Date seeds (*Phoenix dactylifera* L.) consumption as anti-inflammatory and immunostimulant: a systematic review

To cite this article: Saryono *et al* 2019 *IOP Conf. Ser.: Earth Environ. Sci.* **250** 012038

Date seeds (*Phoenix dactylifera* L.) consumption as anti-inflammatory and immunostimulant: a systematic review

Saryono[1], E Dardjito[2], A Proverawati[2], A Sumeru[1], R Setiyani[1], A S Upoyo[1] and R Kamaludin

[1]Nursing Department, Faculty of Health Sciences University of Jenderal Soedirman, Purwokerto
[2]Nutrition Department, Faculty of Health Sciences, University of Jenderal Soedirman, Purwokerto

Email: sarbiokim@gmail.com

Abstract. The low immunity will make the body to be susceptible to various diseases. Trauma, genetic disorders, and microorganisms can reduce immunity status. Until now, drugs have not been effective in improving body immunity, and even tend to reduce immunity. Date seeds contain many polyphenol compounds that can affect the immune system, but the mechanism is unclear. This systematic review aims to explore the potential of date seeds as anti-inflammatory and immunostimulants. Articles obtained from electronic databases such as PubMed, Science Direct and Google Scholar that are published from 2014 to 2018. Keywords are used: dates seed, date seeds and immunity. The result from 5 selected articles showed that date seeds as immunostimulant can increase production of IFN-γ, IL-2, and antioxidant status. Date seeds can also suppress pro-inflammatory mediators (TNF-α, IL-1, IL-1β, IL-2, IL-6), reduce of CRP, inhibit of edema formation, inhibit of NF-kB translocation and suppress of COX2, MMP-9 expression, and IFN-γ. It can be concluded that consumption of date seeds can potentially increase the body's immune status and have a function as anti-inflammatory.

1. Introduction

Immune cells are very important to protect the body from pathogenic microorganism attack, to phagocytes of dead cells and to repair of damaged cells. A low immune system disturbs the body healing process. Imbalance between immune system and causative agent of trauma causes an infection [1]. When infection or trauma occurs, an easily observed of immune response is inflammation. During the inflammatory response, various cytokines are produced [2]. Inflammation is one of the body's defense mechanisms to fight various stimuli (chemical compounds, toxic substances, allergens, microorganism infections, or trauma). Therefore, one of the efforts to keep the body healthy is by increasing the immune system. Some drugs as immunostimulants have dangerous chemical effects. The use of herbal plants is known to have many benefits with minimal side effects, one of them is dates [3].

Secondary metabolites of date seeds such as phenolic and flavonoids show an extraordinary inhibitory effect on inflammation. Research on dates has been done a lot but studies on date seeds are still very limited [4,5]. Date seeds contain lots of flavonoids and other potential compounds as a source of medicine [6]. The active compound in date seeds has a potency as an antioxidant that has

some functions, which are to reduce the body's free radicals, to prevent various diseases due to aging and to protect the body from infection. It has been reported that dates can improve immune system function, but the underlying mechanism is unclear. Previous research shows that date seeds can increase the concentration of hemoglobin, MCH, and MCHC so that it can increase immunity [7].

Date seeds as a drink also contain minerals and vitamins essential for the body to maintain health. The most phytochemical content in dates are flavonoids, anthraquinones, tannins, saponins, alkaloids and terpenoids [8]. Dates also contain lots of potassium, phosphorus, and calcium which are important for the body [9]. Therefore, research needs to be done to explore the potential use of date seeds as an anti-inflammatory agent. This systematic review aims to evaluate the use of date seeds as an anti-inflammatory and improve the body's immune status.

2. Research methods

2.1. Search database

The design used in this study is a systematic review. The steps in this research are summarized in Figure 1. Articles were obtained from electronic databases published in PubMed, Science Direct, and Google Scholar, which were published from 2014 to 2018. The structure of the keywords used to search were "dates seeds" OR “date seed” OR "*Phoenix dactylifera* L." AND "immunity". The inclusion criteria of this study were articles limited in the last 5 years, in English, available in full-text, experimental research, having a control group, and containing the effect of date seeds on the body's immunity.

