

The Effects of *Boswellia serrata* Gum Resin on the Blood Glucose and Lipid Profile of Diabetic Patients: A Double-Blind Randomized Placebo-Controlled Clinical Trial

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Abstract

Regarding preclinical evidence for antidiabetic effects of *Boswellia serrata*, we evaluated antihyperglycemic and lipid-lowering effects of *Boswellia serrata* gum resin in type 2 diabetic patients. Fifty-six diabetic patients were randomly allocated to 2 groups to receive 250 mg of the *Boswellia serrata* gum resin or placebo twice daily for 8 weeks in addition to their routine antidiabetic treatments. Although there was a considerable reduction after the intervention in the field of fasting blood sugar, glycosylated hemoglobin, and triglyceride in the *Boswellia serrata* gum resin group, no significant difference was observed in all outcome measures between the 2 groups at the end of the study. The current study showed that 8 weeks of complementary use of *Boswellia serrata* gum resin with a daily dose of 500 mg had no better glucose and lipid-lowering effect than placebo in diabetic patients.

Keywords

Boswellia serrata, diabetes mellitus, complementary and alternative medicine, herbal medicine

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Diabetes mellitus, as one of the most common noncommunicable and chronic diseases in the world, especially in low/middle-income countries, has a growing prevalence.¹ In 2014, about 387 million people worldwide were afflicted with diabetes, with many cases undiagnosed.² The diabetes prevalence in Iran is estimated to be 7.7% in adults.³ Diabetic patients suffer from a variety of related diseases such as dyslipidemia, which increases their cardiovascular risk. Since diabetic patients with dyslipidemia have a higher mortality rate compared with diabetes mellitus individuals with no dyslipidemia, prevention and management of dyslipidemia in these patients seems to be essential.^{4,5}

Nowadays, there is an increasing interest toward complementary and alternative medicine.^{6,7} Also, because of insufficient efficacy and prominent adverse effects of the current therapies for hyperlipidemia, diabetes and its complications, there is an increasing interest in complementary and alternative therapies especially the use of medicinal plants in treatment of this disease.⁸⁻¹² Because of the mentioned comorbidity of diabetes and hyperlipidemia, medicinal plants with concurrent glucose and lipid-lowering effects are an area of research interest.¹³⁻¹⁵

Boswellia serrata (commonly known as *Salai* in India and *Kondor* in Arabic) is one of the medicinal plants that is traditionally used to treat various diseases, including diabetes.¹⁶⁻¹⁹ Previous studies showed anti-inflammatory, antitumor activities, and anti-cancerous effects of this plant.²⁰ Antihyperglycemic and antihyperlipidemic effects of *Boswellia serrata* in streptozotocin-induced diabetic rats have been shown in other

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studies as well.^{20,21} Moreover, a study showed that *Boswellia serrata* has protective effects on diabetic complications in animal model.²² It also has showed beneficial effects on blood glucose, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) of diabetic patients with the daily dose of 900 mg without any important side effect.^{23,24} According to increase in serum insulin of patients who received *Boswellia serrata*, it is supposed that its antihyperglycemic effect is through increase in insulin secretion.^{23,24}

Regarding previously determined antihyperglycemic effect of *Boswellia serrata* in animal models and also in one dose in human, this study aimed to reevaluate antihyperglycemic and lipid-lowering effects of *Boswellia serrata* gum resin in type 2 diabetic patients in lower dose (500 mg/d) in a double-blind randomized placebo-controlled trial.

Materials and Methods

Preparation of Drugs

The *Boswellia serrata* with certified botanical origin India (standardized for 60% Boswellic acids by Himalayan Herbaria Inc, India), was purchased from herbal market, Karaj, Iran. It was ground into powder. The gum powder as an intervention drug and toast powder due to relative similarity to the gum powder, as a placebo, were separately filled into oral gelatin capsules (250 mg) with identical appearance by using a hand-operated capsule-filling machine (Scientific Instruments and Technology Corporation).

