



## Antidiabetic potential of *Carica papaya* L. and its constituents: From folkloric uses to products development

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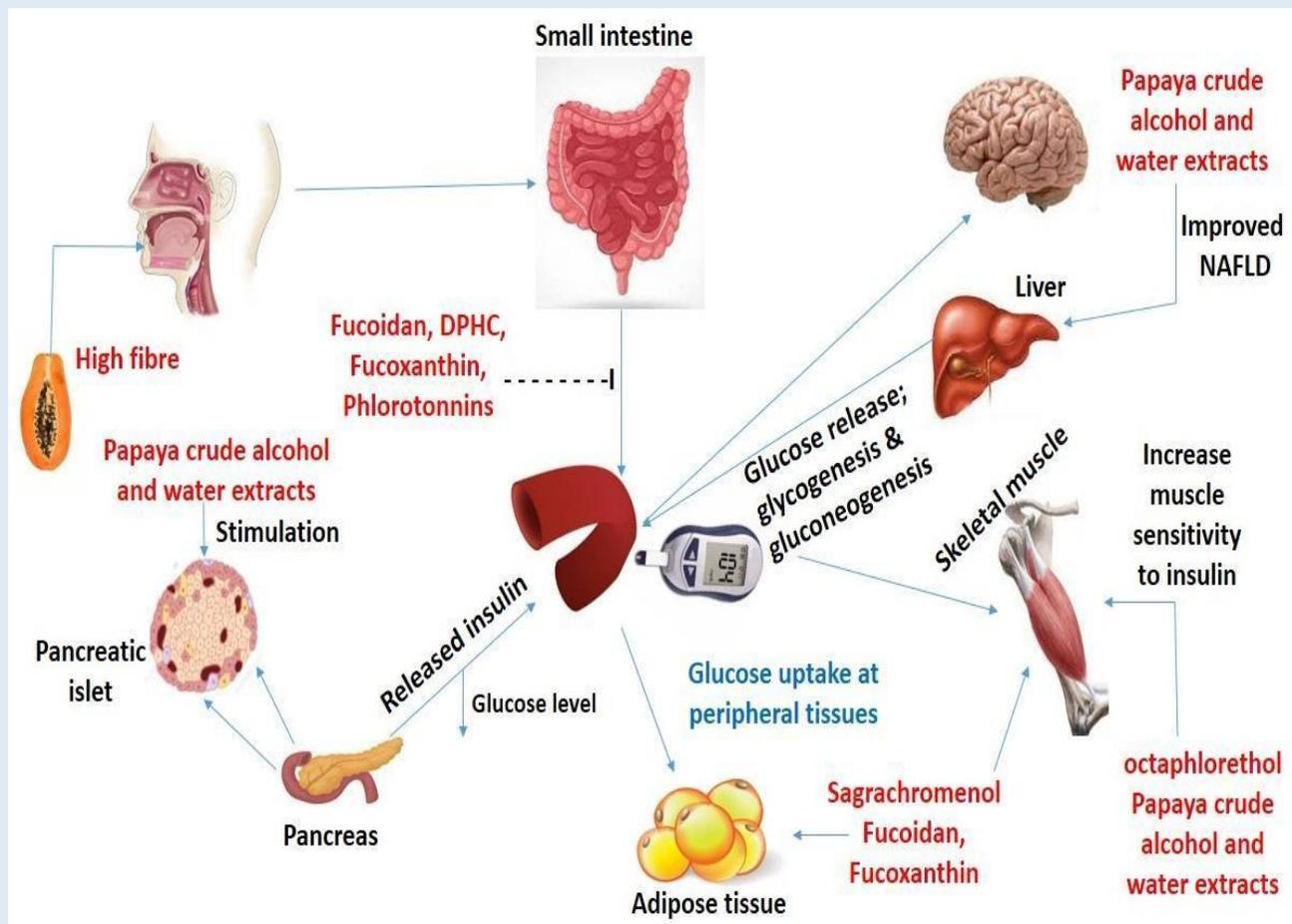
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### ABSTRACT

*Carica papaya* L. is a plant that has a reputation for being antidiabetic. This review is focused on antidiabetic properties of *Carica papaya*. A comprehensive search was performed using various electronic databases including Researchgate, PubMed, Google Scholar, Biomedgrid.com and ScienceDirect. 224 publications were downloaded, out of which one 107 relevant publications were reviewed. The fruit, leaves, and seeds of this plant have been reported to possess antidiabetic properties at different dosages via *in vivo*, *in vitro*, and *ex vivo* studies. Fortified papaya cake, MPPB flour (containing *C. papaya*), and brotowali extract (fortified papaya leaves and sugarcane extracts) displayed significant hypoglycaemic effect. From a clinical trial, the fruit consumed after meals significantly reduced blood glucose level in a quasi-

experimental study. Some bioactive compounds found in the plant's extracts have been linked to the antidiabetic effect of the plant. It has been discovered that the leaf extract contains hypoglycemic saponins, alkaloids, flavonoids, triterpenoids, and tannins. Few compounds with antidiabetic characteristics have been identified from the extracts of this plant's seeds, including hexadecanoic acid, methyl ester, 11-octadecenoic acid, N, N-dimethyl-, n-hexadecanoic acid, and oleic acid. Therefore, pawpaw fruit consumption might help to mitigate the symptoms of diabetes. For the development of new natural remedies for management and prevention of diabetes, additional studies, particularly those on the isolation of antidiabetic principles from various portions of *C. papaya*, will be crucial.

