



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

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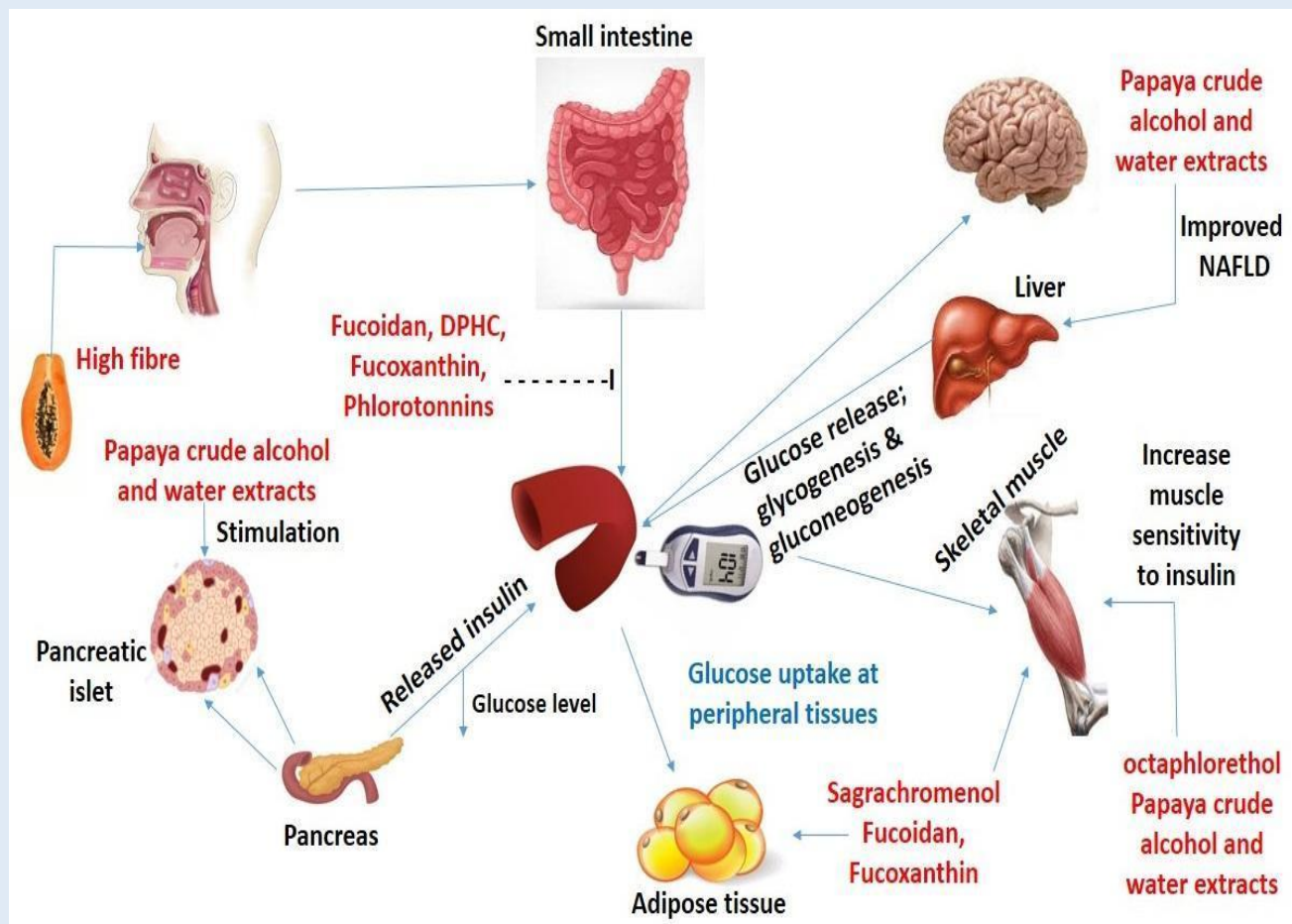
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ABSTRACT

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].

