Tropical Journal of Pharmaceutical Research December 2018; 17 (12): 2455-2461
**ISSN:** 1596-5996 (print); 1596-9827 (electronic)
© Pharmacotherapy Group, Faculty of Pharmacy, University of Benin, Benin City, 300001 Nigeria.

Available online at http://www.tjpr.org
**http://dx.doi.org/10.4314/tjpr.v17i12.22**

**Original Research Article**

# Anti-inflammatory effect of date seeds (*Phoenix dactylifera* L) on carrageenan-induced edema in rats

**Saryono Saryono[1], Warsinah Warsinah[2], Atyanti Isworo[1], Ferry Efendi[3]***
*[1]School of Nursing, [2]School of Pharmacy, Faculty of Health Sciences, University of Jenderal Soedirman, [3]Faculty of Nursing, Universitas Airlangga, Surabaya, Indonesia*

**For correspondence:* ***Email:*** *ferry-e@fkp.unair.ac.id;* ***Tel:*** *+62-31-5913257*

*Sent for review: 25 August 2018* *Revised accepted: 19 November 2018*

## Abstract

***Purpose:*** *To study the anti-inflammatory properties and mechanism of action of date seed extract in carrageenan-induced edema in rats.*
***Methods:*** *In this study with a pre- and post-test control group design, 30 Wistar rats were divided into six groups: Groups C1, C2, and C3 (given 1, 3, and 5 g/kg of soaked date seeds, respectively); positive control (PC, positive control given dexamethasone, 0.5 mg/kg dose), negative control (NC, edema induced by carrageenan), and healthy control (HC, no treatment). In groups C1–3, PC, and NC, carrageenan was administered intraperitoneally prior to date seed, PC and NC treatments. Prostaglandin E2 (PGE-2), cyclooxygenase (COX)-1, COX-2, interleukin (IL)-1β, and IL-12 were measured before and immdiate;y after treatment and compared between the groups.*
***Results:*** *Steeped date seed modulated inflammatory mediators by decreasing IL-1β, COX-1, COX-2, IL-12, and PGE-2 significantly ($p < 0.05$). Its indicated that the steeped date seeds down-regulate pro-inflammatory mediators in a manner similar to that of dexamethasone as positive control.*
***Conclusion:*** *Steeped date seeds possess anti-inflammatory activity similar to that of dexamethasone, through a mechanism involving decreases in pro-inflammatory mediators. Thus, date seeds is a potential source of herbal anti-inflammatory therapy.*

***Keywords:*** *Phoenix dactylifera, Anti-inflammatory, Date seeds, Pro-inflammatory mediators, Dexamethasone*

**This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.**

**Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts**

## INTRODUCTION

Trauma in the human body can cause inflammation. Pro-inflammatory mediators serve to fight infectious microorganisms and repair damaged tissues. However, if inflammation lasts long due to low immunity, healing processes can be inhibited. Infection caused by microorganisms can be prevented by providing antioxidants as anti-inflammatory agents to boost the immune system [1]. One antioxidant of local potency is the date seed (*Phoenix dactylifera* L.). Date seeds have been proven to possess flavonoids, tannins, saponins, glycosides, vitamin C, vitamin E, minerals, and amino acids [1].

The active principles in date seeds are phenolic compounds, flavonoids, minerals, vitamins, and

*© 2018 The authors. This work is licensed under the Creative Commons Attribution 4.0 International License*

crude fiber [2]. These compounds exhibit antioxidant activity [3]. Previous studies have shown that date seeds have anti-atherogenic properties [4].These antioxidants may protect sperm cell membranes from free radical oxidation [5]. Date seeds possess anti-inflammatory and immune-stimulatory activities [6]. However, not much is known about these activities.

Decreases in pro-inflammatory mediators reduce inflammatory processes and mitigate pain and fever. Cyclooxygenase (COX) and pro-inflammatory mediators, including prostaglandin E2 (PGE-2), interleukin (IL)-1, and IL-12, are important inflammatory mediators [7]. However, their excessive activity can disrupt the healing process. The mechanism through which date seeds suppress pro-inflammatory mediators is unknown. Therefore, it is important to research on the anti-inflammatory mechanism of date seeds. This research was conducted to determine the anti-inflammatory mechanism of steeped date seeds in carrageenan-induced edema in rats.

