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Observational study on standardized Salacia root extract in patients with Type-2 diabetes mellitus

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ABSTRACT

Salacia is used by the folklore practitioners of Southern Asia and in classical Ayurvedic text for the management of diabetes. The present observational study was conducted on standardized root extract of *Salacia oblonga* with a primary objective to obtain data on glycemic response and associated symptoms in 100 diabetic patients who were taking *S. oblonga* extract (240 mg/tab) tablet twice daily before meals along with their routine anti-diabetic therapy. The patients were followed up at every month when participants carried on doing their regular activities and other dietary measures. Though the period of follow-up in the current study was very short for just 3 months, the levels of blood glucose post treatment have not reached the normal values; however, a reducing trend was noted in the fasting and postprandial blood glucose levels in the subsequent follow-up visits with a statistically significant reduction at the end of 3 months compared with baseline. Periodical follow-up suggested that there is an improving trend of the quality of life (QOL) in respect of bothering symptoms of diabetes such as fatigability, weakness, increased appetite, increased thirst, tingling sensation, and increased urinary frequency when compared with baseline value measure in visual analog scale. To conclude, standardized *S. oblonga* extract can be a potential promising therapeutic agent useful for prevention and management of diabetes by controlling the blood sugar level and improving symptoms for maintaining the QOL in diabetics. It can be safe and effective option for co-administration with other drugs.

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Introduction

Lifestyle diseases are also called as diseases of longevity or diseases of civilization, which are found to be more widespread in countries, which are more industrialized [1]. Currently, more than 63% of all death worldwide result from chronic non-communicable diseases, i.e., lifestyle diseases [2]. Faulty dietary habits, sedentary lifestyle, and expanded urbanization have intensified the problem further [3]. Diabetes and its complications are included under metabolic diseases. Together the lifestyle diseases contribute to more than 60% of the mortality, i.e., cardiovascular (30%), cancer (13%), diabetes (2%), chronic respiratory diseases (7%), and other chronic diseases (9%) [2]. Diabetes has emerged as a major public health problem today among various life style disorders, affecting a large proportion of the population all over India [4]. Prevalence of type-2 diabetes mellitus (T2DM) has reached epidemic proportions in many countries, which are due to westernization and increased rates of obesity. As per the recent International Diabetes Federation estimates, the number of adults affected by diabetes was 380 million in 2013, which is projected to increase to 590 million by 2035. As per the projections by the World Health Organization (WHO), diabetes will be the seventh leading cause of death in 2030 [5].

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In another perspective in the management of diabetes—because of the associated complications of synthetic drugs—there has been a shift toward locating natural resources showing antidiabetic activity. Effectiveness, less side effects, broad range of action, and relatively low cost make herbal drugs a good option [6]. Therefore, there arises the need to have a natural solution which should have certain attributes such as—can be used as a long-term therapy along with the existing medications and effective in reducing the blood-sugar level. It also should have protective action for the vital organs (especially kidneys and nerves) and reduces the risk factors, helps to either maintain the dosage or able to reduce the existing dosage, and give an overall benefit in improving the quality of life (QOL) of the patients.

Salacia genus (Family-Celastraceae) has been used widely in India, Japan, and Korea for the treatment of diabetes [7,8]. The genus *Salacia* comprises 120 species, out of which *Salacia reticulata, Salacia prinoides*, and *Salacia oblonga* are the predominant species found in India, Sri Lanka, China, Vietnam, Indonesia, and other Asian countries [9]. The Salacia plant is a large woody climber and its root and stem have been extensively used in the traditional Ayurvedic system of Indian medicine for the prevention and treatment of diabetes [7]. In Japan, the extracts of Salacia roots are consumed in commercial foods and dietary supplements for the treatment of diabetes and obesity [10,11].

