Anti-inflammatory activity of Magic Spice Fruits of Sumac (*Rhus coriaria* L)

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Doi: 10.23918/eajse.v8i3p139

Abstract: The goal of this study is to see how effective *Rhus coriaria* L (sumac) is at reducing inflammation caused by formalin in mice. The anti-inflammatory efficacy of sumac ethanol extract was tested in mice with formalin-induced paw edema. Anti-inflammatory activity was assessed in mice (n=6) using a plethysmometer model, and it was compared to morphine. Sumac showed anti-inflammatory effects comparable to morphine in mice with formalin-induced paw edema. In a formalin-induced arthritis model, sumac extracts showed considerable anti-inflammatory efficacy. If the findings of this study are supported by more experimental and clinical research, sumac may have an adjuvant role in the treatment of inflammatory illnesses, particularly when antioxidant qualities are present.

Keywords: Formalin Induced Pain, Paw Edema, Sumac, Plethysmometer Model, *Rhus Coriaria* L

1. Introduction

Non-steroidal anti-inflammatory medications and corticosteroids, which are routinely used in modern medicine to decrease pain and inflammation, only provide symptomatic relief. Long-term use of these medications has been linked to significant side effects. As a result, researchers are still looking for a new, safe analgesic and anti-inflammatory medicine. Touch, pressure, and reflexes are all examples of somatic sensations. Pain has always been a challenging problem in medicine because it plays a vital protective role in preventing or treating existing or possible tissue damage. Despite the fact that nonsteroidal anti-inflammatory drugs and opioids are frequently used to alleviate pain, they have a lot of negative effects and can cause issues with the kidneys and the gastrointestinal system. As a result, most people seek out new treatments that have less side effects, are less expensive, and are more readily available (Baker and Wood 2001).

Although the origin and composition of such plants are largely unknown, there is growing evidence that medicinal plants are frequently given in traditional medicine to treat pain and inflammation. As a result, knowledge of these plants' pharmacological properties can be used as a rational research technique for discovering new medications (Javan et al. and Nafisi 1997). Plants in the *Anacardiaceae* family are considered to provide a variety of pharmacological benefits, including analgesic, anti-inflammatory, and antipyretic properties (Neto et al. 2005; Subasini et al. 2011; Mohammadi et al. 2015). Sumac, also known by its scientific name Rhus coriaria, is a perennial blooming plant of the Anacardiaceous family that comes in over 250 different forms (Kossah et al. 2009). Sumaga, which means "red," is where it gets its name.

Received: June 1, 2022
Accepted: December 1, 2022
Mohammed, S., & Qasm, S., & Hameed, Z., & Walzi, P., & Uthirapathy, S. (2022). Anti-inflammatory activity of Magic Spice Fruits of Sumac (Rhus coriaria L). *Eurasian Journal of Science and Engineering*, *8*(3),139-149.

This Mediterranean-dwelling plant, which is also found in Iraq and Iran, has a latex stem, small, simple or compound leaves, fruits, and a dense cluster (Wetherilt and Pala 1994; and Andrade et al. 2007). The spice product *Rhus coriaria*, which has been employed in spice blends in Asian traditional therapies since ancient times, was given the name "Sumac" after borrowing the Arabic term "summq," which means "dark red." *Rhus coriaria* L. (Sumac) has been used as a folk remedy for centuries. Rhus coriaria L., the only species in Iraq that grows profusely and is cultivated close to localities in the north, has been one of the 91 recognized species names in the Rhus genus. It had been assumed that both pure and blended varieties of sumac were employed as a spice in seasonings. It is traditionally consumed in Iraq together with typical meat meals including kabab, grilled pork, and salads (AL-Maa'thidy 2006).

The antibacterial, antifungal, antiviral, antimalarial, anti-mutagenic, antioxidant, anti-migratory, anti-ischemic, hypoglycemic, and hypolipidimic effects of *Rhus coriaria* extracts have been studied extensively (Abu-Reidah et. al. 2014). As a result, the goal of this study was to assess and compare sumac's anti-inflammatory effectiveness in animal models of inflammation and pain.