## EXPERIMENTAL

### Preparation of date seeds

*Deglet Noor* dates from Tunisia were purchased from a supermarket near Purwokerto. The date seeds were free from physical damage, insect infestation, and fungal infection. The seeds were washed in running water and sun-dried for one day. The dried seeds were roasted at 60 $^{o}$C, ground with a coffee grinder and filtered to obtain 2 kg of fine powder. Hot water was then added, and the mixture was stirred evenly, filtered and stored in a cabinet at 4 $^{o}$C. Each dose was diluted in 3 ml of boiled water.

### Phytochemical screening

Phytochemical screening was performed to identify flavonoids, terpenoids, and saponins, as described in a previous study [8].

### Animals

A total of 30 male Wistar rats aged 3 – 4 months (weighing 250 – 300 g) were obtained from the animal experimental unit of Universitas Gadjah Mada. The rats were placed in separate cages and kept at room temperature (22 – 23 °C) under a 12:12 (dark: light) cycle. They were adapted to the laboratory environment for one week, prior to the study, and were given *ad libitum* access to food and water. The animal experiments were conducted in accordance with the ethics and protocols of animal studies. This study was approved by the Medical Research Ethics Committee of the Faculty of Medicine, University of Sebelas Maret Surakarta (approval no. 331/IV/HREC/2017). All the animal procedures/protocols were performed as per NIH guidelines.

### Study design

In this study with a pre- and post-test with control group design, the 30 Wistar rat strains were divided into six groups: Groups C1, C2, and C3 were given 1, 3, and 5 mg/kg date seeds, respectively; group C4 was the positive control given dexamethasone at a dose of 0.5 mg/kg orally. Group C5 (negative control) and group C6 (healthy control, were without any treatment). Groups C1 – C5 were each administered a single 1-ml dose of carrageenan (0.3 % w/v) intraperitoneally prior to treatment. Two days later, 5 ml blood samples were taken for pre-test. Then, date seeds were given for 14 days, after which blood was taken for tests. The levels of PGE-2, COX1, COX2, IL-1, and IL-12 were measured using an ELISA kit (BT Laboratories, Shanghai) and an ELISA Reader machine (Labtron, Germany) based on the manufacturer's protocols.

### Statistical analysis

The data are presented as frequency distribution tables, and reported as mean ± SD. Normal data were tested using Shapiro–Wilk test and compared between the groups using one-way ANOVA test. Values of $p < 0.05$ were considered statistically significant. Post-hoc test utilized least significant difference (LSD).

## RESULTS

Phytochemical screening showed that Deglet Noor date seed powder contained flavonoids, terpenoids and saponins (Table 1). The total flavonoid content was 24.5 mg/mL. In contrast, previous studies showed that seeds of *Majhoul, Bousthammi* and *Boufgous* dates contained flavonoid levels of 1,659 ± 0.022, 1,844 ± 0.018, and 1,224 ± 0.03 rutin equivalents/100 g dry weight, respectively [9].

Following carrageenan administration, IL-1β levels were increased in groups 1–5 before treatment, when compared with the HC group. The mean IL-1β level in group C6 was 847 ± 105.53 pg/mL. After 14 days of the seed treatment, IL-1β levels were marginally decreased, but there were no significant differences in groups C1–C3 (Figure 1). The date

seeds restored IL-1β close to normal level. There were no significant differences between groups C1, C2, C4, and C6 (Table 2). These findings indicate that the groups receiving 1 and 3 mg/kg of date seeds were comparable to group C4 (positive control given dexamethasone dose (0.5 mg/kg) and group C6 (healthy control).

