



Anti-inflammatory Effect of Apigenin Obtained by *Portulaca oleracea* L in Male Mice

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A B S T R A C T

This study aimed to evaluate the potential anti-inflammatory effects of apigenin, obtained from *Portulaca oleracea* L., using a male mouse model. A total of 56 healthy BLAB/c albino male mice (*Mus musculus*) were used in two experiments. In the first experiment, the xylene-induced ear edema, 28 male mice were randomly divided into four groups (n=7). The negative control group received distilled water, while the positive control, apigenin-treated, and indomethacin-treated groups were exposed to xylene (0.03 mL applied to the anterior and posterior surface of the right ear lobe) to induce inflammation. Subsequently, the apigenin-treated group received orally 50 mg/kg BW apigenin, and the indomethacin-treated group received orally 0.36 mg/kg BW indomethacin. Ear weight difference was calculated as an indicator of anti-inflammatory. For the second experiment, the carrageenan-induced paw edema, a similar experimental design was followed, but carrageenan (50 mg/kg BW of 1% solution) was administered intra-dermally in the right hindpaws. Paw skin thickness difference and differential white blood cells (WBCs) count, along with the quantification of prostaglandin E-2 (PGE-2) and interleukin-6 (IL-6) in serum samples, were used as indicators of anti-inflammatory. Results showed that xylene exposure led to a significant ear weight increase, indicative of inflammation. Conversely, the apigenin-treated group demonstrated a reduction in ear weight compared to the positive control group. Similarly, carrageenan administration resulted in a substantial increase in paw skin thickness and elevated levels of WBCs count, PGE-2, and IL-6. Apigenin treatment significantly mitigated these inflammatory markers, outperforming indomethacin in PGE-2 and IL-6. This study provides evidence supporting the potential of *P. oleracea*-derived apigenin as an effective anti-inflammatory agent, showing comparable or better efficacy than indomethacin.

Keywords: apigenin, *Portulaca oleracea* L, anti-inflammatory, indomethacin, mice

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INTRODUCTION

Inflammation is a natural defence mechanism against harmful stimuli, microbes, and damaged cells (1). Regular physiological and immunological processes are coordinated during inflammation by the immune system signaling soluble molecules, and the relevant cells are then moved to the inflamed regions to treat the abnormal state and ultimately trigger the healing process (2). To prevent

uncontrolled damage and the emergence of other autoimmune illnesses such as systemic lupus erythematosus disease (SLE), rheumatoid arthritis, multiple sclerosis (MS) and psoriatic arthritis, the inflammatory immune response must be controlled after the stimuli have been removed (3).

Although there is overlap between both processes, inflammation is sometimes explained as having distinct acute and chronic phases. Leukocytes, particularly

granulocytes, are present in the acute phase and are responsible for a body's response to chemical, biological, and physical stimulation. Cytokines and acute-phase proteins carefully organize the migration of immune cells to the site of injury following a chemotactic gradient to eliminate the inflammatory stimulus, which may be an infection and foreign materials. The location of the injury responds to a chemical signal gradient to remove the source of inflammation, which could be due to an infection or other factors, or it might be the result of an unusual immune reaction to the body's own molecules. The chronic stage Arthritis, asthma, atherosclerosis, autoimmune disorders, diabetes, cancer, and understanding the function of chronic inflammation in the development of age-related disorders is important because chronic inflammation leads to tissue damage and fibrosis and changes the active immune cell populations to include a mononuclear phenotype (4). TNF- α and IL-6 provide crucial functions in the immune system's inflammatory response to illnesses, and excess IL-6 production has been observed in diseases such as psoriasis, osteoporosis, inflammatory bowel syndrome (IBS), rheumatoid arthritis and Crohn's disease (5).

Non-steroidal anti-inflammatory medications (NSAIDs) are widely commonly used to deal with pain, have a number of undesirable effects, such as renal and hepatic dysfunction, and thus restricted their therapeutic efficacy in pain treatment (6,7). However, these drugs only provide temporary relief for neuropathic in a small percentage of the sick people and frequently cause side effects affecting the central nervous system (CNS), which are severe and dose-limiting (8).

Recently, the use of conventional herbs as effective anti-inflammatory medicines in treatment and prevention methods has drastically expanded (9). Purslane, or *Portulaca oleracea*, is an annual herb from the Portulacaceae plant family. It is on the WHO's list of essential medicines. (10, 11). Many diseases can now be treated more effectively and safely than ever before because of the worldwide shift towards the use of raw plant materials in the creation of pharmaceutical medicines rather than chemicals with hazardous side effects (12). The annual plant *Portulaca oleracea* has been medicinally used for ages to treat a wide range of conditions. *P. oleracea* has been studied for its potential as a medicinal agent due to its anti-fever, anti-inflammatory, and analgesic activities (5). 'The predominant secondary metabolites in *P. oleracea* are alkaloids, terpenes, coumarins, flavonoids, organic acids, and other compounds (13). These metabolites exhibit a range of biological activities, including antibacterial, anti-inflammatory, analgesic, anti-tumor, anti-oxidative, immune-enhancing, and anti-cough effects (14, 15). Additionally, *P. oleracea* is well-known for its potent antioxidant properties, particularly its ability to chelate metal ions, a crucial factor in reducing oxidative stress and inhibiting lipid peroxidation. Its phenolic components and

various fatty acids are responsible for these effects, which include lowering inflammation and pain perception and maybe lowering cancer risk (16).

