Phyllanthus debilis: A poorly investigated plant with antidiabetic effects

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Abstract - *Phyllanthus debilis* (*Ela pitawakka* in Sinhala) whole plant is used as a remedy for diabetes mellitus. However, scientific evidence available on its therapeutic effects is very limited. The aim of this review was to focus on the limited scientific literature available on the antidiabetic effects, phytochemicals and safety of *P. debilis*. According to the reported findings, *P. debilis* has demonstrated evidence to support its hypoglycemic effects, glycation and glycation induced cross-link inhibitory effects and antioxidant effects that are known to minimize diabetic complications. Additionally, anti-inflammatory effects, anticancer effects, antihepatotoxic effects and some phytochemicals present in *P. debilis* have been revealed. More investigations on *P. debilis* need to be carried out.

Key words - *Phyllanthus debilis*, antidiabetic, amylase, glucosidase, glycation, cross-link

1. Introduction

There are approximately 1000 plant species in the genus *Phyllanthus* (Euphorbiaceae) in which diverse types of plants such as trees, shrubs and herbs are found [1]. These plants are widely distributed in most tropical and sub-tropical countries and are traditionally used in the treatment of various diseases including diabetes [2]. *Phyllanthus debilis* Klein. ex.willd (Euphorbiaceae) (*Ela pitawakka/ bim nelli* in Sinhala) [3] is a member of the genus *Phyllanthus* which is an annual plant widely distributed in Sri Lanka, India, Burma, Indonesia, Pacific islands and West Indies [4]. Even though the three species *Phyllanthus amarus*, *Phyllanthus fraternus,* and *P. debilis* were previously referred to as a single species named *P. niruri*, they are now identified as different species [1,5,6]. Many publications published even lately in India on *P. niruri* were found to be referring to any of the three species mentioned above and not on the true *P. niruri* [7]. The true *P. niruri* was identified as a native species in America which does not occur in India [8]. The group of herbs, *P. amarus*, *P. fraternus*, *P. debilis* and *P. urinaria* is known as '*Bhumyamalaki*' in Indian literature which is also known as niruri complex [9]. They are similar in morphology and difficult to identify separately. Specific morphological features which aid the identification of *P. amarus*, *P. debilis, P. maderaspatensis* and *P. virgatus* have been reported [7].

P. debilis (PD) whole plant is used in Sri Lanka to treat diabetes mellitus [3,10]. Furthermore various parts of PD is being used as a remedy for jaundice, sickle-cell anemia, diarrhoea, wounds, inflammation, intestinal worms, scabies, ring worm, gall stones and kidney stones [3,5,11,12].

Even though the closely related species *P. amarus* is well studied on its therapeutic effects including antidiabetic effects, PD is a poorly investigated plant. This review focuses on the limited scientific evidence available on therapeutic effects with a special emphasis on antidiabetic effects, phytochemicals and safety of PD.

2. Antidiabetic effects

2.1. Hypoglycaemic effects

Diabetes mellitus is a global health problem which has affected more than 400 million people in 2015 [13]. Hyperglycemia is a characteristic feature of diabetes [14]. As a result, macromolecules including proteins undergo non-enzymatic glycation at an accelerated rate, leading to chronic diabetic complications such as nephropathy and cardiovascular diseases [15]. The increase in oxidative stress and dyslipidaemia that occur as a result of diabetes also speeds up the occurrence of such complications. Therefore agents that can resist or reverse the metabolic alterations associated with diabetes are invaluable in the treatment of diabetes.

One study has revealed the *in vivo* hypoglycaemic effects of the aqueous extract of PD with evidence of multiple mechanisms of action. In this study, the effects of PD were tested in normoglycemic mice on fasting and random blood glucose levels, oral glucose and sucrose tolerance, amount of glucose absorbed, glycogen content in liver and skeletal muscle and glucose uptake [3]. Findings of this study revealed a dose-dependent reduction in the fasting blood glucose level and improvement of the oral glucose and sucrose tolerance tests when the doses of 497.5, 995 and 1990 mg/kg were used. Almost 50% inhibition of intestinal glucose absorption was detected when PD extract (1990 mg/kg) was given orally. However, no effect was found on glucose uptake and glycogen content when 1990 mg/ kg PD was given for 30 days. In the same study, PD also has increased the HDL level even though the total cholesterol was not changed.

