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Anti-inflammatory and Analgesic Properties of *Salvigenin, Salvia officinalis* Flavonoid Extracted

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ABSTRACT

Background and aims: Inflammation is one of the defense mechanisms of body and unpleasant sensation of pain is caused by tissue damage. Mostly, inflammation occurs through the release of inflammatory mediators. *Salvia officinalis* is one of the most valuable medicinal kind of mint order. *Salvigenin* is one of the active flavonoids existing in this plant. The aim of this study was to evaluate the anti-inflammatory and analgesic effect of *salvigenin, Salvia officinalis* flavonoid extracted.

Methods: In this laboratory experimental study, plant was extracted and the column chromatography was used to purify prepared extracts. 100 male albino mice and 48 male wistar rats were selected. In the hot plate test and in the writhing test, animals were divided randomly into 5 groups. Group 1 (received 10 mg/kg normal saline), groups 2, 3 and 4 (received *Salvigenin* 25, 50 and 100 mg/kg intraperitoneally, respectively), group 5 (received 10 mg/kg morphine in hot plate test and 10 mg/kg indomethacin in writhing test). In the inflammatory test, animals were divided into 6 groups. Group 1 was assigned as a control group which received 0.05 ml of carrageenin. Groups 2, 3 and 4 (received *Salvigenin*, at doses of 25, 50 and 100 mg/kg). Group 5 (received 10 mg/kg indomethacin) and then changes of the volume of all groups were measured. Data were analyzed using ANOVA and Tukey test and $P<0.05$ was considered significant.

Results: In writhing test, *Salvigenin* reduced the number of abdominal contractions at doses of 50 and 100 mg/kg. Increasing dose of *Salvigenin*, with reduction in abdominal cramps resulted in the increasing of pain inhibition, and the percentage of this inhibition was statistically significant ($P<0.001$). In hot plate test, also 30, 45 and 60 minutes after injection of *Salvigenin* and morphine showed significant difference compared to the control group ($P<0.001$). Also, *Salvigenin* increased the maximum percentage of analgesic compared to the control group ($P<0.001$). *Salvigenin* could reduce inflammation and in the group that received *Salvigenin* at 100 mg/kg, the inflammation was significantly lower than the control group ($P<0.05$).

Discussion: Our findings showed that *Salvigenin* has dose-dependent analgesic effect so that it can be useful in controlling of inflammations, acute and chronic pain.

Keywords: *Salvigenin*, Flavonoid, *Salvia officinalis*, Inflammation, Pain.

Original article

INTRODUCTION

Pain and inflammation are of mechanisms of the body's defense which occur after each tissue damage. These inflammatory responses occur in the form of both acute and chronic. Acute form is known as the release of neutrophils and protein

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accumulation, while chronic form is known as accumulation of lymphocytes, macrophages and connective tissue growth. The most effects of inflammation are through the releasing of inflammatory mediators such as histamine, serotonin, bradykinin, nitric oxide and cytokinin from damaged tissues.[1] Nonsteroidal anti-inflammatory drugs are consumed in the US more than 35 million tablets of aspirin, ibuprofen, and naproxen annually without correct prescription. More than one percent of the American people use daily these drugs,[2] but the majority of these drugs can cause undesirable side effects such as gastrointestinal complications, kidney and bone disorders.[3-5] The toxic side effects of these analgesic medications has been well known.[6-8] In addition, production of synthetic drugs is very expensive. In contrast drugs of plant origin have been used for a long time without any significant side effects. So, it seems to be valuable to identify the origin of herbal medicines and their production.[9] Iran is one of the countries that are rich in medicinal herbs and plants, and the need for research on the biological and physiological effects of these herbs are of essential importance. One of the plants with proven anti-inflammatory analgesic effects is *Salvia officinalis*.[10-12]