**Table 1:** Qualitative and quantitative test of phytochemical compound

| Test | Level |
|---|---|
| ***Qualitative test*** | |
| Flavonoids | +++ |
| Terpenoids | ++ |
| Saponins | +++ |
| ***Quantitative test*** | |
| Polyphenol level | 9.27 mg/mL |
| Flavonoid level | 24.5 mg/mL |

**Table 2:** Effect of date seed treatment on IL-1β levels

| Group | C1 | C2 | C3 | PC | NC | HC |
|---|---|---|---|---|---|---|
| C1 | - | 0.956 | 0.115 | 0.061 | 0.030* | 0.507 |
| C2 | 0.956 | - | 0.105 | 0.067 | 0.027* | 0.542 |
| C3 | 0.115 | 0.105 | - | 0.003** | 0.458 | 0.035* |
| PC | 0.061 | 0.067 | 0.003 | - | 0.001** | 0.192 |
| NC | 0.030* | 0.027* | 0.458 | 0.001** | - | 0.008** |
| HC | 0.507 | 0.542 | 0.035* | 0.195 | 0.008** | - |

C1–C3: groups treated with 1, 3 and 5 g/kg date seeds, respectively. NC: negative control, PC: positive control, HC: healthy control. *$p < 0.05$, **$p < 0.01$ {least significant difference (LSD) test}

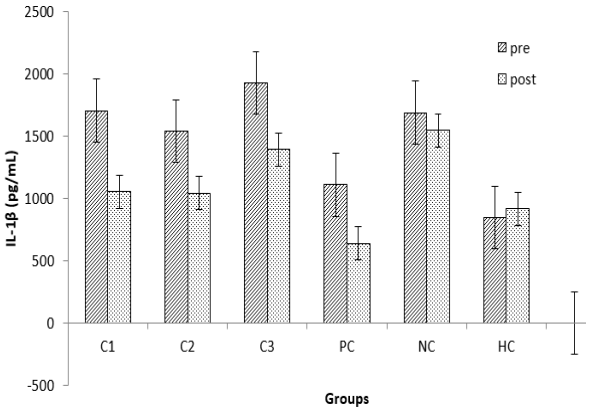


**Figure 1:** IL-1β levels pre- and post-date seed administration (mean ± SD). C1–C3: Groups treated with different doses of date seeds. NC: negative control, PC: positive control, HC: healthy control.

Compared to healthy control group, COX-1 activity after carrageenan administration and before the treatment showed a significant improvement ($p = 0.003$). The level of COX-1 in group C6 was 3.64 ± 0.22 ng/mL. After the treatment, COX-1 levels returned to normal (Figure 2). The LSD post-hoc test results showed no significant difference between the treatment groups and groups C4 and C6 (Table 3) but there were significant differences between the treatment groups and group C5 ($p < 0.05$).

**Table 3:** COX-1 levels after date seed treatment

| Group | C1 | C2 | C3 | PC | NC | HC |
|---|---|---|---|---|---|---|
| C1 | - | 0.419 | 0.389 | 0.327 | 0.003** | 0.157 |
| C2 | 0.419 | - | 0.955 | 0.856 | 0.001** | 0.513 |
| C3 | 0.389 | 0.955 | - | 0.901 | 0.001** | 0.549 |
| PC | 0.327 | 0.856 | 0.901 | - | 0.001** | 0.633 |
| NC | 0.003** | 0.001** | 0.001** | 0.001** | - | 0.008** |
| HC | 0.157 | 0.513 | 0.549 | 0.633 | 0.008** | - |

C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control. *$p < 0.05$, **$p < 0.01$ {least significant difference (LSD) test}.

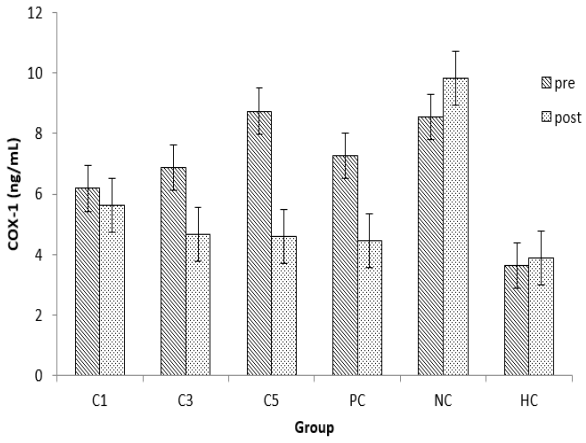


**Figure 2:** COX-1 levels pre- and post-date seed administration (mean ± SD). C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control

The COX-2 activity after carrageenan treatment was increased in groups C3, C4, and C5 but was significantly different from groups C1 and C2 ($p = 0.000$). The mean level of COX-2 was 2.01 ng/mL for group C6. After the treatment, COX-2 levels were decreased (Figure 3). The post-hoc test showed no differences between group C6 and groups C1, C2, and C4 (Table 4). However, group C3 showed a larger decrease than group C4.