**Keywords:** *Carica papaya*; Antidiabetics; Phytoconstituents; Clinical trials; Papaya products

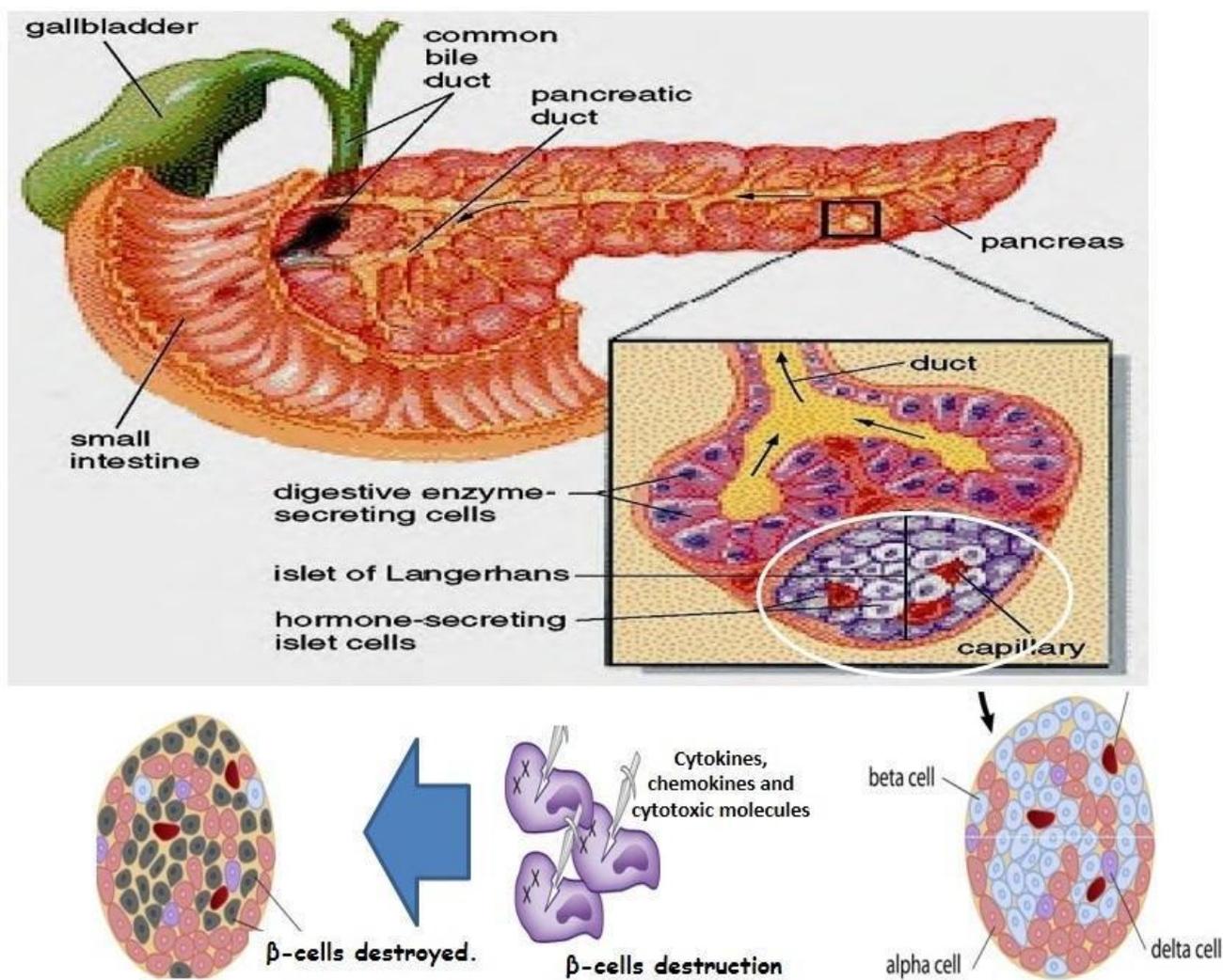


**Graphical Abstract:** Antidiabetic Potential of *Carica papaya* L. and its constituents

**INTRODUCTION**

Diabetes is a long-term metabolic illness marked by high blood glucose levels, which over time cause major microvascular and macrovascular problems including harm to the heart, blood vessels, eyes, kidneys, and nerves. Diabetes can be divided into types 1 and 2, with type 2 being the more prevalent and typically affecting adults. Type 2 diabetes happens when the body develops insulin resistance or doesn't create enough insulin, whereas type 1 diabetes (Figure 1) is a chronic illness in

which the pancreas produces little to no insulin on its own. All income levels of countries now experience a much higher prevalence of type 2 diabetes than they did 30 years ago. The majority of people who have diabetes reside in low- and middle-income nations, where it affects 422 million people and is directly to blame for 1.5 million fatalities each year [1-2]. Over the past few decades, the prevalence of diabetes has been continuously increasing [2].