Salvia officinalis (sage, also called garden sage, or common sage) is a perennial, evergreen subshrub, with woody stems, grayish leaves, and blue to purplish flowers. It is a member of the Lamiaceae family and is native to the Mediterranean region, though it has been naturalized in many places throughout the world. It has a long history of medicinal and culinary use, and today in the modern life it is used also as an ornamental garden plant. The common name "sage" is also used for a number of related and unrelated species.[13,14] *S. officinalis* was described by Carl Linnaeus in 1753. It has been grown for centuries in the Old World for its nutritional and healing properties, and was often described in old herbals for its many miraculous properties.[15] The leaves of this plant have some compounds such as caffeic acid, gallic acid and flavonoids such as Salvigenin, terpenes and tannins and Tvjvn.[16,17] Polyphenols are a group of bioactive compounds which found in plant sources. More than 8000 kinds of polyphenolic compounds are known and flavonoids are one of the most effective of them. A lot of biological activities and a variety of useful properties of polyphenols have been known. Polyphenols are capable to modulating intracellular signaling pathways associated with regulation of metabolism.[18,19] *Salvigenin* (5-Hydroxy-6,7,4′-trimethoxy flavones) is one of the active flavonoids existing in this plant.[20] *Salvigenin* also protects cells against cell death[21] and also present anticarcinogenic[22] and Aorta relaxant activity.[23] Anti-inflammatory activity of flavonoids has been documented.[24] Basic structure of flavonoids Chemically has the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and heterocyclic ring (C). This carbon structure can be abbreviated C6-C3-C6. The three above flavonoid classes are all ketone-containing compounds, and also are anthoxanthins (flavones and flavonols). The three cycle or heterocycles in the flavonoid backbone are generally called ring A, B and C. Ring A usually shows a phloroglucinol substitution pattern.[25,26] In this study, the effects of flavonoids extracted from *Salvia officinalis* have been evaluated. According to the analgesic effect of *Salvia officinalis* that has been evaluated and demonstrated[27] and according to the analgesic effect of flavonoids,[28] it was decided to evaluate the analgesic effect of this flavonoid.

METHODS

In this laboratory experimental study, aerial parts of the plant was dried in the shade under a gentle stream of air. One kilogram of plant was soaked with hexane:

ethyl acetate: methanol (1:1:1) in the laboratory (25 °C). After 72 hours, the mixture was filtered by Buchner funnels using Whatman Filter paper No. 41. Extract was separated using rotary evaporator. The H-NMR Spectroscopy showed that this extract contains flavonoids.

In order to isolate and purify compounds in plant extracts, column chromatography (CC) was used. For this purpose a column of silica gel (100cm × 2cm) with gel 60 (230-400 mesh ASTM) with particle size of 0.040 to 0.063 mm manufactured by Merck mixed with normal hexane were used. Extract was added to the top of the column. For the isolation of natural substances in extracts with different polarity fractions, polarity of the solvent used for washing of column was gradually changed. For this purpose, researchers started with hexane and gradually added certain amounts of ethyl acetate. Thus, the number of fractions was obtained. Similar fractions were mixed together. Then, from isolated fraction with ratio (70:30) hexane-ethyl acetate, yellow crystals were separated after washing with ether. Spectra were obtained using the Mass, one-dimensional and two-dimensional NMR and its structure was determined.

100 male albino mice (25–30 g) and 48 male wistar rats with 6-8 weeks old that were bred in animal house of Shahid Sadoughi Medical School were selected. Animals were kept at controlled temperature (22 ± 2°C) with a 12 h-light/dark cycle and free access to the standard lab chow and tap water. This study was carried out in accordance with current ethical guidelines for the investigation of experimental pain in conscious animals.[29]

In the hot plate test, animals were divided randomly into 5 groups of 10. Group 1 was considered as the control group which received 10 mg/kg normal saline intraperitoneally, groups 2, 3 and 4, received respectively 25, 50 and 100 mg/kg of *Salvignin* intraperitoneally. Group 5 received morphine at a dose of 10 mg/kg. All medications after zero time (initial test hot plate) were performed.