**Table 4:** Effect of date seed extract on COX-2 levels

| Group | C1 | C2 | C3 | PC | NC | HC |
|---|---|---|---|---|---|---|
| C1 | - | 0.474 | 0.015* | 0.324 | 0.000** | 0.777 |
| C2 | 0.474 | - | 0.004** | 0.103 | 0.000** | 0.662 |
| C3 | 0.015* | 0.004** | - | 0.098 | 0.000** | 0.009** |
| PC | 0.324 | 0.103 | 0.139 | - | 0.008* | 0.001* |
| NC | 0.000** | 0.001* | 0.000** | 0.008* | - | 0.265 |
| HC | 0.777 | 0.000** | 0.000** | 0.001* | 0.265 | - |

C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control. *$p < 0.05$, **$p < 0.01$ {least significant difference (LSD) test}

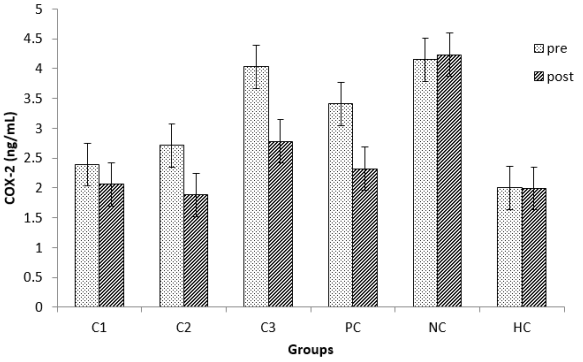


**Figure 3:** COX-2 levels pre- and post-date seed extract administration (mean ± SD). C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control

The IL-12 levels were significantly increased after carrageenan administration ($p$ = 0.000). Results from one-way ANOVA showed significant differences between the treatment groups (C1 – C3) and group C6 ($p$ = 0.000) (Figure 4). The mean level of IL-12 in the healthy control group was 55.00 ± 7 pg/mL. After the treatment, the mean level of IL-12 was significantly decreased ($p$ = 0.000). The LSD post-hoc test showed more significant differences in the treatment groups (C2 and C3) and groups C4 (PC) (Table 5), indicating that date seed doses of 3 and 5 mg/kg exerted better effects than dexamethasone in reducing IL-12 levels.

PGE-2 levels after carrageenan administration were significantly increased, and there was a significant difference between healthy control group (HC) and the other groups given carrageenan (C1-C3) ($p < 0.05$) (Figure 5).

The mean PGE-2 level was 2.67 ± 0.64 ng/mL for the healthy control group. Following the administration of date seeds, PGE-2 levels were significantly decreased, relative to groups C5 and C6. However, there was no significant difference between the treatment groups (C1 – C3) and dexamethasone (group C4) (Table 6). Comparison with the positive control revealed that the mechanism of action of date seeds was similar to that of dexamethasone i.e. through regulation of pro-inflammatory mediators.

## DISCUSSION

Variations in the active phytochemical components of various date species are influenced by soil conditions, geographical location, cultivar type, planting age, plant diseases, storage conditions, and treatments before seed processing [10]. The flavonoids in date include apigenin derivatives and quercetin; proanthocyanidin dimers and trimers, and epicatechin, while the phenolic compounds include several protocatechuic and 5-caffeoylshikimic acids [11].

