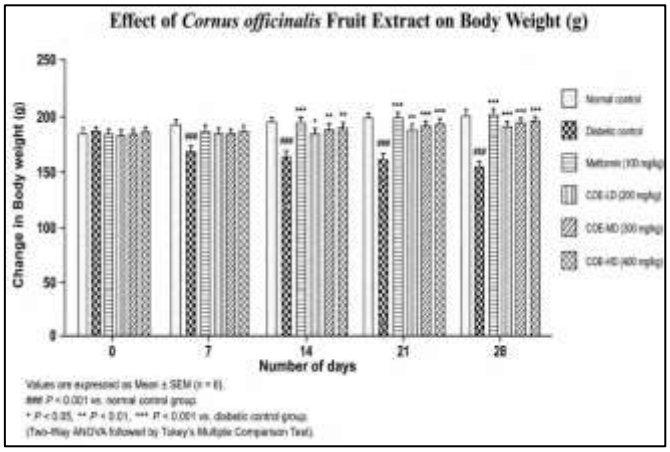

Figure 7: Effect of *Cornus officinalis* Fruit Extract on Body Weight (g)

Serum Glucose and Lipid Profile

Table 12: Effect of *Cornus officinalis* Fruit Extract on Serum Glucose and Lipid Profile

Groups	Serum Glucose (mg/dL)	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
Normal Control	96.33 ± 2.12	84.50 ± 2.11	76.83 ± 1.98	48.16 ± 1.27	21.17 ± 0.84	15.37 ± 0.39
Diabetic Control	348.17 ± 8.33	182.33 ± 4.56###	171.50 ± 4.28###	24.50 ± 0.88###	123.50 ± 3.02###	34.30 ± 0.85###
Metformin (100 mg/kg)	112.66 ± 2.84***	92.17 ± 2.23***	81.17 ± 1.94***	45.66 ± 1.18***	30.27 ± 0.96***	16.23 ± 0.38***

COE-LD (200 mg/kg)	169.17 ± 4.16***	116.50 ± 2.95***	102.66 ± 2.38***	38.17 ± 1.04**	57.80 ± 1.68***	20.53 ± 0.48***
COE-MD (300 mg/kg)	145.50 ± 3.64***	106.33 ± 2.68***	94.17 ± 2.24***	40.83 ± 1.08***	46.67 ± 1.42***	18.83 ± 0.44***
COE-HD (400 mg/kg)	126.33 ± 3.05***	98.66 ± 2.37***	86.50 ± 2.11***	43.33 ± 1.12***	38.03 ± 1.21***	17.30 ± 0.42***

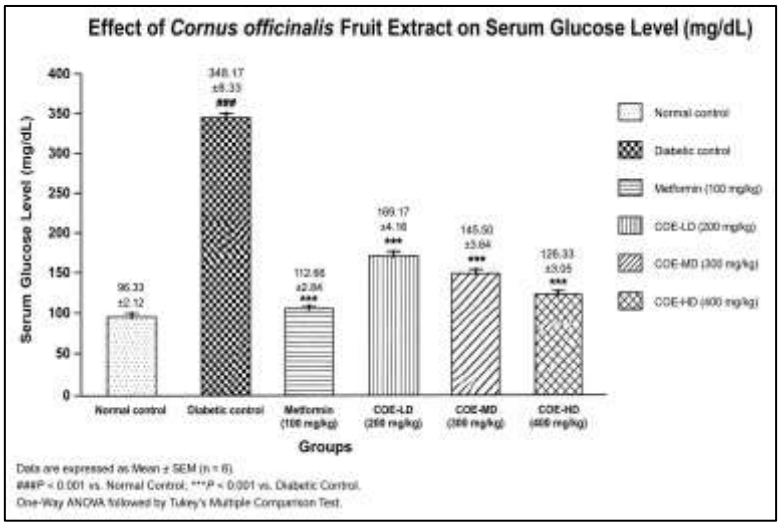

Figure 8: Effect of *Cornus officinalis* Fruit Extract on Serum Glucose (mg/dL)

