Herbal Medicines Journal **2023; 8(1):26-33**
DOI: 10.22087/hmj.v8i1.1011 **ISSN:** 2538-2144

Original Article

The Effect of the Hydroalcoholic Extract of *Quercus infectoria* Fruit Hulls (Jaft-E-Baloot) on Formalin-Induced Inflammation and Pain in Male Mice

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Received: 27.01.2023 Accepted: 18.06.2023

Abstract

Background and Aim: Herbal medicines have been used to alleviate inflammation and pain since ancient times, and their use is even on the rise. The *Quercus infectoria* plant has been commonly used for many years to treat inflammation and pain in alternative medicine. Various species and different parts of this plant have been studied. The present study aimed to investigate the anti-inflammatory and analgesic properties of the extract of the fruit hulls of *Q. infectoria* to find a plant-based alternative to the available drugs with fewer side effects.

Materials and Methods: This study used 60 male NMRI mice with a weight range of 35-40 g. The mice were randomized into a negative control group which only received formalin, a positive control group that received diclofenac 200 µg/kg, and four experimental groups that received 50, 100, 150, and 200 mg/kg of the fruit hulls extraction. Formalin was injected into the paws of the mice to induce inflammation and pain. Then, the paw volume was measured during the first three hours after injection with a digital Plethysmometer. Pain score was also evaluated in three stages at 60-minute intervals.

Results: The results showed that the fruit hulls extract could reduce inflammation at all doses, particularly at 200 mg/kg in comparison with the negative control group ($P< 0.001$). Moreover, the fruit hulls extract relieved pain at different doses in acute and chronic stages.

Conclusion: The fruit hulls extract alleviated the pain and reduced the inflammation in mices' paws depending on the dose. Therefore, it can be considered as a possible alternative to chemical drugs.

Keywords: Analgesic, Anti-inflammatory, *Quercus infectoria*

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Please cite this article as: Karimian A, Nafari A, Sarvestani A, Zamani A, Behnaminia N, Mohammadi R, et al. The Effect of the Hydroalcoholic Extract of *Quercus infectoria* Fruit Hulls (Jaft-E-Baloot) on Formalin-Induced Inflammation and Pain in Male Mice. Herb.

Med. J. 2023; 8(1):26-33.

Introduction

Certain illnesses can be managed with analgesics and anti-inflammatory medications to reduce pain and inflammation. The majority of existing analgesics and anti-inflammatory medications still exhibit a wide spectrum of adverse effects. This circumstance highlights the requirement for the development of new analgesic and anti-inflammatory compounds (1). The oak genus (Quercus) is widely distributed in the Northern Hemisphere (2). The oak acorn is considered a good source of vitamins (mostly A and E), minerals, unsaturated fatty acids, and biologically active compounds such as gallic acid and ellagic acid (3). Oak has been used in China to treat diarrhea and various inflammatory disorders. In Iran, its bark used to be applied as a wound-healing agent (4). Antibacterial (5), anti-inflammatory (6), and anti-fungal (7) properties have also been reported. Different components of oak are broadly utilized in traditional medicine as analgesic, CNS depressant, antidiabetic, and anti-inflammatory medications due to its diverse therapeutic characteristics (8).

Previous studies have investigated the anti-inflammatory and analgesic effects of the *Quercus* species. Despite the ethnobotanical application of the *Quercus infectoria* fruit hulls (Jaft-E-Baloot) in the minimization of inflammation and pain, no scientific study has investigated its potentials. Thus, the present study attempts to assess potential analgesic and anti-inflammatory effects of the hydroalcoholic extract of *Quercus infectoria* fruit hulls on formalin-induced paw edema and pain in male mice.

