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## REVIEW ARTICLE

### PRESENT STATUS OF ANTIDIABETIC PROPERTIES OF *CARICA PAPAYA* L.

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#### Abstract

Rediscovering of natural therapeutics to treat the ruinous diseases became a major concern of the researchers for its outrageous need. Diabetes mellitus (DM) is such an almost incurable disease with enormous secondary complications. In today's fast paced life style DM is the overriding origin of a switch back from life. As the death rate of diabetic patient is increasing the demand of substitute therapies are also increasing hence the use of medicinal plants. Zeroing the secondary complications of chemical treatment is the key factor of using medicinal plants. *Carica papaya* is one such highly prospective anti diabetic tropical plant has been used worldwide as a nutritive food. Thus the different parts of this plant in different formulations have been used to treat diabetes. This review is concerned with the role of *C. papaya* as an antidiabetic agent and the individual investigation of potentiality for different parts of the plant and to highlight the major gaps of the researches.

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#### Introduction:-

*Carica papaya* L. (family- Caricaceae) commonly known as papaya is one such well researched wonder fruit plants of the tropics and sub tropics because of its high nutritive value as well as medicinal value, used for treating many maladies including autoimmune disorders. 'Diabetes mellitus' derived from the two Greek words meaning 'siphon' and 'sugar' is a chronic endocrinal disorder characterised by major derangements in glucose metabolism and abnormalities in fat and protein metabolism. Also it may be defined as the most life threatening disease following cardiovascular disease and cancer. Synchronization of insulin secretion from the beta cell of the pancreas and action to the target organ gets altered in Diabetes mellitus. Depending on the insulin dependency Diabetes mellitus (DM) is classified into Type 1 or insulin-dependent representing 5-10% and Type 2 or insulin-independent comprises about 90-95% of the total diabetic population. World Health Organization (WHO) data suggests that 90% people around the world are suffering from type 2 diabetes (WHO, 2013). A projection report was published by WHO and researchers of Harvard university to summarize the 15 leading causes of deaths in between 2002 and 2030, where they found DM to move up in the list of global mortality and burden of diseases (Mathers and Loncar, 2006). Till date Diabetes mellitus mainly treated by using synthetic drugs but the cost-effectiveness and versatile side effects curve it to develop alternative medicine from the core of our Vedic knowledge of ethnobotanical medicine. More than 1200 plant species are used worldwide in diabetes phytotherapy, among them 150 plants of various families are documented as Indian origin (Maniyar and Bhixavatimath, 2012). The medicinal value of the papaya lies on the phytochemicals- alkaloids, flavonoids, tannins, etc. Papaya fruit is a very rich source of vitamin A (in Sri Lanka regarded as main prevention of vitamin A deficiency), beta- carotene, beta- cryptoxanthin, vitamin C (one piece of

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fruit can supply whole day's requirement), Lutein, zeaxanthin, flavonoids but minute content in sodium, calcium, phosphorus, iron, thiamine, riboflavin, lipids, and calories. This has encouraged many researchers to investigate the antidiabetic property of the papaya. The whole plant parts, fruits, roots, bark, stem, seeds, leaves, latex, are also enriched with those phytochemicals, vitamins, minerals to boost the immune system and positively improve the fitness to maintain the quality of life (Karunamoorthiet *et al.*, 2014). Papaya latex highly enriched with chymopapain and papain, used to treat spinal disorders and digestive disorders (Hewitt *et al.*, 2002). Papaya endopeptidase II and papaya endopeptidase IV were also reported from the latex (Azarkanet *et al.*, 2003). Young leaves contain carpaine, effective antioxidant for the prevention of diabetic heart diseases (Burdick, 1971). Seeds contain myrosinase, caricin and sinigrin glycosides (Raintree nutrition, 2007). This plant is also used in cardiac disorders, rheumatic condition, haemorrhages, ulcers, skin diseases, sickle cell anaemia, digestive disorders etc.