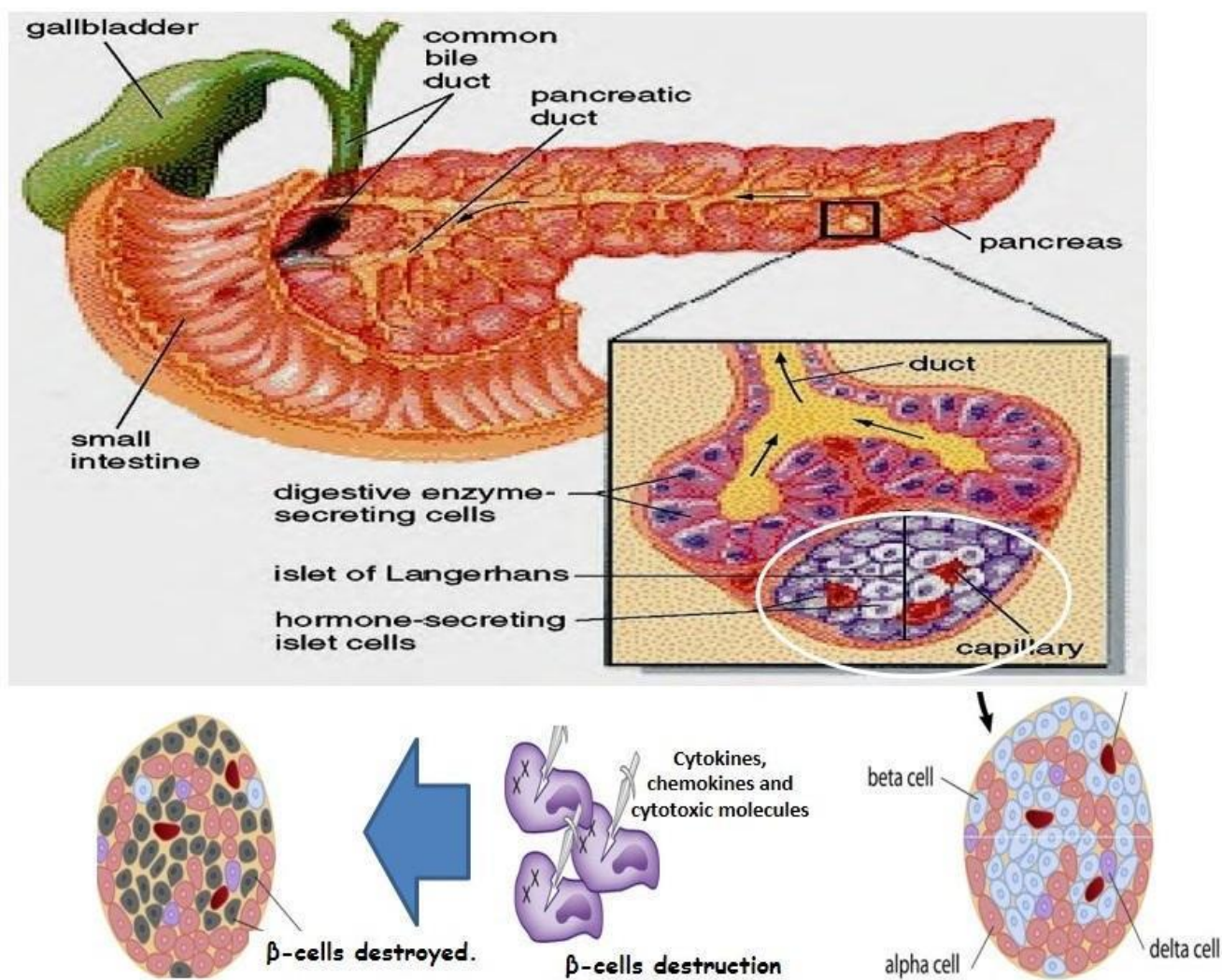


Figure 1: Schematic presentation of aetiology of diabetes

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.

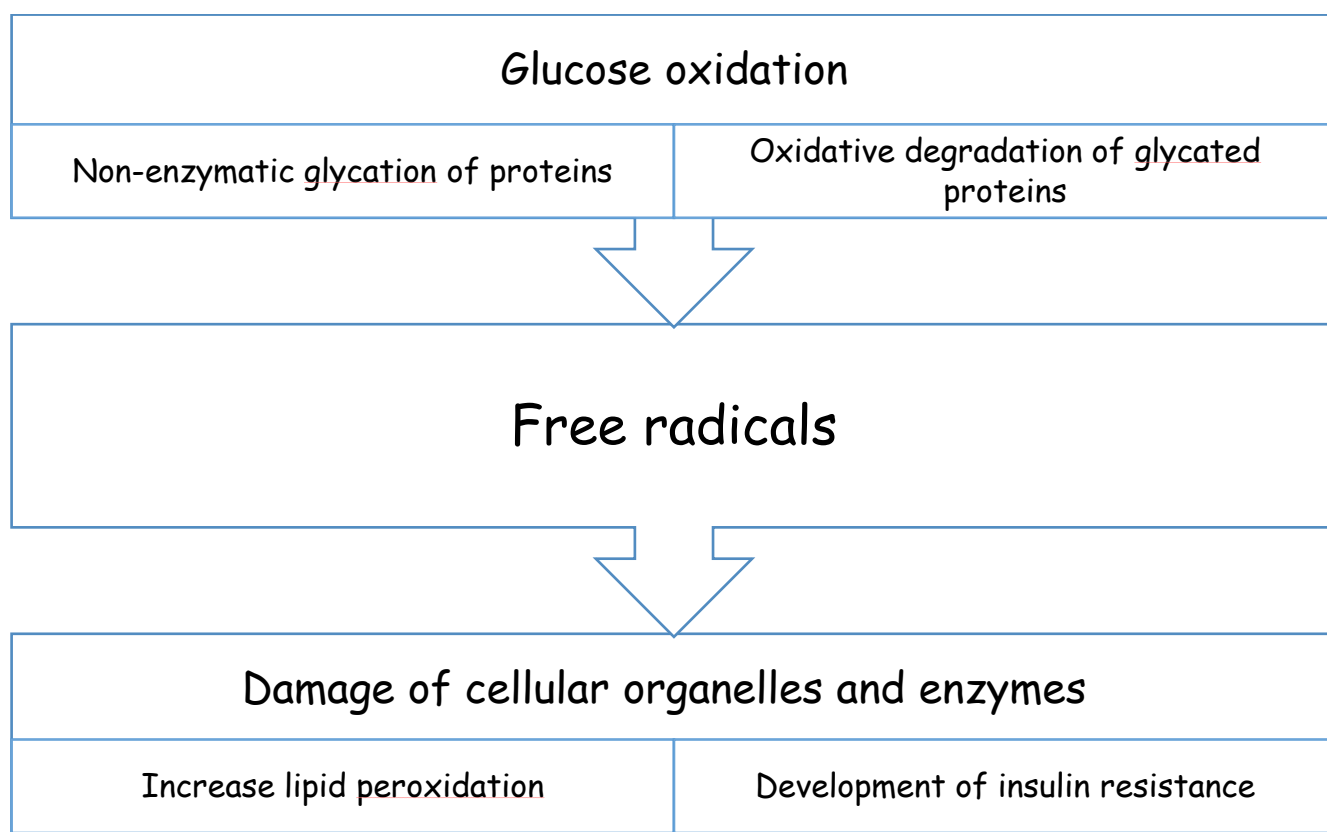


Figure 2: Role of free radicals in the pathogenesis of diabetes.

Table 1: Side effects of known oral hypoglycaemic drugs.

Hypoglycaemic drugs	Mechanism of action	Adverse effects	References
Metformin	Reduce hepatic glucose synthesis and increase insulin sensitivity by acting through AMPK-dependent, as well as AMPK-independent mechanisms.	Lactacidosis	[12-23]
Insulin secretagogues	Enhancement of insulin secretion by pancreatic β -cells	Hypoglycaemia, obesity	
Thiazolidinediones	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	
α-glucosidase and alpha amylase inhibitors	Inhibition of intestinal glucose digestion and absorption	Gastro-intestinal discomforts	
Sulfonylurea	Stimulation of pancreatic beta-cell insulin secretion and inhibition of the enzymes glucosidase and DPP-IV. A carnitine inhibitor.	Potential hypoglycemia and weight gain	
Meglitinides	Stimulates insulin secretion by closing of KATP channels in β 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 3rd of January to 31st 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 μm), total carotene (2740 μm), 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 α -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 ± 0.63 g/mL for ALR1 and 1.22 ± 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 μ g/mL and 46.30 μ 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 α -amylase and α -glucosidase [59]. According to Agada et al. [60], the α -amylase and α -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 α -amylase, with an IC_{50} value of 46.99 ± 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 α -amylase and α -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 glucosinolate-scarposide. 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
Fruit	Alkaloid, fat, fibre, benzyl- β -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- β -D glucosides, octadecanoic acid, molic acid (green fruits), linalol, benzylisothiocyanate, niacin, methyl ester, cryptoxanthin, α ; carpaine, minerals, 2-phenylethyl- β -D-glucoside, 4-hydroxyl -phenyl-2-ethyl-B-D glucoside, Z-11, riboflavin, hexadecenoic acid, and hexadecenoic acid.	[28, 50, 68, 77, 85-99]
Fruit pulp	Glucose-6-phosphate, glutathione peroxidase, glutathione transferase, glutathione reductase, catalase, phenolics, terpenols, alkaloids, flavonoids, and saponins.	
Juice	N-butyric, n-hexanoic acid, myristic acid, n-octanoic acids, vaccenic acid lipids; palmitic, oleic acid, stearic acid, linoleic acid, and linolenic acids	
Seed	Crude fibre, β -carotene, crude proteins, nyrosin, papaya oil, 2,3,4-trihydroxytoluene (caricaphenyltriol), carpaine, benzylglucosinolate, benzylthiourea, palmitic acid, linalool, hentriacontane, β -sistosterol, fatty acids, caricin, β -cryptoxanthine, oleic acid, stearic acid, Tocopherols (α and δ), 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	
Root	Glucosinolatescarposide, benzyl isothiocyanate and carposide, myrosin,	
Leaf	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, β -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,	
Stem bark	Fructose, sucrose, β -sitosterol, glucose, xylitol, and galactose	
Latex	Caricain, papain, glutamine cyclotransferase, protease omega, proteolytic enzymes, peptidase A and B, lysozymes, chemopapain, chymopapain, chymopapain A, B and C,	
Papaya wine	Benzyl isothiocyanate, 3-methylbutyl acetate, ethyl butanoate, ethyl octanoate, (E)- β -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.