2. Material and Methods

2.1 Collection of Plant Materials

Some fresh *Rhus coriaria* fruits were prepared and authenticated by a botanist, after which a voucher specimen number of the plant was deposited in the herbarium of the department of pharmcognosy, Tishk International University, Erbil, Iraq. For preparation of hydro alcoholic extract, *Rhus coriaria* fruits were shed dried at room temperature in the shade, and mechanically pulverized using a grinder. 100 g of powdered *Rhus coriaria* fruits were soaked in a liter of 75 percent ethanol for 72 hours. The resulting mixture was run through a rotating device to get rid of the solvent before being placed in a dish and dried out in a hood for a week. The extract that was left over at the bottom of the container was afterwards dissolved in the small quantity of saline water. In order to provide various doses to the mice.

2.2 Animals

In this investigation, Swiss mice of either gender (weighing 25–30 g) were used. Animals were kept in cages with free access to water and a standard laboratory diet in temperature-controlled, air-conditioned spaces with a 12-hour light/dark cycle. They were instructed to fast the night before the experiment and given a week to become used to the lab environment.

All studies were conducted in compliance with the guidelines established by the Committee for the Purpose of Control and Supervision of Experiments on Animals, and the Institutional Animal Ethics Committee approved the study (CPCSEA). All studies were conducted between the hours of 9 a.m. and 5 p.m. All mice were handled with compassion, and the tests were conducted in compliance with the CPCSEA's manual on the proper care and treatment of laboratory animals (Zimmermann 1983).

2.3 Drugs and Reagents

The animals were put into five equal groups (n = 6 mice per group): control, induction (diseased), sumac extract (150, and 250 mg/kg, i.p), treatment, and morphine (1 mg/kg, i.p.). Morphine, acetic acid and formalin were obtained from Clever Scientific company, Iran.

2.4 Qualitative Phytochemical Test

Using the usual techniques indicated below (Sakhr and Khatib 2020; Ahmad et al. 2013, Asgarpanah and Saati 2014; Shabbir 2012; Lev and Amar 2008; Abu-Reidah 2015), the presence of phytochemical analyses was assessed in Sumac fruit extracts from ethanolic and aqueous solutions. Test for anthraquinones, tannins, saponins, flavonoids, glycosides, terpenoids, steroids and essential oils.

2.5 Acute Toxicity

The acute toxicity of the extract was assessed by injecting different doses of the extract intraperitoneally into male mice. Within 72 hours, the number of animals that died was counted, and the LD50 of the sumac fruit extract was determined (Hashemi, et al. 2008).

2.6 Acute and Chronic Anti-inflammatory Activity

Weigh and number the animals. Make a mark immediately beyond the tibio-tarsal joint on both hind paws (right and left). To ensure continuous paw volume, the paw is dipped in the water column up to a predetermined mark each time. By using water displacement methods, note the initial paw volume for both the right and left legs of each mouse. Divide the animals into five groups of five animals each. Saline was administered into the control group. Animals in the test group were given sumac fruit extract orally, whereas those in the standard group were given morphine 1 mg/kg intraperitoneally (Verma et al. 2005).

An intradermal injection of 0.1 ml of 1 % formalin into the plantar surface of the right hind paw of mice (Winter Risley Nuss 1962) caused paw edema after 30 minutes. The acute phase of the inflammatory reaction occurs before, 30-, 60-, and 120-minutes following formalin administration. i.e., “edema volume of the right hind paw”, was measured using a plethysmometer modified by Hardayal Singh and Ghosh (Ghosh and Singh.1968).

