Original Article

IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

Iranian J Pharmacol Ther. 2017 (August);15:1-6.

Anti-inflammatory and Anti-nociceptive activity of *Rosa Canina* aqueous extract in animal models

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Please cite this article as:
Tabatabaee SM, Yusefi MJ, Motevalian M. Anti-inflammatory and Anti-nociceptive activity of Rosa Canina aqueous extract in animal models. Iranian J Pharmacol Ther. 2017 (August);15: 1-6.

ABSTRACT

Rosa canina has been traditionally used in Iran as herbal medicine for treatment of painful and inflammatory conditions. The aim of this study is to evaluate the analgesic and anti-inflammatory activity of the aqueous extract of the *Rosa canina*in animal models of pain and inflammation. The analgesic effect was evaluated with hot plates a model of visceral pain in mice. Also inflammation produced by injection of formalin in paw of rats and the treatment by extract was assessed. Doses of extract used were 100, 300 and 700 mg/kg. The negative and positive control groups received normal saline and sodium salicylate respectively. The aqueous extract of *R. canina* could increase the latency time in mice in a dose-dependent manner ($P<0.05$). The pretreatment with extract significantly augmented the anti-nociceptive effects of *Rosa canina* and this was comparable with sodium salicylate and even more pronounced than sodium salicylate after 2 hours. Additionally, the inflammation induced by formalin was limited by aqueous extract of *R. canina* during acute and chronic phases of inflammation considered in 7 days period. The results of this study demonstrated the dose-dependent analgesic effects of *Rosa canina*aqueous extract in mice model of pain. And also our data showed dose-dependent anti-inflammatory action of the extract in formalin-induced edema. Our results contribute towards validation of the traditional use of *Rosa canina* in the management of pain and inflammatory conditions.

Conflicts of Interest: Declared None
Funding: Razi Drug Research Center

Keywords
Rosa Canina,
Aqueous extract,
Inflammation,
Nociception

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Received: 10 Feb 2017
Revised: 8 Mar 2017,
Accepted: 17 May 2017

INTRODUCTION

Herbal medicine is among oldest mankind sciences. Oriental scientists like Abu Musa Jabir Ebne Hayyan and Avesina described many of these herbal medicines [1]. *Rosa canina* is a herb used widely in Iranian traditional medicine, but few studies have evaluated its therapeutic properties. *Rosa canina L.* from the family of Rosaceae, known as "dog rose", is a prickly shrub which is 1 to 3meter high with fragrant white or pink flowers [2]. This medicinal plant grows in Mediterranean countries and widely used in northwest of Iran [3]. The rose plant has a pseudo fruit named rose hip (or rose haw). In some species especially *Rosa canina* (dog rose), rose hips are known as valuable sources of vitamin C [4]. A wide array of bioactive ingredients such as fatty acids, minerals, ascorbic acid, flavonoids, tannins, phenols and sugar are responsible for functional properties of *Rosa canina* [5].Especially, an isolated galactolipid from rose hip has been proved to inhibit chemotaxis of human peripheral blood neutrophils [6]. Another study proved that linoleic and alpha-linolenic acids from rose hip inhibit cyclooxygenase-1 (COX-1) and COX-2 activities in vitro [7, 8]. The antioxidant activity of extract of this plant has been reported in several studies and it is shown

that the level of this activity is not correlated to level of vitamin C content [9; 10; 11].Review of trials performed to evaluate the effects of rose hip and seeds extract on osteoarthritis reveals that these compounds are capable of reducing pain in patients and can be promising therapeutic aid for the management of musculoskeletal disorders [4]. More-over, Willich et al performed a double-blind placebo-controlled trial on rheumatoid arthritis patients and revealed improvement of quality of life in patients treated with *Rosa canina* compared to control group[12]. Two studies have investigated the effects of *Rosa canina* alcoholic extract on animal models, but there is no study in literature investigating in-vivo effects of aqueous extract of this plant [13, 14]. This study was designed to evaluate the anti-nociceptive and anti-inflammatory effects of aqueous extract of rose hip using in-vivo experimental models in rat and mice.