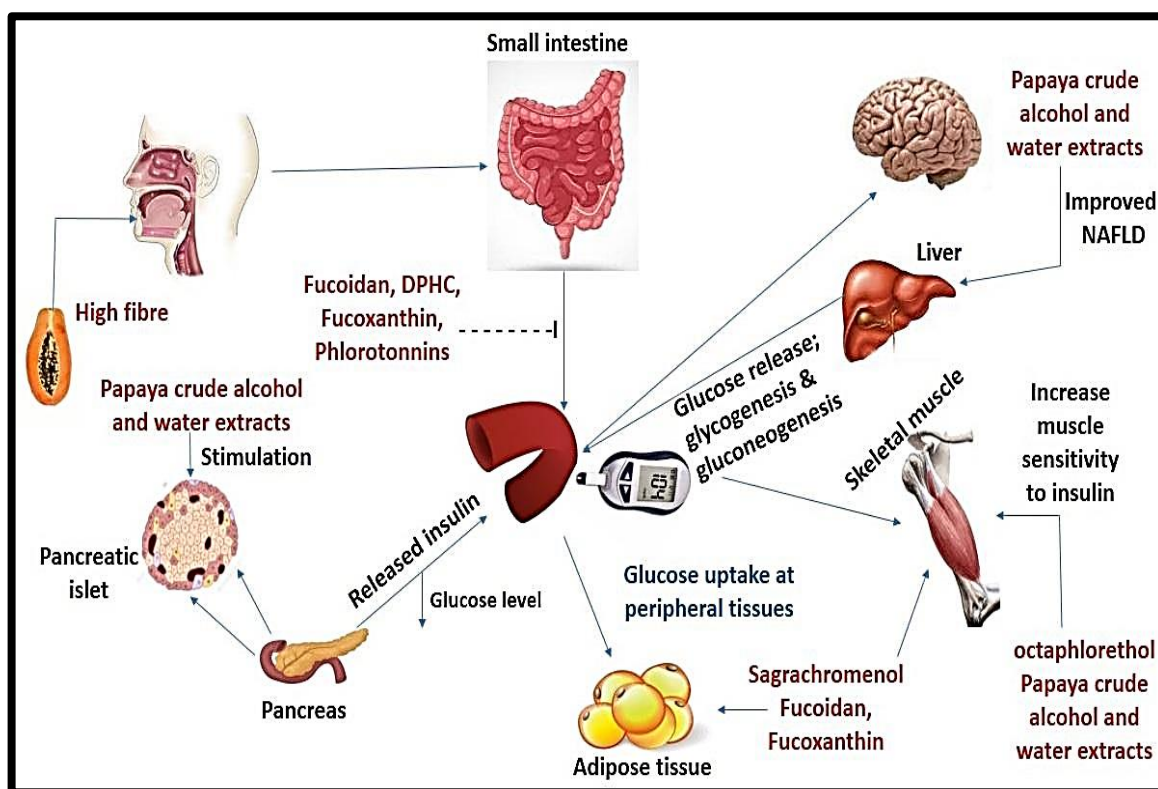


Figure 4: Schematic representation of *C. papaya* antidiabetic mechanisms redrawn from [103]

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 β -cells rejuvenation	[9]
Saponins	Excites exudation of insulin from pancreatic β -cells	[98]
Alkaloids	Arouses production of insulin from pancreatic β -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.

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REFERENCES

- Kumar N, Puri N, Marotta F, Dhewa T, Calabrò S, Puniya M, Carter J. Diabetes: an epidemic with its causes, prevention and control with special focus on dietary regime. *Functional Foods in Health and Disease*. 2017, 7(1):1-6, DOI: <https://www.doi.org/10.31989/ffhd.v7i1.280>
- World Health Organization. Diabetes Mellitus [https://www.who.int/health-topics/diabetes] 2022.
- Rahman MM, Dhar PS, Anika F, Ahmed L, Islam MR, Sultana NA, Cavalu S, Pop O, Rauf A. Exploring the plant-derived bioactive substances as antidiabetic agent: an extensive review. *Biomedicine & Pharmacotherapy* 2022, 152:113217, DOI: <https://www.doi.org/10.1016/j.biopha.2022.113217>
- Boaz M, Leibovitz E, Dayan YB, Wainstein J. Functional foods in the treatment of type 2 diabetes: olive leaf extract, turmeric and fenugreek, a qualitative review. *Functional Foods in health and Disease* 2011, 11:472-81, DOI: <https://www.doi.org/10.31989/ffhd.v11i11.114>
- Maritim A, Dene BA, Sanders RA, Watkins III JB. Effects of β -carotene on oxidative stress in normal and diabetic rats.

