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EVALUATION OF PROPHYLACTIC EFFECT OF HERBAL FORMULATION IN STREPTOZOTOCIN AND HFHF DIET INDUCED DIABETES AND ITS COMPLICATION

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ABSTRACT

Nishamalaki (NA), combination formulation of Curcuma longa and Emblica officinalis effective in diabetes as per Ayurvedic literature. We assessed the time required for development of diabetes and its complication with Streptozotocin (STZ) & High Fat High Fructose (HFHF) diabetic model. Objective was to evaluate NA for prophylactic, therapeutic efficacy and effectiveness in diabetic complication in rats. Diabetes induced in rats with STZ 35mg/kg i.p. + Followed by HFHF Diet till the development of Diabetes. Part I-Nishamalaki started with STZ, in (N= 25) of either sex compared with control rats. Part II- 30 Diabetic rats of either sex, randomly allocated to different groups (n=6), six rats allocated to control group with no diabetes and vehicle treatment. Groups I- vehicle, II- Diabetic Control, III-Nishamalaki (0.9 gm/kg), IV-Nishamalaki (1.8 gm/kg), V-Glibenclamide, VI- Pioglitazone and treated for 8 wks. Body weight, Blood sugar (BSL) & Lipid profile measured. Observed for complications for further 8 months. Statistical Analysis done with ANOVA. Persistent increased levels of BSL obtained in14 days. Nishamalaki achieved Significant ($p<0.01$) lowering of blood glucose and reduced serum cholesterol, triglycerides and LDL compared to diabetic control. Significant reduction in BSL observed in NA-LD ($p<0.05$) & Glibenclamide ($p<0.01$). Results of NA-HD were comparable to Pioglitazone. Serum Cholesterol levels significantly decreased in NA-LD ($p< 0.001$) & NA-HD ($p< 0.01$) than diabetic control. NA-LD, Glibenclamide & Pioglitazone were equal in reducing triglycerides ($p< 0.01$). HDL levels increased with NA-HD ($p<0.001$). Nishamalaki has major prophylactic value & Corrected lipid imbalance. Nishamalaki delayed development & progression of cataract, nephropathy & neuropathy.

KEYWORDS: *Curcuma longa, Emblica officinalis, Lipid profile, Blood sugar, Prophylactic*

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INTRODUCTION

During the last twenty years the prevalence of diabetes has increased dramatically in many parts of the world. Type II diabetes mellitus (T2DM) is a fast-growing epidemic affecting people globally.[1] Type II diabetes is the most common type, which is often resulting from excess body weight, physical inactivity and insulin resistance. India is expected to be world diabetes capital as Indians have genetic predisposition and further precipitated by life style.[2] Increased incidence of diabetes in young age, leads to a serious increase in morbidity. It also increases health care costs and reduces productivity.3 Over a due course of time diabetes can cause complications like blindness, kidney damage, neurological problems and coronary artery disease. In spite of availability of various advanced drugs, prevention of complication is still a challenge.Only way available to postpone the occurrence of complication is the better control of hyperglycemia. Although diabetes cannot be cured, the disease can be managed by non-pharmacological and pharmacological strategies. Improvements in glycemic control is an important factors in delaying the onset and progression of diabetes-related complications.[4]Intense lifestyle modifications like exercise, meditation, dietary modifications etc. are the mainstay of all treatment modalities. They should be encouraged in both populations who are at risk for developing diabetes and patients who are suffering from diabetes.[5] Primary non-pharmacological interventions include appropriate diet and exercise. Diabetes prevention has become a key target for clinicians, patients and policymakers as substantial evidence has accumulated that diabetes can be prevented or delayed if targeted early.[6] Not a single drug is available to prevent or delays occurrence of diabetes and its complications. Herbal preparations are claimed to be more effective in delaying the development of diabetes.[7] Nishamalaki is mentioned in the ancient literature for the diabetes.[8] The combination of Curcuma longa and Emblica officinalis taken early in the morning is beneficial in the diabetes[9] In practice of Ayurveda, Nishamalaki [NA] is used for starting the treatment of diabetes. Various drugs are added according to the disease progression. In our pilot study we observed NA has moderate antidiabetic activity which was comparable to the pioglitazone. Present study was undertaken particularly focusing on the prophylactic aspect of Nishamalaki in Streptozotocin and High Fat and High Fructose HFHF diet induced diabetic Rat model.

