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ORIGINAL ARTICLE

Anti-inflammatory and antinociceptive effects of an ethanol extract from *Senna septemtrionalis*

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Abstract

Senna septemtrionalis (Viv.) H.S. Irwin & Barneby (Fabaceae) is a medicinal plant used as a folk remedy for inflammation and pain. The objective of this study was to evaluate the anti-inflammatory and antinociceptive actions of an ethanol extract of *Senna septemtrionalis* aerial parts (SSE). The in vitro anti-inflammatory effects of SSE were assessed using LPS-stimulated macrophages and the subsequent quantification of the levels of cytokines (IL-6, IL-1β, and TNF-α) with ELISA kits, nitric oxide (NO), and hydrogen peroxide (H_2O_2). The in vivo anti-inflammatory actions of SSE were evaluated with the TPA-induced ear oedema test and the carrageenan-induced paw oedema test. The antinociceptive actions of SSE (10–200 mg/kg p.o.) were assessed using three models: two chemical assays (formalin-induced orofacial pain and acetic acid-induced visceral pain) and one thermal assay (hot plate). SSE showed in vitro anti-inflammatory actions with IC_{50} values calculated as follows: 163.3 µg/ml (IL-6), 154.7 µg/ml (H_2O_2) and > 200 µg/ml (IL-1β, TNF-α, and NO). SSE showed also in vivo anti-inflammatory actions in the TPA test (40% of inhibition of ear oedema) and the carrageenan test (ED_{50} = 137.8 mg/kg p.o.). SSE induced antinociceptive activity in the formalin orofacial pain test (ED_{50} = 80.1 mg/kg) and the acetic acid-induced writhing test (ED_{50} = 110 mg/kg). SSE showed no antinociceptive actions in the hot plate assay. The pre-treatment with glibenclamide abolished the antinociceptive action shown by SSE alone. Overall, SSE exerted in vitro and in vivo anti-inflammatory actions, and in vivo antinociceptive effects by the possible involvement of ATP-sensitive K + channels.

Keywords *Senna septemtrionalis* · Antinociceptive · Anti-inflammatory · Medicinal plant

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Introduction

Approximately 11% of the members of the Fabaceae family are used for medicinal purposes (Allkin 2017). *Senna septemtrionalis* (Viv.) H.S. Irwin & Barneby (Fabaceae), native to North and South America, is a shrub worldwide distributed in warm climates and found between 1600 and 2400 m in altitude. This plant flowers from October to March. In Mexico, *S. septemtrionalis* is commonly known as candelilla or hierba del zopilote, whereas in English it is known as twin-flowered cassia or arsenic bush. *S. septemtrionalis* is used as a garden ornamental plant or as a coffee substitute and is commonly harvested from the wild. Some of the chemical constituents found in this plant include anthraquinones (i.e., chrysophanol, physcion, emodin), flavonoids (ombuin, quercetin), benzoic acids (calendin, syringic acid, vanillic acid), carboxylic acid (cinnamic acid), among others (Singh et al. 1980; Singh 1982; Jones et al. 2000; Alemayehu

et al. 2010). *S. septemtrionalis* is used as a folk remedy for alopecia, cold, rabies, cholera, inflammation, and pain (Aguilar et al. 1994; Jones et al. 2000). *S. septemtrionalis* is also considered an emmenagogue agent (Aguilar et al. 1994). Previously, we have shown that *Senna septemtrionalis* showed low in vivo acute toxicity ($LD_{50} > 2000$ mg/kg p.o. or i.p.) and exerted moderate anxiolytic and anticonvulsant effects, as well as antidepressant effects possibly mediated by α2-adrenoreceptors, and diuretic activity mediated by prostaglandins and nitric oxide (Alonso-Castro et al. 2019). In addition, we showed that the major component (42%) of *Senna septemtrionalis* was D-pinitol. This work evaluated the anti-inflammatory and antinociceptive actions of an ethanol extract of *Senna septemtrionalis* aerial parts (SSE).

Materials and methods

Reagents

Substances used for cell culture were obtained from Gibco-BRL (Grand Island, NY, USA).

Unless indicated, other reagents were from Sigma-Aldrich (St. Louis, MO, USA). ELISA kits used for the quantification of cytokines were purchased from Peprotech® (London, UK).

Plant material

Specimens of *Senna septemtrionalis* were collected in the municipality of Leon, Guanajuato (Mexico), in October 2017. A voucher sample (18,198) was kept at the herbarium of School of Higher Studies at Zaragoza, National Autonomous University of Mexico (FEZA).

