

Effect of NR-Salacia on post-prandial hyperglycemia: A randomized double blind, placebo-controlled, crossover study in healthy volunteers

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ABSTRACT

Background: *Salacia chinensis* (*S. chinensis*) is widely distributed in India and Sri Lanka. Most of the species of genus *Salacia* are known to have effects on blood glucose levels; however, the effects of *S. chinensis* on glucose levels are seldom reported. **Objective:** To evaluate the oral hypoglycemic activity of NR- *Salacia* (1000 mg extract of *S. chinensis*) in healthy adults. **Materials and Methods:** Randomized, double-blind, placebo-controlled, cross-over study was conducted in healthy volunteers. Single dose of NR-*Salacia* (1000 mg extract of *Salacia chinensis*) and placebo were administered before carbohydrate-rich diet. A 6-point plasma glucose profile was performed at different time intervals up to 180 min. **Results:** NR-*Salacia* treatment significantly lowered plasma glucose level at 90 min, and the percentage reduction in glucose concentration was found to be 13.32 as compared to placebo group. A 33.85% decrease in the plasma glucose positive incremental area under curve (AUC) (0 to 180 min) was observed in comparison to placebo. No adverse events were recorded throughout the study period, except for some mild cases of abdominal discomforts like cramping and distention, vomiting, and headache in both placebo and NR-*Salacia*-treated groups. **Conclusion:** The study findings revealed that NR-*Salacia* lowered the post-prandial plasma glucose levels after a carbohydrate-rich meal and can be used as an oral hypoglycemic agent.

Key words: Carbohydrate-rich diet, cross-over, double-blind placebo controlled, hypoglycemic, post-prandial glucose, *Salacia chinensis*

INTRODUCTION

Diabetes was declared as an emerging epidemic by World Health Organization (WHO) in 2006.^[1] In Asia, the proportion of population with type 2 diabetes and obesity increased, and the rate of increase shows minimal signs of slowing.^[2] Clinical use of herbal extracts/supplements is now a popularly accepted practice in the treatment of diabetic and obese patients in many countries.^[3,4] Several investigators^[5-7] explored the pharmacological potentials of medicinal plants/herbal preparations in the control and treatment of diabetes mellitus and obesity. A review

on new bioactive agents isolated from as many as 176 species of hypoglycemic medicinal herbs belonging to 84 families revealed comparatively better anti-diabetic activity than conventional oral medications used in clinical practice. Further, these plant species were found to delay the progress of diabetic complications and correct the metabolic abnormalities.^[8] Inhibition of intestinal digestion and absorption of complex carbohydrates such as oligo- and polysaccharides is proposed as an effective therapeutic means of controlling carbohydrate-dependent metabolic disorders in diabetic or obese patients.^[8-12] Clinical use of various carbohydrate blockers have been extensively studied in the past in relevance to inhibitory actions on intestinal enzymes such as α -glucosidases and α -amylase, which break down complex carbohydrates into easily absorbable monosaccharides.^[4]

Many plant extracts of the genus *Salacia* have been indicated as remedies for various disease conditions and disorders

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in Ayurvedic system of traditional medicine, especially for the prevention of diabetes.^[13,14] *Salacia chinensis* is a woody climber belonging to family Hippocrateaceae found in some regions of India and Sri Lanka.^[13,15] Root of *S. chinensis* reported to possess several pharmacological properties. The safety of *S. chinensis* is well documented in published literature and confirmed in *in vitro* genotoxicity studies. In AMES test and chromosomal aberration assay, *S. chinensis* revealed significant protective effect against *Salmonella typhimurium*-induced mutagenicity.^[16] Ethanolic extract of *S. chinensis* administration at 500 mg/kg bodyweight for 4 days lowered serum SGOT, SGPT, ALP, bilirubin, and established hepatoprotective activity in rats exposed to CCl₄.^[15] Male Sprague-Dawley rats fed with *S. chinensis* extract at 2000 mg/kg/day for 11 weeks revealed no adverse effects on the reproductive outcome. No significant changes in food consumption, body weight gain, gross pathological or histological findings at such high dose were observed in comparison with control group.^[17]

In light of the above considerations, the present investigation was conducted with a primary objective to evaluate the post-prandial glycemic response upon administration of an extract of *S. chinensis* (NR-Salacia) developed by M/s Natural Remedies, Bangalore, India, given orally just before a carbohydrate-rich meal in non-diabetic healthy volunteers. The secondary objectives of the study were to assess the efficacy of NR-Salacia as an oral hypoglycemic agent, to determine the onset, duration of activity, and tolerance in treated individuals.

