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Review Article

Effects of Papaya (*Carica papaya L.*) as Anti-Hyperlipidemia: A Systematic Review

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ABSTRACT

Papaya (*Carica papaya L*) is one of the fruits that is easily found in Asian countries. Papaya has been studied to have good benefits in hyperlipidemia. Papaya contains fiber, vitamins A and C, alkaloids, saponins, and flavonoids which are with antihyperlipidemic properties. The objective of this research was to systematically review studies that have probed into the effect of papaya on triglyceride, total cholesterol, and low-density lipoprotein in hyperlipidemia. This research was conducted to review the effect of papaya fruit as an anti-hyperlipidemic through searching scientific articles related to the topic. Article searches were conducted through Google Scholar, PubMed, and Science-Direct article databases. The selection of articles in the systematic review according to the inclusion criteria was based on articles published from 2016 to 2021, enrolling animals or patients with hyperlipidemia. The experimental design, main outcomes such as triglycerides, total cholesterol, LDL-C, HDL-C and body weight (BW) were investigated. Totally, three articles were reviewed in full to discuss the effect of papaya fruit as antihyperlipidemia in a systematic review. The systematic review reported that administration of papaya juice could improve lipid profiles. The content of fiber, vitamins A and C and phytochemicals in papaya has the potential of anti-hyperlipidemia by improving lipid profile.

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Introduction

Cardiovascular diseases are non-communicable diseases, which result from heart and blood vessel disorders; such as coronary heart diseases, cerebrovascular diseases, and rheumatic heart diseases (1, 2). The World Health Organization (WHO) reported that cerebro- and cardio-vascular diseases are the leading cause of death globally with 17.9 million people every year. Four of 5 cardiovascular deaths are due to heart attacks and strokes (2). In Indonesia, the prevalence of heart and blood vessel diseases increased from year to year, and reached 4.2 million in 2018 (3).

Hyperlipidemia, hyperglycemia, hypertension, and obesity are the risk factors of heart diseases and stroke (2, 4). Unhealthy diet which consists of high saturated fat and low fiber foods will affect the incidence of hyperlipidemia (5). Hyperlipidemia is biochemically characterized by abnormal lipid metabolism, with high total cholesterol, triglycerides,

low density lipoprotein-cholesterol (LDL-C) levels, and low high density lipoprotein-cholesterol (HDL-C) levels (6). Foam cell formation has a vital role in development of coronary artery diseases, because high levels of LDL-C in low levels of HDL-C in peripheral tissues induce inflammation and oxidative stress on endothelial layer of arterial blood vessel walls (6, 7). In addition, the LDL-C components accumulate on the arterial walls to generate plaques, which trigger narrowing and hardening of blood vessels and cause decreased blood flow (8-10). Oxidative stress in blood vessel will produce high reactive oxygen species (ROS), and will worsen tissue damages in the vital organs, such as the heart and brain (11-13).

Fruits and vegetables contain high fibers and antioxidants, which have benefits to improve glucose and lipid metabolism (14-16). *Carica papaya Linn* is one of *Caricaceae* family member of tropical fruits that is widely distributed in several country regions in the world, especially in Central and South America, Asia and other tropical countries. Papaya is included in the tropical fruit group that is widely traded; so that it has a significant effect on the economic sector (17). Indonesia is one of the highest countries with papaya cultivation; so that this fruit is available everywhere and in every season in Indonesia cities and is also relatively cheap (15).

Papaya contains micronutrients and secondary metabolites, which has important properties to reduce lipid and cholesterol in the blood circulation through inhibition of oxidative stress inhibitory pathways. Papaya contains nutrients that are beneficial for health and contains high fibers, lycopene, and vitamins A and C (18). In 100 g of papaya, 0.8 g of fiber, 328 mg of vitamin A, 888 IU of beta carotene, and 61.8 mg of vitamin C exist (18, 19). Several studies demonstrated that papaya fruit contains bioactive components of polyphenols, flavonoids, and triterpenoids. Flavonoid in ripe papaya is 92.95 mg including GAE/100 g dry weight; however, there are no studies to report the polyphenol and triterpenoids contents of papaya (19). The nutritional content and bioactive components of papaya fruit have the potential to provide a reduction in hyperlipidemia (18, 20). A previous study showed that rats induced by a high-fat diet and given 10% papaya juices could improve lipid profile and liver morphology values. The fiber content in fruit can reduce the absorption of fat in the intestines, so that there is a decrease in cholesterol level. During the 24-day intervention, this study showed a decrease in LDL-C, VLDL-C, triglycerides, and total cholesterol, as well as an increase in serum HDL-C levels (20). This study is a systematic review that aims to explore the literature evidence of the potential of papaya fruit as an anti-hyperlipidemia agent. Therefore, this systematic review aimed to investigate the effect of papaya fruit as an anti-hyperlipidemic product.