### Types of Diabetes:-

#### 1. Type 1 diabetes (Insulin Dependent Diabetes Mellitus)

Type 1 diabetes can be defined as the auto-immune mediated destruction of beta cells of pancreas leading to the reduction of insulin secretion and elevation of sugar level in the blood. This form of diabetes is more prevalent in young children and represents 5-10 % of the diabetic population (Singh *et al.*, 2011). T1D is initiated and triggered by several factors like environmental factors (infectious agents, sex hormones, vitamin D etc), genetic factors (Major histocompatibility complex class II, Cytotoxic T lymphocytes antigen 4, insulin regulates immune response) and dysregulation of the immune system influences Type 1 diabetes (Chang *et al.*, 2013). Type 1 diabetes can lead to polydipsia, polyphagia, polyuria due to the deficiency of insulin (Wang *et al.*, 2011).

#### 2. Type 2 diabetes (Non Insulin Dependent Diabetes Mellitus)

Type 2 Diabetes mellitus is characterized by insulin resistance and relative insulin deficiency. Either the pancreas is not producing enough insulin to meet the body's needs or in some cases cells build up a resistance against insulin even though enough insulin is present in the blood stream as a result it takes more insulin to find the right key to unlock the cell for glucose uptake. It is referred to as adult onset diabetes and represents 90-95% of diabetic populations (Singh *et al.*, 2011).

#### 3. Gestational Diabetes mellitus

During Pregnancy (4-5% of all pregnancies), placenta produces some hormones (human placental lactogen) to carry the pregnancy that makes the cell resistant by interfering with the susceptible insulin receptors, causes the elevation of blood sugar (Kadali *et al.*, 2016).

### Commonly Practised Synthetic Remedies Against Diabetes:-

Management of diabetes depends upon the type and severity of the diabetes. Most effectively insulin injections, First generation sulfonylurea- Chlorpropamide, Second generation sulfonylurea- Glibenclamide, oral hypoglycaemic agents like metformin is generally used to treat type 2 diabetes. Dietary changes, regular exercise and stress release are also essentially connected to prevent hyperglycemia thus ultimately help to reduce the microvascular and macrovascular complications. Prolonged use of these synthetic chemicals is associated with undesirable secondary complications which may be sometimes irreversible. Hence, the main challenge in the management of diabetes is the prime concern in our modern life style.

### Plant Based Remedies Against Diabetes:-

There is a long list of plants used to treat diabetes and shows their action by different mechanism like stimulating or regenerating the effect of beta cell. Several plant species have been used for prevention or management of diabetes by the native Americans, Chinese (Foster, 1993; Vuksan *et al.*, 2000), south Americans (Garcia *et al.*, 2001) and Asian Indians (Subbulakshmi and Naik, 2001). A wide range of phytochemicals, mainly alkaloids, glycosides, polysaccharides, hypoglycans, peptidoglycans, glycopeptides, terpenoids, steroids have shown bioactivity against hyperglycemia (Ivorra *et al.*, 1988; Marles and Farnsworth., 1995). In India 60% of the patient uses traditional system of medicine as the treatment of diabetes (Malvi *et al.*, 2011). *Momordia charantia* (bitter melon) widely used natural remedy for treating diabetes. Other plants includes *Musa paradisiaca* (Family-Musaceae), *Cinnamomum tamala* (Family-Lauraceae), *Dillenia indica* (Family-Dilleniaceae), *Annona reticulata* (Family- Annonaceae), *Azadirachta indica* (Family-Meliaceae), *Coccinia grandis* (Family- Cucurbitaceae), *Carica papaya* (Family-Caricaceae) are widely used as antidiabetic plants. Most extensively used hypoglycaemic drug glucophage (metformin) is derived from *Galega officinalis* (Grover *et al.*, 2002).

