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Evaluation of Antidiabetic Activity of Cabergoline and Selegiline in Alloxan Induced Diabetic Rats

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ABSTRACT

The antidiabetic effect of cabergoline and selegiline was investigated in alloxan–induced diabetic rats. Diabetes was induced in albino rats by administration of the single dose of alloxan monohydrate (150 mg/kg i.p.). Cabergoline at dose of 0.6mg/kg i.p. and selegiline at a dose of 0.25 mg/kg i.p. was administered for 14 days. The effect of cabergoline and selegiline on blood glucose level, serum lipid profile [triglyceride and Total Cholesterol), Hepatic Function test [SGOT and SGPT], and Renal Function test [urea and creatinine] were estimated in diabetic rats. Histopathological studies of the pancreas were also carried out. The cabergoline and selegiline significantly reduced the blood glucose level at 7^{th} and 14^{th} day in diabetic rats. Cabergoline and selegiline significantly decreased the triglyceride, total cholesterol, SGOT, SGPT, Urea, and Creatinine in diabetic rats. Histopathological observation of pancreas showed that treatment with metformin, cabergoline and selegiline has recovered the islets from degeneration and enhanced the ability of the cells to proliferate. From the above result it is concluded that selegiline and cabergoline can control diabetes.

INTRODUCTION:

Diabetes is a chronic disease that occurs when the pancreas is no longer able to make insulin, or when the body cannot make good use of the insulin it produces. Insulin is a hormone made by the pancreas that acts like a key to let glucose from the food we eat pass from the bloodstream into the cells in the body to produce energy. All carbohydrate foods are broken down into glucose in the blood. Insulin helps glucose get into the cells. Not being able to produce insulin or use it effectively leads to raised glucose levels in the blood (known as hyperglycemia). Over the long- term high glucose levels are associated with damage to the body and failure of various organs and tissues. [1] The feature of diabetes mellitus is polyuria, polydipsia, weight gain and polyphagia. It is also characterized by chronic hyperglycemia and glucosuria, caused by an absolute or relative deficiency of insulin. [2] This may result in the development of further complications which include hypertension, atherosclerosis, ketosis, gangrene and microcirculatory disorders. [3] It is also associated with long-term complications including retinopathy, nephropathy, neuropathy and angiopathy.[4]

Type 2 diabetes is the most common type of diabetes, accounting for around 90% of all diabetes cases. It is generally characterized by insulin resistance, where the body does not fully respond to insulin. Because insulin cannot work properly, blood glucose levels keep rising, releasing more insulin. For some people with type 2 diabetes, this can eventually exhaust the pancreas, resulting in the body producing less and less insulin, causing even higher blood sugar levels (hyperglycemia).

Type 2 diabetes is most commonly diagnosed in older adults, but is increasingly seen in children, adolescents and younger adults due to rising levels of obesity, physical inactivity and poor diet. The cornerstone of type 2 diabetes management is a healthy diet, increased physical activity and maintaining a healthy body weight. Oral medication and insulin are also frequently prescribed to help control blood glucose levels.[5] Alloxan is the most prominent chemical compound used in diabetogenic research. In research, it is used for induction of Type 1 diabetes. Alloxan is a urea derivative that causes selective necrosis of the β- cells of pancreatic islets. It has been widely used to induce experimental diabetes in animals such as rabbits, rats, mice, and dogs with different grades of disease severity by varying the dose of alloxan used.

Cabergoline is referred for the treatment of hyperprolactinemia and acromegaly. It is a newer D_2 agonist more potent and more D_2 selective and long-acting than bromocriptine and needs

to be given only twice weekly. Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D_2 receptors.[6] Selegiline (L-deprenyl),a proparglyamine derivative of methamphetamine , is a potent, irreversible and selective inhibitor of monoamino oxidase B (MAO- B).[7] Selegiline is a selective MAO-B inhibitor has proved to be useful adjuvant to levo – Dopa therapy and is used as a monotherapy of parkinsonisonis disease. Selegiline bind to brain region with high MAO-B content such as the thalamus, the striatum, the cortex and the brain stem. Selegiline shows the inhibition of MAO-B enzymes which decrease the metabolism of dopamine because MAO-B enzymes metabolite only dopamine. MAO-B enzyme present in liver, brain, platelets. [8] Increased dopamine level cause the decreased insulin resistance, decrease hepatic glucose production, decrease triglyceride, decrease free fatty Acids, by this way they decrease blood glucose levels. [9]