Materials and Methods

The hydroalcoholic extract of *Q. infectoria* fruit hulls used in this study was kindly provided by Dr. Bahram Delfan, and the information on the extraction method and its compounds can be found in a previous study (9). In brief, fruit hulls were gathered from the rural areas of Khorramabad, Lorestan Province, Western Iran. The dried plant materials were milled, and then extracted using methanol and a Soxhlet extractor at 50°C, and then condensed using a vacuum rotary.

Animals

In this study, 60 adults male NMRI mice weighing 35-40 g were used. The animals were kept in a laboratory environment under the same conditions in terms of temperature, length of day and night, and access to the same type of water and food. The animals were divided into twelve groups of 5 (n = 5). Six groups were used for the formalin test and six groups were used to assess anti-inflammatory activities: A negative control group (2.5% formalin, twenty µL, subcutaneously), a positive control group (diclofenac, 200 µg/kg, intraperitoneally), and four experimental groups, which received specified doses of the extract (50, 100, 150, and 200 mg/kg, intraperitoneally). This study was approved by the Ethics Committee of Lorestan University of Medical Sciences (ethics code: IR.LUMS.REC.1400.314).

Evaluation of the Anti-Inflammatory Activities

Paw edema inflammation was measured at specific intervals. At first, the volume of the foot was measured with a digital Plethysmometer (Borj Sanat, Iran). In this method, each mouse's ankle was marked with a marker, and then the paw was put inside a mercury container placed on a digital scale, and the number on the scale was recorded. Thirty minutes after the intraperitoneal injection of different doses of the extract, twenty µL of 2.5% formalin (Sigma-Aldrich, USA) was injected subcutaneously into the mouse's sole in order to induce inflammation. Subsequently, the paw volume of each mouse was measured again in the same way after 60, 120, and 180 minutes. The final volume was obtained by dividing the number read on the scale by 13.6 (the density of mercury) (10, 11).

Assessment of the Analgesic Properties (the formalin test)

The formalin test is a standard and suitable method for measuring the amount of pain caused by a chemical stimulus. A transparent chamber measuring 30 × 30 × 30 was used to perform the test. A curved mirror placed under the chamber was used to observe all movements of the animal's foot. In this experiment, twenty µL of 2.5% formalin was injected into the mice's paws subcutaneously, and they were then immediately transferred to the chamber to observe their behavior. After formalin injection, the animals displayed behaviors that were scored zero to 3: Zero if the animal

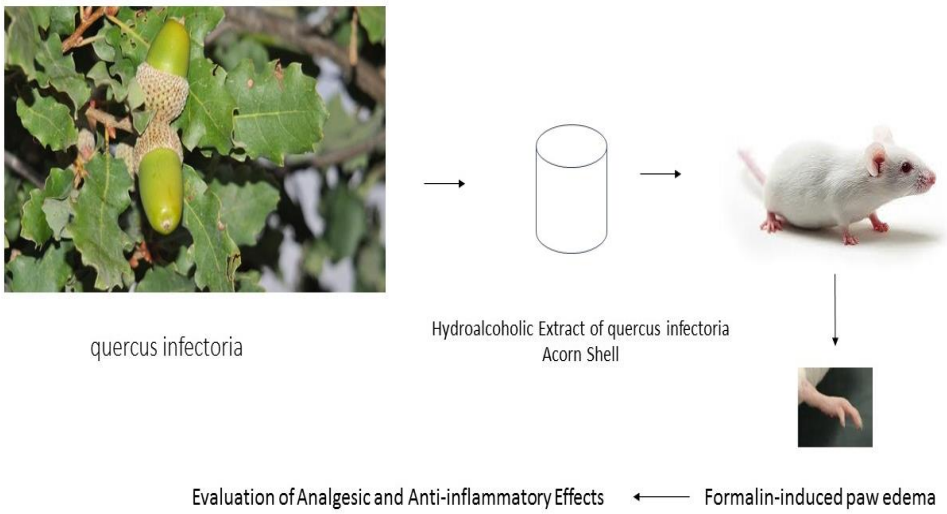

Figure 1. The graphical abstract

Table 1: The effect of the fruit hulls extract on formalin-induced paw edema.

