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Antinociceptive and Anti-inflammatory Effects of Ethanolic Extract of *Salvia syriaca* L. in Mice

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Abstract: The aim of this study was to evaluate the antinociceptive and anti-inflammatory effect of *Salvia syriaca* L. aerial parts ethanolic extract in male NMRI mice. Antinociceptive activity was done using by formalin, hot plate and writhing tests. The effect of ethanolic extract on acute inflammation was studied by xylene edema test in mice. The *Salvia syriaca* L. ethanolic extract (1, 10, 50 and 100 mg kg^{-1} body wt.) was injected intraperitoneally. The control group administrated with saline. Present results showed that the ethanolic extract decreased only second phase of formalin-induced pain. In hot plate test, the ethanolic extract did not raise pain threshold during 60 mins. The ethanolic extract exhibited antinociceptive activity against writhing-induced by acetic acid. In xylene ear edema test, *Salvia syriaca* L. ethanolic extract showed significant activity in the mice. The present data indicated that this plant has antinociceptive and anti-inflammatory effect on the mice but more works are required to be done in order to elucidate the mechanism (s) involved in antinociceptive and anti-inflammatory effects of the *Salvia syriaca* L. extract.

Key words: *Salvia syriaca* L., pain, analgesia, inflammation, formalin, hot plate, abdominal constriction, herbal medicine, mice

INTRODUCTION

Pain is a sensorial modality which in many cases represents the only symptom for the diagnosis of several diseases. It often has a protective function. Throughout history man has used many different forms of therapy for the relief of pain. Medicinal herbs are highlighted due to their wide popular use. In the relief of pain, opiates are generally considered to act on the central nervous system exercising their effects through three opioid receptors (μ, κ and δ), such drugs are especially important for the treatment of chronic pain. Although morphine has reigned for centuries as the king of painkillers, its rule hasn't been totally benign. There are concerns about its addictive properties and side effects which include respiratory depression, drowsiness, decreased gastrointestinal motility, nausea and several alterations of the endocrine and autonomic nervous systems (Almeida *et al*., 2001).

Traditionally, medicinal plants are used throughout the world for a range of pain complications. Plant drugs are frequently considered to be less toxic and free of side effects than synthetic ones. The study of such medicines might offer a natural key to alleviating of pain for the future. *Salvia* is an important genus widely cultivated and used in flavoring and folk medicines. They are used for alimentary, pharmacological and cosmetic purposes (Lawless, 2002; Perry *et al*., 2003; Ulubelen, 2003). *Salvia* species are used as traditional medicines all around the world, possessing antibacterial (Ulubelen *et al*., 2001), antioxidant (Tepe *et al*., 2005; Zupko *et al*., 2001), antitumor (Li *et al*., 2002) and cholinergic binding properties (Ren *et al*., 2004). *Salvia syriaca* L. is a perennial rhizomatous which grows wild in many regions of Iran. Despite its traditional use by native people of Iran, *Salvia syriaca* L. has not been subjected to pharmacological studies. Traditionally, plant medicines are used throughout the world for a range of pain complications. The study of such medicines might offer a natural key to alleviating of pain for the future. Due to the reported use of *Salvia syriaca* in folk medicine for treatment of painful illnesses and the lack of any report on its antinociceptive and anti-inflammatory activities, this study was initiated. In the present study, we have examined the possible antinociceptive and anti-inflammatory effects of the ethanolic extract of *Salvia syriaca* aerial parts in male NMRI mice.

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MATERIALS AND METHODS

Subjects: Male NMRI mice (8 per each group), weighing 25-30 g, were housed in clean plexiglass cages with temperature (22-24°C), 12/12 h light/dark cycle at 21±2°C and relative air humidity 40-60%. The mice were fed with commercial diet (35% carbohydrates, 25% proteins, 7% lipids and 3% vitamins) and tap water *ad libitum*. Each animal was tested once only. This research project was conducted from 1/2/2008 to 1/11/2009. Experimental procedures involving the animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national and international laws and Guidelines for Care and Use of Laboratory Animals in Biomedical Research as adopted and promulgated by the World Health Organization and United States National Institutes of Health, 1985, No. 85-23.

