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Effects of Coadministration of *Eryngium billardieri* and *Boswellia serrata* Extracts on Insulin-Related Biomarkers, Lipid Profile, and Hepatic Enzymes in Patients with Type 2 Diabetes: A Randomized Controlled Clinical Trial

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Abstract

Background: A multifactorial metabolic disorder, diabetes mellitus (DM) is characterized by chronic hyperglycemia. According to the International Diabetes Federation (IDF), this condition is expected to be among the most critical global health concerns in 2045. Despite the recent developments in medications for patients living with type 2 diabetes (T2D), there is still no definitive cure. As nearly all medications have their own complications, some herbs seem beneficial as alternatives. From this perspective, the present study investigated the effects of the coadministration of *Eryngium billardieri* (EB) and *Boswellia serrata* (BS) extracts on biochemical indices in patients with T2D.

Methods: Sixty patients with T2D, aged 35–55, were selected and randomly assigned to two groups: experiment and control. For four weeks, the experimental group was given a combination of the EB (14 cc) and BS (7 cc) extracts in addition to the routine medications. However, the controls only received routine care and medications.

Results: A significant reduction was observed in fasting blood sugar (FBS), homeostatic model assessment for insulin resistance (HOMA-IR), and triglyceride (TG) levels. There was a substantial upsurge in disposition index (DI), homeostasis model assessment of β-cell function (HOMA-β), and quantitative insulin sensitivity check index (QUICKI) levels in the patients in the experimental group. The serum insulin levels showed no major changes.

Conclusion: The study results revealed that the EB and BS coadministration could be a therapeutic approach or a supplement for patients with DM.

Keywords: *Boswellia serrate*, Diabetes, *Eryngium billardieri*, Insulin

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Introduction

A multifactorial metabolic disorder, diabetes mellitus (DM) is characterized by chronic hyperglycemia (1-3). This condition has been categorized into three main types, namely, type 1, which is more common in adolescents due to insufficient insulin production in the pancreas, type 2, which arises from insulin resistance, in which cells become less responsive to insulin, and type 3 or gestational DM, representing hyperglycemia in pregnant women with no medical history of DM (4). According to the International Diabetes Federation (IDF), there were 463 million adults worldwide living with type 2 diabetes (T2D) in 2019, and the number is expected to reach 700 million by 2045, making it one of the most critical global health concerns (5). Patients living with this condition frequently undergo complications, including microvascular and macrovascular issues, which can escalate morbidity and mortality rates. The microvascular problems are more widespread than the macrovascular issues. The microvascular complications might present as nephropathy, neuropathy, and retinopathy, and the macrovascular issues include stroke, cardiovascular disease (CVD), and peripheral artery disease (PAD) (6). Sulfonylurea, metformin, and thiazolidinedione are the most popular medications administered as a treatment for T2D worldwide (7), each with its own side

effects, including peripheral edema (PE), hypoglycemia, and gastrointestinal (GI) discomfort. Against this background, some herbs, specifically *Eryngium billardieri* (EB) and *Boswellia serrata* (BS), containing different phytochemicals and causing fewer complications, were used as medications in this study (8,9).

In this context, EB, which grows in northern Iran, has been documented as a diuretic herbaceous flowering herb from the *Umbelliferae* family with a stem height of 1–2 m. It includes different compounds, such as flavonoids, alkaloids, tannins, saponins, caffeic acid (CA), terpenoids, and beta-carotene. According to previous studies, this herb has various pharmacological advantages, such as antioxidant, cytotoxic, anti-apoptotic, anti-inflammatory, and anti-microbial advantages (10-12). The total phenol and flavonoid content of its extract has also been positively correlated with its antioxidant and anti-microbial properties (13). Moreover, it has positively affected peptic ulcer disease (14).

The roots and leaves of this herb are currently being exploited for their antidiabetic properties (12). According to the most recent literature, EB administration significantly reduces blood sugar levels, hepatic enzymes, and lipid profiles in rats with DM (10).

BS, which grows in India, is a medicinal herb from the *Burseraceae* family (15). It has been used in traditional medicine to improve memory impairment (16). It is also known as an anticancer, antibacterial (17), and anti-inflammatory agent (18). Previous studies have confirmed the positive effect of BS on DM (15). In 2007, an animal study on DM-induced rats demonstrated that taking the extract of the BS leaves and roots for 28 days could decrease serum blood sugar, triglyceride (TG), and cholesterol (Chol) levels (19). Another investigation in 2014 showed that the administration of BS as a supplement for six weeks could reduce Chol, low-density lipoprotein (LDL), and fructosamine levels in patients living with DM (15).

As evidenced in previous research, the administration of BS and EB extracts could positively influence the lives of patients with T2D. However, to the best of our knowledge, no study has been conducted on the effect of the coadministration of such extracts on these patients. From this perspective, the present study investigated the effect of the coadministration of BS and EB extracts on biochemical indices in patients with T2D.