MATERIALS AND METHODS

Participants

A total of 30 healthy volunteers were enrolled based on the inclusion criteria if they (i) were aged between 18-45 years, (ii) had given written consent, (iii) were proven to be healthy after clinical examination by physician, (iv) had normal glycemic response, hematological and biochemical values for blood and urine, and (v) females who had completed family life. Participants were excluded if they (i) had history of diabetes mellitus, allergic to any medication or on medications that interfere with glucose absorption/produce hyperglycemia, (ii) had history of any acute/chronic disorders (including gastrointestinal), (iii) were regular smokers who smoke more than 20 cigarettes daily, (iv) had history of drug dependence or chronic heavy alcohol abuse associated with altered hepatic functions. In addition, volunteers participated in any clinical trial within 6 weeks preceding day 1 of the study and pregnant, lactating women or with anticipated pregnancy were excluded.

Study intervention

NR-Salacia is a hydro alcoholic extract of roots and stems of *Salacia chinensis* Linn. (Family: Hippocrateaceae) commercially manufactured by M/s Natural Remedies, Bangalore, India. The extract was ensured to comply with *in vitro* bioassay specification of α -glucosidase inhibition assay (IC₅₀ < 75 mcg/ml). The extract was also ensured to adhere to the international quality requirements, which included analysis of heavy metals and microbial counts. Placebo capsules contained magnesium carbonate and calcium carbonate. A total of 1000 mg of actives were present in 3 capsules of NR-Salacia. The placebo and NR-Salacia were filled in "0" size black top, red bottom hard gelatin capsules that could not be distinguished from each other.

Randomization and blinding

Participants enrolled were allotted either to placebo or to NR-Salacia. Lists of unique integer random allocation numbers generated using computer-aided random series program were given as participant codes. The code numbers were labeled on participant CRF. NR-Salacia and placebo were packed in identical containers and dispatched to study center. As per the protocol, each coded container was dispensed for administration to the participant. The investigator, study coordinators, and pharmacist remained unaware of treatment assigned throughout the study. Data were collected and sent for statistical analysis.

Study protocol

The study was carried out as a randomized, double-blind, placebo-controlled crossover design. Thirty participants were selected and randomly assigned to either placebo or to NR-Salacia. The study was conducted as a day care procedure at Srinivasa Diabetic Research Center, Bangalore, India after obtaining Institutional Ethics Committee (IEC) approval. Out of 30 participants, three participants dropped out due to collapsible vein line (2) and unwillingness to continue (1).

Volunteers were advised to have a simple diet 3 days prior to administration of study intervention followed by 12 to 14 hour fasting. A carbohydrate-rich diet (approximately 600 Kcal), as designed and recommended by the dietician, was provided on the day of study intervention. Each volunteer was administered with three capsules of placebo or NR-Salacia by a pharmacist under medical supervision. Volunteers were instructed to take rest and restrict their activities after the carbohydrate-rich meal. Heavy physical activities were not allowed in order to maintain uniformity in resting energy expenditure. Participants underwent wash out period for 19 days. Again, the same procedure was repeated with administration of the study intervention *vice versa*.

Blood glucose analysis

Blood samples were collected in the tubes containing sodium fluoride (in order to inhibit glycolysis) at the time intervals of 0, 30, 60, 90, 120, and 180 min and stored at 4°C till further analysis. Samples were centrifuged at 3000 rpm for 10 min. The plasma glucose concentration (mg/dl) was analyzed by glucose oxidase (GOD – POD) enzymatic method, and the intensity of color produced was measured by an auto analyzer. The evaluation of post-prandial plasma glucose response following carbohydrate-rich meal from 0 to 180 min was carried out, and the difference in the glycemic response between the placebo and NR-Salacia-treated group was taken as the measure of efficacy.