The non-inflamed right paw will be used as a comparative point. All of the compounds were given an hour before formalin. Calculate the percent difference in the volume of each mouse's right and left paws in the control and treatment groups. The following formula was used to estimate the percentage inhibition of paw edema. Comparing the average percent change in paw volume between the control and treated groups, and interpreting the results as percentage edema inhibition by conventional medicines and sumac fruit extracts.

$$\text{Percentage of inhibition} = \frac{\text{Td} - \text{Tt}}{\text{Td}} \times 100$$

Where Td represents the paw thickness of mice in the disease (induction) group, and Tt represents the paw thickness of mice in the treatment groups (sumac fruit extract and morphine)

2.7 Principle of Inflammation

Whenever any antigen enters into our body, our bodies protective mechanism starts protecting us, and the inflammation is response of that swelling. We can say that is the part of our own body host defense mechanism. There are several tissue factors which plays active and important role in mechanism of inflammation. These include release of histamine, bradykinin and prostaglandins. Inflammation shows the heat, pain, redness and swelling of the characteristic sign. Those agents which give relief from inflammation are called anti-inflammatory drugs. This drug works by inhibiting the release of histamine and prostaglandins. The inflammation reaction is rapidly produced in mice in the form of

paw oedema, by utilizing the stimulus agent like carrageenan, formalin solution, bradykinin, histamine and egg white. When this irritating agent given as injection in the paw of rat, sudden swelling occurs, because of the release of histamine, 5HT, bradykinin and prostaglandins (Fiorucci 2001).

2.8 Plethysmometer

It is a simple apparatus having two tubes out of which one tube is having water on it; another tube shows the movement or expansion of saline water after placing the fixed length of mice paw. When paw is placed the level of saline water increased due to displacement pressure applied by mice paw. This is lowest prior to inflammation, increases during inflammation, and subsequently decreases when treatment drug is administered (Tjølsen et al. 1992; Shibata et al. 1989).

2.9 Formalin Test

The Dubuisson and Dennis suggested model was used in this experiment to evaluate both acute and chronic pain. The animals were placed in formalin test mice cages one hour before the test to acclimatize them with the environmental conditions. To watch the animal's activities more clearly, the animal cages were created of polypropylene cages with stainless steel top grills (Dubuisson and Dennis 1978).

3. Result and Discussion

3.1 Qualitative Phytochemical Test

The sumac fruit extract contained glycosides, tannins, anthrocyanins, phenolics, flavonoids, saponin, steroids, and essential oil, according to the qualitative phytochemical examination. The presence of these active phytoconstituents revealed that sumac fruit has significant antioxidant effects and can be used as a source for further pharmacological research. In an ethanolic extract of sumac fruits, the results for tannins (greater concentration), flavonoids (higher intensity color), glycosides, terpenoids, and steroids (low concentration) are shown in Table 1. These metabolites' existence suggests that they could be used as an antioxidant and anti-inflammatory (Shafiei et al. 2011; Aliakbarlu et al. 2013; Radmehr and Abdolrahimzade 2009; Zargham and Zargham 2012).

Plant constituents with potential antioxidant action include flavonoids, tannins, and phenolic compounds, which serve as free radical scavengers. Flavonoids are a type of polyphenol found in abundance among secondary metabolites in plants. These substances are important in the medical field because they have antibacterial, antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic, antimutagenic, antimigratory, and anti-ischemic characteristics, and many others (Mahdavi et al. 2018; Chakraborty et al. 2009; Gabr et al. 2014).

Table 1: Preliminary phytochemical screening of fruits of sumac

Chemical test	Sumac phytoconstituents	Colour observations
Dragendorff test	Alkaloids	No orange precipitates (-)
10 ml of bromine water	Tannins	Discoloration of bromine water (+++)
Alkaline Reagent Test	Flavonoids	Light red in colour (++)

2 ml of chloroform +3 ml of H_2SO_4	Terpenoid	grey colour formed (+)
Folin – Ciocalteau regent	Phenolic acid	No colour formation observed (-)
2 ml of chloroform +3 ml of H_2SO_4 and Salkowski's Test.	Steroids	chloroform layer red colour appeared (+)
Liebermann's Test.	Glycosides	Green color showed the entity of aglycone (+)
10 ml of benzene + 10 ml of ammonia	Anthrocyanins	Pink color formation (+)
5 ml of distilled water	Saponins	Formation foam (+)

(-) – absences, +++ - High intensity color, ++ - medium intensity color, + - mild intensity color

3.2 Acute toxicity study (Lethal dose (LD50)

Up to 14 days following the oral dose of 2000 mg/kg, no death was recorded in any of the mice. The clinical sign data analysis showed no aberrant signs or symptoms that could be linked to the drug administration. Tables 2 and 3 provide the comprehensive general clinical examination report. Animals were only completely active for 30 minutes after receiving sumac fruit extract by mouth. Clinical signs and symptoms for up to 14 days after injection. All of the animals showed no aberrant symptoms. Table 4 shows that there was no mortality upto 14 days of administration (Lorke D 1983; Radmehr and Abdolrahimzade 2009).