Methods

Preparation of BS and EB extracts

The toxicological studies on the effect of BS resin on different animals have shown no pathological changes up to 1000 mg/kg. The acute toxicity of this resin has also been documented to occur at doses above 2 g/kg (20). As reported in the related literature, the oral administration of EB extract does not lead to any signs of poisoning or death up to the dosage of 2400 mg/kg (21). As a result, a combination of BS and EB was made based on the principles of traditional medicine and the toxicity dosage of the extracts at a 1:2 ratio. In line with traditional medicine and the toxicity dosage of the herbs, 14 cc of EB (≈0.56 mg) and 7 cc of BS (≈0.35 mg) were mixed, and the patients took one dosage of the BS and EB combination every day after lunch. Each of the substances needed to be prepared separately. To make the BS extract, 1 kg of the herb was added to 40 L of water on a gentle heat for at least 1 hour, and then 20 L of the BS extract was prepared and half of it was evaporated. To provide the EB extract, 1 kg of this herb was added to 40 L of water and heated gently for at least 1 hour, and then 25 L of its extract was obtained (20,21).

Experimental design and ethical statement

This randomized controlled clinical trial was conducted at Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The required approvals were acquired from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (IR.AJUMS.REC.1400.595) and the Iranian Registry of Clinical Trials (IRCT) (identifier: IRCT20111225008515N4).

Based on the standard deviation of fasting blood sugar (FBS) in Khani et al (22) and Ahangarpour et al (15), considering $\alpha = 0.05$ and 90% test power, the sample size in each group was considered as 30 people, accounting for 35% attrition (13,22). In total, 60 patients with T2D were selected. The regimen in the groups was not different. The inclusion criteria were the age range of 35–55, taking only oral medications but not insulin and other supplements, and having 140–250 mg/dL FBS. The exclusion criteria were patients with liver cirrhosis, pregnant and lactating women, smokers and alcohol users, and those suffering from active proliferative diabetic retinopathy and other disorders, such as chronic kidney disease, congestive heart failure, and heart attack over the last six months. All participants were informed about the study objectives, and a written consent form was acquired. The participants were only taking oral hypoglycemic medications, such as metformin and gliclazide, and there were no changes in their dosage during the study. The patients were randomized into two groups. In addition to routine care and medications, those in the experimental group were given a combination of the BS and EB extracts. The demographic data were also collected, including weight, height, body mass index (BMI), and waist-to-hip ratio (WHR). Blood samples were taken at the onset of the study and after four weeks, and the serum was separated via centrifuge and frozen at -70 ˚C.

Insulin-related biomarkers, lipid profile, and hepatic enzyme measurement

First, the biochemical indices, such as FBS, TG, Chol, LDL, high-density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT),

alkaline phosphatase (ALP), blood urea nitrogen (BUN), and creatinine (CR) were measured. Then, the insulin-related biomarkers, viz., quantitative insulin sensitivity check index (QUICKI), homeostatic model assessment for insulin resistance (HOMA-IR), homeostasis model assessment of β-cell function (HOMA-β), and insulin disposition index (DI) were measured using the following formulas (23):

HOMA-IR: FBS (mg/dL) × insulin (μIU/mL) / 405

HOMA-β: 360 × insulin (μIU/mL) / (FBS (mg/dL) - 63)

QUICKI: 1 / [log FBS (mg/dL) + log insulin (μIU/mL)]

DI: HOMA-β / HOMA-IR

Ultimately, the insulin level, lipid profile, hepatic enzyme, and renal function biomarkers were measured using commercial kits (Pars Azmoon Co., Iran) and an auto-analyzer.

Statistical analysis

All study data were analyzed using the SPSS statistics software package as mean ± standard deviation (SD). The paired samples *t* test was also utilized to evaluate the data before and after taking the BS and EB extracts. The independent-sample *t*-test was used to analyze the data between the study groups. A statistical difference smaller than 0.05 was considered significant.

Results

Demographic characteristics data

After four weeks of EB and BS coadministration once a day, as no changes had occurred in the regimen and drugs, no significant changes occurred in weight and BMI.

In this study, 30 male and 30 female patients aged between 35 and 55 were randomly recruited; the participants' demographic characteristics are illustrated in Table 1. Blood samples were also taken at the beginning of the study and after four weeks. Then, the biochemical indices in the experimental group were compared with those in the controls.

Effects of coadministration of EB and BS extracts on insulin-related biomarkers in the experimental group

After four weeks of the EB and BS coadministration once a day, a significant drop was observed in FBS and HOMA-IR ($P < 0.001$). However, there was a considerable increase in DI, HOMA-β ($P < 0.01$), and QUICKI ($P < 0.001$) levels in the patients living with T2D. However, the serum insulin levels showed no major changes (Table 2).