**Table 5:** IL-12 levels after date seed extract treatment

| Group | C1 | C2 | C3 | PC | NC | HC |
|---|---|---|---|---|---|---|
| C1 | - | 0.000** | 0.001** | 0.291 | 0.000** | 0.000** |
| C2 | 0.000** | - | 0.766 | 0.004** | 0.000** | 0.000** |
| C3 | 0.001** | 0.766 | - | 0.006** | 0.000** | 0.000** |
| PC | 0.291 | 0.004** | 0.006** | - | 0.000** | 0.000** |
| NC | 0.000** | 0.000** | 0.000** | 0.000** | - | 0.000** |
| HC | 0.000** | 0.000** | 0.000** | 0.000** | 0.000** | - |

C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control; *$p < 0.05$, **$p < 0.01$ {least significant difference (LSD) test}

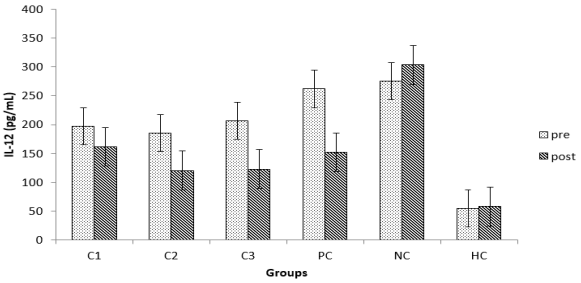


**Figure 4:** IL-12 levels pre- and post-date seed administration (means ± SD). C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg,

respectively. NC: negative control, PC: positive control, HC: healthy control

**Table 6:** PGE-2 level after date seed extract treatment

| Group | C1 | C2 | C3 | PC | NC | HC |
|---|---|---|---|---|---|---|
| C1 | - | 0.627 | 0.689 | 0.898 | 0.004** | 0.000** |
| C2 | 0.627 | - | 0.381 | 0.541 | 0.010* | 0.000** |
| C3 | 0.689 | 0.381 | - | 0.785 | 0.002** | 0.000** |
| PC | 0.898 | 0.541 | 0.785 | - | 0.003** | 0.000** |
| NC | 0.004** | 0.010* | 0.002** | 0.003* | - | 0.000** |
| HC | 0.000** | 0.000** | 0.000** | 0.000** | 0.000** | - |

C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control; *$p < 0.05$, **$p < 0.01$ {least significant difference (LSD) test}

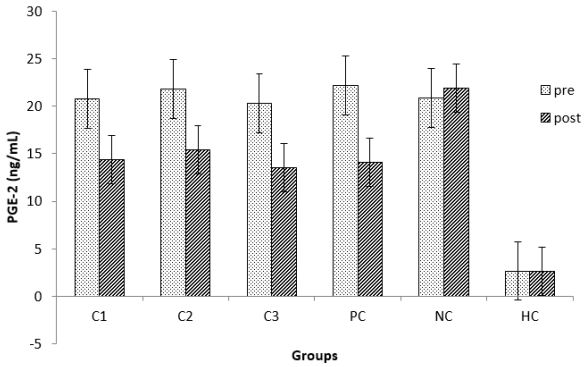


**Figure 5:** PGE-2 levels pre- and post-date seed administration (mean ± SD). C1–C3: groups treated with date seed at doses of 1, 3 and 5 g/kg, respectively. NC: negative control, PC: positive control, HC: healthy control

The levels of vitamin C, alpha-tocopherol, and activities of SOD, catalase, and peroxidase vary widely among date species [12]. Roasting increases the level of caffeine, amount of flavonoids, and antioxidant capacity in dates [13]. Aqueous extracts of date seeds contain higher amount of total phenolics and flavonoids than any other extract type [14].

The data obtained in the present study showed increased pro-inflammatory cytokines after carrageenan administration. The increased levels of COX-1, COX-2, PGE-2, IL-1β, and IL-12 are associated with the induction of pro-inflammatory cytokines by carrageenan leading to their increased expression. Evidence have shown that IL-1β is involved in various biological activities during the inflammatory process [15].

Carrageenan-induced enhancement of pro-inflammatory mediators has been widely reported in previous animal studies [16]. In this study, the inflammatory responses were significantly suppressed by date seeds at all doses tested ($p < 0.05$), as depicted in the differences in enzyme activities between the treatment groups and the negative control group. The anti-inflammatory effects of the seeds may be associated with polyphenolic compounds and flavonoids, as shown in their ability to inhibit the production of nitric oxide (NO), TNF-α, and IL-6 [17].