**Table1:-**Important antidiabetic natural compounds isolated from different plant resource so far

SERIAL NO.	PLANT SOURCE	NATURAL COMPOUND	FUNCTION	REFERENCE
1.	<i>Berberis vulgaris</i>	'Berberine' (alkaloid)	Rectify glucose metabolism in type 2 diabetic patients	Xia <i>et al.</i> , 2011
2.	<i>Ervatamiamicrophylla</i>	'Conophylline' (alkaloid)	Promotes beta cell differentiation	Ogata <i>et al.</i> , 2004
3.	<i>Nymphaeastellat</i>	'nymphayol' (steroid)	increase the number of beta cell mass and insulin content	Subash-Babuet <i>al.</i> , 2009
4.	<i>Anoectochilusroxburghii</i>	'kinsenoside' (glucoside)	Repairing of beta cells and improving its activity	Zhang <i>et al.</i> , 2007
5.	<i>Pinus maritime</i>	'Pycnogenol' (Procyanidin)	Lowering blood glucose level	Singh <i>et al.</i> , 2001
6.	<i>Momordicacharantia</i>	'Vicine' (Pyrimidine nucleoside)	Enhances glucose uptake by cell, ptomotes insulin production	Ahmed <i>et al.</i> , 2001

**Antidiabetic effect of *C. papaya* seeds:-**

In 2013, Venkateswarluet *al.*, studied the anti-diabetic activity of *C. papaya* seeds on Streptozotocin induced type 2 diabetic rats. Dried seeds were powdered and then extracted in boiling water. Streptozotocin and nicotinamide dissolved in citrate buffer separately to inject intraperitoneally to induce diabetes in the experimental rats. Hyperglycemia was confirmed after 7days induction by the elevated glucose levels in the plasma, when it reaches 150mg/dl considered to be diabetic for study. The experiment was carried out against of a standard drug glibenclamide, to stimulate insulin release from pancreatic cells, hence used to treat hyperglycemia. *Carica papaya* seed extract of two different doses 100mg/kg and 200mg/kg body weight were administered and the observation was taken at day1, day7 and day 14<sup>th</sup> to measure the change of blood glucose level by comparing with the standard drug 10mg/kg glibenclamide treated rats. On the 14<sup>th</sup> day blood glucose level of the glibenclamide treated rats were found to be 92.06±5.29 mg/dl from the day 1 (178.50±8.78 mg/dl), whereas *C. papaya* seed extract (200mg) treated rats brought the blood glucose level near to the normal level, viz 128.00±7.34 mg/dl (p<0.01)

**Antidiabetic effect of *C. papaya* Fruit:-**

Papaya fruit was remarkably called "Fruit of the angels" by the legendary explorer Christopher Columbus. Commonly spherical or pear-shaped fruits are 7-20 inches long and 100- 500 gms approximately.

In 2015, the anti-hyperglycemic effect of both single and combined effect of fruit extract of *Carica papaya* Linn. and root extract of *Andrographis paniculata* were investigated (Vigneswaran *et al.*, 2015). Overnight fasted male adult albino wistar rats were injected intra peritonealy with streptozotocin at a dose of 35 mg/kg body weight in 0.1M cold citrate buffer of pH 4.5. Blood Glucose level above 250mg/dl on the third day from injection were subjected to be diabetic for the experiment. These diabetic rats were then treated with *Carica papaya* fruit extract of the following doses at 200mg/kg and 400 mg/kg body weight orally for 21 days by intragastric catheter tube (IGC). Therefore the experimental rats were sacrificed by cervical dislocation and blood collected from heart for further biochemical tests to be performed. Enzymatic Glucose Oxidase Peroxidase (GOD-POD) method was applied for the estimation of serum glucose level and the assay of plasma insulin was carried out by ELISA. Glycosylated haemoglobin test (HbA1c) was performed (Karunanayake and Chandrasekharan *et al.*, 1985), to investigate the number of glucose molecule attached with the haemoglobin over a period of time to evaluate the secondary risk factor of diabetic complications related to heart, kidney, eye etc. Excessive breakdown of tissue protein and fatty acids reduces the body weight by loosing muscle and adipose tissue, a very common phenomenon related to diabetes. Significant reduction of blood glucose level, elevation of serum insulin and maintaining the normalcy of HbA1C observed in high dose of single and combined plant extract treated rats. High AST, ALT and ALP level revealed the damage of liver tissue; it established that the hyperglycemia is responsible for it. The significant reduction of blood glucose level in *Carica papaya* fruit extract (400mg/kg) treated group was found to be 5.15% (p<0.05) as compared to the diabetic control group 8.68% (p<0.001)., eventually a blend of the above mentioned plants at a dose of 200mg/kg works incredibly with a reduction of 11.8% (p<0.001) much higher than the diabetic control group. All these results support the strong anti hyperglycaemic effect of *Carica papaya* fruit along with a new approach of using it as a blend with other plant extract.