Writhing test: In the writhing test, animals were divided randomly into 5 groups of 10. Group 1 was the control group which received 10 mg/kg normal saline intraperitoneally, groups 2, 3 and 4, received respectively 25, 50 and 100 mg/kg of *Salvigenin* intraperitoneally. Group 5 received indomethacin at a dose of 10 mg/kg. All injections were performed 15 minutes before the injection of acid and acetic acid injected at a dose of 0.6 percent intraperitoneally and 5 minutes later, abdominal contractions of the mice were counted for 30 minutes.

In the inflammatory test, animals were randomly divided into 6 groups of 8. Group 1 was assigned as a control group which received 0.05 ml carrageenin in the left foot subcutaneously. Groups 2, 3 and 4, received *Salvigenin*, at doses of 25, 50 and 100 mg/kg intraperitoneally respectively. Group 5 received 10 mg/kg of indomethacin and then changes of the volume of all groups were measured. Extract and drug were injected intraperitoneally 30 minutes before injection.

The hot-plate test was carried out according to the method previously described.[30] Briefly, before the initial of experiment, mice were habituated to a Plexiglas cylinder for 5 minutes. In these experiments, the hot-plate apparatus was maintained at 54 ± 0.1°C. Animals were placed into an acrylic cylinder (20 cm in diameter) on the heated surface, and the time (in seconds) between placement and licking of their hind paws or jumping (whichever occurred first) was recorded as the response latency (reaction time).[31,32] Each mouse served as its own control. A 45-s cut-off was used to prevent tissue damage. After baseline behavior tests, mice were

immediately administered with drugs. The animals were intraperitoneally (i.p.) received vehicle (saline, 10 ml/kg), *salvigenin* at three doses (25, 50, and 100 mg/kg), and morphine (8 mg/kg) 15 min before the test. The reaction time of each mouse was again evaluated at 15, 30, 45, and 60, min after treatment. This was pooled for the mice in each treatment group and the final test mean value for each treatment group at each measurement was calculated. This final test mean value represented after treatment reaction time and was subsequently used to determine the percentage of maximum possible effect (%MPE) by applying the following formula:

$$\%\ MPE = \frac{\text{Test latency (sec)} - \text{Control latency (sec)}}{\text{Cut off (sec)} - \text{Control latency (sec)}} \times 100$$

Acetic acid-induced writhing test: This test was used as visceral pain model in laboratory studies. The abdominal constriction test described by Collier and et al,[33] was used to measure the analgesic activity of *salvigenin*. Male mice were pre-treated with *salvigenin* (25, 50, and 100 mg/kg). Fifteen minutes later, all mice were treated with intraperitoneal injection of 0.6% acetic acid to cause a typical stretching response.[34,35] Five min after acetic acid injection, mice were kept in individual cages and writhing or stretching of each mouse was counted for a period of 30 min by an individual who was unaware of the pretreatment type, to ensure an assessor blind evaluation. The analgesic effect was measured by calculating the mean reduction in the number of abdominal constrictions for each drug as compared to control. The percentage of writhing inhibition was calculated using the following formula:[36]

$$MPE = \frac{\text{Test latency (sec)} - \text{Baseline (sec)}}{\text{Cut off (sec)} - \text{Baseline (sec)}} \times 100$$

Inflammation induction method: Different doses of *Salvigenin* were dissolved in saline carrier. Experimental groups received 25, 50 and 100 mg/kg *Salvigenin* intraperitoneally and the positive control group received 10 mg/kg Indomethacin intraperitoneally and negative control received 5 ml/kg normal saline intraperitoneally. After half an hour, 100 µl of carrageenin (1%) was injected into the right paw of the rats subcutaneously. Right paw volume was measured once every hour for 4 consecutive hours using plethysmometer (model 7140, made in Italy). Immediately before the injection of carrageenin, the volume of the paw was measured as zero time.