Pancreatic α-amylase and α-glucosidase present in the intestinal brush border are key enzymes that are involved in the hydrolysis of dietary starch in to glucose which is the absorbable product, [16,17]. Inhibition of these enzymes serves as therapeutic approaches in lowering the postprandial spikes of blood glucose concentration [18] (Fig. 1).

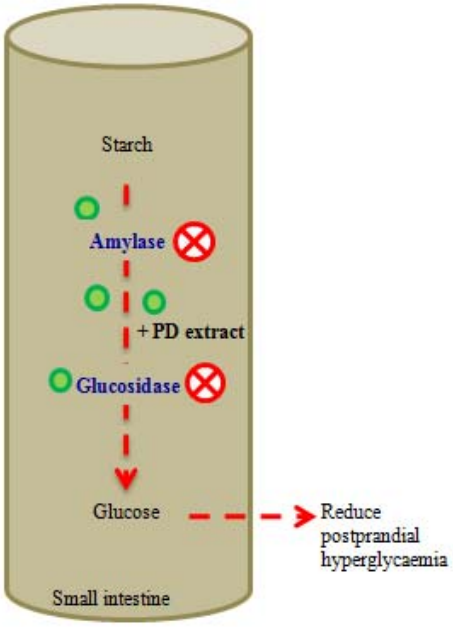

Fig. 1. Inhibition of α-amylase and α-glucosidase in the presence of *Phyllanthus debilis*

Inhibitory effects of both α-amylase and α-glucosidase of the methanol extract of the PD whole plant were revealed *in vitro* [19]. Effect on α-glucosidase was found to be particularly high with an IC_{50} of 0.57 µg/ ml. IC_{50} value against α-amylase was found to be 937 µg/ ml [19]. α-Amylase inhibitory activity of the hexane extract of *P. amarus* was also reported and a mixture of oleanolic acid and ursolic acid was found to be responsible for this effect [20].

2.2. Antiglycation effects

Acceleration of protein glycation leads to the formation of a stable heterogeneous group of complex compounds known as advanced glycation end products (AGEs). Some of the AGEs form protein cross-links leading to dysfunction of the organs involved [21].

Inhibition of glycation by the methanol extract of PD whole plant was revealed using a novel polyacrylamide gel based method *in vitro*. In this study, almost complete inhibition on protein glycation was observed in the presence of 50 µg/ ml PD [15]. In another study, inhibition of glycation induced protein cross-linking of PD whole plant methanol extract was demonstrated *in vitro* using a novel sodium dodecyl sulphate polyacrylamide gel based method [22]. This study revealed almost complete inhibition of the protein cross-linking with 25 µg/ ml PD extract. In both studies on glycation [15,22], PD was among the plants which have produced maximum inhibitory effects. Furthermore, the inhibitory effects on glycation and cross-linking were found to be independent of the known blood glucose lowering effects of PD, as the sugar concentration of the medium was maintained at high concentration in these studies [15,22]. PD whole plant extract was also found to inhibit the formation of early glycation product fructosamine [23]. Thermal stability of the inhibitory compound/s responsible for the prevention of fructosamine formation and glycation induced protein cross-linking was also revealed after heating the extract for 1 h at 95°C [23]. Same study has also revealed that the PD extract is effective in preventing protein cross-linking when added either on day 0 or 1 of the incubation but not when added on day 2 [23].