MATERIAL & METHODS

Animals

Wistar rats of either sex weighing 150-200 g were included in study. Animal coding was done according to standard protocol. Housing was done in standard cage (3 to 4 animals per cage) as per CPCSEA guidelines.

Chemicals

Inj. Streptozotocin (STZ) in powder form (Sigma-Aldrich, USA) was purchased from Sigma- Aldrich, USA.Nishamalaki was obtained from Bharati Vidyapeeth Ayurved College and hospital, Pune. It was authenticated by the Department of Rasashastra & Bhaishajya Kalpana Vigyan, Bharati Vidyapeeth college of Ayurveda, Pune. Other medicines Glibenclamide (Sanofi-Synthelabo) Pioglitazone (Ranbaxy) were obtained from local pharmacy.

Methods

Induction of diabetes in rats [10]

Streptozotocin (STZ) dissolved in citrate buffer (0.01M, pH 4.5) was given to all rats in the dose of 35 mg/kgas an intra-peritoneal injection. It was followed by high fat, high fructose diet. High fat diet was prepared by soaking pellets in the mixture of Coconut oil and Vanaspati ghee in the proportion of 2:3 overnight, before use. Fructose (10%) was given in drinking water.[11]

Part I

Nishamalaki started with STZ to 25 rats of either sex compared with control rats.

Group 1-25 rats from Prophylactic group treated with NA after STZ injection and continued till 12th wk.

Group 2-30 Rats did not receive NA saline treated.

The Rats were anaesthetized using ketamine 100mg/kg IP and blood samples were collected by retro-orbital technique.Slight pressure with a piece of gauze on the eyeball was applied to prevent further bleeding approximately for 30 seconds. The animal was placed back into the cage only when bleeding completely stopped. Blood sugar level (BSL) was measured 12 hourly, till the development of diabetes with Accu-check active strips, i.e. till BSL rose above 250mg% and fortnightly with Glucose Oxidase Peroxidase GOD & POD method. Rats of both the groups were observed for development of diabetes i.e. increase in the blood sugar >250 mg/dl was considered as diabetes mellitus. Persistent rise was observed on14th day in control group. Body weights, BSL, Lipid profile measured in all the rats of both the groups and compared.

Part II

Once diabetes developed, 30 Diabetic rats from the group 2 were further randomly allocated to different experimental groups (n=6)

Group I-No diabetes & vehicle treatment

Group II- Diabetic Control & vehicle treatment

Group III-Nishamalaki (low dose 0.9 gm/kg)

Group IV-Nishamalaki (high dose 1.8 gm/kg)

Group V-Glibenclamide (5mg/kg)

Group VI- Pioglitazone (2.7 mg/kg) &

All the animals treated according to groups for 8 wks.

Parameter studied- Body weight, Blood sugar & Lipid profile

All the animals were observed for the development of complications. Cataract development was assessed with the visual scale and grading was done as follows.

Stages of Cataract[12]

Stage 0 - Clear lens

Stage 1 -Faint peripheral opacity

Stage 2 -Irregular peripheral opacity with slight involvement of the centre of the lens

Stage 3 - Dense nuclear opacity

Stage 4 - A mature cataract

Blood urea nitrogen (BUN) & Creatinine was measured to assess the kidney status.Sensory & Motor component

was assessed with hot plate[13] and walking function test.[14] (Figure -1)

Statistical analysis done with graph pad prism-6, ANOVA followed by Dunnetts' and Tukey's multiple comparison test was used. P < 0.05 was considered as statically significant.

