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Carica Papaya's Anti-Diabetic and Anti-Cancer Properties – A Review

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Abstract

The Carica papaya originates from the Caricaceae family, and various members of this family have been used as treatments for a range of ailments. The perennial plant C. papaya, which is currently found over the whole tropical region, is thought to have originated in the southern region of Mexico. To assess the biological activity of distinct C. papaya sections, several scientific studies have been carried out. Since ancient times, the papaya plant's many components have been employed for medicinal purposes. In this article, the process of extracting Carica papaya leaves as well as the anti-cancer and anti-diabetic properties of papaya leaf activity were all things we wanted to assess. The information for this review paper, which focuses mostly on the therapeutic potential of papaya leaf extract was obtained via researching a collection of wider internet databases, including Google Scholar, PubMed, Science Direct, and Elsevier. The papaya plant, which has different parts such as fruit, leaves, seeds, bark, latex, and other substances, is very important in controlling the spread of illness. Alkaloids, glycosides, tannins, saponins, and flavonoids are just a few of the bioactive constituents in this, we focused on the papaya plant leaf's anti-cancer and anti-diabetic properties. The papaya has a wide range of therapeutic qualities. Papaya is a potent remedy, according to traditional beliefs. Biological activities have been the subject of much research. In the current review, all the pharmacological applications and activities of certain chemical components are discussed.

Keywords: *Carcia papaya leaf, Cancer, Diabetes, Anti-cancer, Anti-diabetic, Animal studies, In-vitro study*

1. Introduction

In contrast to being identified as the papita in Hindi, and erandakarkati in Sanskrit, papaya in English, the Carica papaya Linn plant is a species of the Caricaceae family. The plant was imported through tropical America to India mostly in 16th century. A terminal cluster of massive, long-stalked leaves and a weak, frail, and frequently unbranched stem, which exudes large amounts of white latex, seem to be traits of the plant. These leaves seem to exhibit a fast growth rate and can grow as high as 20 m. In the old days, leaves have been utilized to treat a spectrum of ailments, including as dengue fever, jaundice, malaria, and dengue itself. They also have antiviral, immunomodulatory, and other therapeutic properties (Anjum et al., 2013).

Morphology, distribution, and Taxonomy

Botanical categorization

Flowering plant - Domain

Plantae - Kingdom.

Tracheobionta - Sub Kingdom.

Magnoliopsida - Class

Dilleniidae - Subclass

Spermatophyta - Superdivision

Steptophyta - Phylum

Brassicales - Order

Caricaceae - Family

Genus - Carica

Name of the plant: Carica papaya Linn.

The leaves have too been investigated for their possible therapeutic applications, and it has been noted with in publications as being utilised by locals from many parts of the world for its impact on conditions including cancer, inflammation and diabetes over other things. The hemostatic ability and positive benefits of Carica papaya leaves in treating dengue-infected individuals have recently been documented (Ahmad et al., 2011). Favonoids, cyanogenic glucosides, ascorbic acid and glucosinolates are just a few of the beneficial compounds present in papaya leaves that have been demonstrated to lower lipid peroxidation levels and boost blood total antioxidant capacity. The active components of papaya leaves, such as flavonoids, cyanogenic glucosides, and glucosinolates, papain, ascorbic acid, chymopapain cystatin, -tocopherol, have been shown to increase the blood's total antioxidant capacity and reduce levels of lipid peroxidation (Seigler et al., 2002).

Cancer

Any organ in the human body can be affected by cancer, which is a large category of disorders marked by abnormal body cell proliferation. Another term for cancer that is widely used is a malignant tumour because cancer cells have the propensity to proliferate swiftly from the initial organs to others. As one of the top causes of death today, cancer is thought to account for 10.5 million deaths worldwide annually. It is significant to point out since there have been anecdotal stories of cancer patients of various types obtaining favourable results, such as after taking papaya plant components (Otsuki et al., 2020; Lucas, 1926). Due to the expense, side effects, and continued growth in both new occurrences of cancer and cancer-related mortality, research into the effectiveness of natural remedies for cancer therapy and management is gaining more and more traction. In 2030, estimates show that there will be more than 13.1 million cancer-related deaths worldwide (WHO, 2012).

