

## REVIEW ARTICLE

# The Effects of Papaya Fruit as Anti Diabetes Type 2: A Review

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## ABSTRACT

Diabetes mellitus (DM) is a disease that results in an imbalance in the body ability to use food efficiently caused by the pancreas failure to produce insulin or dysfunction of the body to use insulin properly. Type 2 DM can cause oxidative stress which results in changes in endogenous antioxidant activity and also an increase in oxidative biomolecular damage. This condition causes patients with type 2 DM to require large amounts of exogenous antioxidant intake to inhibit oxidative damage in the body. One of the medicinal plants that has antihyperglycemic activity and high antioxidants is papaya (*Carica papaya Linn*). Based on a review of several studies noted that papaya contains vitamin C, fiber saponins and flavonoids that can lower blood glucose levels. However, to prove this effect, further clinical trials are needed to be done.

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## Introduction

Diabetes mellitus is a disease that is considered as one of the major health problems in the world (1). Diabetes mellitus is caused by a disturbance in the body's metabolism which is characterized by abnormalities in carbohydrate, fat, and protein metabolism caused by impaired insulin secretion, insulin insufficiency or both (2). Complications of diabetes mellitus generally cause death, this can be prevented by the use of traditional medicines using medicinal plants that have antihyperglycemic activities (3). Type 2 DM in its development can cause oxidative stress which is characterized by an imbalance between oxidants and antioxidants in the body. In conditions of oxidative stress decreased endogenous antioxidant activity and increased oxidative damage to biomolecules (4). This is probably due to an increase in controlling

excessive oxidative stress due to abnormalities in glucose metabolism (5).

Several studies have shown that oxidative stress plays a role in systemic inflammation, impaired pancreatic  $\beta$  cell secretion, impaired glucose use in peripheral tissues and endothelial dysfunction. The occurrence of oxidative stress in DM are through three mechanisms of nonenzymatic glycation of proteins, pathways of sorbitol polyols (aldose reductase), and auto glucose oxidation (4). Excessive oxidative stress due to abnormalities in glucose metabolism can be controlled by regulating food intake, especially sources of antioxidants (4-6). DM control in the form of a combination of multiple drugs and lifestyle changes can play a role in preventing vascular complications due to oxidative stress as well as reducing morbidity due to cardiovascular disease and other causes in people with type DM (7, 8).

Increased oxidative stress causes people with type 2 diabetes to require large amounts of exogenous antioxidant intake to inhibit oxidative damage in the body (4-6). Papaya pharmacology and activity from several previous studies showed that papaya extract lowered blood sugar levels, which is thought to have vitamin C, fiber, flavonoid and saponin (9). Besides being rich in nutrients fruits guava and papaya are cheap and affordable fruits, easily available everywhere and a fruit throughout the year. Based on this background, the authors were interested in making a review of the effect of papaya fruit as an anti-diabetes type 2.

### *Papaya Carica Papaya Linn*

*Carica papaya Linn* (Caricaceae) is a type of tropical plant which is the only species in the genus *Carica*. Taxonomy papaya has been described in Table 1 (9). Tropical plants originating from the tropical regions of America are now widely cultivated in other tropical regions of the world (10-15). Papaya fruit can be consumed like a melon, which is available throughout the year (12). The *Carica papaya Linn* tree is an upright tree that grows fast as high as 7-8 m with latex and stems about 20 cm in diameter (2). The stem is hollow cylindrical and supports the leaves (like an umbrella) (13). The leaves are soft, lobed, clustered near the top of the plant, measuring up to 80 cm long (11-15).

The fruit is yellowish to orange in color, long to almost rounded shape, about 7.5-45 cm, with a

**Table 1:** Taxonomy of papaya fruit.

Taxonomy	
Kingdom	Plantae
Division	Magnoliophyta
Subdivision	Spermatophyta
Class	<i>Magnoliopsida</i>
Order	Brassicales
Genus	<i>Carica</i>
Species	<i>Carica Papaya Linn</i>

meat thickness of 2.5–5 cm, sweet and juicy (12). The nutritional content of papaya (*Carica papaya*) in 100 grams of fruit was presented in Table 2. Papaya is one of the fruits that is rich in vitamins and other nutrients, the price is relatively cheap and can be used as a substitute for various health conditions (i.e., constipation, overweight etc.). Other study showed that after consuming papaya fruit as much as 438 g can significantly reduce blood glucose levels (13). Not all fruits that contain sugar should be avoided by diabetics, one of them is papaya. It is safe for diabetics to consume papaya in small portions and preferably in the morning as an energy feeder. Papaya has a glycemic index of 23 which can be categorized as a low glycemic index. A low glycemic index can reduce insulin resistance and insulin levels (13).