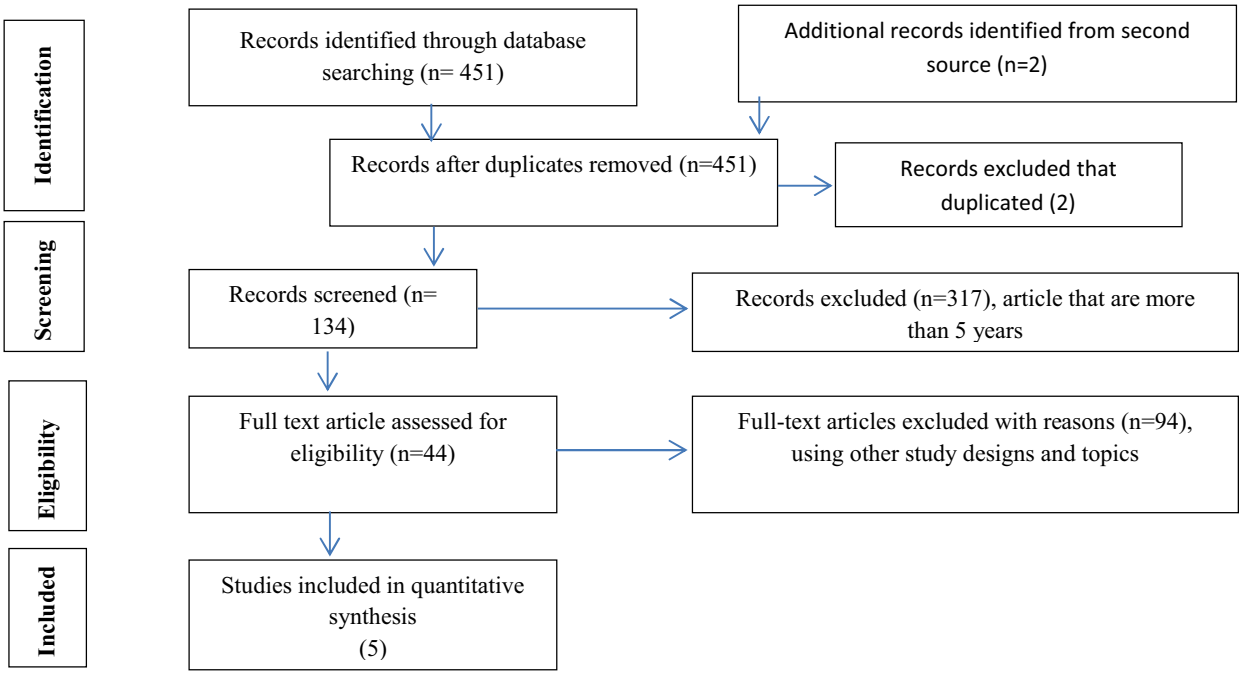

Figure 1. Research flow chart

2.2. *Data extraction and reporting of findings*

The number of articles obtained from the Science Direct database were 33, PubMed 19 and Google scholar 399. The article which double-published and published by Science direct, PubMed, and Google Scholar is selected. After looking at the inclusion criteria, only 451 articles met the criteria. Screening is carried out again by looking at less than five years so it is obtained 134 article and after look for full text, the final article to be 44. After checking again, the reviewer looks back at the abstract of each article to see the indicator variables that indicate the body's immune status and the relevance of the article with systematic review objectives. Reviewers used tools in critical appraisal

journals to evaluate and select article that met inclusion criteria. There are 5 articles that met the inclusion criteria found previously.

3. Results

3.1. Comparison of various types of date seed extract

The total phenolic content (TPC) of date seeds is strongly influenced by the type of solvent. Acetone, ethanol, and methanol solvents are the better solvent in date seeds in extracting phenolic compounds compared to water solvents, but the aqueous extract of date seeds shows a significant effect in showing antidiabetic activity in vitro [10]. The results of several studies show that date seeds are a source of antioxidants because they contain high TPC. The highest water extract in date seeds produce routine and trolox equivalent antioxidant capacity (TEAC) compounds in Ajwa dates [11].

The results of component analysis on date seeds indicate that dates contain alkaloids, flavonoids, tannins, saponins, phenols, sterols, and triterpenes [12]. Total phenolic content, flavonoids and antioxidant activity in date seeds vary widely [13].Genetic factors, differences in the environment of the place of planting, and conditions of growth greatly affect the active substance content. Different extraction methods affect the physicochemical properties and antioxidant activity [14].

