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ANTIDIABETIC EFFECT OF MIXTURE OF *CYATHEA NILGIRIENSIS* (HOLTTUM) AND *PTEROCARPUS MARSUPIUM* ROXB. IN STREPTOZOTOCIN INDUCED DIABETIC RAT MODEL

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Keywords:

Diabetes mellitus, *C. nilgiriensis*, *P. marsupium*, Herbal mixture, Toxicity, Antidiabetic activity.

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ABSTRACT: Diabetes mellitus is a metabolic disorder of the endocrine system and becoming a serious threat to mankind's health in all parts of the world. Herbal remedies are considered convenient for management of diabetes due to their traditional acceptability, availability, and less side effects than oral hypoglycaemic agents. Thus, the present study aims to test the toxic and antidiabetic effect of a traditionally used herbal mixture of *C. nilgiriensis* and *P. marsupium* in STZ induced diabetic rats. No mortality, abnormal behaviour, and physiological changes were noted in all doses of herbal mixture treated rats and did not cause any toxic oriented effects even in the high dose during toxicity studies. Thus 200 mg/kg bwt dose of the herbal mixture was selected to evaluate their antidiabetic activity. Herbal mixture treated rats exhibited a significant reduction in blood glucose level (One way ANOVA, $f_{3,12}$ =525.78; $p<0.005$), HbA_1c level (One way ANOVA, $f_{3,12}$= 87.35; $p<0.005$), and a significant increase in serum insulin level (One way ANOVA, $f_{3,12}$=418.0; $p<0.005$). The herbal mixture also proved its antidiabetic efficiency by restoring the tissue damages in the pancreas, liver, and kidney of diabetic rats.

INTRODUCTION: Diabetes mellitus is a metabolic disorder initially characterized by a loss of glucose homeostasis due to disturbances of carbohydrate, fat, and protein metabolism, resulting from defects in insulin production, secretion and insulin action [1]. Diabetes Mellitus (DM) is the number one killer among all chronic diseases in the world [2] and Asians make up more than 60% of the world's diabetic population [3, 4].

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Uncontrolled diabetes leads to long-term damage to organs, such as the kidneys, liver, eyes, nerves, heart, and blood vessels. Complications in some of these organs can lead to death [5]. Currently available synthetic antidiabetic agents, besides being expensive, produce serious side effects [6].

The apparent reversal of the trend from western to herbal medicine has led to the belief that natural products are safe because they are more harmonious with biological systems [7]. Medicinal plants, since time immemorial, have been used in virtually all cultures as a source of medicine. It has been estimated that about 80-85% of the population, both in developed and developing countries, rely on traditional medicine for their primary health care needs, and it is assumed that a

major part of traditional therapy involves the use of plant extracts or their active principles [8]. For diabetes treatment, before the discovery of insulin by Banting and Best in 1922, the only options were those based on traditional practices [9]. The WHO has listed 21,000 plants, which are used for medicinal purposes around the world [10]. There are about 800 plants that have been reported to show antidiabetic potential [11]. A wide collection of plant-derived active principles representing numerous bioactive compounds have established their role for possible use in the treatment of diabetes [11]. As an increase in demand by patients to use natural products with antidiabetic activity, investigations on hypoglycaemic agents derived from medicinal plants have gained popularity in recent years [12]. So for the present study, we selected a widely used traditional medicinal plant *viz, Cyathea nilgiriensis* (Holttum) belonging to the family Cyatheaceae and *Pterocarpus marsupium* Roxb, belonging to family Fabaceae, as it is used by the traditional healers of Kolli hills to treat diabetes. The aim of the present study was to evaluate the antidiabetic effect of a mixture of *C. nilgiriensis* pith and *P. marsupium* milk in streptozotocin-induced diabetic albino rat models.

MATERIALS AND METHODS:

Selection and Collection of Plant Materials: Based on the ethnobotanical information collected from the tribal people of Kolli hills, tree fern, pith of *Cyathea nilgiriensis* (CYATHEACEAE) (voucher specimen (No.XCH No. 25444) was deposited in department of Botany, St. Xavier's College, Palayamkottai, Tamilnadu) and milk of *Pterocarpus marsupium* (FABACEAE, Indian Kino tree) is given to the diabetic patients either alone as powder form or it was mixed with milk of *P. marsupium.* The stem of *C. nilgiriensis* was cut into pieces, and the central part of the wood (pith) was collected and dried under room temperature and powdered with the help of a mechanical grinder. Further, *P. marsupium* milk was collected from the tree with the help of traditional rural dwellers. The pith powder of *C. nilgiriensis* was pulverized and extracted as a whole preparation in a Soxhlet apparatus. The mixture was prepared by mixing the pith of *C. nilgiriensis* powder, and *P. marsupium* milk in 1:1 ratio (w/v) were concentrated to a dry mass by vacuum evaporator and stored in a desiccator.

Experimental Set-Up: A separate experiment was performed to know whether any toxic effect was produced by mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk. Toxicity determination was conducted using a modified method of Lorke [13]. Normal healthy male albino rats fasted for 12 hours were randomly divided into control and extract treated groups. Rats were divided into three groups (10mg/kg dose = group-II; 100mg/kg dose = group-III and 1000mg/kg dose = group-IV) for each drug formulation, and a separate group was maintained as control (group-I). All the rats were maintained as per the regulations of CPCSEA (Ethical Committee Approval No.790/03/ac/CPCSEA). The rats were observed for clinical signs and symptoms of toxicity and mortality from the time of extract administration to the 30th day. End of the experiment, all the rats were sacrificed. The toxicity of the test drug was confirmed by hematological analysis, liver function marker enzyme analysis, and renal function profile tests.

The antidiabetic effect of the test drug (a mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk) was evaluated on the streptozotocin (STZ) induced diabetic albino rats. Induction of Diabetes to the group-II, group-III, and group-IV rats was made by single intraperitoneal injection of STZ (50 mg/kg of body weight). After 48 hours of injection of STZ, rats with blood glucose levels above 250mg/dl were considered diabetic rats, and they were selected for the experimental studies. They were divided into four groups of 4 rats each and caged in separate cages. The experimental setup was given below.

