

Therapeutic Potential of Star Gooseberry (*Phyllanthus Acidus*, (Skeels)) For Treatment of Diabetes and Related Complications: A Review

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Abstract

Herbal medicines have been used for thousands of years for the management of diabetes due to relatively low incidences of side effects and ease of access in developing countries. The review compiles and analyses the scientific data to emphasise the role of *Phyllanthus acidus* also known as star gooseberry, as a potential therapeutic agent for the treatment of diabetes and related complications. Both *in-vivo* and *in-vitro* studies have shown that the phytoconstituents present in the plant may affect biomarkers of diabetes. The mechanisms of action behind antidiabetic property of the plant and its bioactive constituents are primarily due to α -glucosidase inhibition, curbing of PPAR- γ and increased secretion of insulin. The antioxidant and anti-inflammatory studies pertaining to *P.acidus* also strengthen its claim as an effective antidiabetic agent. Therefore, *Phyllanthus acidus* shows promising therapeutic potential to be used in the treatment of diabetes and its co morbidities.

Keywords: Antioxidant • Anti-inflammatory • α -glucosidase inhibition • Diabetes • Insulin secretagogues *Phyllanthus acidus* • Toxicity

Introduction

Diabetes mellitus a metabolic disorder is one of the major challenges faced by the healthcare industry globally and a major economical and medical burden to the patient. India being home to about 74 million diabetics is considered as the "diabetic capital" sharing a major part of the global burden of diabetes [1]. According to Global Burden of Disease the various micro and macro vascular complications associated with diabetes are retinopathy (moderated to severe low vision and blindness), diabetic neuropathy, amputations resulting from diabetic foot and cardiovascular disorders. Linked with chronic hyperglycemia diabetes is usually classified into Type I, Type II and gestational diabetes. Type I diabetes occurs when the beta cells of the pancreas are damaged and not able to produce insulin in sufficient quantity to maintain blood glucose levels. In this case the patients are entirely dependent on exogenous insulin administration to maintain the blood glucose levels. On the contrary Type II diabetes which is observed in majority of the patients is due to peripheral insulin resistance resulting in diminished insulin sensitivity to skeletal muscle, liver and adipose tissues. Gestational diabetes occurs in pregnant women with no previously diagnosed diabetes [2]. There are various conventional antidiabetic medications available for the treatment and management of diabetes via exogenous supply of insulin, enhancing insulin sensitivity and secretion and stimulating glucose uptake. However prolong use of these medication may lead to adverse events like hepatic failure,

diarrhoea, weight gain, lactic acidosis, tachycardia and hypothyroidism. This has led to an increase in demand of efficient and affordable alternatives with lesser side effects [3].

Traditional medicine has been used for the management of diabetes and its complication in various ethnic cultures like Indian, Chinese, Mexican and Korean for thousands of years. The popularity of these herbal drugs is increasing due to comparatively lower cost, greater patience forbearance, lower adverse events at prescribed dosages and overall acceptance due well established historical usage. There is a renewed interest in plant based pharmaceuticals and lead molecules as alternative medicament for diabetes. Researchers are delving into areas like medicinal chemistry, ethnopharmacology and clinical trials of these traditional medicines validating their clinical usage [4]. Plants comprising of phenolic compound have been found to reduce the risk of cancer, diabetes, inflammation and viral diseases. This property of plants comprising of phenols may be attributed to the free radical scavenging, lowering oxidative stress and antioxidant activity of polyphenolic compounds [5]. In case of diabetes and related complications these compounds have been found to modulate lipid and carbohydrate metabolism by obstructing the effect of digestive enzymes where by reducing postprandial hyperglycemia and dyslipidemia. Polyphenolic compounds have been instrumental in diminishing insulin resistance, ameliorating pancreatic beta-cell function by safeguarding them against oxidative damage and invigorating their insulin [6].

The present review intends to compile scientific investigations pertaining to phytoconstituents and pharmacological studies; supporting the development of drugs, foods and alternate therapies for management of diabetes and related disorders to combat this global pandemic. *Phyllanthus acidus* is an ornamental plant with a long history of culinary and folklore use. Also known as Star gooseberry, Otaheite gooseberry, Malay gooseberry, Tahitian gooseberry, country gooseberry, arbari, West India gooseberry, or simply gooseberry tree has yellow greenish edible berry fruits. The fruits are acidic sour and tart in taste. The plant that is said to have originated in Madagascar is mainly found in the Indian subcontinent and Malay Peninsula [7,8]. It has been used in various traditional system of medicine for treatment of diabetes and other diseases. The aim of this review is to advocate the use of this plant in future scientific investigations and clinical studies and to unlock its true potential as an alternative or complimentary treatment for diabetes.

