Archives of Advances in Biosciences

Original Article:

Anti-inflammatory Activities of *Nannorrhops ritchieana* (Griff.) Aitch Inflorescence Extract in an Animal Model

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Cite this article as: Hashemi Sh, Asgarpanah J, Najafizadeh P, Mousavi Z. Anti-inflammatory Activities of *Nannorrhops ritchieana* (Griff.) Aitch Inflorescence Extract in an Animal Model. Archives of Advances in Biosciences. 2023; 14:E41620. https://doi.org/10.22037/aab.v14i. 41620

https://journals.sbmu.ac.ir/aab/article/view/41620

Article info:
Received: 15 Mar 2023
Accepted: 13 Jun 2023
Published: 27 Oct 2023

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Abstract

Introduction: Given the use of *N. ritchieana* inflorescence (NER) in the folklore medicine of the south of Iran for relieving inflammation and pain in inflammation-based disorders, the current study assessed the anti-inflammatory features of *N. Ritchieana* inflorescence extract (*NRE*) in animal models.

Materials and Methods: The carrageenan-induced paw edema method was used to evaluate the acute anti-inflammatory effects of the *NRE* extract (50,100, and 200mg/kg, i.p.). The postive and negative control groups received mefenamic acid and normal saline, respectively. Then, the rats' paw tissues were removed and collected for studying tumor necrosis factor (TNF-α) level. In addition, the cotton pellet-induced granuloma method was utilized to assess the chronic anti-inflammatory effects of the extract (100 and 200 mg/kg daily for 8 days, i.p.). The postive and negative control groups received indomethacin and saline, respectively. On the last day of the cotton pellet test, the rat's serum was collected for interleukin-1 beta (IL-1β) determination.

Results: In the carrageenan test, the extract significantly reduced the paw edema compared to that of the control ($p<0.05$). The anti-inflammatory activity (100 and 200 mg/kg) of the extract was similar to that of the mefenamic acid group ($P<0.05$). TNF-α levels demonstrated significant anti-inflammatory effects just at the dose of 200 mg/kg. In granuloma induced by cotton pellets, *NRE* was also effective based on the granuloma formation and the transudate amount. The anti-inflammatory activity of the inflorescence extract was found to be the same as the indomethacin group, whereas IL-1β did not represent significant changes.

Conclusion: According to the results, *NRE* had a considerable anti-inflammatory effect.

Keywords: Anti-inflammatory, Inflorescence, IL-1β, *Nannorrhops ritchieana*, Rat, TNF-α

1. Introduction

A group of perennial climbers, caules, shrubs, and trees, the Arecaceae, also called palm trees, include 181 types with almost 2600 species. They exist all over subtropical and tropical areas of the world. The genus *Nannorrhops* belongs to this group in which *Nannorrhops ritchieana (N. Ritchieana)* Griff. is the sole species of this genus.

N.ritchieana is widely distributed in various areas of Baluchistan and Hormozgan provinces in Iran. The young leaves have a sweet astringent taste and are utilized as a purgative in livestock. To treat diarrhea and dysentery, edible fruits are used locally [1, 2].

The flower cluster, the inflorescence, is erect, slender, ramified compound panicle. It is 60 cm to 1 m long and is applied as food and also as an anti-inflammatory natural agent, especially in traditional

medicine. People employ inflorescence in the form of an infusion, decoction, or its extract to relieve inflammation in arthritis rheumatoid, snake and scorpion bites, treatment of urine retention, trauma, and other inflammation-based disorders [3]. Given the widespread use of *N. Ritchieana* inflorescence in Persian traditional medical practices for the treatment of pain and inflammation, the present study aimed to evaluate the anti-inflammatory impact of the extract of *N. ritchieana* inflorescence and study its pharmacological activities as an anti-inflammatory agent. Various standardized experimental test models were used to explore the anti-inflammatory features of the studied extract. This work, to the best of our knowledge, is the first one focusing on the ethnopharmacological features of *N. ritchieana* inflorescence inclusively.

2. Materials and Methods

Chemical

Indomethacin, carrageenan, and diclofenac were purchased from Sigma-Aldrich, Darou-Pakhsh Company (Iran), and Sigma-Aldrich (USA), respectively. Further, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) kits were bought from eBioscience, the USA.

N.ritchieana inflorescence was collected from Hormozgan Province, Iran in the March of 2016. The samples were recognized by N. Kazemivash, followed by depositing the voucher in the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, Islamic Azad University, Tehran, Iran (N.311-PMP/A).

N. ritchieana inflorescence was dried, powdered, and extracted using the maceration method and hydroalcoholic (water and ethanol 80%) solution. The dried crude extract was kept in a clean and dark vial for further biological evaluation.