Preparation of ethanol extract from *Senna septemtrionalis* aerial parts (SSE)

Aerial parts of *Senna septemtrionalis* (300 g) were macerated with ethanol (1800 mL) for 10 days. The extract was concentrated *in vacuo*.

Chemical characterization of SSE

For the chemical analysis of SSE (100 mg), the procedure described by Flores-Ocelotl et al. (2018) was followed using HPLC–PDA-ESI-MSn (negative ionization mode). The identification of the main metabolites in SSE was carried out on a Luna C18 column (250 × 4.6 mm, 5 µm particle size; Phenomenex, Macclesfield, UK).

Animals

Balb/c mice (25 ± 5 g of weight, 6–9 weeks of age) were used in this study. Mice were housed in polypropylene cages, in a room with 12-h light/dark cycle. Animals were handled according to national and international ethical guidelines (NIH, NOM-062-ZOO-1999).

Anti-inflammatory activity

Obtention of peritoneal murine macrophages

The obtention of primary murine macrophages was carried out following the protocol of la Torre Fabiola et al. (2016). Approximately $1x10^5$ cells/per well were seeded in 24-well plates under 5% CO_2 and 37 °C for 48 h. Murine macrophages were treated with 1 µg/mL LPS for 48 h. Then, macrophages received vehicle (DMSO 0.1%) or SSE (10–200 µg/mL) for additional 48 h. The supernatants were collected for further analysis.

Determination of pro-inflammatory cytokines

The quantity of IL-1β, IL-6, and TNF-α in supernatants was determined following the manufacturer's described procedures (Peprotech®, London, UK). The absorbances were measured at 490 nm on a Bio-Rad® iMark microplate reader. The concentrations (pg/mL) of cytokines were calculated by comparison with its respective standard curve.

Measurement of NO production

The Griess reaction described by Zamani Taghizadeh Rabe et al. (2014) was used to evaluate the NO production.

Briefly, equal volumes of the Griess reagent and supernatants were mixed in 96-well plates. The absorbance was recorded at 490 nm, and the nitrites concentration was calculated with a $NaNO_2$ standard curve (0–50 µM).

Analysis of H_2O_2 release

The H_2O_2 release was estimated according to Nathan and Root (1977) protocol. Equal volumes of cell culture supernatants and phenol red solution were mixed in a 96-well plate. After 3 h, 10 µL of NaOH 1 N solution was added and the absorbance was recorded at 620 nm. The H_2O_2 concentration was calculated by a standard curve (0–50 µM).

The experimental protocol of this study was approved by the Institutional Committee on Bioethics in Research of the University of Guanajuato (CIBIUG-P30-2019) prior to the beginning of all experiments.

TPA-induced ear oedema

The acute assay of 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA)-induced ear oedema was carried out as previously described (Inoue et al. 1989). The right ears, internal and external auricular pavilion, of mice ($n = 6$ per group) were administered with 20 µL of vehicle, SSE (2 mg/ear) or indomethacin (2 mg/ear). Thirty minutes later, the right ears of mice were treated with 20 µL of TPA (2.5 µg). After 6 h, the mice were euthanized and a 6 mm sections diameter of ear tissue was acquired from each group of mice.

λ-Carrageenan-induced hind paw oedema

The anti-inflammatory test of λ-carrageenan-induced paw oedema was evaluated according to previously reported technique of Calhoun et al. (1987). Briefly, experimental groups (SSE at 50, 100, and 200 mg/kg p.o.) and two control groups (10 mg/kg indomethacin p.o. as the positive group and saline solution as the vehicle group) were formed ($n = 5$ per group). Thirty minutes after the oral administration of the test samples or vehicle, a suspension of λ-carrageenan at 1% (0.25 µL/paw), in sterile physiological saline solution (0.9%), was injected into subplantar tissue of the right hind paw from each mouse. Measurements of hind paw volume (in mL) were obtained using a digital plethysmometer model LE 7500 (Panlab, Harvard Apparatus, Barcelona, Spain) at each hour for 6 h after extract or vehicle administration. The increase in the mean difference between right and left paw volumes was obtained at each time point indicated the dimension of paw oedema formation.

The percentage inhibition (PI) at each time interval was calculated as follows:

$$\mathrm{PI} = \frac{\left(V_t - V_0\right)\text{control} - \left(V_t - V_0\right)\text{treated}}{\left(V_t - V_0\right)\text{control}} \times 100$$

where V_0 is the mean paw volume at 0 hand V_t, mean paw volume at a particular time interval.