Group I: Control (Non-diabetic rats).

Group II: Diabetic rats (50mg/kg b.wt of streptozotocin).

Group III: Diabetic rats treated with glibenclamide (5mg/kg b.wt).

Group IV: Diabetic rats treated with the mixture (1:1 ratio (w/v) of *C. nilgiriensis* pith powder and *P. marsupium* milk (200mg/kg b.wt).

Antidiabetic activity of the herbal drug was evaluated by analyzing abnormalities in serum blood glucose level, glycosylated hemoglobin

level, serum insulin level, urea level, creatinine level, and uric acid level in experimental diabetic rats were compared with that of normal rats. Further, to know the plant extract's regenerative property in the pancreas, liver, and kidney cells of normal, STZ diabetic albino rats, the tissues were sectioned and observed under the trinocular microscope and microphotographed.

To compare the means of different experimental groups with normal groups, an Analysis of Variance (ANOVA) was performed. The post hoc test (Student-Newman Keuls test; SNK) was performed to investigate the influence of the plant extracts on various biochemical parameters in the extract-treated rats. All statistical analyses were performed by using windows based SPSS package (Statistical Package for Social Sciences / Statistical Product and Service Solutions).

RESULTS AND DISCUSSION:

Toxicity Studies: Herbal medicine preparations are "natural" and are therefore intrinsically harmless. However, their effects can be very powerful and potentially lethal if used incorrectly, and their use as a substitute for conventional medicines may be ineffective [14]. Toxic effects have been attributed to several factors, including hepatotoxicity of main constituents, contamination of preparations by heavy metals or microorganisms, and adverse reactions due to age, and genetic and concomitant disease characteristics of the user [14]. Recently, reports have mounted about hepatotoxicity of herbal remedies, which ranges from mild liver enzyme alterations to chronic liver disease and liver failure [15]. Atta-Ur-Rahman and Khurshid [16] reported the plant extracts containing tannins and alkaloids that have toxic effects on man. Lim and Ho [17] studied that the adverse reactions of pure flavonoids and flavonoid-containing herbs include hemolytic anaemias, thromobocytopaenia, hepatitis and acute renal failure. Knowledge of toxicity is crucial to decrease the risk: benefit ratio; this knowledge defines appropriate conditions for use and strategies for development of safer products.

TABLE 1: STUDENT-NEWMAN-KEULS (SNK) POST HOC TEST RESULT SHOWS THE TOXIC EFFECT OF MIXTURE OF *C. NILGIRIENSIS* AND *P. MARSUPIUM* ON HAEMATOLOGICAL PARAMETERS OF DIFFERENT GROUPS OF THE ALBINO RATS. MEAN VALUES ARE ARRANGED IN ASCENDING ORDER

Student-Newman-Keuls post hoc test				
Parameters	***Groups**			
Total WBC (thousands/mm^3)	6.9 (III)	9.6 (II)	9.8 (IV)	10.6 (I)
Basophil (Arcsine)	0.00 (I)	0.00 (III)	0.00 (II)	0.00 (IV)
Eosinophil (Arcsine)	0.00 (I)	0.01 (IV)	0.01 (III)	0.02 (II)
Neutrophil (Arcsine)	0.03 (I)	0.04 (II)	0.06 (IV)	0.07 (III)
Lymphocyte (Arcsine)	0.39 (III)	0.42 (IV)	0.42 (II)	0.44 (I)
Monocyte (Arcsine)	0.03 (IV)	0.03 (II)	0.04 (III)	0.04 (I)
Total RBC (million/mm^3)	6.2 (I)	6.2 (III)	6.4 (II)	7.6 (IV)
Haemoglobin (gms/dl)	12.1 (I)	14.4 (III)	15.6 (II)	15.8 (IV)

Group I: Control rats
Group II: Mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk treated rats at 10 mg/kg b. wt.
Group III: Mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk treated rats at 100 mg/kg b.wt.
Group IV: Mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk treated rats at 1000 mg/kg b. wt.

Toxic Effect of Test Herbal Drugs on Haematology Parameters: The assessment of haematological parameters could be used to reveal the deleterious effect of toxins, chemicals, and plant extracts on the blood constituents of animals [18]. In the present study, the effects of the mixture of *C. nilgiriensis* and *P. marsupium* milk on hematological parameters were assessed. The WBC count was significantly decreased in the extract-treated rats when compared to control rats. It

showed significant differences (One way ANOVA; $f_{3,12}$ = 39.20; p<0.05) among the groups. In differential WBC count, eosinophil and neutrophil levels were increased in the extract-treated rats compared to control rats. Basophil was absent in the control rats and group-III rats. It showed no significant differences (One way ANOVA; $f_{3,12}$ = 0.73; p>0.05) among all the groups of rats **Table 1**; **Fig. 1**.

Treatment of extracts showed an increase in RBC compared to control rats. Results of the Analysis of variance showed a significant difference in the RBC levels among the groups ($f_{3,12}$ = 6.45; p<0.05). RBC levels in group-IV rats were significantly differed (SNK test; P<0.05) from all other group rats however, no significant differences among group I, group III, and group II (SNK test; P<0.05) **Table 1**; **Fig. 1**.

The haemoglobin of extract-treated rats showed a significant increase when compared to control rats. It showed a significant difference (One way ANOVA; $f_{3,12}$ = 54.63; p<0.05) among the groups **Table 1**; **Fig. 1**. The present results inferred that WBC (TC and DC), RBC, and Hb levels in an extract of *C. nilgiriensis* treated rats were more or less similar to control rats. Thus it is understood that the test herbal drug did not cause a prominent effect on haematological parameters when treated with even a high dose (1000mg/kg body weight).