In this study, volume of paws were not equal at zero time, therefore the following equation was used to calculate the percentage of Edema:

$$\%Relative\ Paw\ Edema = \frac{V_2 - V_1}{V_1} \times 100$$

V_1: paw volume of rats before carrageenin injection
V_2: paw volume of rats after carrageenin injection

To evaluate the percentage of inflammation inhibition in various categories, we use the following equation:

$$\text{Inhibition rate } (I)\% = \frac{E_c - E_t}{E_c}$$

E_c: Edema in the control group
E_t: Edema in the experimental group

Statistical Methods: Results were calculated as mean ± SD. The dataset of experiments were collected and analyzed with prism 5 software. Significant level of Data was Examined with ANOVA and Tukey test and P<0.05 was considered significant.

RESULTS

A. Results of writhing test: According to the results of this research, *Salvigenin* reduced the number of abdominal contractions and increased the percentage of inhibition at doses of 50 and 100 mg/kg compared to the control group (P<0.001) the maximum effect was observed at a dose of 100 mg kg (P<0.001).

Increasing dose of *Salvigenin*, with reduction in abdominal cramps leaded to increasing of pain inhibition, and the percentage of this inhibition was statistically significant (P<0.001). Also, indomethacin in receiver group significantly reduced abdominal contractions compared to the control group and dose of 25 *Salvigenin* (P<0.001).

Table 1: Writhing test; *Salvignin* analgesic effect in mice at different times

Groups	Dose (mg/kg)	Number of writhings SD ± Mean	% of this inhibition	Samples size
Control	10	5.6±5.86	-	10
Salvigenin	25	7.4±54[c]	85.28[c]	10
Salvigenin	50	9.6±5.47[b]	56.43[b]	10
Salvigenin	100	1.3±28[a]	21.68[a]	10
Indomethacin	10	7.1±23.5[a]	69.72[a]	10

[a]: significant difference to the control group (P<0.001); [b]: significant difference to the control group (P<0.01); [c]: significant difference to the indomethacin group (P<0.001).

B. Results of hot plate: According to Table 2, the duration of response to the pain between the groups in the hot plate test at time zero was not significantly different before the injection. It means all groups were similar in terms of pain threshold (P>0.05). 15 minutes after injection, morphine received group had significant difference compared to the control group (P<0.001), also 30 minutes after injection of 100 mg *Salvigenin* and morphine, significant difference was observed in comparison with the control group (P<0.001). 45 minutes after injection of *Salvigenin* at dose 50 mg, a significant difference was seen compared to the control group (P<0.05) and at time 60 minutes after morphine injection, a significant difference was seen compared to control group (P<0.001).

Table 2: Analgesic effect of *Salvigenin* in the hot plate test in mice at different times

Groups	Dose (mg/kg)	Zero time	15 minutes	30 minutes	45 minutes	60 minutes	Samples size
Control	10	10.29	9	10.80	9.5	9.77	10
Salvigenin	25	9.48	9.79	10	11.6	10.51	10
Salvigenin	50	10.25	10.25	11.75	12 [d]	10.25	10
Salvigenin	100	9.73	9.82	14 [a]	14.25 [a]	10.57	10
Morphine	10	9.38	13.82 [a]	16.97 [a]	17.26 [a]	14.55 a	10

[a]: significant difference to the control group (P<0.001); [b]: significant difference to the control group (P<0.01); [c]: significant difference to the morphine group (P<0.001); [d]: significant difference to the control group (P<0.05).

C. MPE (Maximum Possible Effect): The results showed that the percentage of the maximum analgesic effect may be different in experimental groups in time 30 and 45 minutes which used different doses of *Salvigenin*. *Salvigenin* increased maximum percentage of analgesic compared to the control group ($P<0.001$). The percentage of maximum pain suffering in morphine received groups at 15, 30, 45 and 60 minutes after injection were significantly increased compared to the control group ($P<0.001$). Other groups did not show any significant difference compared to control group ($P>0.05$).

