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Evaluation of Anti-inflammatory Activity of Methanol Extract of *Rhus coriaria* L. in Diabetic Rats

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ABSTRACT

Inflammation is an immune system response, which prevents the individual from infection. The use of current anti-inflammatory drugs is often associated with side effects. Therefore, an alternative therapeutic module is necessitated. Herbal medicines are being used against many diseases due to their high efficacy with little or no harmful effects. *Rhus coriaria* has been widely used to treat different diseases including inflammation. The current study evaluated the anti inflammatory activity of *R. coriaria* against carrageenan-induced paw oedema in diabetic rats Male Wistar rats were divided into two parts: healthy and diabetic rats. Each part consisted of five groups. Group 1 received normal saline (negative control) for healthy and diabetic rats. Group 2 received 150 mg/kg acetylsalicylic acid (positive control) for healthy and diabetic rats. Groups 3 4 and 5 were given orally 50, 100 and 200 mg/kg of *R. coriaria* extract for healthy and diabetic rats. Cytotoxicity of *R. coriaria* methanol extract was evaluated against fibroblast cell lines. The results showed that methanol extract of *R. coriaria* at 200 mg/kg significantly decreases paw oedema in diabetic rats ($P< 0.01$) compared to the non-diabetic rats ($P< 0.001$). This finding may indicate that *R. coriaria* has a strong anti-inflammatory activity against carrageenan-induced paw oedema in rats. It was found that 100 µg/mL of *R. coriaria* extract resulted in very low cytotoxicity against fibroblasts with 40.12% inhibition *of* fibroblast proliferation and IC_{50} of 108.4 µg/mL. In conclusion, the extract of *R. coriaria* has a considerable anti-inflammatory activity against carrageenan-induced paw oedema in diabetic rats.

***Keywords*:** *Rhus. Coriaria*, Anti-inflammation, Carrageenan, Rat Paw.

Introduction

Inflammation is an important physiological response to a variety of harmful factors, such as physical trauma, microbial infection, and chemical substances.[1] It limits tissue damage, promotes repair and prevents infection from foreign bodies.[2,3] Previous studies have demonstrated various effective drug strategies for the treatment of diseases such as cancer, diabetes, and inflammation.[4,5] In cancer, the link between inflammation and tumorigenesis has been well established and is supported by genetic, pharmacological, and epidemiological data.[6] At present, the use of medicinal plant extract and their purified components for the treatment of various diseases and disorders is rapidly developing.[7,8]

In addition to the fact that herbal remedy does not have side effects like synthesized drugs, the active ingredients in medicinal plants such as flavonoids, terpenoids, and alkaloids have shown their ability to effectively alleviate various disease symptoms synergistically.[9] However, the study of the use of medicinal plants in treating inflammation needs more scrutiny. Most of the plants that are endemic to Jordan are of Middle Eastern (Mediterranean) habitat, and a number of them are medicinal and show different ways of adaptation through the establishment of biologically active components.

The Sumac plant is one of the most important plants used in Jordanian traditional medicine.[10] *R.coriaria* belongs to the family *Anacardiaceae*, commonly known as Sumac in the Mediterranean countries. It is used as a traditional spice due to its souring taste.[11] It is also used in folk medicine in Jordan as an astringent and anti-inflammatory agent.[12] It has several pharmacological activities including antimicrobial, anti-diabetic, hepatoprotective, hypoglycemic, and DNA protective effect[13, 14] Several studies have demonstrated that the extract of *Rhus* species is a rich source of bioflavonoids,[15,16] hydrolyzable tannins, and gallotannins.[17] Moreover, in order to realize the dietary value of *R. coriaria*, its mineral contents, as well as the physical and chemical properties of gallotannins and flavonoid isomers in its fruits, were characterized.[18, 19]

Additionally, other studies showed that *R. coriaria* extracts have a high potential for wound healing activity in rats and have significant therapeutic activity against dyslipidemia, lipid peroxidation, and hyperglycemia in type 2 diabetic rats.[20] The present study evaluated the efficacy of *R. coriaria* methanol extract against carrageenan-induced paw oedema in an experimental diabetic rat model.