The inflammatory processes involve many mediators such as prostaglandins, prostacyclins, lymphokines, and chemokines (e.g., interferon-γ (IFN-γ), IFN-α, IL-1, IL-8, histamine, hydroxytryptamine, and TNF-α). Date palm contains alkaloid compounds, and alkaloids inhibit COX and lipoxygenase (LOX) pathways [7]. Some alkaloids significantly inhibit PGE-2 production and decrease NF-kB populations. The PGE-2 molecules in the inflammatory processes can stimulate the nervous system, resulting in pain sensations. The biosynthesis of PGE-2 involves two pathways COX-1 and COX-2, and inhibition of these pathways decreases PGE-2 synthesis. In healthy individuals, COX-2 synthesis is low or absent, but it is controlled by pro-inflammatory cytokines, such as IL-1 and TNF-α, in response to infection or inflammation [18].

Inflammation processes produce arachidonic acid oxidation of PGE-2 and lipoxins which are released from infiltrated myeloid cells. Previous studies have also shown that inflammation leads to the suppression of NF-kB, inhibition of COX-1 and COX-2, and regulation of LOX transcription factor [19]. However, studies using steeped date extract as an anti-inflammatory agent have not been previously conducted.

Date seeds contain flavonoids such as quercetin, oleanolic acid, and caffeine. The seed can suppress edema as a result of inflammation due to LOX inhibition. Flavonoids inhibit NO production by affecting the expression of inducible gene NO synthase (iNOS). Another possible mechanism for flavonoids as an anti-inflammatory agent is the inhibition of the synthesis of PGE-2 and COX-2, which leads to the suppression of pro-inflammatory gene expression [7]. Cytokines produced by cells work on other cells to bring changes to target cells. Large amounts of cytokines are produced by different types of cells, including immune cells and epithelial cells. The inhibition of IL-1 and IL-12 pro-inflammatory cytokine activity may decrease inflammation processes and suppress

the T cell activation pathway [18]. Recent studies suggest that flavonoids serve as anti-inflammatory agents [16].

Phenolic compounds are usually found in date palms, and these compounds also act as anti-inflammatory agents [20]. These compounds exert their anti-inflammatory effect by inhibiting leukocyte migration and reducing serum lysozyme, NO, PGE-2, and malondialdehyde levels [7]. The inhibition of TNF-α, decreases the activities in IL-6 and IL-1β and vice versa, and the inhibition of IL-1β decreases IL-6 levels. The inhibition of IL-12 decreases excessive levels of IFN-γ, and B lymphocytes produce TNF-α and IL-1β. Some cytokines work synergistically (e.g. IL-1 and TNF-α, TNF-α and IFN-γ, and IL-1β and IL-6) [21]. Therefore, the inhibition of one component can stop the synergy and reduce the severity of diseases. Phenolic compounds inhibit the expression of IL-1β, and a recent study showed that steeped date seeds decreased IL-6 levels [21].

Phenolic compounds have been grouped into flavonoids and non-flavonoids. Some phenolic compounds such as caffeic acid and quercetin, decrease NF-kB levels, which inhibit NO production via decreased iNOS biosynthesis. Gallic acid inhibits the secretion of histamine and pro-inflammatory cytokines from mast cells. Further, ferulic acid has been described to decrease the activity of NO and PGE-2 in the inflammatory processes [22]. These compounds work in the similar mechanism as non-steroidal anti-inflammatory drugs (NSAIDs) [23].

Date seeds have been shown to contain p-coumaric acid, phenolic compounds, vitamin C, and vitamin E, which act as antioxidants [10]. Their antioxidant properties also contribute to their anti-inflammatory effects [19]. Antioxidants can work as anti-inflammatory agents by inhibiting pro-inflammatory mediators [24]. Several studies have shown that the suppression of pro-inflammatory cytokines in numerous autoimmune diseases is beneficial based on the immunosuppressive properties on some cytokines such as IL-1, IL-6, IL-12, TNF-α, and IFN-γ.