Animals and housing conditions

The samples included Male Wistar albino rats with a weight of 180-220 g. Fifty four animals were kept in a standardized cage for 12 hours in a light/dark cycle (22 ± 2°C). Food *ad libitum* and water were given to the animals.

Carrageenan-induced paw edema test

To evaluate the acute anti-inflammatory effects, the administration-stimulated inhibition of paw edema was considered as 0.1 mL carrageenan 2% into the hind paw of the rats. [4, 5].The male rats were divided into 5 groups each containing 6 rats. The groups were separately given the control (normal saline: 10 mL/kg; i.p.), *N. ritchieana* (50, 100, and 200 mg/kg; i.p.), and mefenamic acid (30 mg/kg; i.p.) 30 min before carrageenan injection. Then, the paw volume was examined by employing a Plethysmometer (Model PM 4500, BorjSanat Company, Iran) 0.5, 1, 2, 3, and 4 hours after the carrageenan prescription. The anti-inflammatory activity was considered the edema inhibition percentage in comparison to the control group. The above-mentioned percentage was measured as follows:

Edema inhibition percentage of100 (1-Vt/Vc)

Where Vt and Vc represent the edema volume in the test and control groups, respectively.

The TNF-α level in the paw tissues were measured using enzyme-linked immunosorbent assay (ELISA). Four hours after the carrageenan challenge, the collected specimens were homogenized in calcium chloride (1.5%). The intended supernatants were prepared using 1 mL $CaCl_2$ per 50 mg tissue and kept at -70°C. Next, the TNF-α level was estimated based on kit brochures presented by the manufacturer (Rat TNF alpha ELISA Kit, eBioscience, the USA 10).

Histopathological examination

Following carrageenan treatment for 4 hours, the rats were euthanized to remove the paw tissues. Subsequently, to fix them, a 10% formaldehyde solution was utilized, followed by fixating the specimens in paraffin wax, cutting them into 5 µm sections, and drying them with hematoxylin and eosin. The inflammatory tissue response was analyzed through qualitative light microscopy considering an area as the representative area.

Cotton pellet-induced inflammation test

To calculate chronic anti-inflammatory activities attributed to the *N. ritchieana* extract, granuloma induced by cotton pellets was considered based on the method presented by Winter and Porter (1957) [6]. Each group contained a total of six animals, and treatment in the groups was performed for seven consecutive days. In addition, *N. ritchieana* (100 and 200 mg/kg; i.p.), indomethacin (5 mg/kg; i.p.), and vehicle (normal saline: 10 mL/kg) were used to treat the rats, followed by anesthetizing them using xylazine 10 mg/kg and ketamine 100 mg/kg on day 8. Surgery was performed to separate cotton pellets and granuloma tissues and remove extraneous tissues. Weighing the wet pellets, they were dried for 24 hours in an incubator at 60°C to achieve a constant weight. The dried pellets were weighed again. To measure the amount of the exudates (mg), the pellet's constant dry

weight was subtracted from its immediate wet weight. To calculate the Granuloma's dry weight, the weight of the cotton pellet was deduced from the constant dry weight of the pellet and was considered as the quantity of granuloma tissue formation. Ultimately, the inhibition percent of the granuloma tissue formation and exudations were computed based on the results.

In this model, the serum IL-1β level was determined by ELISA based on the manufacturer's kit brochures (Rat IL1 beta ELISA Kit).

Statistical analysis

The groups were compared using the one-way analysis of variance (ANOVA), followed by implementing the post hoc Tukey's test. The significant differences in the means were $p<0.05$ and the obtained data were analyzed using Graph Pad Prism 8 statistical software.

3. Results

Effect of *N. ritchieana*, extract on carrageenan-induced paw edema

The results of one-way ANOVA indicated significant differences between control and treatment groups (50, 100, and 200 mg/kg) at 0.5, 1, and 2 hours of the test, while there was a significant difference ($p<0.05$, $p<0.01$, and $p<0.01$; respectively) between all doses and control at the third hour of the test (Figure 1). The anti-inflammatory effects of the extract by 200mg/kg were continued to the fourth hour of the test.

A comparison was also made between the percent of rat paw edema in the carrageenan test at various doses and times (Table 1). The carrageenan-induced paw edema formation in the rats was significantly inhibited ($p<0.05$) by mefenamic acid (30 mg/kg) and the *N. Ritchieana* extract (50,100, and 200 mg/kg). In the third hour of the experiment, the edema peak appeared as 29, 32, 32, and 43% for these injects, respectively. This edema inhibition reached 26, 28, 39, and 44% in the fifth hour of the experiment, respectively (Table 1).