Materials and Methods

Search Strategy

This study was a systematic review using the frameworks from Aghakhani and Massaomi (2019) and Sharafi *et al.* (2019) (21, 22) and conducted using some databases such as Google Scholar, PubMed, and Science-Direct. Search strategy in this study was searching keywords like “papaya”, “lipid”, “hypolipidemic”, “lipid profile” and “anti-hyperlipidemia” for those all databases.

Study Selection

We selected full text articles using the PICOS protocol (Table 1), which met the inclusion criteria enrolling articles published from 2016 to 2021 with Randomized Control Trial (RCT) design in patients or animals with hyperlipidemia. The main outcomes of research study were triglycerides, total cholesterol, LDL-C and HDL-C levels and body weight (BW).

Data Extraction

Two authors worked independently to select all published articles using Zotero software (https://zotero.org). Selected articles were extracted and written by the order of authors, publication year, research subject, intervention, research design, duration, and outcomes after papaya administration in patients/rats with hyperlipidemia.

Table 1: PICOS criteria for selection of full text articles.

Variable	Inclusion criteria	Exclusion criteria
Population	Rats or patients with hyperlipidemia	
Intervention	Papaya fruit or papaya juice	Raw papaya
Comparator	Treatment and control groups	
Outcome	Triglycerides, total cholesterol, LDL-C, HDL-C levels and BW	
Study design	RCT	Non English articles Articles published before 2016 Case reports, review and incomplete articles

PICOS: Population, intervention, comparator, outcome, and study design, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein-cholesterol, BW: Body weight, RCT: Randomized control trial.

Results

Systematic review flowchart for identification and selection full text articles was shown in Figure 1. Totally, 593 full text articles were collected in the initial searches after removal of duplicates. In brief, 583 articles were excluded due to their irrelevant titles and abstracts. The remaining 7 articles were excluded as they did not match the inclusion criteria. Three articles were then fully reviewed to discuss the effect of papaya fruit as anti-hyperlipidemic in a systematic review. Three articles revealed investigation of the effect of papaya (*Carica papaya L.*) as an anti-hyperlipidemic (Table 2).

Triglyceride level

Deenin *et al.* (2021) reported that triglyceride level significantly decreased after administration of 1 mL/100 g BW of papaya juice ($p<0.05$) (23). This is in line with the Od-Ek study (2020) which revealed that serum triglyceride in the group given papaya juice (0.5 mL/100 g BW and 1 mL/100 g BW) for 4 weeks were lower than in the negative control group (24). However, Tijjani *et al.* (2020) reported that administration of 7 mL/kg BW of papaya juice for 14 days significant decreased the triglyceride serum level (25).

Total Cholesterol Level

A significant decrease in total cholesterol level (TC) occurred in the papaya juice group which was given in doses of 0.5 and 1 mL/100 g BW ($p<0.01$; $p<0.001$), when compared to the negative control group. These results indicated that papaya significantly reduced liver TG and TC content (23). These results are also in line with the Od-Ek's study which reported that serum cholesterol in the intervention group showed a significant difference in comparison to the negative control ($p<0.01$) (24). Meanwhile, research by Tijjani *et al.* (2020) reported that giving 7 mL/kg BW of papaya juice significantly decreased by 75.51 mmol/L when compared to the control group ($p<0.05$) (25).

LDL-C Level

Administration of papaya juice could significantly reduce LDL-C level by 77.40 mmol/L ($p<0.05$) (23). It is in line with the Od-Ek's study which found a decrease in LDL-C in rats fed a high-fat diet after being given 0.5 and 1 mL/100 g BW of papaya juice to 178.0 and 187.6 mg/dL, respectively (24). The decrease in LDL-C was statistically significant when compared to the control ($p<0.01$)

Discussion

Based on the systematic review of 3 articles above, the research methods have something in common, namely an experimental design in an *in vivo* study to analyze the effect of papaya administration on