Date seeds also contain tannins which are potent inhibitors of COX-1, and they have anti-phlogistic activities [16]. In other studies, date seed extract significantly decreased the levels of TGF-β, TNF-α, IL-6, and IL-1β ($p < 0.05$) [25].
It has been shown that PGE-2 is a potent inhibitor of IFN-γ and IL-2, and it increases intracellular cAMP by suppressing the production of TNF-α, IFN-γ, and IL-2. Indeed, PGE-2 analogs (e.g., cicaprost and treprostinil) inhibit the pro-inflammatory cytokines IL-12, TNF-α, IL-1α, and IL-6 [21]. The findings of this study supports previous research conducted on broiler chickens. Date seed supplementation acts as immune-stimulant by increasing the levels of IL-2 and IFN-γ [25]. In another study, the administration of dried date extract to mice improved immunity mediated by T and B lymphocytes [21].

The clinical implication of the present research is that date seeds have been proven to serve as anti-inflammatory agents through the suppression of pro-inflammatory mediators. The results indicated that date seeds regulate the expression of COX-1 and COX-2, and the production of PGE-2. In addition, they decrease the synthesis of cytokines (IL-1β and IL-12).

## CONCLUSION

The findings obtained from this study indicate that date seed extract act as anti-inflammatory agents via downregulation of COX-1, COX-2, PGE-2, IL-1β and IL-12. The activity of the compounds in date seeds appears similar to that of dexamethasone. This finding should promote the development of date seed-based products as therapeutic agents for suppressing inflammations.

## DECLARATIONS

### *Acknowledgement*

The authors would like to thank the Indonesian Ministry of Research, Technology, and Higher Education for financially supporting this investigation through PDUPT research funding.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

## REFERENCES

1. *IS Sadiq, T Izuagie, M Shuaibu, AI Dogoyaro, A Garba, S Abubakar. The Nutritional Evaluation and Medicinal Value of Date Palm (Phoenix dactylifera). Int. J. Mod. Chem. 2013; 4: 147–154.*