Current therapy available for diabetes mellitus includes oral hypoglycemic agents. Most of the drugs have failed either due to ineffectiveness or adverse effects. There is no treatment that can completely cure diabetes. This difficulty has highlighted the need for more effective, safer and less costly approaches for the management of diabetes. To overcome these problems and to provide better therapeutic management, there is a need to find out alternative therapies. In this context, the present study aimed is evaluate of antidiabetic activity of cabergoline and selegiline in alloxan-induced diabetic rats.

Materials and Methods:

Drugs and Chemicals:

Alloxan was purchased from Dolphin Pharmacy Instruments Pvt. Ltd. Mumbai. Cabergoline and Selegiline were purchased from Jai Radhe Sales Pvt. Ltd. and LGM Pharma Pvt. Ltd. respectively.

Animals:

Wistar rats (200-250 g) were obtained from Animal House of YSPM's YTC, Faculty of Pharmacy, satara, and were acclimatized in the quarantine area for one week. After acquaintation, animals were kept and maintained under laboratory conditions of temperature 22 ± 2℃, relative humidity 50± 15% and 12 hrs. Light/dark cycle. The animal fed with a standard pellet diet and water *ad libitum*.The experiment was performed as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Experimental Design:

Hypoglycemic Evaluation:

For Hypoglycemic evaluation, Albino Wistar rats were used and divided into three groups, six animals in each group. Animals were kept fasted overnight (18hrs) before treatment. [10]

Group 1 (NC) - Normal Control

Group 2 (Test I) - Normal rats + 0.6mg/kg i.p. Cabergoline

Group 3 (Test II) - Normal rats + 0.25 mg/kg i.p. Selegiline

Oral Glucose Tolerance Test:

For OGTT evaluation, Albino Wistar rats were used and divided into five groups. Each group contained six animals. Animals were kept fasted overnight (18hrs.) before treatment. Glucose (2gm/kg p.o.) was administered to all the groups of rats except group I after half an hour of administration of different drug treatments.

Group 1 (NC) - Normal Control

Group 2 (NC) – Negative Control (Glucose 2g/kg p.o.)

Group 3 (PC) - Positive Control (Glucose 2g/kg p.o. + Metformin 300 mg/kg p.o.)

Group 4 (Test I) - (Glucose 2g/kg p.o. + Cabergoline 0.6 mg/kg i.p.)

Group 5 (Test II) - (Glucose 2g/kg p.o. + Selegiline 0.25 mg/kg i.p.)

Blood glucose was estimated at 0, 30, 60, 90 & 120 min after different drug treatments using the ACCU-CHECK Active Glucometer [11]

Induction of Diabetes

Albino Wistar Rats were made diabetic by intraperitoneal injection of Alloxan monohydrate (150 mg/kg i.p.). Alloxan monohydrate solution was prepared in 0.9% NaCl solution and was administered within 5 minutes at a dose of 150 mg/kg i.p. All the animals except the control group were i.p. administered with Alloxan at a dose of 150mg/kg i.p. once a day for 2 days. After 72 hours of Alloxan administration, rats with moderate diabetes having hyperglycemia (i.e., with a blood glucose level more than 250mg/dl) were taken for the experiment.

Group 1 (NC) - Normal Control

Group 2 (NC) - Negative Control (Alloxan 150 mg/kg i.p)

Group 3 (PC) - Positive Control (Alloxan 150 mg/kg i.p. + Metformin 300 mg/kg p.o.)

Group 4 (Test I) - (Alloxan 150 mg/kg i.p. + Cabergoline 0.6 mg/kg i.p.)

Group 5 (Test II) - (Alloxan 150 mg/kg i.p. + Selegiline 0.25 mg/kg i.p.)

