

Solution for Diabetes Mellitus-Niku Plus

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Abstract

Rigorous and intense scientific evaluation on the anti-diabetic efficacy of Niku plus path breaking Siddha drug formulation was done. Alpha amylase inhibition, alpha glucosidase inhibition, sugar assimilation inhibition, myeloperoxidase inhibition, phagocytosis and clinical evaluation on DM patients were done to establish the efficacy. Findings of the study show that Niku plus is not only effective for the complete management of DM but also can revolutionize the management of DM. The global medical fraternity is coming back to native wisdom and local healing practices which was once fulfilled by the same scientific fraternity. The present study described the scientific details of Niku plus in detail.

Introduction

Diabetes mellitus is a chronic disease condition occurs when the pancreas does not produce enough insulin (a hormone that regulates blood sugar) or alternatively, when the body cannot effectively use the insulin it produces [1].

Diabetes mellitus is majorly classified into three types. Type-I, Type-II and Gestational diabetes. In type- I there is lack of insulin production by pancreas. These patients need to take the insulin to alive. In type II diabetes mellitus, body cannot utilize the insulin produced and this is the most common type of Diabetes mellitus. This majorly linked with the obesity and lifestyle. Gestational diabetes occurs in women during the pregnancy where body will be less sensitive to insulin. Generally, resolves after giving birth [2].

Over 90% of diabetic patients are affected by type-II diabetes. It is also known that diabetic patients more likely to suffer from infections as high blood sugar levels will weaken the immune system. In diabetes immune boosting is also very much required. General medication for type-II diabetes intended to

- Increase insulin output by the pancreas
- Decrease the amount of glucose released from the liver
- Increase the sensitivity (response) of cells to insulin
- Decrease the absorption of carbohydrates from the intestine and
- Slow emptying of the stomach, thereby delaying nutrient digestion and absorption in the small intestine.

Management of Diabetes Mellitus (DM) is quite challenging. Although, glucose absorption and post prandial blood glucose reduction are used as major strategy for the management of DM, the global medical fraternity is coming back to holistic treatment by integrating local health and traditional wisdom that were known to mankind since antiquity.

Niku plus is formulated by Dr. JRK's research and pharmaceuticals by integrating the wisdom of siddha system and modern science. Although such integration was done at herbal level, the finished formulation warrant detailed scientific evaluation to establish the anti-diabetic effect of Niku plus. We have subjected Niku plus to various rigorous scientific evaluations such as

- Alpha amylase inhibition
- Alpha glucosidase inhibition
- Sugar assimilation inhibition
- Myeloperoxidase inhibition
- Phagocytosis
- Clinical evaluation on DM patients

Findings of the study has clearly shown that Niku plus is extremely effective for the management of DM and can be effective for prophylaxis as well. Niku plus in all probability may minimize the threat posed by DM at global level and would revolutionize the treatment per se.

The study was discussed in detail in the present paper.

Materials and Methods

Investigational Product Information

Niku plus is a proprietary siddha medicine (submitted for license) indicated for Diabetes Mellitus [9-12]. The individual herbal drugs used are known to have variety of medicinal values in reduction of postprandial blood glucose levels in diabetic patients. Herbs in it also act against viral fever, chikungunya and dengue [3].

Uses

Niku plus is used to reduce the blood glucose levels in the diabetic patients. It can be used as supportive drug in Diabetes mellitus. It also boosts the immunity and prevents the associated co-morbidities.

Niku plus is composed of *Andrographis paniculata*, *Zingiber officinale*, *Piper nigrum*, *Cyperus rotundus*, *Tinospora cordifolia*, *Adhatoda vasica*, *Syzygium cumini* and *Momordica charantia*.

Scientific validation of the Niku plus was done to establish the efficacy of the product in the maintaining the glucose levels and the mechanism of action.