STATISTICAL ANALYSIS

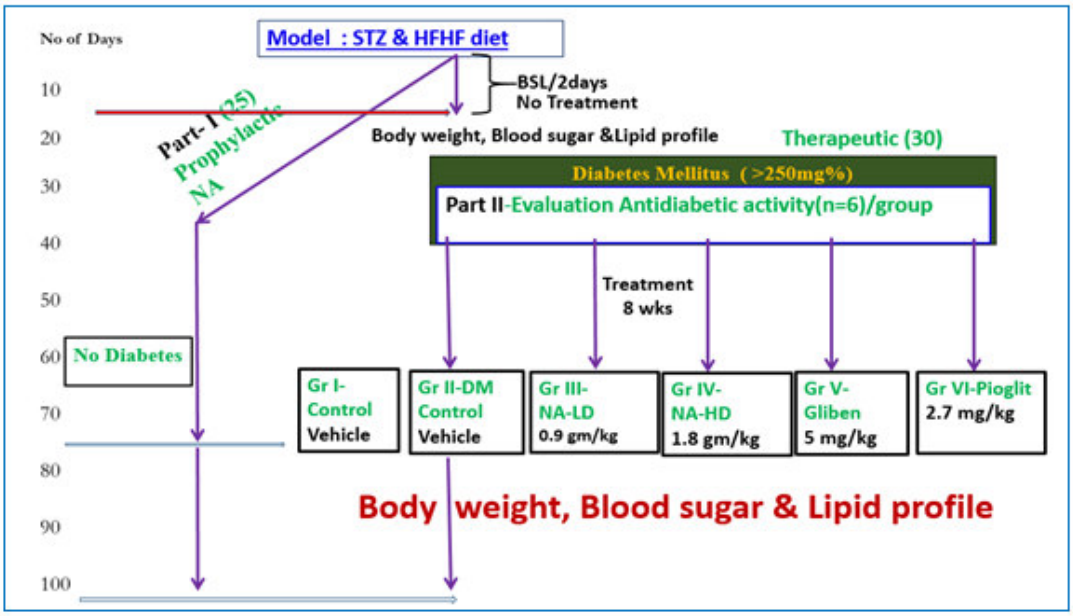
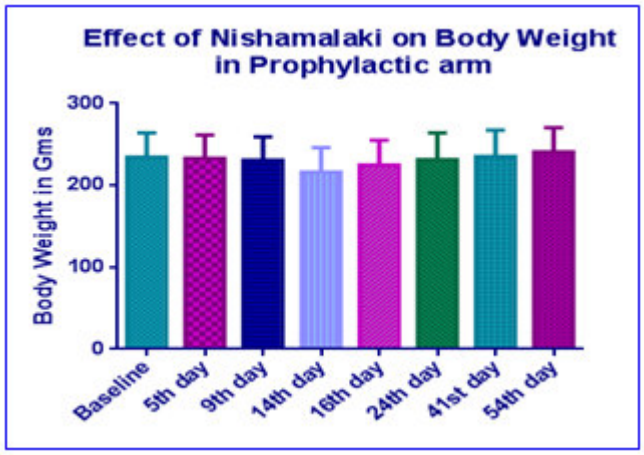


Figure 1
Methodology flow chart

RESULTS

Prophylactic Arm On day 14
Effect of Nishamalaki on body weight in prophylactic arm

Body weight measured throughout the study. On day 14 there was no significant change in body weight. Slight downward trend in body weight was observed towards day 14 but onwards they started again gaining normal weight from all the groups. (Graph-1)

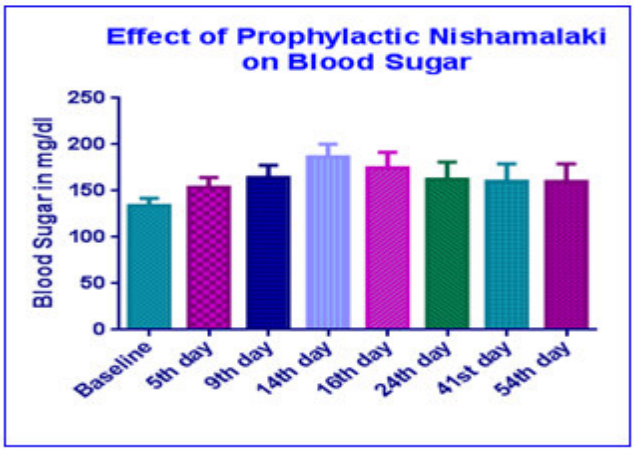


Values expressed as Mean ± SEM . ANOVA followed by Dunnetts' test was used to compare the body weights on study days with baseline readings.