Chemicals: Morphine sulfate was purchased from Temad, Iran. Acetic acid and formalin were purchased from Merck, Germany. Indomethacin and dexamethasone was obtained from Sigma (St. Louis, MO, USA). All other chemicals used were of good quality and analytical grade.

Plant material: Fresh aerial parts of *Salvia syriaca* were collected of Gazvin area of Iran, in June 2008 and scientifically approved in the department of botany of Islamic Azad University (Voucher No.: 05610, deposited in I.A.U Herbarium). The plant was cleaned, shed dried at 25°C and the dried aerial parts of the plant were ground with a blender and the powder was kept in nylon bags in a deep freezer until the time of experiments.

Extraction of ethanolic plant material: Dried and powdered aerial parts of the plant (60 g) were macerated with 300 mL of ethanol (80%) in a Soxhlet apparatus for 72 h. The extract was concentrated in a rotating evaporator under reduced pressure to give a residue (13% w/w). The residue was dissolved in normal saline for final suitable concentrations.

Analgesic activity

Formalin test: The procedure described by Xie *et al.* (2004) was used. Pain was induced by injecting 0.05 mL of 2.5% formalin (40% formaldehyde) in distilled water into dorsal surface of the right hind paw. Mice (eight per group) were pre-treated extract (1, 10, 50 and 100 mg kg^{-1}, i.p.), morphine sulfate (10 mg kg^{-1}, i.p.), indomethacin (10 mg kg^{-1}, i.p.) and saline as vehicle 30 min prior to injecting formalin. All of them were administrated in a volume of 0.2 mL intraperitoneally. Animals were individually placed in a transparent plexiglass cage (30×12×13 cm) observation chamber. The mouse was observed for 45 min after the injection of the formalin and the pain scores in the injected hind paw was recorded. The initial nociceptive scores from 0 to 5 min (first phase) and 15-45 min (second phase) were counted after injection of formalin. These phases represented neurogenic and inflammatory pain responses, respectively. The drugs were administrated 30 min before injection of formalin.

Hot plate test: Mice were placed on an aluminum hot plate kept at a temperature of 55±0.5°C for a maximum time of 30 sec (De´ciga-Campos *et al.*, 2006). Reaction time was recorded when the animals licked their fore-and hind paws and jumped; at before (0) and 15, 30, 45 and 60 min after intraperitoneal zadministration of 1, 10, 50 and 100 mg kg^{-1} of the extract to different groups of eight animals each. Morphine 10 mg kg^{-1} was used as the reference drugs.

Acetic acid-induced abdominal writhing: The writhing test was conducted as described by Fischer *et al.* (2008). Mice were pre-treated with ethanolic extract of *Salvia syriaca* (1, 10, 50 and 100 mg kg^{-1}, i.p.) or indomethacin (10 mg kg^{-1}) 30 min. before the administration of 1.0% aqueous solution of acetic acid (10 mL kg^{-1}, i.p.). Each mouse was placed in a transparent observation box and the number of writhes (full extension of both hind paws) was counted for 30 min after the acetic acid administration. Control animals received a similar volume of saline solution. The number of abdominal writhes (full extension of both hind paws) was cumulatively counted every 5 min over a period of 20 min immediately after the acetic acid injection. The antinociceptive activity was expressed as inhibition percentage of abdominal writhes.

Anti-inflammatory study

Xylene-induced ear edema: Thirty minutes after i.p. injection of the ethanolic extract (1, 10, 50 and 100 mg kg^{-1}, i.p.) and dexamethasone (10 mg kg^{-1}, i.p.), 0.03 mL of xylene was applied to the anterior and posterior surfaces of the right ear. The left ear was considered as control. Two hours after xylene application, mice were sacrificed and both ears removed. Circular sections were excised, using a cork borer with a diameter of 7 mm and weighed. The increase of weight ear caused by the irritant was measured by subtracting the weight of the untreated left ear section from that of the treated right ear section (Hosseinzadeh *et al.*, 2003).