Diabetes Mellitus

In recent decades, interest in traditional plant therapies for diabetes has increased. The goal of this study was to find out whether diabetic rats will respond hypoglycemically to a fluid extract made from C. papaya leaves. The C. papaya plant's different constituents possess antihyperglycemic activity over both animals and people, according to numerous studies (perez et al., 2003; Islam, 2011; Sasidharan et al., 2011; Gaamoussi et al., 2010). Diabetes mellitus is a long-standing ailment, and medicative herb formulations have remained a plentiful supply source of medically beneficial phytocompounds and a workable option in treating a variety of illnesses afflicting humans. Some plants have bioactive chemicals that have reportedly been utilised to cure and prevent diabetes all over the world. The ability of plants to restrict intestinal glucose absorption, boost insulin output, or facilitate metabolites in insulin-dependent activities is directly related to their capacity to recover the performance of pancreatic tissues (Patel et al., 2012).

Extraction Process

Papaya leaves can be extracted in a number of ways, including as the traditional continuous extraction, maceration and percolation techniques as well as by using more advanced tools like ultrasonic cleaners and microwaves. In this presentation, the several papaya leaf extraction techniques and the solvents used in each technique will be presented. Most of the leaves are separated through a maceration process using 96 percent ethanol as the solvent. Maceration is arguably the most popular

kind of treatment because it is less time-consuming and expensive than other approaches. The delicate texture of the leaf may make it simpler for the solution to infiltrate the leaf layers and extract the phytocompounds (Mohammad et al., 2016; Hariono). Water and 96 percent ethanol are the most often used solvents. Since these solvents are safer than alternative options, it is the main justification for picking them (Angkawijaya et al., 2014).

The extraction of papaya leaves involves the process of extracting the phytoconstituents from the different cell layer of the leaves, without causing any damage to the phytochemical constituents. Hence, a special extraction procedure is used during the extraction process of papaya leaf which involves the use of solvents like Methanol, Ethanol and Water. The selection of solvents plays a major role is the process of extraction, hence selective solvents are only used that don't alter the crude drug nature.

- In the first step of extraction cleaning of the papaya leaf is done using ultrasound in the presence of solvents either methanol or 96% ethanol is used to clean the surface of the leaves.
- In the step 2 of the process a hot presser is used to extract the content from the leaves with the help of water as a solvent
- In step 3 in the presence of 70 percent ethanol at first blend and 96 percent ethanol at second blend is done in the blender.
- Maceration is carried out once blending is done with 70 and 80 percent methanol depending upon the blend obtained
- After maceration it is mixed well with cold water or 70 and ethanol or methanol and the sample obtained is microwaved/kept in hot air oven to obtain the pyrogen free product.
- Then the solvent is made up to the volume using hexane/ acetone to make the final product.

Table 1: Extraction of papaya leaf

Extraction Procedure	Solvents
Cleaning using ultrasound	Methanol (Fauziah, 2019) 96 percent ethanol (Utama, 2018)
Hot presser	Water (Kumar, 2020)
Blender	Water (Permadi et al., 2020; Longkala, 2019; Nurjannah et al., 2017) 70 percent ethanol (Megantara, 2018; Pertiwi et al., 2019) 96 percent ethanol (Ugo et al., 2019; Yuliani, 2020)
Maceration	70 percent methanol (Tewari et al., 2014; Kamilla et al., 2021) 80 percent methanol (Nariya, 2017; Anwar, 2019) Water (Anwar et al., 2019)
Mixer	Cold water, cold ethanol, hot water, 70% methanol (Arunkumar, 2009; Liana, 2018)
Microwave	70% ethanol, water (Nisa, 2019)
Soxhlet	Hexane, 60% ethanol, acetone, 40% ethanol, water (Singh et al., 2017)