Effect of *N. ritchieana* extract on the tumor necrosis factor-α level induced by carrageenan in rats' paw tissues

The underlying mechanism under the anti-inflammatory impacts of the *N. ritchieana* extract was evaluated considering the role of TNF-α. Nearly 4 hours following carrageenan-induced inflammation in every treatment group, the rats were killed, and plantar tissue specimens were then assessed in terms of TNF-α. The levels of the plantar tissue of TNF-α in the experimental groups are displayed in Figure 2. The changes of TNF-α in the paw tissue demonstrated that the doses of 50 and 100 mg/kg could not make a significant difference in comparison to that of the control group, but the 200 mg/kg dose could reduce the rate of TNF-α significantly ($p<0.05$).

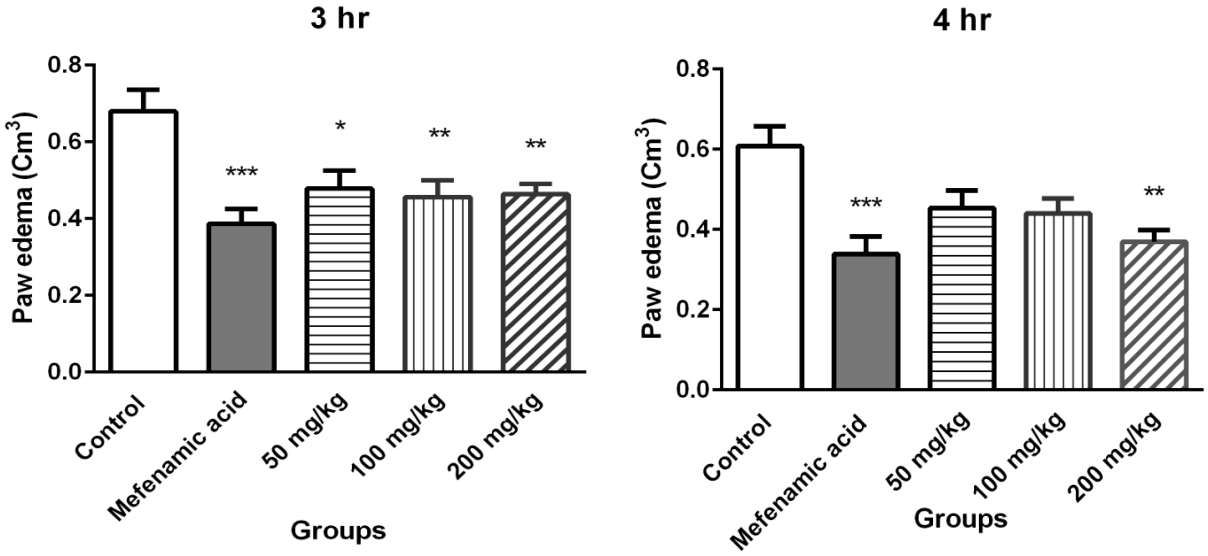

Figure 1. Effect of *N. Ritchieana* extract on the inflammation induced by Carrageenan in rat. Each value represents the mean ± SEM of 6 mice. * P<0.05, ** P<0.01 and *** P<0.001 compared to the control group using one-way ANOVA followed by Tukey's multiple comparison test.

Table 1. *N. Ritchieana* activity on the inflammation caused by carrageenan in rat.

Groups	%Paw edema inhibition in various time intervals				
	0.5 hr	1 hr	2 hr	3 hr	4 hr
Control	*0.25±0.04-*	*0.40±0.06-*	*0.60±0.06-*	*0.68±0.06-*	*0.61±0.05-*
Mefenamic acid	*0.11±0.02* *(55%)*	*0.23±0.03* *(42.5%)*	*0.31±0.04* (48%)	*0.39±0.04* (43%)	*0.34±0.04* (44%)
50mg/kg	*0.23*±0.03 (8%)	*0.38±0.04* (5%)	*0.50±0.06* (16.7%)	*0.48±0.05* (29%)	*0.45±0.04* (26%)
100mg/kg	*0.13*±0.03 (48%)	*0.33±0.06* (17.5%)	*0.51±0.05* (15%)	*0.46*±0.04 (32%)	*0.44±0.04* *(28%)*
200mg/kg	*0.24±0.02* (4%)	*0.38±0.02* (5%)	*0.43±0.03* (28%)	*0.46±0.03* (32%)	*0.37±0.03* (39%)

