



Research Article

BENEFICIAL EFFECT OF NISHAAKATHAKAADHI KASHAYAM ON STREPTOZOTOCIN INDUCED DIABETES AND GLUCOSE METABOLIC ENZYMES

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ABSTRACT

Polyherbal traditional formulation *Nishaakathakaadhi Kashayam* elicit antihyperglycemic effects in streptozotocin induced hyperglycemic rats. *Nishaakathakaadhi Kashayam* 0.6 ml/kg, p.o. significantly reduced the fasted blood glucose level after 60 days of treatment in diabetic rats. The *Kashayam* also reduced serum cholesterol, triglycerides, LDL, VLDL, alanine transaminase, aspartate transaminase, alkaline phosphatase and urea whereas increased HDL, albumin, protein and haemoglobin levels become normal after the treatment. Glycolytic enzyme showed a significant increases in Streptozotocin induced condition while a significant decrease were observed in levels of the gluconeogenic enzymes in *Nishaakathakaadhi Kashayam* treated diabetic rats. The *Kashayam* was non-significantly active with standard drug Glibenclamide (0.6 mg/kg, p.o.). The *Kashayam* has a positive effect on the histopathological changes of the pancreatic beta cells in Streptozotocin induced diabetic rats. The results suggest that *Nishaakathakaadhi Kashayam* possesses potential antihyperglycemic effect by regulating glucose homeostasis in streptozotocin induced diabetic rats. The scientific evidences to antidiabetic use suggest that administration of polyherbal formulation to rats, in a dosage used safely by humans, reduces the production of various diabetes causing biochemical parameters and concomitantly prevents the development of Type 2 (NIDDM) diabetes in established animal models. A combination of different herbs in NKK is used to get the enhanced desired activity.

KEYWORDS: *Nishaakathakaadhi Kashayam*, Diabetes mellitus, Streptozotocin, Rat, NKK.

INTRODUCTION

Diabetes mellitus (DM) is world's largest endocrine disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. In DM, gross abnormalities in glucose homeostasis, protein and lipid metabolism are observed. Decreased physical activity, increasing obesity, and changes in food consumption have been implicated in this epidemic. The World Health Organization predicts that the number of cases worldwide for diabetes is 250 million, 80% of people are living with diabetes and 5% of deaths are reported per year globally and this is likely to increase to 300 million or more by the year 2025^[1,2].

In many parts of the world, traditional medicinal plants have been used for the treatment of diabetes. Satisfactory treatment to most of the severe DM is not available in conventional medicine and continuous intake of conventional medicine produces severe side effects. However, many herbal medicines play a vital role in the management of diabetes mellitus. There are many plants and polyherbal formulations used in traditional systems of medicine such as Ayurveda and Siddha as well as in folklore medicine from time immemorial to treat diabetes mellitus. The pharmacological evaluation using experimental animals also showed some level of antihyperglycemic activities in most of the traditional

antihyperglycemic plants. In this study, antihyperglycemic effect of *Nishaakathakaadhi Kashayam* (NKK) was administered to Streptozotocin induced diabetic rats. *Nishaakathakaadhi Kashayam*, is a decoction popularly used in the treatment of pre-diabetes, diabetes and its complications. It is prepared by boiling coarse powders of rhizomes of *Curcuma longa*, root bark of *Salacia oblonga*, pericarp of *Emblia officinalis*, seeds of *Strychnos potatorum*, roots of *Ixora coccinea*, *Vetiveria zizanioides*, *Aerva lanata* and bark of *Symplocos racemosa*.

MATERIALS AND METHODS

Preparation of Kashayam

All eight raw materials were collected from Kerala Ayurveda, Athani and authenticated by the botanist from CARE Keralam Ltd. A voucher specimen is kept at the centre. The raw materials were air dried, pulverized, homogenized to fine powder and stored in airtight bottles. 100 g each of all eight coarsely powdered raw materials were mixed thoroughly with 12.8 liter of distilled water. This was boiled and reduced to 3.2 liter. Then the decoction was filtered and again reduced to 1.6 liter. The decoction was allowed to cool and kept in airtight bottle in refrigerator^[3].

Chemicals

Streptozotocin (STZ) was purchased from Sigma Aldrich chemical Co (St Louis, MO), USA. Commercial assay kits from Euro Diagnostic Ltd were used to measure the glucose, hepatic marker enzymes, bilirubin, total protein, albumin, urea, haemoglobin and lipid profiles.