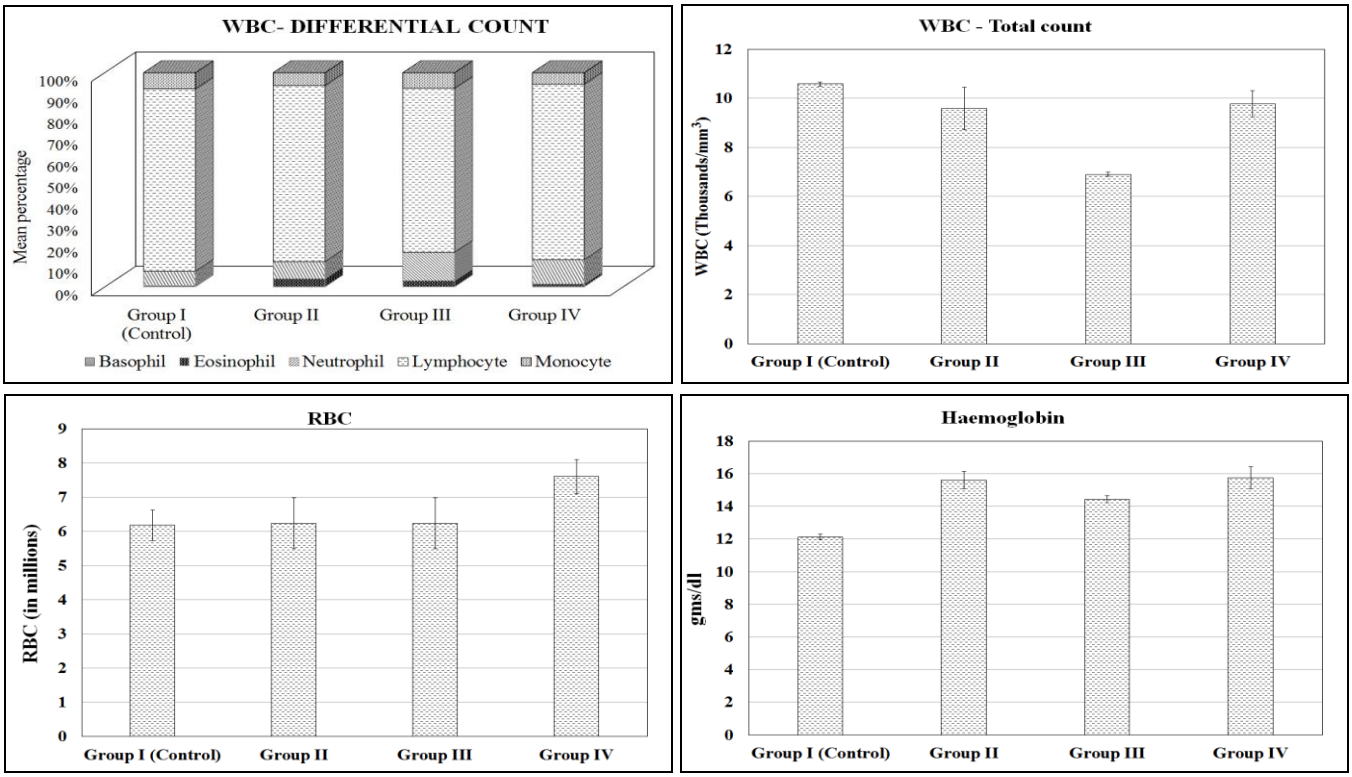


FIG. 1: TOXIC EFFECT OF TEST DRUGS ON WBC TOTAL COUNT, DIFFERENTIAL COUNT, RBC AND HAEMOGLOBIN IN ALBINO RATS

Toxic Effect of Test Herbal Drugs on Liver Marker Enzymes: Liver is a chief organ of protein synthesis; even mild lesions may alter its function [19]. The SGOT and SGPT enzymes are normally contained within liver cells. If the liver is injured or damaged, the liver cells spill these enzymes into the blood, raising the enzyme levels in the blood and signalling liver disease or other organs [20]. Extract administered rats showed a remarkable increase in SGOT levels compared to the control rats. It exhibited a significant difference (One way ANOVA; $f_{3,12}$ = 5.39; p<0.005) among the groups. Treatment of extracts exhibited a significant increase in SGPT levels compared to the control rats (One way ANOVA; $f_{3,12}$ =221.52; p<0.005). Similarly, the ALP level was also significantly increased in the extracts treated rats (One way ANOVA; $f_{3,12}$ = 154.89; p<0.005). ACP level showed a significant decrease in the group III rats while it showed an increase in group-II rats (One way ANOVA; $f_{3,12}$= 27.39; p<0.05) **Table 2; Fig. 2**.

Treatment of extracts increased SGOT and SGPT levels, but they were not exceeded the normal level. Similarly, ALP and ACP levels in test drugs treated rats showed the lowered levels, but they were not exceeded the normal limit. Thus it is concluded that the mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk treatment did not cause any toxic effect with regard to liver marker enzymes.

TABLE 2: STUDENT-NEWMAN-KEULS (SNK) POST HOC TEST RESULTS SHOW THE TOXIC EFFECT OF TEST DRUGS ON HEPATIC MARKER ENZYME LEVELS OF DIFFERENT GROUP OF THE ALBINO RATS. MEAN VALUES ARE ARRANGED IN ASCENDING ORDER

Name of the extracts		Student-Newman-Keuls post hoc test			
Mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk	SGOT (U/L)	36.5 (I)	38.0 (II)	40.0 (III)	42.0 (IV)
	SGPT (U/L)	20.8 (I)	28.8 (III)	40.3 (IV)	43.3 (II)
	ALP (U/L)	28.3 (III)	38.9 (I)	39.6 (IV)	40.5 (II)
	ACP (IU/L)	7.8 (III)	8.3 (I)	8.4 (IV)	9.1 (II)

Horizontal red coloured lines connect similar means. Horizontal red coloured lines connect similar means.