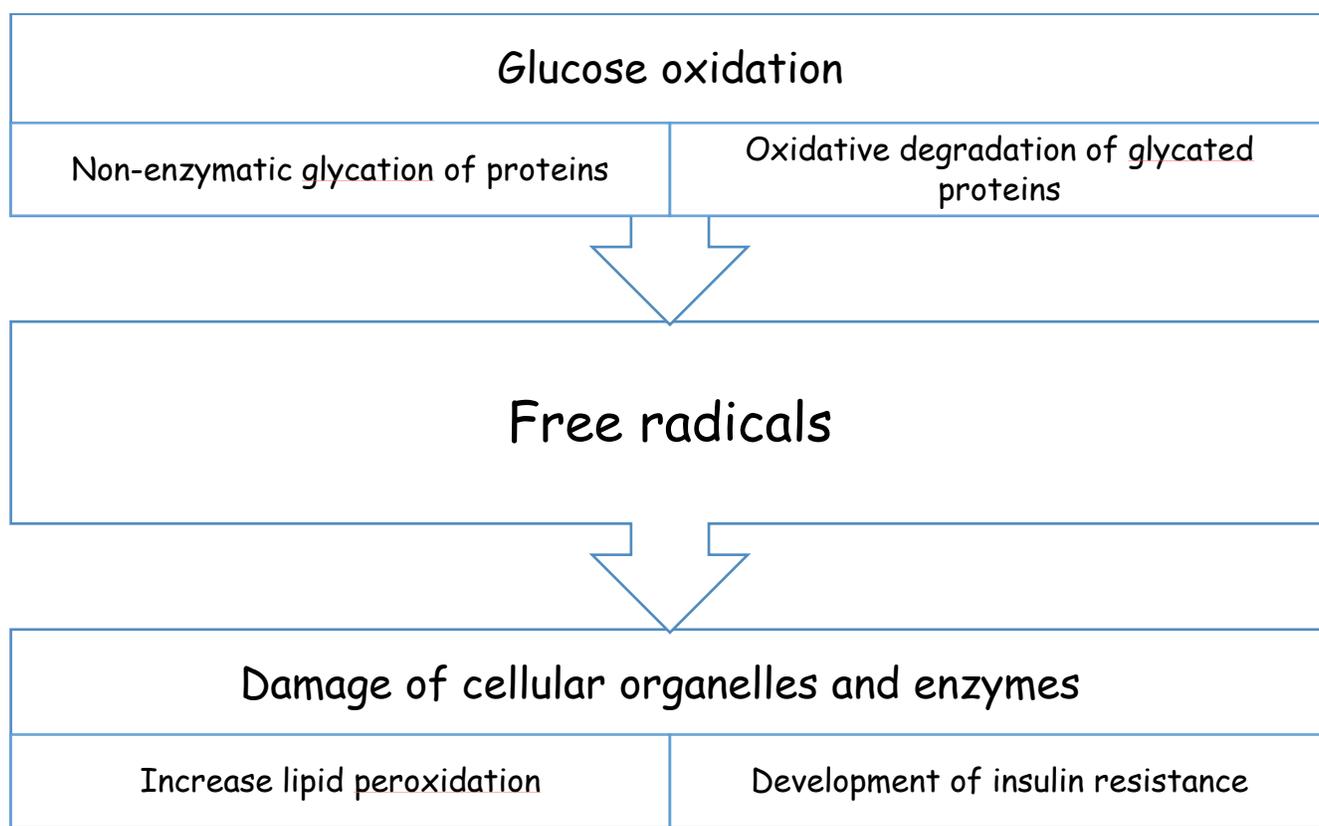
**Figure 1:** Schematic presentation of aetiology of diabetes

The need for alternative plants with little to no side effects for the treatment of diabetes was driven by the

negative effects of well-known oral hypoglycaemic medicines (Table 1) [3-4]. Less than half of the more than

400 traditional plant remedies for diabetes mellitus have undergone scientific validation to determine their effectiveness. Since free radicals have a role in the etiology of diabetes (Figure 2), the majority of these plants exhibit strong antioxidant activity. Many plant-derived substances are helpful in the treatment of diabetes. According to Maritim et al. [5] and Ezeruiké and Preto [6], these substances include active principles that are both alkaloids and non-alkaloids, terpenes, phenolic compounds, and other hydroxylated chemicals. According to studies by Lopez et al. [7] and Nyguyen et al. [8], alkaloids and saponins can help pancreatic beta cells release insulin. Through their antioxidant properties, saponins can significantly alleviate the clinical manifestations of diabetes, while also reducing the

degranulation of insulin. According to Ghorbani [9], triterpenoids help to increase glucose absorption while also acting as insulin sensitizers. Glycosides, alkaloids, and flavonoids are among the metabolites that are found in the majority of plants with hypoglycaemic characteristics [10]. Although a natural insulin alternative is implausible, conventional therapies may offer insightful information that can be used to create new oral hypoglycaemic medicines and dietary supplements [11]. *Carica papaya* L. is a plant that has a reputation for being antidiabetic. For the treatment of diabetes, all of *C. papaya* plant parts have been studied. As a result, this review focused on the antidiabetic potential of all *C. papaya* components and phytoconstituents, as well as the hypoglycaemic potential of its formulations.



**Figure 2:** Role of free radicals in the pathogenesis of diabetes.

**Table 1:** Side effects of known oral hypoglycaemic drugs.

Hypoglycaemic drugs	Mechanism of action	Adverse effects	References
<b>Metformin</b>	Reduce hepatic glucose synthesis and increase insulin sensitivity by acting through AMPK-dependent, as well as AMPK-independent mechanisms.	Lactacidosis	[12-23]
<b>Insulin secretagogues</b>	Enhancement of insulin secretion by pancreatic $\beta$ -cells	Hypoglycaemia, obesity	
<b>Thiazolidinediones</b>	Increased glucose consumption and decreased glucose synthesis by affecting adipose, muscle, and, to a lesser extent, liver, leading to an improvement in insulin sensitivity.	Weight gain	
<b><math>\alpha</math>-glucosidase and alpha amylase inhibitors</b>	Inhibition of intestinal glucose digestion and absorption	Gastro-intestinal discomforts	
<b>Sulfonylurea</b>	Stimulation of pancreatic beta-cell insulin secretion and inhibition of the enzymes glucosidase and DPP-IV. A carnitine inhibitor.	Potential hypoglycemia and weight gain	
<b>Meglitinides</b>	Stimulates insulin secretion by closing of KATP channels in $\beta$ cells	Weight gain	

A comprehensive search was performed using various electronic databases including Researchgate, PubMed, Google Scholar, Biomedgrid.com and ScienceDirect. The keywords “*Carica papaya*”, “biological properties”, “antidiabetic properties” and “bioactive compounds” were explored from 3<sup>rd</sup> of January to 31<sup>st</sup> of March, 2023. 224 publications were downloaded, out of which 107 relevant publications were reviewed.