Ethnomedicine

Prior to examining the scientific evidence pertaining to antidiabetic effect and related activities, it is requisite that we briefly delve into the ethnomedicinal utilization of this herb to prove its historical application. The fruit of *Phyllanthus acidus* is somewhat bitter, aromatic, pungent, and sour and enhances appetite. In Ayurveda it is useful for the treatment of bronchitis, biliousness, urinary concentrations and piles. It also increases "Vata" in yurvedic practices⁷. The fruit is used to enrich the blood and as liver tonic and blood purifier [9]. Latex is said to possess emetic and laxative effect. Coconut oil heated with bark is applied on cracks on hands and feet in Indonesia to treat eruptions. Roots are used as medication for psoriasis. The root extract is utilized to manage asthma, relieving cough and headache. In the Philippines, leaf decoction is utilized for the management of urticaria while bark is used to cure catarrh [10]. Mucilaginous nature of the leaves makes it useful as demulcent in case of treatment of gonorrhoea. The bark has limited use as a tanning agent in India. The tough and durable nature of the wood makes it suitable for making dishes and other items [11]. The culinary use of the sour mature fruits is widespread. It is eaten fresh and used in cooking for flavour. The fruit is used as chutneys, pickles and jams. The fruit juice serves as make cold drinks while fruit is used for manufacturing vinegar. The young leaves are used as vegetables in India, Thailand and Indonesia [12]. The fruit is also used to treat diabetes, relieve cough and enhance memory [13].

Phytochemistry

Preliminary analyses of fruits of *P.acidus* showed that it mostly consist of water, glucose and fructose. It was also rich in ascorbic acid, carotenoids and macro and micro nutrients like calcium, magnesium and iron making it a good candidate for dietary supplements [14-15]. The review of the literature showed that the plant mainly contains phytoconstituents like terpenoid, flavonoids, natural nucleosides, phenolic compounds and volatile oil components Table 1 (Table 1).

Anti-Diabetic Effects of Star Gooseberry

The bioactive components of star gooseberry (*Phyllanthus acidus*) have shown to exhibit antioxidant, anti-inflammatory, hepatoprotective, hypoglycaemic, antimicrobial and cytotoxic properties (Table 2). The evidence provided by these studies indicated that *P.acidus* can modulate molecular mechanisms by affecting transcription factors and different intracellular pathways. This review primarily focuses on the potent antidiabetic potential of this plant. Enhancing the glycemic profile by the star gooseberry bioactive components can control the complications due to diabetes (Figure 1).

In-vivo Hypoglycaemic Studies

Various studies have supported the claim about the ethnomedical application of *P.acidus* for the management of diabetes and related disorders [13]. Extracts of *P.acidus* plant as a whole have shown hypoglycaemic or antidiabetic properties.

Hypoglycaemic activity of etanolic leaf extract of *P.acidus* was demonstrated by using glucose oxidase method, where doses of 200mg/kg p.o and 100mg/kg p.o reduced glucose level after two hours in albino rat. The reduction was found to be more significant for 200mg/kg when compared with standard drug glibenclamide 0.5mg/kg p.o. Furthermore the extracts from leaves of *Phyllanthus acidus* (L.), *Leucaena leucocephala* (Lam.) and *Psidium guajava* (L.)

were found to have considerable hypoglycaemic and hypolipidimic activity and may be utilized as therapeutics for diabetes without compromising haematological standards or kidney functioning. This property may be attributed to hyper insulinemia and antioxidant activity of extracts. The fruit pulp methanolic extract of *P.acidus* showed significant hypoglycaemic activity. The extract also showed effective antiarrheal property and subdued the rate of excretion by 54.24%. The extract also showed considerable analgesic and CNS anaesthetic activity on experimental animals. *P.acidus* seed extract at a dose of 200mg/kg showed decline in blood glucose level after 8 and 12 hours of treatment when compared with glibenclamide as standard.