*Groups- I: Control rats; II: Rats treated at 10 mg/kg body weight; III: Rats treated at 100 mg/kg body weight; IV: Rats treated at 1000 mg/kg body weight

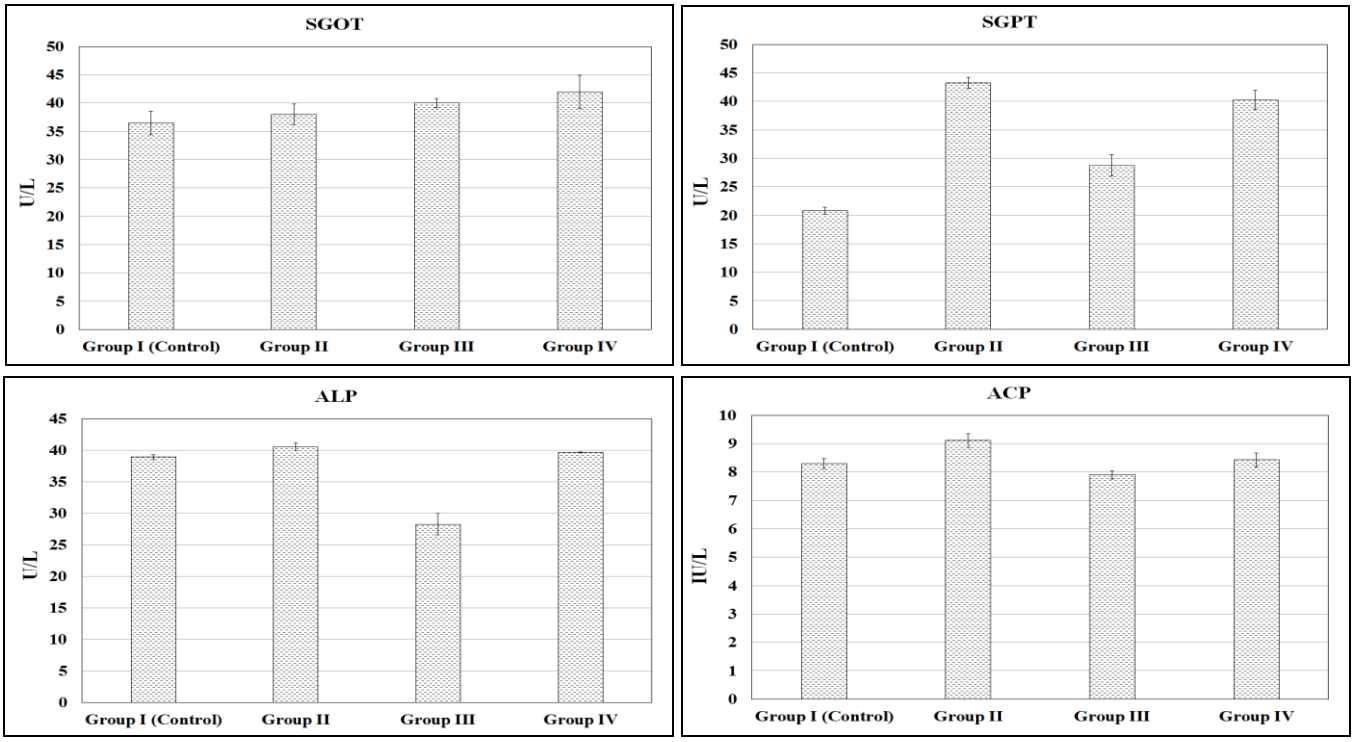


FIG. 2: TOXIC EFFECT OF TEST DRUGS ON LIVER MARKER ENZYMES IN ALBINO RATS

TABLE 3: STUDENT-NEWMAN-KEULS (SNK) POST HOC TEST RESULT SHOWS THE TOXIC EFFECT OF TEST DRUGS ON UREA, URIC ACID, AND CREATININE OF DIFFERENT GROUP OF THE ALBINO RATS. MEAN VALUES ARE ARRANGED IN ASCENDING ORDER

Name of the extracts		Student-Newman-Keuls post hoc test			
Mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk	Urea (mg/dl)	17.3 (I)	17.9 (III)	22.8 (II)	27.9 (IV)
	Uric acid (mg/dl)	3.5 (III)	3.8 (IV)	3.8 (I)	3.8 (II)
	Creatinine (mg/dl)	0.5 (I)	0.6 (IV)	0.6 (III)	0.8 (II)

Horizontal red coloured lines connect similar means.

*Groups I: Control rats; II: Rats treated at 10 mg/kg body weight; III: Rats treated at 100 mg/kg body weight; IV: Rats treated at 1000 mg/kg body weight

Toxic Effect of Test Herbal Drugs on Renal Function: The urea level of test drug-treated rats was increased compared to the control group rats. A slight increase was observed in uric acid and creatinine levels of test drug-treated rats compared to control rats. The one-way ANOVA test revealed significant differences in all renal function tests among all the groups (One way ANOVA; $f_{3,12}$= p<0.005) **Table 3**; **Fig. 3**.