Statistical analysis

Twenty-seven participants were considered for the statistical analysis [Table 1] [Figure 1]. Data were expressed as mean \pm standard error of the mean. Since normality of the data tested by Shapiro-Wilk test indicated non-normal distribution, a non-parametric Wilcoxon signed rank test was used for the analyzes of plasma glucose levels recorded at different time intervals within the group. Similarly, non-parametric, two-sample Kolmogorov-Smirnov test was applied to compare the plasma glucose levels at different time intervals between the groups. Statistical significance was recognized with *P* value \leq 0.05. The above statistical applications were performed using SPSS (Version 10). Positive incremental area under curve (AUC) for both

placebo and NR-Salacia-treated groups were calculated using GraphPad Prism software (version 5.00). Positive incremental AUC values of both the groups were analyzed by two-sample Kolmogorov-Smirnov test. The percentage decrease in plasma glucose level at each time interval and AUC was calculated using following formula.

$$\text{Percentage change} = \frac{[(\text{Control values} - \text{Treated values}) / \text{Control values}] \times 100}{}$$

RESULTS

The baseline hematological, biochemical, and urine estimations carried out before the initiation of the study were

Table 1: Demographic data of volunteers

Group	Male/Female		Total	
	Selected	Completed	Selected	Completed
Placebo	14/01	12/01	15	13
NR-Salacia	13/02	12/02	15	14
Total	27/03	24/03	30	27

Table 2: Hematology and blood biochemistry profile (pretreatment) of healthy volunteers

Parameters	Results
Hematology	
Hemoglobin (g %)	14.57 \pm 0.28
WBC (cells/ μ L)	7176.67 \pm 258.05
Polymorphs (%)	56.67 \pm 1.34
Lymphocytes (%)	33.80 \pm 1.16
Eosinophils (%)	6.63 \pm 1.33
Monocytes (%)	3.29 \pm 0.37
Biochemistry	
Urea (mg/dL)	21.07 \pm 0.79
Creatinine (mg/dL)	1.02 \pm 0.017
Bilirubin - Total (mg/dL)	0.69 \pm 0.016
Bilirubin - Direct (mg/dL)	0.21 \pm 0.004
SGOT (IU/L)	24.83 \pm 1.44
SGPT (IU/L)	22.90 \pm 2.86
Alkaline Phosphatase (U/L)	86.47 \pm 3.02
Total Protein (Serum) (g/dL)	7.56 \pm 0.06
Fasting plasma glucose (mg/dL)	98.97 \pm 2.17

Mean \pm S.E.M; n = 30

Table 3: Results of urinalysis (pretreatment) in healthy volunteers.

Parameters	Mean values
Fasting urine glucose	Nil
Random urinary micro albumin (mg/L)	9.31 \pm 0.41

Mean \pm S.E.M; n = 30

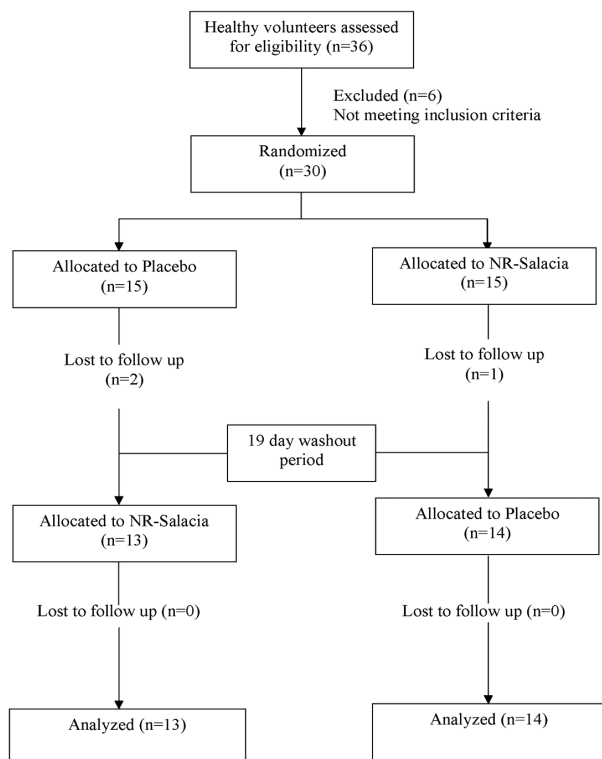


Figure 1: Flow chart of disposition of volunteers

within the normal limits [Tables 2 and 3]. Although clinical examination showed abnormality in respiratory system in two volunteers, each one from placebo and NR-Salacia-treated group with mild pharyngitis, and one with bronchitis (NR-Salacia treated group), they were not excluded from the trial.

