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In vitro Antidiabetic Activity of Seven Medicinal Plants Naturally Growing in Turkey

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ABSTRACT

Objective: Diabetes mellitus is a worldwide metabolic/endocrine disease that causes major medical problems. One of the most important strategies used in the therapy of the diabetes mellitus is the use of inhibition of α-glucosidase and α-amylase enzymes. Therefore, this study aimed to investigate antidiabetic activities of the hexane and methanol extracts of the medicinal plants from Turkey.

Materials and Methods: The hexane and methanol extracts of *Euphorbia helioscopia, Ferula elaeochytris, Sideritis albiflora, Sideritis stricta, Sideritis pisidica, Sideritis leptoclada, Salvia chionantha* plants were prepared at room temperature. Antidiabetic activities of the extracts on α-glucosidase and α-amylase enzymes were determined.

Results: *S. pisidica* hexane extract exhibited higher α-amylase inhibitory activity than acarbose (96.60±0.08 %) used as a standard with an inhibition value of 97.99±0.79 % at 1000 µg/mL concentration. In terms of α-glucosidase inhibitory activities, the extracts were ranked in the following order: *F. elaeochytris* hexane extract > *S. leptoclada* hexane extract > *S. stricta* hexane extract > *E. helioscopia* hexane extract.

Conclusion: In this study, antidiabetic activities of the extracts on α-glucosidase and α-amylase enzymes of the studied medicinal plants were screened for the first time. It has been suggested that *S. pisidica* hexane extract can be used as antidiabetic agent.

Keywords: Medicinal plants, antidiabetic activity, extracts, α-amylase, α-glucosidase

INTRODUCTION

Diabetes mellitus, which is a carbohydrate metabolism disease, causes complications by increasing the risk of neuropathy, retinopathy, and cardiovascular disease if left untreated (1,2). In a report of the World Health Organization, it is reported that these diseases and complications cause direct medical costs, loss of wok and wage losses and significant economic losses (3). Type 2 diabetes is more common among cases of diabetes mellitus and occurs mainly in adults; however, it is becoming increasingly popular in adolescents. Type 2 diabetes, which is caused by insulin resistance or loss of function of pancreatic β-cells, is estimated to affect around 150 million people worldwide (4). Endogenous factors, such as genetic and metabolic abnormalities, and exogenous factors, such as behavior and the environment, constitute the pathogenesis of type 2 diabetes (5). Type 2 diabetes causes increased blood sugar levels in diabetic patients. Today, the most widely accepted method in the treatment of type 2 diabetes is monitoring and controlling hyperglycemia. Digestive enzymes such as α-amylase, and α-glucosidase have a key role in determining blood sugar levels. α-Amylase is involved in the breakdown of long-chain carbohydrates, while α-glucosidase directly converts carbohy-

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drates into glucose in the small intestine (6,7). α-Glucosidase and α-amylase inhibitors delay the digestion of carbohydrates and slow the rate of glucose absorption. This reduces the level of glucose in the blood cells. For the control of postprandial hyperglycemia as well as type 2 diabetes, inhibition of these enzymes has been considered therapeutically (8). Therefore, simultaneous administration of α-amylase and α-glucosidase inhibitors via food is a potential and feasible method for the control of type 2 diabetes (9).

Artificial inhibitors such as voglibose, acarbose and miglitol are used clinically for the treatment of type 2 diabetes. However, due to the observation of side effects of these synthetic inhibitors, such as gas compression in the stomach, hepatotoxicity, diarrhea, abdominal pain and liver diseases, studies focusing on the discovery of new and non-side effects inhibitors from natural sources and plants are being conducted (10-13). Many studies have shown that some plants used in traditional medicine have therapeutic effects on diabetic patients (14,15). More than 400 plants worldwide have been documented as beneficial in the treatment of diabetes (16-19).

Salvia and *Sideritis* genus are the main species belonging to the Lamiaceae family (20). The *Sideritis* genus contains more than 150 species, while the *Salvia* genus is represented by over 900 species in the world (20,21). Both these species are mostly consumed as tea, and used in the treatment of various diseases (22,23). Previous studies have revealed that the *Sideritis* species has various biological properties such antioxidant, anti-inflammatory, antifeedant, antimicrobial, antiviral, antinociceptive and antiulcer (24,25). The *Salvia* species is the medically important plant species due to having numerous pharmacological activities such as antitumor, antioxidant and wound healing, insecticidal, herbicidal, antifungal, antimicrobial and cytotoxic (26). The *Ferula* genus, an important member of the Apiaceae family, consists of more than 170 species. In folk medicine, the *Ferula* species is used in the treatment of indigestion, whooping cough, cramps, inflammation, epilepsy, pain, cholera, flatulent colic and infertility (27). Also, it has been determined that this species has anti-fertility, antifungal, anti-inflammatory, antispasmodic, antitumor, antiviral, antiulcerogenic, cancer chemopreventive and antioxidant effects (28). The *Euphorbia* genus, the most well-known of the Euphorbiaceae family, is represented by approximately 2150 taxa in the world (29). Anti-inflammatory, antiarthritic, antiviral, antitussives, antitumor, antiallergic, antiasthma and antioxidant activities of the *Euphorbia* species have been reported in earlier investigations (30). As a result of the studies carried out so far, it is obvious that these species are included in the class of aromatic plants that are considered biologically and medically important.