#### **Botanical description and geographical distribution of**

***Carica papaya***: *Carica papaya* L. is an herbaceous plant in the Caricaceae family (Table 2; Figure 3). It is found in tropical regions of the world. In English, it is frequently referred to as papaya and is a native of tropical America.

There are more than twenty different species of the plant, but only one *Carica* species is grown for its fruit. According to Alorkpa et al. [24], ornamentals make up the majority of the cultivation of the other three genera, which are *Cyclicomorpha*, *Jarilla*, and *Jacaratia*. The plant grows quickly and has the potential to reach a height of 20 meters. According to Yogiraj et al. [25], it features a terminal cluster of big, long-stemmed leaves that are weak and typically unbranched, generating copious amounts of white latex. It is an herbaceous perennial with profuse milky latex and can grow to 6–10 meters tall [26-27].

**Table 2:** Taxonomic classification of *Carica papaya* [28]

Taxonomy	
Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Brassicales
Family:	Caricaceae
Genus:	<i>Carica</i>
Species:	<i>C. papaya</i> L.

**Figure 3:** Different parts of *Carica papaya* adapted from [29] and [30]

*Carica papaya* is a single-stemmed tree with petioles between one and three feet long, it has whole margins and is palmately lobed or deeply incised. The stems are hollow, 8 inches in diameter, pale green to tan-brown in hue, and heavily scarred [31]. The leaves are simple, lobed, and green in colour with a smooth surface. They have a unique odor and measure 50 to 70 cm in diameter. Transverse sections of the leaves revealed multiple fibers with cluster crystals, lignified xylem cells, 5-7 layers of collenchyma and sclerenchyma encasing the upper and lower epidermis, the lack of pith, and the endodermis, which is made up of parenchymatous cells. During the microscopic examination of the powdered material, vittae, square calcium oxalate crystals, oil

granules, endosperm with aleurone grains, mesocarp, and sclerenchyma cells were all discernible [32].

**Nutritional value of papaya fruit:** The nutrients in 100 g of ripe *C. papaya* are as follows: sodium (3 mg), iron (0.10 g), beta-carotene (888  $\mu\text{m}$ ), total carotene (2740  $\mu\text{m}$ ), vitamin A (1 094 IU), vitamin E (0.73 mg), niacin (3 mg), and water (89%) [33]. In addition to being a good source of vitamins A, B, and G as well as vitamin C (ascorbic acid), it is also high in calcium and iron [33].

**Folkloric application of *C. papaya* for management of diabetes :** The plant *C. papaya* has been proven to have medicinal activities like effect on smooth muscles, antioxidant, wound healing, anti-hypertensive,

anthelmintic, hepatoprotective, antimicrobial, anti-inflammatory, immunomodulatory activity, antifungal, anti-fertility, antiamebic, histaminergic, anti-tumor, diuretic, anti-ulcer activity, antimalarial, hypoglycemic activity, anti-sickling activity [34]. Papaya has been utilized as a nutraceutical in ethnomedicine to prevent and treat a variety of illness. Historically, it has been used as a meat tenderizer, a contraceptive, a treatment for acne, a reliever of menstruation pain, and an appetite stimulant. It has also been discovered that the papaya plant's components contain potent anti-plasmodial, anti-trichomonal, anti-dengue, anti-inflammatory, antiparasitic, antidiabetic, and anti-cancer capabilities [35]. According to Karunamoorthi et al. [36], it has also been employed in the treatment of cardiac illness, gastrointestinal tract disorders, and sickle cell anemia. Papaya's nutritional benefits include prevention of oxidation of cholesterol [37].

#### **Antidiabetic activity of *C. papaya* and its constituents:**

The various components of the *C. papaya* can be used to treat diabetes. The plant's antidiabetic impact (Figure 4) is caused by a variety of phytochemicals, and these vital components may act alone or in synergy to manifest the antidiabetic effect [38].

#### **Antidiabetic effect of different parts of *C. papaya* leaf:**

In alloxan-induced diabetic Wistar rat, the leaf extract decreased blood glucose levels [39]. After 4 days of therapy, Airaodion et al. [10] showed that 600 mg/kg body weight of *C. papaya* leaf extracts reduced blood glucose as much as glibenclamide, the standard drug used to treat diabetes. At dosages of 31 and 62 mg/kg, the leaf chloroform extract considerably decreased serum glucose, triglycerides, as well as transaminases in albino rats, confirming its hypoglycaemic effect [40]. A leaf aqueous extract (5 mg) was found to enhance

glucose absorption in yeast cells in an experiment by Elhaj et al. [41]. This effect may be related to the extract's capacity to bind to glucose and decrease the quantity of glucose that can transit through the intestinal lumen. One important tool for assessing the potential as an antidiabetic herb is the uptake of glucose by yeast cells [42]. In streptozotocin-induced diabetic rats, oral administration of a *C. papaya* leaf aqueous extract (0.11 g/mL) reduced serum glucose, fructosamine, total cholesterol, triglycerides, as well as L-malondialdehyde (MDA) activity while enhancing insulin and high-density lipoprotein cholesterol levels, as well as catalase (CAT) activity. Male diabetic mice were given 250 mg/kg of alloxan monohydrate to induce diabetes [44], while albino rats were given 100, 200, and 400 mg/kg orally to maintain an antihyperglycemic effect [45]. Aqueous papaya leaf extract decreased plasma total cholesterol, triglycerides, as well as phospholipids in these diabetic male mice.