The bioactive ingredients of Salacia are kotalanol, kotalagenin-16 acetate, and mangiferin. Root contains the maximum amount of mangiferin. These bioactive compounds are useful to control the glucose levels by inhibition of the enzymes involved in the glycemic response [12,13]. Many triterpenes, hydrocarbons, and sitosterol have also been reported in the roots and stem barks of different Salacia plants [7,14]. Also, a few different constituents (dulcitol, tannins, kotalagenin maytenfolic corrosive, and soiguesterin) have been isolated from this plant. However, few of them have been pharmacologically evaluated [7,15].

Numerous preclinical and clinical reviews have shown that Salacia roots act through multiple targets such as peroxisome proliferator enacted receptor, alpha-mediated lipogenic gene transcription, angiotensin receptor, alpha-glucosidase, aldose reductase, and pancreatic lipase [16–19]. These multi-target activities may, for the most part, add to Salacia root-initiated change of T2DM and obesity-related hyperglycemia, dyslipidemia, and related cardiovascular complexities found in people and rodents [16].

It was reported that aqueous extract of *S. oblonga* did not possess any change in blood hematology of rats after 14-day oral treatment [20]. In the subchronic 90-day study in rats, no observable adverse effect level was determined to be 2,500 mg/kg/day of alcohol extract of *S. oblonga* [21]. No significant toxicity was exhibited from the result of both acute and sub-acute toxicity study of *S. oblonga*. Therefore, we may suggest that no adverse effects on human health were expected at lower levels of daily dose.

In light of the above considerations, an observational study was conducted with a primary objective to re-establish the efficacy of standardized hydro-alcoholic root extract of Salacia on glycemic response and QOL parameters in diabetic patients.

Materials and Methods

Participants

A total of 100 suboptimal control or freshly diagnosed diabetes individuals were included with a fasting blood sugar level from 99 to 257 mg/dl of either sex, age between 18–70 years, with a present history of intake of anti-hyperglycemic drugs; and currently taking tablet form of *S. oblonga* extract, one tablet twice a day. Remaining others conditions such as advanced or severe or poor control, patients with advanced diabetic complications were excluded. Additionally, patients taking other alternative therapies, pregnant and lactating mothers were not included in the observation study. Flow chart of the study disposition of Type-2 diabetics patients taking *S. oblonga* extract is shown in Figure 1.

Procedures followed for the observational study

The post marketing observational study data were collected from the patients visiting the five centers in and around Hyderabad and Secunderabad during the period of December 2015 to August 2016. The patient data were collected for three subsequent regular follow-up visits with 1-month interval each from the respective outpatient departments, namely J R's Diabetes & Wellness Centre, Karkhana, Secunderabad; Ayuplus Multi Specialty Hospital

