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# Comparative evaluation of Immunomodulatory, Antioxidant, and anti-inflammatory Properties in Degla and Homayra Dates Roub

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**Abstract**

**Aims:** This study aimed to comparatively evaluate the immunomodulatory, antioxidant, and anti-inflammatory properties of two Algerian date (*Phoenix dactylifera L.*) varieties: *Degla* and *Homayra*.

**Methods:** Acute toxicity was assessed using the up-and-down method. The immunomodulatory effect was evaluated via the carbon clearance test in mice. Antioxidant activity was measured by quantifying hepatic glutathione (GSH) levels. Anti-inflammatory activity was determined using the formalin-induced paw edema model.

**Results:** Both date varieties showed no signs of toxicity or mortality at 2000 mg/kg. Significant enhancement of phagocytic activity was observed in treated mice (P = 0.011). The carbon elimination speed was considerably increased at 100 mg/kg for *Degla* (0.0733±0.031) and at 150 mg/kg for *Homayra* (0.076±0.019) compared to the NaCl control (0.029±0.012). Antioxidant activity, indicated by GSH levels, was highest at 100 mg/kg (*Degla*) and 150 mg/kg (*Homayra*) (P = 0.000). Notable anti-inflammatory effects were demonstrated by a significant reduction in paw edema after one week of treatment (P = 0.000).

**Conclusion:** The findings indicate that the Degla and Homayra varieties of *Phoenix dactylifera* exhibit notable immunostimulant, free radical–scavenging, and inflammation-reducing activities, highlighting their potential as candidates for the formulation of natural therapeutic remedies.

**Keywords:** inflammation, GSH, Immune-modulatory, date fruit, Toxicity.

## 1. Introduction

Since ancient times, people have utilized plants as medicine, and this practice continues now. Originally, plants with therapeutic properties were discovered by trial and error, whether for the purpose of curing ailments or just feeling better. Through generations, the application of these herbs has been refined to the point where it is today recognized as traditional medicine in numerous circumstances **(**Salmerón-Manzano *et al*., 2020). By acting as immunomodulatory agents and modifying the immune system, medicinal plants have a significant impact on preventing a variety of diseases and harmful microbes in humans. Plant-based immunomodulatory agents, low-molecular-weight substances like terpenes, phenols, alkaloids, and other nitrogen-containing chemicals, and high-molecular-weight substances like lectins and polysaccharides are commonly employed to modify the immune system **(**Parbat *et al*., 2021). These organic compounds serve a range of biological purposes and are created via secondary metabolism. Among several of these roles, antioxidant and anti-inflammatory qualities are particularly prominent **(**Nunes *et al*., 2020).

Inflammation takes place when the body reacts to infection and damaging external stimuli. Acute inflammation typically goes away on its own and aids in the immune system's reaction to damage. On the other hand, prolonged inflammation led to the overproduction of inflammatory factors, which in turn triggered the cardiovascular system and other inflammatory disorders, such as gouty arthritis, cancer, and chronic gastritis. These inflammatory factors included nitric oxide (NO), tumor necrosis factor α (TNF-α), and cyclooxygenase 2 (COX-2). Diclofenac, aspirin, and ibuprofen are currently the anti-inflammatory medications that are prescribed the most frequently; however, they are frequently associated with side effects and allergic reactions **(**Lu *et al*., 2022).

Usually referred to as the date palm, *Phoenix dactylifera L*. is a significant plant in North Africa and Southwest Asia**.** Since the 20th century, date fruit production has grown dramatically on a global scale; in 2020, it is predicted to reach a value of fourteen billion US dollar **(**Alkhoori *et al*., 2022).With about 930 thousand tons and more than 900 varieties of dates produced annually, Algeria is the third-largest date producer worldwide. Algeria is a large country that grows several different types of dates, such as mech degla, delget nour,

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and degla beida **(**Chergui *et al*., 2021). *Phoenix dactylifera* is a monocotyledonous plant and part of the Arecaceae family. Its species name, phoenix, is derived from the Greek word for purple, while dactylifera translates to "finger-bearing." **(**Oluyele *et al*., 2021). In Algeria, date fruit is widely recognized for its numerous traditional medicinal applications, particularly for nursing mothers who utilize it to increase milk production, treating hair loss and anemia, and speeding up the broken bones healing process. Date fruit is used in traditional medicine all across the world to treat a variety of ailments, such as neurological diseases, and memory issues **(**Sedighi-Khavidak *et al*., 2022). Fresh and dried dates are an integral part of Algerian diets, consumed in a variety of ways, and play an important role in culinary art. Dates are especially important during Ramadan as they are used for breaking the fast, which aligns with religious traditions (Bouguedoura *et al*., 2015). Dates palms serve as an important component of oasis agro-ecosystems, as they help form a microclimate that allows different crops and fruit trees, cereals, and vegetables to thrive. The shade provided by the canopy of date palms protects the soil from evaporation and increases the temperature of the soil that nurtures the crops planted underneath. This stratified plantation pattern maximizes the use of land in these arid regions and is efficient enough for sustainability. Furthermore, date palm cultivation in extreme conditions encourages sustainable agriculture, desertification combat, and hence creates prospects for the rural economies. Indeed, date palms play an important role in the preservation of the environment since they are resilient enough to survive desert conditions (Alotaibi *et al*., 2023; Dhawi and Aleidan, 2024).

In addition to its nutritional and socioeconomic significance, *Phoenix dactylifera L*. has been the focus of numerous scientific investigations highlighting its diverse medicinal properties. Several studies have demonstrated that different parts of the plant—particularly the fruit—exhibit significant antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, and immunomodulatory activities (Al-Snafi and Thuwaini, 2023; Mostafa, 2024; Ahmed and Ali Boutlelis, 2024). Despite these findings, there remains a lack of comparative studies on the bioactivity of specific local varieties, particularly in Algeria, where different ecotypes like Degla and Homayra are traditionally used but scientifically underexplored.