MATERIALS AND METHODS

Plant materials and extract preparation

Rosa canina fruits were collected from northwest of Iran and was authenticated at the pharmacology department of Iran university of medical sciences. The fruits were dried in the dark at room temperature before extraction. Dried fruits (200 g) were crushed and then macerated in water (2 L) for 48 hours on a shaker. The macerated solution was percolated twice and the crushed residue of the fruits was re-macerated in water (1 L) for 24 hours and re-percolated twice. The extract solution was lyophilized under vacuum. The *Rosa canina*aqueous extract was kept in refrigerator at 5˚c before use.

Animals

Thirty five male Wistar rats (weight150-200 g) and 35 male mice (weight 25-30g) were obtained a week before experiment. Rats and mice were randomly assigned to five groups separately (n=7 in each group) and were kept in separate cages under controlled environmental conditions: 22±2°c temperature, 55±5% humidity, a 12 hours light-dark cycle. Throughout the study, animals were fed with standard diet consisting pellets and water ad libitum. All tests were conducted under the guidelines of the International Association for the Study of Pain [15]. All experimental procedures followed the Guidelines on Ethical Standards for investigation of experimental pain in animals and were carried out to a protocol approved by the local Animal Ethics Committee.

Anti-nociceptive activity

In anti-nocicepetive activity assessment, three groups received aqueous extract (100, 300, 700mg/kg) and the other groups received sodium salicylate (300mg/kg) and normal saline as positive and negative control groups respectively. The hot plate test described by Wilson et al. was used for assessment of anti-nociceptive activity [16]. The mice in each group were placed on the hot plate while the temperature of metal surface was set at 50±0.2°c. Response latency was described as the time between placement of mice on hot plate and a discomfort reaction (shaking, licking of the paw and jumping off from the plate). A 15 second cut-off time was chosen to avoid injury. The latency or reaction time was measured before administration and 30, 60, 120 and 180 minutes after intraperitoneal injection of aqueous extract and control compounds. Finally, the percentage of analgesic activity (PAA) was measured using following equation: PAA= [(latency time after injection – latency time before injection)/ latency time before injection] *100.

Anti-inflammatory activity

In the assessment of anti-inflammatory activity, group 1 received the aqueous extract of *Rosa canina* at 100 mg/kg concentration. The second treatment group was given 300 mg/kg and the third 700 mg/kg of extract. Group 4 as positive control was given 300mg/kg sodium salicylate dissolved in water and control group was given normal saline. The anti-inflammatory activity was measured on the basis of formalin induced rat paw edema in two phases; acute and chronic. Thirty minutes before formalin injection, each group received relevant dosages of drug and extract intraperitoneally. Thereafter, rat paw volume was measured using a mercury pletysmometer. The change in volume of the rat hind paw edema was measured by the method described by Winter et al [17]. Afterward, 20 µl of 2.5% formalin was injected in hind paw of all rats. Rat hind paw volume was measured 1, 2 and 3 hour after formalin injections as acute phase and measurements repeated in second to eighth day as chronic phase with pletysmometer. The swelling percent of the paw was determined using Eqn. 1 - Swelling percent = (V-Vi/Vi) ×100. Where V is the paw volume after the formalin injection, and Vi is the initial paw volume. The percent of inhibition of the edema formation was determined using Eqn. 2 - Inhibitory percent = [1-percent swelling]. The average paw swelling in the groups of the drug-treated rats compared torats in control group.

Statistical analysis

The percentage of rat paws swelling and analgesic activity was expressed as mean ± SD. The normal distribution of variables was measured by Kolmogorov Smirnov test. Both comparison of mean paw swelling in the anti-inflammation experiment and analgesic activity in anti-nociception experiment was performed between and within groups using analysis of variances (ANOVA) and repeated measurement ANOVA respectively. The significance was considered at level of $p \leq 0.05$. All calculations were performed using version 18 SPSS software.