Blood samples were collected through the tail veins of rats. Fasting blood glucose estimation was done on 0^{th}, 7^{th}, & 14^{th} day of the study. Blood glucose estimation was done by ACCU-CHECK Active Glucometer using glucose test strips. On the final day, blood was collected from the retro-orbital plexus under mild ether anesthesia from overnight fasted rats and fasting blood sugar was estimated. The study was conducted for 14 days to evaluate the potential of the drug to lower blood glucose levels.

Biochemical Estimation

After 14 days of treatment, blood samples were withdrawn for estimation of Blood glucose level, Lipid profile (cholesterol, Triglycerides), and Liver function test (AST; SGOT, ALT; SGPT, etc.). Renal Function test (Urea, Creatinine) by using diagnostic kits. [12]

Histopathology

At the end of the study animals were dissected and the organs were fixed in 10% formalin for monitoring necropsy or adverse effects of the treatment. The tissues were processed for histopathology starting from trimming, graded alcohol dehydration, embedding in paraffin, sectioning, spreading, fixing in the slides and staining with hematoxylin and eosin. The slides were seen under the microscopy (100 X) for abnormalities and photomicrographs were taken. [13]

Statistical analysis

The results were expressed as Mean ± SEM and were analysed for statistical significance by one-way ANOVA (Dunnett's multiple comparison tests) using Graph pad Prism 5 version. $P < 0.001$ was considered as statistically significant.

Results:

Hypoglycemic Evaluation:

Blood glucose level was not decreased prominently when animals were treated by cabergoline 0.6 mg/kg i.p. and selegiline 0.25 mg/kg i.p. as compared to the normal control group. The results are shown in table 1.

Table 1: Hypoglycemic Effect of Cabergoline and Selegiline in Normal Rats:

Group	TreatmentGroups (n=6)	Fasting Blood Glucose Level (mg/dl)				
		0 min	30min	60 min	90min	120 min
I	NormalControl	70±6.51	68±5.81	67±5.71	66±6.16	68±6.21
II	Test I (Cabergoline 0.6 mg/kg i.p.)	71±7.52	69±7.15	68± 6.73	68±5.21	67±6.84
III	Test II (Selegiline 0.25mg/kg i.p.)	69±8.21	68± 6.21	68± 7.12	65±7.32	65±7.23

The Data are expressed as a mean (n=6) ±S.E.M. $p<0.001$ was considered significant.

Oral Glucose Tolerance Test:

Negative Control (Group II) showed a significant increase in blood glucose level at 60 and 90 min as compared to normal control (Group I). Positive Control (Group III) with Metformin (300 mg/kg p.o.) administration showed a significant decrease in blood glucose level at 60 and 90 min as compared to negative control (Group II). Group IV (Test I) animals treated with cabergoline (0.6 mg/kg i.p.) showed a significant decrease in blood glucose level at 60 and 90 min as compared to negative control (Group II). Group V (Test II) animals treated with Selegiline (0.25 mg/kg i.p.) showed a significant decrease in blood glucose levels at 60 and 90 min as compared to negative control (Group II). The results are shown in table 2.

Table 2: Effect of Cabergoline and Selegiline in the Oral Glucose Tolerance Test

Group	TreatmentGroups (n=6)	Fasting Blood Glucose Level (mg/dl)				
		0 min	30 min	60 min	90min	120 min
I	Normal Control	70±6.83	69±5.92	68±6.12	69±5.82	68±5.91
II	Negative Control (Glucose 2g/kg p.o.)	72±6.53	75±5.25	130±11.12	110±9.21	94±7.42
III	Positive Control (Metformin 300 mg/kg p.o.)	86±7.52	83±5.81	86±7.81	88±7.72	80± 7.05
IV	Test I (Cabergoline 0.6mg/kg i.p.)	79±6.21	84±6.42	92±7.91	91±8.62	85± 8.17
V	Test II (Selegiline 0.25 mg/kg i.p.)	88±6.81	82±7.51	82±7.23	88±7.81	87±7.52

The Data are expressed as a mean (n=6) ±S.E.M. $p<0.001$ was considered significant.