Preparation of Plant Extract

The C. papaya leaves were carefully cleaned under clean running water to eliminate any dirt or debris. The leaves were then rinsed again with DH2O and shade-dried for 10–15 days at ambient temperature (26 ±2◦C). The leaves were then pulverised into a coarse powder. To ascertain the presence of phytochemicals, 100g of leaf powder was separated using a Soxhlet equipment with several vehicles, including chloroform, petroleum ether, water, ethyl acetate and methanol. After the leaf powders had been separated till the solvent inside the thimble had become colorless, Whatman No. 1 filter paper was used to filter it. The leftovers that were left over were kept at 4 °C in amber-coloured glass vials until they were needed (Mohajeri et al., 2021). A randomised controlled experiment demonstrated that children can safely drink the standardised leaf extracts of C. papaya leaves in childrens. Adult humans

could tolerate intake of papaya leaf (in the liquid form as well as standardized aqueous leaf extract) for short intervals of time (approximately five days). The most frequent adverse responses were minor gastrointestinal side effects. Reproductive toxicity and hepatotoxicity are problems with long-term use, according to research on animals. Negative herb-drug interaction including digoxin, metformin, ciprofloxacin, glimepiride and artemisinin were taken into account (Reddy et., 2014).

2. Results and Discussion

Many plant species are beneficial for therapeutic purposes because of phytochemicals, which are chemical elements that are naturally present in various plant sections. As a result of determination of physical properties performed in multiple program of studies that amply established the existence of considerable amounts of phytoconstituents present in it, papaya leaves are in reality recognized to have a variety of health-promoting phytochemicals (Sarkar et al., 2020). Phytochemicals that have been found to be present in leaves include kaempferol 3-(2G-glucosylrutinoside), carpaine, kaempferol 3-(2”-rhamnosylgalactoside), 7-rhamnoside, kaempferol 3-rhamnosyl-(1->2), luteolin 7-galactosyl-(1->6)-galactoside, 11-hydroperoxy-12, Orientin 7-O-rhamnoside, 13-epoxy -9-Octadecenoic acid, 2-Hexaprenyl-6-methoxyphenol and palmiticamide (Li et al., 2015). The leaves of papaya were blended with various medications to treat illnesses. It is combined with other plants in Cameroon to treat malaria and other fungus, and it is used by traditional practitioners in central Africa to treat diabetes. There is proof that native Australians employed the decoction of the leaves as an anti-cancer remedy. The anti-inflammatory as well as anti-cancerous qualities of papaya leaves are mostly due to their saponins, alkaloids, glycosides, phenolic compounds, and flavonoids content (Ayoolo et al., 2020; Dang et al., 2016).

Table 2: List of Phytochemical compounds

Class	Compounds	Pharmacological effect
Flavonoids	Kampferol, deoxyquercetin, galic acid, deoxykampferol, catechin, apigenin, protocatechuric acid	Antio-xidant, anti-bacterial, anti-dengue (Li et al., 2019)
Flavonoid glycosides	Kampferol 3-(2-rhamnosylrutinoside), quercetin 3-(2-rhamnosylrutinoside), myricetin 3-rhamnoside, quercetin 3-rutinoside	Anti-oxidant (Mohammad et al., 2016)
Cyanogenic glycosides	2S-sambunigrin, R-prunasin	Anti-neoplastic (Hariono et al., 2020)
Coumarins	5,7-Dimethoxycoumarin, o-coumaric acid, p-coumaric alcohol, p-coumaric acid	Anti-oxidant (Angkawijaya et al., 2024)
Quinones	• Anthraquinone	Anti-diabetes (Fauziah & Wakidah, 2019)
Cinnamic acids	Chlorogenic acid, E-3-(4-hydroxy3-(3,4,5 trimethoxybenzyl)phenyl)acrylic acid, ferulic acid	
Phenols	2,6-dimethoxyphenol	Anti-oxidant (Utama, 2018)
Alkaloids	pseudo carpaine, dehydro carpaine I, dehydro carpaine II, emetine, carpaine, carposide	Anti-malarial (Kumar et al., 2020)