Materials and Methods

Collection of plant samples

Fruits of *R. coriaria* were collected in August 2020 from theAjloun region north of Jordan and were identified and authenticated by Prof. Sawsan Oran of the Department of Biology, Jordan University. A voucher specimen number (MU2021-22) was deposited in the Department of Biology, Faculty of Science, Mutah University, Jordan.

Preparation of methanol extract of R. coriaria

Fruits of *R. coriaria* were washed, dried, grinded with a blender, and macerated in 96% methanol. The dried fruits (100 g) were soaked in 1 L methanol for 3 days with continuous shaking at 25°C.[21]The filtration of the mixture was done, and the methanol was evaporated using a rotary evaporator at 45°C (Buchi R200C Rotovapor Complete system

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W/ condenser C, V500 pump, and V800 controller).The extract was kept at -20°C in an air-tight container.

Phytochemical analysis of the methanol extracts of R. coriaria
Determination of total phenolic compounds
The whole phenol quantification process was carried out for the methanol extract of *R. coriaria* using the Folin-Ciocalteu method.[22]The crude extract of *R. coriaria* was dissolved in15 mL of Dimethyl sulfoxide (DMSO). Then 0.5 mL extract of *R. coriaria* was added to 2.5 mL of 0.2 NFolin-Ciocalteu reagent and left for 5 min at room temperature, and then 2 mL aqueous solution of sodium carbonate (7.5% w/v) was added. After 2 hours of incubation at room temperature in darkness, the measurements of absorbance were taken at 760 nm employing UV/Visible spectrophotometer (Elico, SL 150, India). Gallic acid concentrations (Sigma-Aldrich, USA) ranged between 0.01-0.05 mg/mL were used for the calibration of a standard curve. The unit (mg gallic acid equivalent/g) was considered as an equivalent for measuring the total phenol content in these experiments.

Determination of total flavonoids
The amount of flavonoid content in methanol extract of *R. coriaria* was estimated according to the procedure of Aryal*et al.*[23] The dissolution of the crude extracts was carried out in 15 mL of DMSO (dimethyl sulfoxide) (Hayman, England), in which 0.5 mL of each extract was mixed with 0.3 mL of 5 g/L sodium nitrite (Labchem, USA), 5 minutes later,a 0.3mLaluminum chloride solution (1g/L) was added. After 6 minutes, 2 mL of 1M NaOH solution was added to the mixture and the total volume was adjusted to 10 ml with distilled water, and then sonication was carried out immediately. The absorbance at 510 nm was taken against tap water as control using a visible/UV spectrophotometer. The Calibration curve was made with a Rutin solution preparation (0-200 µg/mL). The unit mg Rutin/g extract of each plant was used to express the concentrations.

Determination of total tannins
The Folin and Ciocalteu method[24]; was used for the estimation of the total tannins. The methanol extract of *R. coriaria* was analyzed by adding 0.1 mL of previously prepared 15 mL DMSO-crude extract solution dissolved in 7.5 mL of distilled water. To this mixture, 0.5 mL of Folin-Ciocalteau phenol reagent and 1 mL of 35% (w/v) sodium carbonate solution were added and this was made up to 10 mL with distilled water. Samples were well mixed by shaking, left at room temperature for 30 min, and the optical absorbance read at 725 nm. Tap water was used as blank. Pre-treatment was done for a set of standard solutions of gallic acid using the same method mentioned previously with making assessments against blank. The results of tannins were interpreted as the gallic acid equivalent/gram of the gallic acid extract.

Animals
Ninety-five (95) male Wistar rats (150-200 g) were used for testing the toxicity and the anti-inflammatory activity of the methanol extract of *R. coriaria*. The animals were kept in the animal house in standard plastic cages in the Department of Biological Sciences, Mutah University. The temperature was maintained at 23 ± 1°C with a cycle of 12 hr light and 12 hr darkness. The animals had free access to pelleted food and water. Ethical approval with reference number 47-2021 was obtained for the study, and the animals were allowed to adapt to the experimental conditions before conducting the experiments.