Alloxan-Induced Rodent Model of Diabetes:

Negative Control (Group II) with Alloxan (150 mg/kg i.p.) administration showed a significant increase in blood glucose level in comparison to normal control (Group I). Positive Control (Group III) treated with Metformin (300 mg/kg p.o.) showed a significant decrease in blood glucose level as compared to negative control (Group II). Group IV (Test I) animals treated with cabergoline (0.6 mg/kg i.p.) showed a significant decrease in blood glucose level on 7 th and 14 th day as compared to negative control (Group II). Group V (Test II) animals treated with Selegiline (0.25 mg/kg i.p.) showed significant decrease in blood glucose level on 7 th and 14th day as compared to the negative control (Group II). The results are shown in table 3.

Table 3: Effect of Cabergoline and Selegiline on Blood Glucose Level in Alloxan Induced Diabetic Rats

Group	TreatmentGroups (n=6)	Blood Glucose Level (mg/dl)		
		1st day	7th day	14th day
I	Normal Control	79± 6.82	80± 7.81	82± 7.64
II	Negative Control (Alloxan) 150 mg/kg i.p.)	321±22.47	326± 26.08	322± 19.82
III	Positive Control (Metformin 300 mg/kg p.o.)	215±20.81	95± 8.77	90± 8.22
IV	Test I (Cabergoline 0.6 mg/kg i.p.)	299±27.34	296± 19.45	164±14.04
V	Test II (Selegiline 0.25 mg/kg i.p.)	293±28.12	106±8.36	115±10.91

The Data are expressed as a mean (n=6) ±S.E.M. $p<0.001$ was considered significant.

Biochemical Parameter:

Lipid Profile:

Negative control (Group II) with Alloxan (150 mg/kg i.p.) administration showed significant increase in total cholesterol and triglycerides in comparison to normal control (Group I). Positive control (Group III) treated with Metformin (300 mg/kg p.o.) showed significant decrease in total cholesterol and triglycerides as compared to negative control (Group II). Group IV (Test I) animals treated with cabergoline (0.6 mg/kg i.p.) showed a significant

decrease in total cholesterol and triglycerides as compared to negative control (Group II). Group V (Test II) animals treated with Selegiline (0.25 mg/kg i.p.) showed a significant decrease in total cholesterol and triglycerides as compared to negative control (Group II). The results are shown in table 4.

Table 4: Effect of Cabergoline and Selegiline on Serum Lipid Profile in Alloxan-Induced Diabetic Rats:

Group	TreatmentGroups (n=6)	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)
I	NormalControl	128± 9.12	122±10.02
II	Negative Control (Alloxan 150 mg/kg i.p.)	159± 12.83	235±.18.8
III	Positive Control (Metformin 300 mg/kg p.o.)	122±9.76	153±12.34
IV	Test I (Cabergoline 0.6 mg/kg i.p.)	133±7.98	201± 13.28
V	Test II (Selegiline 0.25 mg/kg i.p.)	124±8.68	140±11.75

The Data are expressed as a mean (n=6) ±S.E.M. $p<0.001$ was considered significant.

Hepatic Function Test:

Negative control (Group II) with Alloxan (150 mg/kg i.p.) administration showed a significant increase in SGOT and SGPT in comparison to normal control (Group I). Positive control (Group III) treated with Metformin (300 mg/kg p.o.) showed a significant decrease in SGOT and SGPT as compared to negative control (Group II). Group IV (Test I) animals treated with cabergoline (0.6 mg/kg i.p.) showed a significant decrease in SGOT and SGPT as compared to negative control (Group II). Group V (Test II) animals treated with Selegiline

(0.25 mg/kg i.p.) showed a significant decrease in SGOT and SGPT as compared to negative control (Group II). The results are shown in table 5.