Flavonoids, a type of plant secondary metabolite with a polyphenolic structure, can be found in a wide variety of foods and drinks, including fruits, vegetables, herbs, and even some beverages. Flavonoids have long been known to have anti-inflammatory, antioxidant, analgesic, antiviral, antibacterial, and anti-allergic properties. Flavonoids are one of the most natural substances that minimize the risk of heart disease (17). Polyphenols protect different cell types, such as white blood cells, Platelets, erythrocytes and other types of cells, from hydrogen peroxide (H₂O₂) (18). Flavonoids provide an important nutraceutical component to diet and apigenin is one of them.

Apigenin has the chemical formula C₁₅H₁₀O₅ and is classified as a flavonoid. Apigenin's pure form has a low molecular weight (270.24 daltons) and takes the shape of needles when exposed to light (19,20). Apigenin has also been demonstrated to protect mice from agents-induced liver injury, and its mechanisms are thought to be connected to increased nuclear factor erythroid 2-related factor 2 (Nrf-2) mediated antioxidative enzymes and anti-inflammatory action (21). Apigenin, a flavonoid, has antioxidant, immunomodulatory properties (22) and anticancer *in vivo* (23) and *in vitro* (24).

The anti-inflammatory effect of *P. oleracea* is very well known, with numerous studies evaluating the anti-inflammatory effect, in addition to its anticipative effect. In most of these studies, crude extract (using different extraction methods) has been used (25-29). However, to our knowledge, there are rare studies worked on the investigation of anti-inflammatory potential of apigenin extracted from *P. oleracea*. Thus, the aim of this study was to investigate the anti-inflammatory potential of apigenin extracted from *P. oleracea* in the xylene-induced ear edema and carrageenan-induced paw edema models in mice).

MATERIALS AND METHODS

Ethical Approval

The study was conducted based on the ethical approval received from the local Research Ethics Committee, College of Veterinary Medicine, University of Baghdad (Approval Number 1337 P.G. dated 21st Jun 2023).

Plant Materials and Extraction

The leaves of fresh *P. oleracea* L. plant was obtained by manual harvest from different locations in the province of Baghdad, Iraq, between May, and June. A reference sample was authenticated by the Iraqi National Herbarium, Directorate of Seed Testing and Certification, Ministry of Iraqi Agriculture, Baghdad, Iraq (certification number 3490, dated 22nd November 2022).

At least one plant was pooled to form a single sample after collection. Leaves were dried at room temperature for

one week, then crumpled into a fine powder with a mortar and pestle and stored in a clean container at room temperature before extraction. *P. oleracea* dried leaves powder (35 g) was mixed with 350 mL ethanol (70%, EMSURE, Germany) and extracted in a Soxhlet apparatus (Olympus, Japan) for 6 h at 60 °C, followed using a rotary evaporator (Heidolph, Germany) to eliminate the alcohol. The crude extract was kept in the dark at 4 °C until further use (30).

The yield was calculated based on the formula:

$$\text{Yield (\%)} = \frac{\text{Weight of } P. \textit{oleracea} \text{ leaves extract}}{\text{Weight of dried } P. \textit{oleracea} \text{ leaves powder}} \times 100$$

Isolation of Apigenin from *P. oleracea* L. by HPLC

Apigenin was isolated from the *P. oleracea* ethanolic extract by Shimadzu (Japan) HPLC system following a method previously described (31, 32) at the Department of Chemistry, Ministry of Science and Technology. The HPLC system was equipped with a UV detector and a Shimpack C-18 column (particle size of 3 µm; 50 × 4.6 mm I.D.). The mobile phase consisted of 0.1% phosphoric acid-acetonitrile (52:48, v/v). The flow rate was 1.5 mL/min, and the column temperature was maintained at 25 °C. A 100 µL of the sample and the apigenin standard (10 ppm, Swanson, USA) were injected into the column separately using an autosampler. Peaks were monitored at 285 nm and the fraction corresponding to apigenin was identified by matching its retention time with that of the apigenin standard and collected for further analysis.

The peak areas from the chromatograms were used for the quantification of apigenin. The concentration of apigenin in the sample was determined using the formula:

$$\text{Apigenin (ppm)} = \frac{\text{AUC sample}}{\text{AUC standard}} \times \text{SC} \times \text{DF}$$

Where, AUC sample is area under the curve of sample, AUC standard is area under the curve of standard, SC is standard concentration, DF is dilution factor.

Animals and Experimental Design

A total of 56 healthy BLAB/c albino male mice, aged on average 3 months (±2.8 days) and weighing 27±2 g, were obtained from and kept at the animal house (in a special room belonging to the Department of Physiology, Biochemistry and Pharmacology) of the College of Veterinary Medicine, University of Baghdad. The animals were acclimatized for 7 days, during which they were accommodated in plastic cages (20×30×50 cm³) with stainless-steel wire mesh lids. Commercial rodent feed pellets and tap water were supplied ad libitum. Environmental conditions were maintained at 25 (±5) °C and 50 (±5)% relative humidity, with a 12/12-h light/dark cycle. Ventilation vacuums were regularly used to replace

air, and litter (wood shavings) in the cages was changed regularly.