Animals

Adult male albino Sprague Dawley rats, weighing 180-200 g were used. All animal experiments were approved by the Institutional Animal Ethics Committee, CARE Keralam Ltd and were maintained in accordance with the guidelines of the CPCSEA (1620/PO/c/12/CPCSEA). The animals were housed in polysulfonate individual ventilated cages in a room with a 12 h day-night cycle, temperature of $22 \pm 2^\circ\text{C}$ and humidity of 40-70%. During the experimental period, the animals were fed with a balanced commercial diet (Amrut animal feeds, Bangalore, India) [Composition of the diet: 5% fat, 21% protein, 55% nitrogen free extract and 4% fiber (w/w) with adequate mineral and vitamin contents) and water *ad-libitum*.

Induction of diabetes mellitus, followed by NKK treatment

Experimental animals received a freshly prepared solution of STZ (45 mg/kg) in 0.1 M citrate buffer, pH 4.5, injected i.p in a volume of 1 ml/kg. Normal rats received 1 ml citrate buffer as vehicle^[4,5]. Two days after STZ administration, rats showing moderate diabetes with glycosuria and hyperglycemia (i.e., blood glucose levels of 190-230 mg/dl) were used for the experiment. The animals were fasted overnight and blood samples were collected for blood glucose estimation.

The rats were divided into three groups after the induction of STZ, normal control group used non diabetic rats. In this experiment six rats were used in each group.

Group I : Normal Control (Vehicle treated) rats administrated single daily dose of vehicle for 60 days.

Group II : Diabetic control (Vehicle treated) rats administered single daily dose of vehicle for 60 days.

Group III : Diabetic rats administrated single daily dose of NKK (0.6 ml/kg p.o.) for 60 days.

Group IV : Diabetic rats administrated single daily dose Glibenclamide (0.6 mg/kg p.o.) for 60 days.

Blood samples were drawn at ten days intervals till the end of the experimental period. At the end of the study, all rats were sacrificed by decapitation (euthanasia). Blood samples were collected and serum separated from the blood by centrifugation. Pancreas and liver were dissected, washed in ice-cold saline for biochemical analysis and histopathology.

Biochemical estimation of enzyme activities

Hexokinase activity was assayed by the method of Brandstrup et al.^[6], Glucose-6-phosphatase was assayed according to the method of Koida and Oda^[7] and Fructose-1,6-bisphosphatase was assayed by the method of Gancedo and Gancedo^[8].

Statistical analysis

All data were expressed as mean \pm SD. The statistical significance was evaluated by one-way ANOVA using SPSS version 12 (SPSS, Cary, NC, USA) and the individual comparison were obtained by Duncan's Multiple Range Test (DMRT). A value of $p < 0.05$ was considered to indicate a significant difference between groups. Values sharing a common superscript do not differ significantly with each other at $p < 0.05$.

RESULTS AND DISCUSSION

Table 1 shows beginning to end the fasting blood glucose concentration of normal control rats was 86.2 ± 6.1 to 89.0 ± 10.6 mg/dl. In the present study, Streptozotocin induced rats showed significant increase in blood glucose level and a single dose of Streptozotocin in rates exhibited characteristic signs of diabetic. NKK significantly reduced the blood glucose level from 221.7 ± 18.8 to 118.0 ± 5.6 on 60 days treatment period. Glibenclamide treated group and NKK treated group showed no significant difference between the groups.

Table 1. Effect of NKK in blood glucose level changes in STZ induced Diabetic rats

Groups	Initial Glucose (mg/dl)	10 th day (mg/dl)	20 th day (mg/dl)	30 th day (mg/dl)	40 th day (mg/dl)	50 th day (mg/dl)	61 st day (mg/dl)
Normal control	86.2 ± 6.1^a	91.3 ± 8.8^a	98.6 ± 14.4^a	98.7 ± 11.9^a	99.2 ± 11.8^a	91.4 ± 5.1^a	89.0 ± 10.6^a
Diabetic control	214.3 ± 28.2^b	216.4 ± 20.6^b	212.3 ± 18.2^b	220.4 ± 16.0^b	216.0 ± 21.2^b	220.9 ± 8.6^b	215.4 ± 4.3^b
NKK	221.7 ± 18.8^b	147.8 ± 15.1^c	129.8 ± 18.2^c	123.0 ± 9.6^c	124.2 ± 6.2^c	118.4 ± 7.2^c	118.0 ± 5.6^c
Glibenclamide	190.7 ± 18.5^b	139.4 ± 14.6^c	137.5 ± 11.4^c	120.6 ± 15.3^c	115.2 ± 12.1^c	104.6 ± 11.3^{ac}	102.4 ± 6.1^{ac}

NKK – Nishaakathakaadhi Kashayam

Values are mean \pm SD for 6 rats in each group. ^{a-c} In each column, means with different superscript letter differ significantly at $p < 0.05$ (DMRT).