RESULTS

Hot plate test

This part of study was done on 35 male mice which were divided in 5 groups. As it is shown in Table 1, there were no significant differences in mean of response latency times between the groups before injection (p=0.579).

Table 1. Latency time in response to hot plate in mice received aqueous extract of Rosa canina and control groups

		Time after injection (minutes)				
Drug /extract	Dose	0	30	60	120	180
R. canina aqueous extract	100mg/kg	2.09±1.01	2.16±1.78	1.87±1.23	2.08±1.12	1.31±0.55
	300mg/kg	2.41±1.11	2.58±1.53	3.95±3.18	2.43±1.43	1.75±0.75
	700mg/kg	2.74±1.66	4.98±3.24	3.67±1.48	3.23±0.70	2.65±0.44
Sodium salicylate	300mg/kg	1.99±0.92	1.95±0.84	1.10±0.37	1.00±0.60	2.24±0.81
Normal saline	1 ml	2.30±0.41	1.44±0.42	1.74±0.62	1.12±0.34	1.12±0.33

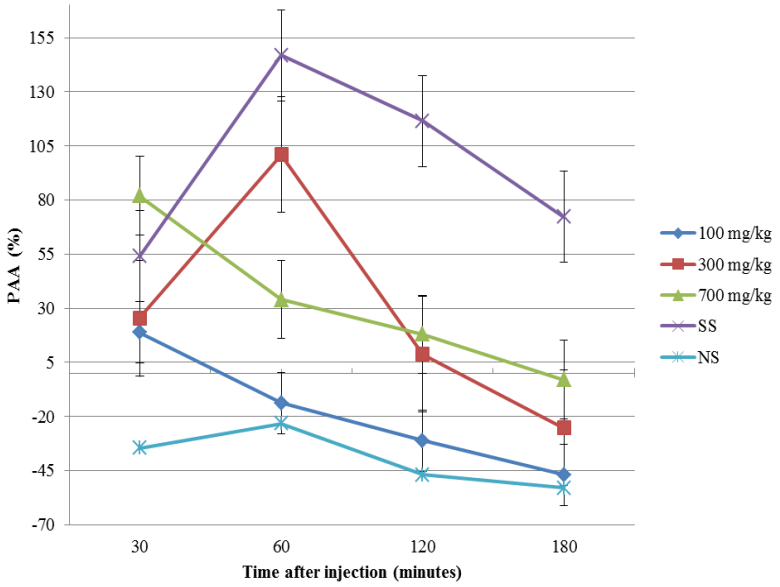

Figure 1. The PAA in mice received aqueous extract of *Rosa canina* and control groups. PAA: Percentage of analgesic activity; SS: Sodium salicylate; NS: Normal saline

Thirty minutes after injections, greatest PAA observed in the group that received 700mg/kg of aqueous extract of *Rosa canina* and this value was statistically significant (p≤0.01) (Fig. 1). This group had greater analgesic activity in comparison to sodium salicylate group as our positive control. The greatest PAA after 60 minutes of injection was seen in 300 mg/kg group (p= 0.013). After 3, analgesic activity decreased in treatment groups and greatest response observed in salicylate group (Fig. 1). The trend of changes in analgesic activity over 3 hours was statistically significant on the basis of repeated measurement analysis (p=0.048).

Rat paw edema test

This experimental study was done on 35 male Wistar rats which were divided in 5 groups. The mean weight of rats was 184±14 g and there was no significant difference in mean weight of rats in five groups (p =0.059).