Antinociceptive activity

Orofacial pain test

The orofacial formalin model was followed according to the report of Barreras-Espinoza et al. (2017). Mice were acclimatized in acrylic cylinders for 3 consecutive days before the experiment. Experimental groups (SSE at 50, 100, and 200 mg/kg) and two control groups (18 mg/kg tapentadol as the positive group and saline solution as the vehicle group) were formed ($n = 8$ per group). Each treatment was orally administered 1 h before the test. Orofacial pain was induced with the administration, using a 30-g needle, of 2% (v/v) formalin (30 uL) into the upper lip of each mouse. Animals were placed in observation chambers and mirrors at a 45º angle to allow a free view of the upper right lip. Nociception was assessed as the rubbing time on the upper right lip, each 3 min for 45 min.

Hot plate test

The hot plate assay was performed following the protocol by Ankier (1974). Experimental groups (SSE at 50, 100, and 200 mg/kg) and two control groups (18 mg/kg tapentadol as the positive group and saline solution as the vehicle group) were formed ($n = 8$ per group). Each treatment was orally administered 1 h before the test. A hot plate apparatus was set at 55 ± 2 °C. Rodents were dropped gently on the hot plate, and those that showed nociceptive response, characterized by jumping or paw licking, between 9 and 15 s were chosen for the experiment. The cutoff period was 30 s. The latency time was recorded before the experiment and at 60- and 120-min post-treatment.

Visceral pain model

The acetic acid-induced visceral pain assay was used (Reichert et al. 2001). Experimental groups (SSE at 50, 100, and 200 mg/kg) and two control groups (18 mg/kg tapentadol as the positive group and saline solution as the vehicle group) were formed ($n = 8$ per group). Each treatment was orally administered 1 h before the test. A solution of 1% acetic acid was intraperitoneally administered (10 ml/kg), and the abdominal contortions were counted for 30 min.

Antinociceptive mechanism of action

Naloxone (5 mg/kg), a blocker of opioid receptors, glibenclamide (10 mg/kg), a blocker of ATP-sensitive K + channel, or methiothepine (0.1 mg/kg), a nonselective antagonist of serotonin, adrenergic, and dopamine receptors, and ondansetron (0.5 mg/kg), an antagonist of 5-hydroxytryptamine-3 (5-HT3) receptors, were used to assess the possible antinociceptive mechanism of SSE. Fifteen minutes after the administration of antagonists, 200 mg/kg SSE was administered at each mouse and the visceral pain model was carried out as described above.

Statistical analysis

Data were analyzed using SigmaPlot Program version 11. The analysis of variance and Dunnett's test were used to compare the doses of SSE against the vehicle group (saline)

in all experimental tests. Values of $p < 0.05$ were considered statistically different.

Results

Chemical characterization of SSE

The main compounds found in SSE corresponded to phenolic compounds, mainly flavonol glycosides, analyzed by HPLC–PDA-ESI-MSn (Table 1 and Fig. 1). Major peaks in SSE were tentatively identified as quercetin rutinoside rutin (8), kaempferol hexoside deoxyhexoside (12), and kaempferol rutinoside (13). These glycosides of flavonols are very common in many botanical and horticultural plants. Other highly glycosylated derivatives of quercetin, kaempferol and isorhamnetin were also detected, but in lesser amounts (e.g., 16, 18, 19).

In vitro anti-inflammatory activity

Macrophages stimulated with LPS increased the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and pro-inflammatory mediators (H_2O_2 and NO), as compared to the LPS-stimulated macrophages without treatment (Fig. 2). The vehicle group (DMSO 0.1%) did not increase significantly the production of pro-inflammatory cytokines, nor H_2O_2 or NO, as compared to the LPS-stimulated macrophages without treatment (Fig. 2). The treatment with SSE significantly ($p < 0.05$) decreased the production of cytokines, NO, and H_2O_2 in a concentration-dependent manner. The IC_{50} values calculated were as follows: 163.3 µg/ml (IL-6), 154.7 µg/ml (H_2O_2), and > 200 µg/ml (IL-1β, TNF-α, NO).

In vivo anti-inflammatory activity

In the TPA assay, SSE (2 mg/ear) decreased the ear oedema formation by 40%. The mice treated with 2 mg/ear indomethacin reduced the inflammation by 58% (Fig. 3a). SSE showed a dose-dependent, time-dependent until the 6th hour, and significant inhibition of λ-carrageenan-induced paw oedema in mice. At 6-h post-treatment, 100 mg/kg and 200 mg/kg SSE showed the maximum anti-inflammatory activity by 46.8% and 58.3%, respectively (Fig. 3b). At 6-h post-treatment, 200 mg/kg SSE showed a comparable effect with that showed by 10 mg/kg indomethacin (61.5%) (Fig. 3b). The ED_{50} value calculated for SEE in this test was 137.8 mg/kg.