**Antidiabetic effect of *C. papaya* Leaf:-**

In 2016, Maniyar *et al.*, performed an experiment in alloxan induced diabetic rats with the treatment of *C. papaya* leaves aqueous extract. The main objective of their experiment was to evaluate the antihyperglycemic and hypolipidemic activity of aqueous extract of *C. papaya* leaves (AECPL). After the surface sterilization with 30% alcohol, dried leaves were grinded to make powder, therefore 50 gm of this powder boiled in hot water for 30 min. Filtrate were taken and evaporated at 40<sup>o</sup>c to produce a brown colored solid film. Healthy wistar albino rats were taken and a single dose of alloxan monohydrate (120mg/kg body weight) was injected. After a week of incubation animals showing above 250mg/dl were selected for experiment. The main key point of this experiment is the availability of data by regular interval of day and hour. Higher dose like 400mg/kg works very well and decreases the blood glucose level at 151.6± 2.6 in 21th day from the beginning 245.3± 11.8. This dose can effectively reduce blood glucose 8.56% within first 6h (p<0.01). The lower dose of 100 and 200 mg was not satisfactory, though 100mg/kg dose showed significant antihyperglycemic effect on day 14<sup>th</sup> and 200mg/kg showed significant result on the 7<sup>th</sup> day (p<0.01). Phytochemical analysis was done by simple and standard qualitative methods as per the "Trease and Evans". Presence of tannins, alkaloids, flavonoids, anthraquinones, saponins, reducing sugar was noted. To determine the non lethal dose of *C. papaya* leaf extract LD50 analysis was done and upto 2000mg/kg was found to be safe. Hyperglycemia and insulin resistance showed elevated plasma cholesterol and triglyceride levels, which triggered the cardiovascular disease along with other major complications of kidney, liver, eye etc. Aqueous extract of 400mg/kg body weight reduces the triglyceride and cholesterol as well as blood glucose level which is the key success of this experiment.

In 2011, Sashidharan *et al.*, studied the efficacy of ethanolic leaf extract of *C. papaya*, they had used another tropical plant *Pandanus amaryfollius* as a diabetic control. The choice of these two plant have been made on the basis of their phytochemical constituent and their incessant use in ethno-botanical medicines to treat many diseases like malaria, obesity, infection, oral drug poisoning, skin diseases etc. Induction of Streptozotocin (60mg/kg body weight) makes distinctive changes between healthy and diabetic mice. According to Akbarzadehet *et al.*, 2007, the tails of healthy mice should be pink and whitish velvety fur coated but after diabetes induction it turns into dark in color and coating becomes pink. Diabetic mice were treated with glyburide (10mg/kg body weight) and *C. papaya* crude extract (100mg/kg body weight). Significant reductions were found in the blood glucose level as a percentage of 58.1% and 50.1% respectively (p<0.05). From this result, it is clear that the active compounds, if purified from the crude extract can act magically as an antihyperglycemic agent. The histological study of the pancreatic cells highly approves the regeneration of beta cells in *C. papaya* treated diabetic mice. In most of the diabetic mice Islets of Langerhans gets shrunken loses its circular shape and well-defined cell-lining leading to the joining of two islets and formation of a large one. Accumulation of red blood cells within these large islets indicates the functional inactivity of beta cell. Though the glyburide treated mice group showed no such difference in the disrupted pancreatic cells but *C. papaya* treated group shows clumping of RBC in disrupted area, prerequisite for the regeneration of beta cells. This phenomenon was supported by Bolkent *et. al.*, (2000)., that medicinal plant therapy can provide blood glucose homeostasis and can induce beta cells to function normally. Liver is the major organ for the metabolism of carbohydrate, proteins, lipids in animals. So that altered metabolism of diabetic mice easily influence the liver tissues. Neither the polyhedral shape of hepatocytes nor the sinusoids were observed in Diabetes mellitus degenerated nucleus. Multiple large vacuole seen over the nucleus. Where the *C. papaya* treated diabetic mice limits the hepatocytes disruption and vacuolation in liver. As well as the diabetic mice treated with *C. papaya* showed a protective effect in kidney by restoring the size and shape of the epithelial cuboidal cells in the medullary region, which gets disrupted in normal diabetes and streptozotocin induced diabetes. Qualitative phytochemical screening indicates the presence of alkaloids, carbohydrate, tannins, flavonoids, saponins in the crude ethanolic extract. This phytochemical analysis strongly supported by a previously conducted study of Mukherjee *et al.*,(2006) where they found that flavonoids and saponins might be responsible for the antidiabetic activity.