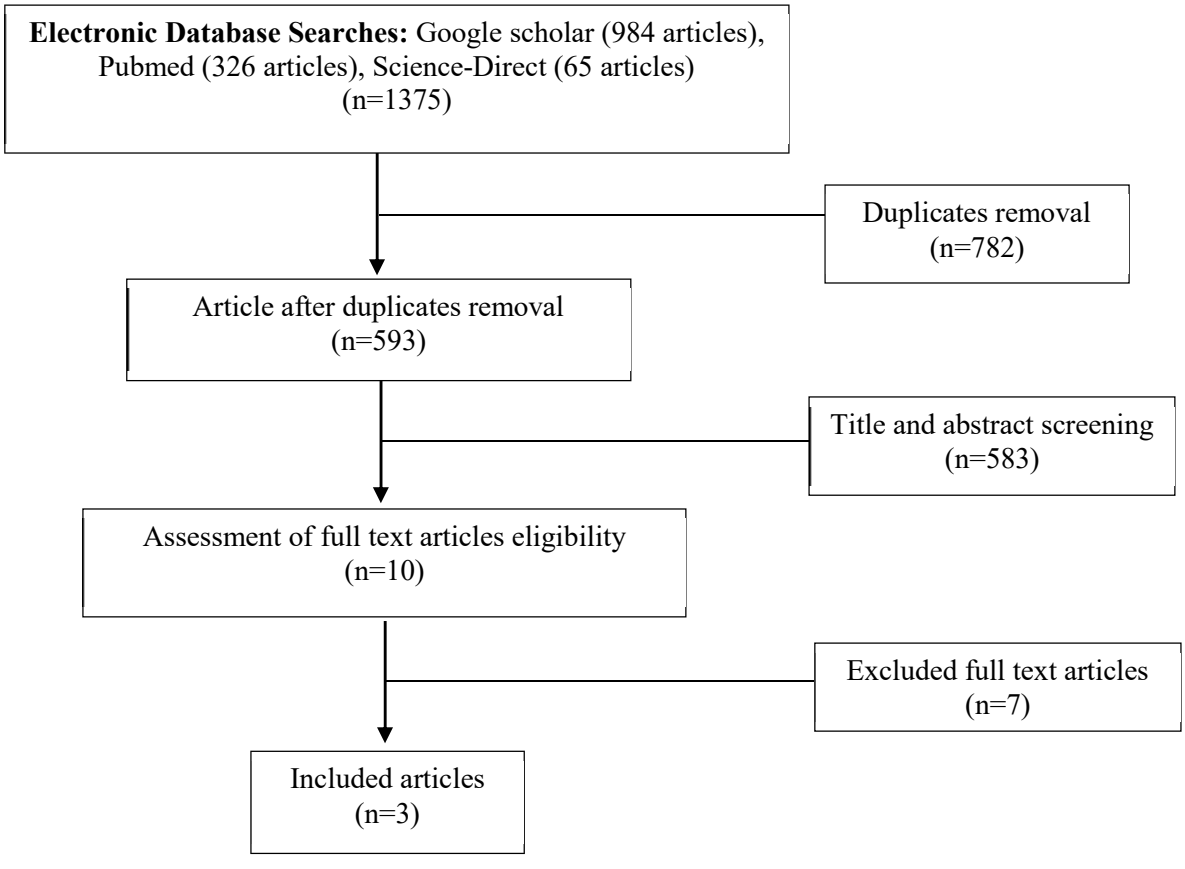

Figure 1: Systematic review flowchart for identification and selection full text articles.

Table 2: The articles that revealed investigation of the effect of papaya (*Carica papaya L.*) as an anti-hyperlipidemic.

Authors, year	Country	Sample	Control	Intervention	Research design	Duration	Findings
Deenin *et al.*, 2021 (23)	Thailand	Sprague-Dawley rats fed a high-fat diet	High fat diet	Papaya juice 0.5 and 1 mL/100 g BW	Experimental design, Post-test only with control group	4 weeks	Administration of 1 mL/kg BW per day for 4 weeks of papaya juice significantly decreased when compared to the control group, The administration of papaya juice could significantly reduce triglyceride level when 1 mL/kg BW of papaya juice was given, while total cholesterol level decreased significantly in both groups (0.5 and 1 mL/kg BW) in comparison to the control group.
Od-Ek et al., 2020 (24)	Thailand	Sprague-Dawley rats fed a high-fat diet	High fat diet	Papaya juice (Holland cultivar) 0.5 and 1 mL/100 g BW	Experimental design, Post-test with only control group	4 weeks	The administration of 0.5 and 1 mL of papaya juice showing a significant decrease in body weight and adipose tissue as well as a decrease in triglycerides, total cholesterol, serum LDL-C and significant increase in HDL-C.
Tijjani et al., 2020 (25)	Nigeria	*Rattus norvegicus* fed a high-lipid-diet	High lipid diet	Papaya juice (pawpaw) 7 mL/kg BW	Experimental design. Post-test with only control group	14 days	Papaya juice significantly reduced total cholesterol, triglyceride, LDL-C and elevated HDL-C levels compared to the control group

BW: Body weight, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol.

lipid reduction or hypolipidemic properties. The content of fibers and antioxidants in fruits can affect reduction of the risk of these diseases. This is evidenced by several other studies showing high intake of fruits could lower the rate of coronary artery diseases and the mortality rate (26). In addition, the content of antioxidants such as vitamins A and C in papaya fruit can affect the improvement of lipid profile values in rats induced by a high-fat diet (24).