- Journal of biochemical and molecular toxicology 2002, 16(4):203-8, DOI: <https://www.doi.org/10.1002/jbt.10038>
6. Ezuruike UF, Prieto JM. The use of plants in the traditional management of diabetes in Nigeria: Pharmacological and toxicological considerations. *Journal of Ethnopharmacology* 2014, 155 (2):857-924; DOI: <https://www.doi.org/10.1016/j.jep.2014.05.055>
 7. López PM, de la Mora PG, Wysocka W, Maiztegui B, Alzugaray ME, Del Zotto H, Borelli MI. Quinolizidine alkaloids isolated from *Lupinus* species enhance insulin secretion. *European Journal of Pharmacology* 2004, 504(1-2):139-42, DOI: <https://www.doi.org/10.1016/j.ejphar.2004.09.008>
 8. Nguyen KH, Ta TN, Minh TH, Nguyen QT, Pham HD, Mishra S., Nyomba BL, Goire G: Nuciferine stimulates insulin secretion from beta cells — An in vitro comparison with glibenclamide. *Journal of Ethnopharmacology* 2012, 142: 488–495, DOI: <https://www.doi.org/10.1016/j.jep.2012.05.024>
 9. Ghorbani A: Mechanisms of antidiabetic effects of flavonoid rutin. *Biomedicine & Pharmacotherapy* 2017, 96:305-12, DOI: <https://www.doi.org/10.1016/j.biopha.2017.10.001>
 10. Airaodion AI, Ogbuagu EO, Ekenjoku JA, Ogbuagu U, Okoroukwu VN: Antidiabetic effect of ethanolic extract of *Carica papaya* leaves in alloxan-induced diabetic rats. *American Journal of Biomedical Science & Research*. 2019, 5(3):227-34, DOI: <https://www.doi.org/10.34297/AJBSR.2019.05.000917>
 11. Bailey CJ, Day C: Traditional plant medicines as treatments for diabetes. *Diabetes care* 1989, 12(8):553-64, DOI: <https://www.doi.org/10.2337/diacare.12.8.553>
 12. Zimmerman BR. Sulfonylureas: Endocrinology and metabolism clinics of North America. 1997, 26(3):511-22, DOI: [https://www.doi.org/10.1016/s0889-8529\(05\)70264-4](https://www.doi.org/10.1016/s0889-8529(05)70264-4)
 13. Kim MH, Jee JH, Park S, Lee MS, Kim KW, Lee MK: Metformin enhances glucagon-like peptide 1 via cooperation between insulin and Wnt signaling. *J Endocrinol* 2014, 220(2):117-28, DOI: <https://www.doi.org/10.1530/JOE-13-0381>
 14. Park J, Rah SY, An HS, Lee JY, Roh GS, Ryter SW, Park JW, Yang CH, Surh YJ, Kim UH, Chung HT: Metformin-induced TTP mediates communication between Kupffer cells and hepatocytes to alleviate hepatic steatosis by regulating lipophagy and necroptosis. *Metabolism* 2023, 141:155516, DOI: <https://www.doi.org/10.1016/j.metabol.2023.155516>
 15. Proks P, Reimann F, Green N, Gribble F, Ashcroft F: Sulfonylurea stimulation of insulin secretion. *Diabetes* 2002, 51(Suppl 3):368-76, DOI: <https://www.doi.org/10.2337/diabetes.51.2007.s368>
 16. Yale JF: Oral antihyperglycemic agents and renal disease: new agents, new concepts. *Journal of the American Society of Nephrology* 2005, 16(Suppl 3):7-10, DOI: <https://www.doi.org/10.1681/asn.2004110974>
 17. Ritz, E., Adamczak, M., Wiecek, A., Kopple, J. D., Massry, S. G., & Kalantar-Zadeh, K: *Carbohydrate metabolism in kidney disease and kidney failure*. Academic Press 2013, 17-30, DOI: <https://www.doi.org/10.1016/B978-0-12-391934-2.00002-3>
 18. Pernicova I, Korbonits M: Metformin—mode of action and clinical implications for diabetes and cancer. *Nature Reviews Endocrinology* 2014, 10(3):143-56, DOI: <https://www.doi.org/10.1038/nrendo.2013.256>
 19. Kalra S, Aamir AH, Raza A, Das AK, Khan AA, Shrestha D, Qureshi MF, Fariduddin M, Pathan MF, Jawad F, Bhattarai J: Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. *Indian journal of endocrinology and metabolism*. 2015, 19(5):577, DOI: <https://www.doi.org/10.4103/2230-8210.163171>
 20. Rena G, Hardie DG, Pearson ER: The mechanisms of action of metformin. *Diabetologia*. 2017, 60(9):1577-85, DOI: <https://www.doi.org/10.1007/s00125-017-4342-z>
 21. Costello, R.A. and Shivkumar, A: Sulfonylureas. In *StatPearls [Internet]*. StatPearls Publishing 2021. PMID 30020597
 22. Scheinberg T, Mak B, Butler L, Selth L, Horvath LG: Targeting lipid metabolism in metastatic prostate cancer. *Therapeutic Advances in Medical Oncology* 2023, 15:17588359231152839, DOI: <https://www.doi.org/10.1177/17588359231152839>
 23. Bagheripour F, Jeddi S, Kashfi K, Ghasemi A: Metabolic effects of L-citrulline in type 2 diabetes. *Acta Physiologica* 2023, 237(3):e13937, DOI: <https://www.doi.org/10.1111/apha.13937>
 24. Alorkpa EJ, Boadi NO, Badu M, Saah SA: Phytochemical screening, antimicrobial and antioxidant properties of assorted *Carica papaya* leaves in Ghana. *Journal of Medicinal Plants Studies* 2016, 4(6):193-8.
 25. Yogiraj V., Kumar Goyal P., Singh Chauhan C., Goyal A., Vyas B: *Carica papaya* Linn: An Overview. *International Journal of Herbal Medicine* 2014, 2 (5): 01-08.