Phytochemical Assay

Thin layer chromatography was used for recognizing chemical components of resin. A variety of indicators, including vanillin sulfuric acid, ferric chloride, and natural product polyethylene glycol were used in this assay. The indicators were sprayed on the prepared thin layers of fractions and observed at 260 and 280 nm wavelengths under ultraviolet light.

Identification of the Volatile Oil Constituents

The volatile essential oils obtained by hydrodistillation of *Boswellia serrata* (volatile oil 10%) were analyzed using an Agilent 6890 GC equipped with BPX5 capillary columns (30 m × 0.25 mm, inner diameter 0.25 µm film thicknesses) and a mass spectrometer column temperature was gradually increased from 50°C to 240°C with a rate of 3°C/min. For gas chromatography/mass spectrometry detection, electron ionization system was used with ionization energy of 70 eV. The injector and ion source temperatures were set at 290°C and 220°C, respectively. One microliter of the sample was injected manually in splitless mode. C9-C20 *n*-alkanes were used as reference points in calculation of the Kovats indices (KI). Tentative identification of the compounds was done based on the comparison of their relative retention time and mass spectra with those of the NIST and Wiley library data of the gas chromatography/mass spectrometry system and literature data.²⁵

Trial Design

The trial is a 2-arm, double-blind randomized placebo-controlled clinical trial using a parallel design with a 1:1 allocation ratio. There was no change in methods after trial commencement.

Participants and Intervention

A total of 384 patients who referred to a private diabetic health care center in Karaj, Iran, during March 2014 and October 2014 were evaluated for inclusion in the study. All the patients were visited by the investigator; if they met the inclusion criteria, they were enrolled in the study. Inclusion criteria for the participants were 18- to 65-year-old patients with type 2 diabetes according to the American Diabetes Association criteria with fasting blood sugar (FBS) = 140-180 mg/dL, glycosylated hemoglobin (HbA1c) 7% to 9%. Exclusion criteria were pregnancy; lactation; nursing women; and patients on insulin, oral and topical steroid, and diuretic agents. Also, patients with serious cardiac, renal, hepatic or hematological diseases, hypothyroidism, tachycardia, vertigo, and seizure were excluded. At last, 56 patients were allocated to the intervention and control groups. The enrolled patients were randomly assigned to receive *Boswellia serrata* gum capsule (n = 27) as the intervention group or placebo (n = 29). Patients received *Boswellia serrata* gum 250 mg capsules or placebo capsules twice daily after meal for 8 weeks. Consumption of conventional oral hypoglycemic agents was continued in the 2 groups simultaneously. The patients' compliance was checked via asking on the number of missed dose in their visit.

Sample Size

The sample size was calculated as 25 patients in each group to estimate 20 mg/dL difference of FBS between the groups, considering type I error = 0.05, 80% power.²⁶

Randomization, Blinding, and Allocation Concealment

Fifty-six eligible patients were randomized after signing the consent form in 2 parallel groups (*Boswellia serrata* gum capsule as the intervention group and placebo group) by the investigator. The randomized list was generated using Microsoft Excel with a block randomization, with block size of 4, as previously shown.²⁷ The investigator, drug deliverers, and statisticians were blind to the allocation of the patients. Moreover, because of the same shape and size of the intervention and placebo capsules, the patients were blind to the drug allocation.

Ethical Considerations

This trial is a 2-arm, double-blind randomized placebo-controlled clinical trial that was registered by the American Economic Association's registry for randomized controlled trials with a code: AEARCTR-0000898. The local Medical Ethics Committee of Qazvin University of Medical Sciences approved the trial protocol (reference number: 2741/20/3) and written informed consent was obtained from each patient prior to the study. This study compared *Boswellia* capsule with placebo and both groups received routine hypoglycemic agents to avoid any deprivation from the standard treatment.

