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Multifunctional Role of *Phyllanthus Acidus* L. as a Therapeutic Agent for Management of Diabetes and Associated Complications: A Review

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Plant based medicines have been used in traditional system of medicines since time immemorial for the treatment of diabetes due to relatively low prevalence of side effects and ease of access in developing countries. The review compiles and analyses the scientific data to accentuate the role of Phyllanthus acidus also known as star gooseberry, as a promising treatment for the management of diabetes and related complications. Several electronic databases like Google Scholar, Pub Med, Scopus, Web of Science, Science Direct etc. and other published data in books and dissertations were utilised to compile this review. Both in-vitro and in-vivo research have indicated that the phytoconstituents present in Phyllanthus acidus may affect the various biomarkers of diabetes. The mode of action behind antidiabetic property of the plant and its biologically active components are mainly due to inhibition of α-glucosidase, suppression of PPAR-γ, and elevate production of insulin. The antioxidant and anti-inflammatory studies pertaining to Phyllanthus 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: Antidiabetic; α-glucosidase; Antioxidant; Anti-inflammatory; Insulin secretion.

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.[2] Linked with chronic hyperglycemia diabetes is usually classified into Type I, Type II and gestational diabetes. Occurrence of Type I diabetes happens when the beta cells present in pancreas are damaged and not able to produce insulin in sufficient quantity to maintain blood glucose levels.[3] 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. Pregnant women who had not been earlier diagnosed with diabetes often suffer from gestational diabetes.[4] 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.[5] This has lead to an increase in demand of efficient and affordable alternatives with lesser side effects.

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 to 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, ethnoparmacology, and clinical trials of these traditional medicines validating their clinical usage.[6] Plants comprising of phenolic compound have been found to reduce the risk of cancer, diabetes, inflammation, and viral diseases.[7] This property of plants comprising of phenols may be attributed to the free radical scavenging, lowering oxidative stress, and antioxidant property of polyphenolic constituents. 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 postparandial 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.[8]

The present review intents 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 Tahitian gooseberry, Star gooseberry, Malay gooseberry, Otaheite 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.[9, 10] It has been utilized in various conventional system of medicine for therapeutics 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.

MATERIAL AND METHODS

Several electronic databases like Google Scholar, Pub Med, Scopus, Web of Science, Science Direct etc. and other published data in books and dissertations were utilised to compile this review. Literature based search, covering reports that have been published regarding the phytochemical, pharmacological and toxicity studies of *P.acidus* was carried out. Emphasis was given to article covering various aspects of antidiabetic potential of *P.acidus*. The search strategy included the use of MESH terms and keywords such as *Phyllanthus acidus*, Diabetes, NIDDM, T2D, Hyperglycemia, 5ØüÞ-glucosidase inhibition, insulin secretagouges, antioxidant, anti-inflammatory, toxicity to search various databases. Studies that were in English language and whose full text were available and reported the relevent *in-vivo* and *in-vitro* studies of antidiabetic, antioxidant, and anti-inflammatory activity of *Phyllanthus acidus* were selected. Exclusion criteria included non-English studies, data for diabetes that could not be separated from other pharmacological activities, and non availability of full-text articles. On the basis of these keywords 110 articles were identified, abstracts of 100 articles were screened and 85 full text articles were scrutinised for eligibility and of these 71 original articles were included in this literature review.

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 Ayurvedic practices.[9] The fruit is used to enrich the blood and as liver tonic and blood purifier.[11] 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.[12] The root extract is utilized to manage asthma, relieving cough, and headache.[10] In the Philippines, leaf decoction is utilized for the treatment of urticaria while bark is used to cure catarrh .[13] Mucilaginous nature of the leaves makes it useful as demulcent in case of treatment of gonorrhoea.[10] 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.[14] 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.[15] The fruit is also used to treat diabetes, relieve cough, and enhance memory.[16]