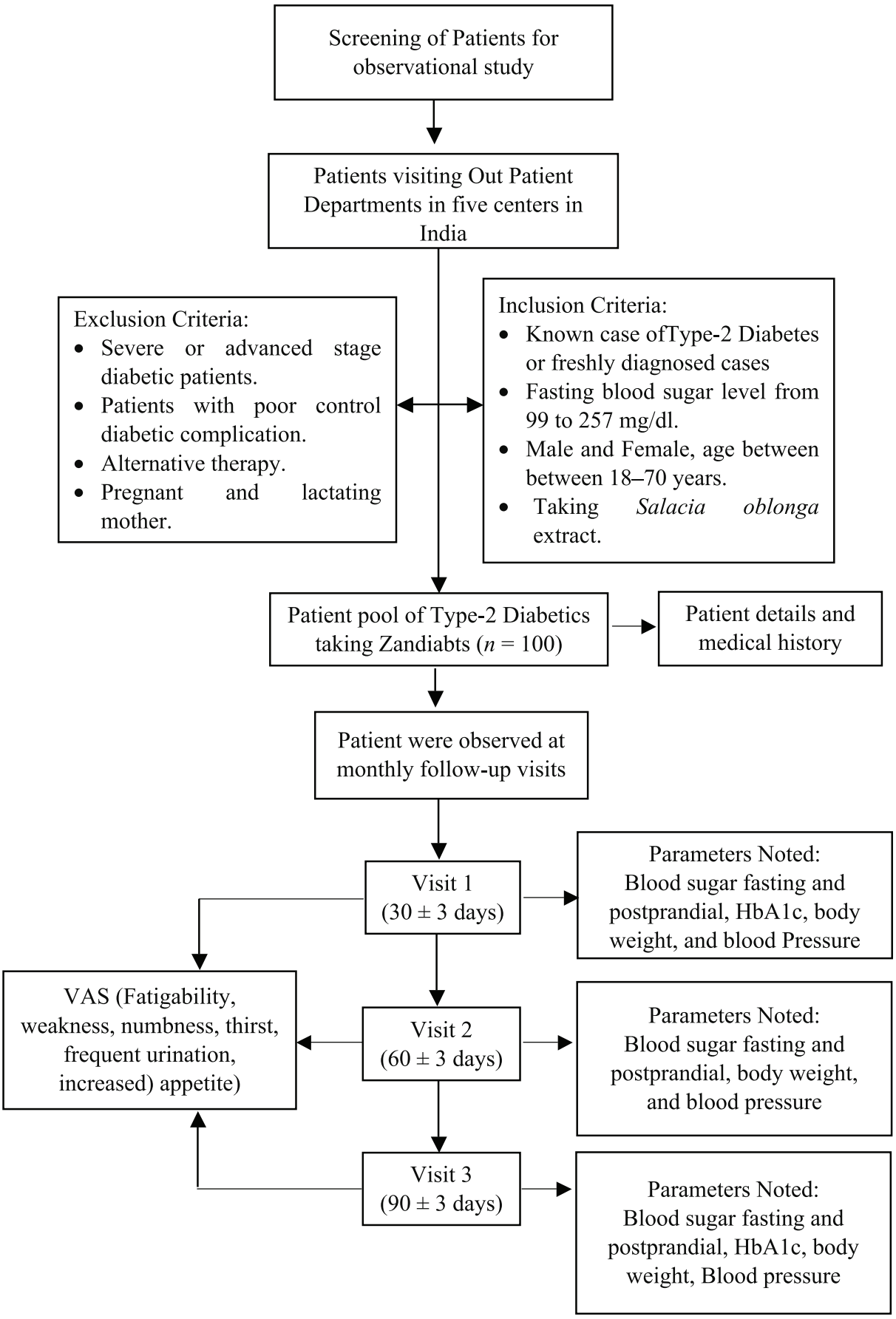

Figure 1. Flow chart of study disposition of type-2 diabetics patients taking *S. oblonga* extract (VAS: Visual analog scale; HbA1c: Glycated hemoglobin A1c).

Table 1. Effect of *S. oblonga* extract on fasting and postprandial blood glucose levels.

Parameter/Event	Baseline	Visit 1 (30 ± 3 days)	Visit 3 (90 ± 3 days)
Fasting blood glucose level (mg/dl)	157.0 ± 35.29	139.4 ± 26*	127.5 ± 34.58*
Postprandial blood glucose level (mg/dl)	224.8 ± 46.70	197.8 ± 41.79*	183.5 ± 38.60*

Values are mean ± SD. Statistically significant difference was denoted with *= $p < 0.001$ *vs.* baseline value.

Diabetology Centre, Nagole, Hyderabad; Sameer Clinic, Kothaguda, Hyderabad; Mitra Hospital, Musheerabad, Hyderabad, and Venkateshwara Clinic, Saleem Nagar, Hyderabad. The data of routine blood parameters, i.e., blood sugar (fasting and postprandial) and glycosylated hemoglobin (HbA1c) were recorded as per the reports brought by the patients at the time of visits. The data of compliance for medications, i.e., *S. oblonga* extract twice daily (Tablet) were reinforced along with the other routine anti-diabetic medications and the same was recorded in a structured format of data record form.