Insulin Secretagogues

Koyoto declaration of 2013, emphasised the importance of insulin secretagogues as treatment for diabetes in Asia, as well as worldwide. The statistical data indicated a distressing need for significant clinical and intrinsic research on diabetes in the Asian region. It was stipulated that the Asian phenotype of diabetes was different than that of other geographical regions as it was mostly non obese and insulin secretory dysfunction rather than the more common type which was obesity and insulin resistance diabetes usually found around the world. The leaf extract of *P.acidus* showed significant hypoglycaemic effects by inducing division of beta cell leading to insulin production in streptozotocin induced diabetic rats. Plant extract at a dose of 250mg/kg was found to be slightly less than that of glibenclamide. Furthermore it was surmised that alcoholic extract of *P.acidus* leaves was at a lesser dose nearly non toxic as the animals endured up to 2000mg/kg of orally administered dose of the extract. Etanolic extract of *P.acidus* was effective in gradually decreasing the blood glucose levels of experimental animals. Histopathological studies also indicated an increase number of beta cells and normalising effect on other factors like body weight, creatine kinase, glycosylated haemoglobin and lactate dehydrogenase affirming the role of this plant for glycemic control.

Table 1: Phytochemical constituents from various parts of *P.acidus*

Plant part	Compounds	References
Roots	Spruceanol, Phyllanes A Phyllanes B Phyllaciduloids A-D, Phyllanthusol A,B, Acidoflavanone, glochidone, lupeol, glochidonol, α -lupene, acidoauronol, 5-O-methylacidoauronol, acidoaurone, acidoisoflavone, acidoflavonol, phyllanthacidoid U	16, 17, 18, 19
Stem/ Bark	Lupeol, β -amyrin, Phyllanthol, Phyllaciduloids A-D phyacidusin A phyacidusin B phyllanthacidoid A-T ,phllanthacidoid N1, phllanthacidoid A1, Phyllanthacid U, phyllanthacidoids A-D, H,L,M,S,T	20, 21, 22, 23,24,331
Leaves	Adenosine, Kaempferol, Hypogallic acid, kaempferol-3-O-(2- α -L-rhamnopyranosyl)- β -D-glucuronopyranosyl methyl ester, kaempferol-3-O-[α -L-rhamnopyranosyl (1 \rightarrow 2)]- β -D-galactopyranoside, kaempferol-3-O-(2- α -L-rhamnopyranosyl)- β -D-glucuronopyranoside, rutin, isoquercitrin, quercitrin, myricitrin 29-norlupane-1 β -hydroxy-3,20-dione, dichapetalins (pacidusins A-D), Phyllane C, ovoideal, spruceanol, fluacinoid	25,26,27
Fruits	Sitosterol- β -D-glucoside, and volatile terpenes, ester, acid and phenols.	28,29,30

Table 2: Therapeutic properties of *Pacidus*

Class of effect	Part Used	Details of effect	Reference
Hepatoprotective activity	Fruit, Leaves	extracts showed decrease of AST, ALP, ALT and total bilirubin, an increase in TP, GSH, SOD, CAT and GPx levels, reduced liver infiltration and focal necrosis	57,58,59
Cytotoxicity and Antiplasmodial Activity	Leaves	MTT assay showed <i>in-vitro</i> cytotoxicity of various extracts, similarly antiplasmodial activity used 3D7 strain, sesquiterpenes isolated from <i>P.acidus</i> showed potential anti-hepatitis B virus (HBV) activities	56,23
Antimicrobial Activity	Leaves, fruit, bark	Disc diffusion, Well diffusion, Steak plate and Dilution method used against various strain of bacteria	64,65,66
Cardiovascular Activity	leaves	chronic doses ensued in diminished serum lipid outline, visceral and subcutaneous fat, alleviating endothelial cells NO ₂ formation	67,68
CNS Activity	Fruit, leaves	Attenuated scopolamine induced dementia and oxidative stress, improved memory and learning.	69
Skin Lightening	leaves	reduce melanogenesis in normal human epidermal melanocytes and a reconstructive dermal prototype	70
Respiratory Activity	Leaves	adenosine, kaempferol, and hypogallic acid in the extract corrects defective electrolyte transfer in cystic fibrosis by alleviating intercellular cAMP and Ca ²⁺ .	71