In vitro Inhibition of α -Amylase

The α -Amylase (0.5 mg/ml) was premixed with extract at various concentrations (100-500 μ g/ml) and starch as a substrate was added as a 0.5% starch solution to start the reaction. The reaction was carried out at 37 °C for 5 min and terminated by addition of 2 ml of DNS (3, 5-dinitrosalicylic acid) reagent. The reaction mixture was heated for 15 min at 100 °C and diluted with 10ml of distilled water in an ice bath; α - amylase activity was determined by measuring spectrum at 540 nm. The % α -amylase inhibitory activity is calculated by the following formula.

$$\% \text{ Inhibition} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

The IC₅₀ value was defined as the concentration of the sample extract to inhibit 50% of α -amylase activity under assay condition [4].

In vitro Inhibition of α -Glucosidase

The enzyme α -glucosidase inhibitory activity was determined by premixing α -glucosidase (0.07 units) with 100-500 μ g /ml of extract.

Then 3 mM p-nitrophenylglucopyranoside was added as a substrate. This reaction mixture was incubated at 37 for 30 min and the reaction was terminated by addition of 2 ml of sodium carbonate. The α -glucosidase activity was determined by measuring the p-nitrophenyl release from p-nitrophenyl glucopyranoside at 400 nm. The % α -glucosidase inhibitory activity is calculated by the following formula.

$$\% \text{ Inhibition} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

The IC₅₀ value was defined as the concentration of the sample extract to inhibit 50% of α -glucosidase activity under assay condition [5].

Sugar Assimilation Assay

Details of the isolates *Candida albicans* used

Twenty-five clinical isolates of *Candida albicans* previously identified by the conventional methods were used for the study. Ten days prior to the start of the study all the isolates were re-tested to confirm their sugar assimilation ability is not lost.

Growth study in Yeast Extract Glucose Medium (YEGM)

The culture suspension adjusted to 104 CFU was inoculated on to a well of 2 mm diameter in YEGM with and without NIKE and Miglitol at 1 mg/ml concentration. 20 ml of medium was used for preparing plates. Simultaneously the organism was also grown in Sabroud's Dextrose Agar medium (SDA) as described above. The plates were incubated at 260 °C for 2 days. The growth characteristics of the organism were studied and noted for 2 days and was compared with the growth of the organism in SDA [6].

Screening of Miglitol, Niku plus and the individual herbs of Niku plus

Miglitol, Niku plus and all the 8 herbs of Niku plus were incorporated separately into YEGM at 1 mg/ml and the organism was inoculated as described above and the plates were incubated at 260 °C for 2 days with complete recording of the growth characteristics of the respective isolates grown in media with Niku plus or the herbs vis-à-vis the growth of organism in YEGM without these herbs. The entire experiment was done in duplicates.

Study of the microscopic characteristics of *Candida albicans* grown in 0.2 %glucose solution with and without Niku plus or Miglitol

The Candida strains were grown in glucose solution containing 1 mg/ml of Miglitol and Niku plus separately and incubated at 260 °C for 2 days. The microscopic appearance of the isolates grown in glucose solution with and without Niku plus or Miglitol was studied using microscope.

Myeloperoxidase assay

Guaiacol was used as substrate. The reaction mixture was prepared with the following chemicals such as 2.5 nM MPO, 1 mM guaiacol (substrate) and 0.5 mM H₂O₂ in 1.0 ml of 50 mM phosphate buffer, pH 7.4.

The mixture was incubated at 37 °C without (control) and with the aqueous preparation of NiKu Plus at the following concentrations such 10, 20, 30, 40, 50 and 100 mg /ml concentrations.

After 5 min, the reaction was initiated by the addition of H_2O_2 , after which the increase of absorbance at 470 nm was recorded continuously for 3 min. MPO activity was calculated from the initial rate of reaction % inhibition = $[1 - (\text{activity of test}) / \text{activity of control}] \times 100$.

Diode Array 8452, a spectrophotometer from Hewlett Packard, equipped with a thermostatic cell, was used for all determinations. Quercetin was used as positive control in this assay [7].