Table 5: Effect of Cabergoline and Selegiline on Hepatic Function Test in Alloxan-Induced Diabetic Rats:

Group	TreatmentGroups (n=6)	SGPT U/L	SGOT U/L
I	NormalControl	43± 3.82	36±3.14
II	Negative Control (Alloxan 150 mg/kg i.p.)	59±5.25	42±3.85
III	Positive Control (Metformin) 300 mg/kg p.o.)	46±4.05	36±2.82
IV	Test I (Cabergoline 0.6 mg/kg i.p.)	48±3.27	41± 2.07
V	Test II (Selegiline 0.25 mg/kg i.p.)	34± 2.86	39±2.53

The Data are expressed as a mean (n=6) ±S.E.M. $p<0.001$ was considered significant.

Renal Function Test

Negative Control (Group II) with Alloxan (150 mg/kg i.p.) administration showed a significant increase in Urea and Creatinine in comparison to normal control (Group I). Positive Control (Group III) treated with Metformin (300 mg/kg p.o.) showed a significant decrease in Urea and Creatinine as compared to negative control (Group II). Group IV (Test I) animals treated with cabergoline (0.6 mg/kg i.p.) showed a significant decrease in Urea and Creatinine as compared to negative control (Group II). Group V (Test II) animals treated with Selegiline (0.25 mg/kg i.p.) showed a significant decrease in Urea and Creatinine as compared to negative control (Group II). The results are shown in table 6.

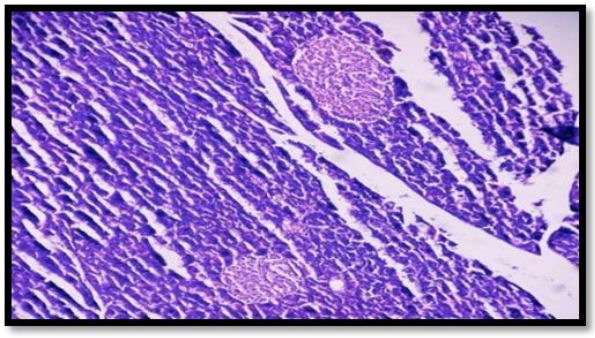
Table 6: Effect of Cabergoline and Selegiline on Renal Function Test in Alloxan-Induced Diabetic Rats

Group	TreatmentGroups (n=6)	Urea (mg/dl)	Creatinine (mg/dl)
I	Normal Control	23± 1.92	0.24±0.01
II	Negative Control (Alloxan) 150 mg/kg p.o.)	45± 4.05	0.88±0.06
III	Positive Control (Metformin 300 mg/kg p.o.)	25± 2.10	0.45±0.03
IV	Test I (Cabergoline 0.6 mg/kg i.p.)	36±3.23	0.78± 0.05
V	Test II (Selegiline 0.25 mg/kg i.p.)	27±1.75	0.72± 0.05

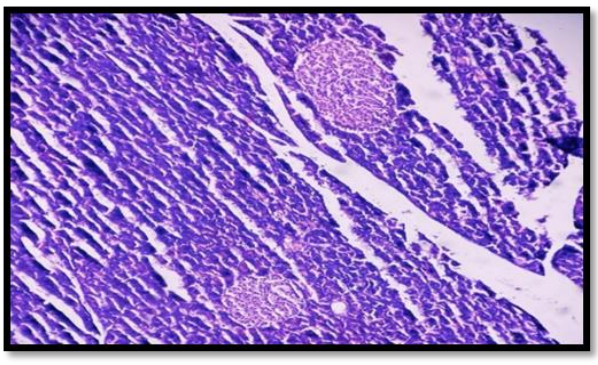
The Data are expressed as a mean (n=6) ±S.E.M. $p<0.001$ was considered significant.