The interest of different scientific fields in natural compounds has increased in recent years. Medicinal plants are considered to be rich sources of biologically active compounds, such as terpenes, alkaloids and phenolics, and are responsible for multifunctional biological effects including anti-inflammatory, antimicrobial, antioxidant and antitumor (31). Also, an inverse relationship between the consumption of fruits, vegetables, and plants in diets and the risk of developing chronic illness such as cancer, diabetes, and cardiovascular diseases has been reported. Therefore, this study aimed to investigate antidiabetic activities on α-amylase and α-glucosidase enzymes of the hexane and methanol extracts *of Euphorbia helioscopia, Ferula elaeochytris, Sideritis stricta, Sideritis leptoclada, Sideritis albiflora, Sideritis pisidica,* and *Salvia chionantha.* [*Euphorbia helioscopia* (EHH, EHM), *Ferula elaeochytris* (FEH, FEM), *Sideritis stricta* (SSH, SSM), *Sideritis leptoclada* (SLH, SLM), *Sideritis albiflora* (SAH, SAM), *Sideritis pisidica* (SPH, SPM), and *Salvia chionantha* (SCH, SCM)]

MATERIALS AND METHODS

Plant Materials

Euphorbia helioscopia was collected from Artvin, Turkey; *Ferula elaeochytris* from Bayburt, Turkey; *Sideritis stricta, Sideritis leptoclada, Sideritis albiflora, Sideritis pisidica* from Muğla, Turkey; and *Salvia chionantha* from Burdur, Turkey. The specimens with voucher numbers have been deposited at Natural Products Laboratory of Muğla Sıtkı Koçman University Herbarium.

Extraction

The dried and powdered aerial parts of plants were extracted with *n*-hexane (4 x 24h) at room temperature. After filtration, the solvent was evaporated on a vacuum by an evaporator to produce hexane extracts. The plant residue was dried and then extracted with methanol (4 x 24h) at room temperature. After filtration, the solvent was evaporated on a vacuum by an evaporator to produce methanol extracts. The hexane and methanol extracts were stored at +4°C for further tests.

Determination of α-Amylase Inhibitory Activity

α-Amylase inhibitory activity of the extracts was tested by using the method previously reported by Quan et al. with slight modifications (31). 25 µL sample solution and 50 µL α-amylase solution (0.1 units/mL) in phosphate buffer (20 mM pH=6.9 phosphate buffer prepared with 6 mM NaCl) were mixed in a 96-well microplate. The mixture was pre-incubated for 10 min. at 37 °C. After pre-incubation, 50 µL starch solution (0.05 %) was added and incubated for 10 min. at 37 °C. The reaction was completed by addition of 25 µL HCl (0.1 M) and 100 µL Lugol solutions. A 96-well microplate reader was used to measure absorbance at 565 nm. Acarbose was used as the standard compound. α-Amylase inhibitory activity results are stated as as inhibition percentage (%) of the enzyme at 1000 µg/mL concentration of the extracts and 50 % inhibition concentration (IC_{50}).

Determination of α-Glucosidase Inhibitory Activity

α-Glucosidase inhibitory activity of the extracts was performed using the method previously reported by Kim et al. with slight modifications (32). 50 µL phosphate buffer (0.01 M pH=6.9), 25 µL PNPG (4-N-nitrophenyl-α-D-glucopyranoside) in phosphate buffer (0.01 M pH=6.9), 10 µL sample solution and 25 µL α-glucosidase (0.1 units / mL) in phosphate buffer (0.01 M pH=6.0) were mixed in in a 96-well microplate. The mixture was incubated for 20 min. at 37 °C. To stop reaction, 90 µL sodium carbonate (0.1 M) was added and a 96-well microplate reader was

used to measure absorbance at 400 nm. Acarbose was used as the standard compound. α-Glucosidase inhibitory activity results are stated as inhibition percentage (%) of the enzyme at 500 µg/mL concentration of the extracts and as 50 % inhibition concentration (IC_{50}).