Table 1 Main compounds found in SSE obtained during LC–ESI–MS analysis

Compounds	Rt (min)	UV_{max} (nm)	[M–H] *m/z* Parental Ions	MSn Fragments *m/z*
(1) *p*-Coumaroyl quinic acid I	10.4	302	337	191
(2) *p*-Coumaroyl quinic acid II	11.8	310	337	191
(3) Quercetin rutinoside hexoside	19.8	266, 346	771	301,300
(4) Unknown	20.2	266, 308	1111	555, 393
(5) Kaempferol rutinoside hexoside	21.2	266, 312	755	575, 285
(6) Quercetin rutinoside pentoside	21.8	266, 354	741	609, 300/301
(7) Quercetin hexoside deoxyhexoside	23.6	266, 356	609	343, 301, 271
(8) Quercetin rutinoside (rutin)	23.9	268, 354	609	301, 271
(9) Quercetin hexoside	24.6	256, 350	463	301
(10) Kaempferol hexoside	25.0	266, 352	447	285
(11) Isorhamnetin rutinoside pentoside	25.4	268, 350	755	623, 315
(12) Kaempferol hexoside deoxyhexoside	25.6	266, 350	593	285
(13) Kaempferol rutinoside	27.0	264, 348	593	285
(14) Isorhamnetin rutinoside	27.8	256, 354	623	315
(15) Kaempferol hexoside	29.3	270, 350	447	285
(16) Quercetin di-(desoxyhexosyl)-pentoxyl-hexoside	29.9	270, 340	887	741, 609, 475, 301
(17) Kaempferol hexoside	30.9	268, 338	447	285
(18) Kaempferol di-(desoxyhexosyl)-pentoxyl-hexoside	32.4	268, 316	871	725, 593, 285
(19) Isorhamnetin di-(desoxyhexosyl)-pentoxyl-hexoside	32.9	268, 318	901	755, 623, 315
(20) Isorhamnetin di-(desoxyhexosyl)-pentoxyl-hexoside	33.3	268, 318	901	755, 623, 315
(21) Emodin derivative (anthraquinone)	34.7	264, 326, 432	589	269, 225
(22) Emodin derivative (anthraquinone)	37.1	264, 348, 432	285	241, 225

