

## The effect of giving dates towards Low-Density Lipoprotein on experimental test: A systematic literature review

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### ABSTRAK

**Latar Belakang:** Peningkatan kadar kolesterol terutama kadar LDL sering dijumpai pada masyarakat umum. Tingginya kadar LDL sering dikaitkan dengan berbagai permasalahan kesehatan seperti Atherosclerosis, Stroke, dan lain sebagainya. Upaya untuk menurunkan kadar LDL terus dilakukan baik dengan menggunakan terapi obat-obatan ataupun terapi alternatif. Para peneliti telah menemukan adanya efek antikolesterol pada buah kurma. Kandungan senyawa penting seperti plant sterol, flavonoid, dan serat pada buah kurma sangat berperan terhadap penurunan kolesterol darah.

**Tujuan:** Menganalisis pengaruh pemberian kurma terhadap kadar LDL pada uji eksperimental hewan coba tikus dan manusia.

**Metode:** Metode penelitian ini menggunakan Systematic Literature Review. Sebanyak 133 artikel menggunakan keywords "The effect" AND "dates" AND "LDL" AND "rats" AND "humans" AND "RCT". Terdapat 7 artikel eksperimental dengan Randomized Controlled Trial (inklusi) yang dipublikasikan melalui Pubmed, Google Scholar, Sciencedirect, EBSCO. Perlakuan intervensi pada hewan uji coba keseluruhan menggunakan ekstrak kurma dengan rata-rata 630,76 mg/kgBB selama 8-15 hari. Sedangkan, responden manusia mengkonsumsi buah kurma dengan rata-rata 70 g/hari selama 21-28 hari.

**Hasil:** Analisis secara deskriptif yang dilakukan pada berbagai artikel bahwa mayoritas pemberian kurma pada subjek hewan uji coba tikus menunjukkan hasil uji  $p < 0,05$  yaitu adanya pengaruh signifikan terkait penurunan kadar LDL. Selain itu, mayoritas hasil pada subjek manusia menunjukkan hasil uji  $p < 0,05$  yaitu adanya pengaruh signifikan terkait penurunan kadar LDL.

**Kesimpulan:** Dari hasil penelitian ini, dapat disarankan untuk dapat mengkonsumsi kurma 7 buah per hari (100 g) dan menerapkan asupan makan dengan tinggi serat, vitamin dan mineral serta memberikan informasi gizi terkait pangan fungsional (kurma) dalam mengurangi tingkat risiko keparahan penyakit.

**KATA KUNCI:** kurma; Low Density Lipoprotein; Randomized Controlled Trial

### ABSTRACT

**Background:** Increased cholesterol levels, especially LDL (Low Density Lipoprotein) levels, are often found in the general population. High levels of LDL are often associated with various health problems such as Atherosclerosis, Stroke, and so on. Efforts to reduce LDL levels continue to be made either by using drug therapy or alternative therapies. Researchers have found an anti-cholesterol effect in dates. The content of important compounds such as plant sterols, flavonoids, and fiber in dates plays a very important role in reducing blood cholesterol

**Objectives:** To analyze the effect of dates on LDL levels in experimental animal rats and humans

**Methods:** His research method uses a Systematic Literature Review. A total of 133 articles used the keywords "The effect" AND "dates" AND "LDL" AND "rats" AND "humans" AND "RCT". There are 7 experimental articles with Randomized Controlled trials (inclusion) published through Pubmed, Google Scholar, Sciencedirect, EBSCO. The overall intervention treatment in experimental animals used date palm extracts with an average of 630.76 mg / kgBB for 8-15 days. Meanwhile, human respondents consumed dates with an average of 70 g / day for 21-28 days.

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**Results:** Descriptive analysis carried out on various articles showed that the majority of dates given to rat experimental animal subjects showed  $p < 0.05$ , which was a significant effect related to the reduction of LDL levels. Also, the majority of the results on human subjects showed  $p < 0.05$ , which was a significant effect on the reduction of LDL levels.

**Conclusions:** From the results of this study, it can be suggested to be able to consume 7 dates per day (100 g) and to implement a diet high in fiber, vitamins, minerals and provide nutritional information related to functional foods (dates) in reducing the risk level of disease severity.