3.2. The action mechanism of date seeds as an anti-inflammatory

The role of free radicals in causing inflammation can be proven from the results of CCl4injection. Carbon tetrachloride is activated by liver microsomal cytochrome to form unstable trichloromethyl and trichloromethyl peroxylm radicals that immediately oxidize polyunsaturated fatty acids (PUFAs) in the cell membrane. Cells become damaged, swell due to changes in cell permeability. This free radical also causes a chain reaction. In this condition, inflammatory markers will be increased [15]. Therefore, inflammation can be treated by giving antioxidants, which can be found in date seeds.

After the trauma, acute inflammation will occur which is marked by vascular changes, recruitment of neutrophils, and chemical mediator production. This response involves macrophages and other cells from releasing pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL-1, IL-6), which triggers inflammatory flow. Pro-inflammatory cytokines can induce leukocyte adhesion on endothelial cells, release of protease enzymes in arachidonic acid metabolism and activate of the coagulation cascade. As a result, some pro-inflammatory mediators are produced, for example, prostaglandins, leukotriene, histamine, and thromboxane along with cytokines and nitric oxide [16].However, as a counterweight in the body, there is a negative feedback mechanism by anti-inflammatory cytokines such as IL-10.

The results of the analysis on scientific articles show that date seeds can be used as an anti-inflammatory and increase the immune response (Table 1). Administration of dates can increase serum IFN-γ and IL-2 significantly [17]. Antioxidants in date seeds have a positive effect in reducing levels of free radicals and further prevent the inflammatory process. Dates are also proven to inhibit NF-kB translocation and suppress COX2 expression [18]. All of these processes are possible through the elimination of free radicals produced by CCl_4.

In CCl_4-induced mice, pro-inflammatory cytokines will increase significantly including TNF-α, IL-1β, and IL-6. However, after administration of date seeds extract, indicators of inflammation in the form of TNF-α, IL-1β and IL-6 decreased[19].The anti-inflammatory effects of dates are related to its polyphenol compounds, which are able to inhibit NO and TNF-α production. Inflammation is often characterized by edema, and study indicate that edema due to inflammation can be eliminated by giving dates [20].

The results showed that the administration of dates seeds could reduce IL-6 and CRP levels, while lymphocyte counts increased in rats after CCl_4 induced [21]. Induction of CCl_4 cause hepatic cell damage, thus stimulating macrophages and neutrophils to produce pro-inflammatory cytokines in the form of IL-6. Interleukin-6 stimulates Kupffer cells to produce CRP [22].When there is inflammation, the body will respond by producing a lot of lymphocytes, but high usage will cause a decrease in

lymphocyte count. Dates contain many flavonoid and phenolic compounds. Several studies have proven that phenolic compounds can regulate pro-inflammatory gene expressions such as COX and LOX.

4. Discussion

Inflammation is part of the body's defense system to eliminate and limit the spread of injury agents. During the inflammatory process, neutrophils and macrophages produce free radical species to fight infectious agents [23]. Inflammation involves several chemical mediators and immune cells in the body's system to respond to dangerous stimuli. Chronic inflammation often induces several factors such as reactive oxygen species (ROS), reactive nitrogen species (RNS), cyclooxygenase (COX) and cytokines that contribute to various health problems [24]. Immunostimulatory effects of date seeds can increase the nonspecific immune response to respond to inflammation [25].

Flavonoids can interact with cell signaling pathways such as protein kinase C, NF-kB, tyrosine kinase and MAP-kinase. NF-kB has been reported to function as a regulator of pro-inflammatory gene expression and synthesis mediators of several cytokines such as TNF-α, IL-1β, IL-6, IL-8. Flavonoids can act as antioxidants, and regulate the activity of enzymes in the metabolic pathways of arachidonic acid (phospholipase A2, COX, LOX) and NOS [26]. Previous studies also showed that flavonoids could serve as an anti-inflammatory agent by regulating inflammatory cells, inhibiting proliferation of T lymphocytes, inhibiting pro-inflammatory cytokines and controlling enzymes of arachidonic acid pathways such as NO formation. Administration of dates seeds has been shown to reduce NO levels of kidney tissue due to inflammation induced by CCl_4 [27]