Xylene-Induced Ear Edema

Twenty-eight male mice were randomly divided into four groups of seven for the first experiment, which was used to evaluate the anti-inflammatory effect by determining xylene-induced ear edema: the negative control group was treated orally with distilled water; the positive control group was treated with 0.03 mL of xylene only (GCC, UK) applied to the anterior and posterior surface of the right ear lobe using a micropipette; third group treated with xylene in the right ear and received 50 mg/kg BW apigenin orally; fourth group treated with xylene and received 0.36 mg/kg BW indomethacin orally. The time interval between substance administration and xylene exposure was 30 min, and the duration of xylene exposure was 1 hour. After 1 hour of xylene application, mice were euthanized by chloroform (CDH, USA), and a 7 mm diameter punch biopsy of the right ear was taken by a cork borer (China) and weighed by sensitive balance (Sartorius, Canada). The ear weight difference was calculated as an indicator of ear edema (33).

Carrageenan-Induced Paw Edema

In the second experiment, twenty-eight male mice were equally divided into four groups to evaluate the anti-inflammatory effect by determining carrageenan-induced paw edema. The groups were as follows: a negative control group treated orally with distilled water; a positive control group subjected to intra-dermal injection in the right hindpaw with a 1% carrageenan solution (Sigma Aldrich, USA); a third group injected intra-dermally in the right hindpaw with the same 1% carrageenan solution and treated orally with apigenin (50 mg/kg BW); and a fourth group injected with the 1% carrageenan solution and treated orally with indomethacin (0.36 mg/kg BW). The time interval between the administration of the substances and the injection of the carrageenan solution was 30 min. For each mouse, 50 µL of the 1% carrageenan solution was injected into the paw. Paw skin thickness was measured before and 5, 10, 15, and 30 min after carrageenan injection using a digital caliper (GUO CAO, China), and the difference in paw skin thickness was calculated as an indicator of paw edema (34).

Blood Sample Collection

Two hours after the last thickness measurement, the animals were anesthetized by chloroform (CDH, Italy) and direct blood draining was conducted from the heart using a disposable syringe. Part of the samples (about 1 mL) of blood was collected into labelled EDTA tubes (AFCO, Jordan) and stored in the refrigerator (-20°C) until the differential white blood cell (WBC) analysis (35). The other blood part (about 1 mL) was collected in a plain gel tube, left at room temperature for 2 h to be clotted, and

centrifuged at 3000 rpm for 15 min. The sera were collected into a labelled Eppendorf tube (Karl, China) and kept frozen at -20 °C until used for measurement of interleukin-6 (IL-6) and prostaglandin E-2 (PGE-2).

Differential White Blood Cell Count

After two hours of carrageenan injection, a single drop of blood was drawn, dropped onto a slide, and spread with a single stroke. Once dried, the slide was stained with Leishman's stain (Sera and Vaccines Institute, Iraq) for ten min before being rinsed in running water. The slide was then viewed under a microscope (with a magnification setting of 100) in a zigzag pattern up and below until 100 cells were counted (cell type identification for percentage calculation) (36).

Quantification of IL-6 and PGE-2

Measurement of serum IL-6 was performed using a Mouse IL-6 enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, USA, Catalog Number: MBS730957). PGE-2 serum level measurement was conducted using a Mouse PGE-2 ELISA kit (MyBioSource, USA, Cat Number: MBS266212). The manufacturer and specifications of the ELISA kits, the preparation and dilution of serum samples, the incubation and washing steps, the addition of substrate and stop solution, and the measurement of absorbance using a microplate reader were followed according to the instructions provided by the kits. The concentrations of IL-6 and PGE-2 in serum samples were calculated using standard curves.

Stock Solutions of Apigenin and Indomethacin

Dilutions of the ethanolic extracted apigenin were prepared by weighing 20 mg and mixed up to 4 mL distilled water. Determination of the final experimental dose was calculated as 0.1 mL/10 g BW, equivalent to the dose of apigenin at 50 mg/kg BW (37-39).

To achieve the final indomethacin experimental dose at 0.36 mg/kg BW, 3.6 mg indomethacin (Samara, Iraq) was diluted to a volume of 100 mL distilled water. After determining the final concentration, the dose was determined to be 0.1 mL/10 g BW (40).

Statistical Analysis

Data were expressed as mean \pm standard error of the mean (SEM). Data for xylene test, differential WBCs count, IL-6 and PGE-2 were subjected to one-way analysis of variance (ANOVA) followed by the post-hoc Least Significant Difference (LSD) test. For carrageenan data the statistical analysis was performed using two-way ANOVA to evaluate the main effects of treatment and time, as well as their interaction on paw thickness, followed by post-hoc comparisons using the LSD test to identify significant differences between groups at each time point. Significance was set at $P \leq 0.05$. All statistical analyses were performed using IBM SPSS 22.0 software (IBM Co., Armonk, NY).

RESULTS AND DISCUSSION

Extraction of *P. oleracea* L

A dark green solution extract was obtained by extracting *P. oleracea* with 70% ethanol weighing 5.25 g (15%) using the Soxhlet procedure.