In 2012, Juarez-Rojop *et al.*, studied the aqueous extract of *C. papaya* leaves for the hypoglycaemic properties. Male Wistar rats were induced diabetes by a single intraperitoneal injection of 60mg/kg Streptozotocin dissolved in distilled water. Blood glucose levels were monitored by using Accu-check sensor comfort glucometer (Roche, Mexico city) and above 250mg/dL were selected for the experiment. Processing of the *C. papaya* leaves includes washing with 1% iodine solution therefore washing and drying preceding homogenization and filtration was done to prepare the extract of 0.75, 1.5 or 3g/100ml. After 30 days of treatment with the above mentioned extracts rats were sacrificed by decapitation. Blood was collected to determine the serum glucose level, cholesterol, triglyceride, high density lipoprotein-cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphate (ALP). These biomarkers are elevated in Streptozotocin induced diabetic rats but when treated with 0.75

and 1.5g/100 ml of *C. papaya* leaf extract significantly reduce the activity of these biomarkers with respect to the diabetic control rats ( $P < 0.001$ ,  $P, 0.001$ ) but when treated with higher dose as 3g/100ml does not work well as the lower dose. Histopathological study of pancreatic tissue reveals that the size, shape and diameter of islets of langerhans are well preserved in *C. papaya* extract treated rats. Whereas the shrunken shape, irregular lining, and reduced size are commonly seen in the untreated diabetic rats. The liver morphology of the untreated diabetic rats showed abundant fat vesicles and glycogen granules in the cytoplasm, sinusoids were not clearly visible but *C. papaya* treated rats exhibits less number of glycogen and fat vesicles content, clearly visible sinusoids. This study strongly suggests that the leaf extract of *C. papaya* can significantly reduce the blood glucose level ( $P < 0.05$ ) in diabetic rats and possibly few surviving beta cells stimulated to produce more insulin, though the exact mechanism yet to be revealed. Several reports are there pointing the regeneration and restoration of beta cell by using plant extracts (Cumaoglu *et al.*, 2011; Nagappa *et al.*, 2003; Chakravarthy *et al.*, 1982).

Though the use of papaya leaf extract on Sprague Dawley rats showed the acute and sub acute oral toxicity in subsequent studies (Halim *et al.*, 2011 and Afzan *et al.*, 2012). Apart from the mild dehydration, there was no acute adverse effects or death was found upto the dose of 2000mg/ kg body weight.

#### **Antidiabetic effect of fortified papaya cake:-**

In 2015, Hanna Afaf-Haniem *et al.*, designed their experiment with papaya powder and papaya puree at different levels of extract 20%, 30%, 50% and 75% to check the antihyperglycemic activity of the Streptozotocin induced diabetic rats. Papaya powder used as an additive to wheat flour in bakery products to enhance the flavour, antioxidant activity and water holding capacity. Seven groups of total thirty five male Sprague Dawley rats were selected and fed with basal diet, 100% wheat flour cake, fortified cake with 20% and 30% papaya powder and fortified cake with 50% and 75% of papaya puree respectively. Induction of diabetes was confirmed by the elevation of serum glucose approximately at 411.25mg and HbA1c levels at 12.30% with respect to the normal control group. After 8 week of incubation, rats were sacrificed to evaluate the biochemical parameters from blood sample. Other body organelles like liver, kidney were also removed for the histopathological examination. Following blood glucose reduction were observed by 59.9%, 56.11%, 55.56% and 53.25% for Cw2, Cs2, Cw1, Cs1 respectively. Significant reduction of HbA1c was also observed in the fortified papaya cake feed diabetic rats. As a consequence of hyperglycemia the untreated diabetic group was found with high triglyceride, LDL-C, VLDL-C, and total lipid. However this remains almost same in the treated groups, remarkably an increase in the HDL-C were also noted, which acts as a scavenger or carry the LDL cholesterol to remove it from the arteries and send back to the liver for removal from the body, a much needed physiological phenomenon to protect from coronary heart disease. Inadequate insulin level may not be able to inhibit hormone sensitive lipase production; therefore free fatty acids can effectively mobilize from the peripheral fat deposits.