Groups/ Times (minutes)	Formalin Mean± Sd	Diclofenac Mean± Sd	50 mg/kg Mean± Sd	100 mg/kg Mean± Sd	150 mg/kg Mean± Sd	200 mg/kg Mean± Sd	P value
0	0.172± 0.008	0.172± 0.004	0.170± 0.003	0.167± 0.009	0.168± 0.005	0.167± 0.003	0.644
30	0.258± 0.010	0.215± 0.005	0.221± 0.004	0.213± 0.012	0.207± 0.005	0.206± 0.004	<0.001
60	0.367± 0.007	0.219± 0.005	0.290± 0.003	0.257± 0.006	0.227± 0.005	0.213± 0.007	<0.001
120	0.334± 0.006	0.212± 0.004	0.267± 0.002	0.241± 0.013	0.213± 0.006	0.208± 0.005	<0.001
180	0.284± 0.015	0.204± 0.005	0.246± 0.012	0.227± 0.009	0.206± 0.006	0.203± 0.004	<0.001

walks normally, 1 if the animal limps mildly, 2 if the animal completely raises one foot, and three if the animal bites or licks its leg or paw. An average of 5 minutes of pain intensity for each animal was recorded individually. A one-hour chart was then drawn for the time since formalin injection. A biphasic nociceptive response was brought on by the injection of formalin. The initial 5-min block was the early phase (0–5 min), while the late phase occurred 15–60 min following the formalin injection (12, 13).

Statistical Analysis

All the results in this study have been expressed as means±S.E.M. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) to test the statistical significance by repeated-measures analysis of variance (ANOVA), followed by Tukey and Dunnett's post-hoc tests. P< 0.05 was considered statistically significant.

This study was approved by the Laboratory Animal Center of Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad

Results and Discussion

Anti-Inflammatory Properties

As shown in Figure 2 and Table 1 and 2, it can be seen that there is a significant difference between the negative control group and the groups receiving different doses of the extract. As shown in Table 2, there is a significant difference in paw edema 30, 60, 120, and 180 minutes after formalin administration in all the groups compared with the formalin group

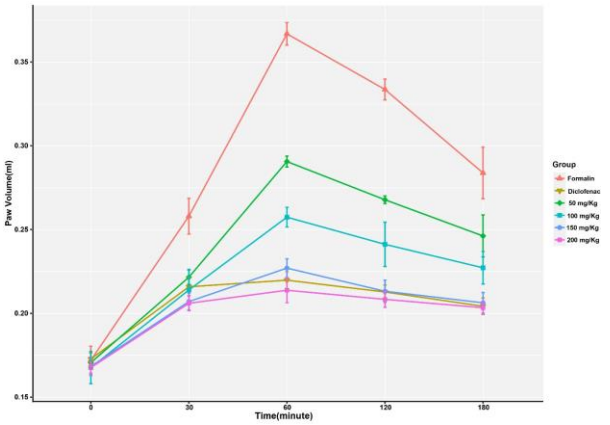

Figure 2. The effect of the fruit hulls extract on formalin-induced inflammation. The animals were divided into six groups of 5 (n=5): negative control (2.5% formalin ,20 µL, subcutaneously), positive control (diclofenac, 200 µg/kg, intraperitoneally), and four groups receiving specified doses of the extract (50, 100, 150, and 200 mg/kg, intraperitoneally).

