

## Topical Anti-Inflammatory Potential of Six *Salvia* Species Grown in Jordan

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### ABSTRACT

Inflammation is a host defense mechanism to get rid of injurious stimuli and to induce tissue healing process. In Jordan, *Salvia* species are traditionally used to treat inflammation and other ailments. The aim of this study was to evaluate the potential of six *Salvia* species grown in Jordan to inhibit cutaneous inflammation. Topical anti-inflammatory activities of hexane (Hex), ethyl acetate (EtOAc) and methanol (MeOH) extracts from *Salvia* species aerial parts (*S. ceratophylla*, *S. dominica*, *S. multicaulis*, *S. palaestina*, *S. spinosa* and *S. syriaca*) were evaluated for the inhibition of croton oil-induced mouse ear oedema. Almost all extracts reduced oedema at the tested dose (300  $\mu\text{g}/\text{cm}^2$ ). Hex and EtOAc extracts exhibited the best anti-inflammatory effect in a dose-dependent pattern. Dose inducing 50% oedema inhibition ( $\text{ID}_{50}$ ) *in vivo* was found to be in the range of 87 - 300  $\mu\text{g}/\text{cm}^2$  and 47-146  $\mu\text{g}/\text{cm}^2$  for Hex and EtOAc extracts, respectively. In comparison with indomethacin ( $\text{ID}_{50}$  96  $\mu\text{g}/\text{cm}^2$ ), *S. palaestina* and *S. multicaulis* EtOAc extracts were two folds more potent ( $\text{ID}_{50}$  47 and 50  $\mu\text{g}/\text{cm}^2$ , respectively). Whereas, the  $\text{ID}_{50}$  of *S. syriaca* Hex extract (87  $\mu\text{g}/\text{cm}^2$ ) was comparable to that of indomethacin. In conclusion, the results illustrated that *S. multicaulis*, *S. palaestina* and *S. syriaca* can be regarded as promising natural sources of anti-inflammatory drugs.

**Keywords:** Croton oil, Lamiaceae, Mouse-ear erythema test, *Salvia*, Topical anti-inflammatory activity.

### 1. INTRODUCTION

Inflammation is a sequential process of responses triggered by several biological stimuli such as ischemia, thermal or physical injury, infectious agents and antigen-antibody interactions manifested as pain fever and oedema. Inflammation is a host defense mechanism to get rid of the injurious stimuli and to induce the tissue healing process<sup>1</sup>.

Steroidal and non steroidal anti-inflammatory drugs

are commonly employed to treat inflammatory symptoms. However, due to their adverse effects, particularly after prolonged use, there is an urgent need for new lead anti-inflammatory compounds<sup>2</sup>. A promising alternative to these drugs are natural products from medicinal plants, which successfully provided us with chemically diverse new drugs. In this respect, the Genus *Salvia* (Lamiaceae), including more than 900 species, can be regarded as a promising source for the discovery of lead anti-inflammatory agents. *Salvia* species (sage) show high diversity in bioactive constituents, mainly flavonoids and terpenoids<sup>3-10</sup>. Jordan's geographic and climatic characteristics allow the growth of a quite diverse group of natural flora. Up to date, twenty *Salvia*

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species were reported in Jordanian flora<sup>11</sup>.

These species are commonly used in traditional medicine of the Middle East to treat inflammations and other ailments<sup>10-17</sup>. In general, the leaves of sage are used to prepare anti-inflammatory mouth gargles, infusions to treat stomach disturbances<sup>17</sup>, rheumatic pain, cough, hyperlipidemia<sup>18</sup> and hypertension<sup>12, 16</sup>. Experimental studies revealed anti-proliferative and antimicrobial properties for the essential oil and the methanolic extract of the aerial parts of *S. Spinosa*<sup>19, 20</sup>. The methanolic extract of *S. Palaestina* aerial parts showed antioxidant and anti-proliferative effects<sup>19</sup>. Moreover, wound healing ointments are prepared from its leaves' extract supporting the reported antimicrobial activity of isolated flavonoids<sup>12,16</sup>. The leaves of the shrub *S. dominica* are used to treat cold, stomach pain and indigestion<sup>17</sup>. In addition, *in vitro* antitumor and antimicrobial activity was reported for the crude extracts<sup>13, 14 21, 22</sup> due to the presence of sesterpenes which inhibit tubulin-tyrosine ligase<sup>23</sup>. The leaves of *S. syriaca* shrub are used as tonic, antispasmodic and to treat gonorrhoea<sup>24, 25</sup>. Hypotensive effect was reported for the isolated diterpenes and steroids from the roots<sup>26, 27</sup>. Biological studies showed antimicrobial, antioxidant, anti-tuberculosis and anti-leishmanial properties for the essential oil of *S. multicaulis* shrub which is commonly used to substitute *S. officinalis*<sup>25, 27-31</sup>. Diterpene from *S. ceratophylla* extracts were shown to exert antioxidant, anti-cholinesterase and

