In vivo Anti-Inflammatory and Antinociceptive Activity Evaluation of Phenolic Compounds from *Sideritis stricta*

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An acetone extract obtained from aerial parts of *S. stricta* Boiss. & Heldr. apud Bentham, its fractions and phenolic compounds were investigated for their *in vivo* anti-inflammatory and antinociceptive activities. For the anti-inflammatory activity and for the antinociceptive activity assessment, carrageenan-induced hind paw edema and *p*-benzoquinone-induced abdominal constriction tests were used, respectively. The acetone extract of the plant and its phenolic fraction exhibited potent inhibitory activity against both bioassay models in mice. From the active phenolic fraction a well-known phenylethanoid glycoside, verbascoside (acteoside) (**1**), and two flavonoid glycosides, isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-*β*-D-glucopyranoside (**2**) and isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-*β*-D-glucopyranoside (**3**), were isolated. During phytochemical studies we also isolated a methoxyflavone, xanthomicrol (**4**), from the non-polar fraction. The structures of the isolated compounds were established by spectroscopic evidence (UV, IR, 1D- and 2D-NMR, MS). Although antinociceptive and anti-inflammatory activities of the phenolic components were found not significant in the statistical analysis, compounds **1** to **3** showed a notable activity without inducing any apparent acute toxicity as well as gastric damage. Furthermore, a mixture of flavonoid glycosides (**2** + **3**) exhibited a significant inhibitory effect in both models at a higher dose.

Key words: Sideritis stricta, Anti-Inflammatory Activity, Antinociceptive Activity

Introduction

The genus *Sideritis* L. (Lamiaceae) comprises at least 150 species mainly distributed in countries of the Mediterranean-Macaronesian region (Obon de Castro and Rivera-Nunez, 1994). Many species of this genus and their particular constituents are reported to have analgesic and anti-inflammatory action. Especially in Spain, some *Sideritis* species are used in popular medicine for their anti-inflammatory and gastroprotective properties (De las Heras *et al.* 1994; Godoy *et al.*, 2000; Navarro *et al.*, 1997, 2001; Hernandez-Perez and Rabanal, 2002; Hernandez-Perez *et al.*, 2004).

In the flora of Turkey, the genus *Sideritis* is represented by 46 species (Huber-Morath 1982; Davis *et al.*, 1988; Duman, 2000; Aytaç and Aksoy, 2000), and in Turkish folk medicine, tea prepared from the aerial parts of *Sideritis* species is popularly used against gastrointestinal disorders such as stomachache, indigestion, and flatulence, to alleviate the symptoms of common colds including fever, flu, sore throath, and bronchitis as well as tonic and diuretic (Ezer *et al.*, 1995; Baytop, 1999). In previous studies were reported diuretic (Başaran *et al.*, 1986), anti-inflammatory (Yeşilada and Ezer, 1989), antispasmodic (Ezer *et al.*, 1992), antibacterial (Ezer *et al.*, 1994) and antioxidant activities (Güvenç *et al.*, 2005) of different extracts from several *Sideritis* species growing in Turkey. Moreover, we have reported anti-inflammatory and antiulcerogenic activity of several flavonoids and phenylethanoids which were isolated from *S. lycia* (Akcoş *et al.*, 1999) and antimicrobial activity of iridoids and essential oils obtained from various *Sideritis* species (Akcoş *et al.*, 1998; Ezer and Abbasoğlu, 1996).

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As a continuation of our studies on *Sideritis* species, we aimed to investigate the possible anti-inflammatory and antinociceptive effects of the acetone extract from *S. stricta*, its main fractions and isolated phenolic compounds in order to assess the above-mentioned folkloric utilizations and biological activities using *in vivo* experimental models, *i.e.*, the carrageenan-induced hind paw edema model for investigating the anti-inflammatory activity and *p*-benzoquinone-induced abdominal constriction tests for the antinociceptive activity.

Material and Methods

Plant material

Sideritis stricta Boiss. & Heldr. apud Bentham was collected in Antalya, Belek, between Belek and Selge in Southern Anatolia, Turkey, in July 1999. Voucher specimens (HUEF 99132) have been deposited at the Herbarium of Faculty of Pharmacy, Hacettepe University, Ankara, Turkey.