In acute phase, the percent of increase in rat paws edema was not significant in the group one (p=0.087) and two (p=0.153) on the basis of repeated measurement ANOVA analysis, But it was statistically significant in the other groups (Table 2). In ANOVA analysis, there was not any significant difference in mean paw volume between different groups. It is shown in Figure 2 that the least rise in the rat paws edema was in the third group (700mg/kg).

The rise in rat paw edema decreased in the next days of chronic phase (Table 3), While the edema in the first and second groups were less than the positive and negative control groups, the least increase in rat paw edema was seen in the 700mg/kg group (Fig. 3). The within group analysis of

Table 2. The percentage of increase in paw volume of rats received aqueous extract of *Rosa canina* and control groups in acute phase (1st, 2nd and 3rd hours after injection).

Groups	*Dose*	*1st h*	*2nd h*	*3rd h*	*P-value*
		Percent of Increase in paw volume			
Rosa canina aqueous extract	100mg/kg	44±19	58±32	56±30	.087
	300mg/kg	42±14	49±14	54±12	.153
	700mg/kg	41±14	45±22	53±20[*a]	.017[*b]
Sodium Salicylate	300 mg/kg	47±20	64±15	73±17	.001[*b]
Normal Saline	1 ml	49±11	60±5	62±9	.033

[a]Comparison between groups 700 mg/kg and sodium salicylate, [b]Significant by P-value≤0.05.

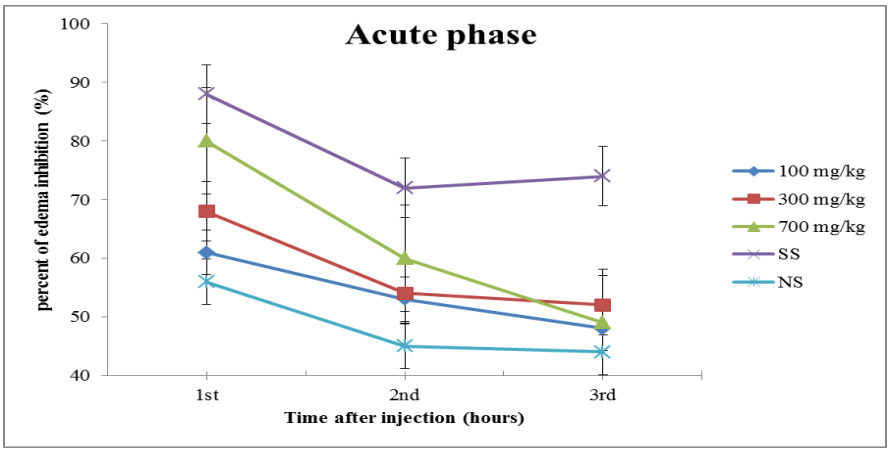

Figure 2. The mean percentage of edema inhibition in rats received aqueous extract of *Rosa canina* and control groups. Data are expressed as mean±sem (n=7). SS: Sodium salicylate; NS: Normal saline

Table 3. The percentage of increase in paw volume of rats received aqueous extract of *Rosa canina* and control groups in chronic phase (2nd, 3rd, 7th and 8th day of injection)

Groups	*Dose*	*2nd day*	*3rd day*	*7th day*	*8th day*	*P-value*[1]
		Percent of Increase in paw volume				
Rosa canina aqueous extract	100mg/kg	65±36	66±28	25±17	21±18	.002*[b]
	300mg/kg	56±13	61±9	22±10	19±9	.001*[b]
	700mg/kg	56±20	58±13	21±25	18±23*[a]	.009*[b]
Sodium Salicylate	300 mg/kg	82±20	71±21	30±18	23±16	.001*[b]
Normal saline	1 ml	79±11	68±12	37±9	29±9	.001*[b]

[a]Comparison between groups 700 mg/kg and normal saline, [b]Significant by P-value≤0.05.