During visits, the details of the patients, food habits, addictions, medical history, and current treatment were recorded. In beginning and at every follow-up, body weight (kg), blood pressure (mm/Hg), blood Sugar (fasting and postprandial) (mg/dl), and HbA1c (%) were recorded. To record the improvement in addition to blood sugar control, the patients were asked to rate their present condition in visual analog scale (VAS) for various symptoms such as fatigability, increased thirst, increased appetite, weakness, increased urinary frequency, and tingling/numbness, with 0 being no symptoms and 10 being the maximum symptoms. The adverse effects were recorded as and when they were reported.

Statistical analysis

Descriptive statistical methods were used for analyses. Data were expressed as a mean ± standard deviation (SD). Shapiro–Wilk and D'Agostino–Pearson tests were used to test for normality of continuous data between male and female patients, such as age and body weight. Paired *t*-test was used to analyze the blood sugar (fasting and postprandial), and for the symptoms measuring the QOL, an analysis was performed by using Kruskal–Wallis test, including treatment and period as fixed effects and subject nested within site as a random effect. GraphPad Prism-6 (GraphPad Software Inc., USA La Jolla, CA) software was used for statistical analysis. A p value less than 0.05 was considered as statistically significant.

Results

Demographic and physiological examination

Out of 100 participants, females and males were 42 and 58, correspondingly. The mean age of a female and a male was 53.2 ± 11.3 and 53.3 ± 11.3 years, respectively. Age and weight of male and female patients were found to be normally distributed when tested with the Shapiro–Wilk and D'Agostino–Pearson tests of normality. The mean body weights of the patients at various stages of treatment were at baseline 70.54 ± 12.37 kg, during the first visit was 70.03 ± 11.48 kg, during the second visit was 69.05 ± 11.21 kg, and at the third visit was 69.23 ± 11.00 kg. There was a statistically significant change in weight ($p < 0.05$) at the end of the study. The mean blood pressure systolic/diastolic (mm/Hg) of the patients at various stages of treatment was recorded at baseline 129.07 ± 14.14/81.85 ± 11.02, during the first visit was 125.91 ± 13.22/81.53 ± 7.77, during the second visit was 125.76 ± 11.89/79.80 ± 7.13, and at the third visit was 124.15 ± 10.23/81.83 ± 6.21. The blood pressure did not fluctuate significantly throughout the study.

Blood glucose level

A reducing trend was noted in the fasting blood glucose levels in the subsequent visits with a statistically significant reduction at the end of 3 months compared with the baseline. A reduction of 18.78% in fasting blood glucose level was observed at the end of 3 months (Table 1). Similar trend was also observed with postprandial blood sugar levels during 3-month treatments, where a reduction of 18.37% was noted at the end of 3-month treatment (Table 1). This observation revealed the potential hypoglycemic effect of the Salacia root extract.

Glycated hemoglobin HbA1c

A reduction of 8.35% as compared with baseline was noted at 3 months of *S. oblonga* extract treatment. A statistically significant reduction ($p < 0.001$) in the HbA1c levels was observed when compared with baseline value at the end of 3 months (Table 2) and suggests that *S. oblonga* extract have the potential for glycemic control in diabetes.

Table 2. Effect of *S. oblonga* extract on HbA1c levels.

Parameter/Event	Baseline	Visit 3 (90 ± 3 days)
HbA1c (%)	8.02 ± 1.55	7.35 ± 0.96*

Values are mean ± SD. Statistically significant difference was denoted with *= $p < 0.001$ *vs.* baseline value.

Qualitative parameters—Visual analog scale (VAS)

Various symptoms, which were rated in 10 points VAS scale in the subsequent visits and the score were compared with baseline (Table 3). Lower the score better is the efficacy and improvement in the condition.

Fatigability

A trend of reduction was noted in the fatigue response in the subsequent visits with a statistically significant reduction ($p < 0.05$) at the end of 3 months compared with baseline. A decrease of 67.46% was observed at the end of 3 months of the study. This observation suggests that daily administration with *S. oblonga* extract helps in reducing the diabetes-associated fatigability.