Identification and Quantification of Apigenin

HPLC results showed distinct chromatographic peaks for different bioactive compounds, including apigenin (Figure 1A). The chromatogram showed apigenin's standard retention time at 16.547 min with an area of 11434.438 mV.s. In our analyzed specimen, the apigenin peak was evident at a retention time of 16.852 min (Figure 1B) and an area of 3036.491 mV.s. This resulted in an estimated apigenin concentration of roughly 2.66 ppm in the sample of ethanolic extract of plant.

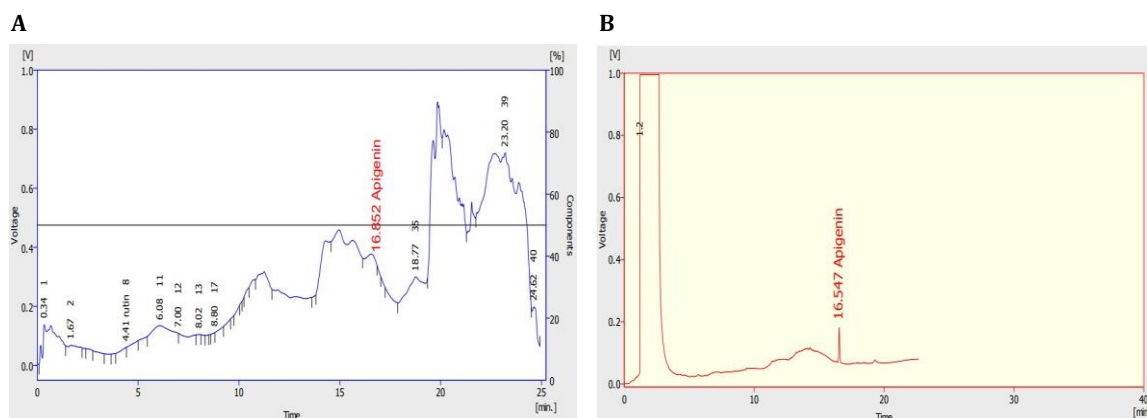


Figure 1. HPLC chromatogram of *Portulaca oleracea* ethanolic extract recorded at 285 nm (A), apigenin standard (B)

The HPLC conditions used in the current study showed specificity and consistency for pinpointing and measuring apigenin. The peak separation met quality standards, and

the retention times were in agreement with those of the standard, validating the methodology (41). The apigenin levels observed in the ethanol extract of *Portulaca oleracea*

L. leaves were consistent with prior studies, reinforcing the plant's potential as a rich source of this pharmacologically significant compound. Apigenin's presence reinforces the plant's medicinal value as it is known to have antioxidative, anti-inflammatory, and anticarcinogenic properties (42).

Xylene Test

As shown in Figure 2, the xylene test results revealed a significant increase ($P<0.01$) in ear weight for the xylene-treated group compared to all other groups, that indicated an elevation in the inflammation. The positive control group recorded the highest ear weight of 0.2914 ± 0.022 g, while the negative control group had the lowest at 0.0353 ± 0.003 g. Both the apigenin and indomethacin-treated groups showed a significant decrease ($P<0.01$) in ear weight compared to the xylene-treated group, demonstrating the anti-inflammatory effect of apigenin to be comparable to indomethacin. Earlier research by (43) reported that the flavonoid apigenin-7-glucoside (AP-7G) has potent analgesic and anti-inflammatory properties when intraperitoneally administered to mice at 30 mg/kg.

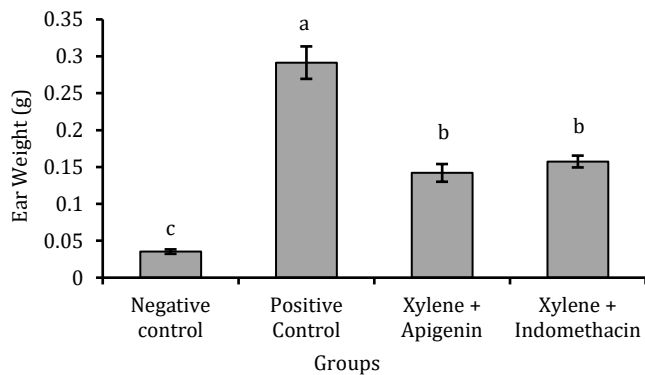


Figure 2. Anti-inflammatory effect of apigenin obtained from ethanolic extract of *Portulaca oleracea* on xylene-induced edema in male mice in comparison with indomethacin. Bars (means) with different letters are statistically significant ($P\leq 0.05$). Error bars represent the standard error of mean (SEM), $n = 7$ per treatment group

The xylene test is a straightforward yet effective approach for evaluating the anti-inflammatory effects of pharmaceuticals or natural substances (44). This method involves the induction of ear edema through xylene application, leading to neurogenic swelling. This process is partially associated with substance P, an eleven-amino acid peptide present in the central and peripheral nervous systems (45). In different physiological processes, substance P acts as a neurotransmitter or neuromodulator. When subjected to stress, neurons in the midbrain release substance P, which then facilitates dopaminergic neurotransmission from sensory neurons in the spinal cord in response to noxious stimuli and excites dorsal neurons. In peripheral tissues, the release of substance P from

sensory neurons leads to vasodilation and plasma extravasations, indicating its involvement in neurogenic inflammation.