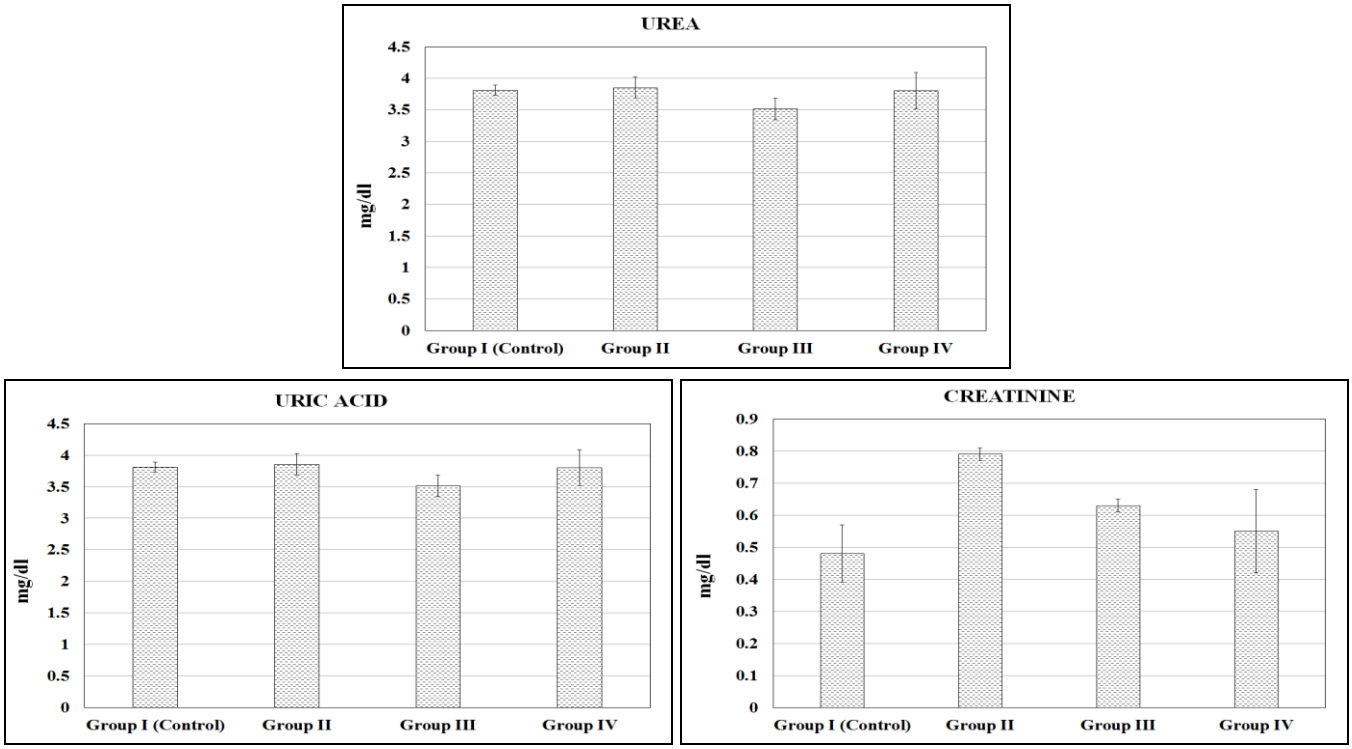


FIG. 3: TOXIC EFFECT OF TEST DRUGS ON UREA, URIC ACID AND CREATININE IN ALBINO RATS

Evaluation of Antidiabetic Activity: Antidiabetic activity of herbal test drugs on the STZ induced rats was evaluated by analyzing abnormalities in serum glucose level, serum insulin level, and glycosylated haemoglobin level **Table 4; Fig. 4**.

Effect of Test Drug on Serum Glucose Level: Streptozotocin was reported to cause a drastic reduction of insulin-producing β cells of islets of Langerhans, thus inducing hyperglycemia [21]. The increased level of blood glucose in the STZ induced diabetic rats might be due to the glycogenolysis or glyconeogenesis [22]. Chronic hyperglycemia, the primary clinical manifestation of diabetes mellitus is associated with the development of micro and macrovascular diabetic complications [23]. Serum glucose levels were highly elevated after intraperitoneal injection of STZ. The glibenclamide and extract-treated group rats exhibited significantly decreased glucose levels compared to diabetic control rats (One way ANOVA; $f_{3,12}$ = 525.78; p<0.05). The SNK multiple comparison tests showed that no significant difference was exhibited among the groups I, III, and IV while the diabetic control group was significantly different from control and from the other groups of rats.

It revealed that the *C. nilgiriensis* pith powder and *P. marsupium* milk mixture has antihyperglyceamic activity by reducing the blood glucose level to near normal level. The antihyperglyceamic activity of herbal drugs could be due to the presence of flavonoids, alkaloids, tannin, steroids, glycosides, phenol, saponin and carbohydrate.

Effect of Test Drug on Serum Insulin Level: Insulin deficiency decreases the uptake of glucose by cells. A partial or total deficiency of insulin causes a derangement in carbohydrate metabolism that decreases the activity of several key enzymes, including glucokinase, phosphofructokinase, and pyruvate kinase resulting in impaired peripheral glucose utilization and augmented hepatic glucose production [24]. The insulin-dependent enzymes are also less active. The net effect is an inhibition of

glycolysis and stimulation of gluconeogenesis, leading to hyperglycemia [25]. Administration of STZ to the rat exhibited insulin deficiency, and produced hyperglycemia was observed in the present study. The serum insulin level was very low in STZ induced diabetic rats compared to control. The serum insulin level of a standard drug (glibenclamide) treated group was significantly increased compared to diabetic control. Similarly, insulin level was increased in test herbal drug-treated diabetic rats which were close to the levels of glibenclamide treated and control rats. The increased insulin level in a mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk treated diabetic rats may be due to increased pancreatic secretion from existing *β* cells. The antihyperglycemic effect of herbal plants is due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose (saponin reduces glucose uptake) or the facilitation of metabolites in insulin-dependent processes. Further, flavonoids are known to regenerate the damaged beta cells in the STZ induced diabetic rats and act as insulin secretagogues [26]. The present phytochemical analysis identified the presence of flavonoids in a mixture of *C. nilgiriensis* pith powder and *P. marsupium* milk. The presence of flavonoids in the *C. nilgiriensis* extracts might be the probable reason for the increase of insulin level in extract-treated rats. It has been isolated from the other plants and found to stimulate secretion or possess insulin-like effect [27]. Hence, treatment with herbal drugs has an effect on protecting β cells and smoothing out fluctuation in glucose levels [28].

Effect of Test Drug on HbA1c: Glycosylated haemoglobin (HbA1C) is now considered the most reliable glycemic control marker in diabetes mellitus [29] and is used to identify the degree of oxidative stress in diabetic conditions [30]. The increased level of blood glucose stimulates non-enzymatic protein glycation, which can lead to irreversible modification observed with the characterization of glycosylated haemoglobin [31].