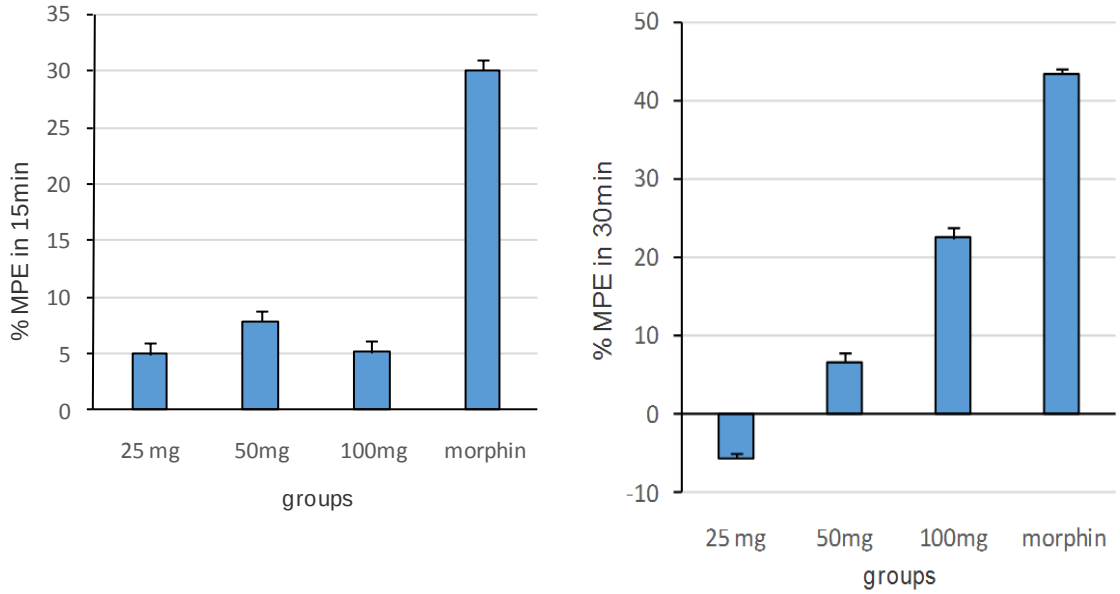

Figure 1: Effect of different doses of *Salvigenin* on the percentage of maximum pain suffering at time 15 and 30 minutes after administration of hot plate test
****: significant difference to the indomethacin group (P<0.001).*