Consequently, it can lead to ear swelling in mice. Apigenin and indomethacin are both known to inhibit the synthesis of prostaglandins by blocking the enzyme cyclooxygenase-2 (COX-2), which is induced by inflammatory stimuli. Apigenin also inhibits the expression of inducible nitric oxide synthase (iNOS), which produces nitric oxide, another pro-inflammatory mediator. It has also been reported that the activation of nuclear factor kappa B was inhibited by the apigenin, which is a transcriptional factor that regulates expressions of different inflammatory agents, including tumor necrosis factor-alpha (TNF- α), IL-1 β , IL-6, and IL-10 (46-48).

The results of the current study align with existing literature documenting apigenin's anti-inflammatory properties in various animal models. These include the carrageenan-induced paw swelling model, the cotton pellet-triggered granuloma formation, and the lipopolysaccharide (LPS) triggered acute pulmonary injury. To our knowledge, our research is pioneering in assessing the anti-inflammatory effect of apigenin sourced from *Portulaca oleracea* L. using the xylene-induced ear edema model. This study introduces new insights, underscoring *P. oleracea* L. as a potent apigenin source. Furthermore, it suggests that apigenin derived from this plant may be as effective, if not more, than indomethacin in mitigating ear inflammation in male mice.

Carrageenan-Induced Paw Edema

The carrageenan-induced paw edema test is a commonly adopted *in vivo* method for assessing the anti-inflammatory effects of substances in cases of acute inflammation (49). Carrageenan administration in the paw leads to edema development in two separate stages (50). The early stage, beginning immediately post-carrageenan injection and lasting up to two hours, involves the release of histamine, serotonin, and bradykinin. The subsequent stage, started after the first and continued for three to five hours, is marked by the secretion of prostaglandins (including PGE-2), protease, and lysosome (51-52). Predominantly, this model is linked with the activation of the cyclooxygenase pathway, integral in the later stage of inflammation in the carrageenan model. This pathway is a key target for numerous NSAIDs (44).

Data presented in Figure 3 showed significant increases in paw thickness at all measured intervals for the positive control group ($P<0.01$), confirming the model's efficacy in inducing inflammation. The maximum increase in paw thickness for this group was recorded at 4.30 ± 0.15 mm at the 30-minute mark, consistent with the expected progression of carrageenan-induced edema as documented in earlier studies (53).

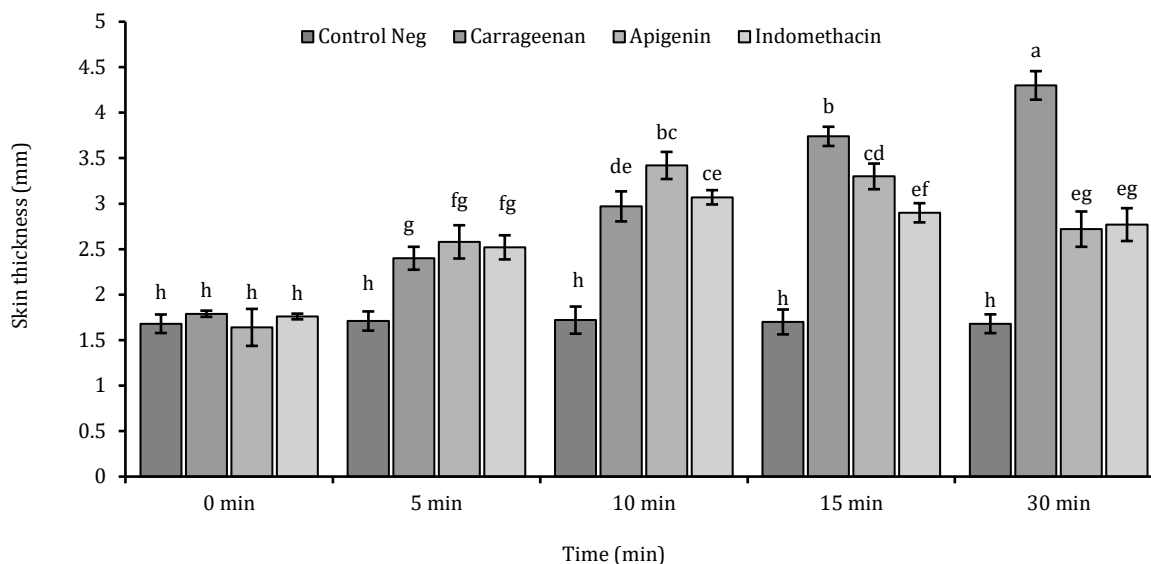


Figure 3. The anti-inflammatory effect of apigenin obtained from ethanolic extract of *Portulaca oleracea* on carrageenan-induced inflammation in male mice in comparison with indomethacin. Bars (means) with different letters are statistically significant ($P \leq 0.05$). Error bars represent the standard error of mean (SEM), $n = 7$ per treatment group

Upon treatment with apigenin, a significant swelling was observed at 10 min, with a peak paw thickness of 3.42 ± 0.149 mm. However, this was followed by a reduction at 15 min and a further decrease to 2.71 ± 0.194 mm at 30 min. This suggests that while apigenin may allow initial inflammation, it appears to exert its anti-inflammatory effects by significantly reducing edema within 30 min of carrageenan administration. In comparison, indomethacin-treated animals also exhibited a peak in paw thickness at 10 min (3.07 ± 0.0788 mm), which then decreased to 2.77 ± 0.181 mm at 30 min. The pattern of response to indomethacin is indicative of its anti-inflammatory activity, which seems to stabilize the paw thickness after the initial inflammatory response.