No significant difference in the baseline plasma glucose levels between the groups was observed. Treatment with carbohydrate-rich meal elevated the plasma glucose level at 30, 60, 90, 120 min significantly in both placebo and NR-Salacia group when compared with baseline value. NR-Salacia-treated group showed reduction in plasma glucose levels at 30, 60, 90, 120, and 180 min intervals as compared to the placebo. A significant reduction in the plasma glucose level was observed at 90 min in comparison with the placebo group, and the percentage reduction was found to be 13.32 [Table 4]. NR-Salacia at 1000 mg dose reduced the post-prandial plasma glucose-positive incremental AUC (0-180 min) by 33.85% compared to placebo [Figure 2]. There were no major adverse events reported throughout the study period, except for some mild cases of abdominal discomforts like cramping and distention, vomiting, and headache in both placebo and NR-Salacia-treated groups. Subjective gastrointestinal intolerance, frequency and intensity of abdominal cramping, abdominal distention, vomiting and headache

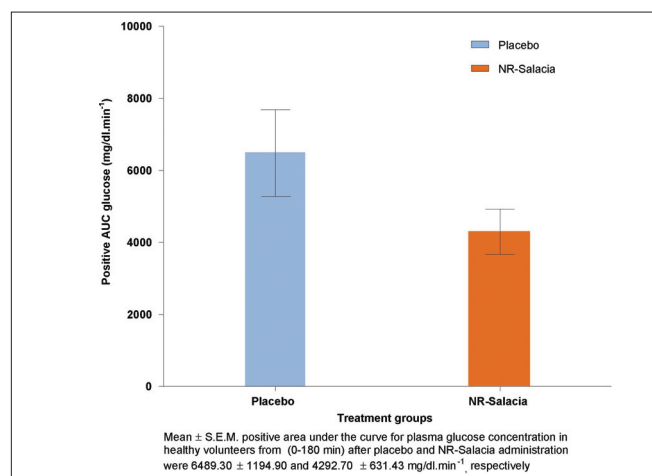


Figure 2: AUC (0-180 min) for plasma glucose values of placebo and NR-Salacia

from both placebo and NR-Salacia-treated group were recorded for the initial period of 48 h after the test substance administration.

DISCUSSION

Inhibition of intestinal enzymes that break down complex sugars restricts the digestion and absorption of complex sugars is considered to be an important method in the treatment of carbohydrate-associated metabolic disorders.^[9-12] Sulfonylureas, biguanides, and thiazolidinediones are other effective glucose-lowering agents^[18] and are associated with hypoglycemia, increase in weight, serious cardiovascular events,^[19] but alpha-glucosidase inhibitors are considered relatively safe intervention in diabetes. Prevalence of diabetes worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030.^[20] With rapidly increasing global occurrence of diabetes,^[20-22] inhibitors of intestinal α -glucosidases and α -amylases like acarbose, voglibose, miglitol etc., have been clinically used as first-line agent or in combination with other anti-hyperglycemic drugs.^[23-27] Blocking of carbohydrate breakdown in the intestinal tract by various herbs such as *Pelvetia*, tochu-cha, welsh onion, and clove are well documented in the published literature.^[28] Several clinical trials have been conducted in the past to determine the efficacy of herbal formulations that lower post-prandial blood sugar levels.^[29,30] Although popularity of herbal medicine is increasing, systematic reviews of scientific reports on the therapeutic usefulness and safety profile of herbal medications suggest the necessity of adequate data still to be generated on this aspect.^[31]

Despite well established preclinical hypoglycemic activity of *S. chinensis*,^[32,33] available literature indicates the lack of adequate clinical studies on the effect of *S. chinensis* in reducing the post-prandial hyperglycemic levels. Keeping in view the rapidly increasing global occurrence of diabetes, a study to investigate the effect of NR-Salacia, an extract of *S. chinensis* on plasma glucose levels in healthy volunteers, was carried out.

The present study revealed beneficial effects of NR-Salacia on post-prandial glycaemia in healthy volunteers. There was no considerable difference in the baseline plasma

Table 4: Post-prandial plasma glucose values of placebo and NR-Salacia at different time intervals

Treatment	Time intervals					
	0 min	30 min	60 min	90 min	120 min	180 min
Placebo	94.96 \pm 1.28	152.15 \pm 6.10 [#]	148.96 \pm 8.25 [#]	140.63 \pm 9.69 [#]	127.19 \pm 9.38 [#]	104.85 \pm 6.05
NR-Salacia	94.52 \pm 1.18	141.37 \pm 5.53 [#]	133.33 \pm 5.26 [#]	121.89 \pm 4.62 ^{#*}	111.15 \pm 4.11 [#]	97.63 \pm 3.18
Percentage reduction	0.46	7.09	10.49	13.32	12.61	6.89