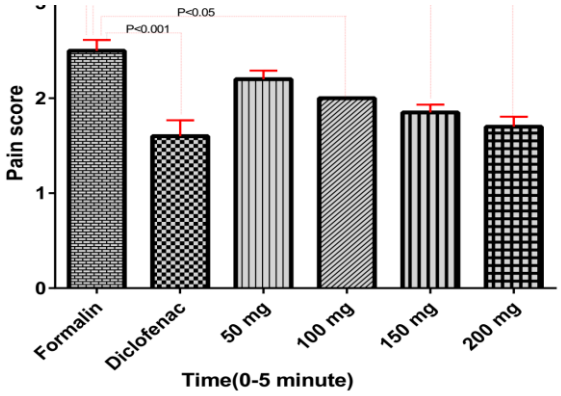

Figure 3. Comparison of the pain level during the first five minutes (the acute pain phase) after the injection of formalin (2.5% formalin, 20 µL, subcutaneously). The animals were divided into six groups of 5 (n = 5) in the negative control group, the positive control group (diclofenac, 200 µg/kg, intraperitoneally), and the experimental groups receiving *Q. infectoria* fruit hulls hydroalcoholic extracts (50, 100, 150, and 200 mg/kg). Values are expressed as mean ± standard error of the mean (SEM) of the standard deviation.

(P<0.001). The 50 mg/kg dose of the fruit hulls extract was significantly less effective compared with diclofenac at 30, 60, 120, and 180 minutes (P<0.001). The 100 mg/kg dose of the fruit hulls extract was also demonstrated as a less effective treatment for formalin-induced paw edema 60,120, and 180 minutes after the administration of formalin (P<0.001). The fruit hulls extract at the 150 mg/kg dose demonstrated the same result. The mice receiving 200 mg/kg of the fruit hulls extract showed similar results to diclofenac. Although not statistically significant, the data analysis showed that the fruit hulls extract was preferable at this dose in reducing formalin-induced inflammation at 30, 60, 120, and 180 minutes, even compared with diclofenac.

Analgesic Properties

After the injection of formalin, the pain experienced by the mice was measured. The lowest pain level was observed in the group receiving diclofenac (positive control), which recovered faster than the other groups as shown in Figure 4. Figure 2 shows acute pain from 0 to 5 minutes after formalin administration. The significance ratio of each group was compared with the negative control group. The best analgesic effect was observed in the positive control group (diclofenac recipients). However, a significant analgesic effect was observed at extract doses of 100,150 and 200 mg/kg. The least effective fruit hulls extract dose was observed in the group receiving 50 mg/kg. The chronic phase can be seen in Figure 3, in which the positive control group and the group receiving 200 mg/kg of the extract displayed the lowest pain level (P<0.001). However, other groups receiving the fruit hulls extract also exhibited a significant reduction in chronic pain (P<0.001).

The results of the inflammation test showed that *Q. infectoria* was significantly effective in reducing inflammation at 50, 100 mg/kg, and 150 mg/kg and were similar to those of diclofenac at the 200 mg/kg

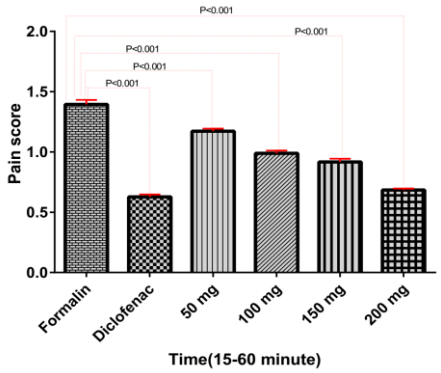

Figure 4. Comparison of the pain level during the time 15-60 minutes after the injection (the chronic stage of pain) of formalin (2.5% formalin, 20 µL, subcutaneously). The animals were divided into six groups of 5 (n=5): the negative control group, the positive control group (diclofenac, 200 µg/kg, intraperitoneally), and the experimental groups receiving the *Q. infectoria* fruit hulls hydroalcoholic extracts (50, 100,150, and 200 mg/kg). Values are expressed as mean ± standard error of the mean (SEM) of the standard deviation.

dose (Figure 5). In a study conducted in 2010, the anti-inflammatory and analgesic effects of the *Quercus brantii* extract on 80 male Wistar rats were investigated. Inflammation was induced by formalin and carrageenan. The extract was studied at 200, 400, and 600 mg/kg doses. Our study demonstrated the best results in the reduction of paw edema at 200 mg/kg ($P<0.001$). However, in a study by Mokhtari, the highest dose had the most significant effect in controlling inflammation and pain (14). In a study conducted in 2018, duloxetine showed no protective effect on formalin-induced paw edema of mice (11).