Outcomes

Mean values for the FBS, HbA1c as primary outcome measures and total cholesterol, LDL, HDL, triglyceride, and insulin level as secondary outcome measures were determined at the baseline and 8 weeks after the intervention in both groups. Blood samples were drawn after an overnight (12 hours) fasting and sent to the hospital's central laboratory. All the blood sample parameters were measured by using

Table 1. Phytochemical Results of the *Boswellia serrata* Gum Resin.

Components	Solvent Systems	Reagents	Result
Terpenoids and phenylpropanoids	n-Hexane:ethyl acetate (7.2:2.8)	Vanillin sulfuric acid	+
Phenolic components	Chloroform:ethyl acetate:formic acid (5:4:1)	Ferric chloride	+
Flavonoids	Ethyl acetate:methanol: water (100:13.5:10)	Natural product reagent	+

Table 2. The Constituents of Essential Oil of *Boswellia serrata* by Gas Chromatography/Mass Spectrometry.

	Components	%
1	α -Thujene	16.12
2	α -Pinene	25.31
3	Myrcene	13.23
4	<i>p</i> -Cymene	10.78
5	Limonene	2.02
6	Methyl chavicol	5.43
7	β -Elemene	4.01
8	Sabinene	2.03
9	Cadinene	2.62
10	Camphene	3.10
11	β -Phellandrene	4.06
12	Unknown components	11.29

DSS Pink-300 test kit (Drew Scientific Limited, UK) kits in the hospital's central laboratory.

Statistical Methods

The descriptive data were presented as numbers, frequencies, means, and standard deviations. The paired and independent Student *t* test and chi-square test were used for statistical comparison of primary characteristics and outcomes between the drug and placebo groups. The intention-to-treat analysis protocol was used for analysis of the data of patients who did not fully adhere to the study protocol. A *P* value less than .05 was considered significant. SPSS software (version 17, IBM Corporation, Armonk, NY) was used for analysis of data.

Results

Phytochemical Assay

Phytochemical assay by thin layer chromatography showed the main components, including phenyl propanoids, terpenoids, phenolic compounds, and flavonoids that were present in the resin (Table 1).

Essential Oil Constituents

The major components of the essential oil of *Boswellia serrata* by gas chromatography/mass spectrometry were α -thujene, α -pinene, myrcene, and *p*-cymene (Table 2).

Baseline Characteristics Data

During the study, a total of 384 patients were assessed for eligibility, and finally 56 of them were included in the trial and randomized to receive the trial or placebo drug. Figure 1 is a flowchart of the group allocation, enrolment, intervention, follow-up, and result analysis. The patients were reassessed 8 weeks after the intervention. No adverse reaction was reported by the patients. Two patients of the placebo group discontinued the study drug, but they were included in the analysis according to intention-to-treat protocol analysis.

The percentage of female study participants in the intervention and placebo groups was 63% and 45%, respectively. Other baseline characteristics for each group (age and duration of the disease) are shown in Table 3 as the mean \pm standard deviation for continuous variables. There was no significant difference between basic characteristics of the 2 groups (*P* > .05).

FBS, HbA1c, Total Cholesterol, LDL, HDL, Triglyceride, and Insulin Levels

There was also no significant difference between the states of outcome measures in the 2 study groups before the intervention (FBS *P* = .54, HbA1c *P* = .98, total cholesterol *P* = .08, LDL *P* = .12, HDL *P* = .60, triglyceride *P* = .20, and insulin *P* = .20).

There was a considerable reduction after the intervention in the field of FBS (*P* = .04), HbA1c (*P* = .02), and triglyceride (*P* = .01) in the *Boswellia serrata* gum resin group. There was no significant change in outcome measures in the placebo group (Table 4).

No significant difference was observed in all the outcome measures between the 2 groups at the end of the study (FBS *P* = .09, HbA1c *P* = .20, total cholesterol *P* = .31, LDL *P* = .49, HDL *P* = .10, triglyceride *P* = .78, and insulin *P* = .86). Table 4 shows the details of the changes of outcome measures.

Adverse Events

There was no reported adverse event by the patients in the 2 groups of the study.