To address this gap, the objective of the present study was to comparatively evaluate (*in vivo* and *in vitro*) the immunomodulatory, antioxidant, and anti-inflammatory effects of the Algerian *Phoenix dactylifera L*. varieties, Degla and Homayra.

## 2. Materials & methods

### *2.1. Plant material*

Date fruits (*Phoenix dactylifera*) of the degla and homayra varieties were picked during the ripening stage from Biskra and Adrar, respectively, to make a date syrup, or "Roub" as it is known in the Algerian local culture. The plant materials used in this study were authenticated as local varieties based on their morphological characteristics and geographical origin. These varieties are well known and widely cultivated in their respective regions, and their identification was confirmed by local agricultural experts.

### *2.2. Roub's Preparations*

The Roub, traditional Algerian date syrup, was prepared using an Algerian conventional method. First, 3 Kg of dates (for each variety) were washed. Then, a large container half-filled with water (twice the dates weight) was warmed to a medium heat (55–65 °C) and left to boil for approximately 90 minutes. Once softened, the fruits were crushed, with the seeds detached, to create a smooth mush, which was then filtered to extract the maximum amount of juice. The extracted juice underwent another heating process at around 65 °C to vaporize extra water, decreasing it to about 1000 g of a dense liquid similar to syrup. Finally, the date's syrup (Roub) was left to reach room temperature before being kept in a sanitized glass container and reserved in a heated, dim place for preservation.

Three doses for each variety (D1DG (100 mg/kg), D2DG (150 mg/kg), and D3DG (200 mg/kg) for the degla variety, and D1HM (50 mg/kg), D2HM (150 mg/kg), and D3DHM (200 mg/kg) for the homayra variety) were utilized in this investigation, and they were made by dissolving the Roub in 10 ml of sodium chloride (NaCl 0.9%).

### *2.3. Animal husbandry*

In this study, adult *Mus musculus* mice weighing between 20 and 30 g and aged between 60 and 75 days were used. The mice were obtained from the central pharmacy of Algeria and housed in polyacrylic cages in regular conditions, which included a cooled room with a 12-hour light and dark cycle. Before the testing started, the animals spent a week acclimating and had unrestricted access to food and drink in the form of dry pellets.

### *2.4. Ethics statement*

The technique for carrying out the animal exploration was based on the research project code (F00920140076), which was acquired from the Ministry of Higher Education and Scientific Research in Algeria. The studies were conducted in accordance with the OECD's ethical rules and principles for overseeing and monitoring animal research (OECD Test No. 420, 2002). All efforts were taken to minimize pain to the animal during experimentation.

### *2.5. Up and down test*

The acute toxicity assessment was conducted using the "Up-and-Down" method, also known as the acute toxicity test (Ezeh *et al*., 2021). Five healthy adult male mice were each administered a high dose of 2000 mg/kg of Roub (from each variety). The mice were weighed the night before treatment, deprived of food, but allowed free access to water. Roub was then administered orally to each mouse. The first mouse received a dose of 2000 mg/kg and was closely observed during the first 60 minutes, then monitored every hour for the next three hours, and intermittently over the following two days for clinical symptoms and mortality. Observations included signs such as unusual aggression, drowsiness, abnormal vocalization, restlessness, and lethargy. If the first mouse survived, four additional mice were given the same maximum dose at two-day intervals. After two weeks of careful observation, the mice were released, and the total number of fatalities

was recorded. If at least three mice survived, the median lethal dose (LD50) was considered to be greater than the maximum dose tested.

*2.6. Phagocytic activity*

Phagocytic activity was assessed by measuring the rate at which the mononuclear phagocyte system cleared carbon from the bloodstream, using a carbon clearance test (Slimani *et al*., 2020). This activity is quantified by three indices: the phagocytic index (K), which reflects the overall function of the mononuclear phagocyte system in its interaction with the blood; the corrected phagocytic index (α), which evaluates this activity relative to the combined weight of the animal's liver and spleen; and the half-life period (T½), representing the time required for the phagocytic system to eliminate carbon from the blood.

The mice were divided into seven groups, as shown in Table 1. Three groups received different doses of *Phoenix dactylifera* (degla variety): D1DG (100 mg/kg), D2DG (150 mg/kg), and D3DG (200 mg/kg). Another three groups received corresponding doses of Phoenix dactylifera (homayra variety): D1HM (100 mg/kg), D2HM (150 mg/kg), and D3HM (200 mg/kg). The control group received 0.5 ml/mouse of 0.9% NaCl solution.

**Table 1.** Animal grouping in the phagocytic activity test

| Phoenix dactylifera varieties | | | | | | Control group |
|---|---|---|---|---|---|---|
| Degla variety | | | Homayra variety | | | |
| **D1DG** | **D2DG** | **D3DG** | **D1HM** | **D2HM** | **D3HM** | 0.5 ml/mouse of NaCl (0.9%) |
| 100 mg/kg | 150 mg/kg | 200 mg/kg | 100 mg/kg | 150 mg/kg | 200 mg/kg | |

**PD1/PD2:** Photographic Densities measured at 5 minutes and 15 minutes, correspondingly.

**K:** Phagocytic index.

The medication was administered via intraperitoneal injection (i.p.). Two days after the injection, each mouse received an injection of an antigenic solution (0.1 ml per 10 g of body weight) through the tail vein. The antigenic solution was composed of carbon ink (3 ml), 3% gelatin solution (4 ml), and saline (4 ml). Blood samples (approximately 15 drops) were collected at five and fifteen minutes after the antigenic solution was administered, and each sample was lysed in four milliliters of 0.1% $Na_2CO_3$ solution. The photometric density (PD) was then measured at 675 nm.