In another study, dehydrocorydaline, an alkaloid compound isolated from *Rhizoma corydalis*, significantly reduced the formalin-induced paw edema in mice by 66% in the 10 mg/kg DHC group after 60 minutes; whereas in our study, the fruit hulls extract decreased paw edema by 42% after 60 minutes at 200 mg/kg (15).

The essential oil of *Pterodon polygalaeflorus* significantly inhibited formalin-induced edema in mice at 60 mg/kg after 15 minutes. However, in our study, 50 mg/kg of the *Quercus infectoria fruit hulls* extract inhibited formalin-induced edema after 30 minutes (16).

In an experiment carried out in 2020, fish oil nano-emulsion at the 100 mg/kg significantly reduced mice paw edema volume ($P\leq0.05$) 30 minutes after formalin injection. However, neither fish oil nano-emulsion, fish oil, nor sunflower oil showed any other significance in a 50-minute assay, whereas in our study the *Quercus infectoria* fruit hulls extract proved to be significantly effective at any dose in the reduction of paw edema after 30 and 60 minutes (17).

The hydroalcoholic extract of pomegranate seed had no significant impact on formalin-induced inflammation after the first hour of injection. However, after the second and third hours, the group receiving 400 mg/kg of the extract showed a significant difference compared with normal saline ($P>0.05$). Nevertheless, there were no significant differences compared with the positive control group (indomethacin). There was a significant reduction of paw volume with a lower dose of the extract with a shorter duration in our study. Moreover, although it was insignificant, the fruit hulls extract dose of 200 mg/kg showed a 20%, 42%, 38%, and 29% paw

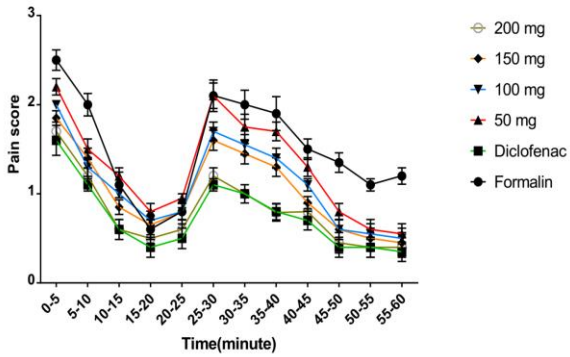

Figure 5. Time courses of the pain scores recorded in six groups of 5 (n=5): the negative control group, the positive control group (f) and the experimental groups receiving the *Q. infectoria* fruit hulls hydroalcoholic extracts (50, 100, 150, and 200 mg/kg) during the formalin test (60 min) divided into 5-min periods. Data are expressed as mean ± standard error of the mean (SEM).

edema reduction, whereas our positive control (diclofenac) showed 17%, 40%, 36%, and 28% edema reduction 30, 60, 120, and 180 minutes after formalin injection, respectively (18).

In another study in 2014, *Q. brantii Lindl.* was used to treat colitis caused by TNBS (2,4,6-Trinitrobenzene sulfonic acid). The extract was injected in two forms (gallstone powder and gall hydroalcoholic extract) for 10 days (500 mg/kg). Ten days after the induction of colitis, the colon's condition was assessed and it was shown that *Q. brantii Lindl*. could exert antioxidant and anti-inflammatory effects on colitis's biochemical and pathological parameters (19).