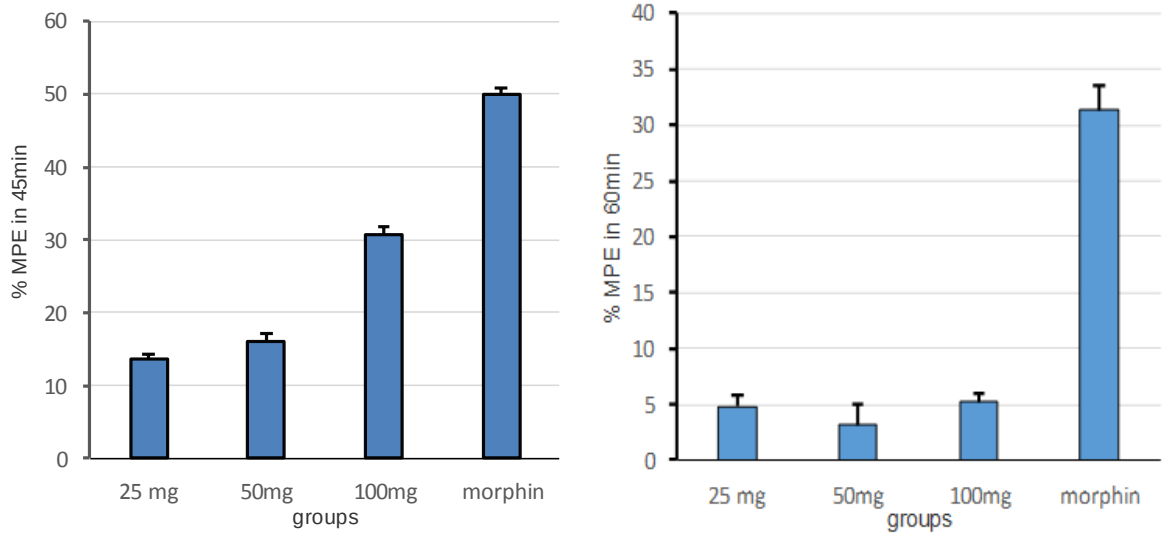

Figure 2: Effect of different doses of *Salvigenin* on the percentage of maximum pain suffering at time 45 and 60 minutes after administration of the hot plate test
****: significant difference to the indomethacin group (P<0.001). **: significant difference to the indomethacin group (P<0.01).*

Table 3: The effect of different doses of *Salvigenin* and indomethacin on edema induced by carrageenan

Groups	Dose (mg/kg)	1 h	2 h	3 h	4 h
Control	10 normal saline	1.5±37.1	7±57.8	3.5±62	4.7±63.2
Salvigenin	25	4.7±36.3	2.4±55.8	5.4±7.59	3.6±61.9
Salvigenin	50	6.7±6.33	8.7±49	8.9±56.1	2±2.57
Salvigenin	100	8.9±28 [a]	9.3±29.1 [a]	6±40.8 [a]	9.2±32.1 [a]
Indomethacin	10	10.7±18.1 [a]	7.5±28.2 [a]	3.6 ±39 [a]	8.5±30.6 [a]

a: Control group (P<0.05).

D. Effects of different doses of *Salvigenin* on carrageenan - induced inflammation: Effects of different doses of *Salvigenin* and indomethacin on edema induced by carrageenin in the paw of rats are presented in Table 3.

As the results showed, after carrageenin injection, volume of all mice paw was increased. Four hours after carrageenan injection, the maximum amount of inflammation was seen in all groups and this level was the highest in the control group. In all three groups, *Salvigenin* could reduce inflammation. In the group that received a dose of 100 mg/kg *Salvigenin*, inflammation was significantly lower than that of the control group (P<0.05). Indomethacin also reduced inflammation more effective than *Salvigenin*.