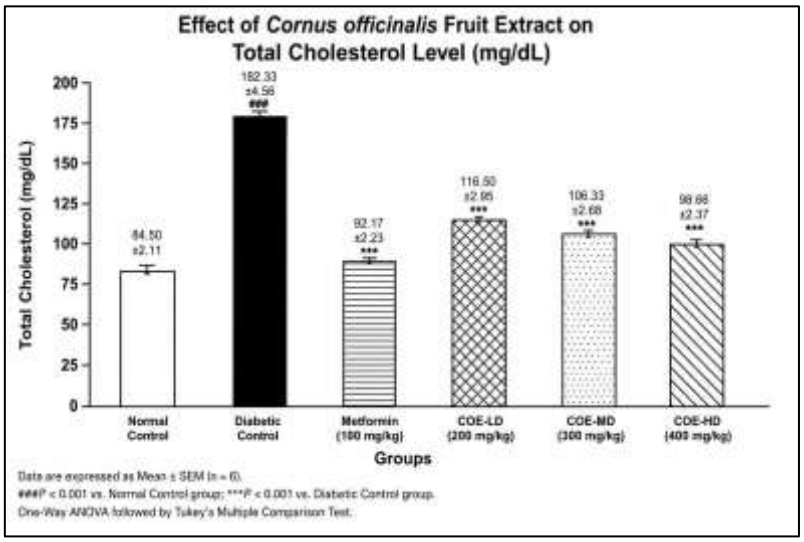

Figure 9: Effect of *Cornus officinalis* Fruit Extract on TC level (mg/dL)

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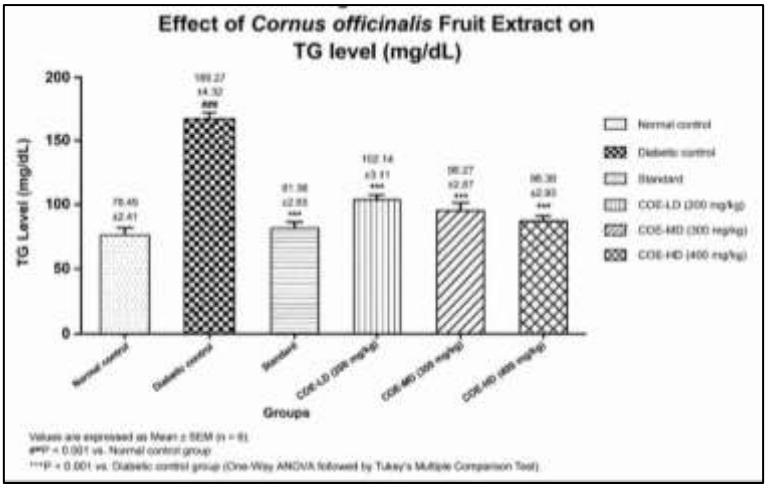

Figure 10: Effect of *Cornus officinalis* Fruit Extract on TG level (mg/dL)

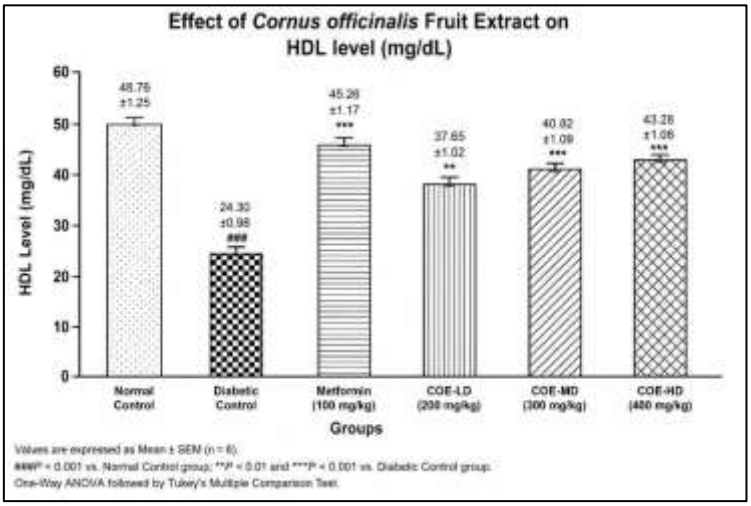

Figure 11: Effect of *Cornus officinalis* Fruit Extract on HDL level (mg/dL)

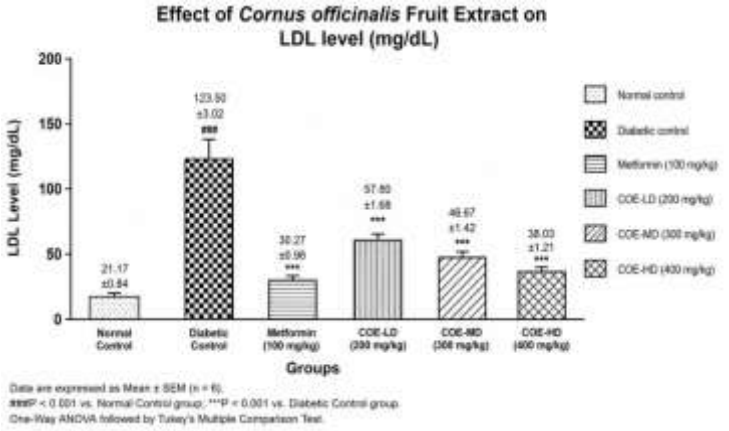

Figure 12: Effect of *Cornus officinalis* Fruit Extract on LDL level (mg/dL)

