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From Tradition to Treatment: The Anti-Diabetic Properties of Carica Papaya Leaves

Bhanu Marwaha

LOVELY professional university, India.

ABSTRACT:

Papaya is a popular fruit in both tropical and sub-tropical countries. Its botanical name is Carica papaya and it belongs to family Caricaceae. The leaves of papaya have long petiole of about 80cm long. Numerous phytochemical studies found that papaya have various enzymes such as papain, chymopapain, alkaloid carpain, nicotine, flavonoids, tannins, and terpinenes. This review focus on evidence-based information about anti-diabetic properties of papaya leaves, collected from online databases (Scopus, ScienceDirect, ResearchGate, google scholar). It has shown a significant impact in normalizing blood glucose level. C.papaya grows quickly and is quite affordable means of treatment for diabetes. Hyperglycemia is a major health issue nowadays around the world. It is a metabolic disorder in which pancreas does not produce enough insulin which results in rise in blood glucose level in body. This in turn leads to many complications including obesity, frequent urination, excessive thirst, and increased appetite. In recent times, there is an increase in demand for organic medicines as compared to antibiotics. Therefore, Papaya leaves are seen to have significant impact in treating diabetes.

KEYWORDS: Papaya, Leaves, Carica papaya, anti-diabetic.

1.INTRODUCTION:

Diabetes mellitus (DM) is a fastest emerging endocrine disorder prevailing worldwide. It affects millions of individuals globally. This condition arises due to disorder in pancreatic secretion of insulin which leads to elevation in blood glucose levels which is commonly termed as diabetes. It also affects blood vessels, kidneys, eyes, heart and nerves [1]. Diabetes increases risk of diseases such as cardiovascular diseases, stroke, ulcers and many more. These diseases can be proven life threatening which increases the mortality rate. Majority of people suffering diabetes are obese and have high blood pressures issues also [2]. Initially, pharmaceutical products are employed for treating blood glucose level to manage symptoms which helps in saving lives. Further aim was to manage chronic diseases symptoms associated with it. These initiatives were considered to increase the life span of diabetic patients. Insulin replacement therapy was used for people diagnosed with type 1 diabetes mellitus whereas lifestyle and dietary modifications were employed for that of patients with type 2 diabetes [3]. Prominent symptoms that can be easily observed in a hyperglycemic person are polyuria, increased appetite, weight-loss and blurred vision [4].

1.1.1CLASSIFICATION:

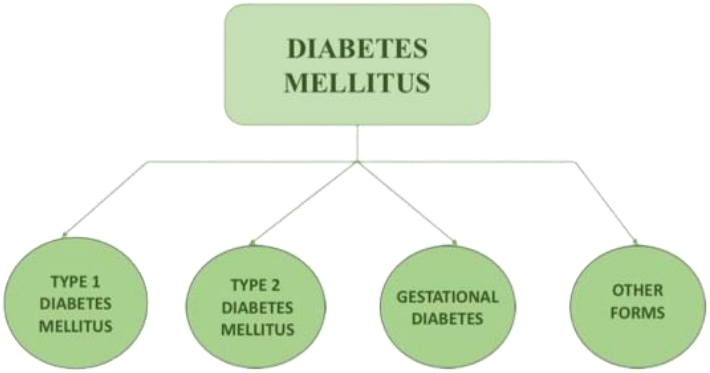

Fig1. Types of diabetes mellitus

I. TYPE 1 DIABETES MELLITUS: also known as juvenile diabetes, commonly seen in young children but can be rarely found in adults also. It is an auto immune disorder in which insulin producing beta cells are destroyed by body's immune cells. This condition may arise due to genetic mutations [5]. T1D can be detected way before its onset commonly before two years of diagnosis a rapid decline in insulin resistance can be noticed. Changes in glucose and protein intake should be done to detect this disorder [6].

II. TYPE 2 DIABETES MELLITUS: The most significant symptom of T2D is defective insulin secretion. Commonly results in insulin resistance. These patients are basically obese and their insulin level is extremely low which reflects the condition of insulin resistance. Responses keep on declining and therefore managing glucose level becomes a huge challenge. The beta cells continue to diminish making condition more worse [6].

III. GESTATIONAL DIABETES MELLITUS: GDM basic symptom is borderline glucose level which leads to hyperglycemia. It is basically found in pregnant women and is resolved after delivery of the baby. GDM increases risk of complications during pregnancy which includes low birth child, preterm delivery, and neonatal hyperglycemia. It has postpartum consequences also such as it severely increases chances of mother developing type2 diabetes mellitus and there are certain chances that the infant may also develop the impaired glucose tolerance. The highest chances of developing GDM are usually during second and third trimester of pregnancy [7].