Statistical analysis: The data were expressed as Mean±SEM. and tested using analysis of one-way ANOVA followed by Tukey post hoc test. The criterion for statistical significance was $p<0.05$.

RESULTS

Analgesic activity

Formalin test: Intraplantar injection of 2.5% formalin evoked a characteristic biphasic nociceptive response. As shown in Fig. 1a and b, pretreatment (30 min) with different doses of *Salvia syriaca* ethanolic extract (at doses 50 and 100 mg kg^{-1}) or indomethacin produced a marked reduction in the duration of nociceptive activity in the second phase. The maximal inhibition of the nociceptive response was achieved at 100 mg kg^{-1}. Morphine was significantly active on the both first and second phases.

Hot plate test: In the hot plate test administration of the ethanolic extracts at doses of 1, 10, 50 and 100 mg kg^{-1} i.p. was not capable of increasing the latency period of pain induced by heating of the plate (Fig. 2).

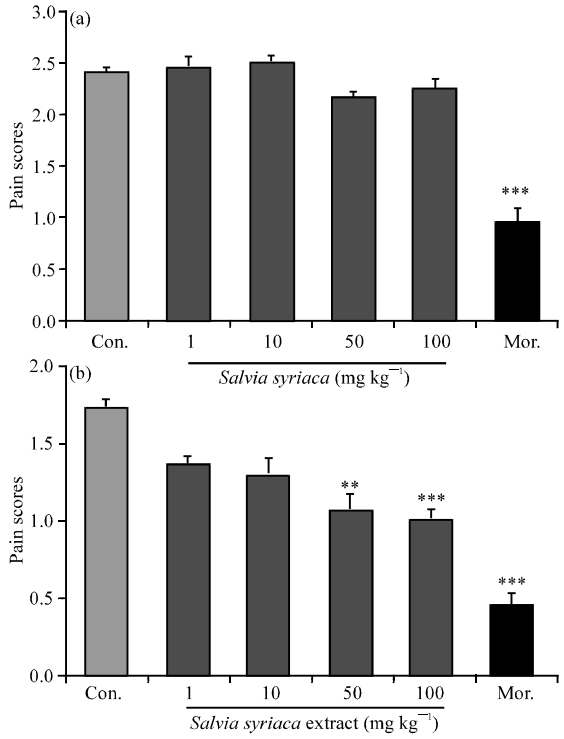

Fig. 1: Effect of *Salvia syriaca* L. extract (1, 10, 50 and 100 mg kg^{-1}) and morphine (10 mg kg^{-1}) on the scores of the first phase (a) and the second phase (b) of the formalin test. The scores were calculated during a period of 300 sec (0-5 min after formalin injection) for the first time and a period of 1800 sec (15-45 min after formalin injection) for the second phase. Values represent the Mean±SEM of nine experiments. **p<0.01, ***p<0.001 compared with control animals

Acetic acid-induced writhing movements: The effect of the *Salvia syriaca* ethanolic extract aerial parts on writhing movements in mice is shown in Fig. 3. The ethanolic extract (at doses of 50 and 100 mg kg^{-1} i.p.) and indomethacin (10 mg kg^{-1}) caused an inhibition on the writhing movements induced by acetic acid. The number of writhing movements/20 min at 50 and 100 mg kg^{-1} of ethanolic extract groups were significantly lower than that of the control (p<0.01).

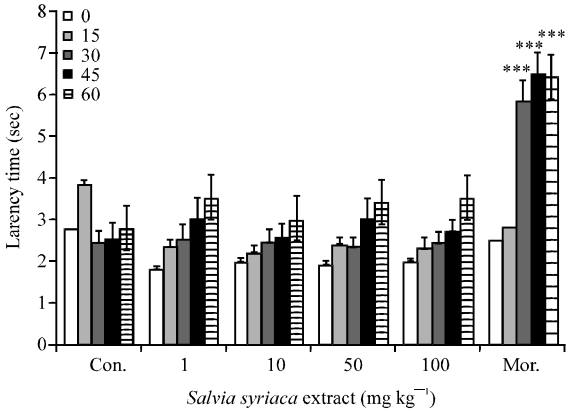

Fig. 2: Effect of *Salvia syriaca* L. extract (1, 10, 50 and 100 mg kg^{-1}) and morphine (10 mg kg^{-1}) on the pain threshold of mice in the hot plate test. Each column represents the Mean±SEM of reaction time of nine experiments. ***p<0.001 compared with control animals