Histopathology of Pancreas:

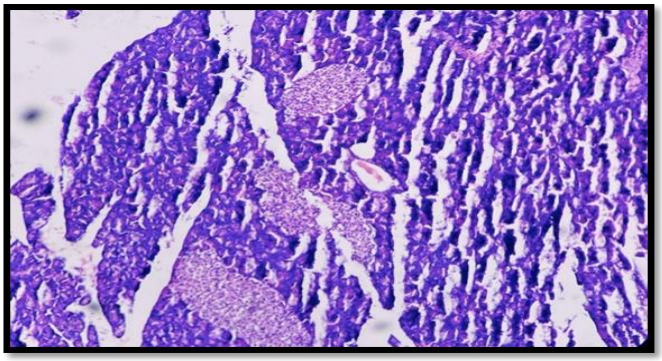
A) Group I- Normal Control



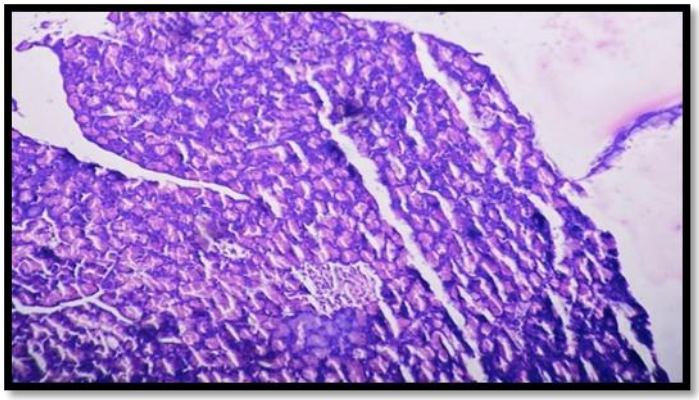
B) Group II – Negative Control



C) Group III - Positive Control



D) Group IV - Test – I



E) Group V – Test II

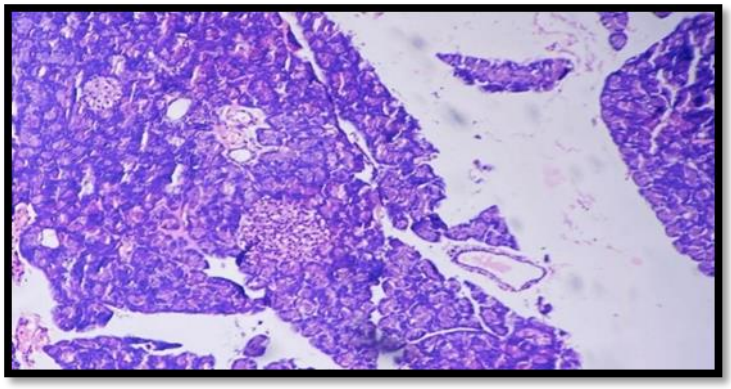


Fig 1-Histopathological Photomicrographs of Pancreas

(A) Group I- Normal Control: The arrow indicates a number of islands and beta cells are normal. No evidence of stromal Infiltration. (B) Group II - Negative Control: arrow indicates total ablation of islands and beta cells are noted. Acinar Degeneration noted. (C) Group III - Positive Control: The arrow indicates Number of islands and beta cells equal or slightly

reduced as compared to control. (D) Group IV - Test I: Number of islands and beta cells are Slightly Reduced as compared to normal. No evidence of stromal Infiltration or regeneration. (E) Group V – Test II: Number of islands and beta cells are Adequate in numbers as compared to normal group and showing proliferation in few islands. Regenerative Changes are noted.

Interpretation

The slides of the pancreas tissue of rats were observed under 100 x magnifications for histopathological changes in the Pancreas. The histopathological observation of the pancreas reveals that the pancreatic islets of the diseased animal were degenerated, with their cell size being shrunken and reduced islets of the pancreas was observed. In the normal control group the cells appeared normal and being proliferated. Treatment with metformin, cabergoline, and selegiline has recovered the islets from degeneration and enhanced the ability of the cells to proliferate and increase the number of islands and beta cells.

DISCUSSION:

Diabetes mellitus is the most common metabolic disorder characterized by hyperglycemia, hyperlipidemia, polyuria etc. The global burden of diabetes continuously increases year by year, 1 out of every 11 people are diabetic. 1.6 million People die due to diabetes. Current therapy available for diabetes mellitus includes oral hypoglycemic agents. Most of the drugs have failed either due to ineffectiveness or adverse effects. There is no treatment that can completely cure diabetes. This difficulty has highlighted the need for more effective, safer and less costly approaches for the management diabetes. To overcome these problems and to provide better therapeutic management, there is a need to find out alternative therapies.