The table 2 shows the level of serum lipid profiles in normal and treated rats. The levels of triglycerides (TG)

and total cholesterol (TC) were significantly increased in diabetic control rats. Administration of NKK and Glibenclamide for 60 days to diabetic rats decreased the TG and TC levels. The effect of NKK was predominant than that of Glibenclamide.

Table 2. Effect of NKK in serum lipid profiles level changes in STZ induced diabetic rats

Groups	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal control	78.1±9.5 ^a	43.8±7.8 ^a	37.7±4.6 ^a	31.5±5.6 ^a	8.8±3.6 ^a
Diabetic control	120.7±11.1 ^b	51.9±5.8 ^b	26.5±6.4 ^b	83.9±6.8 ^b	10.4±1.2 ^b
NKK	78.3±5.0 ^a	38.9±5.9 ^a	34.7±10.7 ^a	35.2±3.2 ^a	7.8±2.0 ^a
Glibenclamide	80.0±3.2 ^a	50.6±5.4 ^b	35.2±10.0 ^a	34.1±3.5 ^a	10.1±1.1 ^b

NKK – Nishaakathakaadhi Kashayam.

Values are mean ± SD for 6 rats in each group. ^{a-b} In each column, means with different superscript letter differ significantly at p<0.05 (DMRT).

The effects of administering NKK to diabetic rats on serum enzymes aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) are given in Table 3. STZ administration increased liver function biomarkers such as ALP, AST and ALP significantly in comparison with normal control rats. The activities of serum enzymes like AST (125.4±9.7), ALT (66.6±7.6) and ALP (223.7±20.7) were significantly increased in the diabetic rats when compared to those of normal control rats. But the activities of serum AST (97.5±7.1), ALT (52.7±8.8) and ALP (194.4±12.7) were significantly decreased in diabetic rats treated with NKK when compared to those of diabetic rats. In addition, the administration of Glibenclamide at the dose of 0.6 mg/kg b.w. also significantly reduced AST, ALT and ALP activities in serum of diabetic rats.

Table 3: Effect of NKK in serum liver marker enzymes, protein, albumin, hemoglobin and urea level changes in STZ induced Diabetic rats

Groups	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Albumin (g/dl)	Protein (g/dl)	Urea (mg/dl)	Hb (g/dl)
Normal control	100.1±12.5 ^a	58.6±7.7 ^a	182.6±17.7 ^a	3.1±0.5 ^a	5.1±1.1 ^a	37.0±5.4 ^a	15.5±2.0 ^a
Diabetic control	125.4±9.7 ^b	66.6±7.6 ^b	223.7±20.7 ^b	2.1±0.3 ^b	4.0±0.7 ^b	44.7±5.1 ^b	6.4±0.5 ^b
NKK	97.5±7.1 ^a	52.7±8.8 ^a	194.4±12.7 ^a	3.9±0.4 ^c	5.6±1.0 ^a	32.6±6.9 ^{a,c}	13.4±0.9 ^a
Glibenclamide	106.8±11.9 ^a	56.7±10.8 ^a	193.4±18.0 ^a	4.0±0.1 ^c	5.7±0.3 ^a	29.6±3.4 ^c	14.2±0.4 ^a

NKK – Nishaakathakaadhi Kashayam.

Values are mean ± SD for 6 rats in each group. ^{a-c} In each column, means with different superscript letter differ significantly at p<0.05 (DMRT).

The serum albumin, protein and urea levels are increased whereas haemoglobin level decreased in STZ induced diabetic control animals. NKK (0.6 ml/kg) 60 days treated in diabetic rats to normalise serum albumin, protein, urea and haemoglobin near to normal level. The Glibenclamide and NKK group rats no significantly differ between the groups.