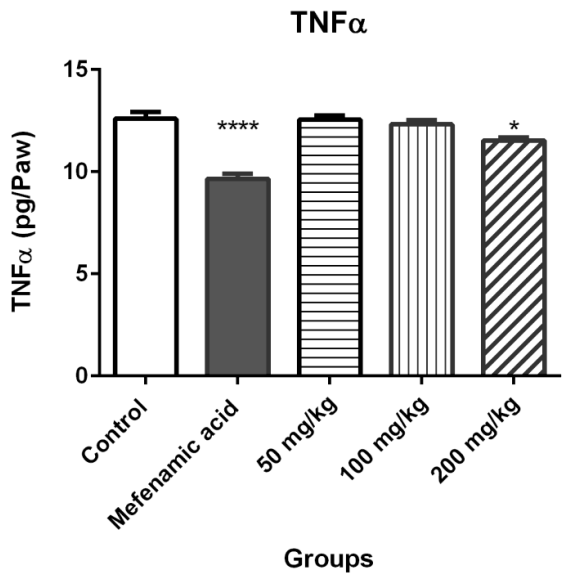

Figure 2. Effect of *N.Ritchieana* extract on carrageenan-induced TNFα in rat paw tissue. The groups received mefenamic acid (30 mg/kg, i.p.), *N. Ritchieana* extract (50,100 and 200 mg/kg, i.p.), and the control (normal saline: 10 mL/kg, i.p.) separately 30 min prior to carrageenan injection.
Each value represents the mean ± SEM of 6 mice. * P<0.05 and **** P<0.0001 compared to the control group using one-way ANOVA followed by Tukey's multiple comparison test.

Histopathological studies

An acute inflammation was found in the paw tissue of vehicle-treated rats with extensive damage in the epidermis layer (Figure 3A). Treating the rats with the *N. ritchieana* extract 50 mg/kg (Figure 3C), mefenamic acid (Figure 3B), 100mg/kg (Figure 3D), and 200mg/kg (Figure 3E) significantly reduced the tissue damage and edema.

Effect of *N. ritchieana* extract on the cotton pellet-induced granuloma and transuda

Based on the findings (Figure 4), granuloma and transudate significantly decreased in the *N. ritchieana* extract-treated (100 and 200 mg/kg; i.p.) group and indomethacin group in the test of inflammation induced by the cotton pellet.

The granuloma inhibition with the *N. ritchieana* extract (100 and 200 mg/kg) was 24% and 36%, respectively, compared to the standard drug indomethacin (39%). Transudate inhibition with the *N. ritchieana* extract (100 and 200 mg/kg) was 36% and 39%, respectively, compared to the standard drug indomethacin (26%), the details of which are presented in Table 2.

Effect of the *N. ritchieana* extract on serum interleukin-1 beta level

The potential mechanism under the anti-inflammatory effects of the *N. ritchieana* extract was considered to evaluate the involvement of the interleukin-1 beta (IL-1β) level.

Figure 5 illustrates IL-1β serum levels in animal groups. Indomethacin could considerably (P<0.0001) reduce the levels of serum IL-1β in the cotton pellet-induced granuloma test in the animal, although the *N. Ritchieana* extract could not cause a significant reduction.

