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## Jackfruit (*Artocarpus heterophyllus*): An Organic Cure against Diabetes



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### ABSTRACT

The Jackfruit (*Artocarpus heterophyllus*) is a mulberry tree species belonging to the Moraceae family. Traditional folk medicine in Indonesia has used plants from the Artocarpus genus as antibacterial, anti-diabetic, anti-inflammatory, antioxidant, and anti-helminthic agents. The purpose of this review was to focus on the anti-diabetic effects of aqueous Jackfruit extract. The blocking of the haemoglobin glycation technique was used to determine the anti-diabetic activity. Carotene and lycopene, two phytochemical constituents, also play a role in diabetic action. Antioxidant activity is also seen in jackfruit. Scavenging hydroxyl radicals has the strongest antioxidant activity, followed by foraging hydrogen peroxide and chelating ferrous iron, which lowers glycated haemoglobin levels (HbA1c) and makes it active against diabetes.



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## INTRODUCTION

Diabetes Mellitus is one of the leading causes of death and chronic disease around the globe. One hundred and fifty million people worldwide suffer from diabetes, over five times the number estimated a decade ago, and this number is expected to treble by 2030<sup>[1]</sup>. India has approximately 77 million diabetics, making it the world's second-largest diabetic population behind China. Diabetes affects one out of every six persons (17%) in the world<sup>[2]</sup>. As of October 2018, India's population accounted for around 17.5 percent of the global total. According to the International Diabetes Federation, the number will rise to 134 million by 2045. Diabetes mellitus, also known as diabetes, is a chronic metabolic disorder of carbohydrate, lipid, and protein metabolism characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance, and occasionally ketonemia due to inadequate or complete stoppage of insulin synthesis or secretion, as well as peripheral insulin resistance<sup>[3]</sup>. Polyuria (excessive urine production), polydipsia (excessive thirst), and polyphagia (excessive eating) are all symptoms of diabetes mellitus. Insulin and oral hypoglycemic medications such as sulfonylureas and biguanides are used to treat the etiology of diabetes mellitus and its consequences<sup>[4]</sup>. However, the majority of these medications caused hypoglycemic coma, insulin resistance, hypersensitivity, cholesterol jaundice, stomach pain, anorexia, and a metallic taste in long-term use<sup>[5]</sup>.

The use of herbal medications in diabetic control has grown in popularity in recent years for a variety of reasons. Natural plant medications are often thought to be safer and have fewer negative effects than synthetic drugs<sup>[6]</sup>. Despite the availability of a significant number of pharmaceuticals on the market, medicinal plant remedies are successfully used to treat the disease<sup>[7]</sup>. Jackfruit is one of the more fascinating fruits (*Artocarpus heterophyllus*). The *Artocarpus heterophyllus* (Jackfruit) is a mulberry tree species belonging to the Moraceae family. There are roughly 60 genera and about 1000 species in it. Many of these species are employed in traditional medicine and as a source of food. Artocarpus species are notable for their big nutrient-dense edible fruits. *Artocarpus heterophyllus*, *Artocarpus altilis*, *Artocarpus hirsutus*, *Artocarpus lakoocha*, and *Artocarpus camansi* are some of the most important species in this genus. Extracts of aerial and underground components, in addition to fruits and seeds, have traditionally been employed in the treatment of diabetes, diarrhoea, dermatitis, malarial fever, asthma, tapeworm infection, anaemia, and many other ailments<sup>[8]</sup>.

The goal of this review is to characterize the anti-diabetic properties of Jackfruit Extracts by looking at their effects on haemoglobin glycosylation inhibition.

## GEOGRAPHICAL DISTRIBUTION

The substantial majority of *Artocarpus* species are found in Asia's tropical and subtropical areas. The jack fruit, *Artocarpus heterophyllus*, is considered to have originated in India's rain forests. Today, jack fruit trees can also be found in Bangladesh, Burma, China, Sri Lanka, Thailand, the Philippines, and other countries of Africa, Australia, Brazil, and Florida. *Artocarpus lacucha* also called monkey jack is widespread throughout South and Southeastern Asia's tropical lowlands, primarily in India, Sri Lanka, Nepal, Myanmar, Indonesia, Vietnam, and Thailand<sup>[9,10]</sup>.