Graph 1
Effect of Prophylactic NA on Body Weight after injection of STZ followed by oral treatment of Nishamalaki

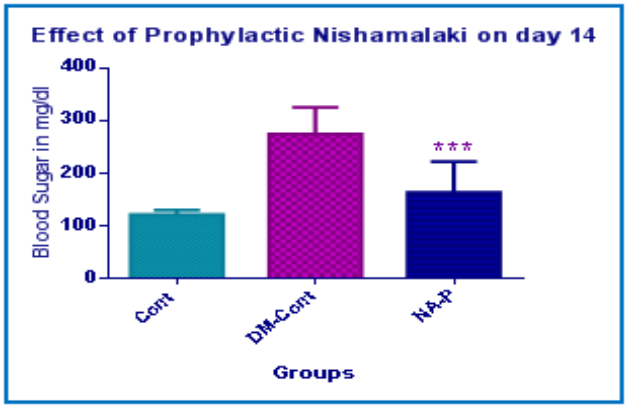
Effect of Nishamalaki on blood Sugar in prophylactic arm

Increase in BSL in prophylactic group (<180mg/dl) was also seen but not reached to level to label them as diabetic (>250mg/dl). (Graph-2) Significant increase in control arm (>250mg/dl) in comparison with prophylactic group and remained persistent. When comparison between Prophylactic & control was done there was statistically significant (p<0.01) difference observed.(Graph-3)



Values expressed as Mean ± SEM . ANOVA followed by Dunnetts' test was used to compare the BSL levels on study days with baseline readings.

Graph 2
Effect of NA on BSL levels after injection of STZ followed by oral treatment of Nishamalaki



*Values expressed as Mean ± SEM, ***p<0.001 in comparison with DM-control group*

Graph 3
BSL on day 14th of treatment

Effect of Nishamalaki on Lipid profile in prophylactic arm

There was increase in cholesterol, LDL and triglyceride level and reduction in HDL level in diabetic control group.In NA prophylactic group, HDL level was increased and TG level was significantly reduced (p<0.001) in comparison to DM control. Down trend was also seen in Cholesterol and LDL levels in Nishamalaki treated group but was not significant. (Table-1)

Table 1
Effect of NA Lipid levels on day 14th of treatment

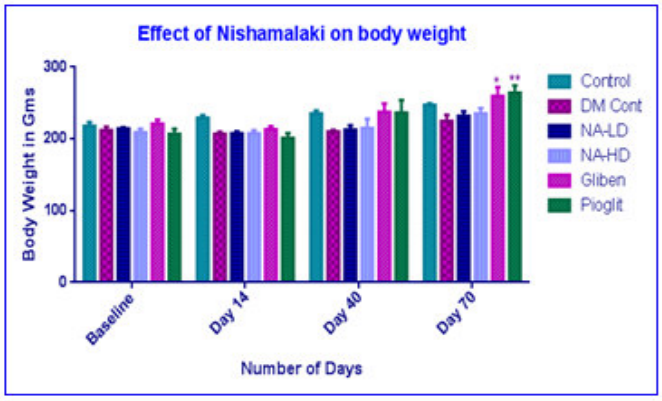
Lipids	Prophylactic	DM Control
CH	49.58±2.83	64.38±6.01
LDL	7.17±1.94	12.11±3.42
TGs	60.79±5.49	117.45±7.96***
HDL	45.01±1.60	25.81±6.53*

*Values expressed as Mean ± SEM, *p<0.05, ***p<0.001 in comparison with Prophylactic group*

Therapeutic Arm

Effect of Nishamalaki on body weight in Therapeutic arm

Weight gain started gradually in Glibenclamide& Pioglitazone group from day 40.In other groups weight gain was slow. On day 70 there was a significant increase in Glibenclamide& Pioglitazone group was observed in comparison with other drug treated groups.Nishamalaki in both doses showed slow weight gain. (Graph-4)