Preparation of plant extracts

The air-dried and powdered aerial parts of *S. stricta* (500 g) were extracted with acetone (2×2500 ml) at room temperature. The combined acetone extract was dried *in vacuo* at 40 °C. The total extract (30 g) was initially fractionated by vacuum liquid chromatography (VLC) on silica gel (petroleum ether to MeOH) to give eight main fractions (Frs. A–H). According to the TLC profile, Fr. B (3.734 g), Fr. C (0.647 g), Fr. E (3.346 g) and Fr. G (6.596 g) were selected and further investigated for their anti-inflammatory and antinociceptive activities.

Extraction and isolation of phenolic compounds

Fr. G was separated by polyamide CC with ethylacetate/methanol/ethylmethylketone/acetone (90:10:5:5 to 80:20:5:5) mixtures. Subfrs. G3 and G5 which were rich in flavonoids were then applied to silica gel CC ($CHCl_3$/MeOH 90:10) affording compound **3** (16 mg) and compound **2** (17 mg), respectively. Compound **1** (55 mg) was purified from Subfr. G6 by Sephadex-LH-20 CC (MeOH). Furthermore, Fr. C was chromatographed by silica gel CC ($CHCl_3$ to $CHCl_3$/MeOH 97:3); then Subfr. C2 was subjected to MPLC (MeOH/H_2O 70:30 to MeOH) to give Frs. C2a–h. Repeated chromatography of Subfr. C2b on a Sephadex column (MeOH) yielded compound **4** (17 mg).

Structure elucidation of the isolated components **1**–**4** was carried out by spectral techniques [UV, IR, 1D- and 2D-NMR (^1H, ^{13}C NMR, DQF-COSY, HSQC, HMBC)] and mass spectroscopy (ESI-MS) and detailed data were recently published elsewhere (Şahin *et al.*, 2006). The structures of compounds **1**–**4** were as follows (Fig. 1): verbascoside (acteoside) (**1**), isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-*β*-D-glucopyranoside (**2**), isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-*β*-D-glucopyranoside (**3**) and xanthomicrol (**4**).

Animals

Male Swiss albino mice (20–25 g) were purchased from the animal breeding laboratories of Refik Saydam Central Institute of Health (Ankara, Turkey). The animals left for 2 d for acclimatization to animal room conditions were maintained on standard pellet diet and water *ad libitum*. The food was withdrawn on the day before the experiment, but free access of water was allowed. A minimum of six animals was used in each group. Throughout the experiments, animals were processed according to the suggested ethical guidelines for the care of laboratory animals.

Preparation of test samples for bioassays

Test samples after suspending in a mixture of distilled H_2O and 0.5% sodium carboxymethyl cellulose (CMC) were given orally to the test animals. The control group animals received the same experimental handling as those of the test groups except that the drug treatment was replaced with appropriate volumes of the dosing vehicle. Either indomethacin (10 mg/kg) or acetyl salicylic acid [Aspirin (ASA)] (100 mg/kg) in 0.5% CMC was used as reference drug.

Antinociceptive activity

The *p*-benzoquinone-induced abdominal constriction test (Okun *et al.*, 1963) was performed on mice for the determination of the antinociceptive activity. According to the method, 60 min after the oral administration of test samples, the mice were intraperitoneally (i.p.) injected with 0.1 ml/10 g body weight of 2.5% (w/v) *p*-benzoquinone (PBQ; Merck) solution in distilled H_2O. Control animals received an appropriate volume of dosing vehicle.

The mice were then kept individually for observation and the total number of abdominal contractions (writhing movements) was counted for the next 15 min, starting on the 5th min after the PBQ injection. The data represent the average of the total number of writhes observed. The antinociceptive activity was expressed as percentage change from writhing controls. ASA at a 100 mg/kg dose was used as the reference drug in this test.

