**Antidiabetic activity and chemical composition of *Teucrium polium***

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**Abstract**

Context: *Teucrium polium* L. (TP) is recommended by herbal and integrative practitioners for the treatment of diabetes. However, to our knowledge, the action mechanism whereby TP exerts its hypoglycemic effects is still unknown.

Objectives: In this *in vitro* study, we tested the chemical composition, cytotoxicity and antidiabetic activity of three TP distinct extracts: water/ethanol (WTP), methanol (MTP) and hexane (HTP).

Methods: TP extracts composition was tested by GC/MS. MTT assay and LDH leakage assay used to assess the extracts toxicity. The efficacy of TP extracts in enhancing glucose transporter-4 (GLUT4) translocation to plasma membrane (PM) was tested in L6 muscle cells stably expressing myc-tagged GLUT4 (L6-GLUT4myc) using cell-ELISA test.

Results: GC/MS phytochemical analysis of MTP and HTP extracts revealed 10 compounds in each. Only palmitic acid was communal in these two extracts. WTP, MTP and HTP extracts where safe up to 63, 63 and 250 µg/mL, respectively. The HTP extract was the most efficient in GLUT4 translocation enhancement and the least was WTP extract. HTP extract increased GLUT4 translocation at 32 µg/mL by 2 - 3 fold relative to the control in the absence and presence of insulin, respectively. Similar result was obtained with the MTP extract at 63µg/mL. A 20% increase of GLUT4 translocation was achieved with 32µg/mL WTP extract in the absence of insulin, however with no effect in the presence of insulin.

Conclusions: These findings indicate that TP antidiabetic activity is mediated in part by enhancing GLUT4 translocation to the PM in skeletal muscle.

**Key words:** GLUT4, GC/MS, phytochemicals, diabetes.

**Introduction**

Herbal-based antidiabetic medicines have been a part of traditional medicine for centuries. The Chinese were the first who detected diabetes mellitus in the third century. They noticed that the sweetness of urine attracts dogs. Later on, Indian physicians in the sixth century related to diabetes as “Honey urine” and prescribed several herbs to treat it ([Saad et al. 2017](#_ENREF_15); [Zaid & Saad 2013](#_ENREF_22)). Later on, diabetes was recognized by medieval Greco-Arab physicians by its main symptoms: increased thirst, frequent urination, and tiredness. Greco-Arab physicians and practitioners had used series of medicinal plants for treating these combined symptoms ([Saad et al. 2013 2017](#_ENREF_15)).

Modern treatment of diabetes mellitus revolves around controlling blood glucose levels either through glucose production or utilizing or through increasing insulin secretion and effectiveness or by reduction of energy intake or increasing energy expenditure ([Kadan et al. 2013](#_ENREF_7); [Zaid et al. 2008](#_ENREF_20)). Unidirectional glucose uptake into skeletal muscle is mediated by the facilitative glucose transporter-4 (GLUT4), a membrane protein that continuously recycles between intracellular vessels and the plasma membrane (PM). Insulin receptor mediated signals significantly enhance the rate of GLUT4 traffic towards and fusion with the PM, a process termed GLUT4 translocation that results in a gain in PM GLUT4 ([Zaid et al. 2008](#_ENREF_20)).

Reports on natural herbs for diabetes treatment focus on lowering blood sugar and reducing the damaging effects of the disease. Interestingly, a single medicinal plant may include biochemically different antidiabetic mechanisms such as enhancing GLUT4 translocation to the plasma membrane, insulin sensitizing, activation of MAPK and PPAR, stimulate insulin secretion, or inhibit intestinal carbohydrate digestion and absorption. Some antidiabetic herbs even possess anti-inflammatory and immunomodulatory action ([Ota & Ulrih, 2017](#_ENREF_13); [Rios et al. 2015](#_ENREF_14); [Saad et al. 2017](#_ENREF_15); [Zaid et al. 2016](#_ENREF_21)).

Insulin sensitizers include plants that increase glucose uptake and disposal by muscle, fat and hepatic cells as well as those that regulate hepatic glycogen metabolism. We had recently tested several medicinal plants extracts mechanisms in increasing glucose uptake and found that *Trigonella foenum-graecum*, *Urtica dioica*, *Atriplex halimus*, and *Cinnamomum officianalis* ([Kadan et al., 2013](#_ENREF_7)) as well as *Ocimum basilicum* ([Kadan et al. 2016](#_ENREF_8)) increase glucose disposal by enhancing the glucose transporter 4 (GLUT4) translocation to the plasma membrane.