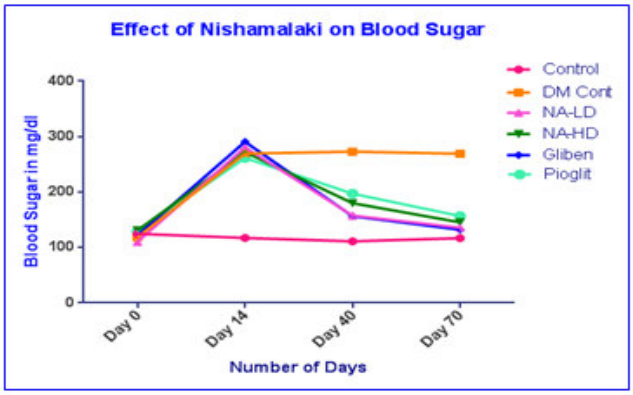


*Values expressed as Mean ± SEM,*p<0.05,**p<0.01 in comparison with NA-HD*

Graph 4
Effect of therapeutic NA on Body Weight

Effect of Nishamalaki on blood Sugar in Therapeutic arm

BSL increased gradually in all STZ & HFHF treated groups and persistent increase in BSL was obtained by 14th day. Throughout the study, gradual and continuous reduction in BSL was seen in all drug treated groups. Reduction in BSL was more with glibenclamide group followed by NA- low dose, NA- high dose and pioglitazone groups Glibenclamide > NA-LD > NA-HD > Pioglitazone Results of NA-HD were comparable to Pioglitazone. In DM control group there was no reduction in the BSL levels throughout the study. (Graph-5)



Cont-Control, DM cont- Diabetes Mellitus control, NA-LD: NA low dose, NA-HD: NA high dose, Glib- glibenclamide, Piog- pioglitazone

Graph 5
Effect of therapeutic NA on Blood sugar levels.

Effect of Nishamalaki on Lipid profile in Therapeutic arm

Lipid levels were significantly raised in DM control group. Serum Cholesterol levels significantly decreased in NA-LD (p< 0.001) & NA-HD (p< 0.01) in comparison to diabetic control. NA-LD, Glibenclamide & Pioglitazone were equi-effective in reducing triglycerides (p< 0.01) . NA-LD was more effective in reducing cholesterol and TG levels than NA-HD.Significant increase (p<0.001) in HDL was seen only in NA-HD group. (Table-2)

Table 2
Effect of NA on Lipid profile

	Control	DM-Control	NA-LD	NA-HD	Glibencl--amide	Pioglit-azone
CH	59.37±1.39	76.64±5.30$$$	26.96±1.31***	49.66±8.93**	64.32±2.47	60.98±5.79
LDL	5.40±0.77	16.91±1.37$$	12.65±3.50	6.10±2.90	16.61±3.26	15.30±4.77
TGs	78.41±3.30	96.56±3.87$	61.42±14.11**	97.65±15.06	51.19±5.04**	51.13±6.84**
HDL	38.28±1.15	29.84±2.11	39.06±2.74	56.62±4.32***	38.45±4.46	37.80±1.99

*Values expressed as Mean ± SEM, $p<0.05, $$p<0.01, $$$p<0.001 in comparison with control &**p<0.01, ***p<0.001 comparison with DM-Control group*

Complications

Cataract

Cataract developed in all animals of diabetic control group of grade III & IV. No cataract was developed in prophylactic group and in NA group it was developed only in 2 rats of grade I in 8 wks. Glibenclamide & Pioglitazone showed similar effect like NA on development cataract.

Nephropathy

No increase in BUN & Creatinine levels was observed in prophylactic group. In DM control group in increase BUN & creatinine level were increased significantly in comparison with NA prophylactic.