The aqueous leaf extract (200 and 400 mg/kg/mL/day) significantly decreased glucose levels, triglyceride, total cholesterol, LDL, and caused an increase in the level of HDL in alloxan-induced diabetic rats [46]. At a dose of 5.0 mg/kg, the ethanolic leaf extract of *C. papaya* significantly reduced blood sugar levels, although the higher dose of 10 mg/kg had no appreciable effects. As reported by Fakeye et al. [47], the leaf extract significantly slows down the commencement of glimepiride's hypoglycaemic activity and intensifies the effect of metformin's hypoglycaemic action. While 50 mg/kg bw of the leaf ethanol extract significantly improved plasma insulin, triglyceride, cholesterol, HDL cholesterol, liver enzymes (ALT, AST, and ALP), bilirubin, as well as blood cells (Red cells, White cells, and Platelets) in streptozotocin-induced diabetic mice, methanol extract of the leaf also inhibits the activity of  $\alpha$ -amylase

and rate of glucose uptake in yeast using in vitro methods [48, 49]. In alloxan-induced diabetic rats, *C. papaya* leaf aqueous extract significantly increased HDL concentration while dose-dependently lowering low-density lipoprotein cholesterol, glucose levels, triglycerides, and plasma total cholesterol [46]. The leaf ethanol extract at doses of 200, 400, and 600 mg/kg lessened the hypoglycaemic and hypolipidemic effects in alloxan-induced diabetic rat [10]. The administration of leaf ethanol extract at a dose of 1000 mg/kg body weight is beneficial in lowering blood glucose levels in alloxan-induced diabetic Wistar mice when compared with glibenclamide at 2 mg/kg. In alloxan-induced diabetic mice, blood glucose levels were decreased after the injection of leaf ethanol extract at doses of 250, 500, and 1,000 mg/kg body weight [39]. Aldose Reductase enzymes were inhibited by the leaves' methanol extract, with  $IC_{50}$  values of  $1.22 \pm 0.63$  g/mL for ALR1 and  $1.22 \pm 0.06$  g/mL for ALR2 [50]. In streptozotocin (STZ)-induced diabetic rats, the leaf's aqueous extract (at concentrations of 0.75 and 1.5 g/100 mL) effectively lowered blood glucose levels ( $p < 0.05$ ). Additionally, it brought down the blood levels of aminotransferases, triacylglycerol, and cholesterol. After therapy, low plasma insulin levels in diabetic rats did not change, but they considerably rose in non-diabetic animals. The extract's ability to aid islet regeneration was demonstrated by the preservation of pancreatic islet cells sizes. It inhibited hepatocyte interruption, glycogen build-up, and lipid accumulation in the liver of diabetic-treated rats [51]. The administration of the leaf ethanol extract to the alloxan-induced diabetic rats considerably decreased glucose levels (from 240 mg/dL to 123.50 mg/dL), total cholesterol (TC), triglyceride (1.24 mg/dl), and low-density lipoprotein cholesterol (LDL-C), while significantly increasing high-density lipoprotein

cholesterol (HDL-C), as well as total protein level (66.51 g/dL). The extract also substantially lowered the levels of blood urea, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in diabetic rats [52].

The metabolism of sucrose was enhanced by the leaf's methanolic extract at doses of 100 mg/kg as well as 200 mg/kg body weight. The leaf extract considerably influenced the blood lipid profile. Additionally, following oral administration of the extract, the levels of C-reactive protein (CRP), serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT) all reverted to normal [53]. When streptozotocin-induced diabetic rats were fed leaf chloroform extract, the fasting glycemia was improved and the quantity and anatomy of pancreatic islets were preserved. After leaf chloroform extract was combined with streptozotocin and given to pancreatic cells in culture, the insulin level increased than when streptozotocin was the only treatment [54]. The ability of albino rats to absorb as well as transmit glucose through the small intestine cell membrane was not significantly affected by the aqueous extract, which is puzzling given the leaf extracts' noteworthy antidiabetic activity [55].

**Fruit:** The fruit juice of the *C. papaya* examined inhibited aldose reductase as well as sorbitol dehydrogenase most efficiently, with  $IC_{50}$  values of  $150.78 \mu\text{g/mL}$  and  $46.30 \mu\text{g/mL}$ , respectively [56]. An alternate method for the metabolism of glucose is the polyol pathway, in which fructose and sorbitol are produced from glucose with the help of the enzymes aldose reductase as well as sorbitol dehydrogenase, respectively. When intracellular glucose levels are elevated, this pathway is triggered in many cells. As a result, sorbitol and fructose build-up, which trigger a variety of pathogenic processes such as oxidative stress and the production of advanced glycation

end products, are produced [57]. The hydroalcoholic fruit extract significantly reduced blood glucose levels ( $p < 0.005$ ). Additionally, the change in lipid metabolism was only partially attenuated, as demonstrated by the decreased serum concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL), and the increased concentration of high-density lipoprotein cholesterol (HDL) in rats with alloxan-induced diabetes [58].

**Seed:** The extract from *C. papaya* seeds may contain bioactive substances that have antidiabetic properties by slowing the breakdown of carbohydrates into absorbable units. The seed methanol extract's ethyl acetate fraction significantly inhibited the activity of the enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase [59]. According to Agada et al. [60], the  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes, as well as oxidative stress associated with diabetes, may be inhibited by the seeds of *C. papaya*, which would explain how they exhibit their antidiabetic effects. In streptozotocin-induced type-II male Sprague-Dawley rats, the aqueous extract of the seed at doses of 100 mg/kg and 200 mg/kg significantly reduced serum glutamate oxaloacetate transaminase, blood glucose levels, serum glutamate pyruvate transaminase, as well as lipid profile [61]. Additionally, a study discovered that seed methanol extract has a strong ability to inhibit  $\alpha$ -amylase, with an  $IC_{50}$  value of  $46.99 \pm 0.018$  g/mL [62]. The seed extract at 100-300 kg/body weight significantly changed the levels of glucose transporter type 4 (GLUT4) in the muscle cells of the skeletal system of fructose-induced diabetic mice [63]. Duration-dependent effects of an aqueous extract of mature *C. papaya* L. seeds include a significant reduction ( $p < 0.05$ ) in fasting blood glucose and lipid profile, as well as a significant rise of serum protein and numerous electrolytes closer to the basal level [64]. The enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase were found to be more effectively inhibited

by the hexane as well as the ethyl acetate extracts [60]. In the animal experiment, rats with normal as well as streptozotocin-induced diabetes received oral administrations of papaya seed extracts for 120 minutes at doses of 250, 500, and 1,000 mg/kg/body weight. Acarbose (100 mg/kg/body weight) and a control group were used to compare the effects of these dosages on postprandial hyperglycemia. At dosages of 250, 500, as well as 1,000 mg/kg/body weight, the ethyl acetate extract considerably lowered postprandial glucose levels in these animals [60].