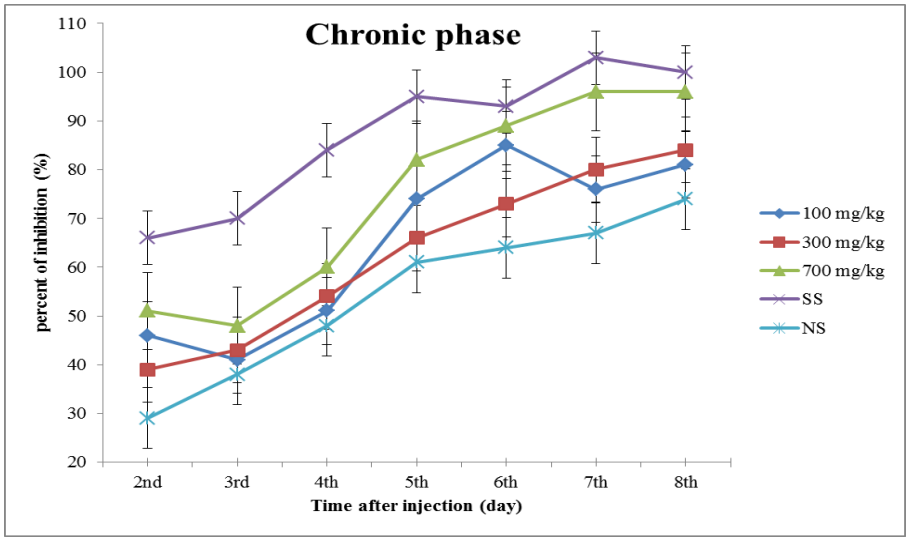

Figure 3. The mean percentage of edema inhibition in rats received aqueous extract of *Rosa canina* and control groups in chronic phase. Data are expressed as mean±sem (n=7). SS: Sodium salicylate; NS: Normal saline

all five groups in the chronic phase were significant. The percent of increase in rat paw edema in the first group was comparable to those of salicylate group and the other treatment groups had greater anti-inflammatory effects than salicylate in the chronic phase.

DISCUSSION

In our experimental study, both anti-inflammatory and anti-nociceptive activities of aqueous extract of *Rosa canina* were measured in vivo. This plant has been used for its

properties traditionally as food and for several therapeutic purposes. Its boiled extract has mild diuretic and laxative properties [4]. *Rosa canina* has also been used for its prevention effects and the treatment of common cold, infectious diseases, general exhaustion, vitamin C deficiency, influenza-like infections, fever, diarrhea, gallstones and gallbladder discomforts, gastric spasms, prevention of gastritis and gastric ulcers, urinary tract diseases and discomforts, inflammatory disorders, arthritis, rheumatism, nephritis, sciatica, gout , inadequate peripheral circulation, diabetes and lung ailments [18].

Several studies have shown in vitro the activity of *Rosa canina* extract on factors released in pain and inflammation. It is shown in a study that aqueous extract at concentration of 500µg/ml and higher can inhibit production of oxygen free radicals in PMNs and decrease chemotaxis in these cells [19]. Another study showed that a galactolipid as an active component is useful in reducing chemotaxis in PMNs [6]. In a study by Tanon and co-workers, Rosa hip and seeds' extract couldn't inhibit platelet activating factor-induced exocytosis of elastase and biosynthesis of prostaglandins[20].However, a short communication report showed that an organic solvent of rose hip extract can inhibit COX-1 and COX-2 in vitro. By the way, the aqueous extract was shown not to be effective in these studies[9]. In a cross-over trial, consumption of 45g of rose hip and seed powder over 28 days and consequent consumption of 10g of powder daily showed dose-dependent reduction of in-vitro chemotaxis of PMNs. In addition, markers of inflammation like C-reactive protein and creatinine decreased in this study [19].