Table 2: Experimental design for Acute toxicity

S. No	Marking	Sex	Dose(mg/kg)
1	Head	F	2000
2	Neck	F	2000
3	Body	M	2000
4	Tail	M	2000
5	Colourless	M	2000

Table 3: Acute toxicity of neurological examination

S. No	Identification	Locomotor activity	Tail elevation	Ataxic gait	Head position
1	Head	Casual	Normal	None	Without tilt
2	Neck	Casual	Normal	None	Without tilt
3	Body	Casual	Normal	None	Without tilt
4	Tail	Casual	Normal	None	Without tilt
5	Colourless	Casual	Normal	None	Without tilt

Table 4: Acute toxicity – Mortality

S. No	Group	No. of animals	Death recorded (Within 24 hours)	% death	Death recorded (within 14 days)	% death
1	Group 1	5	0/5	0	0/5	0

According to the findings of this investigation, the drug's LD_{50} is sumac fruit extract>2000 mg/kg and no significant toxic alterations were noticed clinically or during postmortem examination.

3.3 Acute and Chronic Anti-inflammatory Activity

The baseline mean paw volume was comparable in all groups, as shown in Table 5. The mean paw volume in the three drug-treated groups was considerably lower at 60 and 120 minutes as compared to the control group. At all-time intervals, morphine had a stronger percentage suppression of acute inflammation than sumac extract at a dose of 150 mg/kg. At all-time intervals, the percentage inhibition in the sumac treated group at high dose (250 mg/kg) was larger than that in the sumac treated group at low dose (150 mg/kg) Results are shown in Table 6.

1% of formalin solution was injected into the sub-plantar surface of the animal's left hind paw thirty minutes after the intraperitoneal injection of the drugs, and it was then put back in its cages. The animal's behavior was observed for 60 minutes and labeled as follows: once every 15 seconds, the motor activity to pain was graded and recorded on a scale of 0, 1, 2, and 3. The numbers represent the subsequent reactions: Number 0 indicates that the animal is completely balanced and that its weight is equally distributed across both feet. Number 1 indicates that the animal was unable to support or tolerate the weight of its body on the injected foot. Number 2 indicates that the animal raised its painful claw without making contact with the box. Number 3 indicates that the animal raised its painful claw without making contact with the box and that it then licked, chewed, or moved violently. (Baretta et al. 2009, Khalilpour et al. 2018). Results are shown in Table 7.

Phase 2 (chronic phase) was defined as the average of minutes 15 to 60, while phase 1 (acute phase) was defined as the average of the first five minutes (Shibata et al. 1989). Sumac was given orally at doses of 150 mg/kg and 250 mg/kg during the formalin test, and both of these doses significantly decreased pain scores in the acute and chronic phases as compared to the control group. The morphine group showed a considerably lower pain score when compared to the control group. According to Table 8, an intraplantar injection of formalin stimulates nociception symptoms like flinching and licking of the injected paw early on (phase 1). This is followed by a gradual period with fewer pain-related behaviors and late-hyperalgesic aspects (phase 2), which lasts for about an hour (Table 7). The early phase of nociception, also known as neurogenic nociception, is brought on by the direct activation of peripheral nociceptors, whereas the late phase of nociception, also known as inflammatory nociception, is brought on by the induction of a “spinal state of facilitation, central sensitization, inflammation, and enlargement of receptive fields, as well as the presence of low-level input from both large and small afferents” (Shibata, et al. 1989; Verma et al. 2005).