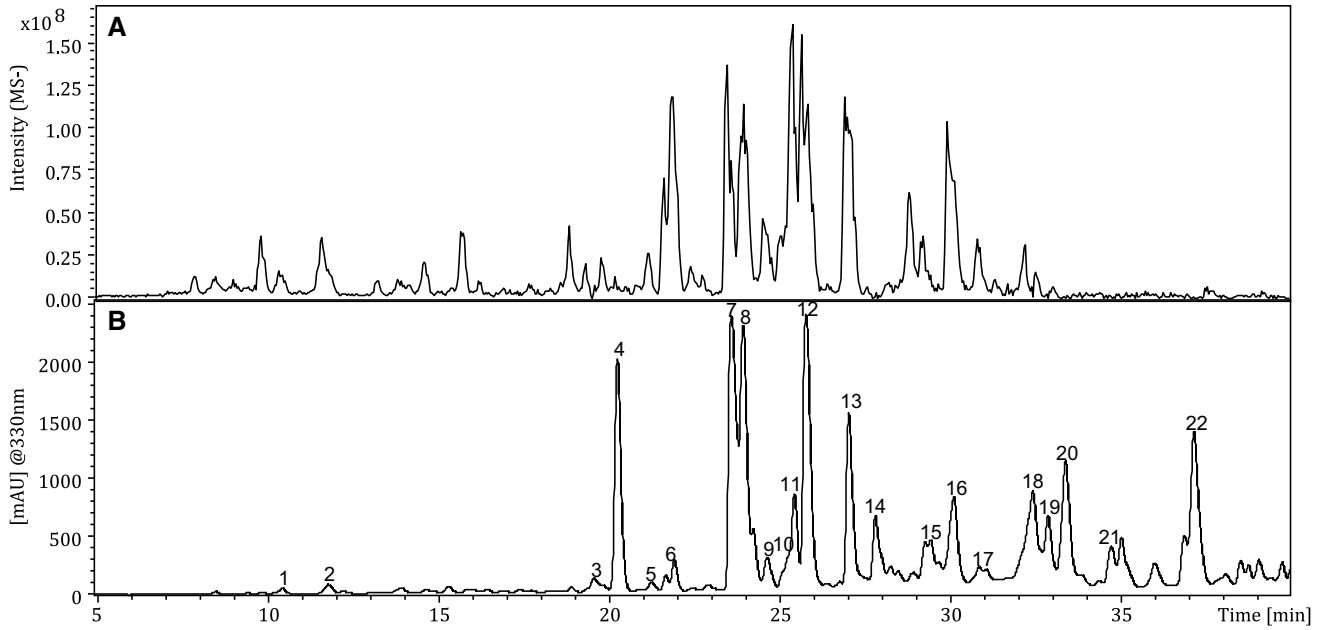


Fig. 1 Type chromatogram obtained during LC–ESI–MS analysis of SSE indicating the ESI–MS (**a**) results of parental ions and the characteristic chromatographic separation (**b**) of peaks registered at 330 ± 16 nm, under the analytical conditions. The tentative identification of the detected peaks (with the numbers) corresponds with the data included in Table 1

Antinociceptive activity

In the orofacial pain test, SSE showed antinociceptive response (ED_{50} = 80.1 mg/kg) with a dose-dependent effect (Fig. 4a). The highest antinociceptive action (69%) of SSE was recorded at dose of 200 mg/kg with similar effect to that obtained with 18 mg/kg tapentadol (77%) (Fig. 4a).

In the hot plate test, SSE did not protect rodents from pain induced by thermal stimuli (Fig. 4b). Tapentadol (18 mg/kg) prolonged the latency time by 29 s at 60- and 120-min post-treatment (Fig. 4b).

In the visceral pain model, SSE decreased the pain in a dose-dependent manner with ED_{50} = 110 mg/kg (Fig. 4c). Tapentadol (18 mg/kg) induced antinociceptive activity by 80% (Fig. 4c).

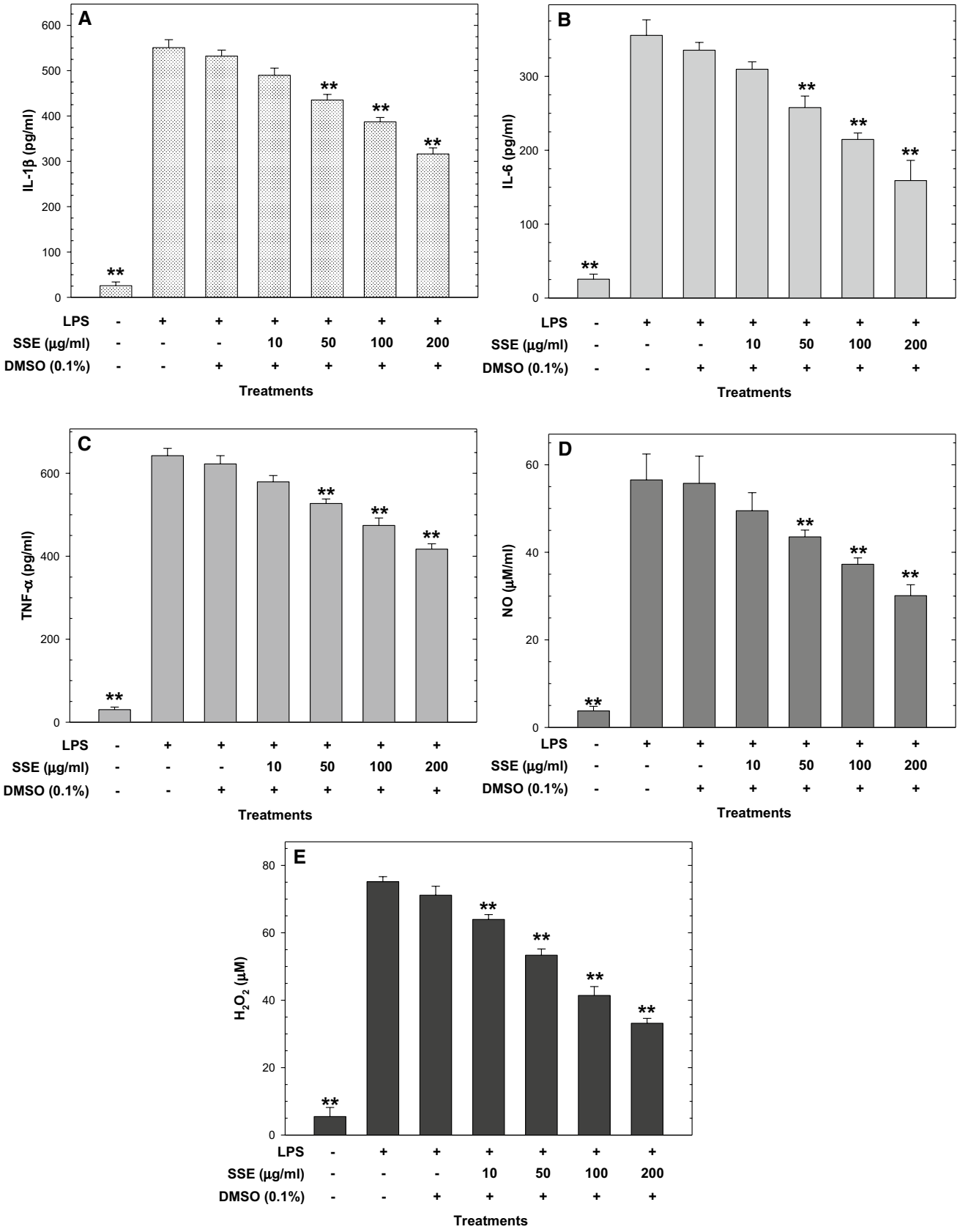
The pre-treatment with glibenclamide abolished the antinociceptive action shown by SSE alone. However, the pre-treatment with methiothepine, naloxone, and ondansetron did not reverse the antinociceptive action of SSE (Fig. 4d).