antibacterial activities<sup>32, 33</sup>. The aim of this study was to evaluate the ability of six *Salvia* species (*S. ceratophylla* L., *S. dominica* L., *S. multicaulis* Vahl., *S. palaestina* Benth., *S. spinosa* L. and *S. syriaca* L.) grown in Jordan to inhibit cutaneous inflammation.

## EXPERIMENTAL

### Plant materials and extraction:

Aerial parts of different *Salvia* species were collected during spring season. *S. syriaca*, *S. multicaulis* and *S. palaestina* were collected from Abu Insair area, Capital Province; *S. dominica* and *S. ceratophylla* from Al-Subayhi area, Al-Balqa Province; *S. spinosa* from Ishtafina, Al-Mafraq Province. Identity of the collected plants was authenticated by Prof. Sawsan Oran and a voucher specimen has been deposited at the Herbarium of Biology Department, Faculty of Science, The University of Jordan.

Air-dried powdered plant material (300 g) was sequentially macerated in 2 L of n-hexane (Hex), ethyl acetate (EtOAc) and methanol (MeOH), at room temperature for one week (each solvent) with frequent agitation. After each step, solutions were paper-filtered, residual filtrates were concentrated under vacuum using rotary evaporator at 35°C and stored in the refrigerator at 4°C. Extraction yields are listed in Table 1.

**Table 1: Percentage yield of crude extracts**

Species	Percentage yield (dry extract :plant material) (w/w)		
	<i>n</i> -Hexane	Ethyl acetate	Methanol
<i>S. ceratophylla</i>	0.7 %	1.3 %	5.5 %
<i>S. dominica</i>	0.6 %	1.4 %	7.1 %
<i>S. multicaulis</i>	0.6 %	2.8 %	0.4 %
<i>S. palaestina</i>	2.1 %	1.5 %	8.8 %
<i>S. spinosa</i>	0.6 %	0.8 %	1.7 %
<i>S. syriaca</i>	1.1 %	0.8 %	1.7 %

**Table 2: Topical anti-inflammatory activity of the tested *Salvia* species extracts**

Substance	Hexane extract <sup>a</sup>		Ethyl Acetate extract <sup>a</sup>		Methanol extract <sup>a</sup>	
	Oedema (mg) m ± S.E.	% Reduction	Oedema(mg) m ±S.E.	%Reduction	Oedema(mg) m ±S.E.	%Reduction
Controls	6.6 ± 0.4	--	6.6 ± 0.4	--	6.2 ± 0.3	--
<i>S. ceratophylla</i>	4.3 ± 0.5*	35	1.2 ± 0.3*	82	5.3 ± 0.4	15
<i>S. dominica</i>	3.6 ± 0.4*	45	2.1 ± 0.2*	68	4.1 ± 0.6*	34
<i>S. multicaulis</i>	3.1 ± 0.2*	53	0.3 ± 0.1*	95	3.3 ± 0.6*	47
<i>S. palaestina</i>	2.1 ± 0.3*	68	0.4 ± 0.1*	94	4.7 ± 0.5*	24
<i>S. spinosa</i>	2.8 ± 0.4*	58	1.7 ± 0.4*	74	2.9 ± 0.5*	53
<i>S. syriaca</i>	0.7 ± 0.2*	89	2.0 ± 0.4*	70	4.8 ± 0.5*	23
Indomethacin§	2.8 ± 0.4*	58				