The anti-inflammatory effects of different parts of *Q. infectoria* have been studied for many years. For instance, a 2009 study investigated the anti-inflammatory properties of this plant's gall for its hepatoprotective potential. Moreover, another study in 2004 which examined the effect of the gall extract of this plant showed that oral administration of its extract significantly inhibited carrageenan, histamine, serotonin, and prostaglandin E2 (PGE2) in induced paw edemas, while the topical application of the gall extract inhibited phorbol-12-myristate-13-acetate (PMA) in ear inflammation (20, 21). In a study in 2017, the effectiveness of *Q. infectoria* in diabetes-induced activity of the Set7 / NF-kB pathway was investigated. The results showed that the *Q. infectoria* extract caused a dose-dependent downregulation in Set7, p65, and inflammatory cytokines compared with the control

Table 2: The effect of the fruit hulls extract on formalin-induced paw edema (***P-value<0.001, **P-value<0.01, *P-value<0.05).

groups	Time (min)	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg	Diclofenac
Formalin	0	0.999	0.867	0.932	0.865	1.000
	30	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
	60	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
	120	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
	180	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
50 mg/kg	0	-	0.973	0.992	0.972	0.993
	30	-	0.631	0.064	0.041*	0.846
	60	-	<0.001***	<0.001***	<0.001***	<0.001***
	120	-	<0.001***	<0.001***	<0.001***	<0.001***
	180	-	0.049*	<0.001***	<0.001***	<0.001***
100 mg/kg	0	-	-	1.000	1.000	0.775
	30	-	-	0.717	0.590	0.999
	60	-	-	<0.001***	<0.001***	<0.001***
	120	-	-	<0.001***	<0.001***	<0.001***
	180	-	-	0.025*	0.008**	0.011*
150 mg/kg	0	-	-	-	1.000	0.865
	30	-	-	-	1.000	0.481
	60	-	-	-	0.016	0.394
	120	-	-	-	0.885	1.000
	180	-	-	-	0.996	0.999
200 mg/kg	0	-	-	-	-	0.773
	30	-	-	-	-	0.363
	60	-	-	-	-	0.581
	120	-	-	-	-	0.919
	180	-	-	-	-	1.000

group in both experimental groups (i.e., the high glucose plus palmitate medium and the high-fat diet group for bone marrow-derived macrophages). These results indicate one of the pathways via which this plant reduces inflammation (22).

The results of the present study showed that increasing the dose progressively decreased the pain experienced by the animals. In the positive control group, the lowest pain level was witnessed compared with the groups receiving the fruit hulls extract, even the group that

received 200 mg/kg. However, all the mice which received the fruit hulls extract significantly experienced reductions in chronic pain. Moreover, the fruit hulls extract proved to be effective in reducing the acute phase at the doses of 100, 150, and 200 mg/kg. Another study conducted in 2009 investigated the *Q. brantii* extract for its analgesic properties. Formalin-induced pain decreased most significantly with an extract dose of 600 mg/kg, which was the highest dose used (P<0.05) (23). Different parts of *Quercus* such as the nutgall, bark, leaf, fruit, and fruit hulls, have been used in alternative medical practices with different therapeutic properties (24). In another study in 2014, the analgesic effect of the methanolic gall extract of *Q. infectoria* in rats was investigated using hot plates and the tail-flick method. The results showed that the methanol extract increased the reaction time of mice to 0.30 seconds 30 minutes after treatment compared with the control group (4.4 seconds) in the tail-flick method, indicating significant analgesic activity (P<0.05). At peak activity (30 min), the extract achieved the maximum possible analgesia (MPA) of 34.2%, and the morphine sulfate reached an MPA of 70.9% (25), which is consistent with the evidence presented in our study.

Conclusion

The *Q. infectoria* fruit hulls extract exhibited analgesic activity against nociceptive responses in mice, and it also showed anti-inflammatory activity against formalin-induced paw edema in very low doses. These results showed that this plant could be further studied as a possible herbal treatment and an alternative to chemical drugs.

Acknowledgment

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

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