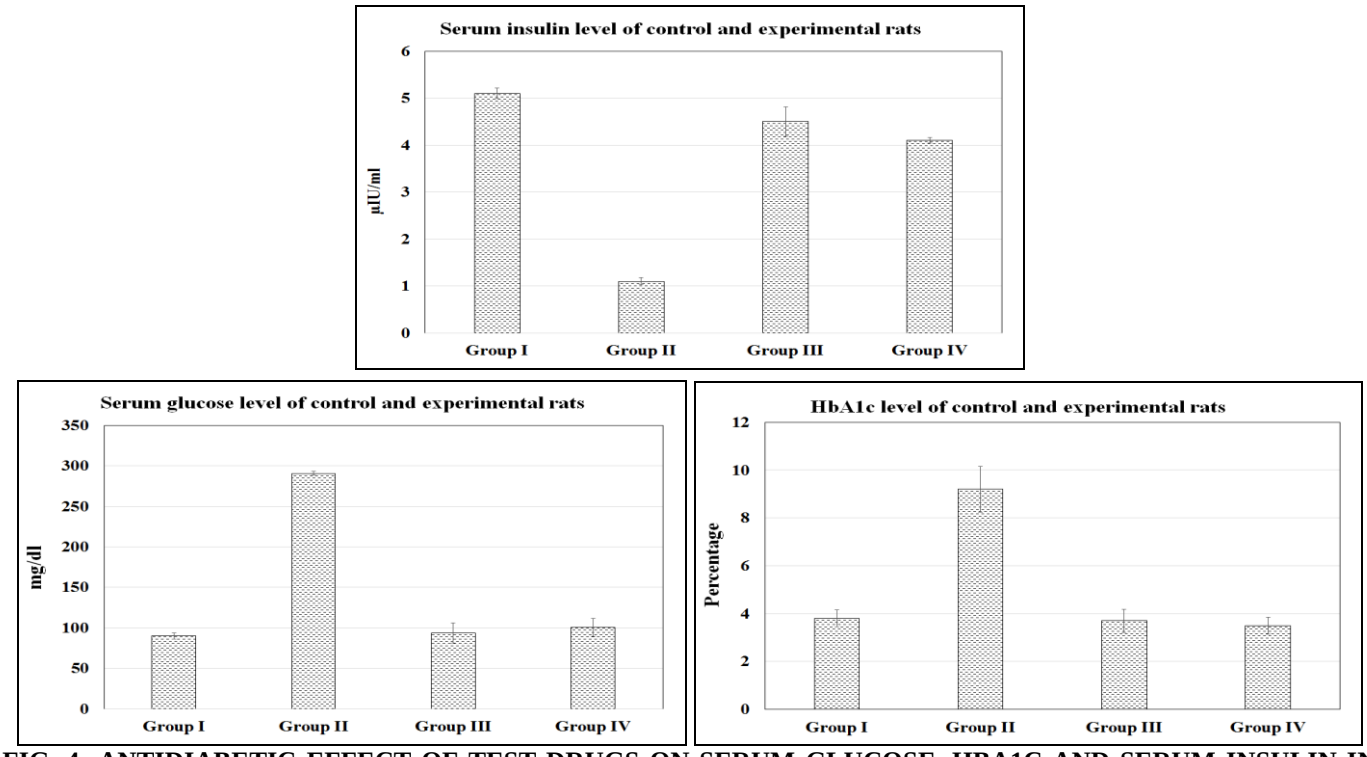


FIG. 4: ANTIDIABETIC EFFECT OF TEST DRUGS ON SERUM GLUCOSE, HBA1C AND SERUM INSULIN IN STZ INDUCED ALBINO RATS

HbA1c level of STZ induced diabetic control rats was significantly increased (One way ANOVA; $f_{3,12}$ = 87.352; p<0.05) compared to control rats. HbA1c level was significantly decreased in standard drug, glibenclamide, and extract-treated group rats compared to the diabetic control rats. The SNK multiple comparison tests showed that no significant difference was exhibited among groups

I, III, and IV. Diabetic rats showed higher levels of glycosylated haemoglobin, indicating their poor glycemic control. The STZ induced diabetic rats shown increased level of blood glucose accompanied by elevated glycosylated haemoglobin and decreased insulin level and liver glycogen in diabetic rats suggest poor glycemic control mechanism. Streptozotocin (STZ) induced diabetes rat enhanced the level of glycated haemoglobin (A1c) due to excessive production of glucose in the blood, which further reacted with blood haemoglobin and prepared the glycated haemoglobin.

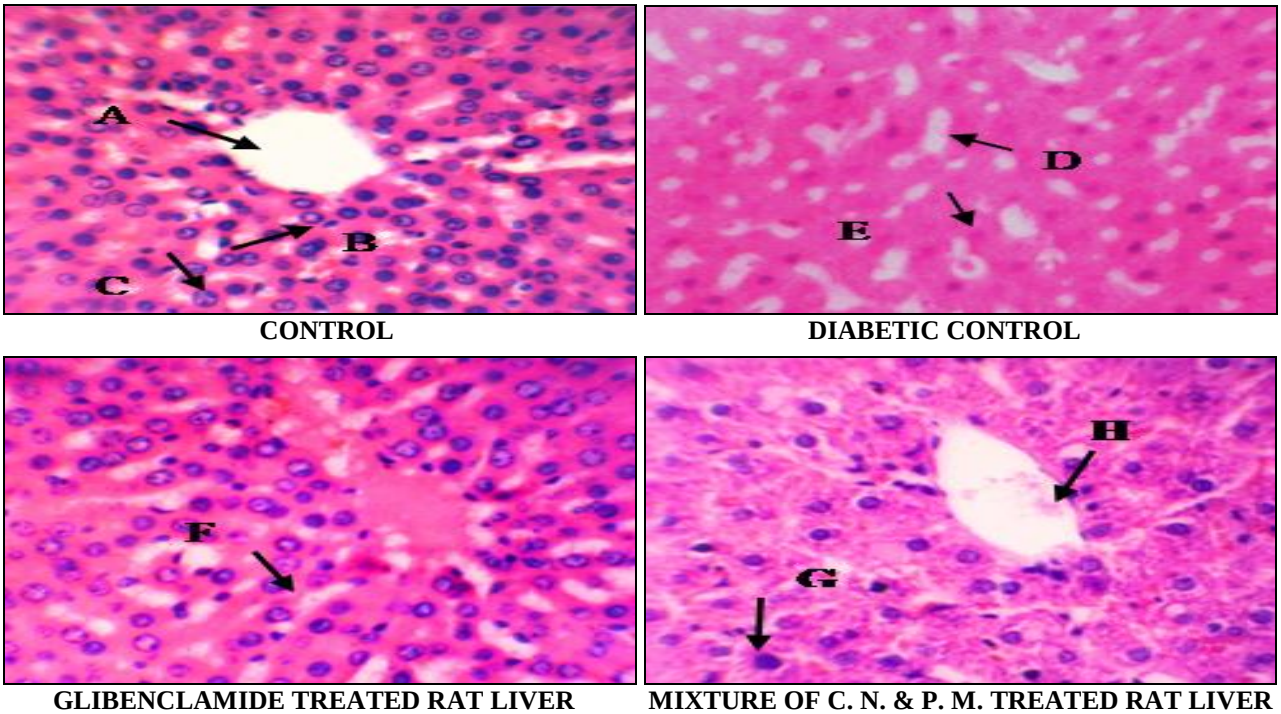
TABLE 4: STUDENT-NEWMAN-KEULS (SNK) POST HOC TEST SHOWS THE ANTIDIABETIC EFFECT OF TEST DRUGS ON SERUM GLUCOSE, HBA1C, AND SERUM INSULIN OF DIFFERENT GROUP OF THE ALBINO RATS. MEAN VALUES ARE ARRANGED IN ASCENDING ORDER