Anti-inflammatory activity

Carrageenan-induced hind paw edema model

The carrageenan-induced hind paw edema model was used for the determination of the anti-inflammatory activity (Yeşilada and Küpeli, 2007). 60 min after the oral administration of the test sample or dosing vehicle, each mouse was injected with a freshly prepared (0.5 mg/25 μl) suspension of carrageenan (Sigma, St. Louis, Missouri, USA) in physiological saline (154 nM NaCl) into the subplantar tissue of the right hind paw. As a control, 25 μl saline solution were injected into the left hind paw. Paw edema was measured every 90 min during 6 h after induction of inflammation. The difference in footpad thickness between the right and left foot was measured with a pair of dial thickness gauge calipers (Ozaki Co., Tokyo, Japan). Mean values of treated groups were compared with mean values of a control group and analyzed using statistical methods. Indomethacin (10 mg/kg) was used as the reference drug.

Acute toxicity

Animals employed in the carrageenan-induced paw edema experiment were observed during 48 h and the morbidity or mortality was recorded, if happens, for each group at the end of the observation period.

Gastric-ulcerogenic effect

After the antinociceptive activity experiment, mice were killed under deep ether anesthesia and stomachs were removed. Then the abdomen of each mouse was opened through the greater curvature and examined under a dissecting microscope for lesions or bleedings. However, *p*-benzoquinone applied i.p. did not induce any irritation on gastric mucosa, but anti-inflammatory agents of COX-1 inhibitors, *i.e.*, aspirin or indomethacine orally, caused a severe bleedings, without repeated administrations.

Statistical analysis

Data obtained from animal experiments were expressed as mean standard error (± SEM). Statistical differences between the treatments and the control were evaluated by ANOVA and Students-Newman-Keuls post-hoc tests. $p < 0.05$ was considered to be significant (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Results and Discussion

An acetone extract from aerial parts of *Sideritis stricta*, main fractions prepared thereof, and the major phenolic constituents **1**–**4** were investigated for their *in vivo* antinociceptive and anti-inflammatory effects. The results, as listed in Tables I and II showed that the acetone extract of *S. stricta* aerial parts and its phenolic fraction (Fr. G) exhibited noteworthy activity in both models employed for the determination of the anti-inflammatory and antinociceptive activity.

For the evaluation of the antinociceptive activity, the *p*-benzoquinone-induced writhing test was used in mice. Results have shown that the acetone extract and Fr. G obtained from this extract possessed 28.0% and 25.8% inhibition, respectively, while ASA, the reference compound, showed 52.6% inhibition at a dose of 100 mg/kg (Table I). Although antinociceptive activity of the isolated phenolic components **1**–**4** at a 50 mg/kg dose was not significant in statistical analysis, the inhibitory rates of compounds **1**, **2** and **3** were at or over 20%. In order to test the dose-dependent activity, a 2-fold higher dose of these compounds was also studied. In spite of a slight increase in the inhibitory rate of **1** (from 21.3% to 23.2%), a mixture of **2** and **3** showed statistically significant activity (29.3% inhibiton) at 100 mg/kg (note: due to the restricted amount of each **2** and **3** as pure compounds a mixture was administered). On the other hand, the acetone extract, fractions, compounds **1**–**4** and (**2** + **3**) were found completely safe in all doses from the viewpoint of gastric damage. Furthermore, no acute toxicity was observed in experimental animals within 48 hours of observation.

Paw edema induced by carrageenan is a well-known *in vivo* model for the evaluation of active non-steroidal anti-inflammatory agents (Ismail *et al.*, 1997). As shown in Table II, acetone extract, Fr. G, compounds **1** and (**2** + **3**) from this extract also exhibited significant inhibition in the carrageenan-induced hind paw edema model, ranging

Table I. Effect of the acetone extract, the fractions and compounds of *S. stricta* against *p*-benzoquinone-induced writhings in mice.

Material	Dose [mg/kg]	Number of writhings ± SEM	Inhibitory ratio (%)	Ratio of ulceration
Control		57.4 ± 4.2		0/6
Acetone extract	200	41.3 ± 3.5	28.0*	0/6
Fr. B	100	54.8 ± 2.9	4.5	0/6
Fr. C	100	47.9 ± 3.1	16.6	0/6
Fr. E	100	46.9 ± 2.9	18.3	0/6
Fr. G	100	42.6 ± 2.0	25.8*	0/6
1	50	45.2 ± 3.9	21.3	0/6
1	100	44.1 ± 3.1	23.2	0/6
2	50	46.1 ± 2.1	19.7	0/6
3	50	43.2 ± 2.5	24.7	0/6
2 + **3**	100	40.6 ± 2.2	29.3**	0/6
4	50	48.9 ± 2.6	14.8	0/6
ASA	100	25.2 ± 2.1	52.6***	4/6

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. SEM, standard error mean.