## PHYTOCHEMICAL CONSTITUENTS

Jack fruit is a nutrient-dense seasonal food that is commonly referred to as "poor man's food" in Southeast Asia. Jack fruit is high in protein, carbohydrate, fat, fiber, calcium, phosphorus, iron, vitamin A, and thiamine in edible portions. The main sugars found in jack fruit are fructose, glucose, and sucrose. Palmitic, oleic, stearic, linoleic, lauric, and arachidic acids are the primary fatty acids present in various regions of the jack fruit. Seeds are high in carbohydrates, protein, minerals, and dietary fiber. Jacalin, a tetrameric two-chain lectin found in the seeds of *Artocarpus heterophyllus*, is a tetrameric two-chain lectin with a heavy chain of 133 amino acid residues and a light chain of 20-21 amino acid residues<sup>[11,12]</sup>.

**Table No. 1:** Specific Phytoconstituents in Jackfruit

Parts	Constituents
Whole Plant	Artocarpine, artocarpetin, artocarpetin A, cycloheterophyllin, artonins A, artonins B, morin, dihydromorin, artocarpin, oxydihydroartocarpesin, cynomacurin, isoartocarpin, cyloartocarpin, artocarpesin, artocarpetin, norartocarpetin, cycloartinone and artocarpanone
Bark	Betullic acid, cycloheterophyllin, cycloartenyl acetate, cycloartenone, heterophylol, and tannin
Leaves and Stem	Sapogenins, cycloartenone, cycloartenol, $\beta$ -sitosterol, and tannins
Roots	$\beta$ -sitosterol, ursolic acid, betulinic acid, cycloartenone, trioxxygenatedflavanones, heteroflavanones A, and heteroflavanones B

## TRADITIONAL MEDICINAL USES OF JACKFRUIT

The use of herbal medications in diabetic control has grown in popularity in recent years for a variety of reasons. Natural plant medicines are frequently thought to be more effective and less toxic, yet with fewer side effects than synthetics [13,14]. Despite the fact that a great number of drugs are available on the market, treatments derived from medicinal plants are used to treat this condition with effectiveness [15]. Traditional folk medicinal treatments use various components of the *Artocarpus* species. Jackfruit leaves, fruits, seeds, roots, and bark are very important in medicine and are used in a variety of Ayurvedic and Unani remedies. The ripe fruits are tasty, refreshing, and laxative, healthful, and it's also utilized to prevent the overproduction of bile. The seeds' extracts are beneficial in the treatment of diarrhoea and other gastrointestinal problems, including dysentery. Roasted seeds are thought to have medicinal properties. These plants have aphrodisiac effects. The leaves are a bright green color. It's thought to be useful in the treatment of asthma, ringworm, diabetes, and gallstones. Leaves contain wound healing activity, vermifuge, anti-psychiatric activity, and induction of lactation in domesticated animals and women. Roots are used to treat a variety of skin conditions, illnesses, diarrhoea, and asthma. The bark of a mature tree is said to be useful in treating dysentery and releasing the cow's placenta after calving. Latex in combination with vinegar is said to aid in the healing of wounds such as abscesses, snakebites, and glandular swellings are also possible causes. The *Artocarpusaltilis* leaves have been traditionally used to cure liver problems, such as cirrhosis, hypertension, and diabetes are all diseases that affect the liver [16].

It is thought to be a good source of nutrients, dietary fiber, carbohydrates, minerals, carboxylic acids, and vitamins like ascorbic acid and thiamine as well [8,17]. Flavonoids of various types are plentiful in the plant of the jack fruit. A few jack fruit products are available on the market such as jack fruit with honey, jack fruit canned, and there are a variety of fruit flavours. Jack fruit powders are used in a variety of recipes [18]. *Artocarpuslakoocha*, sometimes known as Monkey jack, is a Thai plant that is utilized in traditional Thai medicine, used to treat inflammation and as a preventative measure as well as a skin anti-aging agent. The dried-out heartwood aqueous extract has been used as a conventional anti-helminthic. The fruit pulp that can be eaten is used as a liver tonic. The root and bark decoctions are said to be curative towards diarrhoea. When combined with Curcuma and white camphor, the leaves make a beautiful combination and are said to have medicinal properties that are chronic hemorrhage and venereal bubones respectively. The juice extracted from the cooked

fruits is said to stimulate hunger, and when administered to the anus, it also relieves the pain of a hemorrhage. *Artocarpuscamansi* is thought to have comparable characteristics. *Artocarpusaltilis* has therapeutic potential. The seeds are said to be high in protein content than chestnuts<sup>[11,19,20]</sup>.