Neuropathy

No neurological derangement was seen in Prophylactic group, sensory & motor components were normal. Variable range of neurological deficit was observed in all animals of DM control and other drug treated groups. (Figure-2)

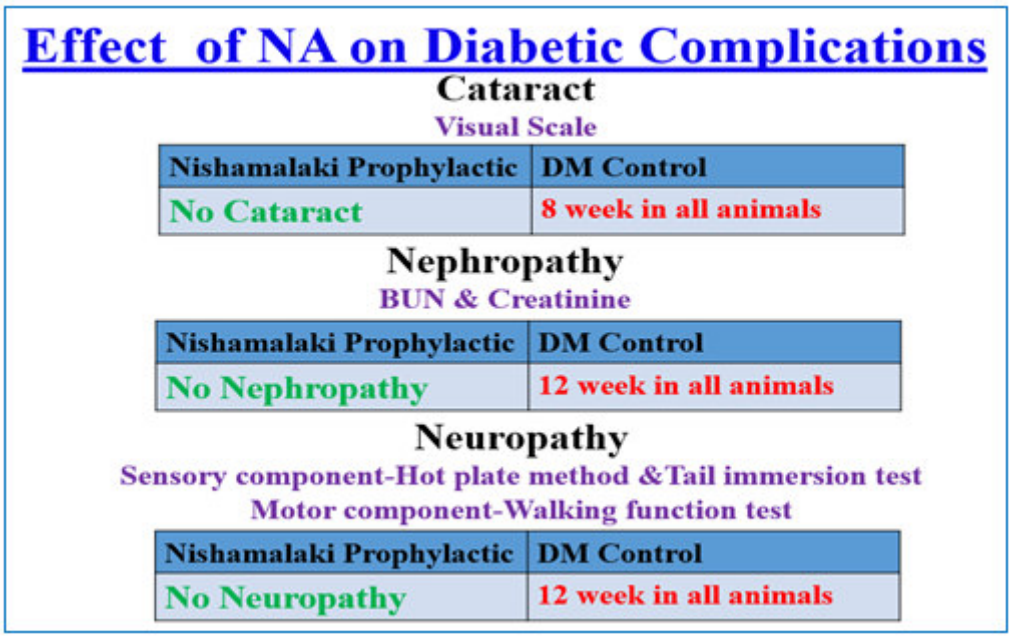


Figure 2
Effect of NA on Diabetic Complications

DISCUSSION

The exact pathophysiology of Type II Diabetes mellitus is not known but there is abnormal insulin secretion &/or increased peripheral resistance have been observed. Impaired insulin secretion and insulin resistance contribute more or less jointly to the development of pathophysiological conditions. What causes insulin resistance is not exactly known. Insulin resistance at liver leads to gluconeogenesis with increase in fasting[15] and also post meal [16] glucose level. Resistance to insulin in the muscle impairs disposal of glucose.[17] The additional pathology is in insulin signal transduction. Routinely, insulin mediates its actions by phosphorylation of tyrosine residue of insulin receptor substrate 1 leading to increased uptake of glucose and other actions including nitric oxide synthesis leading to vasodilatation. It also stimulates mitogen activated protein (MAP) kinase which causes inflammation and atherosclerosis. In insulin resistance, tyrosine phosphorylation reduces, but MAP still is sensitive. So, inflammatory action MAP increases. Fat cells are shown to play crucial role in the pathogenesis of type II diabetes[18] . With insulin resistance, there is increase in lipolysis in the fat tissue to increase free fatty acids (FFA). FFAs get into the circulation and get deposited in many tissues causing lipotoxicity and this is proposed to be the cause of insulin resistance like that of liver, muscle, β cells of pancreas etc. Resistance at adipose tissue causes dysfunction of fat cells leading to inflammation and atherosclerosis. In view of this pathogenesis of insulin resistance and the fact that resistance is first to occur even before the frank diabetes, managing insulin resistance would be effective in the treatment of diabetes and mainly for its prevention. Metformin and thiazolidinediones are the drugs useful in combating resistance. Metformin acts mainly on the liver and to some extent on the muscle by AMPK activation. But it does not act on the pancreas to preserve β cells. Glitazones on the other hand, have excellent action on adipose tissue; has potent action on muscle and liver and importantly, preserve β cell functioning. Glitazones are also reported to reduce the progression if IGT to frank diabetes. At present life style modification is the only non-pharmacological way available to delay the occurrence of the diabetes. Ayurveda emphasized that the first and foremost principle of prevention as well as the treatment of any disease is avoidance of causative factors. Many preparations claimed to be effective for prevention of various diseases[19] Nishamalaki started after the diagnosis of diabetes and later on many different drugs are added according to the progress of the disease.[8] In present study STZ-HFHF model was used, STZ causes β cell death, is used in low dose to keep damage less to the cells and HFHF high fat diet was given to derange