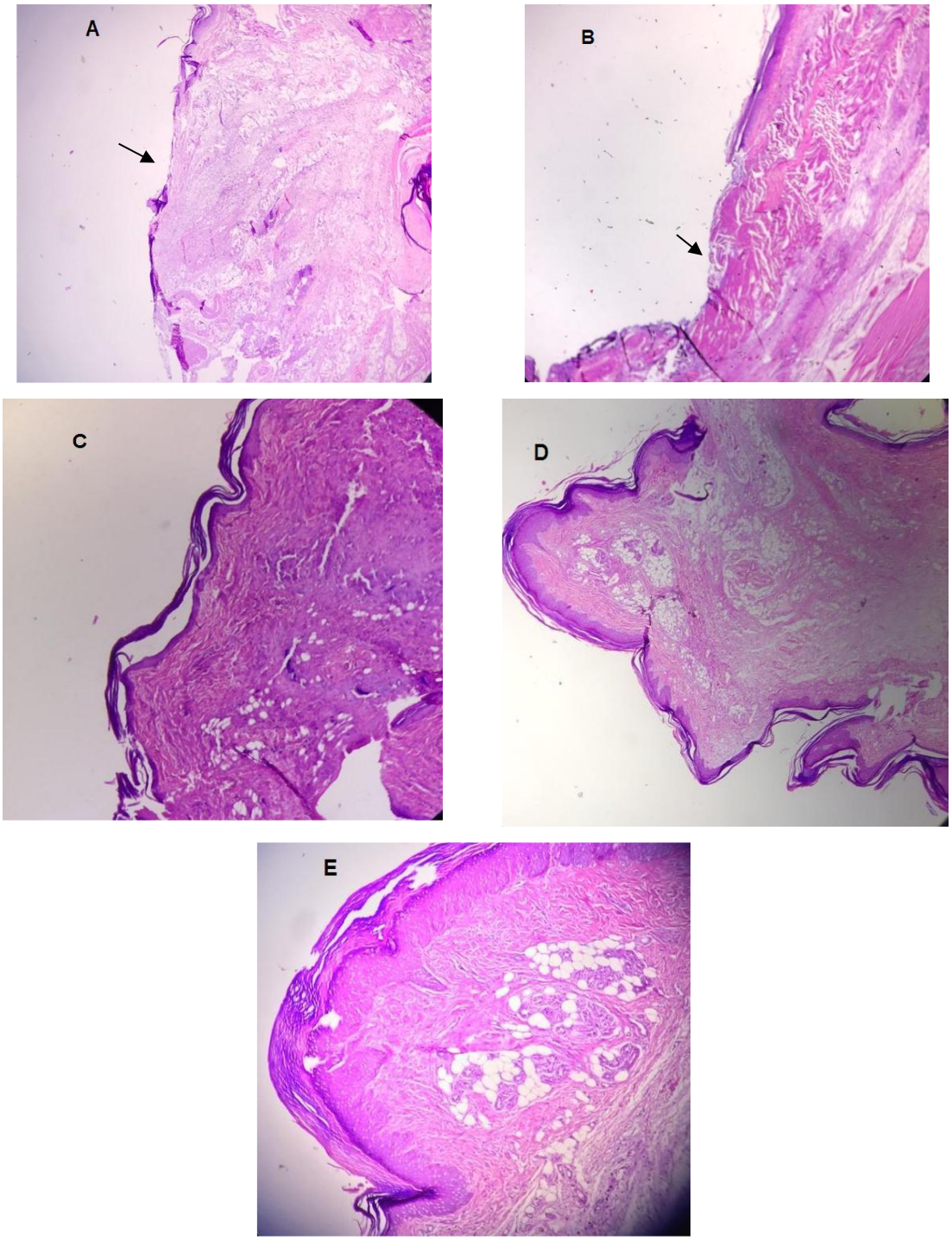

Figure 3. Effect of *N. Ritchieana* extract on histopathological damages induced by carrageenan in paw plantar of the rats. Histopathology examination of paw tissue of rats treated with *N. ritchieana extract*, 4 h after injection of carrageenan. (A): Carrageenan-injected paw tissue in the vehicle group. Vasodilatations with edema were observed. (B, C, D and E): Carrageenan-injected paw of rats treated with mefenamic acid (30 mg/kg, i.p.) and *N. Ritchieana* (50, 100 and 200 mg/kg) respectively. The edema reduced. Sections were stained with H and E, X10.

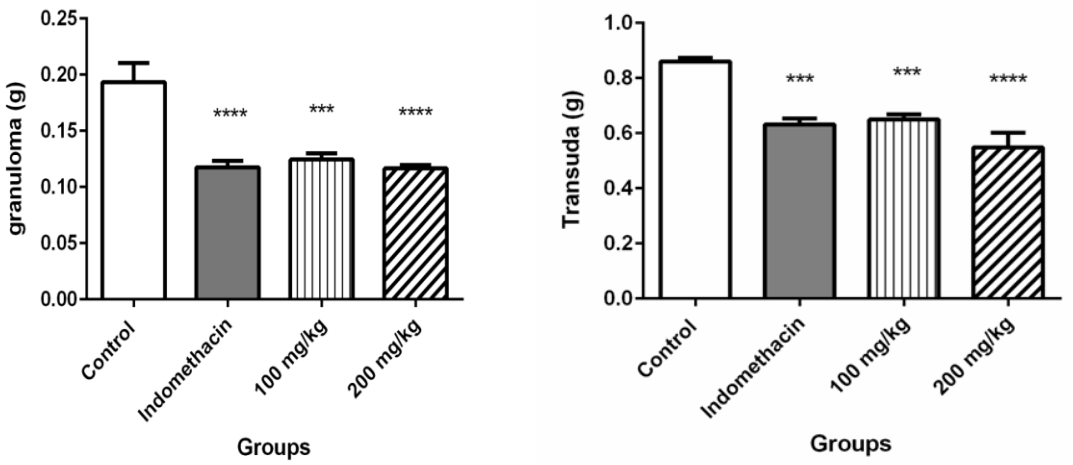

Figure 4: Effect of *N. Ritchieana* extract on the cotton pellet-induced granuloma and transuda in rats.
Each value represents the mean ± SEM of 6 mice. *** p<0.001 and**** p<0.0001 compared to the control groups, using one way ANOVA followed by Tukey's multiple comparisontest.

Table 2. Comparison of *N. Ritchieana* extract activity on inhibition percent of inflammation induced by a cotton pellet.