Fiber is a group of polysaccharide carbohydrates which are divided into soluble and insoluble fibers. The type of fiber in papaya is pectin (27) that can increase bile acid excretion due to increased conversion of cholesterol to bile acids (28). The mechanism of hypolipidemia for papaya fiber is through the decreased absorption of triglycerides in the intestine, increased synthesis and excretion of bile acids, and inhibition of cholesterol synthesis by short-chain fatty acids in the intestine (29, 30). Soluble fibers can trap fat in the small intestine, so that it can reduce cholesterol level in the blood up to 5% (27). The pectin in papaya can affect the absorption of bile acids through gel formation, thereby triggering viscosity, decreasing miscle formation and reducing the fat absorption (28). Thus, dietary fiber is considered capable of reducing cholesterol level in blood plasma, so that it is expected to reduce and prevent the risk of cardiovascular diseases (27, 29).

Vitamin A and beta carotene in papaya have a hypolipidemic effect by inhibiting the lipid peroxidation process and reducing nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) in the process of triglyceride formation (18). Deenin *et al.* (2021) reported that papaya can reduce liver inflammation by inhibiting the overproduction and activity of pro-inflammatory cytokines generated in liver inflammation in high-fat diet-induced rats (23). The mechanism is possible from the indirect action of papaya to reduce reactive oxygen species (ROS) and can modulate the overproduction of cytokines. In addition, papaya itself may play a direct role in the inflammatory process (31).

Vitamin C or ascorbic acid in papaya (61.8 mg/100 g) can increase serum HDL-C values by increasing the rate of cholesterol being excreted in the form of bile acids, resulting in the process of reverse cholesterol transport (32). Reverse cholesterol transport is the removal of unesterified cholesterol level through lecithin cholesterol acyltransferase (LCAT). Cholesterol esters contained in HDL-C are then returned to the liver to be excreted through the bile. HDL oxidation will modify the structure of apolipoprotein A-1 in activating LCAT (22, 32). In addition, vitamin C has been shown to prevent the loss of activity paraoxonase during oxidative stress resulting in attenuating oxidant modification of LDL-C (33).

Many natural products rich in polyphenols, and strong antioxidant activity have been studied for their positive benefits in the treatment of hyperlipidemia. The presence of these bioactive compounds as well as the significant antioxidant activity *in vitro* has been observed in the pulp of papaya (34). Tijjani *et al.* (2020) reported that the phytochemicals detected in papaya fruit consisted of alkaloids, saponins, and flavonoids (25). The benefits of these three secondary metabolites in hypolipidemia are that they can reduce triglyceride level through the activation mechanism of lipoprotein lipase (LPL) receptors, so that they can hydrolyze triglycerides into fatty acids and glycerol. Saponins and tannins can inhibit HMG-CoA reductase activity and increase LDL-C receptor activity (31, 35). Alkaloids are basic nitrogenous organic compounds, which are found in many natural plants. Most alkaloids have a complex cyclic structure and show significant activity in lipid metabolism (36). These natural compounds can increase lipid catabolic metabolism and inhibit anabolic metabolism, thereby limiting the availability of lipids such as fatty acids (37, 38). Saponins were found to inhibit the enterohepatic circulation of bile acids, making them unavailable for intestinal absorption, leading to decreased absorption of cholesterol from the intestine (39). Research by Maisarah *et al.*, 2013 illustrated the total amount of flavonoids in ripe papaya fruit to be 92.95 mg (GAE/100 g dry weight) (19). Flavonoids act as antioxidants, protect LDL-C cholesterol from oxidation, inhibit platelet aggregation and act as an anti-inflammatory and anti-tumor agent (40, 41). Meanwhile, flavonoids also play a role in inhibiting the activity of HMG-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis to prevent the increase in total cholesterol level (35, 42). The limitation of this research is that the search strategy is limited to the last 5 years and has not used Cochrane's search strategy.

Conclusion

The evidence found from the systematic review was based on these 3 articles showing that papaya contains fiber, vitamins A and C, alkaloids, saponins, and flavonoids. The content of fiber, vitamins A and C and phytochemicals in papaya has the potential of anti-hyperlipidemia role by decreasing triglycerides, total cholesterol, LDL-C, VLDL-C, and increasing HDL-C levels. This systematic review on papaya can be used as the basis for further research in developing the right dosage, so that it can be applied for prevention and therapy of hyperlipidemia.

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Conflict of Interest

None declared

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