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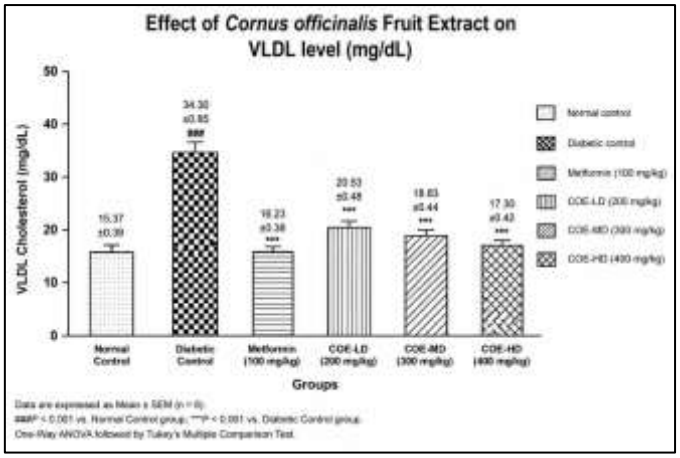

Figure 13: Effect of *Cornus officinalis* Fruit Extract on VLDL level (mg/dL)

Table 13: Effect of *Cornus officinalis* Fruit Extract on Liver Function Parameters

Groups		AST (U/L)	ALT (U/L)	ALP (U/L)
Normal Control		42.16 ± 1.08	31.33 ± 0.84	95.50 ± 2.17
Diabetic Control		88.50 ± 2.37###	76.83 ± 2.08###	181.17 ± 4.83###
Metformin (100 mg/kg)		46.83 ± 1.19***	35.17 ± 0.95***	102.50 ± 2.42***
COE-LD (200 mg/kg)		58.66 ± 1.54***	46.50 ± 1.26***	124.33 ± 3.14***
COE-MD (300 mg/kg)		54.33 ± 1.43***	42.17 ± 1.15***	116.50 ± 2.88***
COE-HD (400 mg/kg)		50.17 ± 1.32***	39.33 ± 1.04***	109.66 ± 2.63***

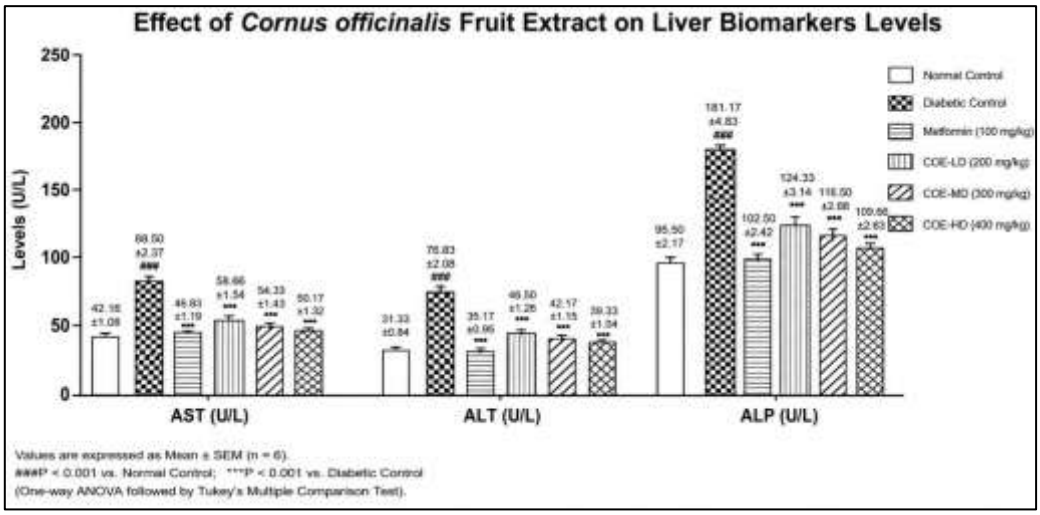

Figure 14: Effect of *Cornus officinalis* Fruit Extract on Liver Function Parameters

Table 14: Effect of *Cornus officinalis* Fruit Extract on Kidney Function Parameters