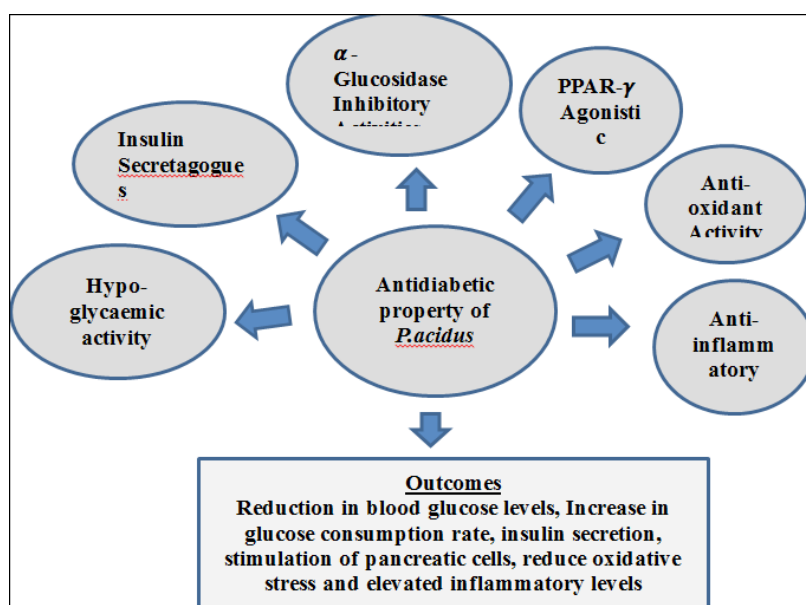


Figure 1: Mechanisms of action of Antidiabetic property of *Phyllanthus acidus*.

α-Glucosidase Inhibitory Activities

Moderation of blood glucose can also be achieved by inhibition of carbohydrate-digesting enzymes such as α -Glucosidase resulting in malabsorption of monosaccharides thus reducing insulin elevation. The inhibition of this enzyme has been found useful for the therapeutics of type 2 diabetic patients. The most widely used synthetic starch hydrolase inhibitors are acarbose, miglitol, and voglibose and have been used as antidiabetic compounds. However, various adverse events are associated with use of synthetic inhibitors like hypoglycaemia at elevated doses, flatulence because of fermentation of intestinal microflora on undigested sugars and diarrhoea. This has led to exploration of natural α -glucosidase inhibitors, a facet under which compounds of *P.acidus* have been explored as well.

Phenolic compounds present in fruit extract of *P.acidus* were analysed using Ultra-high performance liquid chromatography. The fruit extract showed significant α -glucosidase inhibitory activity which may be attributed to phenolic and flavanoidal components like gallic acid, myricetin, quercetin, kaempferol, and dihydroquercetin when compared with forty extracts from tropical fruits from Malaysia⁴³. Derivatives of kaempferol, epicatechin, coumarin and cinnamic acid along with quercetin, citric acid, feruloylactic acid, 4-amino-3-hydroxybutyrate, mucic acid, 2'-*O*-feruloylorientin, diphyllaside B, phyllanthusin E and peonidin-3-glucoside were identified from 50% ethanolic extract that contributed to the α -glucosidase inhibitory activity.

PPAR- γ Agonistic Activity

In the previous decade or so a subfamily of nuclear receptors have emerged as worthy pharmacological receptors whose invigoration can modulate the metabolic disorders and diminish cardiovascular threat factors linked with type 2 diabetes. Thiazolidinediones a synthetic PPAR- γ agonist is an insulin stimulator that rescinds lipotoxicity catalysed insulin resistance in diabetic patients. Nevertheless, like many of the side effects associated with synthetic drugs and an epidemic increase of type 2 diabetes, there is a dire need for novel and safer PPAR agonist with better efficacy and safety. Screening of medicinal plants for PPAR- γ agonist activity seems a logical strategy for finding antidiabetic drugs. After extensive search no investigation into this aspect of diabetes control for this plant could be found. Thus, suggesting an aspect of antidiabetic effect of *P.acidus* plant as PPAR agonist to be explored as possible mechanism of action.

Other Pharmacological Properties of *P.acidus* associated with Diabetes

Production of inflammatory mediators due to oxidative stress results in generation of reactive oxygen species. This link between oxidative stress, inflammation and diabetes is important for the study of therapeutics of

diabetes. Therefore the antioxidant and anti-inflammatory effect of *P.acidus* is examined here, regarding the prospective use of this plant in diminishing the damaging effects resulting from hyperglycemia related oxidative stress and inflammation.