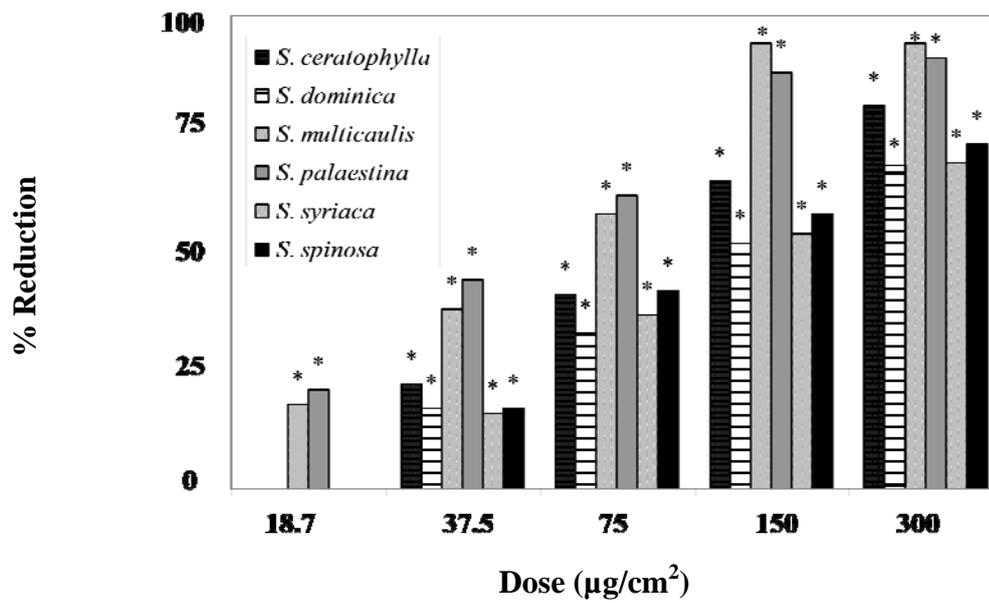
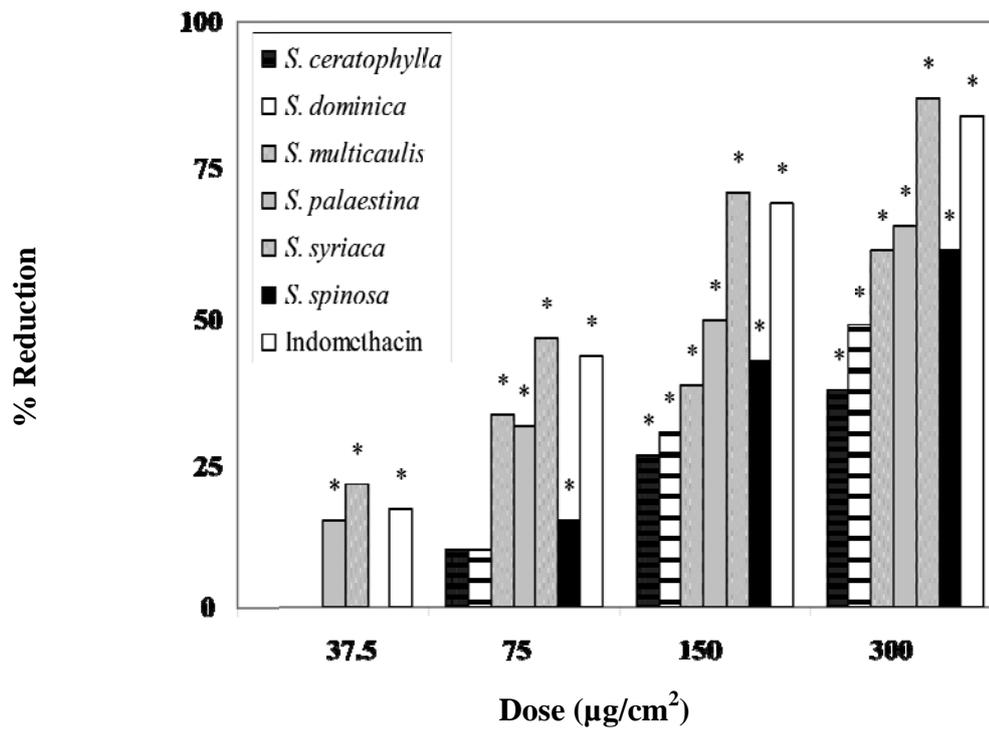
<sup>a</sup> dose: 300 µg/cm<sup>2</sup>