Teucrium polium L. (TP) is one of the mostly used antidiabetic herbs. It is a wild-growing flowering plant in the temperate parts of Europe, Africa and Asia (mainly the Middle East) ([Bahramikia and Yazdanparast 2012](#_ENREF_2)). In Greco-Arab medicine, TP has been used for different pathological conditions including inflammation, gastrointestinal disorders, rheumatism as well as diabetes mellitus ([Saad et al. 2017](#_ENREF_15)).TP antidiabetic activity was evaluated in animal models, some studies in diabetic animal models have shown that intravenous or intraperitoneal as well as oral administration of a TP crude extract to STZ-induced diabetic rats significantly decreased serum glucose levels ([Esmaeili & Yazdanparast 2004](#_ENREF_3); [Gharaibeh et al. 1988](#_ENREF_5); [Shahraki et al. 2007](#_ENREF_18)). Gavage and oral administration of a hydroalcoholic and water extract of TP increased insulin secretion from rat-isolated islets ([Mohseni Salehi Monfared & Pournourmohammadi 2010](#_ENREF_9)) and insulin levels in rats ([Esmaeili & Yazdanparast 2004](#_ENREF_3); [Mohseni Salehi Monfared & Pournourmohammadi 2010](#_ENREF_9); Tabatabaie PS and Yazdanparast R 2017). TP ethyl acetate extract decreased serum, liver and muscle triglyceride content of sucrose-induced insulin resistance in rats ([Mousavi et al. 2012](#_ENREF_10)).

In the present study, we tested the role of GLUT4 translocation in the traditionally known antidiabetic effects of TP. Results obtained in the present *in vitro* study indicate that water/ethanol (WTP), methanol (MTP) and hexane (HTP) extracts significantly increased GLUT4 translocation levels at non-cytotoxic concentrations as measured with MTT assay and the LDH leakage assay.

**Materials and methods**

***Plant extract preparation***

*Teucrium polium* (aerial parts)were purchased from (Al Alim- Medicinal Herb Center, Zippori, Israel). TP air-dried aerial parts (40g) were powdered, packed in an Erlenmeyer, extracted in 500 mL with 50% ethanol in water, methanol, or hexane at room temperature for 72 h to give a dark green extract. The hexane extract was filtered and evaporated to dryness under pressure at 50°C and dissolved in DMSO for further studies. The methanol extract was filtered and concentrated by a rotary vacuum evaporator. The yield of the extracts was 6.3%, 11.1% and 4.6% for WTP, MTP and HTP extracts, respectively. The stock extracts were preserved in airtight glass container and kept at -20°C.

***Gas chromatography-mass spectrometry analysis***

GCMS analysis was performed with HP5890 Series II GC equipped with a Hewlett-Packard MS Engine (HP5989A) single quadrupole MS, HP7673 auto sampler, HP MS-DOS Chemstation, and HP-5MS capillary column (0.25 μm × 15 m × 0.25 mm). The temperature program was as follows: injector temperature, 180°C; initial temperature, 40°C for 6 min; gradient of 20°C/min until 140°C; gradient of 10°C/min until 200°C; and hold time, 3 min. The MS parameters were set as follows: source temperature, 180 °C; transfer line, 280°C; positive ion monitoring; and EI-MS (70eV).

***Identification of components***

The percentage composition of the samples was computed from the GC peak areas. Library searches were carried out using the NIST GC/MS Library or with mass spectra from literature. Component relative percentages were calculated based on GC peak areas without using correction factors.

***Cell culture***

Cells from the rat L6 muscle cell line, stably expressing myc-tagged GLUT4 (L6-GLUT4myc) (Zaid et al. 2009), were maintained in myoblast monolayer culture. All cells were grown under an atmosphere of 95% air and 5% CO2 in *α*-MEM supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin and 0.1 mg/mL streptomycin.

***MTT and Lactate Dehydrogenase Assay (LDH) assays***

Cells were subcultured into 96-well plates with 200 μL of medium (2x104/well) for 24 h and then exposed to (0-1 mg/mL) of TP extracts. Cell viability assessed by following the amount of formazan dye formed in alive cells (MTT) or by calculating the relevant activity of LDH released in dead cells as was described earlier ([Kadan et al. 2013](#_ENREF_7)). MTT and LDH kits were purchased from Promega, (WI, USA).