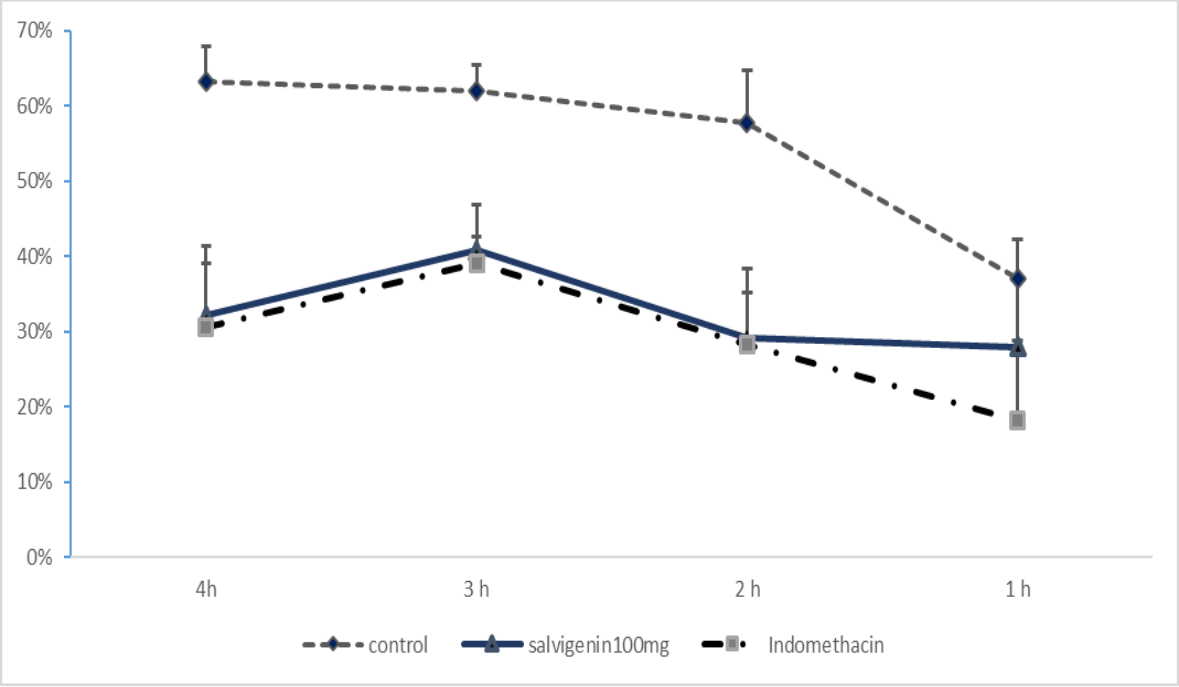

Figure 3: The inhibition of inflammation caused by carrageenan in the positive control group (indomethacin) and *Salvigenin* effective dose (100 mg) in comparison with the control group

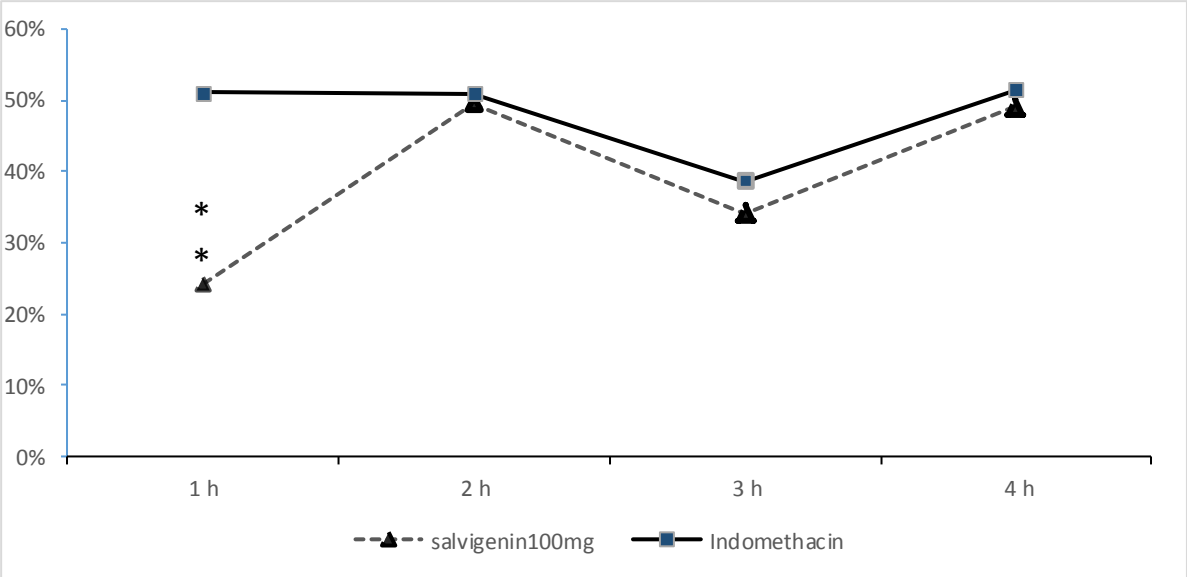

Figure 4: Inhibition of inflammation in group receiving *Salvigenin* compared to the groups receiving indomethacin (P<0.01).