Plants from the *Artocarpus* genus have been used by people for a long time as Indonesian traditional folk medicine against Inflammation, malarial fever, stomach aches, and a lack of urine secretion are all symptoms of a faulty urinary secretion<sup>[21]</sup> as well as skin disorders. *Nangka* (*Artocarpus heterophyllus*) contains antibacterial, anti-diabetic, anti-inflammatory, antioxidant, and anti-helminthic properties<sup>[22]</sup>. Several studies have suggested that jackfruit extracts have anti-diabetic properties, which could be due to their high sugar content, proanthocyanidin, and flavonoid content by preventing lipid peroxide generation and an anti-amylase activity, implying that it could be used as a drug<sup>[23]</sup>. On normal human volunteers, hot water extracts of *Artocarpus heterophyllus* leaves were tested for anti-diabetic efficacy as well as diabetic patients. The extracts have a significant impact on increased glucose tolerance. The anti-diabetic effect of a root methanol extract *Artocarpus integrifolia* bark was studied. The alpha-amylase enzyme is inhibited, that root bark methanolic extract of *A. integrifolia* has the potential to be a valuable resource and further developed into a natural anti-diabetic drug. Several research has been undertaken on a variety of *Artocarpus* species. Anti-inflammatory, antifungal, and sexual effects are some of the additional pharmacological qualities and also, anticholinergic, chelating action, anesthetic agent, performance, immunomodulatory impact, anthelmintic action, ACE inhibitors, Protease inhibitors, melanin biosynthesis inhibition as well as wound healing<sup>[24-27]</sup>.

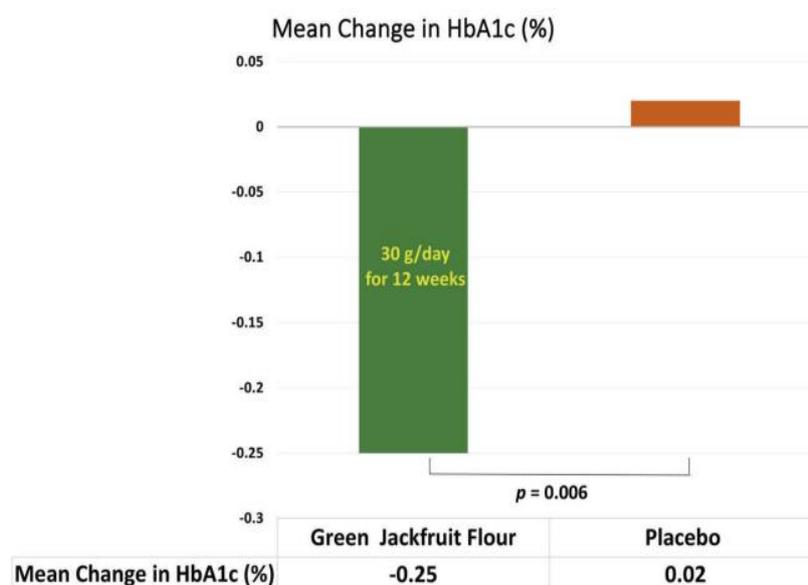
### **ANTI-DIABETIC ACTIVITY OF JACKFRUIT**

Increased glucose content in the blood causes it to bind to haemoglobin, resulting in the generation of reactive oxygen species. Glycation is the term for this process<sup>[14]</sup>. Glycation is a non-enzymatic process that occurs when proteins' free amino groups come into contact with reducing sugars. Maillard's reaction is the name for this reaction<sup>[28]</sup>. Glycation is linked to the development of age- and diabetes-related problems such as neuropathy, angiopathy, and nephropathy<sup>[29]</sup>. This is a typical post-translational alteration of proteins that might cause them to lose their function in living organisms. Glycation is called glycooxidation when an oxidative step is included in the process. During glycooxidation, free radicals, products of the glycating sugar's auto-oxidation, and a heterogeneous set of compounds known as advanced