**Flower:** The papaya (*C. papaya*) flower contains antidiabetic flavonoids, tannins, as well as triterpenoid steroids. The flower extract at 200mg/kg, reduced blood sugar levels by 69.2% in sucrose-induced diabetic male mice [65]. This treatment was administered at a dose of 200 mg/kg body weight [65].

**Stem bark:** In streptozotocin-induced diabetic rats, the stem bark extract at 200 to 400 mg/200 g body weight lowered ( $p < 0.05$ ) cholesterol levels [66].

**Root:** A 100 mg/kg body weight dose of aqueous root extract administered orally every day for 15 days, relative to the untreated diabetic group, significantly lowered blood glucose levels [67]. Alkaline phosphatase (AP), bilirubin, blood sugar, cholesterol, and alanine aminotransferase (ALT) levels were considerably ( $p < 0.05$ ) lowered by male *C. papaya* root aqueous extract after one week of treatment [68-69].

**Clinical trials on antidiabetic activity of *C. papaya*:** In a quasi-experimental study using a pretest post-test control trial design, there was a significant decrease in blood glucose level (14 g/dL) after 14 days of consuming fruit after meals compared to the control group.

Therefore, it may be concluded that papaya helps diabetics in lowering their blood glucose levels [70].

#### **Antidiabetic activity of formulations consisting C.**

**papaya fortified papaya cake:** Papaya fruit powder and papaya puree were used in the experiment by Afaf-Haniem et al. [71] to investigate the antihyperglycaemic effects of the Streptozotocin-induced diabetic rats. The quantities of extract used were 20%, 30%, 50%, and 75%. Papaya powder increases the flavor, antioxidant activity, as well as water-holding capability of baked foods when combined with wheat flour. Male Sprague Dawley rats with diabetes were fed a cake made solely of wheat flour, a cake fortified with 20%, 30%, and 50% papaya powder, respectively, and a cake fortified with 75% papaya puree. When given supplemented papaya cake, diabetic rats' HbA1c levels significantly dropped. Triglyceride, LDL, VLDL, and total lipid levels in these animals are unaffected. Unexpectedly, a rise in HDL-C was also seen. HDL-C is a scavenger or transporter of LDL cholesterol, removing it from the arteries as well as transporting it back to the liver for expulsion from the body. The synthesis of hormone-sensitive lipase may not be inhibited by low insulin levels, allowing for efficient mobilization of free fatty acids from peripheral fat depots [71].

**MPPB flour:** The mixture of unripe *Musa paradisiaca* and *Carica papaya* from *Mucuna cochichinensis* (MPPB) has the highest amount of phytochemicals. Using an Accu-check Active glucometer every day for two weeks, researchers examined the hypoglycaemic activity of MPPB in alloxan-diabetic rats. All of the samples had some level of hypoglycaemia potential, with sample MPPB having the maximum hypoglycaemic activity, lowering the hypoglycaemic blood glucose level from 13.10 mmol/L to 4.33 mmol/L. In male Wistar rats,

alloxan-induced hyperglycaemia was reversed by the MPPB [72]. According to Odom et al. [72], MPPB was more effective than other approaches and may be utilized for both management and prevention of diabetes mellitus.

**Brotowali extract:** The oral treatment of the brotowali extract (fortified papaya leaf and sugarcane extracts) at doses of 250 mg/kg BW as well as 500 mg/kg body weight, respectively, reduced blood glucose levels in mice with alloxan-induced diabetes [73].

**Phytochemistry of C. papaya:** Tannin, saponin, alkaloids, flavonoids, and glycoside are found in papaya leaves, whereas Ca, Fe, Mg, K, Zn, and Mn are found in the shoots. Papain and chymopapain are two examples of the enzymes found in unripe fruit. Carotenoids like carotene and cryptoxanthin are also found in fruit. The root's chemical makeup revealed the presence of benzyl isothiocyanate and glucosinolatecarposide. In addition to other plant parts, enzymes were discovered in latex, including papain, chymopapain, caricain, and protease omega [74-77]. According to Azarkan et al. [78], *C. papaya* latex also contains chitinase, glutaminy cyclase, and cysteine endopeptidases. Resin, anthraquinone, tannin, glycoside, flavonoid, saponin, and steroids were all discovered in n-hexane and methanolic extracts of leaves, according to a different investigation by Musa [79]. El-Mesallamy et al. study [80] revealed that papaya's methanolic leaf extract contains phenolic compounds. According to studies of Nakamura et al. [81] and Rossetto et al. [82], the papaya's seeds, pulp, and pericarp contain benzyl glucosinolate and benzyl isothiocyanate. Oleic acid was extracted from the seed by Ghosh et al. [83]. The seed extract was subjected to a GC-MS analysis, which identified sterol, fatty acids, nitriles, organic acids, fatty aldehydes, as well as amides [84].

Table 3 lists the *C. papaya*'s components.

