



Short Communication

Effect of licorice on patients with HSD11B1 gene polymorphisms- a pilot study

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ABSTRACT

The positive association of HSD11B1 gene polymorphism with type 2 diabetes (T2D) and prediabetic conditions has been revealed. In the current study, we assessed the effectiveness of licorice on the clinical profile of the patients with HSD11B1 gene polymorphism. Licorice (*Glycyrrhiza Glabra*) is a competitive inhibitor of 11 beta-hydroxysteroid dehydrogenase 1 (11 β -HSD1) enzyme and has been traditionally reported as an anti-ulcer, anti-pyretic, anti-thirst, anti-inflammatory, hypoglycemic and hypolipidemic agent. The aim of the study was to assess the effectiveness of licorice on the clinical profile of participants with HSD11B1 gene polymorphism. The study was performed using diabetic patients with HSD11B1 gene polymorphism. Biochemical and anthropometric parameters were measured using standard diagnostic tools. Fourteen patients were divided into two groups by simple randomization, Licorice group (treated with 750 mg licorice/day for three weeks), and placebo group (treated with 750 mg placebo/day for three weeks). Investigations were repeated at the end of three weeks. Licorice showed a significant reduction in serum insulin levels ($p = 0.03$). There was no significant change in any other clinical parameters either by licorice or placebo. Conclusively, licorice moderately improves serum insulin levels in patients with HSD11B1 gene polymorphism. From our pilot study, the safety of licorice is confirmed at a dose of 750 mg/day. However, the study can be repeated at a higher dose to show its effectiveness and safety. © 2020 The Authors. Published by Elsevier B.V. on behalf of Institute of Transdisciplinary Health Sciences and Technology and World Ayurveda Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Overexpression of 11 β -HSD1 is involved in the onset of obesity, insulin resistance, diabetes and prediabetic conditions [1]. HSD11B1 gene that encodes 11 beta hydroxysteroid dehydrogenase type 1 (11 β -HSD1) enzyme, influences the circulating cortisol levels, insulin levels, blood sugar, lipid profile and other associated components [2]. HSD11B1 polymorphisms have shown positive association with type 2 diabetes and prediabetes conditions such as metabolic syndrome in the South Indian population [3]. Blood sugar and lipid levels are higher in patients with raised 11 β -HSD1 levels. 11 beta-hydroxysteroid dehydrogenase type 1 (11 β -HSD1)

enzyme inhibition has been recommended as an ideal therapeutic target for the treatment of type 2 diabetes (T2D) [4].

Licorice is a natural inhibitor of 11 β -HSD1, with hypoglycaemic and hypolipidemic properties [5]. In Ayurveda, it is used as a haemostatic, diuretic, bronchodilator, laxative, as an anti-ulcer, anti-pyretic, anti-inflammatory agent [6]. The mechanism of inhibition is by competitive inhibition of 11 β -HSD1 and pretranslational inhibition of 11 β -HSD1 [7].

Animal studies have shown that the licorice significantly decrease serum lipid levels [5,8,9]. In fifteen healthy patients, Armanini et al. showed that the consumption of licorice reduced body fat mass [10]. In another study of Fuhrman et al. licorice (0.1 g/day for four weeks) decreased plasma blood sugar and lipid levels [11].

No reports are available in literature regarding the impact of licorice on the patients with the HSD11B1 gene polymorphism. Consequently, we assessed these issues in the reduction of

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endpoints in patients with HSD11B1 gene polymorphisms with the 11 β -HSD1 inhibitor Licorice study.