glycation end products (AGEs) are generated<sup>[30,31]</sup>. The presence of phytochemical constituents in jackfruit extracts may be responsible for the increased concentration of glycated haemoglobin that can be controlled by them. Many etiological and pathophysiological human diseases, such as diabetes, are known to be caused by reactive oxygen species (ROS). ROS, or oxygen-free radicals, can cause lipid peroxidation, which then promotes protein glycation<sup>[28]</sup>. Glycation is a non-enzymatic process that occurs when proteins' free amino groups come into contact with reducing sugars<sup>[30]</sup>. This reaction results in the creation of reversible Schiff bases, which are then transformed into stable, covalently bonded amadori products through intermolecular reconfiguration<sup>[32]</sup>. These products undergo a glycoxidation process and further change over time, resulting in the creation of advanced glycation end products (AGEs)<sup>[33]</sup>. On normal human subjects and diabetic patients, hot water extracts of *Artocarpus heterophyllus* leaves were tested for anti-diabetic efficacy. The extracts significantly increased glucose tolerance in both healthy people and diabetics. The inhibition of  $\alpha$ -amylase was used to test the anti-diabetic effects of a methanol extract of *Artocarpus integrifolia* root bark<sup>[19]</sup>. Bhuiyan A.*et.al.* have shown that *Artocarpus heterophyllus* was found to have a considerable anti-glycation effect, suggesting that it could be used as a traditional medicine to treat chronic diabetes mellitus<sup>[34]</sup>. Another study looked at the anti-diabetic effect of *Artocarpus heterophyllus*. Bark extracts were used as an edible medicine by local tribal people in Vellore districts, in streptozotocin-induced diabetic rats. The percentage reduction in fasting blood glucose level was used to examine the hypoglycaemic actions of extract-treated diabetic rats<sup>[35,36]</sup>. Bhuiyan A. *et. al.* studied that, when compared to the husk of *Artocarpus heterophyllus* seed (18%), the crystal of the tegmen of *Artocarpus heterophyllus* seed demonstrated the best anti-diabetic action (55%). When the concentration of the sample was raised, the anti-diabetic activity of the crystal of tegmen of *Artocarpus heterophyllus* seed rose. When compared to our standard sample, vildagliptin, which exhibited 60% anti-diabetic activity at the highest concentration, the anti-diabetic activity of crystal of tegmen of *Artocarpus heterophyllus* seed showed reduced anti-diabetic effect<sup>[36]</sup>.

The most successful experiment done by Rao AG *et alin* the year 2021 was the efficacy of green jackfruit flour as a medical nutrition therapy replacing rice or wheat in patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study, which revealed the efficacy of jackfruit flour meal as a supplement for type-2 diabetes mellitus patients. Between May 2019 and February 2020, a randomized, double-blind, placebo-

controlled research was conducted. Patients of either sex, aged 18 to 60 years, who had been diagnosed with T2DM for more than a year and were taking oral antihyperglycemic drugs were randomized (1:1) to receive jackfruit flour 30 g/day (Group A) or placebo flour (Group B) (breakfast and dinner) daily for 12 weeks, replacing an equal amount of rice or wheat flour. A mean change in glycosylated haemoglobin was the primary outcome (HbA1c) that is depicted in Fig:1. Mean changes in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), lipid profile, and body weight were the other outcomes. The results show that a total of 40 patients (n = 20 each) were enrolled using the independent t-test to compare changes between the groups. From baseline to week 12, Group A had a considerably larger reduction in HbA1c than Group B [2.73 mmol/mol (0.25 percent) vs. 0.22 mmol/mol (0.02 percent), p = 0.006]. The mean change in FPG and PPG in Group A was substantially larger than in Group B (p = 0.043 and p = 0.001, respectively). The continuous glucose monitoring showed a fall in mean blood glucose within 7 days of administration of jackfruit flour meal<sup>[37-39]</sup>.