***Determination of surface GLUT4myc***

Surface myc tagged GLUT4 was measured in intact, non-permeabilized cells. Cells grown in 24-well plates for one day followed by addition of the plant extracts for 20 h and serum-starved for 3 h were treated without or with 1 µM insulin for 20 min. GLUT4myc on the plasma membrane was then detected as previously described ([Zaid et al. 2009](#_ENREF_25)). Briefly, the cells were reacted with polyclonal anti-*myc* antibody (1:200) for 1 h at 4 °C, washed with PBS and reacted with horseradish peroxidase-bound goat anti-rabbit secondary antibody (1:1000) for 1 h at 4 °C, and washed with PBS. Cells then incubated with 0.5 ml *o*-phenylenediamine dihydrochloride reagent and allowed to develop for 20–30 min in the linear range in the dark at room temperature. The reaction was stopped with 0.5 mL/well of 3 N HCl. Supernatants were collected and absorbance was measured at 492 nm. Background absorbance obtained in the absence of anti-*myc* antibody was subtracted from all values.

***Statistical analysis***

Error bars were plotted and represent simple standard deviations of the mean. When comparing different samples, results were considered to be statistically different when P < 0.05. Statistical calculations were conducted using SPSS version 21.0.

**Results**

The current study evaluated the chemical composition, cytotoxicity and antidiabetic activity of three Teucrium polium L. (TP) distinct extracts: water/ethanol (WTP), methanol (MTP) and hexane (HTP).

**Teucrium polium L. chemical composition**

The chemical compounds in the HTP and MTP extracts were identified by GC/MS (Table 1). Nineteen chemical compounds were detected by GC/MS analysis in TP extracts; they contain a complex mixture of chemical compounds, aromatic, saturated and unsaturated fatty acids, and phenolic compounds. Ten compounds were detected in MTP extract and 9 compounds in the HTP. Only one mutual compound was found in the two extracts, namely palmitic acid (Table 1). Interestingly, palmitic acid was recently reported by our group to be found in three deferent *Ocimum basilicum* L. extracts (methanol, hexane and dichloromethane). *Ocimum basilicam*-derived palmitic acid was suggested to play an essential anti- diabetic role which seems to be mediated through GLUT4 translocation ([Kadan et al. 2016](#_ENREF_8)).

As seen in Table 1, (5E,8E,11E)-methyl heptadeca-5,8,11-trienoate (5.6%) and (9Z,12Z)-octadeca-9,12-dienoic acid (4.5%), 3,7,11-trimethyldodeca-1,6,10-trien-3-ol (4.4%) and Palmitic acid (4.2%) are the major compounds in the MTP (Fig. 2C). In the HTP, cis-vaccenic acid (20%), butyl (2-ethylhexyl) phthalate (12.2%) and Palmitic acid (7.2%) are the main components (Fig. 3C). Some of the detected compounds were reported to possess antidiabetic activity, namely, thymol ([Saravanan & Pari 2015](#_ENREF_17)), carvacrol ([Ezhumalai et al. 2014](#_ENREF_4)), eugenol ([Jeong et al. 2014](#_ENREF_6)) and cis vaccenic acid ([Alstrup et al. 2004](#_ENREF_1)).

**Teucrium polium L. extracts toxicity**

MTT and LDH leakage assays were used to evaluate the nontoxic concentrations of the three TP extracts. The plant extracts toxicity was tested *in vitro* in L6-GLUT4myc cells. Cells were seeded in 96 well plates and were subjected to increasing concentrations of the extracts (0-1 mg/mL) for 24 hours. Extracts concentrations that led to less than 10% cell death were considered as safe. WTP (Fig. 1A), MTP (Fig. 2A) and HTP (Fig. 3A) extracts were found to be safe up to 63, 63 and 250 µg/mL, respectively. The efficacy studies were performed at concentrations equal or less than the safe concentration for each extract.

**Effects of Teucrium polium extracts on GLUT4 translocation**

Skeletal muscle and liver are the primary tissues responsible for dietary glucose uptake and disposal. In muscle, hepatic and adipose tissues, insulin promotes the exocytic traffic of intracellular GLUT4 vessels towards the plasma membrane to elicit a rapid increase in glucose uptake ([Osorio-Fuentealba & Klip 2015](#_ENREF_12); [Zaid et al. 2008](#_ENREF_20); [Zierath et al. 1996](#_ENREF_26)). In insulin resistance and diabetes type 2, insulin fails to promote GLUT4 translocation to the PM. Some of the antidiabetic synthetic drugs and medicinal plants-based products bypass the insulin resistance by increasing GLUT4 translocation in insulin dependent or independent pathway ([Zaid et al. 2012](#_ENREF_24)).