There is significant difference in the body weight, food and water intake of DM with that of NKK. Hence it is concluded that NKK is having efficacy in regulating the bodyweight. Animals maintained a remarkable, stable body weight (Fig. 1).

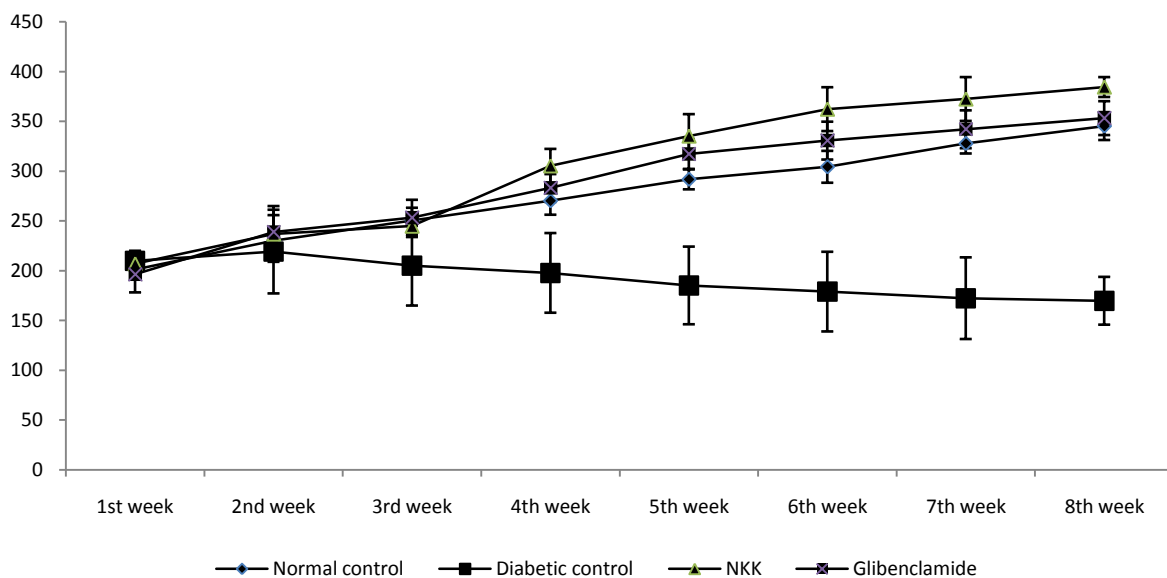


Fig.1: Effect of NKK in body weight changes in STZ induced diabetic rats

Table 4 depicts the activities of carbohydrate metabolizing enzymes in liver of normal and treated rats. The activities of enzyme hexokinase was significantly decreased whereas the activities of gluconeogenic enzymes: glucose-6-phosphatase and fructose-1,6- biphosphatase were significantly increased in diabetic control rats. NKK administration to diabetic rats reversed the above changes in a significant manner when compared to diabetic control rats. Histopathological evaluation of rat pancreas by H and E staining showed pancreas with normal acini and also many islet cell clusters in control groups, acinar cells in clusters surrounded by fat globules diabetic group and NKK group and glibenclamide group showed pancreatic acinar cells with normal morphology separated by fat lobules (Fig. 2).

Table 4. Effect of NKK in liver glucose metabolic enzymes level changes in STZ induced Diabetic rats

Groups	fru-1,6 bi p ase (Units ¹ / mg protein)	Glu 6 p ase (Units ² / mg protein)	Hexokinase (Units ³ /g protein)
Normal control	0.2±0.05 ^a	0.15±0.01 ^a	141.3±3.1 ^a
Diabetic control	0.5±0.04 ^b	0.27±0.02 ^b	105.5±9.2 ^b
NKK	0.23±0.03 ^a	0.17±0.03 ^a	136.2±8.3 ^a
Glibenclamide	0.25±0.01 ^a	0.16±0.01 ^a	138.8±7.4 ^a

NKK – Nishaakathakaadhi Kashayam

Values are mean ± SD for 6 rats in each group. ^{a-b} In each column, means with different superscript letter differ significantly at p<0.05 (DMRT)