Phagocytosis Assay

Principle of the study

Macrophages play an important role in the elimination of antigen/pathogen. Therefore, any enhancement in the performance of macrophages would result in the elimination of pathogen/allergen in the blood as the macrophages are always present in the blood stream [8].

Study of phagocytosis

Phagocytes were cultured in standard tissue culture medium and were treated separately with three antigens such as bacteria, yeast cells and carbon particles. The rate of ingestion by the treated and untreated phagocytes was recorded and accordingly the efficacy was interpreted. The concentration of the products shown activity was 500 mg/ml. Below which they did not show activity. Above the concentration, the cells were destroyed.

Clinical Evaluation

Objective

Primary Objective: To assess the post prandial blood sugar levels of the subjects in the study groups from baseline upto one-week time period on 1st, 3rd, 6th and 7th day.

Secondary Objective: To monitor the occurrence of any adverse events.

Methodology

- Type of Study:** Prospective interventional proof of concept clinical end point study (Pilot study).
- Study Design:** A randomised open label parallel group clinical study.
- Study Population:** Type 2 Diabetes mellitus patients.
- Sample Size:** 24 patients with type 2 diabetes mellitus satisfying the selection criteria were enrolled in the study.

Selection Criteria

➤ Inclusion Criteria

- Proper written informed consent obtained from the patient before any procedure is being performed.
- Male or female Type 2 DM patients on oral hypoglycemic agents, in the age group of 18-45 years.
- Patient should have not participated in any other clinical trial during the past 3 months.

➤ Exclusion Criteria

- Patient who are unable to consume solid and liquid orals.
- Patients who are having complications of Diabetes mellitus and suffering from other co morbid conditions.
- Patients who are unable to sign informed consent.
- Patient unwilling or unable to comply with study procedure.

Intervention

- Subjects randomized onto two groups with 12 subjects in each.
- Group 1 received one tablet of NiKu plus orally after food along with their routine Oral hypoglycemic drugs thrice daily orally for 1 week (5).
- Group 2 received only their routine Oral hypoglycemic agents for 1 week.
- Baseline assessment (on day 0) of body weight, Blood sugar levels (fasting and post prandial) and HbA1c levels were estimated.
- On day 0 fasting and post prandial blood sugar levels were estimated.
- Post Prandial blood sugar levels were monitored on day 1, day 3 and day 6.
- At the end of 1-week time (day 7) the baseline parameters and fasting and post prandial blood sugar assessment were repeated.

Data Collection Procedure

Data collected include

- Body weight of the patients.
- Fasting and post prandial blood sugar levels (total venous blood sample of 15 ml).

Blood sugar levels will be analysed using glucose oxidase method by means of auto analyser.

Confidentiality: The identity of the subjects, who have participated in the clinical trial is kept confidential.

Statistical Analysis: With the help of the mean and standard deviation of the data collected, two-tailed student t test followed by Mann-Whitney U test was applied to analyse the results statistically, using Graph Pad Prism 7.03 software. P value <0.05 was considered as statistically significant.

Results

Inhibition of alpha amylase and glucosidase

Alpha amylase and alpha glucosidase are the two important enzymes that help in maintaining the glucose levels. Niku plus (Proprietary siddha drug under licensing process) was evaluated for the efficacy Table 1.

S.no	Sample details	IC 50 values	
		Alpha amylase	Alpha glucosidase
1	<i>Andrographis paniculata</i>	4 mg/ml	8 mg/ml
2.	<i>Cyperus rotundus</i>	2 mg/ml	3 mg/ml
3.	<i>Justicia adhatoda/ Adhatoda vasica</i>	2 mg/ml	2 mg/ml
4.	<i>Tinospora cordifolia</i>	5 mg/ml	6 mg/ml
5.	<i>Zingiber officinalae</i>	10 mg/ml	13 mg/ml
6.	<i>Piper nigrum</i>	8 mg/ml	7 mg/ml
7.	<i>Syzygium cumini</i>	5 mg/ml	8 mg/ml
8.	<i>Momordica charantia</i>	6 mg/ml	6 mg/ml
9.	NIKU PLUS	0.4 mg/ml	0.6 mg/ml

Table 1: Inhibition of alpha amylase and alpha glucosidase.