The amount of inflammation caused by carrageenin in the positive controls (indomethacin) and *Salvigenin* at effective dose (100 mg) compared to the control group are presented in figure 3. Figure 4 presents the inhibition of inflammation among the *Salvigenin* received groups and indomethacin received groups. It showed that indomethacin inhibited inflammation more effective than the other groups. This inhibition was more than *Salvigenin* (100 mg) in the first hour after carrageenin injection.

DISCUSSION

Salvigenin has a significant analgesic effect like morphine. *Salvia officinalis* is the most valuable type of mint with anticonvulsant, antipyretic, diuretic effect and facilitates the digestion process. Consuming this plant is useful for relieving of unilateral headaches and headaches with neurological origin.[37] Qnais and colleagues proved the analgesic and anti-inflammatory effects of this plant.[38] Uydeş-Doğan and colleagues reported relaxant effect of *Salvigenin* on rat aorta.[23] However, analgesic effects of *Salvigenin* has not been evaluated yet. Flavonoids are plants Polyphenol compounds that have analgesic and anti-inflammatory effects.[39]

Flavonoids are able to cross the blood-brain barrier and through several mechanisms including the effect on GABA receptors, opioids receptors and alpha-adrenergic receptors can inhibit enzymes involved in inflammation and pain in different parts of the nervous system including the ventral medulla oblongata (medulla Rostral ventrolateral), the alpha-adrenergic, GABA receptors reported. Stimulation of this receptor can induce analgesia.[40]

Flavonoids in inflamed tissue inhibit Cyclooxygenase, so they can prevent the formation of prostaglandins. Prostaglandins stimulate pain receptors in brain. Many plants containing flavonoids present these functions by inhibiting cyclooxygenase.[41]

Flavonoids inhibit nitric oxide synthesis that inhibits NO production. Thus, it is leading to decrease analgesic activity. Other studies have shown that flavonoids can decrease intracellular calcium with inhibition of

N-Methyl-D-aspartate receptor. So, synthesis of nitric oxide and phospholipase A and activity of NO decrease analgesic effect of NO and prostaglandins appear. Inhibition of phospholipase A2 leads to inhibiting of the conversion of phosphatidic acid to arachidonic acid, therefore prostaglandin synthesis inhibit.[42] According to the available evidence, flavonoids also can inhibit cyclooxygenase enzyme with inhibition of tumor necrosis factor (TNF) secretion, so they can control and inhibit inflammation.[43]

Flavonoids like apigenin reduce accumulation of lipids which are necessary to pain signal. Therefore, flavonoids reduce inflammatory pain receptors by inhibiting the accumulation of receptors and signaling cascades.[44] Furthermore, studies have shown that quercetin can inhibit lipoxygenase and cyclooxygenase activity. So, it can decrease the inflammation. Inhibition of eicosanoids biosynthesis is one of the other mechanisms of flavonoids anti-inflammatory operation.[45]

Our findings showed that *salvigenin* has dose-dependent analgesic effect So that 100 mg/kg was the most effective dose among different studied doses. This dose had no mortality or significant adverse effects in treated mice. According to the previous researches, inhibition of prostaglandins and nitric oxide production are possible mechanisms of this flavonoid. The results of this study showed that *salvigenin* can control acute and chronic pain. However, the tests used in this study were general, so it is suggested that more similar studies be conducted in other pain models. Based on above studies, *Salvigenin* has anti-inflammatory and high antioxidant activity. Since, anti-inflammatory of these flavonoids have not been checked, the aim of this study was to demonstrate anti-inflammatory effect of *salvigenin* intraperitoneally. The results of this study are in accordance with other studies. With more basic and clinical studies, we can suggest that flavonoids can be combined with other anti-inflammatory herbal alternative medicine as anti-inflammatory drugs.

CONFLICT OF INTEREST

There is no conflict of interest associated with this study.

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