\* p<0.05 at the analysis of variance, as compared with controls;

§ dose: 100 µg/cm<sup>2</sup>

**Table 3: ID<sub>50</sub> values of the tested *Salvia* species extracts**

Salvia species and Reference drug	ID <sub>50</sub> (µg/cm <sup>2</sup> )	
	Hexane	Ethyl Acetate
<i>S. ceratophylla</i>	>300	98
<i>S. dominica</i>	>300	146
<i>S. multicaulis</i>	202	50
<i>S. palaestina</i>	160	47
<i>S. spinosa</i>	207	117
<i>S. syriaca</i>	87	134
Indomethacin	96	



**Figure 1: Topical anti-inflammatory activity of Hex extracts (upper), EtOAc extracts (lower) and indomethacin: dose-effect relationship**

### Chemicals:

Croton oil and indomethacin were purchased from Sigma Aldrich (Milan, Italy) and Merck. Ketamine HCl was purchased from Virbac (Milan, Italy). Solvents used were of analytical grade and were purchased from Sigma Aldrich (USA).

### Topical anti-inflammatory activity:

The topical anti-inflammatory activity was evaluated as inhibition of the croton oil-induced ear oedema in mice<sup>34</sup>. The *in vivo* experiments complied with the Italian DL 116 of 27.01.1992 and associated guidelines in the European Communities Council Directive of 24.11.1986 (86/609 ECC), concerning animal welfare. Male CD-1 mice (28–32 g; Harlan Italy, Udine, Italy) were kept for 1 week before the experiment, at constant conditions of temperature (21±1 °C) and humidity (60–70%), and a fixed artificial light cycle (7.00 am–19.00 pm). Inflammation was always induced in the late morning (10.00 am–12.00 am) and was anaesthetized by intraperitoneal injection of ketamine HCl (145 mg/kg).

Two vehicles were used to prepare croton oil (5 mg/mL) solutions A and B. In solution A, croton oil was dissolved in acetone. Solution B was prepared by suspending croton oil in 42 % aqueous ethanol v/v. Anti-inflammatory test solutions of hexane, ethylacetate extracts (20 mg /mL) and the reference, non-steroidal anti-inflammatory drug (NSAID) indomethacin (8mg/mL) were prepared by dissolving in stock solution A, while methanol extract (20 mg /mL) was dissolved in stock solution B.

Cutaneous inflammation in the control mice group was induced by applying 15 µl of the croton oil acetone solution (5 mg / mL) to the inner surface (about 1 cm<sup>2</sup>) of the right ear of the mice. The left ear remained untreated and acted as a reference. In addition, a group of 5 mice were treated with 15 µl of the vehicles to test any possible biological interference.

Anti-inflammatory effect of the prepared extract solutions, indomethacin and croton oil solutions A and B were evaluated by applying 15 µl to the right ear of the mice. After six hours, mice were sacrificed and a plug (6 mm Ø) was removed from the treated and the untreated ears. The oedematous response was measured as weight

difference between the two plugs.

The anti-inflammatory activity was expressed as percent reduction of oedema with respect to the control croton oil group. All experiments were carried out using a group of 5 mice and were conducted in triplicates<sup>34</sup>. Five different doses of indomethacin and *Salvia* extracts in the range of 10–300 µg/cm<sup>2</sup> were used to find out the dose-effect curve.

### Statistical analysis:

Data were analyzed by one-way analysis of variance followed by the Dunnett's test for multiple comparisons of unpaired data, and a probability level lower than 0.05 was considered as significant. The ID<sub>50</sub> values (dose giving 50 % oedema inhibition) were calculated by graphic interpolation of the logarithmic dose-effect curves.