**KEYWORD:** dates; Low Density Lipoprotein; Randomized Controlled Trial

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## INTRODUCTION

Cholesterol is needed to form membranes, steroid hormones, and bile acids (1). Cholesterol is insoluble in water, so it requires transporters called lipoproteins. LDL (Low-Density Lipoprotein) is one type of cholesterol that has the largest cholesterol content which can be a risk factor for atherosclerosis (2).

Based on the World Health Organization (WHO) data 2016 (3), more than 1,9 billion (39%) of the world's population aged  $\geq 18$  years were overweight and 650 million (13%) were obese. Indonesia was in fourth place (14.3%) with the highest obesity rate in Southeast Asia in 2016. According to Riskesdas 2018 (4), obesity is a health problem that continues to increase in Indonesia. The obese adults population prevalence in Indonesia continues to increase, from 2007 which is 18,8%, there is an increase in 2013 which is 26,6% to reach 31,0% in 2018. The obese adults prevalence in East Java were 22%. In fact, obesity generally causes an increase in the total body fat especially in the abdominal area, which is 120% greater than the recommended weight gain according to age, height, and weight (5).

Various ways to prevent obesity complications have been carried out, including increasing the intake of endogenous antioxidants that can naturally overcome free radicals. The limited amount of endogenous antioxidants in the body, requires supplement intake that contains antioxidants (6).

Dates were proven to contain many nutrients such as carbohydrates, protein, fat, fiber, minerals, vitamins, and antioxidants. Dates have flavonoids that can reduce total cholesterol, triglycerides, and LDL levels in the blood. Flavonoids will increase the release of cholesterol from macrophages and increase the production of Apo A-1 which is a precursor to HDL (good cholesterol). The fiber contained in dates also lower the lipid profile of total cholesterol, triglycerides, and LDL, otherwise increasing HDL level (7).

The LDL reducing effect by dates was proven and expected to be an option in dyslipidemia prevention and promotion, with research interest in anti-cholesterol effects of dates admission the researchers wanted to identify the effect of giving dates on LDL levels in experimental tests.

## MATERIALS AND METHODS

This research was a descriptive approach study using a Systematic Literature Review method. The selection of research data was adjusted to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Data were obtained through the search engine (Google Chrome) (8) an update of the QUOROM guidelines for reporting systematic reviews and meta-analyses. Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their specialty, 1 2 and they are often used as a starting

point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research,<sup>3</sup> and some medical journals are moving in this direction.<sup>4</sup> As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews. Several early studies evaluated the quality of review reports. In 1987 Mulrow examined 50 review articles published in four leading medical journals in 1985 and 1986 and found that none met all eight explicit scientific criteria, such as a quality assessment of included studies.<sup>5</sup> In 1987 Sacks and colleagues evaluated the adequacy of reporting of 83 meta-analyses on 23 characteristics in six domains.<sup>6</sup> Reporting was generally poor; between one and 14 characteristics were adequately reported (mean 7.7, standard deviation 2.7).

The research results were national and international articles (scientific journals and scientific articles) on the effect of giving dates to find out whether dates admission would reduce LDL (Low-Density Lipoprotein) levels in animals, especially rats and human respondents. Research data source are also published through databases including Google Scholar, Pubmed, Sciencedirect, EBSCO. The selected journal has a range of the last 10 years (2011-2020).

The data search used relevant keywords and included all English title variables namely dates, LDL, rats, humans, randomized controlled trials. The search strategy uses Boolean operators, which are the relationships between different search words to help the search strategy. The words used are simple, namely AND, OR, and NOT. This strategy can help with more focused and productive results.

In this study, the inclusion and exclusion criteria for the study were determined. The following are the inclusion criteria and exclusion criteria in the research articles used in the systematic review, namely:

Inclusion criteria: 1. Research using experimental research design with RCT

(Randomized Controlled Trial), 2. Research with the topic of the effect of giving dates on LDL levels, 3. Research using rats and humans as research subjects, 4. Research published in the last 10 years, 5. Research published on a national and international scale, 6. Research using English and Indonesian

Exclusion criteria: 1. Research using animals other than rats (rabbits, etc.). 2. Treatment or research interventions other than dates. 3. Inaccessible research articles and in the form of reviews. 4. Research that discusses HDL levels, cholesterol, and triglycerides.