Antioxidant Activity of *P.acidus*

The in-vivo radical scavenging activity of extract of bark, roots, leaves and fruit of *P.acidus* against superoxides, DPPH, hydroxyl radicals etc. is used to evaluate its antioxidant property. NO scavenging activity was observed in 50% ethanolic extract of leaf of *P.acidus*. The methanolic extract of fruits of *P.acidus* was found to possess antioxidant activity due to presence of phenolic compounds. Due to higher phenolic content ethanolic extract of bark showed remarkable antioxidant activity. The extract showed ABTS radical scavenging at 90% at dose of 50 μ g/mL. Analysis of the extract also revealed the presence of well known antioxidant compounds like gallic acid, rutin, quercetin, myricetin, luteolin, coumaric acid and hydroxyl benzoic acid. The leaf and fruit of *P.acidus* were found to check oxidative damage induced due to free radical. This can be utilized to treat cardiovascular and inflammatory disease. The alcoholic and aqueous extracts of fruits of *P.acidus* were evaluated for their antioxidant and cytotoxic activity. The study also showed that aqueous extract showed more potent pharmacological activity than ethanolic extract.

Anti-inflammatory Activity of *P.acidus*

The *P.acidus* leaf extract exhibited notable analgesic and anti-inflammatory action. The ethanolic extract of the leaves also showed significant anti-inflammatory and anti-nociceptive activity due to high flavanoid and phenolic compounds and can be considered as a medicine against pain, oxidative stress and inflammatory diseases. Aqueous extract of *P.acidus* fruit was utilized for silver nanoparticles (AgNP) green synthesis from aqueous AgNO₃. These characterized AgNP showed remarkable anti-inflammatory activity through scavenging nitric oxide and super oxide anions. The AgNP's did not offset the viability of peritoneal macrophages and can be utilized for the treatment of inflammatory diseases by attenuating the expression of IL-1 β . Methanolic extract of *P.acidus* showed both in vivo and in vitro anti-inflammatory activity. The orally administered extract also restored the HCl/ethanol-induced gastric damage and acetic acid vascular permeability. The compounds identified were flavonoids, kaempferol and quercetin.

Toxicity Studies

Limited literature exists relating to the toxicity studies of *Phyllanthus acidus*. Although considered toxic in Malay few citations are available regarding the toxicity studies of this plant. The safety profile of ethanolic extract of *P.acidus* leaves was established through subchronic toxicity assay. The outcome showed that not only the extract could reduce the body weight as

compared to the control group but all the other haematological parameters after administration of the extract were similar to that of control group. There was no change in the levels of alanine aminotransferase, glucose, blood urea nitrogen levels but an elevated aminotransferase, creatinine and urine volume. The examination of the various organs showed that though the organ/body weight ratios of heart and liver were unaltered at all doses however the liver was enlarged and kidney shrunken. The result indicated that the extract was relatively safe at subchronic doses but at higher doses the liver and kidney need to be critically monitored. In an earlier study to establish the antiplasmodial activity of the various extracts of *P.acidus* it was found that the extracts were non toxic up to a concentration of 50µg/ml when tested for cytotoxicity on Vero normal cell lines.

Conclusions

The various evidences collected from the scientific publications establishes the worthiness of *P.acidus*, to be investigated and advocated as complementary or alternate therapy for management of diabetes and its complications. More in-depth studies are required to determine the phytoconstituents responsible for hypoglycaemic activity of this plant. The aspect of insulin resistance, a major characteristic of type 2 diabetes and the ability of *P.acidus* to combat it need to be evaluated. Genetically altered rat models like Goto-Kakizaki model can be utilized to determine the insulin resistance in type 2 diabetes. Another aspect which needs to be explored is the isolation of bioactive constituents responsible for pancreatic regeneration of the β cell utilizing both in-vivo and in vitro studies. However in comparison to the plants employed in traditional system of medicine for treatment of diabetes, it is possible that *P.acidus* has progressed sufficiently in terms of scientific evaluations including pharmacognostic evaluation of crude drug, isolation of bioactive constituents and exploring the mechanism of therapeutic activities. Although the use of *P.acidus* may be advocated for treatment of hyperglycemia, its use for the purpose of overall health and wellbeing should also be encouraged. In spite of plethora of research available on *P.acidus* it is imperative that pharmacological and toxicological facet of the plant are also studied through in-vivo and clinical studies. There is also a need to determine the recommended dosage and intake limit prior to its utilization as antidiabetic agent.

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