The parameters for evaluating phagocytosis efficiency were calculated using the following equations:

$$K = \frac{LOG\,PD1 - LOG\,PD2}{15 - 5} \qquad T^{1}/_{2} = \frac{0.693}{K}$$

$$\alpha = \sqrt[3]{K}\,\frac{Body\ weight\ of\ the\ animal}{liver\ weight\ +\ spleen\ weight}$$

*2.7. Hepatic GSH test*

By measuring hepatic glutathione (GSH) spectrophotometrically with the DTNB (5,5-dithio-bis-(acide 2-nitrobenzoïque) reagent (Vuolo *et al*., 2022), the anti-oxidant impact was evaluated.

*2.8. Formalin-induced paw edema test*

The formalin-induced paw edema test in mice was performed to evaluate the anti-inflammatory effects of *Phoenix dactylifera* Roub *in vivo*. The progression of inflammation was monitored by measuring paw edema with a digital caliper. After a one-week acclimatization period, the mice were divided into five groups:

- Negative Control (C-): Received only flour treatment.
- Positive Control (C+): Treated with 2% formalin (0.05 ml).
- DG Group: Administered 100 mg/kg of *Phoenix dactylifera* (Degla variety).
- HM Group: Administered 150 mg/kg of *Phoenix dactylifera* (Homayra variety).
- DEC Group: Received 10 mg/kg of Diclofenac sodium (50 mg).

All treatments were given orally for seven consecutive days.

*2.9. Histological study of the mice inflamed paw*

The histological examination of the inflamed mouse paw was performed according to the hematoxylin and eosin staining protocol described by Fischer *et al*., (2008).

*2.10. Statistical data analysis*

Tukey's multiple comparison test and one-way ANOVA were used to analyze differences between groups during the dietary treatments (IBM SPSS version 20). P-values less than 0.05 were considered statistically significant.

## 3. Results

*3.1. Up and down test*

The results offered in Table 2 show that, in the acute toxicity test, administering a 2000 mg/kg dose of both *Phoenix dactylifera* varieties did not result in any deaths or apparent marks of toxicity. Five adult male mice received the same Roub orally at this dose and were monitored for two weeks. By the end of the observation period, all five mice survived.

**Table 2.** Toxic effect of *Phoenix dactylifera* varieties

| Limit dose | | Signs of toxicity (2 weeks) | | Signs of mortality (2 weeks) | | Number of mice survived during (2 weeks) | |
|---|---|---|---|---|---|---|---|
| DG | HM | DG | HM | DG | HM | DG | HM |
| 2000 mg/kg | | No toxicity | | No mortality | | all mice | |

**DG:** degla variety; **HM:** homayra variety

*3.2. The Phoenix dactylifera immunomodulatory activity*

*3.2.1. Phagocytic index K*

In Figure 1, the results indicate a statistically important difference in the (K) values between the experimental groups (P = 0.011). Furthermore, the findings indicate that

*Phoenix dactylifera* at the D2HM and D1DG has the highest K (K D2HM = 0.076 ± 0.019, K D1DG= 0.073 ± 0.031) compared to the control (K NaCl = 0.029 ± 0.012) and the other treated groups D1HM (K = 0.06 ± 0.025), D3HM (K = 0.048 ± 0.0148), D2DG (K = 0.053 ± 0.016), D3DG (K = 0.041 ± 0.013).

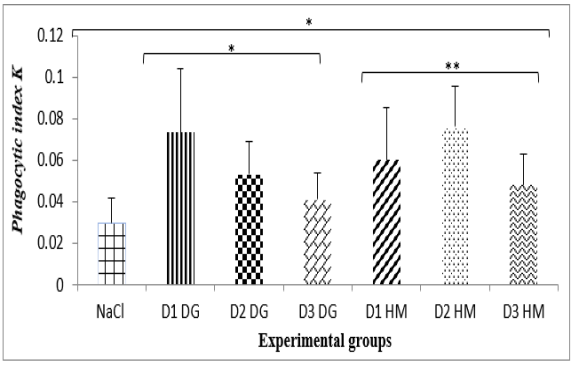


**Figure 1**. Impact of different *Phoenix dactylifera* varieties on (K).

Data are Mean ± Standard Deviation (n=5), with significant deviations from the NaCl group as *P<0.05, **P<0.01, ***P<0.001

NaCl: Control; D1DG D2DG D3DG: (100, 150, 200) mg/kg of *P. dactylifera* (degla variety); D1HM, D2HM, D3HM: (100, 150, 200/kg) mg/kg of *P. dactylifera* (homayra variety)

*3.2.2. Carbon clearance time (T½)*

Findings in Figure 2 expose a highly significant reduction in carbon clearance period among the groups (P = 0.002). In addition to that, the results show that the carbon clearance was quicker in the group treated with D2HM (T½ = 9.788 ± 2.596 min) and D1DG (T½ = 10.517 min ± 3.23) compared to the other treated groups: D3HM (T½ = 16.652 ± 4.946 min); D1HM (t½ = 13.586 ± 4.964 min); D2DG (T½ = 14.006 min ± 3.7); D3DG (T½ = 18.43 min ± 6.24), and the control NaCl (T½ = 27.179 min ± 12.05).