Parameters	Groups			
Serum glucose	90.0	93.7	100.5	290.7
	(I)	(III)	(IV)	(II)
HbA1c	3.5	3.7	3.8	9.2
	(IV)	(III)	(I)	(II)
Serum insulin	1.1	4.1	4.5	5.1
	(II)	(IV)	(III)	(I)

Horizontal red coloured lines connect similar means.

*Groups I: Control rats; II: STZ treated diabetic rats; III: Glibenclamide treated diabetic rats; IV: Extract treated rats.

Effect of Test Herbal Drug on Histoarchitecture of Liver, Kidney, and Pancreas: The liver is the vital organ involves in maintaining the optimum blood glucose levels within narrow limits. The liver and kidney exhibited numerous morphological and functional alterations during diabetes [32]. Hyperglycemia-induced free radical toxicity causes severe damage to vital organs, especially the liver. In the present study, STZ induced diabetic rat's liver showed much necrosis in liver cells. Diabetic liver showed dilations in hepatic sinusoids and kupffer cell hyperplasia. The restoration of damages in the liver of diabetic rats treated with a mixture of *C. nilgiriensis* and *P. marsupium* milk and glibenclamide may be due to improved glycemic control and thereby control over free radical production and glycation of protein **Plate 1**.

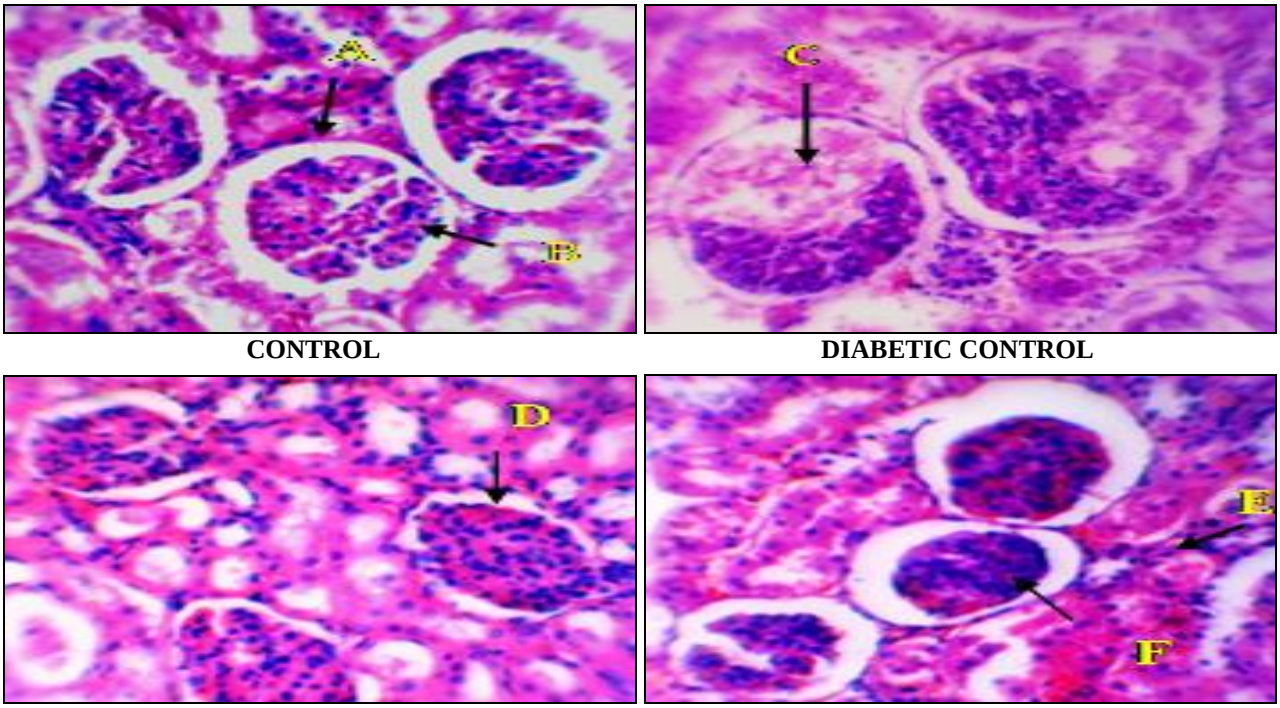


CONTROL **DIABETIC CONTROL**

GLIBENCLAMIDE TREATED RAT LIVER **MIXTURE OF C. N. & P. M. TREATED RAT LIVER**

PLATE 1: TOXIC EFFECT OF HERBAL DRUG ON HISTOARCHITECTURE OF LIVER

(A) Central vein, (B) Normal sinusoids, (C) Hepatic nuclei, (D) Cellular debris, (E) Degenerated hepatocytes, (F) Sinusoids, (G) Central vein, (H) Kupffer cells