26. Fayziyeva FA, Nazarova FA: Bioecology and useful properties of papaya or melon tree. *ACADEMICIA: An International Multidisciplinary Research Journal*. 2021, 11(3):1778-85.
27. Carvalho FA, Renner SS: A dated phylogeny of the papaya family (Caricaceae) reveals the crop's closest relatives and the family's biogeographic history. *Molecular Phylogenetic and Evolution* 2012, 65:46-53, DOI: <https://www.doi.org/10.1016/j.ympev.2012.05.019>
28. Santana LF, Inada AC, Espirito Santo BL, Filiú WF, Pott A, Alves FM, Guimarães RD, Freitas KD, Hiane PA: Nutraceutical potential of *Carica papaya* in metabolic syndrome. *Nutrients* 2019, 11(7):1608, DOI: <https://www.doi.org/10.3390/nu11071608>
29. Hidayati TK, Susilawati Y, Muhtadi A. Kegiatan Farmakologis Dari Berbagai Bagian *Carica Papaya* Linn. Ekstrak: Buah, Daun, Benih, Uap, Kulit Dan Akar. *Jurnal Riset Kefarmasian Indonesia*. 2020, 17:2(3):211-26, DOI: <https://www.doi.org/10.33759/jrki.v2i3.97>
30. Iordănescu OA, Băla M, Gligor D, Zippenfening SE, Cugorean MI, Petroman MI, Hădărugă DI, Hădărugă NG, Riviş M: A DPPH-kinetic approach on the antioxidant activity of various parts and ripening levels of papaya (*Carica papaya* L.) ethanolic extracts. *Plants*. 2021, 10(8):1679, DOI: <https://www.doi.org/10.3390/plants10081679>
31. Arvind G., Debjit B., Duraivel S., Harish G. Traditional and Medicinal uses of *Carica papaya*, Medicinal uses of *Carica papaya*. *J Med Car Pap* 2013, 1(1):2320-3862.
32. Donga S, Pande J, Chanda S: Pharmacognostic investigations on the seeds of *Carica papaya* L. *Journal of Pharmacognosy and Phytochemistry* 2019, 8(5):2185-93.
33. Vij T, Prashar Y: A review on medicinal properties of *Carica papaya* Linn. *Asian Pacific Journal of Tropical Disease* 2015, 5(1):1-6, DOI: [https://www.doi.org/10.1016/S2222-1808\(14\)60617-4](https://www.doi.org/10.1016/S2222-1808(14)60617-4)
34. Singh P, Singh RL, Pathak N, Singh PK, Tripathi M, Mondal S. Phytochemistry and nutraceutical properties of *Carica papaya* (Linn.): A review. *Dietary Supplements and Nutraceuticals*. 2022, 1(9):1-5. DOI: <https://www.doi.org/10.31989/dsn.v1i9.991>
35. Karunamoorthi, K., Kim, H.M., Jegajeevanram, K., Xavier, J., Vijayalakshmi, J: A gifted nutraceutical plant - a critical review of recent human health research. *TANG. Papaya*: 2014, 4(1):1-15, DOI: <https://www.doi.org/10.5667/tang.201>
36. Herviana H, Indarto D, Wasita B, Pasaribu SF: Effects of Papaya (*Carica papaya* L.) as Anti-Hyperlipidemia: A Systematic Review. *International Journal of Nutrition Sciences*. 2022, 7(1):19-25, DOI: <https://www.doi.org/10.30476/IJNS.2022.94129.1168>
37. Kumar S., Nandi G: Present status of antidiabetic properties of *carica papaya*. *Int. J. Adv. Res.* 2017: 5(7), 495-502, DOI: <https://www.doi.org/10.21474/IJAR01/4744>
38. Solikhah TI, Setiawan B, Ismukada DR: Antidiabetic activity of papaya leaf extract (*Carica papaya* L.) isolated with maceration method in alloxan-induced diabetic mice. *Systematic Reviews in Pharmacy*. 2020, 11(9):774-8, DOI: <https://www.doi.org/10.31838/SRP.2020.9.109>
39. Juárez-Rojop IE, Tovilla-Zárate CA, Aguilar-Domínguez DE, Roa-de la Fuente LF, Lobato-García CE, Blé-Castillo JL, López-Meraz L, Díaz-Zagoya JC, Bermúdez-Ocaña, DY: Phytochemical screening and hypoglycemic activity of *Carica papaya* leaf in streptozotocin-induced diabetic rats. *Brazilian Journal of Pharmacognosy*. 2014, 24(3): 341-347, DOI: <https://www.doi.org/10.3892/etm.2017.5640>
40. Elhaj R., Ya'akob H., AbdMalek R: Evaluation of antidiabetic activity of *Carica papaya* leaves extract using yeast cells method. *Food Research* 4. 2020 (Suppl. 2): 67-70, DOI: [https://www.doi.org/10.26656/fr.2017.4\(S2\).S01](https://www.doi.org/10.26656/fr.2017.4(S2).S01)
41. Nair SS, Kavrekar V, Mishra A: In vitro studies on alpha amylase and alpha glucosidase inhibitory activities of selected plant extracts. *European Journal of Experimental Biology*. 2013, 3(1):128-32.
42. Hashem M, Ismail S. Clinicopathological Studies on The Effect of Papaya on experimentally induced short term hyperglycemia in rats. *Zagazig Veterinary Journal*. 2019 Mar 1;47(1):45-56, DOI: <https://www.doi.org/10.21608/zvjz.2019.6088.1011>
43. Sinha RK, Pratap R, Varma MC: Lipid-lowering effect of aqueous leaf extract of *Carica papaya* on alloxan monohydrate induced male diabetic albino mice. *International Journal for Advance Research and Development*. 2018, 3(6):38-41.
44. Ahmed SK, Sampath D, Cheekavolu C, Sunil M, Naveen A: Evaluation of Antihyperglycemic activity of aqueous extract of *Carica papaya* Linn. leaves in Alloxan induced diabetic Albino rats. *Journal of Medical Science and Clinical Research*, 2017, 5(11): 30915-30922, DOI: <https://dx.doi.org/10.18535/jmscr/v5i11.187>