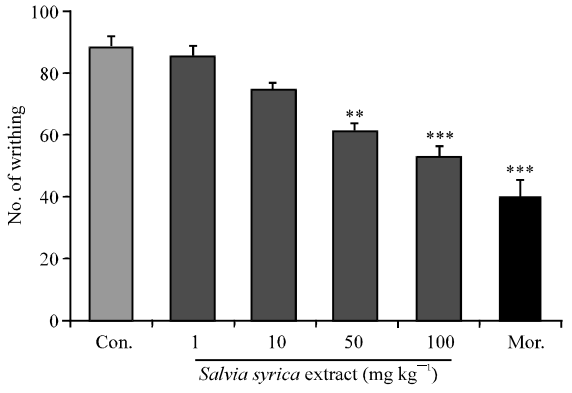

Fig. 3: Effect of *Salvia syriaca* extract (1, 10, 50 and 100 mg kg^{-1}) and morphine (10 mg kg^{-1}) on acetic acid-induced writhing response of mice. Drugs were orally administered 30 min prior to the peritoneal injection of acetic acid. Each column represents the Mean±SEM. **p<0.01, ***p<0.001 compared with control animals

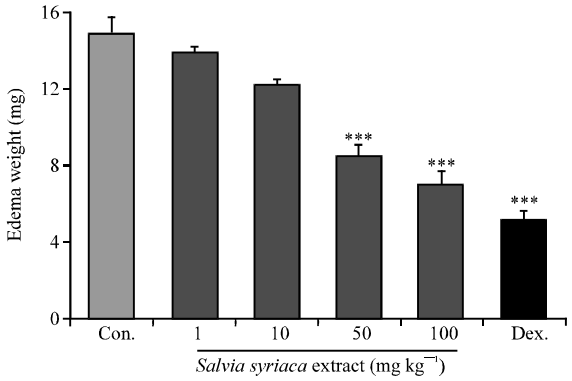

Fig. 4: Effect of *Salvia syriaca* extract (1, 10, 50 and 100 mg kg^{-1}) and morphine (10 mg kg^{-1}) on inhibition of xylene-induced ear edema of mice. Drugs were orally administered 30 min prior to the administration of xylene. Each column represents the Mean±SEM. ***p<0.001 vs. control animals

Anti-inflammatory activity

Xylene-induced ear edema: Results obtained from xylene-induced mice ear edema are shown in Fig. 4. The dexamethasone and ethanolic extract (at doses of 50 and 100 mg kg^{-1} i.p.) significantly reduced the ear edema induced by the xylene.

DISCUSSION

The present results indicate that ethanolic extract of aerial parts of *Salvia syriaca* have marked peripheral antinociceptive activity. The extract also showed activity against inflammation. The antinociceptive effect was assessed by three different models: the formalin test, hot plate test and acetic acid-induced writhing test in mice, whereas the anti-inflammatory effects were examined with ear edema model.

The formalin test is a valid and reliable model of nociception and is sensitive for various classes of analgesic drugs. Formalin is known to produce biphasic pain behaviors (Abbadie *et al*., 1997). The first transient phase is ascribed to the direct effect of formalin on sensory C fibers and the second prolonged phase is associated to the development of an inflammatory response and the release of analgesic mediators (Buritova *et al*., 2005). It was reported that substance P and bradykinin participate in the manifestation of the first-phase responses and histamine, serotonin, prostaglandin and bradykinin are involved in the second-phase responses (Otuki *et al*., 2001; Choi *et al*., 2003).

The hot plate test measures the response to a brief, noxious stimulus; the formalin test, on the other hand, measures the response to a long-lasting nociceptive stimulus and thus may bear a closer resemblance to clinical pain (Marchioro *et al*., 2005). Present results showed that the administration of the extract did not significantly raise the pain threshold in comparison with control. Morphine, used as a reference drug, produced a significant antinociceptive effect during all the observation times when compared with control values (Hiruma-Lima *et al*., 2000).