Discussion

In the present study, we evaluated antihyperglycemic and lipid-lowering effects of *Boswellia serrata* gum resin in type 2 diabetic patients in a double-blind randomized placebo-controlled clinical trial. Results of this trial showed that although there was a reduction after the intervention in the field of FBS (*P* = .04), HbA1c (*P* = .02), and triglyceride (*P* = .01) in the *Boswellia serrata* gum resin group, these changes were not statistically significant compared with the placebo group. Thus, use of *Boswellia serrata* gum resin in 500 mg daily dose for 8 weeks failed to demonstrate significantly better effect on glycemic control and lipid profile in diabetic patients compared with the placebo group.

Multiple herbal remedies have been assessed previously for their antihyperglycemic and lipid-lowering effects. In Chinese herbal medicine, *Xianzhen Pian*, *Qidan Tongmai*, and *Liuwei*

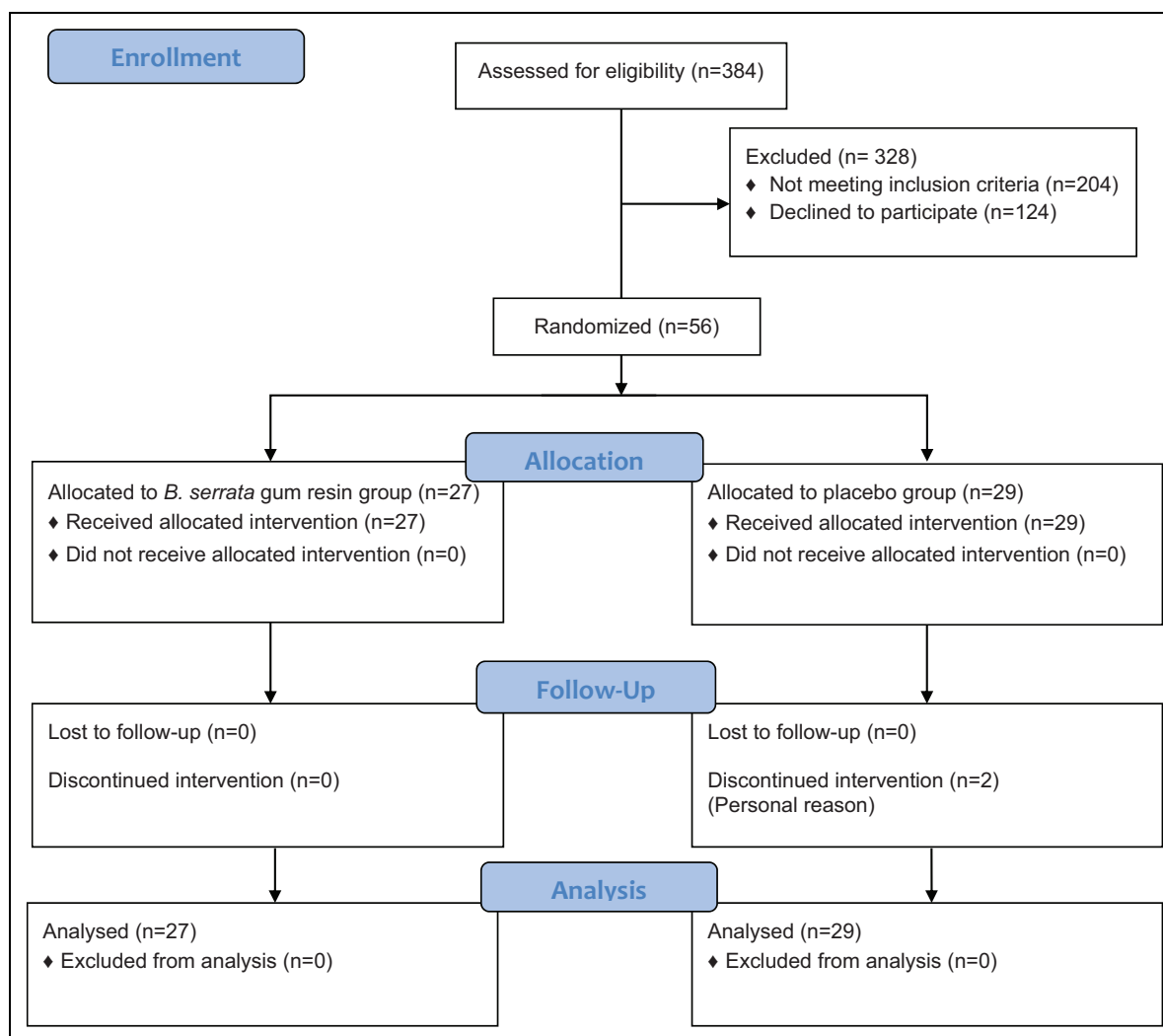


Figure 1. Flowchart of study inclusion, allocation, and follow-up.

Table 3. The Baseline Demographic Information of the Patients in *Boswellia serrata* Gum Resin and Placebo Groups.

Basic Characteristics	<i>Boswellia</i> Gum Resin	Placebo	<i>P</i>
Sex, women, %	63	45	.17
Age, years, mean \pm SD	57.07 \pm 10.08	52.68 \pm 10.69	.16
Duration of diabetes, years, mean \pm SD	11.44 \pm 6.80	10.82 \pm 6.00	.81
Mean body mass index, kg/m ² , mean \pm SD	26.01 \pm 2.42	25.06 \pm 2.03	.13