C-reactive protein (CRP) is a plasma protein synthesized by the liver which can be used as a marker that sensitive to inflammation [28]. CRP levels in the body's circulation will increase during the acute phase to serious infection. CRP activate immune cells in tissues that are inflamed by secretion of other inflammatory molecules. Thus, CRP can be called a direct pro-inflammatory factor in the pathogenesis of inflammatory diseases. In previous studies, it was shown that administration of dates can reduce CRP significantly compared to the control group. The active compound in date palm seeds inhibits the filtration of immune cells to the site of inflammation. Inflammation occurs because it is triggered by a vascular response followed by leukocyte infiltration which secretes major inflammatory mediators such as TNF-α, plasminogen activator inhibitor-1 (PAI-1), IL-1β, IL-6, IL-8, IL-15, IL-10, complement factor and prostaglandin E2 (PGE2). This mediator stimulates the liver to produce acute phase proteins in the form of CRP into the plasma [29].

Date seeds also contain sterols which can reduce levels of CRP, IL-6, TNF-α, phospholipase A1 and fibrinogen. This effect is assumed due to changes in the composition of the cell membrane, affecting membrane fluidity and sensitivity and signaling pathways. All of these changes will support the immune response by influencing the synthesis and secretion of eicosanoids, leukotrienes, and prostaglandins. Flavonoids and polyphenols are believed to play an important role in anti-inflammatory activity [30].

LOX and NF-kB transcription factors play an important role in the process of inflammation, cancer, and other degenerative diseases [31]. Modulation in transcription factors is an important step in treating and preventing disease. Active compounds in some herbal products can suppress transcription factors (NF-kB) and work as an anti-inflammatory [18]. Date seeds contain phenolic and flavonoids which can inhibit the lipid peroxide cyclooxygenase enzyme (COX-1 and COX-2). Some studies also show that date seeds can regulate cytokine expression. Other findings indicate that the use of date seeds can reduce foot swelling and plasma fibrinogen.

Table 1. Date seeds using to influence immune system activity

References	Aim	Designs/ samples	Intervention	Indicator variable	Result
[17]	to assess the effect of methanol extract of date palm seeds (DPS) in comparison to mannan-oligosaccharides (Bio-Mos) and β-glucan over antioxidant anti-immunity events that have effect on growth and carcass performances of broilers	This trial with post-test only with control design Samples: Broilers	The chicks were allocated into control (received the basal eating program), Bio-Mos (containing 0.1% Bio-Mos), β-glucan (containing 0.1% β-glucan), DPS2 (2% date crushed seeds), DPS4 (4% date crushed seeds), and DPS6 (diet 6% date seeds powder) groups from 1st to 42nd days of age.	interferon-gamma (IFN-γ), interleukin-2 (IL-2), nitric oxide (NO) levels,	IFN-γ, IL-2 and antioxidant status increases NO levels decreases
[18]	to assess the potential effects of aqueous extract of date fruits, either flesh (DFE) or pits (DPE), on oxidative DNA damage and liver inflammation induced by carbon tetrachloride (CCl_4) and whether they are related to inhibition of nuclear factor-κB pathway.	Experiment with control groups. Sampel: Rats	Rats were divided into the following groups: normal control, model control (CCl_4 only), CCl_4 +DFE, CCl_4 + DPE and CCl_4 + coffee. Coffee was used as a positive control	NF-κB COX2 Heme oxygenase-1 (HO-1) Tissue inhibitor Metalloproteinase -1 and -2 (TIMP-1 and TIMP-2) Matrix Metalloproteinase-9 (MMP-9)	DPE inhibited NF-kB translocation and alleviated COX-2 expression. DPE also attenuated the levels of TIMP-1 and -2 expression. DPE decreases MMP-9 and restoration of HO-1 activity.
[19]	to assess the influence of flesh or pits on CCl_4-induced liver fibrosis in rats. Inactivation of HSCs and suppression of TGF-β, TNF-α, IL-1β,and IL-6 (as inflammatory mediators), and VEGF, VEGFR-1, and CD31 (as angiogenic markers) were taken as target mechanisms.	Experiment with control group Samples: rats	Rats were divided into Group I: normal, control with no treatment. Group II: control treated with CCl_4 only. Group III: CCl_4 treated with coffee. Group IV: CCl_4 treated with aqueous extract of date flesh (DFE). Group V: CCl_4 treated with aqueous extract of date pits (DPE).	tumor necrosis factor-α, interleukin-6, and interleukin-1β.	The decreasing in the levels of TNF-α, IL-1β, and IL-6 were observed by the simultaneous administration of DFE and the combination of coffee + DFE and coffee + DPE ($p < 0.001$) and by DPE and coffee ($p < 0.01$)compared to CCl_4-intoxicated rats.