45. Ukpabi CF, Chukwu M, Onyemaechi JN, Ibe P, Onuh EF: Antidiabetic and antihyperlipidemic effects of aqueous extract of *Carica papaya* leaf on the experimental model against single alloxan toxicity. *World Scientific Research*. 2019, 6(1):14-8, DOI: <https://www.doi.org/10.20448/journal.510.2019.61.14.18>
46. Fakeye TO, Oladipupo T, Showande O, Ogunremi Y: Effects of coadministration of extract of *Carica papaya* Linn (family Caricaceae) on activity of two oral hypoglycemic agents. *Tropical Journal of Pharmaceutical Research*. 2007, 6(1):671-8, DOI: <https://www.doi.org/10.4314/tjpr.v6i1.14645>
47. Ogundele AV, Otun KO, Ajiboye A, Olanipekun BE, Ibrahim RB: Antidiabetic Efficacy and Phytochemical Screening of Methanolic Leaf Extract of Pawpaw (*Carica papaya*) Grown in North Central Nigeria. *Journal of the Turkish Chemical Society Section A: Chemistry*. 2017, 4(1):99-114, DOI: <https://www.doi.org/10.18596/jotcsa.52813>
48. Sobia K, Javaid MA, Ahmad MS, Rehmatullah Q, Hina G, Iram B, Pervaiz A, Farhana B, Nyla J, Gulfranz M: Assessments of phytochemicals and hypoglycemic activity of leaves extracts of *Carica papaya* in diabetic mice. *International Journal of Pharmaceutical Sciences and Research*. 2016, 7(9):3658, DOI: [https://www.doi.org/10.13040/IJPSR.0975-8232.7\(9\).1000-08](https://www.doi.org/10.13040/IJPSR.0975-8232.7(9).1000-08)
49. Adewole E, Ojo A, Omoaghe AO, Enye LA, Sumera Z. Aldose Reductase Inhibitory Effect and Identification of Bioactive Compounds in *Carica Papaya* Extract. *Der Pharmacia Lettre* 2018, 10(2):73-78, DOI: <https://www.doi.org/10.4172/2153-2435.1000576>
50. Juárez-Rojop IE, Díaz-Zagoya JC, Ble-Castillo JL, Miranda-Osorio PH, Castell-Rodríguez AE, Tovilla-Zárate CA, Rodríguez-Hernández A, Aguilar-Mariscal H, Ramón-Frías T, Bermúdez-Ocaña DY. Hypoglycemic effect of *Carica papaya* leaves in streptozotocin-induced diabetic rats. *BMC complementary and alternative medicine*. 2012, 12:1-1, DOI: <https://www.doi.org/10.1186/1472-6882-12-236>
51. Adenowo AF, Ilori MF, Balogun FO, Kazeem MI. Protective effect of ethanol leaf extract of *Carica papaya* Linn (Caricaceae) in alloxan-induced diabetic rats. *Tropical Journal of Pharmaceutical Research*. 2014, 13(11):1877-82, DOI: <https://www.doi.org/10.4314/TJPR.V13I11.15>
52. Bhuiyan MR, Maniruzzaman M, Akter S, Mehjabin S, Rana MR, Jaman MS. Drug Promising Effect for Diabetic Mice of *CARICA PAPAYA* Leaves. *European Journal of Pharmaceutical Research*. 2022, 2(3):1-5, DOI: <https://www.doi.org/10.24018/ejpharma.2022.2.3.47>
53. Miranda-Osorio PH, Castell-Rodríguez AE, Vargas-Mancilla J, Tovilla-Zárate CA, Ble-Castillo JL, Aguilar-Domínguez DE, Juárez-Rojop IE, Díaz-Zagoya JC. Protective action of *Carica papaya* on β -cells in streptozotocin-induced diabetic rats. *International journal of environmental research and public health*. 2016, 13(5):446, DOI: <https://www.doi.org/10.3390/ijerph13050446>
54. Renganathan S, Yunivita V, Martiana A, Suraya N. Effect of *Carica Papaya* L Leaf Infusion on Transporting Glucose across Small Intestine Cell Membrane of Wistar Rats Model. *Althea Medical Journal*. 2019, 6(1):42-5, DOI: <https://www.doi.org/10.15850/amj.v6n1.512>
55. Kazeem MI, Adeyemi AA, Adenowo AF, Akinsanya MA. *Carica papaya* Linn. fruit extract inhibited the activities of aldose reductase and sorbitol dehydrogenase: possible mechanism for amelioration of diabetic complications. *Future Journal of Pharmaceutical Sciences*. 2020, 6:1-7, DOI: <https://www.doi.org/10.1186/s43094-020-00118-x>
56. Lorenzi M: The polyol pathway as a mechanism for diabetic retinopathy: attractive, elusive, and resilient. *Journal of Diabetes Research* 2007: DOI: <https://doi.org/10.1155/2007/61038>
57. Sureddi J, Sharma P: Evaluation of hypoglycemic, anti hyperglycemic and antihyperlipidaemic activity of hydroalcoholic extract of *carica papaya* l. In alloxan induced diabetic rats. *World Journal of Pharmacy And Pharmaceutical Sciences*, 2021, 6; 5(10):1017-1030
58. Agada R, Usman WA, Shehu S, Thagari D: In vitro and in vivo inhibitory effects of *Carica papaya* seed on α -amylase and α -glucosidase enzymes. *Heliyon*. 2020, 6(3):e03618, DOI: <https://www.doi.org/10.1016/j.heliyon.2020.e03618>
59. Agada R., Thagriki D., Lydia E., Khusro A., Alkahtani J., Alshaq M., Alwahibi S., Elshikh M: Antioxidant and antidiabetic activities of bioactive fractions of *Carica papaya* seeds extract. *Journal of King Saud University - Science*. 2021, 33 (2):101342, DOI: <https://www.doi.org/10.1016/j.jksus.2021.101342>
60. Venkateshwarlu E, Dileep P, Sandhya P: Evaluation of anti-diabetic activity of *Carica papaya* seeds on streptozotocin-induced type-II diabetic rats. *Journal of advanced scientific research*. 2013, 4(02):38-41.
61. Pokhrel S, Karki P: Phytochemical screening, antioxidant and antidiabetic activities of extracts of leaves and seeds of