2. Materials and methods

2.1. Study design and selection criteria

This study is a randomized, double blind, placebo controlled, parallel arm, phase 2 clinical testing to compare the effectiveness of treatment with licorice and the treatment with matching placebo. Newly diagnosed T2D patients, aged 18 to 75, male or female, with HSD11B1 gene polymorphism willing to provide written informed consent before participating in the trial were included. The T2D was confirmed before assessing HSD11B1 gene polymorphism based on the clinical symptoms, fasting blood sugar (FBS) \geq 126 mg/dL, postprandial (PPBS) and random blood sugar (RBS) \geq 200 mg/dL, glycosylated hemoglobin (HbA1c) level \geq 6.5%, following the criteria of the American Diabetes Association. The cases with type 1 diabetes, malignancy, acute infections, inflammation, endocrine disorders, patients on insulin therapy, and chemotherapeutic agents, old, sick and pregnant patients were excluded.

2.2. Patients

All participants were recruited from the inpatient and outpatient department of Kasturba Medical College, Mangalore. Patients of our previous study who showed positive association of HSD11B1 gene polymorphism with T2D and prediabetic conditions were used for licorice study [3]. The study protocol was approved by the Manipal University Ethics Committee (IEC no. ECR/191/Inst/KL/2013) and the trial has been registered in the Clinical trial registry of India (CTRI/2015/09/006171).

2.3. Licorice intervention

The standardized preparation of solid licorice root powder enclosed in the hard gelatin capsule was procured from the Himalaya Drug company whose products comply with standards of Ayurvedic pharmacopoeia of India. Each capsule contains 250 mg of licorice root powder extract. The company has quality management system for physiochemical standardization of raw material, quality assessment, and purity analysis under the directives of the department of AYUSH, certified with GLP, GMP (Good Manufacturing Practices), issued by the Licensing Authority, Directorate of Indian Systems of Medicine. Hydroalcoholic extract method involves crushing of the dried roots and rhizomes and extraction with 70% v/v ethanol, concentration of the hydro-alcoholic extract under reduced pressure and evaporation in air to get a dry powder to be enclosed in the hard gelatin capsule [12]. Standardization and determination of their phytochemical profile is performed by HPTLC (High Performance Thin Layer Chromatography, and MS (Mass Spectrometry).

2.4. Intervention study procedure

Fourteen T2D patients with HSD11B1 gene polymorphism were randomized arbitrarily into licorice and placebo groups by simple block randomization. All the participants received either Licorice or placebo in a dose of three capsules (250 mg) thrice daily, for three weeks. All participants underwent clinical examination and evaluation of weight, waist circumference (WC), blood pressure, fasting blood sugar (FBS), lipid levels (total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, triglycerides (TG)), serum cortisol, serum insulin, serum sodium (Na⁺) and potassium (K⁺) levels on entry. Serum electrolyte levels (Sodium and potassium) and blood

pressure were monitored at weekly intervals. All participants continued their routine diets during the study. Adverse effects if any were recorded. Clinical investigations were repeated at the end of 3 weeks to observe improvements in clinical profile. The consort flow diagram illustrates the progress through the phases of this study (Fig. 1).

2.5. Primary and secondary outcome measure

The primary end-points in this study were the decrease of baseline weight, blood sugar, lipid levels, serum insulin and cortisol levels. The licorice safety and toxicity profiles were secondary end points.

3. Statistical analysis

All statistical analyses were performed using SPSS version 20 for windows (SPSS, Chicago, Illinois, USA) and SNPstat Software [13]. A Paired t-test was used to compare the improvement in clinical parameters by the licorice and placebo. The sample size was calculated using the formula $n = (2 * (Z_{\alpha} + Z_{\beta})^2 * \sigma^2) / d^2$ at 95% confidence interval, 80% power, based on the study of Fuhrman et al. [11] with the effect size of 14 and standard deviation of 9. All the values are represented as a mean \pm standard deviation. The p values less than 0.05 were considered statistically significant.

4. Results

4.1. Clinical profile after licorice and placebo intervention

The licorice showed significant reduction in the serum insulin levels ($p = 0.03$) in participants with HSD11B1 gene polymorphism (Table 1). However, there was no improvement in other clinical parameters by licorice. Placebo did not significantly change any clinical parameters in participants with HSD11B1 gene polymorphism.