At the 30-minute point, when compared to the peak inflammation observed in the carrageenan group, both apigenin and indomethacin treatments demonstrated a reduction in paw thickness with very close values, indicating a comparable level of efficacy in the context of this study. While apigenin showed a slightly lower mean paw thickness (2.71 ± 0.194 mm) compared to indomethacin (2.77 ± 0.18 mm), the small difference suggests that their effects are quite similar.

These results supported the anti-inflammatory potential of apigenin, which has been previously reported to modulate the production of inflammatory mediators. (36) used carrageenan-induced paw edema to measure the anti-inflammatory effect of apigenin (50 mg/kg BW as isolated from red alga *Acanthophora spicifera* collected from Al-Shoaiba coast, Red Sea, Saudi Arabia). Mice orally treated with this compound inhibited the synthesis of prostaglandin, bradykinin, histamine, and serotonin, five

important factors in the inflammatory process. Furthermore, apigenin's impact on cellular processes, including the inhibition of mucopolysaccharide and collagen production by fibroblasts, underscores its therapeutic potential in acute inflammatory conditions (54). In light of these results, it appears that both apigenin and indomethacin demonstrate efficacy in reducing acute inflammatory responses, as observed in the carrageenan-induced paw edema experiments. This suggests their potential utility in addressing inflammatory conditions.

Differential WBCs Count

To our knowledge, this is the first investigation to examine the impact of *P. oleracea* L.-sourced apigenin on WBC differential count in the carrageenan-induced paw edema model. WBC count changes can be used as an indicator of the inflammatory state (55). Different cell types of WBC, including lymphocytes, monocytes, neutrophils, eosinophils, and basophils, play definite roles in immune response (55). Cell numbers and ratio fluctuations reveal inflammation intensity and nature (50). Compared to the negative control group, the carrageenan-treated group showed statistically significant ($P < 0.01$) increases in the percentages of lymphocytes, monocytes, eosinophils, and basophils (Table 1), suggesting a significant inflammatory response. Additionally, a marked decrease ($P < 0.01$) in neutrophils was observed in the carrageenan group compared to the control, suggesting a transition from acute to chronic inflammation. Groups treated with apigenin, and indomethacin showed a significant reduction ($P < 0.01$) in lymphocytes, monocytes, eosinophils, and basophils, hinting at diminished inflammation.

Table 1. Anti-inflammatory effect of apigenin obtained from ethanolic extract of *Portulaca oleracea* on differential WBCs (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) in male mice in comparison with indomethacin

Groups	Lymphocytes	Monocytes	Neutrophils	Eosinophils	Basophils
Negative Control	22.2 ± 0.614 ^c	3.33 ± 0.201 ^{bc}	73.5 ± 0.515 ^a	0.22 ± 0.007 ^c	0.14 ± 0.001 ^b
Positive Control	24.7 ± 0.327 ^b	4.92 ± 0.359 ^a	69.4 ± 0.496 ^b	0.73 ± 0.015 ^a	0.28 ± 0.034 ^a
Apigenin	28.4 ± 0.399 ^a	2.97 ± 0.123 ^c	68.1 ± 0.404 ^b	0.49 ± 0.047 ^b	0.03 ± 0.003 ^c
Indomethacin	25.9 ± 0.641 ^b	3.99 ± 0.487 ^{ab}	69.5 ± 0.471 ^b	0.43 ± 0.038 ^b	0.210 ± 0.04 ^{ab}
P-value	<0.001	0.002	<0.001	<0.001	<0.001

Values are means ± SEM, n=7. Means in a row without a common superscript, small letters and capital letters in the same column differ ($P < 0.05$). Negative Control treated orally with distilled water; Positive Control received 50 μ L intra-dermally 1% carrageenan only in the right hindpaw and received no treatment; Apigenin, received 50 μ L intra-dermally 1% carrageenan and treated after 30 min with apigenin at a dose of 50 mg/kg BW orally; Indomethacin, received 50 μ L intra-dermally 1% carrageenan and treated after 30 min with Indomethacin at a dose of 0.36 mg/kg BW orally

Nonetheless, the neutrophil percentages remained largely unchanged across all groups. The apigenin group presented the lowest basophil percentage ($0.03 \pm 0.003\%$), which is key in allergic responses, hinting at apigenin's potential anti-allergic capabilities. Apigenin is reported to modulate basophil functions in allergic reactions by hindering IL-4 and IL-13 production from activated basophils (56) and suppressing Fc ϵ RI α expression on basophils, essential for histamine and other inflammatory mediators' release (57). The indomethacin group, however, displayed a high neutrophil percentage ($69.5 \pm 0.471\%$), suggesting an immunostimulatory effect, as neutrophils are crucial in phagocytosis and bacterial elimination