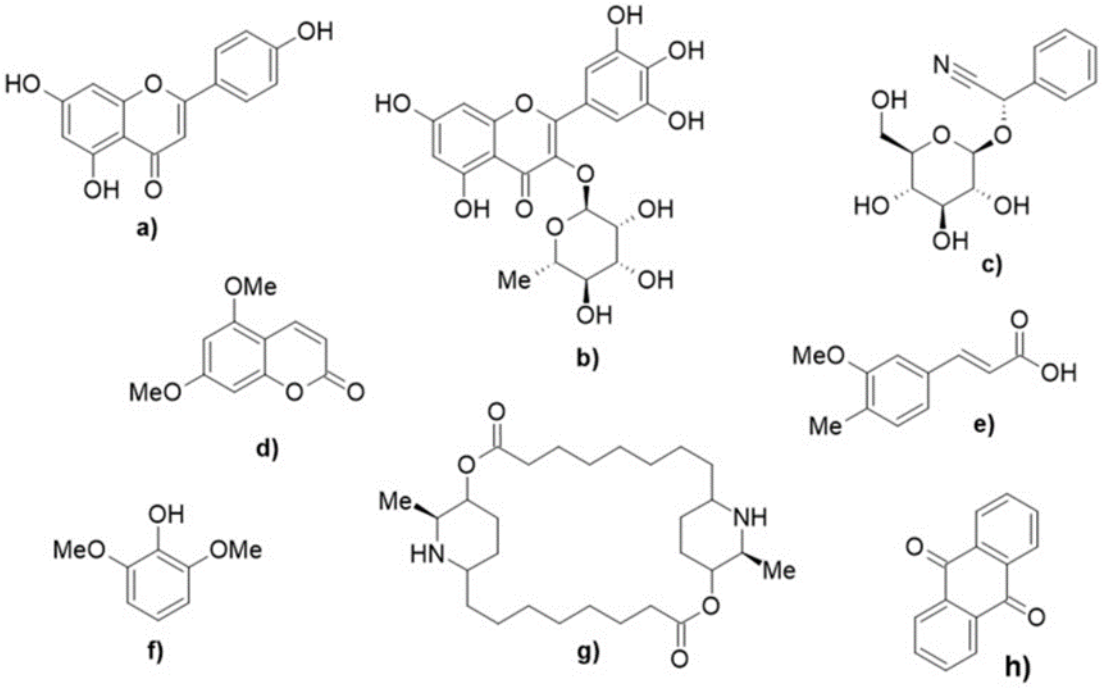

Figure 1: Chemical structure of phytochemical compounds

Apigenin, Myricetin 3-rhanmnoside, 2S-Sambunigrin, 5,7-Dimethoxycoumarin, Ferulic Acid, 2,6-Dimethoxyphenol, Carpaine, and Anthraquinone are the typical components found in papaya leaves from each class (Ugo et al., 2019). Additionally, potential anti and anti-helminthic activities of carpaine have been reported. The benefits of papaya leaf (Carica papaya) against diabetes and cancer will be discussed here.

Papaya leaf extract's anti-cancer properties

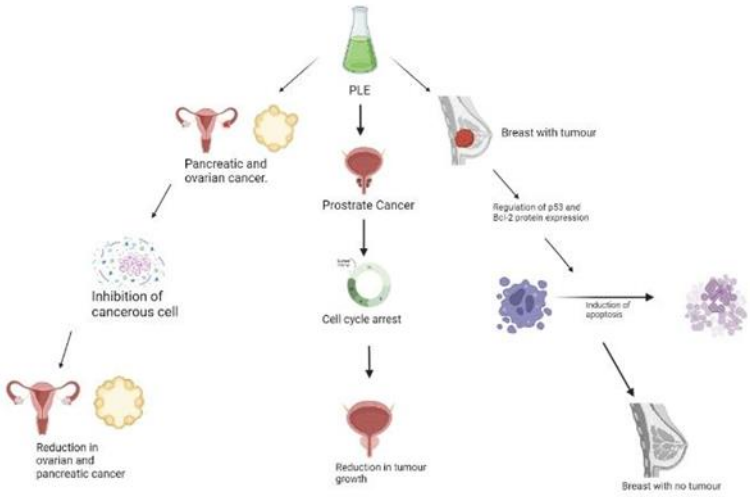

Figure 2: Anti-cancer properties of PLE

Cancer, a broad class of diseases characterized by uncontrollable cellular proliferation in the body, can damage any organ. Another term for cancer that is widely used is a malignant tumour, because cancerous cells have the ability to quickly spread from their initial organ to others. A current major cause of mortality, malignancy is thought to account for 8.97million deaths annually worldwide (Pertiwi et al., 2019). While females are more prone to acquire colorectal, breast, thyroid, lung, and cervical cancers, men are more likely to suffer liver, lung, stomach, prostate, and colorectal cancers (Sandhanasamy et al., 2021; Lim et al., 2021; Alara et al., 2022). Financial and emotional toll that