The adjusted data will be selected and assessed for study quality based on the CASP (Critical Appraisal Skill Program) to assess the quality of the selected studies (9). After that, the data will be extracted and synthesized using the PRISMA method. Data extraction can be done if all the data meet the classified requirements. Furthermore, the data will be extracted by combining data following the inclusion criteria, where the data analysis method uses descriptive methods.

## RESULTS AND DISCUSSIONS

### Prism diagram

In the Systematic Review research, several studies were collected from the Google Scholar, Pubmed, Sciencedirect, EBSCO databases which were summarized in the PRISMA diagram (**Figure 1**). There were 133 articles according to the research title, then the title and abstract were screened to produce 119 articles that did not match the title, abstract, and in the form of a review/book chapter. The results from data extraction obtained 14 articles that match the inclusion criteria. After that, it was screened again based on the full text of the journal and produced 7 articles that could be reviewed for discussion.

### Research Characteristics

In this study, the data on the characteristics of the research were presented for the experimental test of rats (**Table 1**) and the experimental test of the respondent's subject (Human) (**Table 2**).

From the search results of research articles, the effect of dates on LDL levels in experimental animal mice and human respondents obtained 7 research articles. Each of the materials or research treatments from the seven articles used date palm extraction in mice, while human respondents used dates directly.

The entire research article was conducted in 6 different countries, namely India, Pakistan, Jordan, Arab, Indonesia, and Algeria. This study uses the outcome, namely identifying LDL levels in experimental animal trials of mice and human respondents.

#### **The effect of giving dates on LDL levels in experimental rats**

The results of the research on the effect of giving dates on LDL levels in experimental rats are described in detail in Table 3. Musa's research (9), showed that there was no effect on giving date palm extracts on LDL levels ( $P > 0.05$ ). However, there was a change in the reduction of LDL levels in group 3 by 18 mg/dl (extract 2000 mg/kg) and group 4 by 26.67 mg/dl (extract 3000 mg/kg) in this study.

Ahmed, et al research (10) insulin resistance, hyperlipidemia and fatty liver disease. Especially high serum lipid levels are directly connected to the progression of cardiovascular disorders, which are the leading cause of death all over the world. Date palm fruit (*Phoenix dactylifera*, found a significant effect of 300 kg/BW dates suspension compared to the control group ( $P < 0.005$ ). This indicates a decrease in LDL levels with animals receiving 300 mg/kg of date palm suspension, namely 14 mg/dl. In animals receiving 600 mg/kg of date palm suspension, they also experienced a significant reduction compared to the group of animals induced

by hyperlipidemia, namely 33.75 mg/dl.

Ahmad, et al research (9), showed a decrease in LDL levels after consuming khalal and tamr dates. In contrast to the cholesterol-induced group, showed a significant increase in LDL levels. The results of statistical tests ( $p > 0.05$ ), showed no effect on the distribution of dates on LDL levels. Puspa et al research (11), showed a significant effect on giving dates to LDL levels. This research shows that giving date palm ethanolic extract, significantly can reduce LDL levels ( $P < 0.05$ ).

#### **Effect of giving dates on LDL levels in experimental test of respondent subject (humans)**

The effect of giving dates on LDL levels in the experimental test of respondent subjects (Humans) is described in full in Table 4. Alawan, et al research (12) nevertheless, contain more than 70% sugar. This study aims to assess the effects of date consumption (three dates daily, showed a significant effect on the intervention of dates on LDL levels. This suggests that there was a decrease in LDL levels in the intervention group compared to the control group ( $P < 0.05$ ).

Adzani et al research (13), showed that there is no effect on giving dates on LDL levels. This indicates an increase in LDL levels after the intervention of giving dates. Grouchala, et al research (14), showed that there was a difference between Tamr and Ghars dates, where according to the research results, Tamr dates had the effect of significantly reducing LDL levels after being given intervention ( $P < 0.05$ ). Meanwhile, Ghars dates showed an increase in LDL levels although it had no significant effect ( $P > 0.05$ ).