**Table 3:** Chemical composition of various parts of *Carica papaya* L.

Part	Constituents	References
<b>Fruit</b>	Alkaloid, fat, fibre, benzyl- $\beta$ -D glucoside, protein, carbohydrates, calcium, phosphorus, Octadecanoic acid, Z-11, methyl ester, iron, vitamin C, thiamine, and caroxene, amino acid, cis and trans 2, 6-dimethyl-3,6 epoxy-7 octen-2-ol, citric acids, four isomeric malonated benzyl- $\beta$ -D glucosides, octadecanoic acid, molic acid (green fruits), linalol, benzylisothiocyanate, niacin, methyl ester, cryptoxanthin, $\alpha$ ; carpaine, minerals, 2-phenylethyl- $\beta$ -D-glucoside, 4-hydroxyl -phenyl-2-ethyl-B-D glucoside, Z-11, riboflavin, hexadecenoic acid, and hexadecenoic acid.	[28, 50, 68, 77, 85-99]
<b>Fruit pulp</b>	Glucose-6-phosphate, glutathione peroxidase, glutathione transferase, glutathione reductase, catalase, phenolics, terpenols, alkaloids, flavonoids, and saponins.	
<b>Juice</b>	N-butyric, n-hexanoic acid, myristic acid, n-octanoic acids, vaccenic acid lipids; palmitic, oleic acid, stearic acid, linoleic acid, and linolenic acids	
<b>Seed</b>	Crude fibre, $\beta$ -carotene, crude proteins, nyrosin, papaya oil, 2,3,4-trihydroxytoluene (caricaphenyltriol), carpaine, benzylglucosinolate, benzylthiourea, palmitic acid, linalool, hentriacontane, $\beta$ -sistosterol, fatty acids, caricin, $\beta$ -cryptoxanthine, oleic acid, stearic acid, Tocopherols ( $\alpha$ and $\delta$ ), linoleic acid, 1,2,3,4-tetrahydropyridin-3-yl-octanoate, glucotropacolin, benzylisothiocyanate, glyceryl-1-(2',3',4'-trihydroxybenzoyl)-2,3-dioleate (papayaglyceride), 4-terpinol, benzyl isothiocyanate glucosinolates, and fatty acid	
<b>Root</b>	Glucosinolatescarposide, benzyl isothiocyanate and carposide, myrosin,	
<b>Leaf</b>	Methyl gallate, kaempferol 3-rhamnosyl-(1->2)-galactoside-7-rhamnoside, quercetin-3-O-rutinoside, flavonoids, orientin 7-O-rhamnoside, saponins, phytol, oxalic acid, 6-ethyloct-3-yl isobutyl ester, 3-methyl-2-(2-oxopropyl)Furan, carbonic acid, 7-rhamnoside, 1H-Imidazole, 1(1-oxooctadecyl), pseudocarpain, isobutyl undec-10-enyl ester, isoquercetin, p-coumaric acid, carpaine, choline, lycopene, caffeic acid, benzyl isothiocyanate, vitamin C and E, D-mannitol, 1 decylsulfonyl kaempferol, kaempferol 3-rutinoside, quercetin 3-(2G-rhamnosylrutinoside), quercetin 3-rutinoside, myricetin 3-rhamnoside, lycopene, zeaxanthin, cryptoxanthin, $\beta$ -carotene, violaxanthin, quercetin, 5,7-dimethoxy coumarin, dehydrocarpaine I and II, pro-anthocyanin, chlorogenic acid, alkaloids carpain, protocatechuic acid, nicotiflorin, quercetin-3-O-1C4-rhamnopyranoside, quercetin-3-O-glucopyranoside, Polyphenols, trans-ferulic acid, kaempferol 3-(2G-glucosylrutinoside), kaempferol 3-(2''-rhamnosylgalactoside), luteolin 7-galactosyl-(1->6)-galactoside, 11-hydroperoxy-12,13-epoxy-9-octadecenoic acid, palmitic amide, carposide, 2-hexaprenyl-6-methoxyphenol, loliolide, rutin, clitorin, kaempferol-3-O-neohesperidoside, and isorhamnetin-3-O-D-glucopyranoside,	
<b>Stem bark</b>	Fructose, sucrose, $\beta$ -sitosterol, glucose, xylitol, and galactose	
<b>Latex</b>	Caricain, papain, glutamine cyclotransferase, protease omega, proteolytic enzymes, peptidase A and B, lysozymes, chemopapain, chymopapain, chymopapain A, B and C,	
<b>Papaya wine</b>	Benzyl isothiocyanate, 3-methylbutyl acetate, ethyl butanoate, ethyl octanoate, (E)- $\beta$ -damascenone, ethyl hexanoate, and	

**Phytoconstituents with antidiabetic activity:** There were significant bioactive chemicals in the fruits, seeds,

roots, leaves, stems, and latex of the *C. papaya* plant, which may have an antidiabetic impact (Table 4).

Alkaloids, flavonoids, triterpenoids, tannins, and saponins are among the substances present in the *C. papaya* leaf extracts (Table 4). These substances have a known hypoglycaemic impact [7, 9, 39, 49, 100-101]. Figure 4 shows the mechanisms of action of the fruit. Different bioactive chemicals were found in the ethyl acetate extract fraction of *C. papaya* seeds, according to the GC-MS chromatogram. The main antidiabetic chemicals in *C. papaya* seed are 11-octadecenoic acid,

oleic acid, hexadecanoic acid, methyl ester, N, N-dimethyl-, methyl ester, as well as n-hexadecanoic acid. According to Agada et al. [102], these chemicals may be the reason for the plant's antidiabetic effects. According to Juarez-Rojop et al. [40], the high content of steroids in *C. papaya* leaves may be the cause of the chloroform extract's hypolipidemic and hypoglycaemic effects on diabetic rats. The antidiabetic compounds from *C. papaya* are listed in Table 5.