chronic illness takes on patients, their families, and healthcare systems throughout the world, particularly in low- and middle-income nations, is continually rising. Additionally, Researchers found that high saponin papaya leaf extracts with ethanol were more effective at inhibiting malignant cell lines than aqueous extracts.

To estimate the impact of papaya capsule on cancer patients, a recent study divided cancer patients into age groups (paediatric: 4–9 years and adult: 19–73 years), gender groups, body mass categories, and social groups. Patients who received papaya leaf extract experienced a considerable decrease in malignant growth of 0.16 g/kg body mass as relative to the placebo group. Their research showed that extract of papaya leaves significantly impacted antitumor treatment for the management and cure of prostate tumour as a result of phytocompounds (flavonoids, amino acids, phenolics and alkaloids). In vitro tests have conclusively shown that this herbal extract considerably benefitted several cancer cell lines. To ascertain the effectiveness of the extract of papaya leaves in cancer prevention as well as its precise mode of action, more research is still needed. The therapeutic potential of a leaves extract from Carica papaya L. against thrombocytopenia brought on by viruses.

Table 3: In vivo research on the anti-cancer effects of Carica papaya leaf extract

Treatment	Effect on malignant cells
The C. papaya leaf isolate in aqueous solution (1.25–27 mg/mL).	(i) On tumor cell lines (including the ovarian tumor cell line Dov-13, the colon tumor cell line DLD-1, the stomach tumor cell line AGS, the pancreatic tumor cell line Capan-1, the lymphoma cell line Karpas, and the breast tumor cell line MCF-7) it demonstrated an effective anticancer property (ii) limiting the incorporation of 3H-thymidine to minimize DNA synthesis (Soib et al., 2020).
C. papaya leaf extract in water (0.625–20 mg/mL).	(i) Malignant and hemopoietic cell lines' proliferative responses are inhibited (ii) immunological modulatory gene expression is increased (Juarez et al., 2014) .
Juice from brewed leaves (20 mg/mL).	(i)Prostate malignant cells were effectively inhibited from proliferating (ii) SCC25 cell proliferation was inhibited in a dosage-dependent manner (iii) 20 percentage of the total SCC25 cell and 70 percentage of malignant-free individual keratinocytes HaCaT cells survived by a dosage of 25 mg/mL (Nisa et al., 2017)
Extract of C. papaya leaves in water (659.63 µg/mL).	(i)Papaya leaf extract demonstrated antiproliferative and apoptotic triggered action suppresses cellular expansion in breast cancer in individuals. MCF-7 cell line death was seen in extracts from papaya leaves (22.54%) (Singh et al., 2017)
The extracts of papaya leaves (0.25–0.1 mg/mL).	(i)Prostate cancerous cells that can be effectively inhibiting from proliferating (ii)Except for the normal (Prostate epithelial transformed by HPV and Myofibroblast cell line) cells, all prostate cells show strong growth inhibitory and cytotoxic actions. s(iii) The intermediate polar fraction prevented the metastatic PC-3 cell from migrating and adhering (Sandahasamy et al., 2021)
C. papaya leaf juice (0.01–1 mg/mL) action in prostate epithelium cancerous cells and benign	(i)Reduced the growth of cancer cells (ii) stopped the S phase of the cell cycle

tumour.	(iii)Cell death of prostate cancerous cells (Lim et al., 2021)
Silver nanoparticles (AgNPs) with leaf extract of papaya (0.5, 1, 2.5, and 5 μg/mL) at 24 hours and 48 hours on human prostate tumor DU145 cells.	Apoptosis followed by decreased cell growth in human prostate cancer DU145 cells (Alara et al., 2022).