**Fig. No. 1:** Mean change in HbA1c for 12 weeks after administration of jackfruit flour meal in comparison with placebo meal<sup>[39]</sup>

## OTHER PHARMACOLOGICAL ACTIVITIES OF JACK FRUIT

Various preclinical studies showed the beneficial properties of jack fruit in humans. Some of them are as follows:

**a. Anti-Inflammatory:** In RAW264.7 cells, extracts of jackfruit pulp showed anti-inflammatory action by reducing the formation of nitric oxide and prostaglandin E2 reactive oxygen species generated by lipopolysaccharide (LPS)<sup>[40]</sup>. With an IC50 value of 23.3  $\mu$ M, artocarpanone and artocarpin suppressed myeloperoxidase activity in human phagocytes and have the potential to be developed into effective anti-inflammatory drugs. Ethanolic extracts of the spine, skin, and rind of the jack fruit have anti-inflammatory properties<sup>[41]</sup>. The results showed that skin extract had the most anti-inflammatory action, rind inhibited Cyclooxygenase-2 preferentially, and inhibition of both Cyclooxygenase-1 and 2 *in vitro* was shown by skin<sup>[42]</sup>.

**b. Anti-Oxidant Activity:** Many carotenoids, including all-trans-beta carotene, are found in jackfruit and have vital antioxidant properties for human health<sup>[25,43,44]</sup>. Jackfruit not only has free radical scavenging properties, but it also worked as a significant protective agent against DNA damage caused by H<sub>2</sub>O<sub>2</sub> + UV and irradiation<sup>[45]</sup>. Polysaccharides are extracted from jackfruit pulp as a dietary source of antioxidants and phytochemicals that survive digestion. The antioxidant activity of jackfruit rind and rachis extracts is aided by protocatechuic acid and chlorogenic acid<sup>[46]</sup>. The antioxidant activity of flavonoids from *A. heterophyllum* leaf, root, and bark methanol extracts was dramatically increased. As a result, jackfruit extract has antioxidant properties because it reduces the generation of reactive oxygen species<sup>[47]</sup>.

**c. Anti-Microbial Activity:** Because of the presence of quinic acid, catechin, and chlorogenic acid, jackfruit leaves had antifungal efficacy against *Colletotrichum gloeosporioides* and *Penicillium italicum*<sup>[48]</sup>. Protease from jackfruit latex was tested for antimicrobial action and the results showed that it could suppress the development of *Pseudomonas aeruginosa* ATCC 27853 and *Candida albicans* at low inhibitory doses. From the heartwood of *A. heterophyllum*, antibacterial chemicals such as cycloartocarpin, artocarpin, artocarpanone, and cyanomaclurin were identified. *Streptococcus mutans*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* were the microorganisms with the strongest antibacterial activity<sup>[49,50]</sup>.

**d. Anti-Cancer Activity:** The addition of jackfruit pulp to one's diet may assist to inhibit and control the development of some malignancies<sup>[51]</sup>. The number of revertants produced by aflatoxin B1 (AFB1) and the growth of cells M12. C3.F6 were both lowered by organic extracts derived from jackfruit pulp<sup>[52]</sup>. The proliferation of the PC-3, NCI-H460, and/or A549 cancer cell lines was inhibited by bioactive chemicals from *A. heterophyllum* leaves. On

human T47D breast cancer cells, artocarpin caused a concentration-dependent reduction in cell viability as well as changes in cell and nuclear morphology. In cancer cell lines such as T47D, TH29, and B16F10, jackfruit seeds extract was beneficial [53,54].

**e. Anti-osteoporotic activity:** Cathepsin-K (Cat-K) is a key player in osteoclast-mediated bone resorption and has been identified as a promising target for osteoporosis treatment. Flavonoids from *A. heterophyllus* were discovered to reduce Cat-K, with IC50 values ranging from 1.4 to 93.9  $\mu\text{M}$  [55].

## CONCLUSION

The review concludes that jackfruit extract inhibits haemoglobinglycation. The presence of phytochemical constituents in jackfruit extracts, such as carotene and lycopene, may be the reason for the inhibition. Furthermore, because jackfruit extract contains ascorbic acid, it has antioxidant action and can prevent haemoglobinglycation. As a result of the extract's ability to decrease glycated haemoglobin levels, this review implies that jackfruit extract has the potential as a diabetic agent (HbA1c). Irrespective of that jackfruit also shows its efficacy in the other pharmacological conditions because of its nutrient-rich properties.

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## CONFLICT OF INTEREST

No conflict of interest.

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