The results of hypoglycemic study have shown that Group II and Group III treated with cabergoline (0.6 mg/kg i.p.) and Selegiline (0.25 mg/kg i.p.) respectively did not show significant change in blood glucose levels compared to normal control group.

OGTT for nondiabetic rats were performed according to the standard method (Du Vigneaud and Karr, 1925). [14] Oral glucose tolerance test (OGTT) was performed to check the glucose tolerance capacity and to confirm the development of diabetes. Animals were fasted for 18h and glucose was administered orally at a concentration of 2 g/kg. Blood samples were collected from the tail of the animals by tail vein puncture method at the time intervals of 0,

30, 60, 90 and 120 min and the blood glucose concentration was checked. Data were expressed as mean ± standard error of mean (SEM).

The Oral glucose tolerance test in normoglycemic rats, blood glucose level was significantly greater in the glucose-loaded animals at 60 and 90 min as compared to normal control. A positive control group with metformin (300 mg/kg p.o.) administration showed significant decrease in blood glucose level at 60 and 90 min as compared to the negative control group. Group IV treated with cabergoline (0.6 mg/kg i.p.) showed a significant decrease in blood glucose level at 60 and 90 min as compared to the negative control group. Group V treated with Selegiline (0.25 mg/kg i.p.) showed significant decrease in blood glucose level at 60 and 90 min as compared to the negative control group.

Alloxan is a beta–cytotoxin that has been demonstrated to cause chemical diabetes in variety of animal species by causing damage to the pancreas insulin-secreting beta cells .This damage a high number of beta cells, resulting in reduction in endogenous insulin production. As a result, rats given alloxan become hyperglycemic in a short time, followed by hepatic glucose overproduction. After a single dosage of 150 mg/kg body weight alloxan injection, we noticed a significant increase in rat's blood glucose levels. The rise in glucose levels was due to alloxan-induced reactive oxygen species , as well as a large rise in cytosolic calcium concentration , which resulted in the rapid death of pancreatic islets cells and reduction in insulin synthesis and release. [15]

Negative Control (Group II) with Alloxan (150 mg/kg i.p.) administration showed a significant increase in blood glucose level in comparison to normal control group. Positive control (Group III) treated with metformin (300 mg/kg p.o.) showed significant decrease in blood glucose level as compared to negative control group. Group IV treated with cabergoline (0.6 mg/kg i.p.) showed significant decrease in blood glucose level on 7^{th} and 14^{th} day as compared to the negative control group. Group V treated with Selegiline (0.25 mg/kg i.p.) showed significant decrease in blood glucose level on 7^{th} and 14^{th} day as compared to the negative control group.

Mechanisms of cabergoline are like the secretion of prolactin by the anterior pituitary is mainly under hypothalamic inhibitory control, likely exerted through the release of dopamine by tuberoinfundibular neurons. Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D_2 receptors. [16] Mechanism of Selegiline shows the inhibition of MAO-B enzymes which decrease the metabolism of dopamine because MAO-B enzymes metabolite

only dopamine. MAO-B enzyme present in liver, brain, platelets.[17] Increase Dopamine level cause the decrease insulin resistance, hepatic glucose production, triglyceride, decrease free fatty Acids, by this way they decreased blood glucose level. [9]

Diabetes mellitus has been reported to impair lipid metabolism as the hyperglycemia is accompanied by a significant increase in the level of triglycerides, total cholestrol which result in the development of atherosclerosis and another cardiovascular disease. Thus, it is rational to infer that the ability of the fraction at suitable doses to prevent hyperglycemia could be the major reason for the decreased triglycerides, total cholesterol levels in rats. [18]

Negative Control (Group II) with Alloxan (150 mg/kg i.p.) administration showed a significant increase in total cholesterol and triglycerides in comparison to normal control group. Positive control (Group III) treated with metformin (300 mg/kg p.o.) showed significant decrease in total cholestrol and triglycerides as compared to negative control group. Group IV treated with cabergoline (0.6 mg/kg i.p.) showed significant decrease in total cholesterol and triglycerides as compared to negative control group. Group V treated with Selegiline (0.25 mg/kg i.p.) showed a significant decrease in total cholestrol and triglycerides as compared to negative control group.