Papaya leaf extract may lessen metastatic cancer by functioning as an anti-cancerous agent by reducing the extracellular matrix content, which also attracts PC-3 cells for adherence and migration (Soib et al., 2020). As a result, the extraction suggests the ability to stop DNA synthesis and stop the reproduction of cancer cells.

Papaya leaf extract's anti-diabetic properties

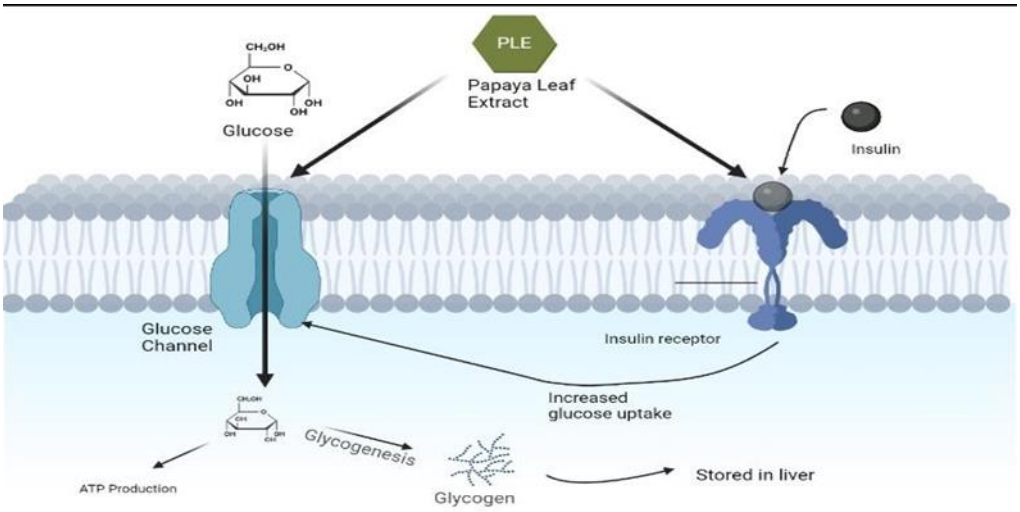

Figure 3: Anti-diabetic property of PLE

Diabetes mellitus has been around for a while, and herbal extracts continue to be a valuable source of medically helpful phytochemicals and effective options in treating the different illnesses that plague humans. There are certain plants that have bioactive components that have reportedly been utilised to cure and prevent diabetes all over the world. The capacity of plants to restore pancreatic tissue function through increased insulin secretion, inhibition of intestinal glucose absorption, or stimulation of metabolites in insulin-dependent processes is directly related to their anti-hyperglycaemic qualities (Juarez et al., 2014). Carica papaya is one of the fruit and vegetable-friendly plants in the Cariaceae family. People have recently started eating these leaves to treat dengue fever and manage their platelet levels (Zhang et al., 2011). The word "diabetes mellitus" itself implies a wide range of conditions marked by improper glucose metabolism and hyperglycemia. It is linked to variable degrees of resistance to insulin action as well as impairment in insulin secretion. Diabetes also raises the chance of other illnesses and conditions like weight, ageing, inheritance, and hereditary insulin receptor and beta-cell dysfunction. Both conventional and contemporary medicine highlight the powerful anti-diabetic phytonutrients found in a variety of plants.

Numerous studies have shown that plant part extracts have strong anti-diabetic properties and can be used to treat diabetes due to the tendency toward lower blood glucose levels in the treated animals that consumed plant part extracts. Papaya leaves, among other plant components, have been included in conventional Ayurvedic treatments for diabetes (Nalamolu, 2006). Papaya leaf extracts have been shown to have an anti-diabetic impact on diabetic rats in preclinical experiments that have been published, but no clinical research on humans has yet been conducted to test this effect. Papaya leaves have no adverse effects, according to researchers, making them a potential alternative therapy for the treatment of diabetes. This leaf extract has a large number of phytochemicals, which has a substantial impact on lowering various secondary issues brought on by diabetes (Sobia et al., 2016). In 2007, the initial analysis of papaya leaf extract's effects on Wistar diabetic rats was completed. In the course of

the study, papaya ethanol extract of leaves (5.0 mg/kg BW) was administered to male Wistar rats. After giving diabetic rats an oral dose for 24 hours, the researchers saw a dramatic drop in blood glucose levels, which range between 12.75 to 1.23 mmol/L (Fakeye et al., 20017).