The involvement of glucose transporter (GLUT4) in the observed antidiabetic effects of *Teucrium polium* extracts was evaluated here by applying the GLUT4 translocation assay. Insulin increases GLUT4 translocation to the myoblasts surface, and thus enhancing glucose uptake ([Osorio-Fuentealba & Klip 2015](#_ENREF_12); [Zaid et al. 2008](#_ENREF_20)). L6 skeletal muscle cell lines expressing myc epitope at the exofacial loop of the glucose transporter-4 (GLUT4), named L6-GLUT4myc were used as a model to follow GLUT4 translocation to the plasma membrane ([Zaid et al. 2008](#_ENREF_20)). The extracts were added to the L6-GLUT4myc cells in the absence or presence of insulin and the translocation of GLUT4myc to the plasma membrane was assessed as described in the Methods section. Results obtained indicate that, in muscle L6-GLUT4myc cells, insulin-independent (basal) as well as insulin dependent GLUT4 translocation to the PM is significantly increased in response to TP extracts, especially the methanol and hexane extracts. The WTP extract was found to have the lowest effects on GLUT4 translocation, and only 20% of GLUT4 translocation was obtained at 32 µg/mL of WTP extract in the absence of insulin. No effect was observed in the presence of insulin.

MTP extract (63 µg/mL) increased GLUT4 translocation to the PM by 2, and 3 times in the absence and presence of insulin, respectively (Fig. 2B). HTP extract (at 32 µg/mL) led to similar results (Fig. 3B) obtained with MTP extract (at 63 µg/mL). These findings indicate The HTP extract was the most efficient one in GLUT4 translocation enhancement.

**Discussion**

*Teucrium polium* L is one of the traditional medicinal plants well known for its antidiabetic property in the Middle East (Saad et al. 2017). TP antidiabetic activity was evaluated in animal models. Gavage and oral administration of a hydroalcoholic and water extract of TP increased insulin secretion insulin levels in the circulating blood in rats (Esmaeili & Yazdanparast 2004; Mohseni Salehi Monfared & Pournourmohammadi 2010; Tabatabaie PS and Yazdanparast R 2017). TP was reported as insulin secretion enhancer by regulation transcription factors of the JNK pathway in the pancreatic β-cells (Tabatabaie PS and Yazdanparast R 2017). However, TP effect on glucose disposal in muscle cell line was not reported. To our best of knowledge, this is the first report on the efficacy of TP extract on GLUT4 activity and translocation to the PM.

Glucose transporter-4 (GLUT4) continuously recycles between the PM and intra cellular vesicles. Insulin shifts GLUT4 translocation towards the PM. Glucagon on the other hand shifts GLUT4 translocation towards the intracellular stores (Osorio-Fuentealba & Klip 2015; Zaid et al. 2008; Zierath et al. 1996). We and others have tested several traditional used antidiabetic medicinal plants hypoglycemic activity through increasing glucose transporter (GLUT) translocation to the plasma membrane in muscle and hepatic tissue (Kadan et al. 2013, 2016; Ota & Ulrih 2017; Zaid et al. 2015, 2016). Although, TP is recommended by herbal and integrative practitioners for the treatment of diabetes (Mousavi et al. 2015; Saad et al. 2017), the action mechanism whereby TP exerts its hypoglycemic effects is still unknown. Therefore, the present study was conducted to evaluate the role of GLUT4 translocation in the observed antidiabetic TP effects. Three TP extracts (water/ethanol, methanol and hexane) were prepared and their effects on GLUT4 translocation were measured in L6 skeletal muscle cell line, in the present and absence of insulin.

The extent of increase in insulin-stimulated GLUT4 translocation was additive to that of basal GLUT4 translocation in TP-exposed cells, suggesting possible synergistic effects between TP active ingredients and insulin. Alternately, TP active ingredients might activate GLUT4 translocation in non-insulin dependent pathway (e.g. AMP-Kinase). It is possible then that, TP active ingredients might possess ‘insulin-like’ or ‘insulin-sensitizing’ activity/compounds. It is essential to dissect TP active compounds in order to identify its cellular molecular target and point out its specific antidiabetic mechanism and cellular pathway(s).

Insulin enhances mobilization of GLUT4-containing vesicles from intracellular stores to the muscle cell surface and thus promotes glucose uptake. Notably, the gain in GLUT4 at the muscle membrane is reduced in primary cells from diabetic animals as well as human diabetic subjects (Shamni et al. 2017; Zaid et al. 2008; Zierath et al. 1996). Hence, unraveling antidiabetic medicinal plants action mechanism and pointing out their potential active ingredients, is of paramount importance to develop antidiabetic new drugs.

**Conclusions**

Phytochemical analysis with GC-MS technique revealed various phytochemicals identities in both MTP and HTP extracts. Some antidiabetic compounds were identified in TP extracts, these compounds maybe responsible on GLUT4 translocation. Further studies regarding the chemical profile of the most active extract (HTP) will be performed in order to identify the bioactive compound(s).

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