4.2. Presentation of side effects

During the three-week treatment, patients on licorice showed signs of gastro intestinal (GI) (burping, flatulence), oedema and musculo-skeletal (back pain) pain. Two patients on placebo complained of excess hunger and weight gain (Table 2).

5. Discussion

Herbal and Ayurveda therapies are unlikely to have the adverse effects of conventional treatments for T2D and have been widely researched, especially in India. Here, in our study the Ayurveda capsules of drug licorice (Himalaya Drug Company, Mangalore, Karnataka), was evaluated for use in diabetic patients having HSD11B1 gene polymorphism. We found a significant decrease in serum insulin level by licorice. Similar decrease in serum insulin levels were observed in mice by the study of Sil et al. and Kamisoyama et al. [14,15]. In our study, licorice did not significantly improve any other clinical parameters. Contradictory to this, licorice brought significant decrease in FBS ($p < 0.01$), TC ($p < 0.01$), LDL ($p < 0.01$), and TG ($p < 0.01$) in 12 hypercholesteraemic Israeli patients [11]. However, their study population was different, which may be the reason for discrepancy.

Licorice is a natural 11 β -HSD1 inhibitor. No studies have reported the effect of licorice in Indian population. To the best of our knowledge, this is the first study on the effectiveness of licorice on patients with HSD11B1 gene polymorphism. In our previous studies, we observed positive association of HSD11B1 gene