Diabetes is one of the common causes for a liver disease which includes abnormal liver enzymes, cirrhosis, hepatocellular carcinoma and acute liver failure. Glucocorticoids increase lipid catabolism leading to increase in lipolysis result in a massive release of fatty acids that are accumulated in the liver. Thus, increase in the transaminases leads to hepatotoxicity.[19] The organ liver plays a vital role in governing carbohydrate metabolism. The maintenance of blood glucose and also the supply of blood glucose to other organs are regulated by the liver. Intolerance to the blood glucose may cause liver damage. [20]

Negative control (Group II) with Alloxan (150 mg/kg i.p.) administration showed significant increase in SGOT and SGPT in comparison to the normal control group. Positive control (Group III) treated with metformin (300 mg/kg p.o.) showed significant decrease in SGOT and SGPT as compared to the negative control group. Group IV treated with cabergoline (0.6 mg/kg i.p.) showed significant decrease in SGOT and SGPT as compared to the negative control group. Group V treated with Selegiline (0.25 mg/kg i.p.) showed significant decrease in SGOT and SGPT as compared to the negative control group.

Renal failure and toxicity is one of the serious complication caused by the DM. Oxidative stress also plays an important role in the development of renal damage. The high glucose content leads to the development of high free radicals production and lead to the development of renal failure.[20]

Negative control (Group II) with Alloxan (150 mg/kg i.p.) administration showed a significant increase in urea and creatinine in comparison to normal control group. Positive control (Group III) treated with metformin (300 mg/kg p.o.) showed significant decrease in urea and creatinine as compared to the negative control group. Group IV treated with cabergoline (0.6 mg/kg i.p.) showed significant decrease in urea and creatinine as compared to the negative control group. Group V treated with Selegiline (0.25 mg/kg i.p.) showed significant decrease in urea and creatinine as compared to the negative control group.

In the histopathological study the fine section of Normal Control diabetic rat's pancreas on microscopic examination using H & E stain, 100X showed the presence of islets of Langerhans, blood vessels, connective tissues, inter and arrangement of islets of Langerhans was normal with tightly arranged cells and even distribution throughout the lob-necrosis.[21]

Also, the Pancreas Exocrine portion is predominantly and composed of lobules, each of which is surrounded by connective tissue septa through which run blood vessels, nerves, lymphatics, and interlobular ducts. Adequate islets of beta and alfa cells were seen. No evidence of stromal Infiltration was seen.

The histological observation of the pancreases of the normal control group, Normal control group I showed Exocrine portion predominantly and composed of lobules formed by acinar structure, each of which is surrounded by connective tissue septa through which run blood vessels, nerves, lymphatic's, and interlobular ducts. Number of islands and beta cells are normal. No evidence of stromal Infiltration. Negative control group treated with alloxan shows that the total Ablation of islands and beta cells are noted. Acinar Degeneration was observed.

The treatment with metformin showed number of islands and beta cells equal or slightly reduced as compared to the control. The treatment with cabergoline showed Number of islands and beta cells is Slightly Reduced as compared to normal. No evidence of stromal Infiltration or regeneration. The treatment with selegiline showed Number of islands and beta

cells is Adequate in numbers as compared to normal group and showed proliferation in few islands. Regenerative Changes are noted.

CONCLUSION:

The present study concludes that, in the hypoglycemic study, no significant effect on blood glucose levels was found when animals treated with cabergoline and selegiline. Cabergoline and selegiline decrease the blood glucose level significantly in the alloxan-induced diabetic rats. Cabergoline and selegiline significantly decreased total cholestrol, triglyceride, SGOT, SGPT, Urea, and Creatinine level in alloxan induced diabetic rats. Selegiline had a prominent effect on blood glucose, lipid profile, hepatic function test, and renal function test as compared to cabergoline. Selegiline possesses significant antidiabetic activity and it may prove to be effective for the treatment of diabetes mellitus.

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