Sugar assimilation assay

Growth morphology of *Candida albicans* in media with and without sugar in **YEGM (Yeast Extract Glucose Medium)** Candida cells show characteristic rich, mucoid colony. The growth pattern of Candida in YEM without glucose exhibited very weak, transparent, button like colony. The growth characteristics of Candida in YEGM media was comparable with that of SDA (**Sabroud's dextrose agar**).

YEGM media	YEM without glucose	SDA	SDA with NIku	SDA with Miglitol
Rich, mucoid colony	Transparent, weal, button like colony	Rich, extended mucoid colony	Sparse colony, appear weak	Improvised colony with transparent appearance

Table 2: Growth pattern of *Candida albicans* (25 isolates) after 2 days.

Anti-diabetic benefit of Niku plus in comparison with Miglitol by exploring the sugar assimilation inhibition of *Candida albicans* was studied.

S.No	Name of test material	Extent of inhibition of growth of Candida grown in YEGM
1	<i>Andrographis paniculata</i>	-
2	<i>Syzygium cumini</i>	-
3	<i>Tinospora cordifolia</i>	++
4	<i>Momordica charantia</i>	++
5	<i>Cyperus rotundus</i>	+++
6	<i>Zingiber officinale</i>	-
7	<i>Piper nigrum</i>	-
8	<i>Adhatoda vasica</i>	++
9	Miglitol	+++
10	NIku plus	++

+++ indicates inhibition of growth,
++ Minimum inhibition of growth,
- Indicates no inhibition

Table 3: Extent of inhibition of growth of Candida grown in YEGM.

Growth morphology of *Candida albicans* (25 isolates) in YEGM with 1 mg/ml of Niku plus and its individual ingredients

Microscopic characteristics of *Candida albicans* grown in 0.2% glucose solution with and without Niku plus and or Miglitol. The microscopic characteristics of *Candida* cells grown in 0.2% glucose solution were well grown well matured with abundant blastospore formation. When the *Candida* cells were grown in 0.2% solution with 1mg/ml concentration of Niku plus and or Miglitol exhibited highly impoverished state indicating some inhibition of sugar assimilation due to Niku plus.

Microscopic characteristics of *Candida albicans* (25 isolates) grown in 0.2 % glucose north with and without Niku plus

0.2% glucose solution	0.2% glucose solution+1 mg/ml Niku plus	0.2% glucose solution + 1mg/ml Miglitol
1. Gorged cells with well spread and rich cytoplasmic inclusions 2. Even and uniformly sized cells 3. Abundant blastospore all around the cells	1. Miniaturized cells 2. Condensed cellular inclusions showing impoverished state of the cells 3. Increased vascular space	1. Miniaturized sparse cells 2. Highly condensed cellular inclusions showing impoverished state of the cells 3. Increased vacuolar space

Table 4: Microscopic characteristics of *Candida albicans*.

Myeloperoxidase assay

In Diabetic patients, Myeloperoxidase may cause insulin inactivation due to infiltration of circulating neutrophil concentrations and accumulate in adipose tissues. This may also lead to insulin sensitivity and diabetic patients may suffer from MPO co-morbidities like atherosclerosis etc.

Time in Seconds	20 mg/ml	Time in Seconds	30 mg/ml
	% inhibition		% inhibition
0	-	0	-
20	11	20	17
40	15	40	19
60	20	60	24
80	19	80	22
100	21	100	30
120	19	120	29
140	23	140	26
180	20	180	27
200	22	200	25

NiKu plus inhibited 30% activity of MPO at 30 mg/ml concentration.

Table 5: Inhibition of Myeloperoxidase.