Dihuang Tang are common herbs that are traditionally used and have approved antihyperglycemic effect.²⁸ Also, in non-Chinese traditional medicine such as traditional Persian medicine, there are several herbs that were significantly effective in reduction of blood glucose such as *Citrullus colocynthis* L., *Silybum marianum*, *Psyllium*, *Teucrium polium*, and pomegranate.^{9,29} Dill, fenugreek, ginger, ginseng, green tea, and *Nigella* are also reported to have hypolipidemic effects.³⁰

Many herbs have been used to control the blood sugar and approved their effects. However, diabetic patients usually have multiple comorbidities, which lead to polypharmacy and increase the risk of drug interactions,³¹ so the trend of researches in the field of herbal medicine is toward the herbs that affects multiple metabolic targets. For example, researches on *Aloe vera* L, *Brassica napus*, *Trigonella foenum-graecum*, *Juglans regia* L, and *Hibiscus sabdariffa* have shown positive effects on lipid profile in addition to antihyperglycemic effects in diabetic patients.^{32–37} *Boswellia serrata* gum resin is one of these herbs that has shown its antihyperglycemic and lipid-lowering effects in animal studies.^{21–24,38} It also has shown glucose-lowering effect in patients with diabetes through increase in insulin secretion in a clinical report.²⁴ In another clinical trial on patients with diabetes, *Boswellia serrata* gum resin supplementation with the daily dose of 900 mg for 6 weeks showed HDL increasing and LDL decreasing effect.²³ These effects may be attributed to the main components of this resin, including phenyl propanoids, terpenoids, phenolic compounds, and flavonoids, which were detected by phytochemical

Table 4. Mean Values (\pm SD) for Fasting Blood Sugar, HbA1c, and Lipids Profile in *Boswellia serrata* Gum Resin and Placebo Groups Before and After the Intervention.