Weakness

A trend of reduction was noted in the weakness levels in the subsequent visits with a statistically significant reduction ($p < 0.05$) at the end of 3 months compared with baseline. A reduction of 68.01% was noted at the end of 3 months of the study. This observation suggests that daily administration with *S. oblonga* extract helps in reducing the diabetes-associated symptom of weakness.

Increased appetite

In people with diabetes, increased craving for food is usually noted. During the study, a trend of reduction was noted in the increased appetite levels at the end of 3 months compared with baseline and a decrease of 81.27% was observed after 3-month treatment. This observation suggests that daily administration with *S. oblonga* extract helps in reducing the diabetes-associated symptom of "increased appetite."

Increased thirst

A trend of reduction was noted in the excessive thirst levels at the end of 3-month treatment and a reduction of 97.96% as compared with baseline was observed.

Tingling/Numbness

A trend of reduction was noted in the mild tingling/numbness sensation in the subsequent visits with a statistically significant reduction ($p < 0.05$) at 3 months compared with baseline. A reduction of 93.96% was noted at the end of 3 months of the study.

Increased urinary frequency

The frequency of urination was also reduced in the subsequent visits with a statistically significant reduction ($p < 0.05$) at 3 months compared with baseline. A decrease of 96.97% was noted at the end of 3 months of the study. This result suggested that patient's improvement in the diabetes associated symptom of "increased urinary frequency."

Physician response to overall quality of life assessment

At the end of 3 months therapy, physician noted a good to significant improvement in the various symptoms and overall QOL. The majority of patients were on either of the various concomitant anti-diabetic therapies such as glimepiride, metformin, glizide, voglibose, glynase, and sitagliptin. The patients were also using the other medication such as atorvastatin, losartan, telmisartan, and salbutamol as co-therapy. Thus, it can be suggested that Salacia can be taken along conventional anti-diabetic medicines.

Adverse events

No patient experienced any serious adverse event. Out of 100 patients, nine patients reported of dyspepsia and two patients complained of occasional gastrointestinal upset.

Table 3. Effect of *S. oblonga* extract treatment on various qualitative parameters.

S. No	Parameters	VAS score			
		Baseline	Visit 1 (30 ± 3 days)	Visit 2 (60 ± 3 days)	Visit 3 (90 ± 3 days)
1.	Fatigability	8.36 ± 8.80	5.45 ± 2.03	4.260 ± 2.37	2.72 ± 1.67*
2.	Weakness	6.94 ± 2.21	4.87 ± 1.61	3.56 ± 1.90	2.22 ± 1.96*
3.	Increased appetite	5.50 ± 2.44	4.15 ± 2.37	3.30 ± 2.08	1.03 ± 1.22*
4.	Increased thirst	6.40 ± 2.48	3.87 ± 2.68	3.43 ± 2.20	0.13 ± 0.34*
5.	Tingling/Numbness	4.47 ± 3.21	3.29 ± 2.37	2.57 ± 1.87	0.27 ± 0.78*
6.	Increased urinary frequency	6.27 ± 2.50	3.71 ± 2.53	3.02 ± 2.00	0.19 ± 0.60*

Values are mean ± SD. Statistically significant difference was denoted with *= $p < 0.05$ *vs.* baseline value.

Discussion

It is a well-known fact that, since prehistoric times, Salacia species have been widely used by the folklore practitioners for the treatment of hyperglycemia and obesity. This paper deals with the effect of *S. oblonga* root extracts—240 mg/tab twice daily on blood glucose levels, glycated hemoglobin (HbA1c), and qualitative parameters of improved life in diabetes mellitus patients. The selected dose of the herbal *S. oblonga* extract had significant effects on fasting and postprandial glucose levels and also improves the QOL in patients suffered with diabetes mellitus. The dosage of 240 mg twice daily was kept basis the randomized clinical study evaluating the effect of a high-carbohydrate meal on postprandial glycemia and insulinemia in 66 patients with type 2 diabetes. The dosage of 480 mg *Salacia* extract showed maximum response in lowering acute glycemia and insulinemia after a high-carbohydrate meal [10].