Unit ¹µmoles of inorganic phosphorus liberated/hour/mg protein

Unit ²µmoles of inorganic phosphorus liberated/min/mg protein

Unit ³µmoles of glucose phosphorylated/min/g protein

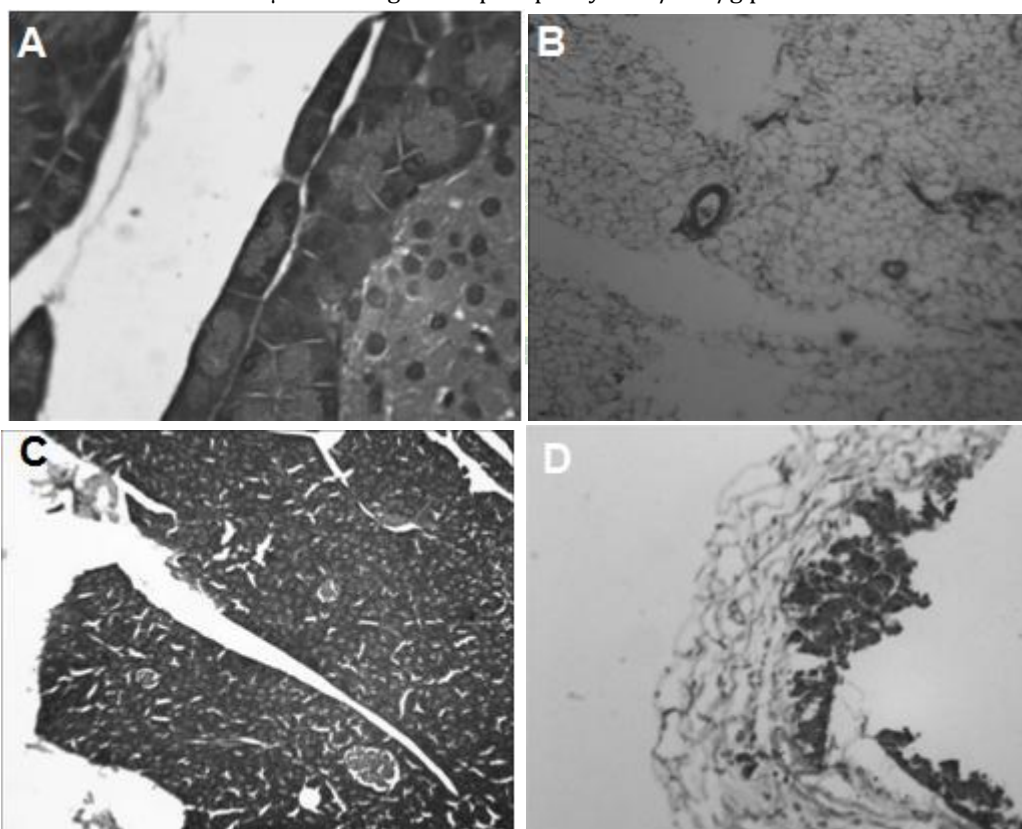


Fig. 2: Histology of pancreatic sections stained with haematoxylin and eosin (A) Normal rat pancreas section shows pancreas with normal acini & also many islet cell clusters; (B) Diabetic rat pancreas section shows fat lobules, islet cells are shrinkage & few congested vessels; (C) NKK group pancreas section shows pancreatic tissue with normal acini and lobules of mature adipocytes are seen; (D) Glibenclamide group pancreas section shows pancreatic acinar cells in clusters surrounded by fat globules.

Diabetes mellitus (Type II) comprises a heterogeneous group of hyperglycemic disorders characterized by loss of glucose homeostasis and disturbances of carbohydrate and lipid metabolism. Patients with diabetes are at increased risk of atherosclerosis and its clinical effects: coronary, renal, peripheral vascular and cerebrovascular diseases. Concurrently, the most common cause of death in persons with diabetes is myocardial infarction. The pathogenesis, progression and epidemiology of atherosclerotic disease

are distinct in patients with diabetes. Several therapeutic agents are used for solving this problem. Streptozotocin is a frequently used drug that exerts a diabetogenic effect through a specific damage of the pancreatic Beta-cells, mimicking type 1 diabetes mellitus [9,10]. Blood glucose needs to be individually tailored as part of a comprehensive cardiovascular risk management strategy. Chronic administration of NKK to STZ-induced diabetic rats showed significant and consistent decrease in fasting blood glucose levels at different time intervals throughout the period of study as compared to the vehicle treated diabetic controls, indicating its potent antidiabetic activity.