Groups	Urea (mg/dL)	Creatinine (mg/dL)
Normal Control	28.16 ± 0.84	0.62 ± 0.03
Diabetic Control	68.50 ± 2.08###	1.82 ± 0.06###
Metformin (100 mg/kg)	31.17 ± 0.96***	0.71 ± 0.03***
COE-LD (200 mg/kg)	41.33 ± 1.14***	1.08 ± 0.04***
COE-MD (300 mg/kg)	37.16 ± 1.07***	0.94 ± 0.03***
COE-HD (400 mg/kg)	34.83 ± 1.01***	0.82 ± 0.03***

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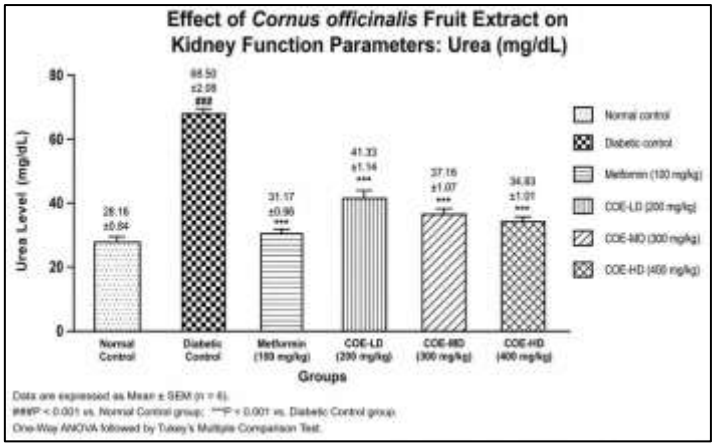

Figure 15: Effect of *Cornus officinalis* Fruit Extract on Kidney Function Parameters Urea (mg/dL)

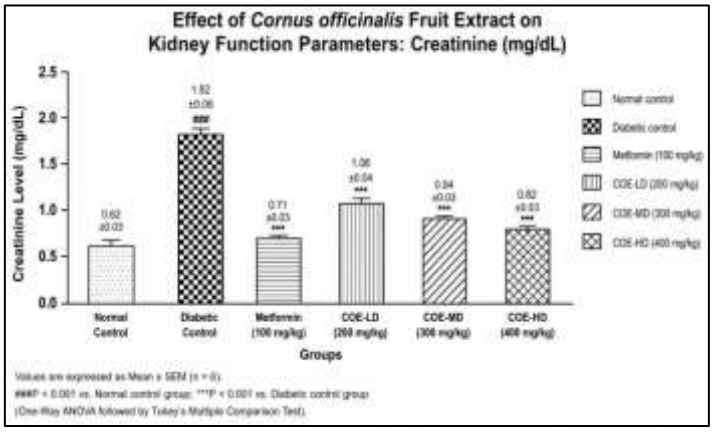

Figure 16: Effect of *Cornus officinalis* Fruit Extract on Kidney Function Parameters Creatinine (mg/dL)

Table 15: Effect of *Cornus officinalis* Fruit Extract on Antioxidant Parameters

Groups	SOD (U/mg protein)	CAT (µmol/min/mg protein)	GSH (µg/mg protein)
Normal Control	12.84 ± 0.36	61.33 ± 1.48	8.17 ± 0.21
Diabetic Control	5.16 ± 0.18$^{###}$	28.66 ± 0.87$^{###}$	3.21 ± 0.12$^{###}$
Metformin (100 mg/kg)	11.83 ± 0.31***	58.50 ± 1.26***	7.74 ± 0.19***
COE-LD (200 mg/kg)	8.84 ± 0.25***	45.33 ± 1.07***	5.83 ± 0.16***
COE-MD (300 mg/kg)	9.75 ± 0.27***	49.83 ± 1.12***	6.46 ± 0.17***
COE-HD (400 mg/kg)	10.66 ± 0.29***	54.17 ± 1.18***	7.02 ± 0.18***