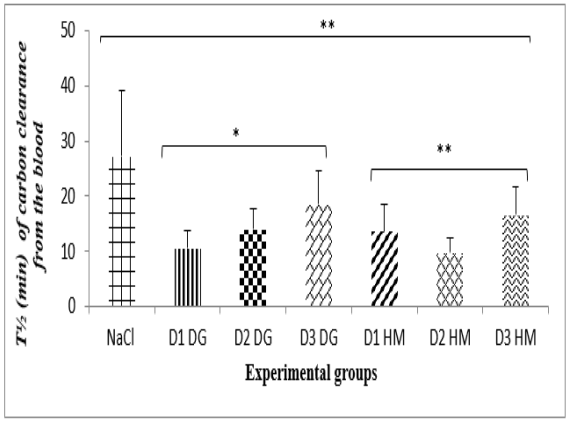


**Figure 2.** Impact of different *Phoenix dactylifera* varieties on the (T½)

Data are Mean ± Standard Deviation (n=5), with significant deviations from the NaCl group as *P<0.05, **P<0.01, ***P<0.001

NaCl: Control; D1DG D2DG D3DG: (100, 150, 200) mg/kg of *P. dactylifera* (degla variety); D1HM, D2HM, D3HM: (100, 150, 200/kg) mg/kg of *P. dactylifera* (homayra variety)

*3.2.3. Corrected phagocytic index*

The findings presented in Figure 3 reveal a statistically significant dissimilarity (P = 0.000) among the treated groups. The corrected phagocytic index α of the groups treated with the homayra variety (D1HM = 6.126 ± 0.616; D2HM = 7.172 ±0.731; D3HM = 6.128 ±0.418; P = 0.000) was considerably greater than that of the degla variety (D1DG = 4.406 ± 0.65; D2DG = 3.518 ± 0.66); D3DG (3.107± 1.23) P = 0.016.

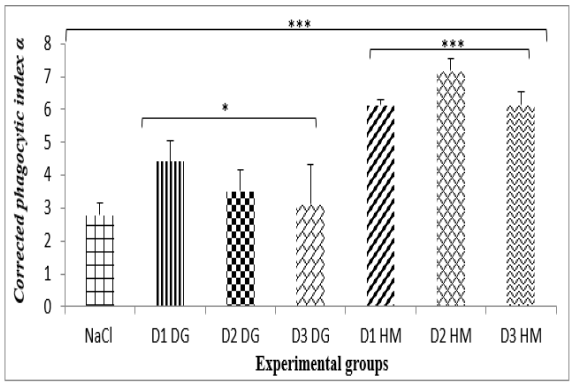


**Figure 3.** Impact of different *Phoenix dactylifera* varieties on α.

Data are Mean ± Standard Deviation (n=5), with significant deviations from the NaCl group as *P<0.05, **P<0.01, ***P<0.001

NaCl: Control; D1DG D2DG D3DG: (100, 150, 200) mg/kg of *P. dactylifera* (degla variety); D1HM, D2HM, D3HM: (100, 150, 200/kg) mg/kg of *P. dactylifera* (homayra variety)

*3.3. The Phoenix dactylifera antioxidant activity*

Figure 4 results demonstrate that there is a significant difference (P = 0.000) in the glutathione values between the treated groups with both varieties of *Phoenix dactylifera*. Glutathione values were significantly higher in the groups treated with the homayra variety (D2HM = 1.57 nmol/mg ± 0.128; D1HM = 1.652 nmol/mg ± 0.386; D3HM = 1.83 nmol/mg ± 0.088; P = 0.000) than the NaCl group (0.000235 nmol/mg ± 9.5154E$^{-05}$) and the groups treated with the degla variety (D1DG = 0.039 nmol/mg ± 0.003; D2DG = 0.0160 nmol/mg ± 0,001; D3DG = 0.0010 nmol/mg ± 0.0006) P = 0.035.

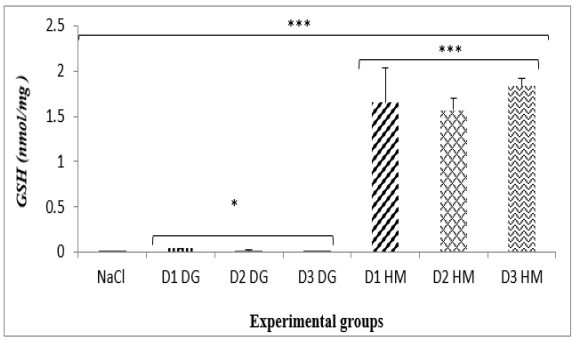


**Figure 4**. Impact of different *Phoenix dactylifera* varieties on hepatic glutathione.

Data are Mean ± Standard Deviation (n=5), with significant deviations from the NaCl group as *P<0.05, **P<0.01, ***P<0.001

NaCl: Control; D1DG D2DG D3DG: (100, 150, 200) mg/kg of *P. dactylifera* (degla variety); D1HM, D2HM, D3HM: (100, 150, 200/kg) mg/kg of *P. dactylifera* (homayra variety)

### 3.4. The Phoenix dactylifera anti-inflammatory activity

Results in Figure 5 demonstrate a greatly significant dissimilarities in edema size among the groups over the seven-day experiment (P = 0.000). This reduction in edema size was evident from the difference in diameters between inflamed and non-inflamed paws treated with both *Phoenix dactylifera* varieties (HM and DG) as well as Diclofenac (DEC). Moreover, a substantial decrease in edema size was observed in the HM, DG, and DEC groups from the fourth day of inflammation until the seventh day, when it reached its lowest level:

DG: Day 4 (3.34 mm ± 0.281), Day 7 (3.245 mm ± 0.310), P = 0.035

HM: Day 4 (3.52 mm ± 0.157), Day 7 (3.29 mm ± 0.235), P = 0.000

DEC: Day 4 (3.02 mm ± 0.164), Day 7 (2.74 mm ± 0.065), P = 0.000

Conversely, the C+ group exhibited significantly larger edema compared to the control and other treated groups: C+: Day 4 (4.35 mm ± 0.42), Day 7 (3.76 mm ± 0.58), P = 0.000.

These findings suggest that treatment with *Phoenix dactylifera* varieties and Diclofenac effectively reduced edema size over time.