The study was designed in such a way that one value of HbA1C after baseline is captured to get an idea on the control of glycemia after treatment with Salacia. Therefore, the total follow-up with the patients was planned for 3 months. There is a limitation for this data collection procedure and warrants a well-designed randomized clinical trial with longer duration of active treatment and follow-up.

The reported observations in many pre-clinical and clinical studies of its efficacy against diabetes are attributed to its insulinogenic action, suggesting that Salacia root extracts might stimulate insulin secretion from the pancreatic β-cells and be causing β-cell regeneration in the pancreas [14,22–25]. In one such study, Williams et al. have reported that the extract of *S. oblonga* brings down postprandial glycemia and insulinemia after a high-carbohydrate meal in 66 patients with type 2 diabetes (mean age of 61 years) in a randomized, double-blind crossover study [10]. In another study, Koteshwar et al. also demonstrated the oral hypoglycemic activity of Salacia extract in 30 healthy adults in a randomized double blind, placebo-controlled, crossover study, where a single dose of Salacia extract (1,000 mg/day) significantly lowers the plasma glucose level after 90 minutes of carbohydrate rich meal [23]. The results of the study showed that the Salacia extracts significantly lowered the fasting, as well as postprandial glucose levels and also lowered the HbA1c levels compared with the baseline. Observations reported in this communication encouraged us for the quest of the mechanism of antidiabetic action and safety indication of Salacia root extract. The present study was in concurrence with this assumption, and Salacia extracts may likewise, be used for a long-standing glycemic control.

Shivaprasad et al. evaluated the efficacy and safety of Salacia leaves and root extracts in 29 patients with pre-diabetes and mild to moderate hyperlipidemia in a randomized, double-blind, placebo-controlled study, where the authors showed that the Salacia extracts at dose 500 mg/day significantly lowered the lipid profile and glycemic levels after 6 weeks. There were no adverse events reported and all safety parameters were within the normal range [26]. A similar trend of lowering of body weight was noticed in our observational study with the mean body weights loss of the patients at various stages of treatment during the treatment period. Moreover, during the entire duration of therapy, there was a constant control of blood pressure in patients. Therefore, in the current observational study, there appears some hope that *S. oblonga* extract might be a useful choice in management of the pre alarming symptoms of diabetes, as hypertension with increase in lipids and body weight are considered as risk factors.

These observations additionally supported that Salacia extracts might be advantageous in the postprandial glucose control. Postprandial hyperglycemia is an excellent indicator of progression to diabetes and key marker for glycemic control. The quality of life (QOL) is defined by the WHO as "an individual's perception of his/her position in life in the context of the culture and value systems". Diabetic mellitus has profound effects on the social, psychological, and physical wellbeing of a person making the management of diabetic patients a complicated and tedious process for the health care professionals [27]. The reported observations have revealed that continuous daily administration with Salacia extracts not only lowers the blood glucose levels but also improved the other conditions like fatigability, weakness, appetite, and urinary frequency, which are often experienced by diabetes patients. In all the patients, continuous daily administration with *S. oblonga* extract at a dose 240 mg twice in a day also improved the QOL in comparison with the baseline. Along these lines, the long-term benefits of this homegrown medication on glycemic control were investigated inside this populace to discover its incentive in the realm of diabetic treatment.

Conclusion

It can be concluded on the basis of the observational study that *S. oblonga* extract can be a potential choice of therapy in management of diabetic along with other conventional anti-diabetic therapy safely. Moreover, the data indicated that *S. oblonga* extract may be useful in improving health standard in diabetic.

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Conflict of interest

The authors declare that they have no conflict of interest.

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