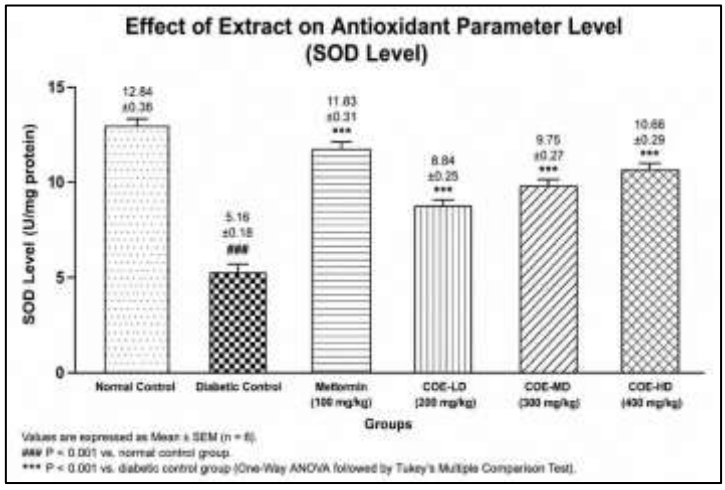

Figure 17: Effect of *Cornus officinalis* Fruit Extract on Antioxidant Parameters SOD (U/mg protein)

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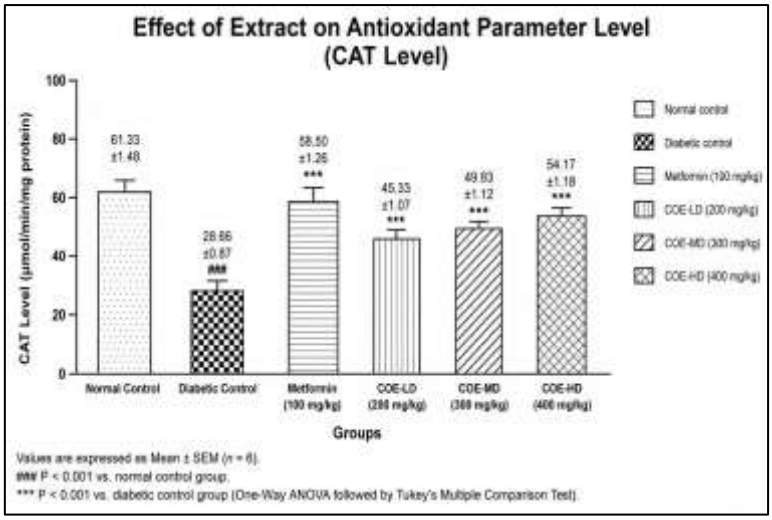

Figure 18: Effect of *Cornus officinalis* Fruit Extract on Antioxidant Parameters CAT (µmol/min/mg protein)

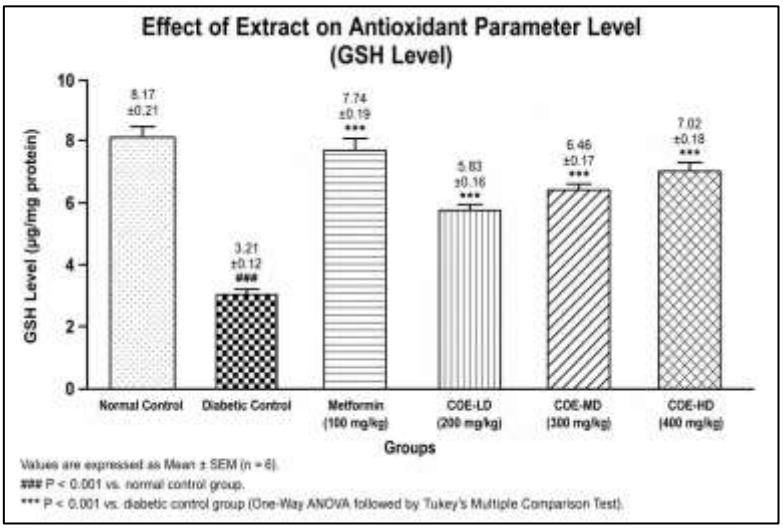

Figure 19: Effect of *Cornus officinalis* Fruit Extract on Antioxidant Parameters GSH (µg/mg protein)

Table 16: Effect of *Cornus officinalis* Fruit Extract on Lipid Peroxidation Marker

Groups	MDA (nmol/mg protein)
Normal Control	1.84 ± 0.08
Diabetic Control	6.92 ± 0.24$^{###}$
Metformin (100 mg/kg)	2.18 ± 0.11***
COE-LD (200 mg/kg)	3.64 ± 0.15***
COE-MD (300 mg/kg)	3.08 ± 0.13***
COE-HD (400 mg/kg)	2.63 ± 0.12***