### *Benefits of Vitamin C*

Other studies have shown that papaya has more vitamin C content than soursop (*Annona muricata*), langsung and sugar apple (14). Papaya contains 61 mg

**Table 2:** Nutritional content of papaya fruit (16, 17).

Nutrient content	Levels per 100 grams of fruit	Unit
Energy	163	KJ
Protein	2.01	Gram
Carbohydrate	16	Gram
Fat	0.2	Gram
Fiber	5.9	Gram
Vitamin C	61.8	mg
Vitamin B6	0.1	mg
Niacin (vitamin B3)	0.38	mg
Vitamin A	328	µg
Thiamin (vitamin B1)	0.2	mg
Folate (vitamin B9)	38	µg
Riboflavin (vitamin B2)	0.05	mg
Lycopene	3.4	mg
B-carotene	0.5	mg
Phenol	171	mg
Flavonoids	20.47	mg
Iron	0.1	mg
Calcium	31	mg
Carotene	0.8	mg
Potassium	275	mg
Magnesium	10	mg

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of vitamin C every 100 grams of fruit (15, 16). In some literature sources has been stated that the dose of vitamin C per day for adults is 70-90 mg/dl, so that papaya can be used as an alternative sufficient vitamin C patient with type 2 diabetes mellitus (17). Man cannot produce vitamin C in the body because they do not have the L-gulonolactone oxidase enzyme that catalyzes the final step in the synthesis of ascorbic acid so that it needs food intake from outside the body (18).

Vitamin C is an important nutrient for human that acts as a reducing agent in the oxidation process of free radicals, so it can be said that vitamin C can act as an antioxidant (18). The role of vitamin C or ascorbic acid in diabetes is as an inhibitor of the aldose reductase enzyme, so that the reduced equivalent use of reducing (19). The availability of equivalent reducing agents is useful for oxidized glutathione conversion (GSSG) to reduced glutathione (GSH). This is what can then prevent the accumulation of sorbitol in the network. Another benefit of using antioxidants is minimizing the formation of AGEs (advance glycosylation end products). This condition is analogous to the use of vitamin C in minimizing the browning process in food. The mechanism of minimizing the formation of AGEs is inseparable from the role of vitamin C in the pathway of sorbitol polyols (aldose reductase). Reducing the accumulation of sorbitol in the tissue will suppress fructose, so that the non-enzymatic replication process is also suppressed (4, 19).

Vitamin C is an important micronutrient that dissolves in water and participates in a number of enzyme reactions. Vitamin C is an antioxidant that prevents oxidative damage from free radicals, which protect tissues from oxidative stress. One of the roles of antioxidant activity is to prevent the occurrence of oxidative stress (20). Vitamin C is a non-enzymatic antioxidant that has an important role in protecting cell damage from free radicals. Vitamin C can reduce insulin resistance by improving endothelial function and reducing oxidative stress. Vitamin C reduces glucose toxicity which contributes to preventing a decrease in  $\beta$  cell mass and insulin levels. Increased insulin-mediated vitamin C work is mainly due to an increase in non-oxidative glucose metabolism (21).

### Benefits of Fiber Use

Food fiber is a part of plants that can be consumed and consists of carbohydrates which have resistance to digestion and absorption in the small intestine (22). Since the mid-1970s, dietary fiber has been known to reduce blood sugar levels, as evidenced by a 6-week long-term clinical trial which showed that diets high in soluble fiber can reduce blood sugar

profiles. Dietary fiber is classified into two namely soluble fiber and insoluble fiber. The benefits of soluble fiber are slowing down gastric emptying, so it can reduce the response of postprandial blood sugar (23). Other studies have shown that 7.5 grams of soluble fiber can reduce postprandial glycemia, which is associated with slowing gastric emptying. Diabetes with complications or relative hyperglycemia showed a significant delay in gastric emptying by soluble fiber (24).

Another study, the therapeutic effect of water soluble fiber for patients with type 2 diabetes in 120 respondents in China proved that soluble fiber with a content of 20 grams was able to improve postprandial 2-hour blood sugar, fasting insulin levels, insulin resistance index, and effectively maintaining glycemic control without affecting the function secretion of the islets of Langerhans (25). Eating foods high in fiber can control blood glucose and reduce insulin requirements. Consumption of fiber, especially insoluble fiber contained in grains and some plants, can help prevent the occurrence of diabetes by increasing the work of the hormone insulin in regulating blood glucose in the body. Insoluble fiber can pass through the digestive system as a whole and can provide a longer and satisfied taste and help control appetite (26). Another benefit of insoluble fiber is that it can reduce the risk of type 2 diabetes and can also increase insulin sensitivity (27). The results of other studies also obtained the same findings, namely the finding of a positive relationship between fiber intake and blood sugar levels of type 2 diabetics, which means lower fiber intake, the higher blood sugar levels of diabetics with the strength of the relationship in a strong category (28).