IV. OTHER FORMS OF DIABETES: Other forms of diabetes are genetic diabetes, exocranial pancreatic disorders, endocrine diseases, chemical induced diabetes, infection and unusual form of immune mediated diabetes [8].

1.2 Carica papaya LEAVES:

C. papaya leaves are used as a medicinal plant from ancient time. These were consumed orally in infused forms to manage blood pressure and blood glucose. In addition, these have potential to treat fever, increasing platelet count mostly in case of dengue. These are proven effective in treating hyperglycemia and hyperlipidemia. Leaves have several phytochemical contents which are responsible for its important characteristics. WHO reports highlights safety of herbal medicines are comparable to conventional methods [9].

In recent times, prevalence of chronic diseases is increasing tremendously worldwide. Therefore, it is becoming an important matter of concern to manage these diseases with the help of dietary modifications. Plant based remedies have lesser side effects and are effective against chronic diseases such as type 2 diabetes mellitus, obesity and other infectious diseases. Papaya leaves has emerged as one of the most efficient functional crops in treatment of chronic diseases [10].

Carica papaya is also known as papaya or pawpaw, its all parts have essential properties. It is a tropical plant and is grows well during winters. Although all parts of papaya were considered in studies but most importantly leaves and fruit were found to be most effective and can be used in foods, medicines, pesticides and cosmetics. Papaya leaves extract was proven to be effective in managing hyperglycemia by increasing glucose transporter 4 (GLUT4). This mechanism takes place in skeletal muscles which inhibits cell atrophy [11].

1.2.1 BOTANICAL FEATURES:

Pawpaw tree is a long herbaceous tree which is single stalked. It attains an approximate length of 20-30ft., it has large sized leaves and petiole is of about 2-3ft long. The stem color is green to tan brown and is hollow having a diameter of about 8cm and have leaf scars [12].

DIFFERENT PARTS OF *C. papaya* ADAPTED FROM [12]

This review mainly focus on *Carica papaya* leaves aqueous extract. How it helps in management and prevention of diabetes.

2.HYPOGLYCEMIC EFFECT OF PAWPAW LEAVES:

Diabetes is a metabolic disorder which arises due to problem in insulin secretion by beta cells of pancreas. There are several responsible factors for elevation of this including sedentary lifestyle, unhealthy eating habits, obesity and malnourishment related problems. India is considered to diabetic capital of world. There are other plants also which shows anti-hyperglycemic effects such as garlic, ispaghula seeds and bitter melon.
Several studies were conducted which shows anti-diabetic effects of papaya leaf extract in diabetes induced rats. It increases secretion of insulin from beta cells of pancreas [13].

3. MATERIALS AND METHODS:

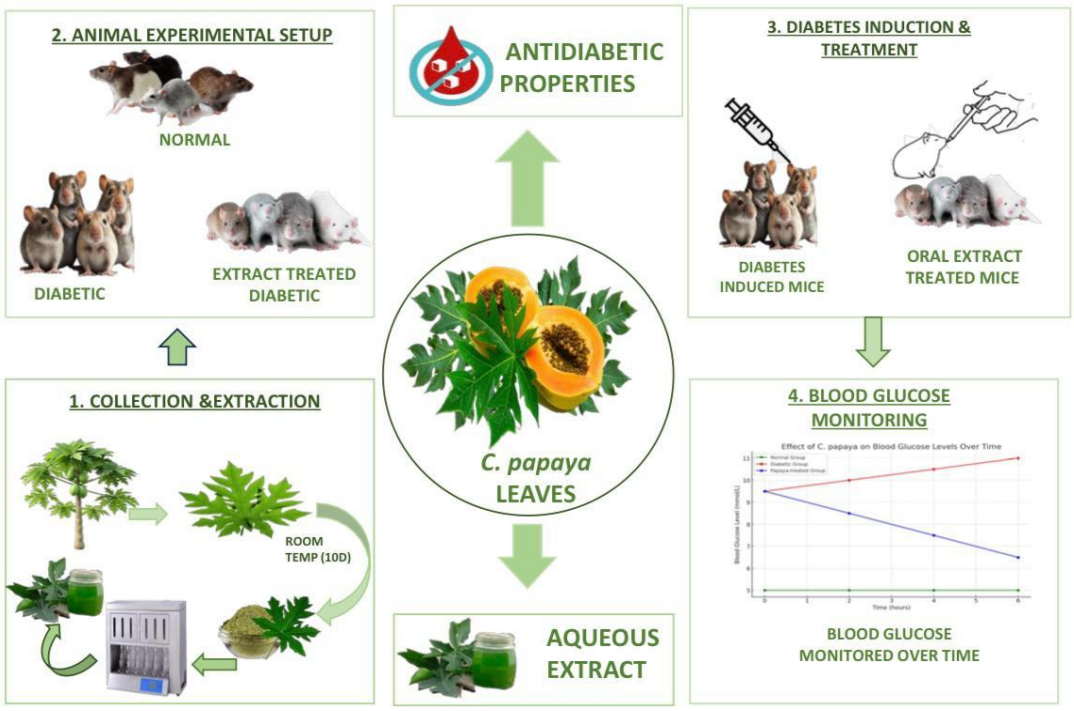

Fig2. Graphical Abstract

3.1 PLANT MATERIAL:

Leaves of *C. papaya* were collected from botanical garden, nearby parks and from college gardens. A specimen was deposited in herbarium.