## RESULTS AND DISCUSSION

The topical anti-inflammatory activity of the plant extracts, administered at the dose of 300 300 µg/cm<sup>2</sup> are reported in Table 2. Test extracts provoked oedema reduction, which ranged from 20 % for *S. palaestina* and *S. syriaca* MeOH to 90 % for *S. multicaulis*, *S. palaestina* EtOAc and *S. syriaca* Hex extracts. Apparently, EtOAc extracts were the most active and illustrated a significant oedema reduction in the range of 70–95 % followed by Hex extracts (35–90 % reduction), and MeOH extracts (20–50 % reduction). As reference, the non steroidal anti-inflammatory drug indomethacin (100 µg/cm<sup>2</sup>) induced 60 % reduction as shown in Table 2.

A dose-dependent oedema reduction was observed for all tested extracts as shown in Figure 1. The rank order of the topical anti-inflammatory effect for the Hex extracts was: *S. syriaca* > *S. palaestina* > *S. spinosa* > *S. multicaulis* > *S. dominica* > *S. ceratophylla*. However, for EtOAc extracts the rank order was: *S. multicaulis* > *S. palaestina* > *S. ceratophylla* > *S. spinosa* > *S. syriaca* > *S. dominica*. Whereas MeOH extracts rank order was: *S. spinosa* > *S. multicaulis* > *S. dominica* > *S. palaestina* > *S. syriaca* > *S. ceratophylla*.

The ID<sub>50</sub> values (dose inducing 50 % oedema inhibition)

for the tested Hex and EtOAc extracts are shown in table 3. The EtOAc extracts of *S. multicaulis* and *S. palaestina* (ID<sub>50</sub> of 50 and 47 µg/cm<sup>2</sup> respectively) were almost two folds more potent than indomethacin (ID<sub>50</sub> = 96 µg/cm<sup>2</sup>), while *S. ceratophylla* and *S. spinosa* (ID<sub>50</sub> = 98 and 117 µg/cm<sup>2</sup> respectively) were comparable to indomethacin.

Hexane extracts of *Salvia* species showed interesting activity (ID<sub>50</sub> values ranging from 87 to 207 µg/cm<sup>2</sup>) except for *S. ceratophylla* and *S. dominica* (ID<sub>50</sub> > 300 µg/cm<sup>2</sup>).

Phytochemical studies revealed the presence of phenolic and terpenoidal bioactive secondary metabolites (lupeol, ursolic acid, apigenin, eupatilin, luteolin, eupatorin, cirsimaritin and chrysoeriol) in different medicinal plants possessing anti-inflammatory effect, often due to different mechanisms of action<sup>4, 9, 12, 13, 16, 35-40</sup>. Accordingly, it could be speculated that, such bioactive compounds play a role in the observed topical anti-inflammatory effect of *S. palaestina*, *S. multicaulis*, *S. syriaca* and *S. ceratophylla* aerial parts Hex and EtOAc extracts. For example, eupatorin and salvisyriacolide were identified in *S. syriaca*<sup>40, 41</sup>. The phenolics, salpalaestinin; methyl 3-O-methylrosmarinate and the flavonoids luteolin dihydroxyphenyl caffeate; diosmetin; apigenin; clinopodic acid B were reported from *S. palaestina*<sup>42, 43</sup>. Kaempferol and its glucopyranoside, in addition to the isoflavone pseudobaptigenin were reported from *S. ceratophylla*<sup>44</sup>. Diosmetin, hymenoxin, norwogonin,

cirsimaritin, baicalin, pinocembrin, naringenin, isorhamnetin, fisetin-3-*o*-glucoside flavonoids were reported from *S. multicaulis*<sup>44, 45</sup>. β-Ocimene, valerate, β-Caryophyllene terpenes were reported in *S. spinosa* aerial parts volatile oil<sup>46</sup>.

## CONCLUSION

The six tested *Salvia* species from Jordan possess topical anti-inflammatory properties by inhibiting croton oil-induced ear oedema in mice. This finding would support their use in the treatment of inflammatory affections. In addition, the differences observed in the anti-inflammatory properties among various species would certainly strengthen the evidence that *S. Multicaulis*, *S. palaestina* and *S. syriaca* could be considered natural resources of new lead anti-inflammatory agents. However, further studies are recommended to identify the relevant bioactive principles in the active extracts.