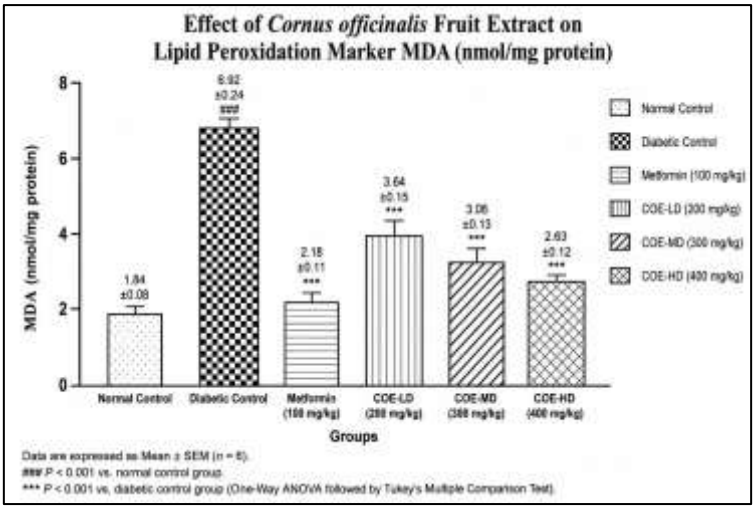

Figure 20: Effect of *Cornus officinalis* Fruit Extract on Lipid Peroxidation Marker MDA (nmol/mg protein)

Histopathological Scoring of Pancreatic Tissue

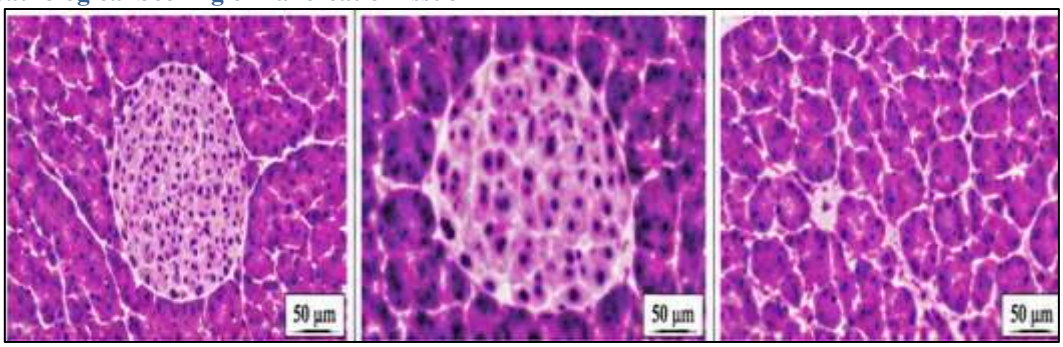

Figure 21: Histopathological section of pancreas from Normal Control group showing normal architecture of pancreatic islets and intact β-cells (H&E, 400×).

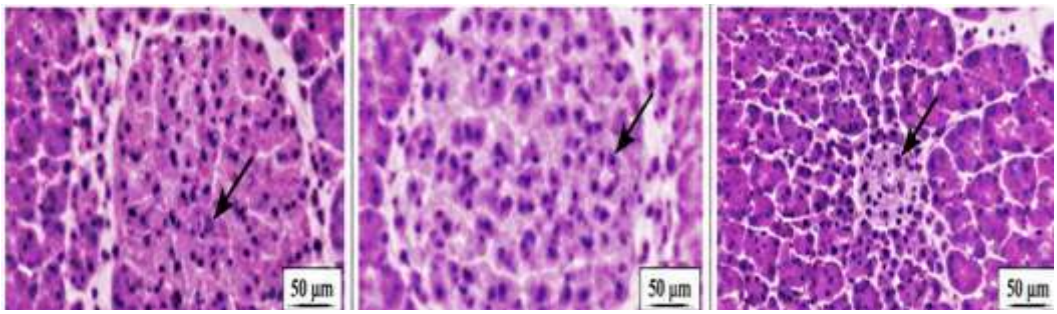

Figure 22: Histopathological section of pancreas from Diabetic Control group showing severe degeneration of β-cells, islet shrinkage and necrosis (H&E, 400×).

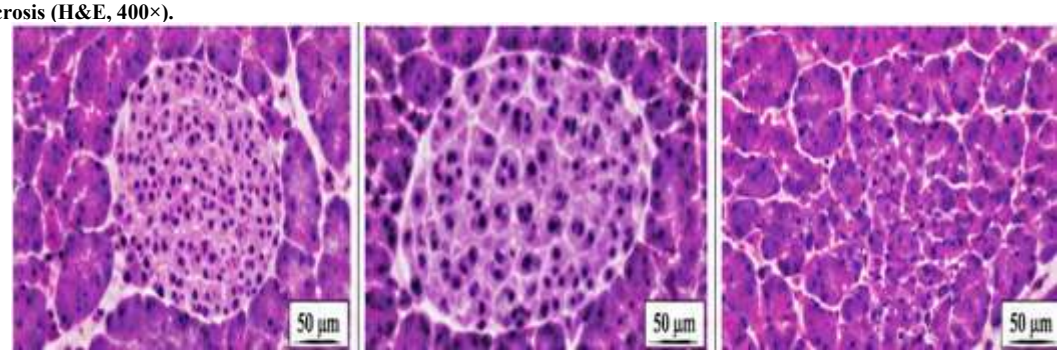

Figure 23: Histopathological section of pancreas from Metformin-treated group showing restoration of islet architecture and β-cell regeneration (H&E, 400×).