Apigenin is recognized for its anti-inflammatory, antioxidative, and anticancer properties. It modulates WBC function, impacting various cell signaling pathways. The findings of this study align with previous research on apigenin's influence on WBC differential counts in various inflammation models like LPS-induced sepsis, DSS-induced colitis (58), allergic rhinitis (59), ulcerative colitis (60) (58), and acute lung injury (61). These studies demonstrated apigenin's capacity to reduce lymphocytes, monocytes,

neutrophils, eosinophils, and basophils, linked with chronic and allergic inflammation, and increase acute and bacterial inflammation-involved cells. Apigenin also inhibited pro-inflammatory cytokines (like IL-6, IL-1 β , and TNF- α) while enhancing anti-inflammatory cytokines (IL-4, IL-10, and TGF- β) production (62-63).

Serum IL-6 and PGE-2

Serum concentrations of IL-6 and PGE-2 serve as key indicators of the body's inflammatory condition. IL-6, a cytokine with pro-inflammatory attributes, is produced by cells such as monocytes, macrophages, lymphocytes, and fibroblasts in response to inflammatory triggers. It plays a role in stimulating acute phase proteins like C-reactive protein (CRP) and is implicated in fever and pain mechanisms (64). PGE-2, synthesized from arachidonic acid by COX-2, is a pro-inflammatory prostaglandin known to increase vascular permeability, sensitize pain receptors, and activate immune cells (65). The serum levels of IL-6 and PGE-2 mirror the intensity and persistence of inflammation (50).

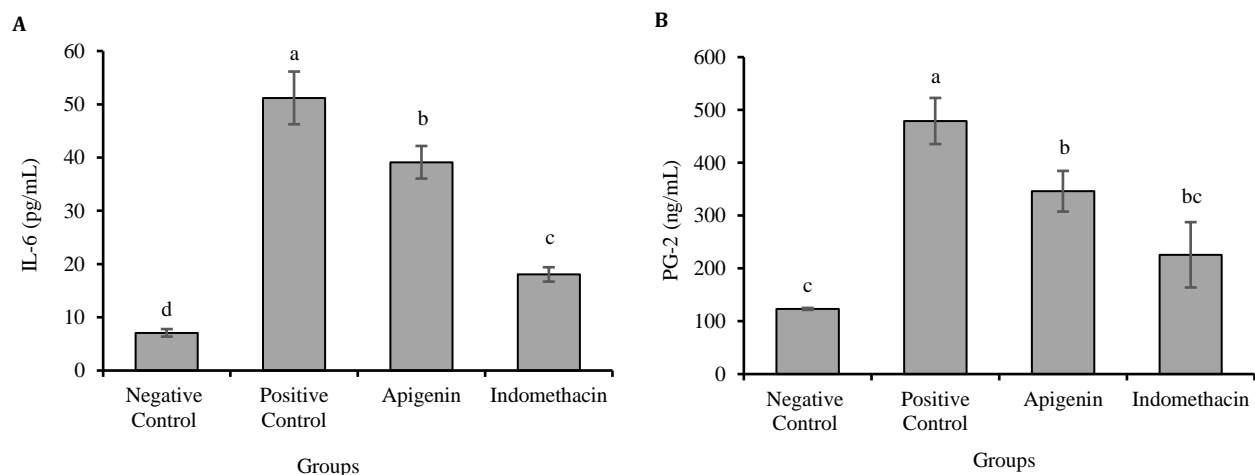


Figure 4. The anti-inflammatory effect of apigenin obtained from ethanolic extract of *Portulaca oleracea* on serum levels of (A) interleukin 6 (IL-6) and (B) prostaglandin E-2 (PGE-2) in male mice in comparison with indomethacin. Bars (means) with different letters are statistically significant ($P \leq 0.05$). Error bars represent the standard error of mean (SEM), n = 7 per treatment group

According to Figure 4, significant variances ($P < 0.001$) were noted in serum IL-6 and PGE-2 levels among different groups. The positive control group displayed a notable

elevation ($P < 0.001$) in IL-6 and PGE-2 levels compared to the negative control, signaling severe inflammation. Specifically, the highest levels were seen in the positive

control group with IL-6 at 51.2 ± 4.95 pg/mL and PGE-2 at 479 ± 43.6 ng/mL, while the negative control exhibited the lowest at 7.08 ± 0.712 pg/mL for IL-6 and 123 ± 1.86 ng/mL for PGE-2. Both apigenin and indomethacin groups showed a significant reduction ($P < 0.001$) in IL-6 and PGE-2 levels compared to the positive control, indicating decreased inflammation. The apigenin group had the lowest IL-6 (18.1 ± 1.36 pg/mL) and PGE-2 (162 ± 11.4 ng/mL) levels, whereas the indomethacin group had intermediate levels (IL-6: 39.1 ± 3.06 pg/mL, PGE-2: 346 ± 38.5 ng/mL).