2. C Platat, HM Habib, FD Maqbali, NN Jaber, WH Ibrahim. Identification of Date Seeds Varieties Patterns to Optimize Nutritional Benefits of Date Seeds. J. Nutr. Food Sci. 2014; 1: 1-8.
3. Saryono, D Hisni, E Rahmawati, A Proverawati, A Hidayat. Plasma Malondialdehyde and Vitamin E Levels after Date Palm Seeds (Phoenix dactylifera) Steeping Administration. Asian J. Clin. Nutr. 2017; 9: 131-136.
4. Saryono, J Eliyan, D Herdiati, A Khikmatullah, C Silvana, H Adi. Anti-atherogenic properties of Deglet Noor Date seeds (Phoenix dactylifera) Methanol extract on Diet-Induced Hypercholesterolemic Rats. IOP Conf. Ser. Mater. Sci. Eng. 172 (2017). doi:10.1088/1742-6596/755/1/011001.
5. Saryono, H Retnani, D Santoso. Date Seeds Steeping (Phoenix Dactylifera) Strengthen Sperm Cells Membrane and Reduce Malondialdehyde Level. J. Ners. 2015; 10: 355–359.
6. KH Eddine, S. Zerizer, Z. Kabouche. Immunostimulatory Activity Of Phoenix Dactilifera. Int. J. Pharm. Pharm. Sci. 2014; 6: 7–10.
7. S Beg, S Swain, H Hasan, MA Barkat, MS Hussain. Systematic review of herbals as potential anti-inflammatory agents Recent advances, current clinical status and future perspectives. Pharmacog Rev. 2011; 5: 120–137.
8. J Bruneton. Pharmacognosy, phytochemistry, medicinal plants. Technique et Documentation Lavoisier, 1993.
9. RDV Sundar, G Segaran, S Shankar, S Settu, L Ravi. Bioactivity of Phoenix dactylifera seed and its phytochemical analysis, Int. J. Green Pharm. 2017; 2017: 1–6.
10. MRS Ardekani, M Khanavi, M Hajimahmoodi, M Jahangiri, A Hadjiakhoondi. Comparison of antioxidant activity and total phenol contents of some date seed varieties from Iran, Iran. J. Pharm. Res. 2010; 9: 141–146.
11. BR Yasin, HAN El-Fawal, SA Mousa. Date (Phoenix dactylifera) polyphenolics and other bioactive compounds: A traditional islamic remedy's potential in prevention of cell damage, cancer therapeutics and beyond. Int. J. Mol. Sci. 2015; 16: 30075–30090. doi:10.3390/ijms161226210.
12. MS Baliga, BRV Baliga, MS Khandathil, HP Bhat, PK Vayalil. A review of the chemistry and pharmacology of the date fruits (Phoenix dactylifera L.). Food Res. Int. 2011; 44: 1812–1822. doi:10.1016/j.foodres.2010.07.004.
13. R Paranthaman, P Praveen Kumar, S Kumaravel. HPLC and HPTLC Determination of Caffeine in Raw and Roasted Date Seeds (Phoenix Dactylifera L). Doi:10.4172/Scientificreports.249. 2012; 1: 1–4. doi:10.4172/scientificreports.24.
14. A Thouri, H Chahdoura, A El Arem, AO Hichri, R Ben Hassin, L Achour. Effect of solvents extraction on phytochemical components and biological activities of Tunisian date seeds (var. Korkobbi and Arechti). BMC Complement. Altern. Med. 2017; 17: 1–10. doi:10.1186/s12906-017-1751-y.
15. J Ji, LEI Su, Z Liu. Critical role of calpain in inflammation. Biomed. REPORTS. 2016; 5: 647–652. doi:10.3892/br.2016.785.
16. MH Hossain, F Jahan, MSI Howlader, SK Dey, A Hira, A Ahmed, RP Sarkar. Evaluation of Anti-inflammatory Activity and Total Flavonoids Content of Manilkara zapota (Linn.). Int. J. Pharm. Phytopharmacol. Res. 2012; 2: 35–39.
17. K Choi, Y Son, J Hwang, B Kim, J Lee, Y Son, J Hwang, B Kim. Antioxidant, anti-inflammatory and anti-septic potential of phenolic acids and flavonoid fractions isolated from Lolium multiflorum. Pharm. Biol. 2017; 55: 611-619. doi:10.1080/13880209.2016.1266673.
18. CA Dinarello. Anti-inflammatory Agents: Present and Future. Cell. 2013; 140: 935–950. doi:10.1016/j.cell.2010.02.043.Dinarello.
19. C Zhang, S Aldosari, P Vidyasagar, K Nair, M Nair. Antioxidant and anti-inflammatory assays confirm bioactive compounds in Ajwa date fruit. J. Agric. Food Chem. 2013; 61: 5834–5840.
20. C Zhong, D Hu, L-B Hou, L-Y Song, Y-J Zhang, Y Xie, L-W Tian. Phenolic Compounds from the Rhizomes of Smilax china L. and Their Anti-Inflammatory Activity, Molecules. 2017; 22: 1–8. doi:10.3390/molecules22040515.
21. S Saryono, A Sumeru, A Proverawati, F Efendi. Decreasing Carbon Tetrachloride Toxicity using Date-seed (Phoenix dactylifera L.) Steeping in Rats. Toxicol. Environ. Heal. Sci. 2018; 10: 139–145. doi:10.1007/s13530-018-0357-1.
22. T Vezza, A Rodríguez-nogales, F Algieri, MP Utrilla, ME Rodriguez-cabezas, J Galvez. Flavonoids in Inflammatory Bowel Disease : A Review. Nutrients. 2016; 8: 1–22. doi:10.3390/nu8040211.
23. DL Ambriz-pérez, N Leyva-lópez, EP Gutierrez-grijalva, JB Heredia. Phenolic compounds : Natural alternative in inflammation treatment. Cogent Food Agric. 2016; 41: 1-14. doi:10.1080/23311932.2015.1131412.
24. A Li, S Li, Y Zhang, X Xu, Y Chen, H Li. Resources and Biological Activities of Natural Polyphenols. Nutrients. 2014; 6: 6020–6047. doi:10.3390/nu6126020.
25. NM Al-Rasheed, HA Attia, RA Mohamad, NM Al-Rasheed, MA Al-Amin, A Al-Onazi. Aqueous Date Flesh or Pits Extract Attenuates Liver Fibrosis via Suppression of Hepatic Stellate Cell Activation and Reduction of Inflammatory Cytokines, Transforming Growth Factor-β1 and Angiogenic Markers in Carbon Tetrachloride-Intoxicated Rats Extract, Evidence-Based Complement. Altern. Med 2015; 2015: 1-19. doi:10.1155/2015/247357.