- Carica papaya. Nepal Journal of Science and Technology. 2021, 20(1):126-35, DOI: <https://www.doi.org/10.3126/njst.v20i1.43362>
62. Wulansari DD, Basori A, Suhartati S: Effect of Papaya Seed Extract (*Carica papaya* Linn.) on Glucose Transporter 4 (GLUT 4) Expression of Skeletal Muscle Tissue in Diabetic Mice Induced by High Fructose Diet. *MajalahObatTradisional*. 2017, 22(2):131-8, DOI: <https://www.doi.org/10.22146/tradmedi.27926>
 63. Morolahun EA, Ajao FO, Pemba SK: Antidiabetic effect of aqueous extract of ripe *Carica papaya* Linnaeus seed in alloxan-induced diabetic albino rats. *Journal of Diabetes and Endocrinology*. 2019, 10(2):13-7, DOI: <https://www.doi.org/10.5897/JDE2018.0127>
 64. Marpaung FS, Andika MI, Lubis YE, Mutia MS: The Effectiveness Test of Papaya (*Carrica Papaya* L.) Flower Extract on Blood Sugar Level Of The Sucrose-Induced Male Mice (*Mus Musculus* L.): UjiEfektivitasEkstrakBungaPepaya (*Carrica Papaya* L.) Terhadap Kadar GulaDarahMencit (*Mus Musculus* L.) Jantan Yang DiinduksiSukrosa. *Biospecies*. 2021, 14(1):24-31., DOI: <https://www.doi.org/10.22437/biospecies.v14i1.11175>
 65. Safrida S, Sabri M: Effect of carica papaya I. stem bark extracts on cholesterol concentration in rats induced with streptozozin. In *Proceedings of E3S Web of Conferences 2020* (Vol. 151, p. 01011). EDP Sciences, DOI: <https://www.doi.org/10.1051/e3sconf/202015101011>
 66. Tiwari Mandvi, Kuldeep Singh, Raksha Mishra and Raj K. Prasad: Antidiabetic activity and chemical characterization of aqueous root extract of *carica papaya* in alloxan induced diabetic rats. *European Journal of Biomedical and Pharmaceutical sciences* 2017, 4(5); 298-302
 67. Ezekwe SA, Chikezie PC: GC-MS analysis, hypoglycemic activity of aqueous root extract of *Carica papaya* and its effects on blood lipid profile and hepatorenal tissues biomarkers of diabetic rats. *Journal of Diabetes and Metabolism*. 2017, 8(5):740-8, DOI: <https://www.doi.org/10.4172/2155-6156.1000740>
 68. Nimenibo-Uadia R, Nwachukwu K: Antidiabetic effect of aqueous root extract of *Carica papaya* L. in alloxan induced diabetic rats. *J Natl Sci Res*. 2020, 10:2224-3186, DOI: <https://www.doi.org/10.7176/JNSR/10-6-01>
 69. Ismawanti Z, Suparyatmo JB, Wiboworini B: The Comparative Effect of Red Guava (*Psidiumguajava* L.) with Papaya (*Carica papaya*) on Blood Glucose Level of Type 2-Diabetic Patients. *Romanian Journal of Diabetes Nutrition and Metabolic Diseases*. 2020, 27(3):209-13, DOI: <https://www.doi.org/10.46389/rjd-2020-1032>
 70. Afaf-Haniem, M. R., HanaaF.El-Mehiry., Madiha, M., Abd El-Hay: Effect of Fortified Cake with Papaya (*Carica papaya* L.) on Hypoglycemia of Streptozotocin (STZ) Induced Diabetic in Experimental Rats. *World Applied Sciences Journal* 2015, 33(7): 1142-1153, DOI: <https://www.doi.org/10.5829/idosi.wasi.2015.33.07.14592>
 71. Odom TC, Udensi EA, Ogbuji CA: Evaluation of hypoglycemic properties of mucunacochichinensis unripe carica papaya and unripe musaparadisiaca flour blends. *European Journal of Biology and Medical Science Research*. 2013, 1(1):15-22.
 72. Purnamasari AB: Effect of Brotowali Extract Fortification of Papaya Leaves and Sugar Cane Caries on Diabetes Mellitus Type II. In *Journal of Physics: Conference Series 2021 Feb 1* (Vol. 1752, No. 1, p. 012051). IOP Publishing, DOI: <https://www.doi.org/10.1088/1742-6596/1752/1/012051>
 73. Brocklehurst, K., Salih, E., McKee, R., Smith, H: Fresh non-fruit latex of *Carica papaya* contains papain, multiple forms of chymopapain A and papaya proteinase omega. *Biochem. J.* 1985, 228, 525–527, DOI: <https://doi.org/10.1042/bj2280525>.
 74. Dubois, T., Jacquet, A., Schnek, A.G., Looze, Y: The thiol proteinases from the latex of *Carica papaya* L. I. fractionation, purification and preliminary characterization. *Biol. Chem. Hoppe. Seyler*. 1988. 369, 733–740. DOI: <https://www.doi.org/10.1515/bchm3.1988.369.2.733>
 75. Dubois, T., Kleinschmidt, T., Schnek, A.G., Looze, Y., Braunitzer, B: The thiol proteinases from the latex of *Carica papaya* L. III. The primary structure of chymopapain. *Biol. Chem. Hoppe. Seyler*. 1989, 370, 425–434, DOI: <https://doi.org/10.1515/bchm3.1989.370.1.425>
 76. Azarkan, M., El Moussaoui, A., Van Wuytswinkel, D., Dehon, G., Looze, Y: Fractionation and purification of the enzymes stored in the latex of *Carica papaya*. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 2003, 790, 229–238, DOI: [https://doi.org/10.1016/S1570-0232\(03\)00084-9](https://doi.org/10.1016/S1570-0232(03)00084-9)
 77. Azarkan, M., Garcia-Pino, A., Dibiani, R., Wyns, L., Loris, R., Baeyens-Volant, D: Crystallization and preliminary x-ray analysis of a protease inhibitor from the latex of *Carica papaya*. *ActaCrystallogr. Sect. F Struct. Biol. Cryst. Commun.* 2006,62:1239–1242, DOI: <https://doi.org/10.1107/S1744309106046367>.