Table II. Effect of the acetone extract, the fractions and compounds of *S. stricta* against carrageenan-induced hind paw edema in mice.

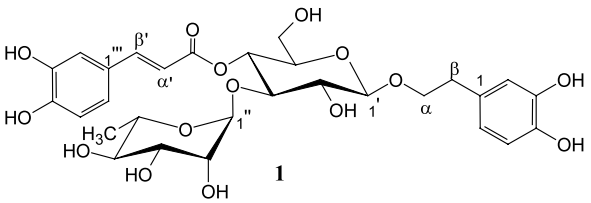
Material	Dose [mg/kg]	Swelling thickness ($\times 10^{-2}$ mm) ± SEM (% inhibition)			
		90 min	180 min	270 min	360 min
Control		53.2 ± 3.9	59.7 ± 3.1	65.8 ± 3.7	69.2 ± 3.3
Acetone extract	200	45.6 ± 3.7 (14.3)	50.1 ± 3.9 (16.1)	50.4 ± 3.6 (23.4)*	50.8 ± 3.0 (26.6)*
Fr. B	100	53.7 ± 2.5	61.2 ± 2.9	68.8 ± 3.4	71.2 ± 3.3
Fr. C	100	43.2 ± 2.1 (18.8)	49.4 ± 2.5 (17.3)	52.6 ± 3.0 (20.1)	53.9 ± 3.1 (22.1)
Fr. E	100	48.3 ± 3.2 (9.2)	53.7 ± 3.1 (10.1)	59.6 ± 3.8 (9.4)	61.2 ± 3.2 (11.6)
Fr. G	100	46.9 ± 2.3 (11.8)	51.2 ± 2.7 (14.2)	55.1 ± 2.5 (16.3)	53.1 ± 2.9 (23.3)*
1	50	49.4 ± 3.7 (7.1)	53.8 ± 3.2 (9.9)	56.4 ± 3.4 (14.3)	55.3 ± 3.1 (20.0)
1	100	45.1 ± 2.9 (15.2)	49.7 ± 2.6 (16.8)	51.5 ± 2.4 (21.7)	53.2 ± 2.0 (23.1)*
2	50	45.8 ± 3.7 (13.9)	51.2 ± 3.1 (14.2)	55.6 ± 3.4 (15.5)	57.5 ± 3.1 (16.9)
3	50	47.6 ± 2.4 (10.5)	54.2 ± 3.0 (9.2)	58.4 ± 3.2 (11.2)	59.1 ± 3.0 (14.6)
2 + **3**	100	43.5 ± 2.1 (18.2)	45.8 ± 2.7 (23.3)	49.1 ± 3.2 (25.4)*	52.2 ± 2.3 (24.6)*
4	50	49.7 ± 3.1 (6.6)	54.3 ± 3.5 (9.0)	60.1 ± 3.8 (8.7)	62.4 ± 3.3 (9.8)
Indomethacin	10	35.1 ± 2.0 (34.0)**	36.7 ± 2.3 (38.5)**	36.9 ± 2.1 (43.9)***	41.4 ± 2.5 (40.2)***

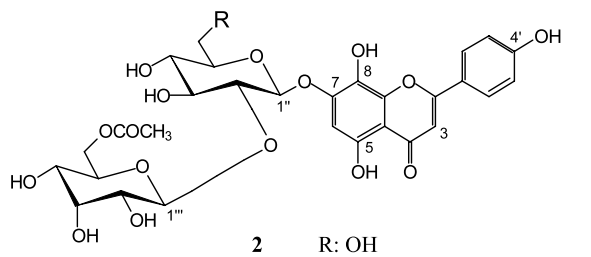
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. SEM, standard error mean.

between 14.3 and 26.6% for the acetone extract at 200 mg/kg, 11.8 and 23.3% for Fr. G, 15.2 and 23.1% for compound **1**, and 18.2 and 24.6% for the mixture (**2** + **3**) at 100 mg/kg. The results were quite comparable to indomethacin (34.0–40.2% inhibition).