Statistical Analysis

All data on the antidiabetic activities were determined as the averages of three parallel sample measurements. The data were registered as the mean ± S.E.M. Student's t test was used to evaluate important differences between the means, and *p* values <0.05 were accepted as substantial.

RESULTS

The hexane and methanol extracts of *E. helioscopia, F. elaeochytris, S. albiflora, S. stricta, S. pisidica, S. leptoclada, S. chionantha* plants were prepared at room temperature. α-Amylase and α-glucosidase inhibitory activities of the extracts were tested spectrophotometrically. Acarbose was used as the standard compound. Table 1 shows α-amylase and α-glucosidase inhibitory activities of the extracts of the studied plant species. The inhibitory activities on α-amylase of the hexane extracts of the plant species are given in Figure 1. The inhibitory activities on α-glucosidase of the hexane extracts of the plant species are given in Figure 2. The hexane extracts showed higher inhibitory activity on α-amylase than the methanol extracts. The highest inhibitory activities on α-amylase at 1000 µg/mL concentration were observed in *S. pisidica* hexane

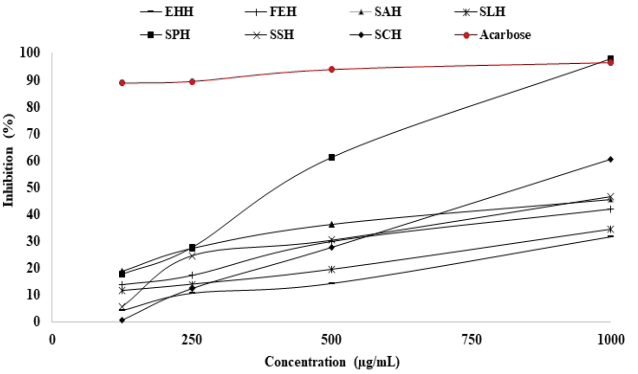

Figure 1. α-Amylase inhibitory activities of the hexane extracts of plant species. EHH: *E. helioscopia* hexane extract, FEH: *F. elaeochytris* hexane extract, SAH: *S. albiflora* hexane extract, SLH: *S. leptoclada* hexane extract, SPH: *S. pisidica* hexane extract, SSH: *S. stricta* hexane extract, SCH: *S. chionantha* hexane extract

Table 1. α-Amylase and α-glucosidase inhibitory activities of the extracts of plant species[a]

			α-Amylase Inhibitory Activity		α-Glucosidase Inhibitory Activity	
Plants species	**Extracts**	**Code**	**Inhibition (%) (at 1000 µg/mL)**	**IC_{50} (µg/mL)**	**Inhibition (%) (at 500 µg/mL)**	**IC_{50} (µg/mL)**
E. helioscopia	Hexane	EHH	31.58±0.17	>1000	1.95±0.06	>500
	Methanol	EHM	11.85±0.56	>1000	NA[b]	>500
F. elaeochytris	Hexane	FEH	42.14±0.30	>1000	14.24±0.82	>500
	Methanol	FEM	8.62±0.00	>1000	NA[b]	>500
S. albiflora	Hexane	SAH	45.45±0.22	>1000	NA[b]	>500
	Methanol	SAM	21.94±0.95	>1000	NA[b]	>500
S. leptoclada	Hexane	SLH	34.68±0.34	>1000	11.08±0.73	>500
	Methanol	SLM	20.09±0.05	>1000	NA[b]	>500
S. pisidica	Hexane	SPH	97.99±0.79	413.53±0.18	NA[b]	>500
	Methanol	SPM	17.11±0.15	>1000	NA[b]	>500
S. stricta	Hexane	SSH	46.77±1.04	>1000	7.10±0.81	>500
	Methanol	SSM	18.21±0.70	>1000	NA[b]	>500
S. chionantha	Hexane	SCH	60.68±0.04	>1000	NA[b]	>500
	Methanol	SCM	6.35±0.11	>1000	NA[b]	>500
Standard	Acarbose		96.60±0.08	21.63±0.01	67.01±2.28	378.66±0.14

[a] Values represent the means ± SEM of three parallel sample measurements ($p < 0.05$).
[b] NA: not active.