lipid & glucose homeostasis. Adipose dysfunction leads to release of TNFα and other cytokines leading to insulin resistance, impairment in TG storage, and lipolysis resulted in increase in free fatty acids (FFAs) i.e. inflammatory state in adipocytes.[20]The standard comparator Glibenclamide and Pioglitazone was used. Glibenclamide is a Sulfonylurea, which act by increasing insulin secretion & peripheral glucose uptake. While Pioglitazone is a Thiazolidinedione acts as PPARγ agonist by reducing insulin resistance, increasing glucose uptake & triglyceride without much change in LDL also it has anti-oxidant effect.But has limited clinical utility due to hepatic and cardiac adverse drug reactions.[21]Nishamalaki is a combination of Curcuma & Emblica. Both the ingredients has antioxidant activity. Curcuma has been proved to have PPARγ agonist action by which it reduces insulin resistance, increase insulin release & reduce FFA.[22] Emblica increase insulin release [23] & Inhibition of α glucosidase and amylas [24]In the preparation number of carbon double bonds were more than the market preparation showing enhanced antioxidant action. Antioxidant and antidiabetic properties of Emblica recently have been attributed to the tannoid complexes.[25]*Emblica officinalis* also has hypolipidemic activity in combination with curcuma longa, it was found to be effective in the long term treatment of diabetes.[26]Streptozotocin (STZ) is a toxic glucose and N-acetyl glucosamine (GlcNAc) analogue that is accumulated preferentially in pancreatic β-cells via GLUT 2 transporter uptake. Accumulated STZ produces free radicals which damages DNA of β cells of Pancreas, leading to reduced number of β cells.

STZ→ Free radicals →DNA break →PARP activation →NAD depletion →Necrotic cell death.[27]

In Diabetes mellitus there is an increased production of reactive oxygen species and a reduction in antioxidant activity.[28]Both the ingredients of Nishamalaki possess antioxidant activity[29] which is observed in present study, when given prophylactically inhibited the free radical generation. Curcuma has been shown to inhibit PARP (Poly ADP ribose polymerase) activation[30] preventing depletion of NAD (+) and ATP in cells exposed to STZ. This could be the reason that in prophylactic group blood sugar increased, but it did not reach diabetic level as seen in control (NA untreated) group.Antidiabetic agent's sulfonylureas and thiazolidinediones shows increase in body weight[31] when used for treatment of diabetes mellitus. In our study in therapeutic arm increase in body weight was seen with Glibenclamide & Pioglitazone not with NA. Nishamalaki also showed effects on the lipids.Cholesterol levels were decreased with NA but not seen with other agents. Triglycerides levels were lowered by Nishamalaki, Glibenclamide & Pioglitazone. Blood sugar levels were decreased with all drug treatment groups, marked effect was seen with Glibenclamide and NA-LD.Blood sugar lowering effect of Nishamalaki was moderate but NA- LD was more effective than Pioglitazone in lowering BSL. Even if NA has multitude of actions, its antidiabetic efficacy is less than that of Sulfonylurea compounds. Development of cataract was seen in all the animals of DM-Control group in 8th week, rise in the blood urea nitrogen 10th week and neurological derangement observed in the 12th week. No complications were observed in the prophylactic group till 12th week. Thus Nishamalaki has major prophylactic value and mainly correcting lipid imbalance. It has also delayed development of diabetic complications.

CONCLUSION

Nishamalaki was effective in preventing the occurrence of DM and predominant action on lipids in prophylactic arm. Antidiabetic efficacy of Nishamalaki in diabetic rats is comparable to Pioglitazone. It has also improved the lipid profile in diabetic rats in therapeutic arm. This preparation shows preventive potential in Diabetes. It will be very useful to delay the diabetes and its complications in individuals having family history of diabetes. Further studies are required to explore complete profile of Nishamalaki.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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