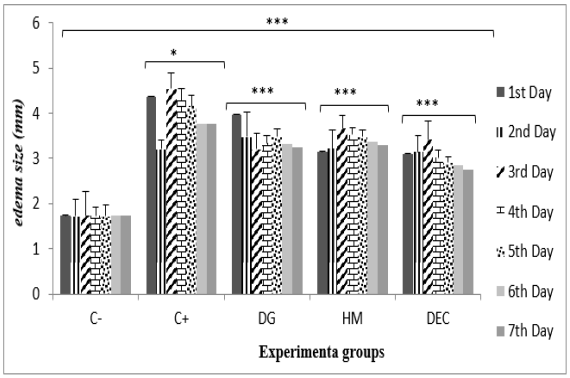


**Figure 5:** Impact of different *Phoenix dactylifera* varieties on the edema size.

Data are Mean ± Standard Deviation (n=5), with significant deviations from the NaCl group as *P<0.05, **P<0.01, ***P<0.001

C-: Negative Control; C+: Positive Control; DG: 100 mg/kg of *P. dactylifera* Degla variety;

HM: 150 mg/kg of *P. dactylifera* Homayra variety; DEC: 10 mg/kg of Diclofenac sodium (50 mg).

### 3.5. The histology study

Figures 6A and 6B illustrate cellular desquamation of the synovial membrane and paw degeneration in the (C+) group, which received a subplantar injection of formalin. In contrast, the normal (C-) group exhibited an intact paw structure, with clearly visible joint components, including calcified cartilage, spongy bone, and hyaline cartilage.

Figures 6C and 6D display histological sections of the joint paw treated with *Phoenix dactylifera* (Degla and Homayra varieties). These sections revealed intact articular cartilage with a preserved articular surface. Similarly, the Diclofenac sodium-treated group showed intact hyaline cartilage with no signs of erosion on the articular surface (Figure 6E).

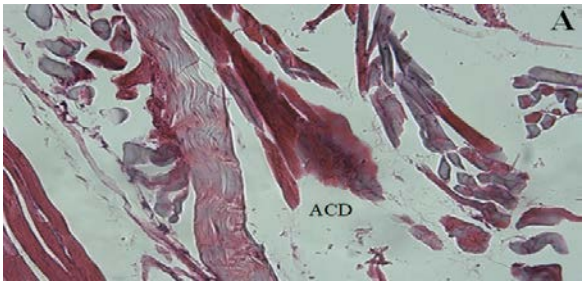


**Figure 6A**: Histological section of a mouse paw following seven days of inflammation in the C+ group, stained with H&E (X100).

ACD: Articular Cartilage Degenerated

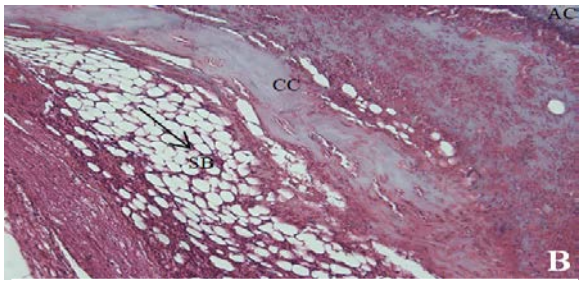


**Figure 6B**: Histological section of a mouse paw following seven days of inflammation in the (C-) group stained with H&E (X100).

AC: Articular Cartilage; CC: Calcified Cartilage; SB: Spongy Bone.

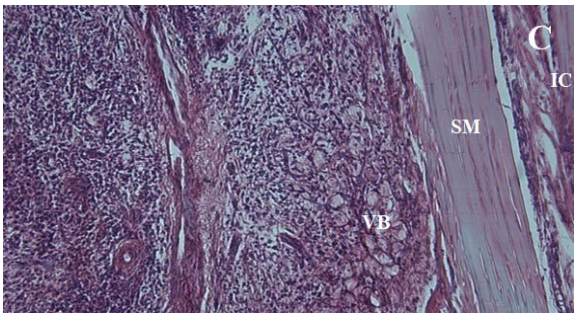


**Figure 6C:** Histological section of a mouse paw following seven days of inflammation in the (DG) group stained with H&E (X100).

IC: Intact cartilage; SM: Synovial Membrane;

VB: Vascularized Bone

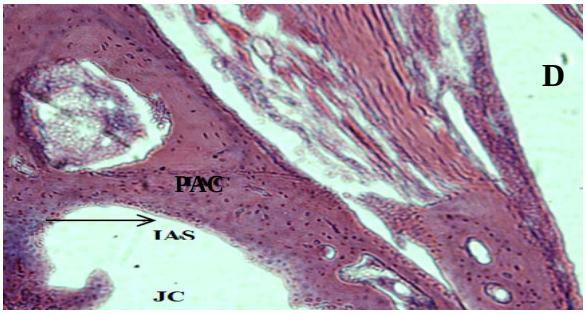


**Figure 6D:** Histological section of a mouse paw following seven days of inflammation in the (HM) group stained with H&E (X100).

PAC: Preserved Articular Cartilage; **IAS:** Intact Articular Surface; JC: Joint's Cavity.

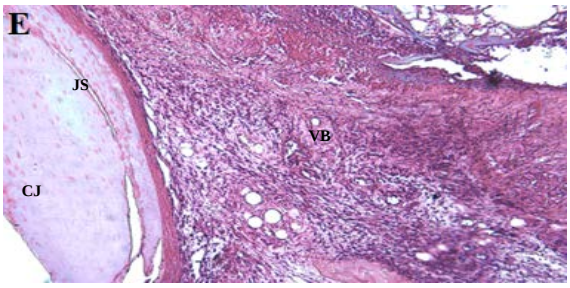


**Figure 6E:** Histological section of a mouse paw following seven days of inflammation in the (DEC) group stained with H&E (X100).