Induction of diabetes
Diabetes was induced in 35 rats using an intraperitoneal injection of 60 mg/kgbw of streptozotocin. The development of diabetes was tested after 3 days and was confirmed by measuring the fasting blood glucose level.[31] Animals with blood sugar levels more than 200 mg/dL were considered diabetic.[32]

Induction of hind paw oedema and extract treatment
Seventy (70) male Wister rats were used to evaluate the anti-ooedematous activity of methanol extractof *R. coriaria*. The animals were divided into two parts, the first part consisted of healthy rats, and the second part was diabetic. Each part consisted of five groups and in each group seven rats. Group 1, controls for both healthy and diabetic rats: was administered orally 1 mL of saline. Group 2, for each healthy rat and diabetic rats received 150 mg/kg acetylsalicylic acid (positive control). Groups 3, 4, and 5 for each healthy rat and diabetic rats received orally 50, 100, and 200 mg/kg of *R. coriaria* extract.
The plant extract dissolved in 1 mL of saline using oral gavage needles. After 1 hour, 0.1 mL of 1% carrageenan was subcutaneously injected into the footpad of the rat hind paw. Paw thickness was measured at 0, 3, and 7 hours after carrageenan injection.[25, 26] The carrageenan-induced oedema was evaluated as the percentage increase in the paw thickness as compared to control groups.

Toxicity study
Twenty-five (25) overnight-fasted male rats (150-200 g) were used for toxicity study. The animals were divided into five groups (n = 5). Groups 1 to 4 received orally 100, 200, 400, and 800 mg/kg of the *R. coriaria* methanol extract dissolved in 1 mL normal saline, respectively using animal oral gavage feeding needles. Group 5 was used as control and received 1 mL orally normal saline. The symptoms of toxicity and mortality were observed in each group after 24 hrs. The survived animals were observed for any signs of delayed toxicity for two weeks.

In vitro cytotoxicity test
Cytotoxicity of *R. coriaria* extract was assessed against fibroblast cell lines. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 100 µg/mL of penicillin and streptomycin antibiotics. The cells were grown in humidified 5% CO2 incubator at 37°C. Cells were fractionated every 3-4 days by discarding the culture media followed by cell separation with 1-2 mL trypsin and the addition of a fresh warm DMEM medium.[27] Concentration ranges tested were between 10-100 µg/mL for plant extract. All cultures were performed in triplicates. IC_{50} was calculated from the dose-response curve.

Culturing of cell lines
The cytotoxicity of *R. coriaria* extract was determined microscopically. Different concentrations of the samples (10, 25, 50, and 100 µg/mL) were applied into 24-well culture plates containing 5×10^4 cells/mL of the tested cell line. The cells were incubated at 37°C and in a humid atmosphere harboring 5% carbon dioxide. The test was done in duplicate and the cytotoxic effect was observed daily up to 72 hr of cultivation.[28,29] Changes in cell shape morphology including loss of monolayer, rounding, and shrinking was considered signs of cytotoxic effect of the tested samples under microscopy. Cultures of cell line without tested extract was used as a negative control.

Antiproliferative Assay
Following the cultivation of cell lines with tested compounds, the inhibition of cell proliferation was monitored using the Giemsa staining method.[30]The media from wells were aspirated followed by washing with 0.5 mL PBS and fixation with 0.3 mL methanol for 10 min at 37°C. Methanol was aspirated and the plates were left for 2 min to dry. Giemsa stain (0.5 mL of 1:10 dilution in PBS) was applied to each well and left for 10 min, after which, the stain was aspirated and the wells were washed with 0.5 mL deionized water. The bounded stain was extracted using 0.3 mL of 0.1N HCl and antiproliferative activity was estimated using an enzyme-linked immunosorbent assay (ELISA) microplate reader at 630 nm. Cell viability was shown as a percentage of live cells versus control. The percentage of cell death was estimated using the formula:

$$Dead\ cells\ (\%) = \frac{Absorbance\ of\ control - Absorbance\ of\ treated\ cells}{Absrobance\ of\ control}\ x\ 100$$

Statistical analysis
Data were presented as means ± SD. The statistical significance of differences between groups was assessed by one-way analysis of variance (ANOVA) with Tukey's HSD post-hoc test using Graph Pad Prism version 7. $P < 0.05$ was considered significant.