Previous studies have shown the analgesic and anti-inflammatory activities of several *Sideritis* species and their particular constituents, such as flavonoids and terpenoids (Yeşilada and Ezer, 1989; Alcaraz *et al.*, 1989; Navarro *et al.*, 1997; De las Heras *et al.*, 1994, 2001; Akcoş *et al.*, 1999; Aboutabl *et al.*, 2002; Hernandez-Perez and Rabanal, 2002; Hernandez-Perez *et al.*, 2004; Bas *et al.*, 2006). In addition, anti-inflammatory and antinociceptive activities of lipid and sterol fractions from several *Sideritis* species were reported (Godoy *et al.*, 2000; Navarro *et al.*, 2001; Hernandez-Perez *et al.*, 2004).

The results reported in the present study pointed out significant anti-inflammatory and antinociceptive activities of an acetone extract of *Sid-*





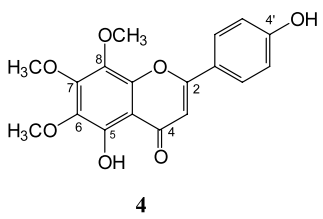


Fig. 1. Chemical structures of compounds **1**–**4.**

eritis stricta and its phenolic fraction. The phytochemical analysis conducted on the active phenolic fraction (Fr. G) revealed the existence of a phenylethanoid glycoside, verbascoside (acteoside) (**1**), and two flavonoid glycosides, isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-*β*-D-glucopyranoside (**2**), and isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-*β*-D-glucopyranoside (**3**) (Fig. 1). In addition to these compounds, a methoxyflavone, xanthomicrol (**4**), and four well-known diterpenes, sideridiol (**5**), isosidol (**6**), isolinearol (**7**), and linearol (**8**), were isolated from a non-polar fraction (Fr. C) (Şahin *et al.,* 2006). However, because of the limited quantities of these diterpenoids obtained, it was not possible to test the pharmacological effects in this study.

The phenylethanoid glycoside verbascoside (**1**) was also found as the anti-inflammatory and antinociceptive component of several plant remedies. Andary *et al.* (1982) reported the antinociceptive along with antihypertensive activities, while Akcoş *et al.* (1999) and Schapoval *et al.* (1998) showed anti-inflammatory activity in the carrageenan-induced hid paw edema model. In the study of Diaz *et al.* (2003) who evaluated the potential inhibitory activity of several phenylethanoids from *Scrophularia scorodonia* (Scrophulariaceae) including verbascoside on some macrophage functions involved in the inflammatory process, verbascoside showed a significant inhibitory effect on thromboxan B_2 (TXB_2) release, tumour necrosis factor-α (TNF-α), nitric oxide and lipopolysaccharide-induced PGE_2 in a concentration-dependent manner. Penido *et al.* (2006) revealed that verbascoside exhibited a potent inhibitory effect on LPS-induced total leucocyte, neutrophil and eosinophil accumulation in the pelural cavity along with a potent antiulcerogenic activity against diclofenac-induced gastric ulcers at 100 mg/kg. Due to the ulcerogenic toxicity of known anti-inflammatory agents in the current therapy, this specification has a critical importance.

On the othe hand, isoscutellarein, a 5,7,8,4′-tetrahydroxy flavone, has a very close chemical structure to hypolaetin, a 5,7,8,3′4′-pentahydroxy flavone, which was previously reported as the active anti-inflammatory and antiulcerogenic constituent of *Sideritis mugronensis*, a Spanish folk remedy (Villar *et al.*, 1984).

In conclusion, compounds **1**–**3** appear to be among the constituents implicated in pharmacological activities displayed by the acetone extract of *Sideritis stricta.* A well-known phenylethanoid glycoside, verbascoside (**1**), showed significant anti-inflammatory activity, while the mixture of two isoscutellarein derivatives of flavonoid glycosides (**2** + **3**) was found to possess significant anti-inflammatory and antinociceptive activities at a 100 mg/kg dose without inducing any apparent acute toxicity as well as gastric damage. Further studies are entailed for the detailed activity assessment of the plant as well as participation of other constituents of the plant.

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