Table 1. Demographic characteristics of the patients with T2D

Demographic characteristics data	Mean ± SD
Age (y)	49.65 ± 5.31
Weight (kg)	83.63 ± 12.53
WHR	0.96 ± 0.12
BMI	29.66 ± 3.81

BMI, body mass index; WHR, waist-hip ratio.

Effects of coadministration of EB and BS extracts on lipid profile in the experimental group

Other indices, such as lipid profile, were measured, and a significant reduction was observed in the TG levels, but there were no substantial changes in Chol, HDL, and LDL (Table 3).

Effects of coadministration of EB and BS extracts on hepatic enzymes and renal function biomarkers in the experimental group

No significant changes were seen in AST, ALT, ALP, BUN, and CR, indicating that the coadministration of the BS and EB extracts did not lead to hepatotoxicity or nephropathy (Table 3).

Effects of coadministration of EB and bs extracts on insulin-related biomarkers, lipid profile, hepatic enzymes, and renal function biomarkers in experimental and control groups

According to the comparison between the biochemical indices in both study groups, the coadministration of the BS and EB extracts significantly reduced FBS, HOMA-IR, Chol, TG, and LDL, but there was a considerable increase in DI and HOMA-β (Table 4).

Discussion

Despite the development of many medications to treat T2D, no definitive cure has been found. The number of patients is expected to increase dramatically in the future, and there are significant concerns about this global health concern. On the other hand, most medications have side effects. In light of this, there is a need to conduct more investigations to find safer treatments (24-26). According to the American Diabetes Association (ADA), research, technologies, and new treatments have thus far improved DM care, resulting in higher patient quality of life (27). The present study investigated the effects of the coadministration of the BS and EB extracts on biochemical indices in patients with T2D. The beneficial effect of the BS and EB extracts had been previously evaluated in separate studies with promising results; however, further investigations were required to confirm

Table 2. Comparison of mean ± SD values of insulin-related biomarkers before and after BS and EB coadministration

Variables	Baseline	After four weeks	*P* value
FBS (mg/dL)	171.26 ± 12.44	140.814 ± 6.71	< 0.001
Insulin (μIU/mL)	25.17 ± 1.00	25.217 ± 0.89	> 0.05
HOMA-IR	12.77 ± 1.5	8.882 ± 0.56	0.04
DI	9.4 ± 0.55	18.550 ± 2.46	< 0.01
HOMA-β	109.52 ± 11.9	136.092 ± 11.93	< 0.01
QUICKI	0.279 ± 0.003	0.284 ± 0.003	< 0.001

FBS: fasting blood sugar; HOMA-IR: homeostatic model assessment for insulin resistance; DI: disposition index; HOMA-β: homeostasis model assessment of β-cell function; QUICKI: quantitative insulin sensitivity check index.

Table 3. Comparison of mean ± SD values of biochemical indices before and after BS and EB coadministration

Variables	Baseline	After four weeks	*P* value
Chol (mg/dL)	151.437 ± 15.353	147.750 ± 10.948	*P* > 0.05
TG (mg/dL)	209.176 ± 29.320	164.705 ± 13.705	0.048
HDL (mg/dL)	38.764 ± 2.502	39.235 ± 3.343	> 0.05
LDL (mg/dL)	78.200 ± 10.660	76.623 ± 7.200	> 0.05
BUN (mg/dL)	16.444 ± 1.435	15.000 ± 1.224	> 0.05
CR (mg/dL)	0.941 ± 0.044	0.985 ± 0.070	> 0.05
ALT (U/L)	24.266 ± 1.683	25.133 ± 2.069	> 0.05
AST (U/L)	24.066 ± 1.402	24.466 ± 1.864	> 0.05
ALP (U/L)	200.538 ± 18.310	188.153 ± 10.987	> 0.05

Chol: cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BUN: blood urea nitrogen; CR: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase.

the results (15,10,26). The novelty of this study was in the coadministration of BS and EB extracts for four weeks, succeeding in reducing FBS with antidiabetic properties. The insulin levels did not change, but there was an increase in DI, QUICKI, and HOMA-β, indicating an improvement in the health and function of insulin-producing cells (28,29). However, Mehrzadi et al reported that using 250 mg of the BS gum in the experimental group or the placebo in the controls twice a day for eight weeks did not lead to any changes in FBS and TG between the study groups (18). In agreement with the present study, Zarei et al (12) and Jyothi et al (30) reported a decrease in HOMA-IR. Khani et al assessed the lipid profile, revealing a drop in TG and LDL but a rise in HDL after treating rats with DM with EB root extract. However, the present study found no remarkable LDL, HDL, or Chol changes. However, there was a reduction in TG, probably related to the reduced fat absorption and the antidiabetic and hypolipidemic effects of EB (10).