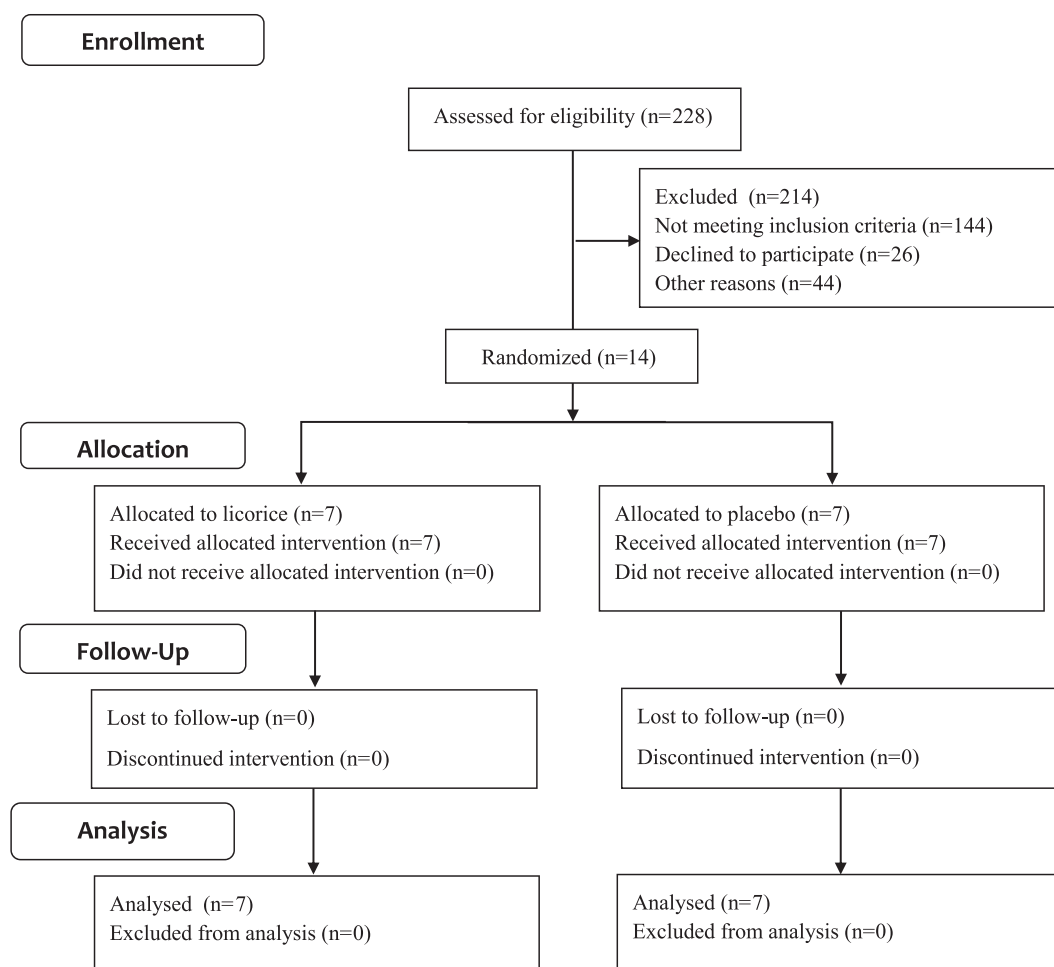


Fig. 1. CONSORT Flow Diagram.

polymorphism with T2D, prediabetic conditions, and their clinical profile [3,16,17]. Therefore, we assessed the influence of the licorice on clinical profile of patients with HSD11B1 gene polymorphism. In our study, 71% of cases on licorice showed marginal weight reduction compared to 14% of cases on placebo. Reduction in body weight has been previously reported in high fat diet induced obese rats by Eu et al. [18]. Hypertension is considered to be the common side effect of licorice. However, 86% cases of our study on licorice

showed decrease in BP. A study by Fuhrman et al. also showed decrease in SBP in hypercholesterolaemic patients treated with licorice [11]. In another study, Sharma et al. studied the effect of licorice in combination with 23 other Ayurveda formulation on T2D Indian patients for 3 months and the patients showed improvement in clinical profile from second month onwards [19]. However, it's uncertain that the improvement was mediated by licorice alone, as it was administered with other formulation. The knowledge of

Table 1

Effect of licorice and placebo on clinical parameters of T2D patients with HSD11B1 gene polymorphism.

Parameters	Licorice treated group			Placebo treated group		
	Before trial	After trial	p	Before trial	After trial	p
Weight (kg)	69.28 ± 11.18	68.38 ± 10.28	0.132	65.72 ± 6.78	66.04 ± 6.87	0.483
WC (cms)	89.07 ± 16.22	88.35 ± 15.73	0.601	85.57 ± 3.99	87.5 ± 3.92	0.161
FBS (mg/dL)	97.28 ± 14.56	101 ± 12.19	0.62	103.71 ± 11.2	111.14 ± 17.08	0.089
TC (mg/dL)	183.85 ± 29.61	186.28 ± 33.88	0.699	195.85 ± 45.97	194.1 ± 51.55	0.853
HDL (mg/dL)	51.11 ± 10.21	52.14 ± 9.88	0.482	50.18 ± 12.77	48.8 ± 16.28	0.483
LDL (mg/dL)	117.55 ± 30.21	124.52 ± 37.78	0.279	128.3 ± 48.17	131.31 ± 51.66	0.706
TG (mg/dL)	94.57 ± 37.84	90.14 ± 25.68	0.547	144.7 ± 64.26	130.57 ± 45.02	0.396
SBP mmHg	121.71 ± 11.85	118.57 ± 13.45	0.481	129.28 ± 10.17	128.57 ± 24.10	0.925
DBP mmHg	81.14 ± 9.08	77.28 ± 9.74	0.236	77.14 ± 7.55	77.14 ± 7.55	1.00
K+ nmol/L	4.4 ± 0.3	4.6 ± 0.42	0.141	4.44 ± 0.43	4.38 ± 0.45	0.577
Na+ nmol/L	140 ± 2.08	139.14 ± 1.21	0.225	139.66 ± 2.8	139.33 ± 1.03	0.765
Serum Insulin ulu/mL	16.70 ± 6.22	12.42 ± 3.80	0.03*	20.25 ± 6.42	19.09 ± 6.77	0.73
Serum cortisol ng/mL	82.75 ± 48.87	81.98 ± 41.76	0.957	104.54 ± 52.49	111.04 ± 51.29	0.541

Data are shown as mean ± Standard deviation. *Significant p value < 0.05. WC, waist circumference; FBS, fasting blood sugar; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; K+, serum potassium; Na+, serum sodium.