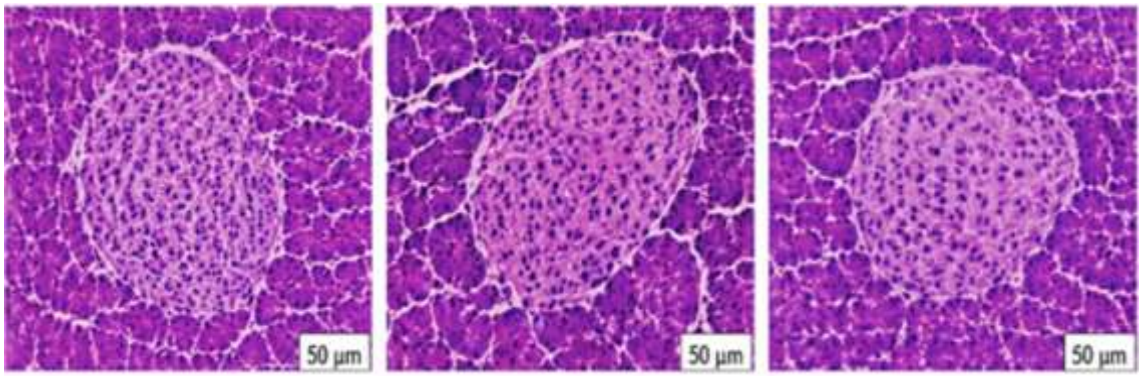

Figure 24: Histopathological section of pancreas from Cornus officinalis extract low-dose group showing moderate regeneration of β-cells and improved architecture (H&E, 400×).

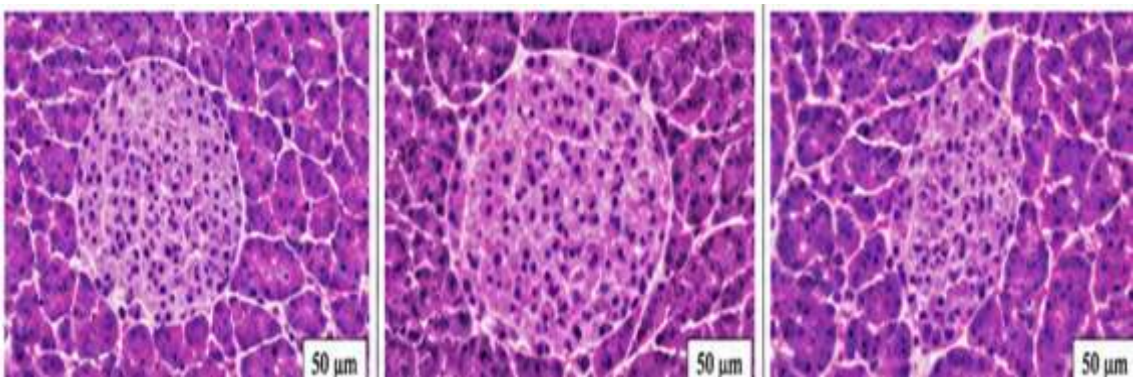

Figure 25: Histopathological section of pancreas from Cornus officinalis extract Medium-dose group showing moderate regeneration of β-cells and improved architecture (H&E, 400×).