	Bacteria		Yeast		Carbon Particles	
	Test products	Phagocytic index	% Difference between control and treated	Yeast	% Difference between control and treated	Carbon particles
NIKU plus	10		150	8	700	40
Untreated control	4		-	1	-	4

Table 7: Phagocytosis assay.

Clinical evaluation

Diabetic patients of both the gender was taken for the study. Fasting and post prandial blood glucose levels was evaluated.

Blood sugar levels of Control group (No. of patients=12)

SUBJECTS	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
DAYS	FBS	PPBS										
Day 0	110	150	120	172	124	200	100	145	114	187	112	176
Day 1	108	156	116	166	120	196	102	151	100	176	107	167
Day 3	116	140	108	180	118	184	106	136	110	180	100	160
Day 6	114	162	112	176	120	195	110	160	96	166	108	191
Day 7	106	155	115	178	122	203	104	154	102	180	114	171

Table 8: Blood sugar levels of the control group (patients 1-6).

SUBJECTS	Patient 7		Patient 8		Patient 9		Patient 10		Patient 11		Patient 12	
DAYS	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS
Day 0	120	168	96	135	124	180	100	143	120	165	100	150
Day 1	132	204	90	128	114	172	96	140	110	163	96	160
Day 3	128	188	103	137	110	186	103	150	108	158	90	145
Day 6	130	197	100	130	120	182	110	153	100	160	110	157
Day 7	124	190	92	126	118	175	108	145	112	154	115	162

Table 9: Blood sugar levels of the control group (patients 7-12).

TEST GROUP (NiKu PLUS) (n=12): Blood sugar levels

SUBJECTS	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
DAYS	FBS	PPBS										
Day 0	121	184	88	180	113	128	90	145	100	157	120	190
Day 1	115	180	86	180	110	129	96	140	105	155	110	180
Day 3	118	174	95	177	106	120	100	135	110	154	126	182
Day 6	110	172	110	176	118	118	92	132	107	153	130	176
Day 7	112	171	86	172	105	116	97	131	110	153	125	177

Table 10: Blood sugar levels of the test group (patients 1-6).

SUBJECTS	Patient 7		Patient 8		Patient 9		Patient 10		Patient 11		Patient 12	
DAYS	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS	FBS	PPBS
Day 0	130	200	110	166	116	158	109	150	120	166	100	142
Day 1	124	197	100	154	110	158	110	144	118	162	96	140
Day 3	120	179	124	154	109	157	115	146	118	158	94	140

Day 6	130	176	116	153	112	155	106	142	116	160	90	136
Day 7	125	173	108	153	114	150	102	138	110	152	90	132

Table 11: Blood sugar levels of the test group (patients 7-12).

Control Group

DAYS	Mean+ SD	
	% ↓ in FBS	% ↓ in PPBS
Day 1	3.65 + 5.6	-0.57 + 7.76
Day 3	2.66 + 7.78	2.07 + 6.19
Day 6	0.25 + 9.56	-3.23 + 7.68
Day 7	0.29 + 7.06	-1.19 + 6.06

Table 12: Mean Percentage reduction in blood sugar levels: (n=12).

TEST GROUP: NiKu PLUS: (Mean Percentage reduction in blood sugar levels): (n=12)

DAYS	Mean+SD	
	% ↓ in FBS	% ↓ in PPBS
Day 1	2.51 + 4.77	2.39±4.86
Day 3	-1.85 + 7.64	4.58±3.57
Day 6	-1.98 + 9.36	5.95±2.42
Day 7	2.25 + 6.46	7.53±1.83