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.[17, 18] The review of the literature showed that the plant mainly contains phytoconstituents like terpenoid, flavonoids, natural nucleosides, phenolic compounds, and volatile oil components as shown in 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 reinforced the affirmation about the ethnomedical application of *P.acidus* for the management of diabetes and related disorders.[16] 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 employing glucose oxidase procedure, where doses of 200mg/kg p.o and 100mg/kg p.o reduced glucose level after two hours in albino rat. Where, the reduction was found to be more significant for 200mg/kg when compared with standard drug glibenclamide 0.5mg/kg p.o.[35] Furthermore the extracts from *Phyllanthus acidus (L.), Leucaena leucocephala (Lam.) and Psidium guajava (L.)* leaves were found to have considerable hypoglycaemic and hypolipidimic activity and may be utilized as therapeutics for diabetes without compromising haematological standards or kidney functioning.[36] 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 antidiarrheal property and subdued the rate of excretion by 54.24%.[37] The extract also showed considerable analgesic and CNS anaesthetic activity on experimental animals. *P.acidus* seed extract at a dose of 200mg/kg exhibited decline in blood glucose level after 8 and 12 hours of treatment. When compared with glibenclamide as standard.[38]

Insulin Secretagogues

Koyoto declaration of 2013 emphasised the importance of insulin secretagouges 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 [39]. 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.[40] 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.[41] Histopathological studies 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**.**[42]

a-Glucosidase Inhibitory Activities

Moderation of blood glucose can also be achieved by inhibition of carbohydrate- digesting enzymes such as a-Glucosidase resulting in malabsorption of monosaccharides thus reducing insulin elevation.[43] The inhibition this enzyme has been found useful for the therapeutics of type 2 diabetic patients.[44] The most widely used synthetic starch hydrolase inhibitors are acarbose, miglitol, and voglibose and have been used as an 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.[45] This has led to exploration of natural a-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 a-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 Malaysia.[46] Derivatives of kaempferol, epicathechin, coumarin and cinnamic acid along with quercetin, citric acid, feruloylacetic acid, 4-amino-3-hydroxybutyrate, mucic acid, 2''-*O*-feruloylorientin, diphylloside B, phyllanthusiin E and peonidin-3-glucoside were elucidated from 50% ethanolic extract that ascribed to the a-glucosidase inhibitory activity.[47]

PPAR-g 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.[48] Thiazolidinediones a synthetic PPAR-ã agonist is an insulin stimulator that rescinds lipotoxicity catalysed insulin resistance in diabetic patients.[49] 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-ã agonist with better efficacy and safety. Screening of medicinal plants for PPAR- ã 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-ã 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.[50] Plants comprising of phenolic and flavonoidal constituents have been found to reduce the risk of cancer, diabetes, inflammation and viral diseases. This property of plants comprising of phenols and flavonoids may be attributed to the free radical scavenging, lowering oxidative stress and antioxidant activity of these polyphenolic compounds.[51] Occurrence of oxidative stress due to persistent hyperglycemia is one of the causes of onset of diabetes and its complications. Mechanisms that are responsible for increased oxidative stress are metabolic stress, auto-oxidation of glucose and increased non-enzymatic glycosylation of glucose.[52] *P.acidus* is rich in terpenoids, phenols and flavonoids like gallic acid, rutin, quercetinls, myricetin etc. and possesses antioxidant activity due to the presence of hydroxyl groups which help in scavenging of free radicals.[53]Inhibition of antioxidant enzymes caused by elevated free radicals is reduced resulting in antioxidant activity. This further leads

to reduction of lipid peroxidation in tissues.[54]As it is evident that Type II diabetes mellitus is an inflammatory disease that leads to increase in the presence of cytokines and oxidative stress related to them, resulting in an increase in the stress activated signalling pathways. The entire process initiates insulin resistance and decreased glucose tolerance in humans.[55] Presence of compounds like flavonoids, kaempferol, and quercetin in *P.acidus* was responsible for the scavenging of Nitric