Plasma glucose values are expressed as mean \pm S.E.M; n = 27, [#]P \leq 0.05 plasma glucose levels of 0 min Vs 30, 60, 90, 120, 180 mins, ^{*}P \leq 0.05 placebo Vs NR-Salacia

glucose levels between the study groups. The treatment group showed significant reduction in the post-prandial plasma glucose levels at 90 min, and the percentage reduction was found to be 13.32. The study revealed that NR-Salacia at 1000 mg reduced positive plasma glucose incremental AUC by 33.85% in comparison to placebo. Similar findings were reported in a double-blind, randomized crossover study to evaluate the effect of 1000 mg *Salacia* extract on post-prandial glycemic level in non-diabetic adults (n = 39). The study revealed a decrease in the plasma glucose incremental AUC (0 to 120 min post-prandial) by 23% as compared to the control.^[4] Another study that evaluated the effectiveness of *Salacia* extract (1000 mg) on post-prandial glycemia, insulinemia, and breath hydrogen responses in healthy subjects (n = 43; 20 men and 23 women) by Collene *et al.* exhibited a decrease in plasma glucose AUC by 27% (0 to 120 min) and 24% (0 to 180 min), insulin AUC by 35% and 36%, respectively, and significantly higher breath hydrogen excretion (more than 60%) compared to control.^[34] An analogous study of *Salacia* in type 2 diabetic patients (n = 66; 53 men and 13 women) confirmed the hypoglycemic effect on post-prandial glucose levels. *Salacia* extract, at both doses, significantly reduced the post-prandial positive glucose AUC by 14% (240 mg extract) and 22% (480 mg extract) and the adjusted peak glucose response (19% for the 240 mg dose and 27% for the 480 mg dose) to the control meal.^[35] The study on acute glycemia by Williams *et al.*, in diabetic patients demonstrated a 14% significant decrease in positive serum glucose AUC (0-180 min) which can be attributed to the large sample size (n = 66). The decrease in the post-prandial glycemia, positive incremental AUC, and the gastro-intestinal symptoms observed in present study corroborates the α -glucosidase inhibitory activity of NR-Salacia. Inhibitory activity of enzyme are in compliance with the *in vitro* α -glucosidase inhibition assay ($IC_{50} < 75$ mcg/ml) (unpublished data). Alpha-glucosidase activity of *Salacia* species is well documented,^[36] similarly *S. chinensis* demonstrated substantial inhibitory activity on intestinal α -glucosidase. Methanolic extract from *S. chinensis* stem exhibited intestinal α -glucosidase activity.^[33] Polyphenols from *S. chinensis* showed inhibitory activity of carbohydrate metabolizing enzymes (sucrase, maltase, isomaltase, α -amylase, and aldose reductase).^[36]

A systematic review and meta-analysis revealed that α -glucosidase inhibitors exhibit beneficial effect on fasting and post-load blood glucose and post-load insulin, and the effects are comparable to metformin or thiazolidinediones, but seemed to be less as compared to sulfonylureas.^[27,37] In a study on healthy volunteers, 100 mg of acarbose administration prior to 75 g glucose load showed 20.27% reduction in the AUC (0-180 mins) for glucose as compared

to placebo^[38] while NR-Salacia administration decreased the plasma glucose AUC by 33.85%. In the present study, no major adverse events were reported throughout the study period, except for few cases of mild abdominal discomforts like cramping and distension, vomiting and headache in both placebo and NR-Salacia-treated groups. Similar incidences of gastro-intestinal symptoms associated with α -glucosidase inhibitors were reported in previous studies also. Mild to moderate increases in intensity of flatulence and distension in individuals treated with 1000 mg *Salacia* extract were observed.^[4,34] A placebo-controlled, double blind clinical trial on long-term use of acarbose in subjects with non-insulin-dependent diabetes mellitus also exhibited gastrointestinal discomforts.^[39]

CONCLUSION

In conclusion, from our research findings, it can be stated that NR-Salacia attenuated the post-prandial plasma glucose levels and was well tolerated. In view of growing interests in herbal medicines, NR-Salacia can be used as an oral hypoglycemic agent. In addition, further studies can focus on optimizing dose of NR-Salacia for reducing glycemia in diabetic patients.

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