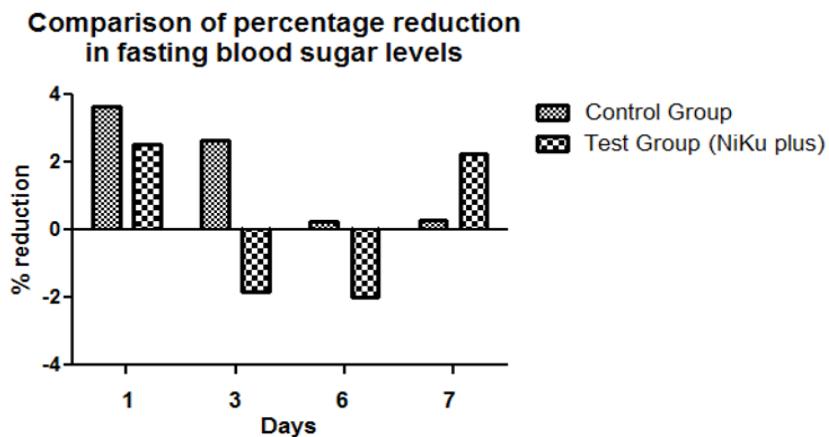
Table 13: Mean Percentage reduction in blood sugar levels: (n=12).

Comparison of percentage reduction in fasting blood sugar levels:

DAYS	CONTROL GROUP (N=12)	TEST GROUP (NiKu PLUS) (N=12)	P value	Significance
	Mean + SD	Mean + SD		
ON DAY 1	3.65 + 5.6	2.51 + 4.77	P > 0.05	NS
ON DAY 3	2.66 + 7.78	-1.85 + 7.64	P > 0.05	NS
ON DAY 6	0.25 + 9.56	-1.98 + 9.36	P > 0.05	NS
ON DAY 7	0.29 + 7.06	2.25 + 6.46	P > 0.05	NS

Statistics: Ordinary Two-tailed student t test followed by Mann-Whitney U test. P value (0.34) <0.05 is considered statistically significant. NS- Not significant.

Table 14: Percentage reduction in the fasting blood glucose levels.



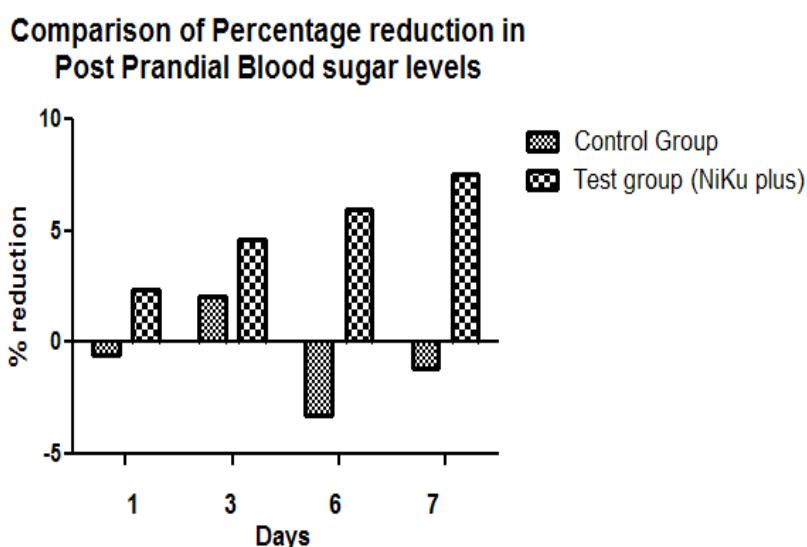
Graph 1: Percentage reduction in the fasting blood glucose levels.

Comparison of percentage reduction in post prandial blood sugar levels:

DAYS	CONTROL GROUP (N=12)	TEST GROUP (NiKu PLUS) (N=12)	P value	Significance
	Mean + SD	Mean + SD		
ON DAY 1	-0.57 + 7.76	2.39±4.86	P <0.05	Significant
ON DAY 3	2.07 + 6.19	4.58±3.57	P <0.05	Significant
ON DAY 6	-3.23 + 7.68	5.95±2.42	P <0.05	Significant
ON DAY 7	-1.19 + 6.06	7.53±1.83	P <0.05	Significant

Statistics: Ordinary Two-tailed Student t test, followed by Mann-Whitney U test. P value (0.0286) <0.05 is considered statistically significant.