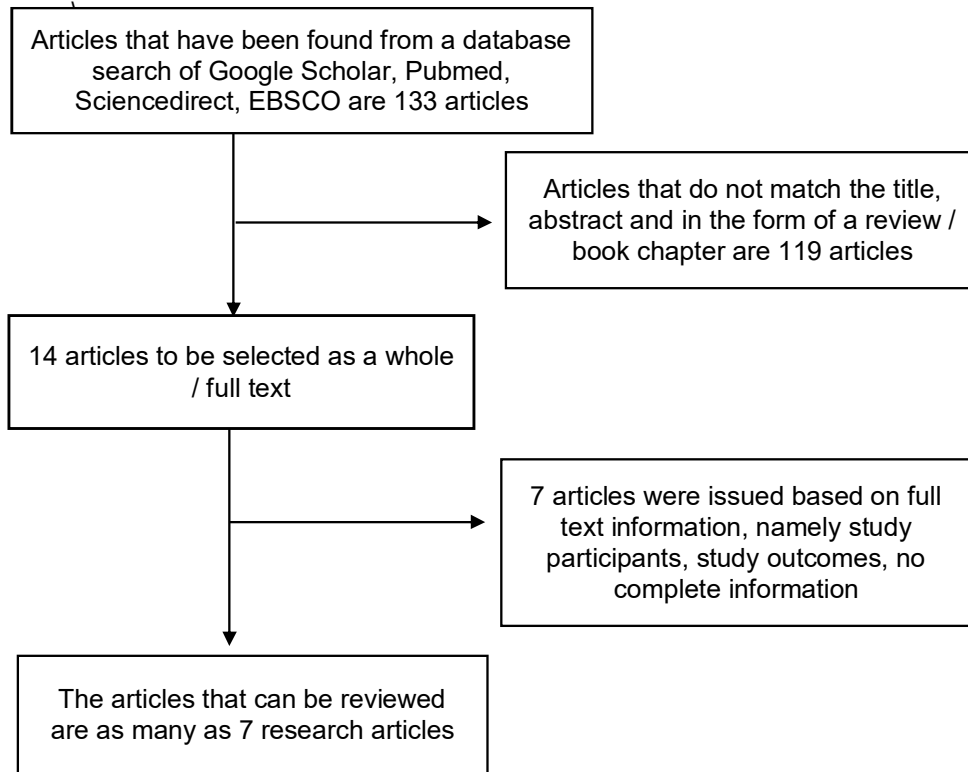


Figure 1. Flowchart of the Effect of Dates on LDL Levels in Experimental Tests

Table 1. Research Characteristics Effect of Dates on LDL Levels in Experimental Rats

Reference	Year of Publication	Research Samples	Research sites	Research design	Research Materials	Outcomes
Musa, Aminu Isa	2018	Albino rats weighing 100-200 kg	Jaipur India	Experimental	Date palm extract	LDL Level
Ahmed, Shadab., <i>et al</i>	2016	Albino rats weighing 250 - 300 g	Animal house of Hussein Ibrahim Jamal (HEJ) Research Institute of Chemistry, Pakistan	Experimental	Dates oral suspension	LDL Level
Ahmad, Mousa Numan., <i>et al</i>	2015	Sprague Dawley rat	The University of Jordan, Amman, Jordan	Experimental	Dates at 2 stages of maturity: Khalal and Tamr	LDL Level
Puspa, <i>et al</i>	2015	Albino rats weighing 120-150 g	Tamilnadu, India	Experimental	Date ethanol extraction	LDL Level

**Table 2. Research Characteristics The Effect of Giving Dates on LDL Levels in Experimental Test of Respondent Subjects (Humans)**

Reference	Year of Publication	Research Samples	Research sites	Research design	Research Materials	Outcomes
Alalwan, <i>et al</i>	2020	Respondents / subjects with a diagnosis of type 2 diabetes	University of Bahrain, Arab	Eksperimental - RCT	Dates	LDL Level
Adzani, Siti Binayu	2015	Student of PSPD UIN Jakarta	UIN Jakarta	Eksperimental - RCT	Dates	LDL Level
Freha, Grouchala., <i>et al</i>	2013	Respondents / healthy subjects (15 - 66 years)	Ibn Khaldoun Univeristy, Algeria	Eksperimental - RCT	Dates (Ghars and Tamesrit)	LDL Level