Discussion

The main metabolites found in SSE were flavonol glycosides. Other bioactive compounds detected and identified in SSE were the peaks (20) and (21), which correspond to emodin derivatives, formed fragments m/z 269, and subsequent fragment ions at m/z of 225 and 241, by the neutral loss of a CO and CO_2, respectively. The fragmentation of these anthraquinone derivatives was previously reported (Qiu et al. 2013). One peak of different characteristics and in high amount in the extract was the peak (4), unidentified compound with a fragmentation pattern that was not coincident with common flavonoids. The compound [M–H] of m/z 1111 produced fragments in MS2 and MS3 of 555 and 393 and was designated as "unknown," and the spectrum of absorbance was not a typical spectrum of flavonoid either; nonetheless, the abundance of the peak in the context of the extract is relevant and merits future isolation and purification of this fraction to properly identify this chemical entity.

Rutin and kaempferol-rutinoside-related compounds, two of the main compounds found in SSE, have been previously reported to exert anti-inflammatory (Guardia et al. 2001; Selloum et al. 2003; Yoo et al. 2014; do Nascimento et al. 2018) and antinociceptive (Wang et al. 2014; Hernandez-Leon et al. 2016; Alonso-Castro et al. 2017) activities. It is probable that the anti-inflammatory and antinociceptive actions shown by SSE could be attributed to the presence of rutin and related compounds of kaempferol rutinoside.

The anti-inflammatory effects of SSE were evaluated on in vitro and in vivo assays. The in vitro anti-inflammatory activity of SSE was mediated, mainly, by the reduction in the release of IL-6 and H_2O_2. IL-6 is a key factor in the progression of acute inflammation (Dinarello 1999). LPS stimulates the overproduction of H_2O_2, a marker of oxidative stress, in macrophages. Previously, we showed that SSE showed in vitro antioxidant activity (Alonso-Castro et al. 2019). The


A
IL-1β (pg/ml)
B
IL-6 (pg/ml)
C
TNF-α (pg/ml)
D
NO (μM/ml)
E
H2O2 (μM)
LPS
SSE (μg/ml)
DMSO (0.1%)
Treatments
**

◂**Fig. 2** In vitro anti-inflammatory actions of SSE. The effects of SSE on the production of IL-1β (**a**), IL-6 (**b**), TNF-α (**c**), NO (**d**), and H_2O_2 (**e**) in LPS-stimulated macrophages. The results represent the mean ± SEM of three independent experiments ($n = 3$). Data were analyzed using the ANOVA test followed by Dunnett's post hoc test with $p < 0.05$

results here described corroborate that SSE exerts protection against oxidative stress.

TPA induces local inflammation by the formation reactive species of oxygen, prostaglandins, and leukotrienes, and the subsequent induction of oedema (Inoue et al. 1989). SSE induced anti-edematogenic effect with similar activity compared to indomethacin. Carrageenan injection promotes the release of histamine and serotonin, which triggers to paw oedema (0–1 h). Subsequently, the release of prostaglandins, oxygen-derived free radicals, cytokines (IL-6 and TNF-α), and NO produces the migration of leukocytes, which leads to the inflammatory reaction (1–6 h). The antioxidant effects of SSE previously reported (Alonso-Castro et al. 2019), as well as the inhibition of IL-6 on the in vitro assays, could be associated with the decrease in inflammation in the carrageenan-induced paw oedema. The results indicated that SSE (100 mg/kg) exhibited a prominent anti-inflammatory effect in the second phase of the carrageenan test. SSE showed anti-inflammatory response on the in vivo acute assays. Therefore, the in vivo findings were supported by the in vitro results.