Since lipid abnormalities accompanied by premature atherosclerosis are the major cause of cardiovascular diseases in diabetic patients ideal treatment should have a effect on lipid profile. Cardiovascular diseases are listed as the cause of death in 65% people suffering from diabetes[11]. NKK not only lowered the TC, TG, VLDL and LDL levels but also enhanced the cardio protective lipid HDL in diabetic rats, after 60 days of treatment. Several studies have shown that an increase in HDL-cholesterol is associated with a decrease in coronary risk[12] and most of the drugs that decrease total cholesterol also decrease HDL cholesterol[13]. In the present study NKK not only decreased the total cholesterol but also enhanced HDL-cholesterol significantly.

In the present study the activities of AST, ALT and ALP in serum were altered in diabetic animals. The changes in the levels of AST, ALT and ALP are directly related to changes in metabolism in which the enzymes are involved. The increased activities of transaminases, which are active in the absence of insulin due to the availability of amino acids in the blood of demand, are also responsible for the increased gluconeogenesis and ketogenesis[14]. AST and ALT levels also act as an indicator of liver function. Hence restoration of normal level of these enzymes indicates the normal functioning of liver. Increased activities of serum ALP have been observed in STZ diabetic rats. STZ treated diabetes caused lipid peroxide mediated tissue damage in the pancreas, liver, kidney, and heart. The increase in the levels of these enzymes in diabetes may be as a result of the leaking out from the tissues and then migrating into the blood stream. Diabetes and hyperlipidaemia also cause cell damage by altering the cell membrane architecture, which results in enhanced activity of ALP in diabetic rats. The cell damage might be reverted NKK and glibenclamide treated groups and this may leads to the decreased activity of ALT, AST and ALP. Therefore, the present study clearly indicates that NKK possess hypoglycaemic and hypolipidaemic activities in STZ induced diabetic rats.

Polyphagia, polydipsia, polyuria, increased water intake and weight loss are established classical symptoms and signs of diabetes mellitus. The decrease in body weight in diabetic rats clearly showed a loss or degradation of structural proteins. Individuals with untreated diabetes mellitus also experience significant weight loss due to the inability of cells to utilize glucose for energy production.

Hexokinase is the prime enzyme catalysing glucose phosphorylation. Impairment of hexokinase activity suggests the impaired oxidation of glucose via glycolysis leading to its accumulation resulting in hyperglycemia. Insulin influences the intracellular utilization of glucose in a number of ways. Insulin increases hepatic glycolysis by increasing the activity and amount of several key enzymes including glucokinase and phosphofructokinase[15]. Hexokinase is universally present in cells of all types. Hexokinase catalyses the conversion of glucose to glucose 6-phosphate and plays a central role in the maintenance of glucose homeostasis[16-18]. In our present study hexokinase activity was decreased in diabetic control rats. Decrease in hepatic hexokinase has been reported in STZ diabetic rats. Administration of NKK to diabetic rats enhanced the hexokinase activity and suggests greater uptake of glucose from blood by liver cells and increased glycolysis. In addition, NKK may regulate the activity of hexokinase by maintaining the critical levels of glucose-6-phosphate needed to be catabolized to produce ATP and NAD.

Activation of gluconeogenic enzymes is due to state of insulin deficiency since under normal condition insulin functions as a suppressor of gluconeogenic enzymes. Administration of NKK significantly depressed the activities of gluconeogenic enzymes in diabetic rats. The effect of NKK may be primarily modulating and regulating the activities of the two gluconeogenic enzymes, either through regulation of cAMP or any other metabolite activation/inhibition of glycolysis/gluconeogenesis. The reduction in the activities of gluconeogenic enzymes can result in the decreased concentration of glucose in blood[19,20].

CONCLUSION

The findings provide scientific evidences to antidiabetic use of a traditional formulation and suggest that administration of polyherbal formulation to rats, in a dosage used safely by humans, reduces the production of various diabetes causing biochemical parameters and concomitantly prevents the development of Type 2 (NIDDM) diabetes in established animal models.

A combination of different herbals in NKK is used to get the enhanced desired activity and eliminate unwanted side effects. In the present study, NKK produced significant antidiabetic activity in experimental animals and is also effective in case of glucose metabolic enzymes. Hence NKK can be effectively used in the treatment of diabetes mellitus. However the studies on diabetic patients are under progress to establish its effectiveness in human volunteers.

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