Table 15: Percentage reduction in the post prandial blood sugar levels.



Graph 2: Percentage reduction in the post prandial blood glucose levels.

Discussion

The present study clearly reveals that NIKU plus is effective for the management of diabetes mellitus.

NIKU plus has exhibited activity against alpha amylase and alpha glucosidase at 0.4 and 0.6 mg/ml respectively. Both alpha amylase and alpha glucosidase plays a significant role in blocking the absorption of glucose at intestine, thus reducing the glucose burden in the blood after food. High post prandial blood glucose burden is the principle cause for various diseases of infective and non-infective origin associated with diabetes mellitus. Therefore, the use of safe alpha amylase and alpha glucosidase inhibitors are greatly required for managing the post prandial blood sugar in diabetic patients.

The sugar assimilation assay was done using *Candida albicans* and tested with Niku plus and its individual ingredients. Study showed that Niku plus blocked the sugar assimilation pathway resulting in growth inhibition of the organism and impoverished colonies comparable with Miglitol, a proven anti-diabetic drug. The above candida based study reconfirms the enzymatic activities of Niku plus against alpha amylase and alpha glucosidase.

In diabetes mellitus condition, the patients have infections more often than the non-diabetic patients. The increased occurrence of infection is mainly due to the adherence of microorganism in the high glucose environment. Niku plus also exhibited immune boosting effect as revealed by Phagocytosis assay. This suggests that Niku plus besides addressing the problem of high glucose burden also offers immune protection extremely necessary for Diabetic patients.

To understand the utilization of free form of glucose by *Candida albicans*, the following study was done. The growth characteristic of *Candida albicans* cells grown in 0.2 % of glucose solution with 1 mg/ml of NIKU Plus extract showed miniaturized cells, condensed cellular inclusions showing impoverished state of cells and increased vacuolar space indicating inhibition of sugar assimilation pathway whereas in the control showed Candida cells were well grown, matured and abundant blastospore formation. This shows the Niku plus effectively inhibits glucose assimilation pathway.

In type 2 diabetes patients, increased MPO activity was reported, resulting in generation of Reactive Oxygen Species (ROS) and higher the risk of cardiovascular diseases & other inflammatory condition, thereby inhibition of MPO is necessary for Diabetes mellitus patients. NIKU plus showed inhibition of Myeloperoxidase (MPO) at 30 mg/ml concentration. MPO plays an essential role in the innate immune system by catalyzing the production of Hypochlorous Acid (HOCl) which acts as potent bactericidal agent.

In type2 diabetes condition it is already reported the presence of lower percentage of activated macrophages and thereby increased the risk of infections. NIKU plus showed phagocytic activity which is essential for diabetic patients.

In vitro and enzymatic studies on Niku plus proven to reduce the blood glucose levels and the possible co-morbidities. To reconfirm the efficacy of the Niku plus, a 7day clinical trial was conducted on DM patients (both genders).

Patients are on their regular drugs in control group and in the test group along with regular medication, Niku plus was given twice a day after food. The results showed that there is a great improvement in the post prandial blood glucose when compared to control group. The results showed the statistical significance (P value (0.0286) <0.05) in the two arm clinical study.

The clinical trial has reestablished the role of Niku plus in management of Diabetes mellitus. Niku plus also play a significant role in reduction of the possible risk of co-morbidities by inactivating the myeloperoxidase. It also plays a greater role in boosting the immunity by increasing the phagocytosis thus reduces the occurrence of infections.

Conclusion

From the present study Niku plus is proven to decrease the alpha amylase, alpha glucosidase and thus prevents the glucose conversion. It also decreases the myeloperoxidase and improves phagocytosis thus helps in the preventing the co-morbidities and improve the first line of immunity. Niku plus was clinically proven to decrease the post prandial blood glucose level in diabetic patients. Niku plus is scientifically proven proprietary siddha medicine which shows the broad spectrum anti-diabetic benefit and may likely revolutionize the treatment of DM.

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