### Benefit of Flavonoids

Flavonoids are phenyl propanoid compounds with a carbon frame C6-C3-C6. Flavonoids are a group of secondary metabolites that are widely found in plants, especially from the *legiminoceae* group. Flavonoids are generally bound or conjugated with sugar compounds. Flavonoid compounds have many activities, one of which is antihyperglycemic. Flavonoids have activities to reduce blood sugar levels by being able to regenerate pancreatic beta cells and increase insulin secretion, also increase cell sensitivity to insulin. Another mechanism of flavonoids that shows hypoglycemic effects is reducing glucose absorption and regulating the activity of expression of enzymes involved in carbohydrate metabolism (29).

Flavonoids are effective as exogenous antioxidants which can have a curative effect on pancreatic beta cells and improve insulin sensitivity

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by reducing oxidative stress and reducing reactive oxygen species (ROS). This mechanism dampens free radicals directly by donating hydrogen atoms. Flavonoids will be oxidized by radicals to be more stable and less reactive compounds (30). Flavonoids also inhibit GLUT-2 in the intestinal mucosa. This inhibitory mechanism is non-competitive so it can reduce glucose absorption and blood glucose levels can decrease (31).

Flavonoids can also inhibit phosphodiesterase, so that it can cause insulin secretion by pancreatic beta cells. Flavonoids are alpha-glucosidase inhibitors which inhibit the alpha-glucosidase enzyme needed for carbohydrate breakdown before being absorbed as monosaccharide. The mechanism of action above results in a decrease in blood glucose (32). The inhibitory mechanism of flavonoids for the  $\alpha$ -glucosidase enzyme is through hydroxylation bonds and substitution on the  $\beta$  ring. The principle of this inhibition is to produce a delay in carbohydrate hydrolysis and glucose absorption and to inhibit sucrose metabolism into glucose (33). Antihyperglycemic activity analysis was also carried out on papaya fruit, with a dose of 100–400 mg / kg, intra-peritonally for 21 days. The test results showed a decrease in blood glucose levels (34).

In the mechanism of healing diabetes, flavonoids are thought to play a significant role in increasing the activity of antioxidant enzymes and are able to regenerate damaged  $\beta$ -pancreatic cells so that insulin deficiency can be overcome. The flavonoids contained in plants are thought to also improve the sensitivity of insulin receptors (35). Flavonoids can inhibit  $\beta$  cell damage on the pancreatic Langerhans island which produces insulin and stimulates the release of insulin in pancreatic  $\beta$  cells to be secreted into the blood, in addition flavonoids can also restore insulin receptor sensitivity to cells (36).

### Benefits of Saponin

Saponins are natural glycosides that are bound to steroids or triterpene. Saponins have activities such as insulin, can inhibit lipolysis, increase glucose uptake by adipose cells. A study shows that saponin compounds can improve insulin resistance (37). Saponins function as inhibitors of the  $\alpha$ -glucosidase enzyme. The enzyme plays a role in converting carbohydrates to glucose, if this enzyme is inhibited, the blood glucose level in the body will decrease (38). It was shown that saponins can reduce blood glucose levels by stimulating insulin release (39). Saponin works by preventing the absorption of blood glucose by preventing glucose transport to the intestinal border brush in the small intestine which is the place for glucose absorption. The mechanism

that saponin is also thought to have a role in reducing blood glucose levels (40).

The mechanism of saponin with the occurrence of pancreatic regeneration which causes an increase in the number of pancreatic  $\beta$  cells and islands of Langerhans, so that insulin secretion will increase. Increased insulin secretion will help reducing blood glucose levels. Regeneration of pancreatic  $\beta$  cells occurs because of the presence of quiescent cells in the pancreas which have the ability to regenerate (41). The results of other researchers showed that there was a significant decreased blood glucose concentration by the papaya extract. The results of phytochemical analysis of papaya leaf extract are known to contain flavanoids, saponins, one of which has antihyperglycemic activity (15). A dose of 5000 mg/kg BW was shown to reduce blood glucose levels. A decrease in blood glucose levels in Wistar rats was demonstrated due to the active substance content in papaya of saponins and alkaloids that induced hypoglycemia. In addition, the active substances contained in papaya also played a role in stimulating insulin release from pancreatic beta cells and somatostatin release, but suppressed glucagon secretion (42).

### Conclusion

Papaya contains nutrients that are beneficial for diabetes mellitus. But to prove these effects, it is needed to undertake further clinical trials.

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### Conflict of Interest

None declared.

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