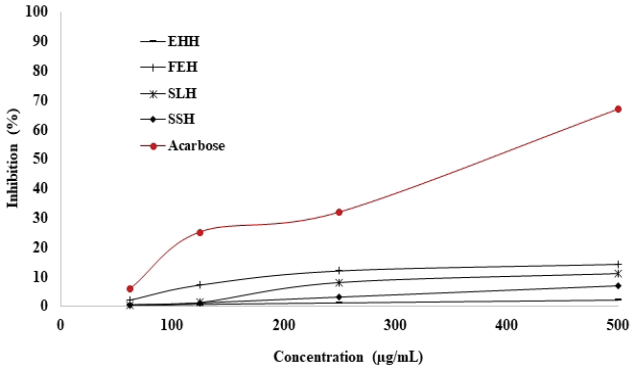

Figure 2. α-Glucosidase inhibitory activities of the hexane extracts of plant species. EHH: *E. helioscopia* hexane extract, FEH: *F. elaeochytris* hexane extract, SLH: *S. leptoclada* hexane extract, SSH: *S. stricta* hexane extract

extract (SPH) (97.99±0.79 %), *S. chionantha* hexane extract (SCH) (60.68±0.04 %), *S. stricta* hexane extract (SSH) (46.77±1.04 %) and *S. albiflora* hexane extract (SAH) (45.45±0.22 %), respectively (Table 1). Also, against α-amylase, SPH extract was found to be more active than acarbose (96.60±0.08 %) with an inhibition value of 97.99±0.79 % at 1000 µg/mL concentration. In terms of inhibitory activities on α-glucosidase enzyme, the extracts were ranked in the following order: *F. elaeochytris* hexane extract (FEH)> *S. leptoclada* hexane extract (SLH)> *S. stricta* hexane extract (SSH)> *E. helioscopia* hexane extract (EHH). The other extracts showed no α-glucosidase inhibitory activity. The highest activity of the hexane extracts is considered to be related to the non-polar compounds contained.

DISCUSSION

Enzyme inhibition, considered a significant area of pharmaceutical research, has allowed the discovery of a wide variety of drugs that have previously been useful in a number of diseases. The activity of the enzymes is blocked by the interaction of their specific inhibitors. Enzyme inhibitors, which have been used to treat a wide range of physiological conditions, are of great importance as drugs (33). Currently, one of the therapeutic methods used in the therapy of type 2 diabetes is the inhibition of α-amylase and α-glucosidase to reduce the reabsorption of glucose in the intestine. α-Amylase is the enzyme responsible for the initial stage of hydrolysis of complex carbohydrates to an oligosaccharide and disaccharide mixture in the intestinal mucosa. These sugars are broken down into monosaccharides by the effect of α-glucosidase (34).

Medicinal plants are extremely important natural resources for discovering new drug molecules due to the pharmacologic properties such as antioxidants, cytotoxic, antimicrobial, anti-inflammatory and antidiabetic activities (35,36). In this current research, *in vitro* inhibitory activities on α-amylase and α-glucosidase enzymes of the hexane and methanol extracts of *E. helioscopia, F. elaeochytris, S. stricta, S. leptoclada, S. albiflora, S. pisidica, S. chionantha* were evaluated. According to the obtained results, when SPH extract displayed the highest α-amylase inhibitory activity, FEH extract showed the best α-glucosidase inhibitory activity. The hexane extracts were found to have higher antidiabetic activity when compared to the methanol extracts. This highest activity of the hexane extracts is considered to be related to the non-polar compounds contained.