3.2 PREPARATION OF EXTRACT:

The surface leaves are sterilized by using 30% alcohol, and is dried in shade. The leaves after dried are grind using grinder and passed through sieve. The powder formed is then boiled in hot water and after that it is filtered in cotton gauze. Brown color residues are produced after evaporation at 40^0C. The extract formed is then kept in an airtight container and stored in refrigerator at 4^0C. Fresh preparation can be made from this sample whenever required [14].
The leaves of papaya were chopped into small pieces and washed thoroughly with tap water. After air drying the sample was crushed and is placed inside Soxhlet apparatus. Extraction process was carried out for 8hr along with 500ml chloroform. Further process was carried under vacuum till the extract was completely dry and preserved at -20°C. Chloroform extract of leaves was used to final concentration of 1mg/ml [15].
The leaves of papaya are dried continuously for 6days and is converted to powder. The sample was extracted with methanol for 72hours and obtained extract was filtered. The crude extract was concentrated under decreased pressure to remove solvents from methanol extract. Further the extract is kept inside an air tight container for future use [16].
Collected leaves were washed in 1% iodine solution afterwards with distilled water. Then the leaves are chopped, dried and powdered using pastel and mortar. About 50g of powder is added into a conical flask then added 450ml of distilled water and stirred for 8minutes, then is covered using a cork and left undisturbed for 14hours. The solution was filtered using filter paper and stored in refrigerator at 4°C [17].

The pawpaw leaves were washed and oven dried at 50°C and is then powdered using waring blender. Reflux method was employed for making aqueous extract. Then filtration was done using Whatman No.1 filter paper. Evaporation was carried out in rotatory evaporator under vacuum at 50°C. The dried extract was stored at 20°C for further usage [18].

The leaves are dried and powdered and the extraction is carried out with hexane, chloroform, ethyl acetate and methanol by using Soxhlet method. The remains after extraction with methanol are drained out using water. Filtrations is done and extract is concentrated using Rota vapor and is freezer till next use [19].

The sample is cleaned and dried and is converted into powder and is sieved. Before filtration the 10g of powder is boiled in 100ml water foe 30minutes and then passed through cotton gauze. Further the extract was stored in an air tight container at 4°C. Fresh extract was made after every 5th day till 21stday of research [20].

Proper cleaning of leaves was done and were dried under optimum conditions and stored in a container. 80g of powder was taken separately and 400ml solvent was added. The mixture was stored in a vessel and is covered properly with cotton and aluminum foil for 15days and stirred at regular intervals. Then the extract is filtered and heated at 390°C under reduced pressure in a rotatory evaporator. The remnants were stored in sterile conditions [21].

Washing was done in order to clean the papaya leave then the leaves were dried for 24hours.followed by oven drying at 40°C for 24hours. Powder was made in blender and liquified with 96% ethanol for 3x24hours. The filtrate is then evaporated in a rotatory evaporator at 50°C. and is put into an oven and converted into paste [22,23].

3.3 ANIMALS:

Healthy Wistar albino rats were used and were kept under normal conditions. Weighing between 150-300g and fed with normal rat diet and water for different intervals [14,15,17,20,21,22].

3.4 INDUCTION OF DIABETES:

A single dose of alloxan monohydrate dissolved in saline was employed for type 2 diabetes induction. Induction was done in rats after overnight fasting. Stabilized conditions were provided for 3,4,7,10 days respectively and rats were selected on the bases of blood glucose level more than 250mg/dl [14,15,17,21].

3.5 EXPERIMENTAL DESIGN:

Rats were fasted overnight for 12hours were randomly divided into 6 groups with 6 rats in each group. Group 1-3 were non diabetic rats and group3 was taken as standard group. Further group 4,5,6 was treated with different doses of aqueous extract. Fasting blood glucose levels were measured after 0,2,4, and 6 hours after treatment. The process was carried out for 21 days the estimation of glucose was done at 0, 1, 7, 14, and 21 days [14,17].