Prior studies corroborated these findings regarding the impact of apigenin on IL-6 and PGE-2 levels (46) highlighted apigenin's ability to hinder the expression of proinflammatory cytokines by deactivating nuclear factor-kappa beta (NF- κ B) via the suppression of transcription factor p65 phosphorylation (47) further reinforced these findings, demonstrating apigenin's anti-inflammatory effects in human periodontal ligament cells stimulated by nicotine and lipopolysaccharide, as it inhibited the production of NO, PGE-2, IL-1 β , TNF- α , IL-6, and IL-12. Mushtaq et al. (42) delved deeper into apigenin's mechanism, elucidating how it suppresses a range of proinflammatory cytokine secretions, including TNF- α , IL-1 β , IL-6, and IL-10, and blocks nitric oxide-mediated cyclooxygenase-2 expression and monocyte attachment, vital in inflammatory responses. These effects, observed in microglial and macrophage mouse cells, highlight apigenin's extensive anti-inflammatory capabilities. Furthermore (66) noted apigenin's role in modulating the expression and activity of enzymes and proteins associated with oxidative stress, apoptosis, autophagy, and metabolism, such as heme oxygenase-1 (HO-1), COX-2, inducible nitric oxide synthase (iNOS), Nrf2, PPAR- γ , and AMPK. This multifaceted approach positions apigenin as a notable compound for further investigation in anti-inflammatory therapeutics. Findings from the current study, supported by the broader scientific literature, underscore apigenin's significant anti-inflammatory potential. Its effectiveness, comparable to established drugs like indomethacin and its influence on various inflammatory pathways makes it a promising candidate for future drug development in anti-inflammatory treatments.

Based on the findings from the xylene-induced ear edema, carrageenan-induced paw edema, differential WBC count, and IL-6 and PGE-2 level assessments, it is evident that apigenin obtained from ethanolic extract of *P. oleracea* L. holds significant promise as an anti-inflammatory agent. Not only did apigenin demonstrate comparable efficacy to indomethacin, a well-established anti-inflammatory drug, but it also exhibited a broad spectrum of action affecting both cellular and molecular markers of inflammation. Particularly notable was its ability to modulate immune cell populations, as evidenced by the differential WBC count, and its potent efficacy in acute inflammatory models.

In conclusion, these findings suggest that apigenin could serve as a multifaceted, natural alternative to traditional anti-inflammatory medications. Further research is warranted to explore its full therapeutic potential and mechanisms of action.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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تأثير المضادات الالتهابية للأبيجينين الذي تم الحصول عليه من البقلة في ذكور الفئران

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الخلاصة

هدفت هذه الدراسة إلى تقييم التأثيرات المحتملة للمضادة للالتهابات للأبيجينين، التي تم الحصول عليها من أوراق البقلة، باستخدام نموذج ذكور الفئران. تم استخدام ٥٦ فأراً ذكراً أمهيق في تجربتين. في التجربة الأولى، اعتمد على وذمة الأذن التي يسببها الزيلين، تم تقسيم ٢٨ ذكراً من الفئران عشوائياً إلى أربع مجموعات (العدد=٧). تلقت مجموعة السيطرة السلبية الماء المقطر، في حين تعرضت مجموعة السيطرة الإيجابية والمجموعات المعالجة بالأبيجينين والإندوميثاسين إلى الزيلين (٠,٠٣ مل يطبق على السطح الأمامي والخلفي لفص الأذن الأيمن) للحث على الالتهاب. بعد ذلك، تلقت المجموعة المعالجة بالأبيجينين عن طريق الفم ٥٠ ملجم/كجم من الأبيجينين في وزن الجسم، وتلقت المجموعة المعالجة بالإندوميثاسين عن طريق الفم ٠,٣٦ ملجم/كجم من الإندوميثاسين في وزن الجسم. تم حساب فرق وزن الأذن كمؤشر على مضاد للالتهابات. بالنسبة للتجربة الثانية، وذمة مخلب مستحثة بالكاراجينان، تم اتباع تصميم تجريبى مماثل، ولكن تم إعطاء الكاراجينان (٥٠ ملجم/كجم من محلول ١٪) داخل الجلد في الكفوف اليمنى. تم استخدام اختلاف سمك جلد المخلب وعدد خلايا الدم البيضاء التفاضلية (WBCs)، جنباً إلى جنب مع القياس الكمي للبروستاجلاندين (PGE-2) و E-2 (PGE-2) والإنترلوكين ٦ (IL-6) في عينات المصل، كمؤشرات على مضادات الالتهاب. أظهرت النتائج أن التعرض للزيلين أدى إلى زيادة كبيرة في وزن الأذن، مما يدل على الالتهاب. على العكس من ذلك، أظهرت المجموعة المعالجة بالأبيجينين انخفاضاً في وزن الأذن مقارنة بمجموعة السيطرة الإيجابية. وبالمثل، أدى إعطاء الكاراجينان إلى زيادة كبيرة في سمك جلد المخلب ومستويات مرتفعة من عدد خلايا الدم البيضاء، PGE-2، و IL-6. خفف علاج الأبيجينين بشكل كبير من هذه العلامات الالتهابية، متفوقاً على الإندوميثاسين في PGE-2 و IL-6. تقدم هذه الدراسة أدلة تدعم إمكانات المستمدة من أبيجينين كعامل فعال مضاد للالتهابات، مما يدل على فعالية مماثلة أو أفضل من إندوميثاسين.

الكلمات المفاحية: أبيجينين، البقلة، مضاد للالتهابات، إندوميثاسين، فئران