78. Musa, Y.M: Isolation and purification of flavonoids from the leaves of locally produced *Carica papaya*. Int. J. Sci. Technol. Res 2015, 4:282–284, DOI: <https://www.doi.org/10.1016/j.crbiot.2020.11.001>
79. El-Mesallamy, A.M.D., Hussein, S.A.M., Abd El Azim, M.H.M., El-Gerby, M: Phenolic composition and biological activities of methanolic extract of *Caricapapaya*. Nat. Prod. Indian J. 2015,10:91–98.
80. Nakamura, Y., Yoshimoto, M., Murata, Y., Shimoishi, Y., Asai, Y., Eun, Y.P., Sato, K., Nakamura, Y: Papaya seed represents a rich source of biologically active isothiocyanate. J. Agric. Food Chem. 2015, 55: 4407–4413, DOI: <https://doi.org/10.1021/jf070159w>
81. Rossetto, M.R.M., Oliveria Do Nascimento, J.R., Purgatto, E., Fabi, J.P., Lajolo, F.M, Cordenunsi, B.R: Benzylglucosinolate, benzylisothiocyanate, and myrosinase activity in papaya fruit during development and ripening. J. Agric. Food Chem. 2008, 56: 9592–9599, DOI: <https://www.doi.org/10.1021/jf801934x>
82. Ghosh, S., Saha, M., Bandyopadhyay, P.K., Jana, M: Extraction, isolation and characterization of bioactive compounds from chloroform extract of *Carica papaya* seed and it's in vivo antibacterial potentiality in *Channa punctatus* against *Klebsiella* PKBSG14. Microb. Pathog. 2017, 111:508–518, DOI: <https://doi.org/10.1016/j.micpath.2017.08.033>
83. Sani, M.S.A., Bakar, J., Rahman, R.A., Abas, F: Effects of coated capillary column, derivatization, and temperature programming on the identification of *Carica papaya* seed extract composition using GC/MS analysis. J. Anal. Test. 2020, 4:23–34, DOI: <https://doi.org/10.1007/s41664-020-00118-z>.
84. Nadkarni K., Pop PraPvt Ltd, Bombay. *Indian material medica* 1954, 1:273-277.
85. The Wealth of India – 1992: A dictionary Indian raw materials and industrial products: Raw material series, Ca-Ci, publications and information directorate, CSIR . 3:276-293.
86. Bruneton J: *Tech Docu Fra.Carica papaya*, In: Pharmacognosy phytochemistry of medicinal plants. 1999, 2:221-223
87. Chandrika, U.G., Jansz, E.R., Wickramasinghe, S.M.D.N., Warnasuriya, N.D., 2003.Carotenoids in yellow- and red-fleshed papaya (*Carica papaya* L). J. Sci. Food Agric. 83, 1279–1282, DOI: <https://doi.org/10.1002/jsfa.1533>.
88. Canini, A., Alesiani, D., D'Arcangelo, G., Tagliatesta, P: Gas chromatography-mass spectrometry analysis of phenolic compounds from *Carica papaya* L. leaf. J. Food Compos. Anal. 2007, 20:584–590, DOI: <https://doi.org/10.1016/j.jfca.2007.03.009>.
89. Pino, J.A., Queris, O: Characterisation of odour-active compounds in papaya (*Carica papaya* L.) wine. Int. J. Food Sci. Technol. 2012, 47:262–268, DOI: <https://doi.org/10.1111/j.1365-2621.2011.02834.x>
90. Adachukwu, I., Ogbonna, A., Faith, E: Phytochemical analysis of paw-paw (*Carica papaya*) leaves. Int. J. Life Sci. Biotechnol. Pharma Res. 2013, 2:347–351, DOI: <https://www.doi.org/10.23910/1.2023.3374a>
91. Nwofia GE, Ojmelukwe P, Eji C: Chemical composition of leaves, fruit pulp and seeds in some *Carica papaya* (L) morphotypes. International Journal of Medicinal and Aromatic Plants. 2012, 2(1):200-6.
92. Roshan A, Verma NK, Gupta A. A brief study on *Carica Papaya*-a review. International Journal of Current Trends in Pharmaceutical Research. 2014, 2(4):541-50.
93. Nugroho, A., Heryani, H., Choi, J.S., Park, H.J: Identification and quantification of flavonoids in *Carica papaya* leaf and peroxynitrite-scavenging activity. Asian Pac. J. Trop. Biomed. 2017, 7:208–213, DOI: <https://doi.org/10.1016/j.apitb.2016.12.009>
94. Anjum, V., Arora, P., Ansari, S.H., Najmi, A.K., Ahmad, S: Antithrombocytopenic and immunomodulatory potential of metabolically characterized aqueous extract of *Carica papaya* leaves. Pharm. Biol. 2017, 55:2043–2056, DOI: <https://doi.org/10.1080/13880209.2017.1346690>.
95. Wang, X., Hu, C., Ai, Q., Chen, Y., Wang, Z., Ou, S: Isolation and identification carpaine in *Carica papaya* L. leaf by HPLC-UV method. Int. J. Food Prop. 2015, 18:1505–1512, DOI: <https://doi.org/10.1080/10942912.2014.900785>.
96. Soib, H.H., Ismail, H.F., Husin, F., Abu Bakar, M.H., Yaakob, H., Sarmidi, M.R: Bioassay-guided different extraction techniques of *Carica papaya* (Linn.) leaves on in vitro wound-healing activities. Molecules 2020, 25:1–13, DOI: <https://doi.org/10.3390/molecules25030517>
97. Teng, W.C., Chan, W., Suwanarusk, R., Ong, A., Ho, H.K., Russell, B., Rénia, L., Koh, H.L: In vitro antimalarial evaluations and cytotoxicity investigations of *Carica papaya* leaves and carpaine. Nat. Prod. Commun. 2019, 14:33–36, DOI: <https://doi.org/10.1177/1934578X1901400110>

98. Hamed AN, Abouelela ME, El Zowalaty AE, Badr MM, Abdelkader MS: Chemical constituents from *Carica papaya* Linn. leaves as potential cytotoxic, EGFR wt and aromatase (CYP19A) inhibitors; a study supported by molecular docking. *RSC advances*. 2022, 12(15):9154-62, DOI: <https://www.doi.org/10.1039/d1ra07000b>
99. Pandit DN, Singh S, Sinha US, Singh RR: Impact of *Carica papaya* L. Fruit juice on plasma variables and tissue glycogen of induced hyperglycemic albino rats. *Animal Research International*. 2019, 16(2):3361-6.
100. Ugbogu EA, Dike ED, Uche ME, Etumnu LR, Okoro BC, Ugbogu OC, Adurosakin OE, Chinma CE, Ohaeri E, Iweala EJ: Ethnomedicinal Uses, Nutritional Composition, Phytochemistry and Potential Health Benefits of *Carica papaya*. *Pharmacological Research-Modern Chinese Medicine*. 2022 :100266, DOI: <https://www.doi.org/10.1016/j.prmcm.2023.100266>
101. Agada R., Usman W., Shehu S., Thagariki D: *Heliyon*. *In vitro* and *In vivo* inhibitory effects of *Carica papaya* seed on α -amylase and α -glucosidase enzymes. 2020, 6(3): e03618, DOI: <https://www.doi.org/10.1016/j.heliyon.2020.e03618>,
102. Nyakundi BB, Yang J: Uses of Papaya Leaf and Seaweed Supplementations for Controlling Glucose Homeostasis in Diabetes. *International Journal of Molecular Sciences*. 2023, 24(7):6846, DOI: <https://www.doi.org/10.3390/ijms24076846>,
103. Adewole E: Characterization and aldose reductase inhibitory effect of carica papaya extract. *Pharm Anal Acta*. 2018, 9(576):2, DOI: <https://www.doi.org/10.4172/2153-2435.1000576>
104. Prasetya T: Isolation and identification of active compounds from papaya plants and activities as antimicrobial. In *IOP Conference Series Materials Science and Engineering*. 2018, 349(1): 012007, DOI: <https://www.doi.org/10.1088/1757-899X/349/1/012007>
105. Khaw K., Parat M., Shaw P., Nguyen T., Pandey S., Thurecth K., Falconer J: Factorial design assisted supercritical carbon-dioxide extraction of cytotoxic active principles from *Carica papaya* leaf juice. *Sci. Rep.* 2019, 9:1 -12, DOI: <https://www.doi.org/10.1038/s41598-018-37171-9>
106. Khaw K., Chear N., Maran S., Yeong K., Ong Y., Goh B: Butylcholinesterase inhibitory activity and GS-MS analysis of *Carica papaya* leaves *Nat. Prod. Sci.*. 2020, 26:65-170, DOI: <https://www.doi.org/10.20307/nps.2020.26.2.165>