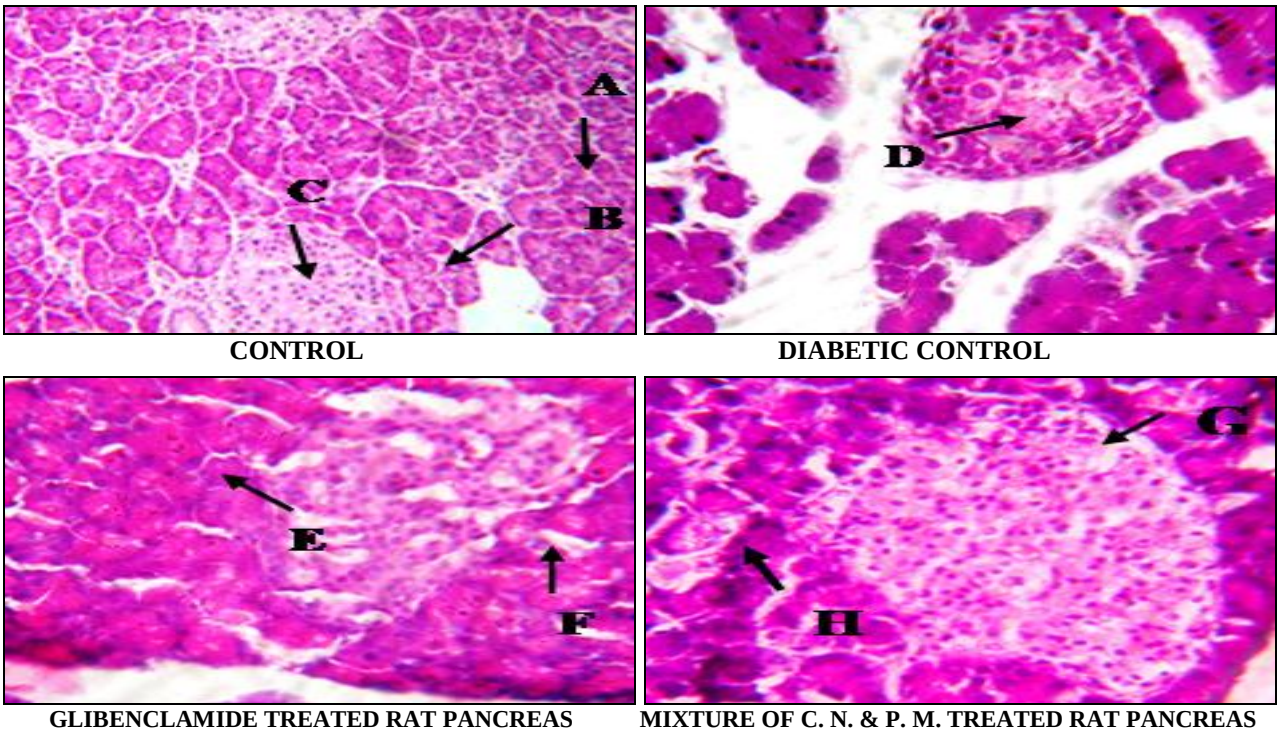


CONTROL **DIABETIC CONTROL**

GLIBENCLAMIDE TREATED RAT KIDNEY **MIXTURE OF C. N. & P. M. TREATED RAT KIDNEY**

PLATE 2: TOXIC EFFECT OF HERBAL DRUG ON HISTOARCHITECTURE OF KIDNEY

(A) Renal Corpuscle, (B) Bowman's Capsule, (C) Destruction of glomerular cells, (D) Distal Convoluted Tubule, (E) Dexta glomerular cells, (F) Mesangium



CONTROL **DIABETIC CONTROL**

GLIBENCLAMIDE TREATED RAT PANCREAS **MIXTURE OF C. N. & P. M. TREATED RAT PANCREAS**

PLATE 3: TOXIC EFFECT OF HERBAL DRUG ON HISTOARCHITECTURE OF PANCREAS

(A) Pancreatic duct, (B) Acinar cells, (C) Islets of Langerhans, (D) Dysfunction of islets of Langerhans, (E) Exocrine, (F) Endocrine, (G) Islets, (H) Intercalated duct

Histopathological studies of the kidney showed damaged tubules, lesions, and fatty infiltration in diabetic rats. The kidney of diabetic rats showed an increase in mesangial cell and matrix of glomeruli with an increase in glycogen deposition and hyalinization of arterioles with thickened basement membranes of proximal and distal convoluted tubules. Hyperglycemia and glycation of proteins

are the main causes for the damage occurred in diabetic rat's kidney. Moreover, the fatty acid composition also altered in diabetic conditions leading to increase severity of damages in kidney structure.

These results were well supported by the previous investigators [33]. Most of the tissue damage is caused by free radicals by attacking membranes through the peroxidation of unsaturated fatty acids [34]. Hyperglycaemia was responsible for the dilatation of proximal and distal tubules in the cortex [35]. The recovery of damages in the kidney of diabetic rats treated with mixture of *C. nilgiriensis* and *P. marsupium* and glibenclamide may be due to controlled free radical toxicity and prevention of disintegration of tissue membranes **Plate 2**.

Streptozotocin selectively destroys the pancreatic insulin-secreting beta cells [36]. The ultrastructure of the STZ diabetic pancreas showed considerable reduction in the islets of Langerhans and depleted islets. The diabetic rats showed pancreatic islet regeneration. The regenerative effect of the pancreatic cells by the mixture of *C. nilgiriensis* and *P. marsupium* was noted *in* **Plate 3**. The herbal mixture also proved its antidiabetic efficiency by restoring the tissue damages in the pancreas, liver, and kidney of diabetic rats.

CONCLUSION: The mixture of *C. nilgiriensis* and *P. marsupium* extract proves that it is one of the best promising and emerging drugs against diabetes mellitus. Thus the findings of the present study provide a base for designing new safe antidiabetic drugs.

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CONFLICTS OF INTEREST: Nil

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