CJ: Cavity of the Joint; JS: Joint Surface; VB: Vascularized Bone

## 4. Discussion

Therapeutic plants and their derivatives have been found to influence both humoral and innate responses by engaging with the immunoregulatory cascade and modifying immune cell multiplication, phagocytic activity, toxicity function, and the expression of cytokines, cellular co-receptors, and immunoglobulins (Alanazi *et al*., 2023, Shen *et al*., 2023). The study aimed to comparatively evaluate the immunomodulatory, antioxidant, and anti-inflammatory properties of Algerian date (*Phoenix dactylifera*) varieties, degla and homayra.

To assess the impact of date Roub on the mononuclear phagocyte system (a network of cells specialized in phagocytosis), a test for carbon elimination was executed. Upon the direct injection of carbon elements (the ink) into the systemic circulation, macrophages and other phagocytic cells initiate the process of clearing carbon from the blood.

The doses of *Phoenix dactylifera* varieties used in the treatment groups influenced the immune system by

stimulating the phagocytic system to accelerate carbon clearance from the blood and affecting liver GSH levels. The most significant effect was observed at 100 mg/kg for the Degla variety and 150 mg/kg for the Homayra variety. These findings show similarities with those of Oriade *et al*. (2021) who reported that the immunological responses of the groups fed with 0.5 and 2.0% date revealed noticeably higher levels of antibody and phagocytic activity, respectively. Furthermore, the results agree with the study of Merza Mahmood *et al.* (2016) The study examined the immunomodulatory effects of date fruit water extract in mice, revealing an increase in the amount of IFN-γ, CD4 (cluster of differentiation), CD49b, IL-12, and CD11b cells compared to normal after treatment. Moreover, Ahmad Mohd Zain *et al*. (2022) highlight the date palm's many health advantages, including how it strengthened the immune system during the COVID-19 epidemic.

Substances that can activate the immune system's innate or adaptive arms are known as immunostimulants. Pharmaceutical companies release a lot of synthetic immunostimulants, but they have a lot of adverse effects (Alhazmi *et al*., 2021, Wang *et al*., 2024). On the other hand, As a result of containing components such as polysaccharides, lectins, saponins, and flavonoids, among others, certain plant products are thought to strengthen the body's innate defense against infection. While some of these merely engage the immune system's cellular components, others promote both humoral and cell mediated immunity (Santiago *et al*., 2021).

The results also show that, the Roub of *Phoenix dactylifera* (degla and homayra varieties) is capable of improving antioxidant activity by increasing hepatic GSH levels. These results show some similarities with the results of Saryono *et al*. (2019). The study revealed that when 5 g/kg of steeped date seeds are administered, TNF-α is decreased while GSH and IFN-γ are increased. In addition to that, the results also agree with those of Roshankhah *et al*. (2020) who indicated that by strengthening the liver's antioxidant defenses, Middle Eastern *Phoenix dactylifera* can lessen the negative structural alterations and oxidative stress caused by mercury in the testis. According to Gad El-Hak *et al*. (2022), date palm extracts, such as methanolic date flesh extract, can ameliorate hepatic injury induced by toxins like cisplatin and help to restore GSH levels, reduce oxidative stress, and decrease inflammatory biomarkers in the liver.

Results from the last section of the study demonstrated that from the second day until the end of the test, *Phoenix dactylifera* (degla and homayra varieties) greatly decreased formaldehyde-induced edema. The test results may be attributed to the influence of *Phoenix dactylifera* on the release of inflammatory mediators and its potential to act correspondingly to non-steroidal anti-inflammatory drugs in both phases of inflammation. The results agree with Saryono *et al*. (2019) who reported that *Phoenix dactylifera* seeds have anti-inflammatory and immunostimulant properties. As an anti-inflammatory effect, date seed inhibits the formation of edema and IFN-γ and suppresses inflammatory cytokines like IL-6, IL-1, and TNF-α . The study of Bouhlali *et al*. (2020) suggested that *Phoenix dactylifera* seed extracts mediate anti-inflammatory properties through the stabilization of lysosomal membranes, prevention of protein denaturation, and inhibition of fibrinogen formation and C-reactive protein.

It should be noted that many plants' biological effects, including their ability to reduce inflammation and arthritis, have been linked to their triterpene or flavonoid concentrations. Furthermore, it has been shown that a number of flavonoids, including luteolin, quercetin, and rutin, as well as biflavonoids and triterpenoids, including ursolic acid, exhibit notable anti-nociceptive and/or anti-inflammatory properties (Kaushik *et al*., 2021, Sivasakthi *et al*., 2021). From that point of view, *Phoenix dactylifera* is known for its exceptional nutritional and functional properties, being abundant in tannins, phenolics, flavonols, and flavonoids **(**Chenini *et al*., 2021, Harkat *et al*., 2022), proteins, lipids, fibers, vitamins, minerals **(**Alahyane *et al*., 2021, Shahab Uddin and Nuri, 2021), simple carbohydrates, primarily glucose, fructose and other secondary metabolites (Bano *et al*., 2022).

## 5. Conclusion

The present synthetic drug-based therapy method for diseases including diabetes, cancer, and rheumatoid arthritis is costly. Date fruit preparations from Algeria are a cheap and useful treatment. This study demonstrated the beneficial effects of *Phoenix dactylifera* (homayra and degla varieties) on the management of diseases due to its anti-inflammatory properties, anti-oxidant, and immunostimulation qualities, which inspire hope for a novel therapeutic approach. Despite the promising results obtained in this study, several limitations should be acknowledged. First, the investigation was limited to acute in vivo models, and long-term or chronic effects of the extracts were not assessed. Second, while the study demonstrated significant immunomodulatory, antioxidant, and anti-inflammatory activities, the underlying molecular mechanisms and specific bioactive constituents responsible for these effects were not explored. Additionally, the evaluation was conducted solely in animal models, which may not fully replicate the complexity of human biological responses. Therefore, further studies are recommended to isolate and characterize the active phytochemicals in these date varieties, examine their molecular targets and pathways, and assess their efficacy and safety in chronic disease models. Ultimately, clinical trials will be essential to validate their therapeutic potential in humans.

## Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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## Author contributions

Conceptualization: Kehili Houssem Eddine; Methodology: Kehili Houssem Eddine, Zerizer Sakina, Kanouche Zahia; Formal analysis and investigation: Kehili Houssem Eddine, Meriem Mokrane, Samah Sayoud, Amira Teldjoune; Writing - original draft preparation:

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## References


Ahmed G, and Ali Boutlelis D. 2024. Protective and antioxidant capacity of date palm seeds (*Phoenix dactylifera L.*) On hepatotoxicity in rats. *FARMACIA*, **71(2): 303-311**.

Alahyane A, Harrak H, Elateri I, Ayour J, Ait-Oubahou A, and Benichou M. 2021. Evaluation of some nutritional quality criteria of seventeen Moroccan dates varieties and clones, fruits of date palm (*Phoenix dactylifera* L.). *Braz J Biol.*, **82**. http://dx.doi.org/10.1590/1519-6984.236471.

Alanazi HH, Elasbali AM, Alanazi MK, and El Azab EF. 2023. Medicinal herbs: Promising immunomodulators for the treatment of infectious diseases. *Molecules*, **28(24)**. http://dx.doi.org/10.3390/molecules28248045.

Alhazmi HA, Najmi A, Javed SA, Sultana S, Al Bratty M, and Makeen HA. 2021. Medicinal plants and isolated molecules demonstrating immunomodulation activity as potential alternative therapies for viral diseases including COVID-19. *Front Immunol.*, **12(637553)**. http://dx.doi.org/10.3389/fimmu.2021.637553.

Alkhoori MA, Kong AS-Y, Aljaafari MN, Abushelaibi A, Lim S-H, and Cheng W-H. 2022. Biochemical composition and biological activities of date palm (*Phoenix dactylifera* L.) seeds: A review. *Biomolecules*, **12(11)**. http://dx.doi.org/10.3390/biom12111626.

Alotaibi KD, Alharbi HA, Yaish MW, Ahmed I, Alharbi SA, Alotaibi F, and Kuzyakov Y. 2023. Date palm cultivation: A review of soil and environmental conditions and future challenges. *Land Degradation & Development*, **34: 2431–2444**. doi:10.1002/ldr.4619.

Al-Snafi AE, and Thuwaini MM. 2023. *Phoenix dactylifera*: traditional uses, chemical constituents, nutritional benefit and therapeutic effects. *Traditional Medicine Research* ., **8(4): 20**. https://doi.org/10.53388/TMR20221110001.

Bano Y, Rakha A, and Khan M. 2022. Chemical composition and antioxidant activity of date (*Phoenix dactylifera* L.) varieties at various maturity stages. *Food Science and Technology*, **42**.

Bouguedoura N, Bennaceur M, Babahani S, and Benziouche SE. 2015. Date palm status and perspective in Algeria. In *Date Palm Genetic Resources and Utilization*, edited by Al-Khayri JM, Jain SM, and Johnson DV, **125–168**. Dordrecht: Springer Netherlands.

Bouhlali EDT, Hmidani A, Bourkhis B, Khouya T, Ramchoun M, and Filali-Zegzouti Y. 2020. Phenolic profile and anti-inflammatory activity of four Moroccan date (*Phoenix dactylifera* L.) seed varieties. *Heliyon*, **6(2)**: e03436.

Chenini-Bendiab H, Djebli N, Kara Y, Uçar M, and Kolayli S. 2021. An investigation of Algerian dates (*Phoenix dactylifera* L.); antioxidant, anti-inflammatory properties and phenolic compositions. *Emir J Food Agric.*, **33: 629**. http://dx.doi.org/10.9755/ejfa.2021.v33.i8.2737.

Chergui D, Akretche-Kelfat S, Lamoudi L, Al-Rshaidat M, Boudjelal F, and Ait-Amar H. 2021. Optimization of citric acid production by *Aspergillus niger* using two downgraded Algerian date varieties. *Saudi J Biol Sci.*, **28(12)**: 7134–7141. http://dx.doi.org/10.1016/j.sjbs.2021.08.013.

Dhawi F and Aleidan MM. 2024. Oasis agriculture revitalization and carbon sequestration for climate-resilient communities. *Frontiers in Agronomy*, **6**: 1386671. doi:10.3389/fagro.2024.1386671.

Ezeh GC, Udeh NE, Ozioko CA, Onoja SO, Eze RE, and Omeh YN. 2021. Acute and sub-acute toxicity profile of methanol extract of *Hura crepitans* leaf on Wistar rats. *Not Sci Biol.*, **13(2)**: 10939. http://dx.doi.org/10.15835/nsb13210939.

Fischer AH, Jacobson KA, Rose J, and Zeller R. 2008. Hematoxylin and eosin staining of tissue and cell sections. *CSH Protoc.*, **5**. http://dx.doi.org/10.1101/pdb.prot4986.

Gad El-Hak HN, Mahmoud HS, and Ahmed EA. 2022. Methanolic *Phoenix dactylifera* L. extract ameliorates cisplatin-induced hepatic injury in male rats. *Nutrients*, **14(5)**. http://dx.doi.org/10.3390/nu14051025.

Harkat H, Bousba R, and Benincasa C. 2022. Assessment of biochemical composition and antioxidant properties of Algerian date palm (*Phoenix dactylifera* L.) seed oil. *Plants*, **11(3)**: 381. https://doi.org/10.3390/plants11030381.

Kaushik S, Jain P, Satapathy T, Purabiya P, and Roy A. 2021. Evaluation of anti-arthritic and anti-inflammatory activities of *Martynia annua* L. ethanolic extract. *Clin Phytoscience*, **7(1)**. http://dx.doi.org/10.1186/s40816-021-00250-y.