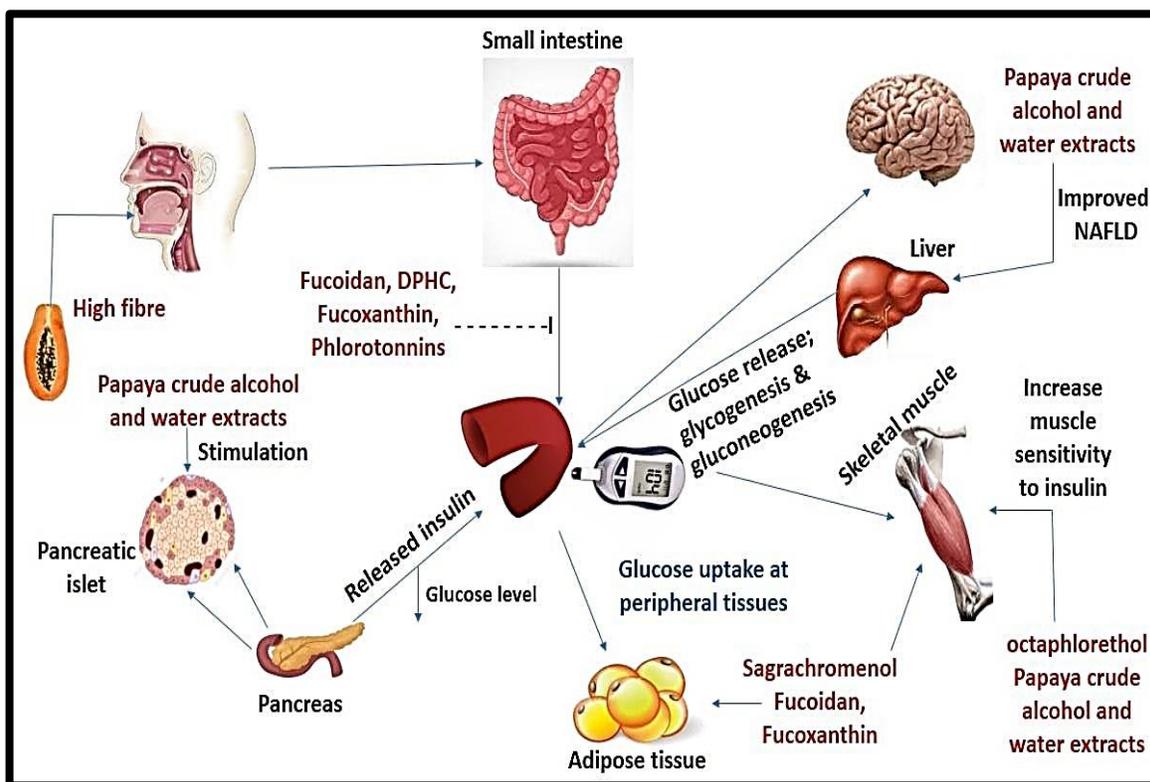


Figure 4: Schematic representation of *C. papaya* antidiabetic mechanisms redrawn from [103]

Table 4: Mechanism of action of class of compounds in *Carica papaya* as antidiabetics

Bioactive compounds	Mechanism of antidiabetic activity	References
Steroids	Reduce glucose production in the liver	[49]
Tannins	Inhibit loss of glucose transport which produces insulin	[100]
Flavonoids	Pancreatic $\beta$ -cells rejuvenation	[9]
Saponins	Excites exudation of insulin from pancreatic $\beta$ -cells	[98]
Alkaloids	Arouses production of insulin from pancreatic $\beta$ -cells	[104]
Terpenoids	Caused glucose absorption to increase. Insulin sensitizer	[98]

**Table 5:** Antidiabetic compounds in *Carica papaya*

Part	Compound	Mechanism	References
Leaf	Oxalic acid, Phytol, 3-methyl-2-(2-oxopropyl)Furan, 6-ethyloct-3-yl isobutyl ester, isobutyl undec-10-enyl ester, Carbonic acid, 1H-Imidazole, 1(1-oxooctadecyl), D-mannitol, 1 decylsulfonyl	Promising inhibitory aldose reductase	[104-105]
Seed	Oleic acid, methyl ester, Heexadecanoic acid, 11-octadecenoic acid, N, N-dimethyl-, methyl ester, n-hexadecanoic acid.	Antidiabetic effects	[101, 106-107]

## CONCLUSION

This review focused on *Carica papaya*'s antidiabetic properties. The fruit, leaves, seeds, and formulations of this plant have shown antidiabetic activities at various dosages in *in vivo*, *in vitro*, and *ex vivo* experiments. It has been discovered that the leaf extract contains hypoglycaemic saponins, alkaloids, flavonoids, triterpenoids, and tannins. A few compounds with antidiabetic characteristics have been identified from the extracts of this plant's seeds, including oleic acid, methyl ester, hexadecanoic acid, N, N-dimethyl-, 11-octadecenoic acid, and n-hexadecanoic acid. For the development of new natural remedies for both the management and prevention of diabetes, additional studies, particularly those on the isolation of antidiabetic principles from various portions of *C. papaya* will be crucial.

**Abbreviation:** DPP-IV: Dipeptidyl peptidase 4; KATP: ATP-sensitive potassium channels; MDA: L-malondialdehyde; CAT: catalase; LDL: Low density lipoprotein; HDL: High density lipoprotein; TC: total cholesterol; TG: triglycerides; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALR: Aldose Reductase; CRP: C-reactive protein; SGPT: serum glutamic pyruvic transaminase; SGOT: serum glutamic oxaloacetic transaminase; GLUT4: glucose transporter type 4; MPPB: *Musa paradisiaca* and *Carica papaya* from *Mucuna cochichinensis*; BW: Body weight.

**Competing interests:** Authors do not have any conflict of interests to declare.

**Authors' contribution:** The study was conceived by ADO, who also contributed to its planning and design. The manuscript was created by TRO and ADO. The final paper was read, amended, and approved by all authors.

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