In a previous report of Adımcılar et al. IC_{50} value of *S. chionantha* methanol extract was calculated as 43.3±2.5 µg/mL in α-glucosidase inhibitory assay (37). α-Amylase and α-glucosidase inhibitory activities of the water, methanol and dichloromethane extracts of *Salvia modesta* were investigated. The dichloromethane extract showed the highest antidiabetic activity with a mean value of 0.64 and 9.48 mmol ACAE/g sample on α-amylase and α-glucosidase, respectively (38). Water, ethyl acetate and methanol extracts of *Salvia cadmica* were tested to evaluate their α-amylase and α-glucosidase inhibitory activities. The methanol extract exhibited considerable α-amylase inhibitory activity (102.28±2.09 µmol ACEs/g dry plant) and α-glucosidase inhibitory activity (869.21±19.55 µmol ACEs/g dry plant) (39). The methanol extracts of *Euphorbia denticulata* parts (mix of aerial part, stem, flowers, leaf) were used to evaluate inhibitory activities on α-glucosidase and α-amylase enzymes by Zengin et al. (40). *E. denticulata* flower extract indicated the highest activity in the α-glucosidase assay with an inhibition value of 10.59±0.01 mmolACAE/g while *E. denticulate* mix extract was found to be the most active extract in α-amylase with an inhibition value of 0.77±0.04 mmol ACAE/g. α-Glucosidase and α-amylase inhibitory activities of dichloromethane and methanol extracts of *Euphorbia milli* aerial and root parts were investigated in the study of Sallem et al. (41). For α-glucosidase inhibition, both aerial methanol (1.9±0.01 mmol ACAE/g extract) and root methanol (1.79±0.02 mmol ACAE/g extract) extracts exhibited higher inhibitory potential than dichloromethane extracts. In the case of α-amylase, dichloromethane extracts (0.62±0.02 mmol ACAE/g extract for aerial part, 0.55±0.01 mmol ACAE/g extract for root part) showed higher inhibition than the methanol extracts. Inhibitory activities on α-glucosidase and α-amylase enzymes of the methanol, acetone and chloroform extracts of *Ferula halophila* were investigated. When the chloroform extract demonstrated the highest α-amylase inhibitory activity (1.04±0.04 mmol ACAE/g extract), the methanol extract expressed potent α-glucosidase inhibitory activity (43.02±0.45 mmol ACAE/g extract) (42). In another study, the highest α-amylase inhibitory (0.71±0.02 mmol ACE/g extract) and α-glucosidase inhibitory (5.66±0.04 mmol ACE/g extract) activities were observed in *Sideritis galatica* petroleum ether extract (43). α-Glucosidase and α-amylase inhibitory activities of the ethyl acetate, methanol and water extracts of *Sideritis ozturkii* were evaluated by Zengin et al. (44). The higher inhibitory activity on glucosidase was found for the methanol (13.33 mmol ACAE/g extract) and ethyl acetate (13.81 mmol ACAE/g extract) extracts, while the water extract (3.60 mmol ACAE/g extract) was the least active. α-Amylase inhibitory activities of *S. ozturkii* extracts ranged between 0.11 and 0.63

mmol ACAE/g extract. α-Glucosidase and α-amylase enzymes were used for assessing the antidiabetic activities of the hexane, chloroform and methanol extracts of *Calamintha origanifolia*, *Satureja thymbra*, *Prangos asperula, Sideritis perfoliata*, *Asperula glomerata, Hyssopus officinalis, Erythraea centaurium, Marrubium radiatum* and *Salvia acetabulosa*. Among the studied plant species, *M. radiatum* methanol extract exerted the highest inhibitory activity against both α-amylase and α-glucosidase with IC_{50} values of 61.1 and 68.8 µg/mL, respectively (45). Ekin et al. (46) had described antidiabetic activities of the ethanol extracts of *Lamium purpureum* var. *purpureum*, *Origanum onites, Salvia sclarea, Salvia virgata* and *Thymus zygioides* var. *lycaonicus* at 2000 µg/mL concentration. α-Glucosidase inhibitory activities of the extracts followed the order: *T. zygioides* var. *lycaonicus* (85.28±0.89%)> *O. onites* (77.39±0.76%)> *S. sclarea* (leaves) (72.95±1.0%)> *S. sclarea* (flowers) (64.72±1.06%)> *S. virgata* (61.15±2.03 %)> *L. purpureum* var. *purpureum* (46.75±1.54%). α-Amylase inhibitory activity of all tested extracts were found between 2.30±0.21 and 8.93±1.73% (46). The obtained antidiabetic activity results are in agreement with the literature.

When the literature studies are examined, it is seen that there are studies on bioactive properties of *E. helioscopia, F. elaeochytris, S. albiflora, S. leptoclada, S. stricta, S. pisidica, S. chionantha* species, such as antioxidant, anti-tyrosinase, anticholinesterase, anti-urease, antibacterial, antinociceptive, anti-inflammatory, antimicrobial and anti-pyretic (22,23,47-53). This is the first study on antidiabetic activities of the hexane and methanol extracts *of E. helioscopia, F. elaeochytris, S. albiflora, S. leptoclada, S. pisidica,* and *S. stricta*. The results of this study may be useful in investigating specific enzyme inhibitors from the medicinal plant extracts for efficient management of type 2 diabetes mellitus and relevant complications.

CONCLUSION

In this study, α-glucosidase and α-amylase inhibitory activities of the hexane and methanol extracts *of E. helioscopia, F. elaeochytris, S. albiflora, S. leptoclada, S. stricta,* and *S. pisidica* were screened for the first time. The hexane extracts showed notable α-amylase inhibitory activities. Against α-amylase, *S. pisidica* hexane extract was found to be more active than acarbose used as the standard. This study suggests that the hexane extracts (especially *S. pisidica* hexane extract) can be used in the pharmaceutical industry as a potential α-amylase inhibitor of natural origin.

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