			Group VI: CCl_4 treated with combination of coffee + DFE. Group VII: CCl_4 treated with combination of coffee + DPE.		
[20]	To determine the date seeds phytochemical composition and the effect of its different solvents extraction on its antioxidant activity, in vitro antidiabetic and in vivo anti-inflammatory properties	Experiment with control groups. Sample: Rats	Male Wistar rats were divided into different groups of 6 animals. The control group received 2.5 ml/kg of saline, the standard group received the reference drug (acetylsalicylate of lysine (ASL), 300 mg/kg) and the test groups received different date seeds extracts at a dose of 100, 200 and 300 mg/kg.	The paw volume was measured by plethysmometer.	The aqueous extract of date seeds can inhibit edema formation.
[21]	to prove the decreasing of carbon tetrachloride toxicity using date seed (Phoenix dactylifera L.)	Experiment with control groups. Sample: Rats	Rats were grouped into 6 groups, healthy control (HC), negative control (NC), positive control (PC), treatment dose 1 g/kg (T1), treatment dose 3 g/kg (T3), and treatment dose 5 g/kg (T5). Each group was replicated five times.	IL-6 Lymphocyte count, CRP	Date-seed steeping can inhibit the rate of IL-6 and CRP levels. The lymphocyte count that decreases after CCL_4 induction can be increased again by giving date seed steeping.

Other compound of date seeds are coumaric acid, vanillic acid, caffeic acid, quercetin, gallic acid, and routine[32,33]. Several studies clearly state that polyphenol compounds such as caffeic acid and quercetin can reduce NF-kB, which then inhibits NO production through reduction of iNOS biosynthesis. Gallic acid also shows the inhibitory effect of histamine secretion and pro-inflammatory cytokines on mast cells [34]. Ferulic acid has been reported to reduce SOD activity, myeloperoxidase (MPO), nitric oxide (NO), and prostaglandin E2 during acetic acid-induced inflammation. Ferulic acid can also reduce the signs of inflammation of hs-CRP and TNF-α[35]. Other studies have shown that ferulic acid can reduce TNF-α and IL-1β macrophage cells that activated by LPS [36].

Previous studies have shown that a combination of gallic acid, ferulic acid, and caffeic acid as a component of phenolic acids can reduce COX-2 [35]. Routine has also been shown to have high inhibitory activity against COX-1, COX-2 and 15-LOX [37]. Flavonoid compounds in date seeds can also act as antimicrobials[38].

Date seeds can increase immune cells, including NK cells, macrophages, and dendritic cells in Peyer's patches and spleen. The levels of IFN-γ, clusters of differentiation of CD4, CD49b, IL-12 and CD-11b increased compared to normal controls after giving date seeds [39]. Interleukin-12 stimulates T cell and NK cell activation to synthesize various pro-inflammatory mediators, especially IFN-γ. Therefore, an increase in the number of immune cells shows the role of date seeds as immunostimulant.

5. Conclusion

Up to now, the sources of medicinal plants to improve the body's immune system are still very few. Date seeds can be used as anti-inflammatory and immunostimulant. As anti-inflammatory agent, date seed suppress pro-inflammatory mediators (TNF-a, IL-1, IL-1β, IL-2, IL-6), inhibiting edema formation, inhibiting NF-kB translocation and suppress COX2, MMP-9 expression and IFN-γ. As an immunostimulant agent, date seeds can increase IL-2, and IFN-γ synthesis, indeed decrease NO.

Acknowledgment

The authors are grateful to the Research and Community Service section of the University of Jenderal Soedirman for financial support of this project.

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