**Table 3. Research Results from The Effect of Dates on LDL Levels in Experimental Rats**

Reference	n	Research Samples	Independent Variable		Dependent Variable / Outcomes	p-Value	
			Variable	Group	Intervention		LDL Level (mg/dL)
Musa, Aminu Isa (2018)	16	Albino rats weighing 100-200 kg	Date water extraction	Control / Group 1	Normal Water	27.33 ± 3.21	<i>P</i> > 0.05
				Group 2	1000 mg/kg extract	30.00 ± 15	
				Group 3	2000 mg/kg extract	26.67 ± 18.58	
				Group 4	3000 mg/kg extract	18.00 ± 8.4	
Ahmed, Shadab., <i>et al</i> (2016)	40	Albino rats weighing 250 - 300 g	Dates oral suspension	Group 1 (Control)	Destilation water	11.00 ± 2.62**	<i>P</i> < 0.005
				Group 2	Hyperlipidemia induction	43.50 ± 14.51	<i>P</i> < 0.005
				Group 3	Atorvastatin induction	14.00 ± 2.93**	
				Group 4	Suspention 300 mg/kg	14.00 ± 2.51**	
				Group 5	Suspention 600 mg/kg	33.75 ± 17.88	
Ahmad, Mousa Numan., <i>et al</i> (2015)	60	Sprague Dawley rat	Dates at 2 stages of maturity: Khalal and Tamr	Free Cholesterol Group	Control (0%)	16.2 ± 2.5	<i>P</i> > 0.05
					Khalal 5%	22.1 ± 1.7	
					10%	18.7 ± 1.8	
					Tamr 5%	14.0 ± 1.6	
				The group with cholesterol supplementation (cholesterol induction)	10%	14.4 ± 1.9	
					Control (0%)	35.9 ± 4.4	
					Khalal 5%	40.4 ± 3.1	
					10%	42.4 ± 1.8	
Tamr 5%	35.9 ± 4.6						
10%	37.7 ± 4.1						
Puspa, <i>et al</i> (2015)	24	Albino rats weighing 120-150 g	Date ethanol extraction	Group I (Control)	Normal water	26.18 ± 2.52	<i>P</i> < 0.05
				Group II	200 mg/kgBB extract	30.70 ± 2.95	
				Group III	Triton WR (400 mg/kgBB)	158.59 ± 15.26	
				Group IV	Triton WR (400 mg/kgBB) + extract (200 mg/kgBB)	31.93 ± 3.07	

**Tabel 4. Research Results The Effect of Giving Dates on LDL Levels in Experimental Test of Respondent Subjects (Humans)**

Reference	n	Research Samples	Independent Variable			Dependent Variable / Outcomes	p-Value
			Variable	Group	Intervention	LDL Level (mg/dL)	
Alalwan, <i>et al</i> (2020)	100	Respondents/ subjects with a diagnosis of type 2 diabetes	Dates	Control	-	2.36 ± 0.70	P -0.226 (p < 0.05)
				Intervention	3x/dayt in 16 week	2.3035 ± 0.92*	
Adzani, Siti Binayu (2015)	13	Student of PSPD UIN Jakarta	Dates	Intervention (7 fruit each day in 28 day)	day-0 day-29	99.63 ± 9.65 100.23 ± 11.69	P > 0.05
Freha, Grouchala., <i>et al</i> (2013)	52	Respondents / healthy subjects (15 - 66 years)	Dates (Ghars and Tamesrit)	Group T (Tamr)	Befofre After (71 g/day)	1.26 ± 0.21 1.11 ± 0.19*	P < 0.05  P > 0.05
				Group G (Ghars)	Before After (69 g/hari)	1.07 ± 0.16 1.11 ± 0.30	

### Effect of Giving Dates on LDL Levels in Experimental Rats

Based on the results of the systematic literature review that has been done, it states that giving dates can reduce LDL levels. Dates are extensively used as edible fruit. All parts of the dates contain carbohydrates, steroids, alkaloids, and tannins. The phenolic profile of this plant shows the presence of cinnamic acid, flavonoid glycosides, flavonols, and anthocyanins (15).

Musa's Research show there is no significant differences between lipid profile parameters due to differences in the varieties of dates used (16). This has been described following previous studies by Bhathena and colleagues research (17). Rock's *et al* (18), also reported that after 4 weeks of consuming dates, LDL levels were reduced by 8 - 15%. As it is known that fiber can reduce the concentration of LDL levels by absorbing cholesterol and bile acids and increasing HD receptor activity (18) Other studies have shown that dates may have a protective effect against hyperlipidemia through improved lipid profiles (19).