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Results and Discussion

R. coriaria has long been used as a spice, in the medical fields and even in some industries such as the leather industry. This plant is known to have various medicinal uses; as antioxidant, antibacterial, antifungal, anti-inflammatory, and hypoglycemic agent. These biological activities may be attributed to the presence of some important phytochemicals such as phenolic compounds.[33-35]

Phytochemical analysis and DPPH radical scavenging ***activity*** of *methanol extracts of R. coriaria*

The methanol extracts of *R. coriaria* were approximately 13.4% w/w on a dry weight basis. The results of this study showed that the methanol extracts of this plant containedphenolic compounds (34.53±0.35 mg GAE/g), flavonoids (29.29±0.98 mg QE/g), and tannins. (7.425±0.81 mg GAE/g)(Table 1). These results show the great potential of the plant as antioxidants, antimicrobials, antiparasitics, and anti-inflammatory agent. Most flavonoids have been reported to have antioxidant activity and the ability to scavenge free radicals as well as having anti-inflammatory activity.[36-42] The value of DPPH radical scavenging activity was perceived to be 119.15±1.33GAE mg/g in the methanol extract of *R. coriaria*.

Toxicity study

Acute toxicity studies showed that all the oral administration doses of the *R. coriaria* methanol extract used (100, 200, 400, and 800 mg/kg) were safe and non-toxic. This agrees with previous study that showed the extract is non-toxic even at doses higher than 800 mg/kg body weight.[43]

Antiproliferative assay

Fibroblast cell proliferation was stimulated when treated with 100 mg/mL of *R. coriaria* extract after 24 hours compared to the control group. The cytotoxicity activity of methanol extract of *R. coriaria* against fibroblasts revealed that 100 µ/mL of *R. coriaria* extract resulted in very low cytotoxicity against fibroblasts with 40.12%, and IC_{50} of 108.4 µ/mL. The study showed that 200 mg/kg methanol extract caused significant inhibition ($P < 0.001$) of the rat paw oedema. It is known that the anti-inflammatory drugs which are currently used are often associated with many side effects.[44,45]The methanol extract *of R. coriaria* showed more effect compared with acetylsalicylic acid as a standard anti-inflammatory agent. Thus, the significant effect of this extract reveals for the first time that compounds contained in the methanol extract of *R. coriaria* exert an anti-inflammatory effect. The anti-inflammatory activity could be related to the presence of flavonoids.[46]

Evaluation of hind paw oedema

The maximum increase in hind paw oedema demonstrated by the paw thickness was obtained in rats 7 hours after the injection of carrageenan (Tables 2 and 3). From the results, it is noted that all the concentrations used (Table 2) in the treatment (50 to 200 mg/kg) led to an inhibition of paw oedema in non-diabetic rats with a more effective degree ($P < 0.001$) than of that obtained when using acetylsalicylic acid (150 mg/kg) as a control. Moreover, the concentration of 200 mm/kg caused a 1.5-fold better than acetylsalicylic acid as control. Also, when looking at the effect of the methanol extract of *R. coriaria* on carrageenan induced paw oedema in diabetic rats (Table 3), it is still more efficient than acetylsalicylic acid (150 mg/kg) as a control ($P < 0.01$)**.** The development of carrageenan-induced oedema is characterized by two-phase. The initial phase starts within one hour, which is due to the release of mediators, such as serotonin, histamine, bradykinin, and substance P.[47]

However late long-lasting phase forms after one hour and is mainly due to the infiltration of neutrophils at the site of injury. This phase is due to the production of large amounts of pro-inflammatory mediators such as Prostaglandin(PGE2) and various cytokines including interleukins (IL-1β, IL-6, IL-10) and tumor necrosis factor(TNF-α).[48] The present study showed that methanol extract of *R. coriaria* has an effective anti-inflammatory activity by reducing carrageenan induced inflammation at both phases. Methanol extract may have inhibited the synthesis and/or release of inflammatory mediators such as histamine and serotonin after 3 and 7 hours of treatment. It has been reported that alcoholic extract of *R. coriaria* fruit significantly reduced the level of mRNA of the pro-inflammatory cytokines IL-18 and IL-1β, in lipopolysaccharide-stimulated synoviocytes extracted from joint and fluid of limb of the 8-month-old healthy calf.[49]