Lu Q, Li R, Yang Y, Zhang Y, Zhao Q, and Li J. 2022. Ingredients with anti-inflammatory effect from medicine food homology plants. *Food Chem.*, **368**: 130610. http://dx.doi.org/10.1016/j.foodchem.2021.130610.

Mahmood M, Ramadan F, and Hassan M. 2016. Therapeutic effect of *Phoenix dactylifera* against cryptosporidiosis in immunocompromised mice. *Global Advanced Research Journal of Medicine and Medical Sciences*, **5(3)**: 88–95.

Mohd Zain A, Kari MR, and Dawood Z. 2022. Bioactivity and pharmacological potential of date palm (*Phoenix dactylifera* L.) against pandemic COVID-19: A comprehensive review. *Appl Biochem Biotechnol.*, **194(10)**: 4587–4624. http://dx.doi.org/10.1007/s12010-022-03952-2.

Mostafa MYA. 2024. Evaluation of Antioxidant, Anti-Inflammatory, and Anticancer Activities of Palm Heart (*Phoenix dactylifera L.*) *In Vitro. J. of Food and Dairy Sci., Mansoura Univ.,* ***Vol. 15 (9):123 – 132.***

Nunes CR, Arantes MB, Pereira SMF, Cruz LL, Passos MS, and Moraes LP. 2020. Plants as sources of anti-inflammatory agents. *Molecules*, **25(16)**: 3726. http://dx.doi.org/10.3390/molecules25163726.

Oluyele O, Oladunmoye MK, and Ogundare AO. 2022. Toxicity studies on essential oil from *Phoenix dactylifera* (L.) seed in Wistar rats. *Biologics*, **2(1)**: 69–80. http://dx.doi.org/10.3390/biologics2010006.

Oriade TO, Alao OS, and Afolayan FID. 2023. Immunostimulatory effect of *Phoenix dactylifera* supplemented diet on *Aeromonas hydrophila* infected *Clarias gariepinus*. *Pan African Journal of Life Sciences*, **15(1)**. http://dx.doi.org/10.36108/pajols/1202/50.0160.

Parbat AY, Malode GP, Shaikh AR, Panchale WA, Manwar JV, and Bakal RL. 2021. Ethnopharmacological review of traditional medicinal plants as immunomodulator. *World J Bio Pharm Health Sci.*, **6(2)**: 43–55. http://dx.doi.org/10.30574/wjbphs.2021.6.2.0048.

Roshankhah S, Abdolmaleki A, and Salahshoor MR. 2020. Anti-inflammatory, anti-apoptotic, and antioxidant actions of Middle Eastern *Phoenix dactylifera* extract on mercury-induced hepatotoxicity in vivo. *Mol Biol Rep.*, **47(8)**: 6053–6065. http://dx.doi.org/10.1007/s11033-020-05680-4.

Salmerón-Manzano E, Garrido-Cardenas JA, and Manzano-Agugliaro F. 2020. Worldwide research trends on medicinal plants. *Int J Environ Res Public Health*, **17(10)**: 3376. http://dx.doi.org/10.3390/ijerph17103376.

Santiago LÂM, Neto RNM, Ataíde ACS, Fonseca DCSC, Soares EFA, and Sousa JCS. 2021. Flavonoids, alkaloids and saponins: Are these plant-derived compounds an alternative to the treatment of rheumatoid arthritis? A literature review. *Clin Phytoscience*, **7**. http://dx.doi.org/10.1186/s40816-021-00291-3.

Saryono S, Dardjito E, Proverawati A, Sumeru A, Setiyani R, and Upoyo AS. 2019. Date seeds (*Phoenix dactylifera* L.) consumption as anti-inflammatory and immunostimulant: A systematic review. *IOP Conf Ser Earth Environ Sci.*, **250**: 012038. http://dx.doi.org/10.1088/1755-1315/250/1/012038.

Saryono S, Taufik A, Proverawati A, and Efendi F. 2019. Dietary supplementation of *Phoenix dactylifera* L. seeds decreases pro-inflammatory mediators in CCl4-induced rats. *J Herbmed Pharmacol*., **8(3)**: 212–217. http://dx.doi.org/10.15171/jhp.2019.31.

Sedighi-Khavidak S, Shekarbeygi N, Delfani M, and Nejad FH. 2022. Nutritional and medicinal values of dates (*Phoenix dactylifera* L.) from the perspective of modern medicine and Iranian traditional medicine. *Complementary Medicine Journal*, **12(1)**: 44–55. https://doi.org/10.32598/cmja.12.1.1101.2.

Shahab Uddin M and Nuri ZN. 2021. Nutritional values and pharmacological importance of date fruit (*Phoenix dactylifera* Linn): A review. *Journal of Current Research in Food Science*, **2(1)**: 27–30.

Shen L, Luo H, and Fan L. 2023. Potential immunoregulatory mechanism of plant saponins: A review. *Molecules*, **29(1)**. http://dx.doi.org/10.3390/molecules29010113.

Sivasakthi P, Priya ES, and Selvan PS. 2021. Molecular insights into phytochemicals exhibiting anti-arthritic activity: Systematic review. *Inflammation Research*, **70**: 665–685. http://dx.doi.org/10.1007/s00011-021-01471-0.

**Slimani W, Zerizer S, and Kabouche Z. 2020. Immunomodulatory and anti-arthritic activities of *Stachys circinata*. *Jordan Journal of Biological Sciences*, 13(2): 183–189.**

Vuolo MM, da Silva-Maia JK, and Batista ÂG. 2022. The GSH colorimetric method as measurement of antioxidant status in serum and rodent tissues. *Methods Protocols Food Sci*., 187–194.

Wang G, Wang Y, and Ma F. 2024. Exploiting bacterial-origin immunostimulants for improved vaccination and immunotherapy: Current insights and future directions. *Cell Biosci.*, **14(1)**: 24. http://dx.doi.org/10.1186/s13578-024-01207-7.