#### **Antidiabetic effect of fermented papaya preparation (FPP) to reduce the cancer:-**

It has been postulated that FPP is an excellent nutraceutical, functional food, or a supplement, which acts in both nutritional and physiological terms (Rafaelli *et al.*, 2015). In 2006, Danese *et al.*, investigated the collateral effect of fermented papaya preparation in the reduction of plasma glucose level. For this purpose, 50 subjects, divided in two groups, were enrolled. First group includes 25 patients of different sex are affected by type 2 diabetes mellitus under the treatment of oral anti diabetic drug glibenclamide and the another group is for the control consists of 25 clinically healthy subjects irrespective of their age. During lunch they were feed with 3 grams of fermented papaya preparations for the two months. A significant decrease in plasma glucose level was seen in both the groups. This hypoglycaemic effect induces the diabetic patient to reduce the dose of chemical drugs which helps to promote lesser side effects.

In 2014, Arumoa *et al.*, gone through with the research of fermented papaya preparation for its antidiabetic effect as well as to reduce the risk factor of pancreatic, colorectal, breast and liver cancer. Excessive inflammation of pancreas, liver, bladder and beta cell disruption has the direct influence and prolonged use of antidiabetic drugs has the indirect effect over the development of cancer. Hyperglycemic conditions favour the cell-growth, anti-apoptosis increased cell-motility and high degree of invasiveness are the major contributing factor of the association between diabetes (Type 2) and cancer. In this study Yeast Fermented papaya preparation (ISO 9002 and 14,001 certified) was used as a dietary supplement, commercially sold in Japan and Philippines. Though the chemical modifications of the biofermentation of *C. papaya* are not yet fully characterize. Radiation and chemotherapy are advanced technique to treat the cancer, thus, these therapies have a large spectrum of secondary complications including skin reactions, gastrointestinal discomfort, site-specific mucosal reactions, vomiting, nausea, headache etc. Clinical trial assessed

that the latex derived enzyme chymotrypsin and papain can reduce these acute side effects (Mukherjee *et al.*,2006). Several investigations (Juarez-Rojop *et al.*,2012; Cumaoglu *et al.*, 2011; Li *et al.*, 2012) suggested that the aqueous extract of papaya contains novel bioactive component benzyl glucosinolate can suspend the growth of tumour cell lines. Fermented papaya preparation can effectively restores the internal redox balance by reducing the oxidative stress build up within the tissue of major organs on the onset of cancer. Thus proves the fermented papaya preparation has a beneficial prophylactic potential for the dietary management of both diabetes and cancer.

### Conclusion:-

In this review we have discussed the antidiabetic effect of the different parts of the *Carica papaya*. As this chronic disease is turning out to be a great threat of our life and the synthetic drugs are emerging enormous secondary complications, researchers are need to formulate feasible herbal inhibitors. An attempt has been made through this review to investigate the *Carica papaya* as a formidable antidiabetic medicinal plant. Thus, satisfying from all the researches, different parts of the *Carica papaya* can be successfully used to treat diabetes. *Carica papaya* is a rich source of various phytochemicals, these different compounds may act either separately or together to exert their antidiabetic effect. Amount of these bioactive compounds are highly variable in different varieties of papaya, researchers must look on this. Though the exact mechanism by which they exert their biochemical activities or the chemical properties of the responsible phytochemicals having antidiabetic effect is still under investigation. In addition, excessive consumption of papaya can induce carotenemia so the determination of dose is highly important.

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