The antinociceptive actions of SSE were evaluated using three models: two chemical assays (formalin-induced orofacial pain and acetic acid-induced visceral pain) and one thermal assay (hot plate). Orofacial pain test mimics postinjury pain in humans (Siqueira-Lima et al. 2014). This test is composed of two phases: The first phase involves the participation of nociceptors (including c-fibers, bradykinin, among others), and the second phase includes the involvement of both nociceptors and second-order neurons, as well as the participation of N-methyl D-aspartate (NMDA) receptors, serotonin, histamine, among others (Siqueira-Lima et al. 2014). SSE showed antinociceptive actions in the orofacial test with a dose-dependent effect and $DE_{50} = 80$ mg/kg. The hot plate test is useful to detect compounds that have affinity to opioid receptors (Ankier 1974). SSE did not increase the latency in the hot plate test, which suggests that this extract might not have central antinociceptive effects. This hypothesis was further tested. Acetic acid-induced writhing response, a peripheral pain stimulus, is promoted by the release of prostaglandins, kinin, substance P, among others in the mouse viscera (Reichert et al. 2001). SSE decreased

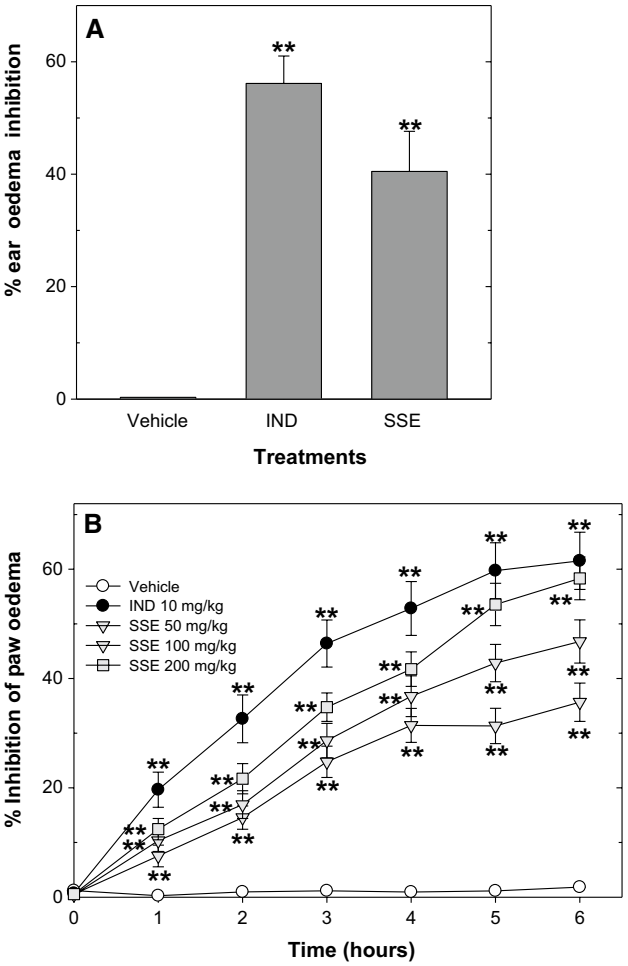


Fig. 3 In vivo anti-inflammatory actions of SSE. The effects of SSE on the TPA-induced ear oedema (**a**) and the λ-carrageenan-induced hind paw oedema (**b**) tests. The inhibition of ear oedema and paw oedema was estimated as described in Materials and methods. The results represent the mean ± SEM of two independent experiments ($n = 8$). Data were analyzed using the ANOVA test followed by Dunnett's post hoc test with $p < 0.05$

the abdominal constrictions in mice by the probable participation of ATP-sensitive K + channels, which indicates peripheral antinociceptive effects. The possible participation of opioid receptors was rejected since the pre-treatment with naloxone did not abolish the antinociceptive action of SSE. In addition, a sedative action by SSE in its antinociceptive action is rejected, since we recently reported that SSE did not affect locomotor coordination or induce sedation in mice (Alonso-Castro et al. 2019).