Groups	% Inhibition Granuloma	% Inhibition Transudate
Indomethacin (5 mg/kg)	39.00	26.51
N. Ritichieana (100 mg/kg)	24.50	36.00
N. Ritichieana (200 mg/kg)	36.00	39.00

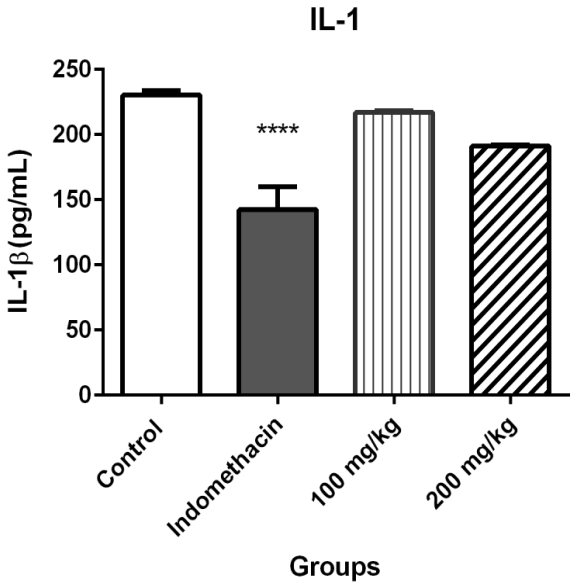

Figure 5. Effect of *N. Ritchieana* extract on cotton pellet-induced IL-1β level in serum of rats.
The groups received indomethacin (5 mg/kg, i.p.), *N. ritchieana*(100 and 200 mg/kg, i.p.), and the control (normal saline: 10 mL/kg, i.p.) for 8 days in rats. Value represents the mean ± SEM of 6 mice. **** P<0.0001 compared to the control group using one-way ANOVA followed by Tukey's multiple comparison test.

4. Discussion

Inflammation is the response of the immune system against harmful stimuli such as damaged cells, irradiation, pathogens, or toxic compounds, and acts by the removal of injurious stimuli and initiation of the healing procedure; on the other hand, uncontrolled acute inflammation may be chronic, causing various chronic inflammatory diseases.

Although there are varied and new approaches for the treatment of inflammation, extensive research field exists in this area to investigate the increased pharmacological response, as well as the least level of unwanted side effects.

In the current study, the first report was presented on the anti-inflammatory activities of the *N. ritchieana* extract (*NRE*) on acute and chronic inflammation experiment models in rodents.

According to our results, the rat hind paw edema induced by intra-plantar injection of carrageenan was suppressed by *NRE* significantly. The inhibitory activity observed in *NRE* (200 mg/kg) in a 4-hour period in paw inflammation induced by carrageenan is equalled to the standard drug (mefenamic acid). Additionally, it was revealed that *NRE* produced anti-inflammatory impacts in rat paw edema triggered by

carrageenan based on the dose.

Based on the findings of present study, in the acute inflammation model, it was found that the greatest changes in the volume of the foot caused by the injection of carrageenan occur in the third hour (*NRE* at doses of 50, 100, and 200 mg/kg) compared to that in the negative control group (normal saline), had a significant difference at the same hour, and could inhibit inflammation by 29, 32 and 32%, respectively. Although this anti-inflammatory effect was unstable at doses of 50 and 100 and decreased in the fourth hour, at the dose of 200 mg/kg, this effect continued until the fourth hour and seemed to be able to reduce inflammation in a stable manner.

As mentioned earlier, the present study further evaluated the *NRE* anti-inflammatory effect to clarify the underlying mechanisms under this animal model. It was demonstrated that the effect may be caused by inhibiting the release of pro-inflammatory cytokines, including TNF-α. Moreover, it was indicated that *NRE* could prevent carrageenan-induced inflammatory damage through the inhibition of TNF-α production.

Further, histological studies demonstrated that in the group receiving the extract, epidermis layers retained their original shape compared to that of the control group. Based on the histological comparison, in the extract group 200 mg/kg the amount of the epidermis remained healthy to a greater extent compared to the 50 and 100 mg/kg extract groups.

According to our results, the dose of 200 mg/kg has a significant role in reducing acute inflammation, and this effect is stable. In addition to reducing the amount of the TNF-α molecular mediator, it can reduce edema and inflammation and cause tissue healing.

The carrageenan test is regularly utilized as an acute inflammation model, representing a higher sensitivity rate to non-steroidal anti-inflammatory drugs (NSAIDs). The carrageenan-induced inflammatory response has a complicated mechanism, requiring the release of various mediators for acute inflammation and incremented vascular permeability. The increased IL-1β, TNF-α, and IL-6 levels, along with cytokine, were found in the inflamed paw [7-10]. It was revealed that TNF-α significantly contributed to the formation of edema more critically to the neutrophil migration and mechanical allodynia after administrating carrageenan [11]. Additionally, the carrageenan-triggered paw edema in rats significantly increased the nitric oxide serum and TNF-α levels [12].