Oral doses of papaya aqueous chloroform extract were given to rats. Similarly same doses were given to non- diabetic rats. For every group the body weight was measured every week. The experiment was continued for 20days followed by 12h fasting and rats were sacrificed [15].

Mice were divided into 5groups, the classification was done as follows [16]:

S no.	**GROUP**	**CLASSIFICATION**	**FEED**
1	**GROUP 1**	**NORMAL CONTROL**	**CONVENTIONAL PELLET DIET AND WATER**
2.	**GROUP 2**	**DIABETIC CONTROL**	**NO MEDICATION**
3.	**GROUP 3**	**POSITIVE CONTROL**	**GLIBENCLAMIDE DOSE (5mg/kg)**
4.	**GROUP 4**	**TREATED 1**	**AQEOUS EXTRACT WITH METHANOL**
5.	**GROUP 5**	**TREATED 2**	**DOUBLE DOSE OF EXTRACT**

Table : Classification of mice

3.6 ESTIMATION OF BIOCHEMICAL PARAMETERS:

On 21st day, blood sample was collected from overnight fasted rats using orbital plexus puncture method and was kept for clotting for about 30min. The sample was employed to centrifugation at 6000rpm for 20min. Serum was separated and sent for analysis [14].

Blood was collected and serum was frozen at -70°C before biochemical analysis was done. Glucose test was done [15].
On day 1, 5, 10, 15 and 21 the blood was collected from vein of tails in fastening mice from each. Mice were given anesthesia and blood was collected from heart. At the end of experiment the mice were sacrificed [21].

3.7 STATISTICAL ANALYSIS:

I. ANOVA Test followed by Dunnett's test [14,49].
II. ANOVA test followed by Tukey's test to compare differences [15].
III. Phytochemical analysis was done [16]
IV. ANOVA method was used [17]
V. The individual groups were analyzed using the analysis of variance procedure of SPSS software 20 Version (IBM) [18,39].
VI. Phytochemical analysis was done [19]
VII. Analyzed using SPSS version 16.0 and an independent T-test [20]
VIII. Data analysis was confirmed with IBM SPSS 12.0 version [21].

4.RESULTS:

A. The dose of 100gm/kg extract shows effect on 14th day of experiment whereas that of 200mg/kg shows its effect on 21stday [14].
B. There was a reduction in weight of chloroform treated aqueous extract apart from that it shows reduction in blood glucose level [15].
C. The methanol extract of papaya leaves shows ability to manage blood glucose [16].
D. Extract have ability to manage insulin secretion and shows decline in hyperglycemic effect [17]
E. Aqueous extract inhibits increasing of glucose uptake in the blood [18]
F. Due to presence phytochemical compounds pawpaw leaves show ability to regulate blood glucose level [19,42].
G. There was a significant decrease in level of glucose seen in extract treated rats as compared to diabetes induced rats in addition to that plasma insulin level was elevated in extract treated rats as compared to other once [20].
H. Methanol extract of *C. papaya* treated groups show decrease in hyperglycemic condition as compared to other groups [21,35]
I. Papaya leaves extract help in repairing pancreatic cells [22].
J. Ethanol and methanol extracts elevate glucose absorption in cells hence managing diabetes [23,24].

5.DISCUSSIONS:

In modern times there is an increase in demand of organic treatments for chronic diseases as compared to antibiotic treatments. The presence of phytochemical compounds in papaya leaves it shows a significant impact in reduction of blood glucose levels of extract treated rats as compared to diabetic rats. The studies nowadays are focusing more on developing remedies from natural substances for diabetes and its complications. Carica papaya leaves extract also shows antioxidant properties also which helps in defense against diseases helps in immune responses[25,26]. Aqueous extract treated mice also shows decline in body weight also hence showing another effect of these in management of complications related to diabetes. Additionally, extract have ability to repair more pancreatic cells hence managing insulin secretion. The demand for development of organic remedies is a recent trend in market for management of diabetes as people are aware about side effects of chemical treated medicines. Therefore, plant-based medicines have minimal side effects[26-28]. Patients with mild hyperglycemia can be treated with the help of dietary products. Further, these are quite convenient and affordable for each group of individuals [14-23].

6.CONCLUSION:

From the above discussions, it can be concluded that diabetes mellitus is the most prevalent diabetic disorder in the world. It has different types. And have various causative factors such as lifestyle, and dietary habits, can be genetic also. As the trend for natural plant-based medicines is increasing, therefore, various studies have been conducted. Papaya leaves aqueous extract found to have potential in the management of diabetes and its complications such as obesity. The extract was obtained using different methods and positive results were observed. The Papaya tree is grown worldwide and has various benefits. Additionally, every part of this plant has its benefits. Its aqueous extract not only manages blood glucose levels it also has an antioxidant effect.

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