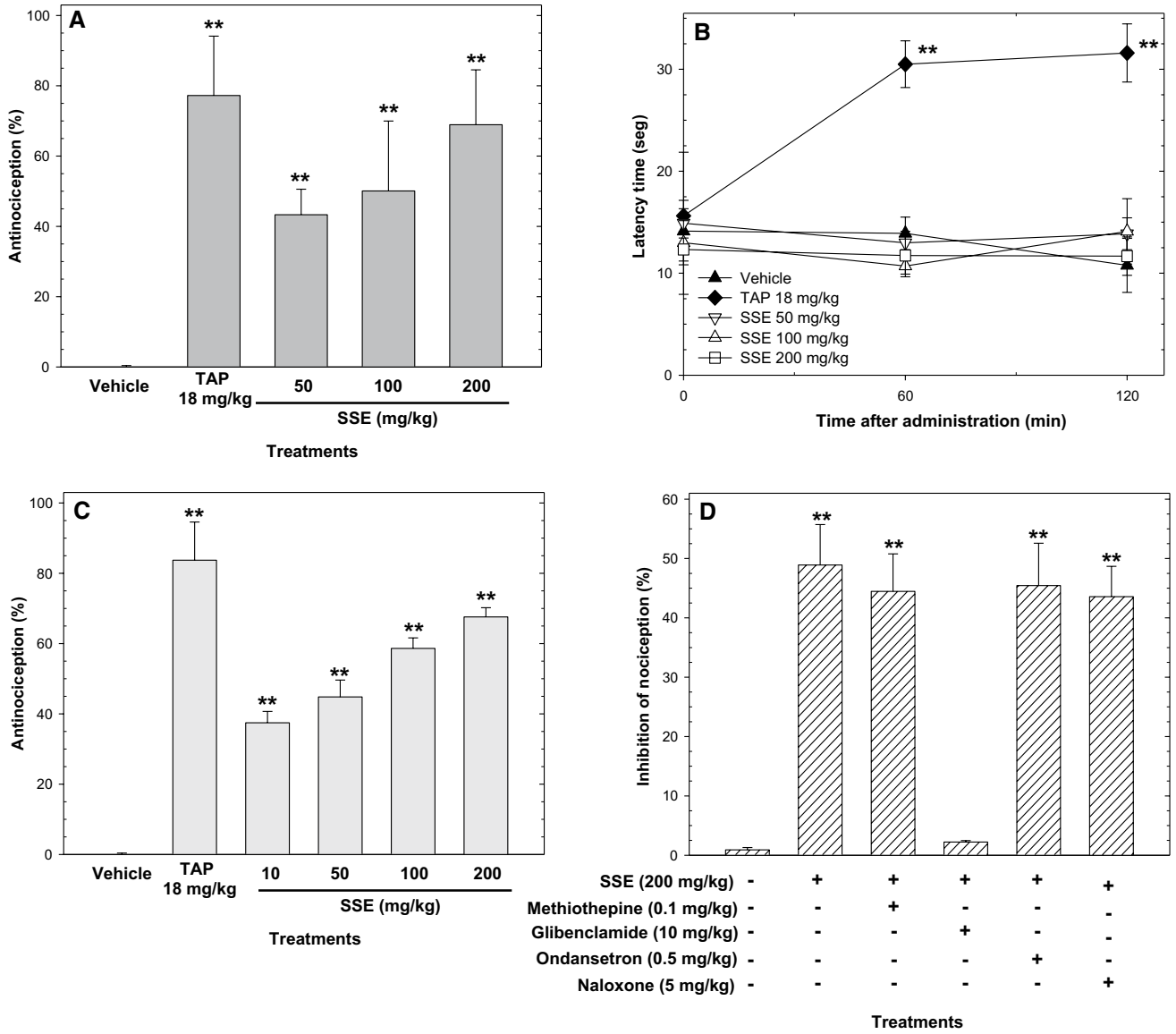


Fig. 4 Antinociceptive actions of SSE. The following assays were used to evaluate the antinociceptive effects of SSE: Formalin-induced orofacial test (**a**), hot plate test (**b**), acetic acid-induced writhing test (**c**), and the possible mechanism of action in the acetic acid-induced writhing test (**d**). The results represent the mean ± SEM of two independent experiments ($n = 8$). Data were analyzed using the ANOVA test followed by Dunnett's post hoc test with $p < 0.05$

Conclusion

The folk medicinal use of *Senna septemtrionalis* for the treatment of pain and inflammation has been corroborated in this study. SSE exerted in vitro and in vivo anti-inflammatory actions, and in vivo antinociceptive effects possibly mediated by ATP-sensitive K + channels.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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