A randomized, double blinded placebo controlled trial on 10 osteoarthritis patient reported that consumption of 1g of standardized rose hip powder in 4 months can improve hip and shoulder movements and daily activity and increased quality of life and reduced pain intensity [21]. In two other RCTs performed on osteoarthritis in which 120 [22] and 97[23]patientsconsumed 5g of standardized rose hip powder, results showed that pain and general physical conditions improved in patientsand moreover, no adverse effects observed in these studies.

In present study, anti-nociceptive activity measured with hot plate method. The greatest analgesic activity in the 30, 60 and 120 minutes after intra-peritoneal injection of extract was seen in the 100, 300 and 700 mg/kg groups respectively, But 360 minutes after injection, sodium salicylate as positive control had the greatest anti-nociceptive activity. These results show time and dose-dependent activity of aqueous extract. In the formalin induced rat paw edema test, the anti-inflammatory activity was measured in two phase. In both acute and chronic phases, the third group which was given 700mg/kg of extract had the least increase in rat paw volume. Normal saline as negative control group has the greatest increase in paw volume in both acute and chronic phases and salicylate as positive control has less inhibitory effect than three extract-treated groups.

To date, there are two studies on the in vivo anti-inflammatory effect of *Rosa canina* using animal models. Orhan et al in 2007 assessed anti-inflammatory and anti-nociceptive activities of *Rosa canina* while lattanzio et al in 2011 evaluated just anti-inflammatory activity. Orhan and colleagues used mice and measured the foot pad thickness. Because of mice small foot, these measures can be creating errors but we used rats in rat paw edema model to increase study precision. Moreover, Lattanzio and colleagues measured the anti-inflammatory effects from 30 minutes to 210 minutes after injection and Orhan et al measured the edema up to 360 minutes of study but we continued the rat paw edema measurement until day 8 after injection. This time can help to increase the accuracy of study and to differentiate between acute (few hours after injection) and chronic (few days after injection) phases. Although Orhan et al used aqueous and hydroalcoholic extract of *Rosa canina* together, Lattanzio et al used just hydroalcoholic extract. In this study, we assessed aqueous extract of *Rosa canina* for its anti- inflammatory effects on rat and anti-nociceptive effects on mice.

The only study on effects of Rosa canina extract on anti-nociceptive activity is Orhan's study, which used writhing test. In our study, hot plate technique was used and we repeated our measurements 180 minutes after injections.

The formalin induced rat paw edema is a two phase process. Acute phase which occurs in first hours of inflammation is due to release of histamine, serotonin and the other similar substances. Kinin-like substances, prostaglandins, proteases and lysosomes are responsible for chronic phase which occurs in following days after induction of inflammation. These substances are derived from arachidonic acid. *Rosa canina* extract has greater effect on acute phase than chronic phase and this probably might be due to greater effect of extract on histamine and serotonin than arachidonic acid derived factors. Since existing anti-inflammatory drugs act on the second phase and inhibit the arachidonic acid cascade, we can conclude that aqueous extract of *Rosa canina* can be used as an alternative in similar situations. According to previous in vitro studies, we can speculate that the effect of *Rosa canina* extract can be for components like linoleic acids, alpha-linoleic acids and tritrepene acids which can inhibit the arachidonic acid cascade [7-9]. Moreover, it is shown that *Rosa canina* extract is full of polyphenols, flavonoides and phenolic acids, which can have anti-inflammatory effects [24-27].

In addition, flavonoids can inhibit nitric oxide synthetase [28]. Because nitric oxide has an important role in pain pathway [29], inhibition of this substance can precede analgesic activity. New researches show that flavonoids can have analgesic activity by inhibiting opioid and adrenergic system [30].

CONCLUSION

According to result of this study, aqueous extract of *Rosa canina* can have great anti-inflammatory and anti-nociceptive activities, but further high quality human studies are necessary.

ACKNOWLEDGMENT

This study was funded and supported by Razi Drug Research Center (Grant No. 12674).

CONFLICT OF INTEREST

The authors declare that this research does not have any conflict of interest with anyone or any institute.

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