The results show that sumac extracts have a pain-inhibiting effect. The sumac fruit extracts studied showed antinociceptive efficacy in both phases of formalin-induced pain in rats. It was found that the lowering effect is stronger in the chronic stage than in the acute phase. Sumac fruit extracts appear to have some antinociceptive effects because they prevent the chronic phase of the formalin test. This is because central nociceptive neurons release modest amounts of substances such prostaglandins

throughout this process (Verma et al. (2005). Herbs' biologic or therapeutic function is closely linked to their chemical combinations (Trease and Evans 1989; Di Carlo et al. 1999). “Organic acids, phenolic acids and derivatives, hydrolysable derivatives, anthocyanins and derivatives, flavonoids and isoflavonoid derivatives, terpenoid derivatives, and other compounds have been identified in Rhus coriaria, all of which have “antioxidant, anti-inflammation, and antinociception properties” (Hashemi and Davoodi 2011, Anwer et al. 2013).

Flavonoids and isoflavonoid derivatives are the active ingredients or key bioactive components of Rhus coriaria that provide a morphine-like antinociceptive action. Sumac yielded 61 flavonoid compounds, which were identified and characterized. “Apigenin-7-O- (6% O-galloyl) is a -D-glucopyranoside that is structurally similar to apigenin” (Abu-Reidah et al. 2014; Mahdavi et al. 2018; Nagib 2017). Euphoria has this chemical listed as an active ingredient. Similarly, dihydrotamarixetin galloyl-hexoside was proposed as a candidate for this action (Abu-Reidah et al. 2015). As far as we are aware, this plant doesn't contain any morphine-like alkaloids (Duke 2002, Di Carlo et al. 1999). Many flavonoids and tannins can dismutase reactive oxygen species (ROS) by chelating free radicals like hydroxyl radicals (Hashemi and Davoodi 2011). By the way, tannins have been reported to have antinociceptive and anti-inflammatory properties. As a result, tannins included in sumac fruit extract contribute to the extract's antinociceptive impact.

Table 5: Effect of sumac drugs on paw volume in formalin induced paw edema in mice

S. No.	Control group Volume (ml)	Induction group Volume (ml)	Standard group (morphine 1mg/kg) Volume (ml)	Treated group (sumac 150 mg/kg) Volume (ml)	Treated group (sumac 250 mg/kg) Volume (ml)
1.	1.26	2.45	1.72	2.12	1.88
2.	1.24	2.57	1.75	1.99	1.90
3.	1.24	2.56	1.73	2.25	1.88
4.	1.23	2.47	1.75	2.09	1.97
5.	1.24	2.57	1.73	1.98	1.96
Average	1.242	2.524	1.736	2.086	1.918

Table 6: Percentage inhibition of formalin induced paw edema by different drugs

Groups	% Inhibition at 30 min	% Inhibition at 60 min	% Inhibition at 120 min
Standard group Morphine	31.22	47.22	56.22
Treated group – Sumac at 150 mg/kg	17.35	31.25	43.67
Treated group – Sumac at 250 mg/kg	24.00	48.32	54.78

Table 7: Animal behavior and Score values (motor response to pain rate)

Score values	Animal behaviors	Stage of Phase
0	The mouse moves in perfect equilibrium, with its weight evenly distributed on both feet.	Phase 1 was defined as the average of the first five minutes of grades (acute phase)
1	The mouse could not take the burden of its body on the injected foot or care for it.	
2	The uncomfortable claw of the mouse has been elevated and has made no touch with the cage bottom.	Phase 2 was defined as an average of 15 to 60 minutes (chronic phase)
3	The mouse licks the injured claw that has been bitten or stretched.	

4. Conclusion

The antinociceptive action of this fruit sumac extract may be attributed to its phytoconstituents of tannins and flavonoids, according to the findings of this study. In this study, suppression of both phases of the formalin test served as evidence of *Rhus coriaria's* antinociceptive efficacy. *Rhus coriaria* is a significant resourceful plant in the current period because of its potential sources of potential vital nutrients for nutraceuticals, as well as trustworthy *Rhus coriaria* pharmaceutical and multifunctional food preservative industries. Finally, we conclude that the extract has anti-inflammatory properties, which are most likely due to "inhibition of prostaglandin synthesis and central and peripheral nervous system inhibition". As a result, this extract could be used to reduce inflammatory nociception.

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