Outcomes	Groups		<i>P</i> ^a
	<i>Boswellia</i> Gum Resin	Placebo	
Fasting blood sugar (mg/dL)			
Before	171.82 \pm 60.78	162.18 \pm 56.37	.54
After	149.86 \pm 26.19	165.77 \pm 43.13	.09
<i>p</i> ^b	.04	.67	
Insulin (UI/L)			
Before	7.37 \pm 4.14	5.97 \pm 4.01	.20
After	8.15 \pm 4.90	8.39 \pm 5.48	.86
<i>p</i> ^b	.48	.13	
HbA1c (%)			
Before	8.17 \pm 1.88	8.17 \pm 1.58	.98
After	7.60 \pm 1.34	8.09 \pm 1.48	.20
<i>p</i> ^b	.02	.86	
Triglyceride (mg/dL)			
Before	162.13 \pm 53.53	141.07 \pm 64.81	.18
After	135.93 \pm 31.92	139.74 \pm 66.22	.78
<i>p</i> ^b	.01	.88	
Total cholesterol (mg/dL)			
Before	196.65 \pm 35.74	179.44 \pm 37.65	.08
After	184.27 \pm 29.78	173.96 \pm 44.79	.31
<i>p</i> ^b	.06	.43	
Low-density lipoprotein (mg/dL)			
Before	104.13 \pm 24.23	93.55 \pm 26.71	.12
After	97.72 \pm 34.13	91.81 \pm 29.72	.49
<i>p</i> ^b	.21	.68	
High-density lipoprotein (mg/dL)			
Before	44.48 \pm 10.44	46.03 \pm 11.73	.60
After	47.44 \pm 7.09	43.44 \pm 10.87	.10
<i>p</i> ^b	.22	.20	

^aIndependent sample *t* test.^bPaired sample *t* test.

assay by thin layer chromatography and previously showed to have hypoglycemic effects.³⁹ The major components of the essential oil (α -thujene, α -pinene, myrcene, and *p*-cymene) were also present in *Anethum graveolens* L (dill) seed, another popular antidiabetic plant.⁴⁰

Boswellia serrata gum resin was known as a hot and dry temperament drug and has been recorded as antipyretic, emmenagogue, carminative, antiobesity, and cardiogenic in traditional medicine texts⁴¹; *Boswellia serrata* gum resin, especially in traditional Persian medicine, is known as an herbal drug for increasing memory power.⁴² Although it is usually used in combination with multiple other herbs as compound formulations for treatment of gastrointestinal diseases, eye diseases, wounds, and inflammatory diseases, such as osteoarthritis.⁴² But in the current study, we evaluated antihyperglycemic and lipid-lowering effects of *Boswellia serrata* gum resin as a single herb.

An important limitation of this trial was the short duration of the study. The best median time for following the changes in laboratory test results after pharmacotherapy in diabetic

patients is over 2 months.⁴³ Moreover, the narrow range of inclusion criteria could lead to some limitations in the generalizability of the study results to all diabetic patients.

Nonresponsive results in our study may be due to small sample size of our study. Within group analysis showed a significant reduction after the intervention in the field of FBS (*P* = .04), HbA1c (*P* = .02), and triglyceride (*P* = .01) in the *Boswellia serrata* gum resin group, while between groups analysis did not show any statistically significant difference, so small sample size of the study could be one of the causes of this negative results. Moreover, given that positive results of previous studies on antihyperglycemic and lipid-lowering effects of *Boswellia serrata* gum resin, inadequate prescribed drug dose (500 mg daily) in this study may be another reason for ineffective results.^{19,23,35}

As a conclusion, the current study showed that complementary use of *Boswellia serrata* gum resin capsule with a dose of 250 mg twice daily did not have better outcomes compared with the placebo in FBS, HbA1c, total cholesterol, LDL, HDL, triglyceride, and insulin levels in diabetic patients.

Author Contributions

The work presented in this article was carried out through collaboration between all authors. HFH and BT made the initial hypothesis. All authors participated in defining the research theme and provided the proposal. SM, SHM, MH, and BT performed the experiments, collected the data, analyzed the data, and wrote the article. HFH and BT conceptualized the study, critically analyzed and discussed the data, and corrected and reviewed the article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This trial is a 2-arm, double-blind randomized placebo-controlled clinical trial that was registered by the American registry for randomized controlled trials with a code: AEARCTR-0000898. The local Medical Ethics Committee of Qazvin University of Medical Sciences approved the trial protocol and written informed consent was obtained from each patient prior to the study. This study compared *Boswellia* capsule with placebo and both groups received routine hypoglycemic agents to avoid any deprivation from the standard treatment.

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