Treatment	Results
Streptozotocin-induced diabetics were given an ethanol liquid extract of C. papaya (100 mg/kg) together with water for five days.	(i) Lower levels of blood glucose after the conclusion of the fifth treatment day. (ii) Significant regeneration of liver tissue. (iii) The renal tissues show significant improvement in the cuboidal tissue (Sasidhran et al., 2011).
0.75 and 1.5 grammes per 100 millilitres of C. papaya aqueous extract for a month.	(i) A lag in amiodarone, extract, and amiodarone reaching their maximum plasma concentrations enhanced the drug's bioavailability. (ii) Significantly higher blood glucose levels (434.0 mg/dL) compared to animals who weren't receiving treatment (iii) A substantial reduction in glucose level in the blood to 306.00 10.2 mg/dL (Juarez et al., 2012).
For 21 days, diabetic albino rats were given an liquid extract of C. papaya leaf (400 mg/kg BW).	(i) The antidiabetic and hypolipidemic capabilities result in a substantial drop in serum lipid profiles and blood sugar levels. (ii) After the course of therapy, leaf extract revealed a 38.19% reduction in blood glucose levels (Maniyar, 2012).
Using an ethanolic extract of C. papaya leaves for 21 days (250-500 mg/kg BW of diabetic rats induced with alloxan).	(i) Significantly lower levels of serum urea (12.35 mg/dL), total cholesterol, and triglycerides (1.24 mg/dL), as well as glucose (123.50 mg/dL). (ii) Significantly higher levels of total protein (66.51 g/dL) and HDL cholesterol. (iii) A significant drop in alanine aminotransferase, aspartate aminotransferase, creatinine, and LDL cholesterol (Adenowo et al., 2014).
50, 150, and 300 mg/kg BW of C. papaya ethanolic leaf extracts were administered to diabetic mice.	(i) Positive impacts on HDL cholesterol, plasma insulin, cholesterol, and triglyceride levels. (ii) The hypoglycemic impact of various dosages of C. papaya extract on rats treated (Sobia, 2016).
For 18 days, albino rats were given an aqueous extract of C. papaya leaf at a dose of 120 mg/kg BW.	Significantly decreased total cholesterol, total glycerides, and LDL cholesterol levels from 117.70 to 98.50 mg/dL, 107.10 to 97.21 mg/dL, and from 49.44 to 44.01 mg/dL (Ukpabi et al., 2019)
Feeding diabetic Wistar mice ethanol extract from papaya leaves at a dose of 1000 mg/kg body weight.	lower levels of blood glucose in Wistar mice with diabetes was found (Solikhah et al., 2020).

To minimize the breakdown of disaccharides and triglycerides into simpler, more rapidly digestible free fatty acids and monosaccharides, papaya leaves diminish the efficiency of both the fat and carbohydrate hydrolytic enzymes with in small intestines (Juarez et al., 2014). To demonstrate papaya leaf extracts' positive benefits as a hypoglycemic agent but before include it as an anti-diabetic component, more comprehensive, exhaustive cell line or animal study research is required.

3. Conclusion

Papaya leaves offer a lot of potential for treating viral infections and boosting immunity, in addition to having anti-inflammatory, anti-cancer, anti-diabetic, and numerous other disease-preventive characteristics, Further research is required to determine the major pathways of action of the phytonutrients contained in the leaf extract of papaya as medicinal agents. Numerous studies have shown that papaya leaf extract decreases blood sugar levels and inhibits the growth of cancer cells. To describe how papaya plant pieces affect cancer cells and people with diabetes, a further descriptive

clinical study should be conducted. Eating papaya leaves has shown to greatly hasten the recuperation from viral infections such as dengue fever. There are presently no antiviral drugs available to treat severe corona virus-like illnesses, thus the hunt for an alternative therapy has become a major priority in recent years. Rising viral infections are now considered to be of great significance on a global scale.

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