Table 1. Phytochemical constituents of different parts of *P. acidus*

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, , phyllanthacidoid U	19, 20, 21, 22
Stem Bark	Lupeol, β-amyrin, Phyllanthol, Phyllaciduloids A-D phyacidusin A phyacidusin B phyllanthacidoid A-T ,phllanthacidoid N1, phllanthacidoid A1	23, 24, 25, 26,27
Leaves	Adenosine, Kaempferol, Hypogallic acid, kaempferol-3-*O*-(2-α-L-rhamnopyranosyl)-β-D-glucuronopyranosyl methyl ester, kaempferol-3-*O*-[α-L-rhamnopyranosyl (1→2)]-β-D-galactopyranoside, kaempferol-3-*O*-(2-α-L-rhamnopyranosyl)-α-D-glucuronopyranoside, rutin, quercitrin, myricitrin29-norlupane-1β-hydroxy-3,20-dione, dichapetalins (pacidusins A–D),Phyllane C, ovoideal, spruceanol, fluacinoid	28,29,30
Fruits	Sitosterol-β-D-glucoside, and volatile terpenes,ester, acid and phenols.	31,32,33
Stem	Phyllanthacoid U ,phyllanthacidoids A-D, H,L,M,S,T	34,25

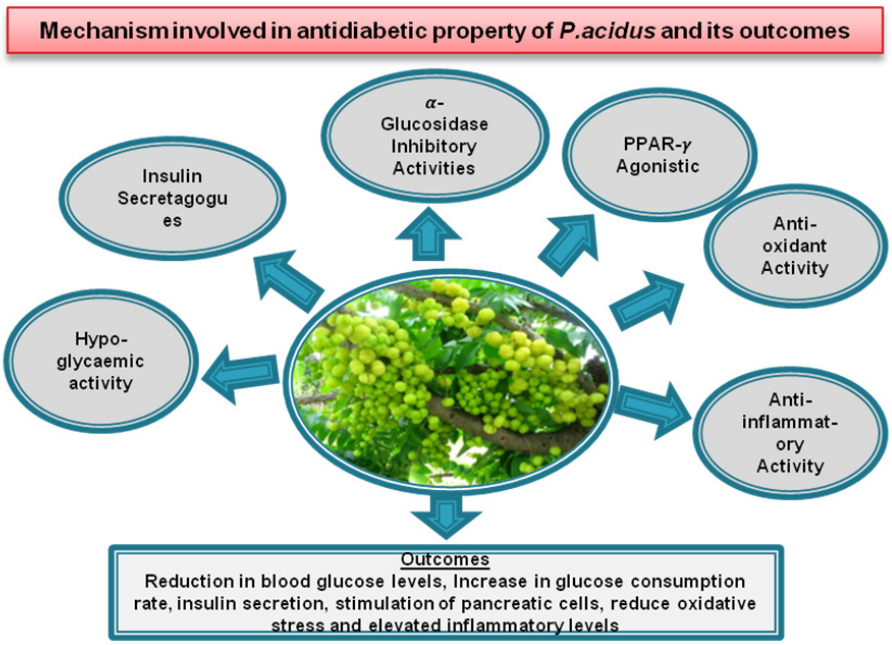

Fig. 1. Mechanisms of action of Antidiabetic property of *Phyllanthus acidus*

Oxide (NO) and superoxide anions responsible for inflammatory response. Furthermore *P.acidus* also attenuated the expression of inflammatory markers like IL-1â.[61]Therefore the anti-inflammatory and antioxidant effect of *P.acidus* is examined here, regarding the prospective use *P.acidus* in diminishing the damaging consequences due hyperglycemia related oxidative stress and inflammation.