Previous studies showed similar results in terms of its anti-inflammatory activity using the carrageenan-induced foot oedema model. An example is the use of *Rhus toxicodendron* and the methanol extract of *Rhus tripartita*, which showed significant inhibition of inflammation in the carrageenan-induced foot oedema model.[50,51] The using of methylene chloride extract of *Rhus retinorrhaea* at doses of 100 and 200 mg/kg body weight significantly inhibited carrageenan-induced foot oedema and lumbar granulomas in rats. Furthermore, acute toxicity tests showed no mortality or morbidity in rats up to a dose of 3 g/kg body weight.[52] *R. coriaria* fruit extract has positive effect as preventive agent in the treatment of keratinocyte inflammation through their inhibitory effect on the production of skin pro-inflammatory mediators.[53]

Mononuclear phagocytes are principally responsible for the production of TNF-α (nuclear transcription factor-alpha) and this results in an immune response by promoting T cells, macrophages, and the secretion of other inflammatory cytokines.[54]Signal pathways of protein kinase which are activated by mitogen and the nuclear transcription factor-kappa B (NF-κB) are duo major signaling pathways engaged in the response of inflammations.[55]The activation of NF-κB, the main transcription factor enhances the pro-inflammatory expression by cytokine related genes, such as TNF-α, IL-6, and IL-1*β*.[56]

Table 1: Antioxidant activity and phytochemical analysis of *R. coriaria* methanol extract

Plant	Antioxidant activity (GAE mg/g)	Phytochemical analysis Total phenols (GAE mg/g)	Total falvonoids (Rutine qu. mg/g)	Tannins (GAE mg/g)
R. coriaria	119.15±1.33	34.53±0.35	29.29±0.98	7.425±0.81

Table 2: Effect of *R. coriaria* methanol extract and acetylsalicylic acid on carrageenan-Induced paw ooedema in non-diabetic rats

S/N	Group	Time (hour) 0	3	7
1	Carrageenan (1%)	9.48 mm ± 0.11	7.22 mm ± 0.34	5.79 mm ± 0.49
2	6.05 mm ±0.16 *	6.62 mm ± 0.48	5.48 mm ± 0.12	2 Acetylsalicylic acid (150 mg/kg)
3	5.95 mm ± 0.18	6.15 mm ± 0.6	5.33 mm ± 0.34	3 *R. coriaria* (50 mg/kg)
4	5.65 mm ± 0.17	5.98 mm ± 0.16	5.25 mm ± 0.53	4 *R. coriaria* (100 mg/kg)
5	4.21 mm ± 0.40 **	5.96 mm ± 0.17	5.36 mm ± 0.2	*5 R. coriaria* (200 mg/kg)

Values are mean±S.D. of 7 individual rats. * $P < 0.01$, ** $P < 0.001$.

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Table 3: Effect of *R. coriaria* methanol extract and acetylsalicylic acid on carrageenan-induced paw ooedema in diabetic rats

		Time (hour)		
S/N	**Group**	**0**	**3**	**7**
6	1% carrageenan	5.47 mm ± 0.42	8.49 mm ± 1	10.10 mm ± 0.21
7	(150 mg/kg acetylsalicylic acid)	10 mm ±0.27	7.33 mm ± 0.55	6.44 mm ±0.17 *
8	*R. coriaria* 50 mg/kg	5.14 mm ±0.14	7.85 mm ± 0.21	8.35 mm ± 0.32
9	*R. coriaria* 100 mg/kg	5.08 mm ± 0. 3	7.46 mm ± 0.45	7.84 mm ± 0.61
10	*R. coriaria* 200 mg/kg	5.00 mm ± 0.41	7.23 mm ± 0.47	6.02 mm ± 0.16 *

* Values are mean±S.Dof 7 individual rats, (P< 0.01).

Conclusion

The results showed that *R. coriaria* methanol extract possesses anti-inflammatory activity against carrageenan-induced hind paw ooedema in both diabetic and non-diabetic rats.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Ethical Clearance

All experimental protocols were approved under the Department of Biology, Mutah University, Jordan, and all experiments were carried out in accordance with the guidelines established by the FIOCRUZ Committee of Ethics for the Use of Animals (CEUA LW16/14).

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