Ahmed *et al* (10) insulin resistance, hyperlipidemia and fatty liver disease. Especially high serum lipid levels are directly connected to the progression of cardiovascular disorders, which are the leading cause of death all over the world. Date palm fruit (*Phoenix dactylifera*, using organic solvents (ethanol) with dates in the form

of suspension showed that the effectiveness of suspension dates is comparable to the standard drug Atorvastatin which shows that phytoactive ingredients from dates are effective in reducing hyperlipidemia, especially LDL levels. Dates are rich in phytochemicals such as phenolic acids, sterols, carotenoids, procyanidins, anthocyanins, and flavonoids. Date fiber can also help in lowering LDL by reducing the absorption of the gastrointestinal tract (7).

Ahmad *et al* (9), using treatment with 2 types of dates for 6 weeks (khalal and tame) obtained insignificant results. Khalal dates are dates with early stages of maturity while tamr dates are dates with the final stage of maturity (dry dates). The likelihood of inadequate dietary intake, differences in experimental protocols and procedures, duration of feeding, and nutritional imbalances affecting outcomes are not significant.

Puspa *et al* (11), using 20 g of date powder extracted in 200 ml of 70% ethanol using the Soxhlet apparatus showed hypolipidemic activity in the ethanol extract of dates against a hyperlipidemic mouse model. The results of the literature study were partly less significant (p > 0.05), due to the possibility of differences in biochemical composition (antioxidant activity, polyphenols, glucose, fructose, sucrose, soluble fiber, insoluble fiber, water, and protein content) in various dates. In this case, the intervention in the form of fruit is also thought to be

less effective than that in the form of date extracts.

### **Effect of Giving Dates on LDL Levels in Experimental Tests for Human Respondents**

Based on the results of a systematic review of human subjects, researchers argue that dates contain flavonoids, high fiber content, and long-chain fatty acids so that they can improve lipid profiles, namely lowering LDL, Triglycerides, cholesterol, and increasing HDL levels.

Alalwan et al (12) nevertheless, contain more than 70% sugar. This study aims to assess the effects of date consumption (three dates daily research on the effect of giving dates on LDL levels by paying attention to the number of dates given and the duration of the intervention showed that the consumption of dates in subjects with type 2 diabetes mellitus was associated with a decrease in LDL. Dates known are a good source of dietary fiber, and can be hypocholesterolemic.

Grouchala et al (14), reported that the Ghars variety did not cause significant variation in lowering LDL levels, while the Tamr variety reduced LDL levels, thereby increasing the HDL profile. The difference in LDL results in the two types is probably because the Tamr type contains polyphenols and higher antioxidant activity than the Ghars type. Several epidemiological studies suggest this effect is related to the soluble fiber content contained in dates. Also, proper dietary intake is essential in preventing disease progression (20).

Siti Binayu research shows that dates cannot significantly reduce LDL and even tend to increase. Several confounding factors can cause inaccurate interpretation of LDL results in this study, such as the consumption of high-fat foods that can increase LDL levels (13).

### **CONCLUSIONS AND RECOMMENDATIONS**

Studies on experimental animals using date suspension/syrup with an average dose of 200 - 300 mg/kg showed a significant effect on reducing LDL levels. Studies on respondents (humans) who were given dates with an average of 7 dates per day for 21-28 days showed a significant effect in reducing

LDL levels. The results of this study are expected to be the basis for developing further research related to the addition of total cholesterol variables (HDL and triglycerides) with the treatment of giving dates and evaluating or identifying food intake other than consumption of dates. The benefits of dates that have been proven in this study can be a recommendation for sufferers of high cholesterol to consume as many as 7 dates per day (100 g of dates) as recommended by the Prophet's sunnah.

Medical personnel, especially nutritionists, are expected to be able to provide the right service or the right diet, one of which is an alternative to giving dates to high cholesterol patients. Also, there needs to be nutrition education or counseling related to the intake of foods high in fiber, vitamins, and minerals for patients with complications from high cholesterol complaints, so that patients or respondents can get wider exposure to nutritional information.

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