Previous studies have reported that BS gum resin has hepatoprotective effects against chemical damage (30). Ahangarpour et al also demonstrated the hepatoprotective effects of BS as a supplement in patients with T2D. A reduction in AST and ALT was also observed after six weeks (15). Another study on rats with DM receiving EB reported a fall in AST and ALT (10). The present study showed no changes in AST, ALT, and ALP after the coadministration of the BS and EB extracts, implying that such herbs had no hepatotoxic side effects.

Moreover, BUN and CR showed no significant changes, demonstrating that the coadministration of EB and BS extracts had no side effects on the kidneys. In agreement with these results, Marefati et al found that the BS gum resin (100 mg/kg) administered in rats with lipopolysaccharide-induced inflammation did not change BUN and CR. However, it ameliorated hepatic and renal function at 200 mg/kg (31).

Table 4. Comparison of mean ± SD values of insulin-related biomarkers, lipid profile, and hepatic enzymes between study groups

Variables	Control group	Experimental group (after 4 weeks)	*P* value
FBS (mg/dL)	198.77 ± 15.6	140.814 ± 6.711	< 0.001
Insulin (μIU/mL)	25.11 ± 0.93	25.217 ± 0.887	> 0.05
HOMA-IR	12.18 ± 1.03	8.882 ± 0.564	< 0.01
DI	8.76 ± 1.08	18.550 ± 2.462	< 0.001
HOMA-β	85.30 ± 7.35	136.092 ± 11.931	< 0.001
QUICKI	1.82 ± 0.02	0.284 ± 0.003	> 0.05
Chol (mg/dL)	201.07 ± 10.74	147.750 ± 10.948	< 0.01
TG (mg/dL)	242.85 ± 23.7	164.705 ± 13.705	< 0.01
HDL (mg/dL)	41.03 ± 1.74	39.235 ± 3.343	> 0.05
LDL (mg/dL)	110.96 ± 7.05	76.623 ± 7.200	< 0.01
BUN (mg/dL)	23.95 ± 3.9	15.000 ± 1.224	> 0.05
CR (mg/dL)	1.33 ± 0.18	0.985 ± 0.070	> 0.05
ALT (U/L)	23.74 ± 0.23	25.133 ± 2.069	> 0.05
AST (U/L)	23.96 ± 0.22	24.466 ± 1.864	> 0.05
ALP (U/L)	204.14 ± 1.94	188.153 ± 10.987	> 0.05

FBS: fasting blood sugar; HOMA-IR: homeostatic model assessment for insulin resistance; DI: disposition index; HOMA-β: homeostasis model assessment of β-cell function; QUICKI: quantitative insulin sensitivity check index; Chol: cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BUN: blood urea nitrogen; CR: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase.

Conclusion

According to the results of this study on 60 patients with T2D, the coadministration of EB (14 cc) and BS (7 cc) extracts for four weeks reduced FBS and TG levels. Based on the HOMA-β outcomes, it also improved the function of pancreatic beta cells, although it did not cause changes in the serum insulin levels. Moreover, the absence of noticeable changes in AST, ALT, ALP, BUN, and CR indicated that EB and BS coadministration was safe for the kidney and liver. Therefore, such herbs could be used as novel supplements for patients with DM.

However, further information is still required to determine the benefits and side effects of the coadministration of the EB and BS extracts and estimate the proper dosage for each patient.

Authors' Contribution

Conceptualization: Sorour Rajabalipour, Akram Ahangarpour, Fatemeh Bineshfar.

Data curation: Sorour Rajabalipour, Akram Ahangarpour, Mehrnoosh Zakerkish.

Formal analysis: Akram Ahangarpour.

Funding acquisition: Sorour Rajabalipour.

Methodology: Sorour Rajabalipour, Akram Ahangarpour, Mehrnoosh Zakerkish.

Investigation: Sorour Rajabalipour, Akram Ahangarpour, Fatemeh Bineshfar.

Project administration: Akram Ahangarpour.

Supervision: Akram Ahangarpour.

Visualization: Sorour Rajabalipour, Akram Ahangarpour, Fatemeh Bineshfar.

Writing–original draft: Sorour Rajabalipour, Akram Ahangarpour.
Writing–review & editing: Sorour Rajabalipour, Akram Ahangarpour, Fatemeh Bineshfar.

Competing Interests
The authors declared no conflict of interest.

Ethical Approval
This research was conducted as a clinical trial at Ahvaz Jundishapur University of Medical Sciences. The university's Ethical Committee (IR.AJUMS.REC.1400.595) and the Iranian Registry of Clinical Trials have approved the study (IRCT20111225008515N4).

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