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## دراسة فعالية ستة أنواع من فصائل المريمية التي تنمو في الأردن في قدرتها على التثبيط الموضعي للالتهابات الجلدية

ميادة شحادة<sup>1</sup>، سيلفيو سوسة<sup>2</sup>، غدير سعيفان<sup>1</sup>، رولى درويش<sup>3</sup>، آنا ججيانجاسبرو<sup>4</sup>، انطونيو فاسالو<sup>4</sup>، لورا ليبوري<sup>4</sup>،  
سوسن العوران<sup>5</sup>، هنا حماد<sup>5</sup>، اورليا تويارو<sup>2</sup>، تينا دي توماسي<sup>4</sup>، روبرتو ديللا لوجيا<sup>2</sup>

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<sup>3</sup> كلية الصيدلة، الجامعة الأردنية

<sup>4</sup> كلية الصيدلة، جامعة ساليرنو، ساليرنو، إيطاليا

<sup>5</sup> كلية العلوم، الجامعة الأردنية، عمان، الأردن

### ملخص

الالتهاب هو آلية دفاع الجسم الحي للتخلص من المحفزات الضارة وتحفيز عملية التئام الأنسجة. تستخدم أصناف المريمية (*Salvia*) في الأردن بأنواعها المختلفة في الاستطبانات الشعبية لعلاج الالتهابات وأمراض أخرى. تهدف هذه الدراسة إلى تقييم فعالية ستة أصناف مختلفة من المريمية التي تنمو في الأردن، من حيث قدرتها على تثبيط الالتهابات الجلدية. تم تقييم قدرة مستخلصات الأجزاء الهوائية من الأصناف التالية:

(*S. ceratophylla*, *S. dominica*, *S. multicaulis*, *S. palaestina*, *S. spinosa* and *S. syriaca*) المحضرة باستخدام الهيكسان (*hexane*)، الإيثيل اسيتيت (*ethyl acetate*) والميثانول (*methanol*) على تثبيط الالتهابات الناجمة عن تعرض أذن الفأر لزيت الكروتون (*Croton oil*) باستخدام الاختبار الحيوي المعروف ب اختبار الأذن الاحمراري "Mouse Ear-Erythema test".

أوضحت نتائج البحث قدرة جميع المستخلصات التي تم تقييمها باستخدام جرعة ( $300 \mu\text{g}/\text{cm}^2$ ) على تثبيط الالتهاب الجلدي، ولكن بنسب مختلفة. أظهرت النتائج أن مستخلصات الهيكسان والإيثيل اسيتات سجلت أعلى فعالية تراوحت بين ( $87 \mu\text{g}/\text{cm}^2$  -  $300 \text{ ID}_{50}$ ) و ( $146 - 47 \mu\text{g}/\text{cm}^2$   $\text{ID}_{50}$ ) على التوالي، بنمط يعتمد على الجرعة.

سجل مستخلص الإيثيل اسيتات لفصيلتي *S. palaestina* ( $47 \mu\text{g}/\text{cm}^2 \text{ ID}_{50}$ ) و *S. multicaulis* ( $50 \mu\text{g}/\text{cm}^2 \text{ ID}_{50}$ ) تأثيراً مضاعفاً لتثبيط الالتهاب الجلدي، مقارنةً بالدواء المعروف اندوميثاسين ( $96 \mu\text{g}/\text{cm}^2 \text{ ID}_{50}$ )، بينما سجل مستخلص الهيكسان لنبات *S. syriaca* فعالية مماثلة لدواء اندوميثاسين ( $87 \mu\text{g}/\text{cm}^2$ ). ويخلص البحث أن فصيلتي *S. palaestina* و *S. multicaulis* يمكن اعتبارهما مصدرين طبيعيين للحصول على مركبات ذات فعالية ضد التهابات الجلد الموضعية.

**الكلمات الدالة:** اختبار الأذن الاحمراري، العائلة الشفوية، المريمية، زيت كروتون، مضاد الالتهاب، الجلدي الموضعي.

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