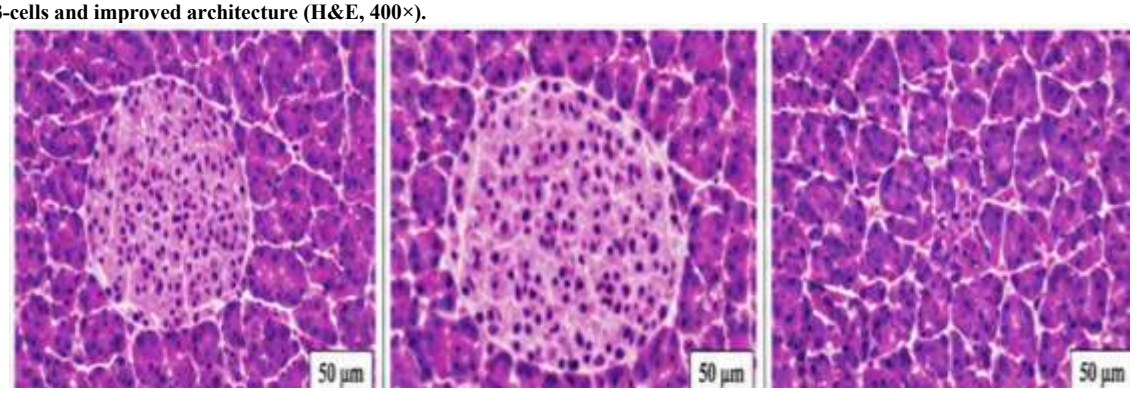

Figure 26: Histopathological section of pancreas from Cornus officinalis extract high-dose group showing marked regeneration of β-cells with near-normal architecture (H&E, 400×).

Histopathological examination revealed severe β-cell degeneration, necrosis, and islet destruction in the diabetic control group. Treatment with *Cornus officinalis* extract showed dose-dependent restoration of pancreatic architecture, with the high-dose group demonstrating marked β-cell regeneration and near-normal islet morphology comparable to metformin treatment.

4. DISCUSSION:

The present study demonstrated the significant antidiabetic and pancreatic β-cell regenerative potential of Cornus officinalis fruit extract in streptozotocin (STZ)-induced diabetic Wistar rats. Streptozotocin is a well-known diabetogenic agent that selectively destroys pancreatic β-cells through oxidative stress, DNA alkylation, and free radical generation, resulting in persistent hyperglycemia and metabolic disturbances. In the current investigation, STZ administration produced marked elevation in fasting blood glucose levels along with reduction in body weight, altered lipid profile, and elevated liver function parameters, confirming successful induction of diabetes. Treatment with Cornus officinalis extract significantly reduced fasting blood glucose levels in a dose-dependent

manner throughout the 28-day treatment period. The high-dose group (400 mg/kg) exhibited maximum glucose lowering activity, which was comparable to the standard drug metformin. Improvement in body weight observed in extract-treated groups further indicates better glycemic control and restoration of metabolic functions.

The extract also significantly improved serum lipid profile by reducing total cholesterol, triglycerides, LDL, and VLDL levels while increasing HDL levels. Diabetes-associated dyslipidemia is a major risk factor for cardiovascular complications, and normalization of lipid parameters suggests the protective effect of the extract against diabetic complications. In addition, reduction in AST, ALT, and ALP levels indicated hepatoprotective activity and improvement in hepatic function.

In vitro antioxidant studies revealed strong DPPH free radical scavenging activity, while α-amylase and α-glucosidase inhibitory assays demonstrated significant enzyme inhibition activity. These effects may contribute to delayed carbohydrate digestion and reduced postprandial hyperglycemia. Preliminary phytochemical screening confirmed the presence of flavonoids, phenolics, tannins, glycosides, alkaloids, and saponins in the methanolic extract. These phytoconstituents are known for their antioxidant and cytoprotective properties and may protect pancreatic β-cells from oxidative damage.

Histopathological examination further supported the biochemical findings by showing regeneration of pancreatic β-cells and restoration of normal pancreatic architecture in extract-treated groups. Overall, the study suggests that Cornus officinalis possesses potent antidiabetic, antioxidant, and pancreatic protective activities, supporting its therapeutic potential in the management of diabetes mellitus.

5. CONCLUSION

The present study demonstrated that the methanolic extract of *Cornus officinalis* possesses significant antioxidant and antidiabetic activity in streptozotocin-induced diabetic Wistar rats. The extract exhibited strong DPPH free radical scavenging activity along with notable α-amylase and α-glucosidase inhibitory effects, indicating its potential to reduce oxidative stress and postprandial hyperglycemia. Oral administration of the extract significantly reduced fasting blood glucose levels, improved body weight, restored altered lipid profile parameters, and protected against diabetes-induced hepatic dysfunction in a dose-dependent manner. Histopathological evaluation further confirmed marked regeneration and restoration of pancreatic β-cell architecture in extract-treated groups, particularly at higher doses, comparable to metformin treatment. The observed pharmacological effects may be attributed to the presence of flavonoids, phenolics, tannins, and other bioactive phytoconstituents present in the extract. Overall, the findings suggest that *Cornus officinalis* may serve as a promising natural therapeutic agent for the management of diabetes and associated complications.

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