Table 2

Number of patients in licorice and placebo groups with presentation of side effects.

Side effects	Licorice group (n)	Placebo group (n)
GI side effects (Burping, flatulence) and oedema	1	0
Musculo-skeletal pain (Back pain and left side body pain)	2	0
Excess hunger	0	1
Weight gain	0	1

the consequences of licorice-anti-diabetic drug interactions is essential so that a unique combination of the licorice and modern medicine could be achieved [20]. Currently, there is limited clinical evidence to support serious licorice–drug interactions, especially the interaction with anti-diabetic drugs. There has been a report of the inhibitory effect of licorice–warfarin interaction on the hepatic microsomal enzyme system and risk of blood clotting [21]. In another study licorice induced hypokalemia in one patient presenting digoxin toxicity [22]. However, our study participants were not on digoxin and did not show hypokalemia. Table 3 shows probable effects of licorice interaction with known drugs.

Since there is a great individual variation in the susceptibility to licorice, it is difficult to determine precisely the dose of licorice required [24]. In previous studies, side effects of oedema and hypertension were observed in those patients whose daily intake of licorice was in the range from 1.5 to 250 gm/day [24]. Half of the lower limit of this dose was used in our study.

Since this is the pilot comparative study and considering patient's safety as well as acceptability, we used smaller sample size and shorter duration. Except for serum insulin levels, licorice did not improve any clinical parameters. However, the study needs to be replicated with the larger sample size and longer study duration to study the effectiveness of licorice. The study with higher doses of licorice is necessary with precautions as the current dose decreases only insulin but not FBG in Indian population with HSD11B1 gene polymorphism.

According to Ayurveda our study participants showing HSD11B1 polymorphism belong to the Kapha constituent [25,26]. In colder climates, licorice may induce nasal congestion, sinusitis, running nose, in patients with kapha constitution. However, in normal climatic conditions and in other prakritis, licorice may prevent *nasal sinusitis*, severe acute respiratory syndrome, and even the coronavirus by preventing fusion of the virus with the membrane of the host cell [27,28]. Thus future studies must include patients showing HSD11B1 polymorphisms, exhibiting pitta body constitution, and pitta symptoms, as licorice may provide better results in these conditions according to Ayurveda. Since the anti-inflammatory effect of licorice is confirmed [29], it is also worthwhile to assess even the inflammatory markers like CRP, IL-6, and TNF- α in the T2D patients who generally show higher levels of inflammation in their bodies [30]. While licorice is indispensable against various ulcers

and infections, the glycyrrhizin component of licorice may show aldosterone-like effects if consumed at higher dose [31]. Removal of the glycyrrhizin compound will eliminate the risk altogether [31].

From our study, safety of licorice for pilot study is confirmed and the study can be repeated with the higher dose. Many pharmaceutical companies are developing potential 11 β -HSD1 inhibitors to treat obesity and T2D. Studies in mice have yielded promising results with reduction in body weight and FBS in obese and diabetic mice strains [18,32]. While human studies using novel 11 β -HSD1 inhibitors are awaited, in this study we have used the licorice as a 'prototype' to assess the clinical effects of 11 β -HSD1 inhibition on metabolic profile of patients with HSD11B1 gene polymorphism.

6. Conclusion

In conclusion, licorice moderately improves serum insulin levels in patients with HSD11B1 gene polymorphism. From our pilot study, safety of licorice is confirmed at a dose of 750 mg/day. However, the study can be repeated at a higher dose to show its effectiveness and safety.

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Conflict of interest

None.

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Table 3

Licorice-drug interactions.

Interacting drug	Significance	Reference
Warfarin	Decreased blood clotting, potentiation of the effect of Warfarin therapy, inhibition of hepatic microsomal enzyme system	[21]
Digitalis	Congestive heart failure by digitalis toxicity in elderly man	[22]
Digoxin	Hypokalemia, high blood pressure	[23]

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