Antioxidant Activity of *P.acidus*

The *in-vivo* scavenging activity of free radicals by various 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*.[47] The methanolic extract of fruits of *P.acidus* was found to possess antioxidant activity owing to the various phenolic compounds found in it.[56] Due to higher phenolic content ethanolic extract of bark showed remarkable antioxidant activity. The extract showed ABTS radical scavenging at 90% at dose of 50µg/mL. Investigation of the methanolic extract also revealed the presence of prominent antioxidant compounds like quercetin, gallic acid, rutin, , myrcetin, luteolin, coumaric acid, and hydroxyl benzoic acid.[42] 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.[57] The alcoholic and aqueous extracts of *P.acidus* fruits were evaluated for their antioxidant and cytotoxic activity. The study also showed that aqueous extract exhibited more potent pharmacological effect than ethanolic extract.[58]

Table 2. Therapeutic properties of *P.acidus*

Class of effect	Part Used	Details of effect	Ref
Hepatoprotective activity	Fruit, Leaves	Various extracts showed decrease of AST, ALP, ALT and total bilirubin. There was an increase in TP, GSH, SOD, CAT and GPx levels, reduced liver infiltration and focal necrosis	65,66,67
Anti-diabetic	Fruit, leaves	Both *in-vitro* and *in-vivo* research exhibited the lowering of blood glucose level by various intrinsic mechanisms.	45,47,35, 36,38,40
Antioxidant Activity	Leaves, barks and fruit	*In vivo* assays like DPPH radical, Superoxide anion, Nitric oxide radical, hydrogen peroxide scavenging assays showed prominent inhibitions of these free radicals by various extracts of *P.acidus.*	68,69,70, 71,47,42
Cytotoxicity and Antiplasmodial Activity	Leaves	MTT assay was employed to determine the *in-vitro* cytotoxicity of various extracts, similarly antiplasmodial activity used 3D7 strain, Norbisabolane sesquiterpenes isolated from *P.acidus* showed potential anti-hepatitis B virus (HBV) activities	64,25
Antimicrobial Activity	Leaves, fruit and Bark	Disc diffusion, Well diffusion, Steak plate and Dilution method used against various strain of bacteria	72,73,74
Cardiovascular Activity	leaves	chronic doses ensued in diminished serum lipid outline, visceral and subcutaneous fat, rats influenced vascular function by alleviating endothelial cells NO2 formation	75
CNS Activity	Fruit, leaves	attenuated scopolamine induced dementia and oxidative stress, improved memory and learning.	76
Skin Lightening Activity	leaves	reduce melanogenesis in normal human epidermal melanocytes and a reconstructive dermal prototype	77
Respiratory Activity	Leaves	adenosine, kaempferol, and hypogallic acid present in the extract corrects defective electrolyte transfer in cystic fibrosis by alleviating intercellular amount of cAMP and Ca2+.	78

Anti-inflammatory Activity of *P.acidus*

The *P.acidus* leaf extract exhibited notable anti-inflammatory and analgesic action.[59] The etanolic extract of the leaves also exhibited notable anti-inflammatory and anti-nociceptive property due to high flavanoid and phenolic compounds and can be considered as a medicine against pain, oxidative stress, and inflammatory diseases [60]. Aqueous extract of *P.acidus* fruit was utilized for silver nanoparticles (AgNP) green synthesis from aqueous AgNO3.[61] These characterized AgNP showed remarkable anti-inflammmatory 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 therapeutics of inflammatory diseases by attenuating the expression of IL-1â.[61] Methanolic extract of *P.acidus* showed both *in vivo* and *in vitro* anti-inflammatory activity. The orally administered extract also restored the HCl/ ethanol- instigated gastric damage and acetic acid vascular permeability. The compounds identified were flavonoids, kaempferol and quercetin.[62]

Toxicity Studies

Limited literature exists relating to the toxicity studies of *P.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.[63] 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 extracts were non-toxic up to concentration of 50µg/ml when tested for cytotoxicity on Vero normal cell lines.[64]

CONCLUSIONS

The various evidence 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 â cell utilizing both in vitro and in-vivo studies. However in comparison to the plants employed in conventional system of therapeutics for mitigation of diabetes, *P.acidus* has progressed credibly in terms of research based evaluations including pharmacognostic appraisal of raw drug ,isolation of bioactive components, 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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Conflicts of Interests

The authors declare that they do not have any Conflicts of Interests.

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