Our results in the model of chronic inflammation by the foreign body granuloma method (the cotton pellet test) showed that *NRE* (100 and 200 mg/kg) could significantly reduce the amount of granuloma and transudate, which is comparable to the effect of indomethacin. Therefore, it is effective in chronic inflammatory conditions, demonstrating possible efficiency in inhibiting the increased fibroblasts and synthesis of mucopolysaccharides and collagen when forming granuloma tissues.

In the examination of serum IL-1β changes, indomethacin could significantly decrease the level of IL-1β. However, the extract could not produce a significant change. The studied doses of the ethanolic extract of *N. ritchieana* reduced chronic inflammation, but could not significantly change the molecular mediator IL-1β.

The cotton-pellet granuloma test is a common technique to evaluate chronic anti-inflammatory materials [5, 13, 14]. The dry weight of the pellet and the quantity of the granulomatous tissue are correlated, along with the pellets' wet weight and transudate. Developing proliferating cells led to chronic inflammation. Proliferating cells might be in spread or granuloma forms. Accordingly, the chronic anti-inflammatory effects of the extract are probably related to the inhibition of cell infiltration or the proliferative phase. The mechanism of action can be more accurate and can be reported with more certainty considering that in any case, the extract of the plant has controlled the inflammation, and the intended extract has different effective components, perhaps by increasing the dose or purifying the components and examining the effects of the components.

This result confirms the *NRE*'s efficacy in controlling inflammation through the regulation of inflammatory reactions. It was found that *NRE* is probably involved in arachidonic acid metabolites, which produce the dependency of edema on neutrophil mobilization. Moreover, the anti-inflammatory effect of *NRE* is possibly related to the scavenging of acute-phase inflammatory mediators, decreasing the growth of edema. *NRE* may contribute to the regulation of free radical reactions, which is undoubtedly incorporated in inflammatory procedures.

Hence, the dose of the 200 mg/kg extract has an acceptable and highly favorable response in both acute and chronic inflammation models, which is comparable to standard NSAID drugs. In the phytochemical analysis of *N. Ritchieana* leaves, it has been reported that the plant has alkaloids, flavonoids, phenol, phytosterols, tannins, and terpenoids. It also has an anti-microbial effect due to the presence of these components [15].

Another report in the same field indicates that the

leaves of *N. Ritchieana* contain 22 types of phenolic compounds, mostly ellagic acid, and 21 types of flavonoid glycosides and aglycones were also identified in them, mainly including Kaempferol 3-O-(2-ρ-coumaroyl) glucoside [1].

The results of a review study by Rahmani et al. (2014) about the fruit of the *Phoenix Dactylifera* plant showed that this plant can be effective in preventing diseases in which the inflammatory process plays a role, and this plant has anti-inflammatory, antioxidant, and anti-tumor effects [16].

Reports of the anti-inflammatory effect of plants related to *N. ritchieana* are available, including the anti-inflammatory effect of the *Phoenix Dactylifera* pollen extract in the testosterone-induced prostate hyperplasia model, which effectively reduced the level of pro-inflammatory cytokines [17].

5. Conclusion

Therefore, according to findings of the present and previous studies and reports on plant components, including flavonoids and tannins, the extract of the *N. Ritchieana* plant has obvious anti-inflammatory effects; this warrants more research in relation to the active substance of the plant and the mechanism of the anti-inflammatory impact.

Ethical Considerations

Compliance with ethical guidelines

The experiments were conducted according to guidelines provided for laboratory animals presented by the Faculty of Pharmacy. The Research and Ethics Committee of Tehran Medical Sciences, Islamic Azad University, Tehran, Iran (IR.IAU.PS.REC.1397.271) proved the experiments.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Author's contributions

Shahrzad Hashemi performed the laboratory work and collected the data. Jinous Asgarpanah contributed to the project idea, preparing the plant materials and writing the manuscript. Parvaneh Najafizadeh and Zahra Mousavi contributed to providing the equipment for the experiments, data collection, and writing the paper. All authors have approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

Acknowledgments

This study was conducted as part of a Pharm.D. Student thesis project in Faculty of Pharmacy and Pharmaceutical Sciences, University of Medical Sciences. We would like to appreciate the Faculty of Pharmacy and Pharmaceutical Sciences for their support.