In the present study, acetic acid injection was demonstrated to induce a characteristic writhing response in the mice. Acetic acid-induced writhing is a highly sensitive and useful test for analgesic drug development especially peripherally acting analgesics. Acetic acid induces pain by liberating endogenous substances (bradykinin, serotonin, histamine, substance P) (Lu *et al*., 2007; Bars *et al*., 2001). Hyperalgesia induced by the injection of acetic acid is characterized by contraction of the abdominal muscle accompanied by an extension of the forelimbs and body elongation. These peripheral nociceptive fibers are sensitive to both narcotics analgesic (morphine) and non-steroid anti-inflammatory drugs like aspirin (Ridtitid *et al*., 2008). It is therefore possible that the extract exerts an analgesic effect probably by inhibiting synthesis or action of prostaglandins. It was reported that prostaglandin biosynthesis plays an important role in the nociceptive mechanism in this pain model (Franzotti *et al*., 2002). In addition to prostaglandins, several other inflammatory mediators, including sympathomimetic amines, tumour necrosis factor-α, interleukin-1β and interleukin-8 have been reported to be associated with the nociceptive response to acetic acid in mice (Ribeiro *et al*., 2000a). It is reported that writhing response induced by acetic acid is highly dependent on both peritoneal macrophages and mast cells (Ribeiro *et al*., 2000b). The ethanolic extract produced a significantly analgesic effect on the number of writhes induced by acetic acid suggesting that the extract might have a role to inhibit the synthesis of prostaglandins.

The ear edema model permits the evaluation of antiinflammatory steroids and is less sensitive to non-steroidal anti-inflammatory agents. In xylene-induced ear oedema test, mediators of inflammation are released following stimulation. This leads to dilation of arterioles and venules and to increased vascular permeability (Vogel and Vogel, 1997). The extract had significant anti-inflammatory effects in this test, thus it may have a membrane-stabilizing effect that reduces capillary

permeability and/or has inhibitory effects on mediators. Intraperitoneal administration of the extract, 30 min before topical application of xylene, dose dependently inhibited the development of ear edema. The inhibition produced by 100 mg kg^{-1} of the extract was similar to that produced by 1 mg kg^{-1} dexamethasone. The effect of the extract in this model suggests inhibition of phospholipase A_2.

The main constituents of *Salvia syriaca* were thymol, α-pinene and isobornyl acetate (15.5, 12.6 and 12.0%, respectively) (Flamini *et al*., 2007). The essential oil from the aerial parts of *Salvia syriaca* growing in Iran was composed, mainly, of germacrene B (34.8%), germacrene D (29.2%), α-ylangene (3.6%) and spathulenol (3.4%) (Sefidkon and Mirza, 1999), whereas other authors reported germacrene D (33.8%) and bicyclogermacrene (12.5%) as principal volatiles (Baser *et al*., 1996). Other chemicals isolated from this species were salvisyrianone, ferruginol, 3β-hydroxystigmast-5-en-7-one (Ulubelen *et al*., 2000), scutellarein 4′,7-dimethylether, apigenin 4′,7-dimethylether, salvigenin, 6-methoxyluteolin 3′,4′,7-trimethylether, eupatorin and salvisyriacolide (Rustaiyan and Sadjadi, 1987). It has been demonstrated that some flavonoids exert antinociceptive activity in mice (Ramesh *et al*., 1998).

Antinociceptive and/or anti-inflammatory activities have been reported for some *Salvia* genera such as *Salvia hemaematodes* (Akbar *et al*., 1984), *Salvia aethiopis* (Hernandez-Perez *et al*., 1995), *Salvia leriifolia* (Hosseinzadeh *et al*., 2003; Hosseinzadeh and Yavary, 1999) and other genera (Zargari, 1995). This study on *Salvia syriaca* and other research also confirm that *Salvia* genera are good candidates for anti-inflammatory and analgesic uses. Further pharmacological investigations are required to identify the active constituents of the plant extract responsible for the antinociceptive and anti-inflammatory and effects.

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