References

[1] Essa AF, Mohamed T, Haggag E, Elkhrisy EE-D. Flavonolignans and biological activity of Nannorrhops ritchiana leaves. J Adv Pharm Educ Res. 2018; 2:44-55. [DOI: 10.21608/aprh.2017.4721]

[2] Kazemi MD, Beyzaei H, Ebrahimnezhad Z. Chemical composition, antioxidant potential, and antimicrobial activity of nannorrhops ritchiana (Griff) Aitch. *Arch Adv Biosci*. 2021; 14:1-5. [DOI:10.22037/aab.v13i.39282]

[3] Marwat SK. Ethnophytomedicines for treatment of various diseases in DI Khan district. Sarhad J Agric. 2008; 24:306-16. https://www.researchgate.net/profile/Muhammad-Zafar-23/publication/265113602

[4] Winter CA, Risley EA, Nuss GW. Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. Proc Soc Exp Biol Med. 1962; 111:544-7. [DOI: 10.3181/00379727-111-27849] [PMID]

[5] Jahandar F, Asgarpanah J, Najafizadeh P, Mousavi Z. Anti-inflammatory activity and chemical composition of Pycnocycla bashagardiana fruit's essential oil in animal models. Iran J Basic Med Sci. 2018; 21:188. [DOI: 10.22038/IJBMS.2017.20860.5426.] [PMID] [PMCID]

[6] Winter CA, Porter CC. Effect of alterations in side chain upon anti-inflammatory and liver glycogen activities of hydrocortisone esters. J Am Pharm Assoc. 1957; 46:515-9. [DOI: 10.1002/jps.3030460902] [PMID]

[7] Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A, Ghorbanzadeh B. A study of the mechanisms underlying the anti-inflammatory effect of ellagic acid in carrageenan-induced paw edema in rats. Indian J Pharmacol. 2015; 47(3):292-8. [DOI: 10.4103/0253-7613.157127] [PMID] [PMCID]

[8] Sadeghi H, Hajhashemi V, Minaiyan M, Movahedian A, Talebi A. Further studies on anti-inflammatory activity of maprotiline in carrageenan-induced paw edema in rat. Int Immunopharmacol. 2013; 15(3):505-10. [DOI: 10.1016/j.intimp.2013.01.018] [PMID]

[9] Annamalai P, Thangam EB. Local and systemic profiles of inflammatory cytokines in carrageenan-induced paw inflammation in rats. Immunol Invest. 2017; 46(3):274-83. [DOI: 10.1080/08820139.2016.1248562] [PMID]

[10] Chitsaz R, Zarezadeh A, Asgarpanah J, Najafizadeh P, Mousavi Z. Rubiadin exerts an acute and chronic anti-inflammatory effect in rodents. Braz J Biol. 2021; 83. [DOI: 10.1590/1519-6984.243775] [PMID]

[11] Rocha AC, Fernandes ES, Quintão NL, Campos MM, Calixto JB. Relevance of tumour necrosis factor-α for the inflammatory and nociceptive responses evoked by carrageenan in the mouse paw. Br J Pharmacol. 2006; 148(5):688-95. [DOI: 10.1038/sj.bjp.0706775] [PMID] [PMCID]

[12] Kataoka T, Teraoka J, Sakoda A, Nishiyama Y, Yamato K, Monden M, et al. Protective effects of radon inhalation on carrageenan-induced inflammatory paw edema in mice. Inflammation. 2012; 35(2):713-22. [DOI: 10.1007/s10753-011-9364-y] [PMID]

[13] Ismail TS, Gopalakrishnan S, Begum VH, Elango V. Anti-inflammatory activity of Salacia oblonga Wall. and Azima tetracantha Lam. J Ethnopharmacol. 1997; 56(2):145-52. [DOI: 10.1016/s0378-8741(96)01523-1] [PMID]

[14] Dzoyem J, McGaw L, Kuete V, Bakowsky U. Anti-inflammatory and anti-nociceptive activities of African medicinal spices and vegetables. Medicinal spices and vegetables from Africa: Elsevier; 2017. [DOI: 10.1016/B978-0-12-809286-6.00009-1]

[15] Mahmood A, Sharif M, Ahmad Q, Mahmood R, Riaz S, Zafar M. Phytochemical analysis and comprehensive evaluation of antimicrobial activity of Nannorhops ritchiana leaves (Mazari palm). World J Pharm Pharmaceut Sci. 2017; 6:173-89. https://www.researchgate.net/profile/Qurratulain_Ahmad4/publication/333678628

[16] Rahmani AH, Aly SM, Ali H, Babiker AY, Srikar S. Therapeutic effects of date fruits (Phoenix dactylifera) in the prevention of diseases via modulation of anti-inflammatory, anti-oxidant and anti-tumour activity. Int J Clin Exp Med. 2014; 7(3):483-91. [PMID] [PMCID]

[17] Elberry AA, Mufti ST, Al-Maghrabi JA, Abdel-Sattar EA, Ashour OM, Ghareib SA, et al. Anti-inflammatory and antiproliferative activities of date palm pollen (Phoenix dactylifera) on experimentally-induced atypical prostatic hyperplasia in rats. J Inflamm. 2011; 8(1):1-13 [DOI: 10.1186/1476-9255-8-40] [PMID] [PMCID]