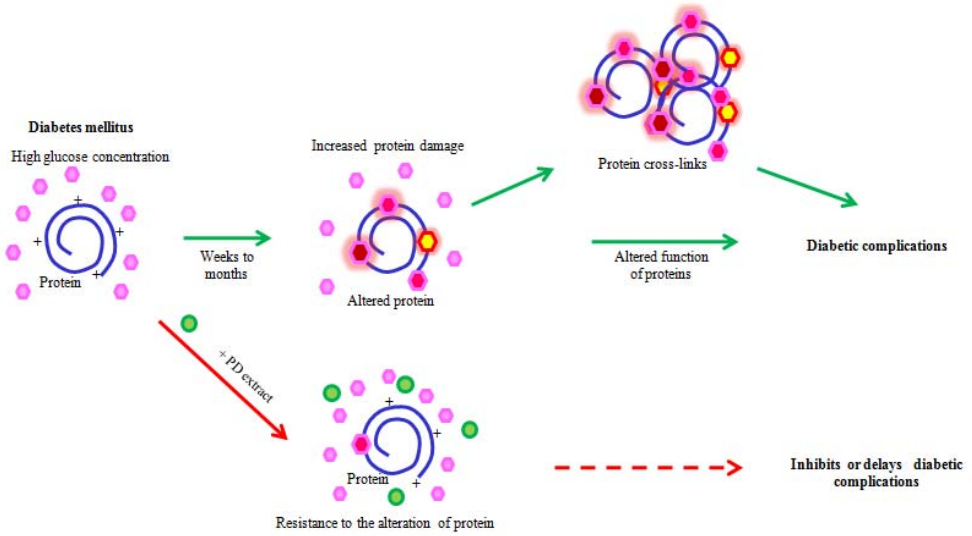

Fig. 2. Inhibition of protein glycation and glycation induced protein cross-linking in the presence of *Phyllanthus debilis*

2.3. Antioxidant effects

It was reported that free radical generation is increased and the protective mechanisms are impaired in diabetes with an increase in the oxidative stress [24]. Oxidative stress is identified as a contributing factor in the causation of chronic diabetic complications [25].

Several studies have revealed the protective role of PD against oxidative stress. PD was found to show maximum antioxidant activity when compared with *P. amarus, P. maderaspatensis, P. urinaria,* and *P. virgatus* [26]. Antioxidant activity of these plants was found to be due to the presence of phenolic compounds [26]. Ethanolic extracts of PD shoot was identified as a rich source of phenolic compounds [4]. Antioxidant activity of the methanol extract of PD dried leaves was shown in another study [27]. Ethanolic extract of seven species of the genus *Phyllanthus* including PD have shown the presence of phenolic compounds and antioxidant effects. However, in this study, the content of such compounds and the antioxidant activity of PD were found to be lower than that of *P. amarus* [28], in contrast to the findings of Kumaran and Karunakaran [26].

3. Other therapeutic effects

3.1. Anti-inflammatory effects

The anti-inflammatory potential of PD was revealed using two different models, carrageenan-induced paw oedema model and cotton pellet-induced granuloma model [29].

3.2 Anticancer effects

When *P. urinaria, P. amarus* and *P. debilis* extracts were investigated for anticancer activity by assessing the antiproliferative and proapoptotic effects, highest inhibition of cell proliferation was observed with the PD extracts. All extracts were capable of inducing apoptosis of hepatocarcinoma cells though induction of TNF-α. All three extracts also inhibited expression of proteins cyclooxygenase (COX) 2, Bcl-2 and IL-8 which protect the cells from apoptosis while inducing Bax which promotes apoptosis [30]. Effects on DNA protection and life span extension were found to be high in the presence of both PD and *P. amarus* [28].

4. Phytochemicals

Even though phytochemical investigation of species such as *P. emblica, P. niruri* and *P. amarus* has been carried out extensively, investigations carried out on *P. debilis* (Table 1) is incomplete [31]. More than 500 compounds have been isolated from the large genus *Phyllanthus* in which majority were found to be lignins, triterpenoids, flavonoids and tannins [12]. Lignins and tannins are reported to exhibit number of biological activities. The three most prevalent compounds found in this genus are corilagin, geraniin, and gallic acid [12]. Phyllanthin, niranthin and geraniin were the compounds which were mainly focused in the pharmacological research [12]. Phyllanthin was found to show maximum number of medicinal effects [1].

Arial parts of PD were found to contain unidentified flavonoids [26]. Two major lignans found in the phyllanthus genus, phyllanthin and hypophyllanthin were not detected in methanol extract of PD leaf and stem extracts [27,32]. However, one study reported the identification of phyllanthin, hypophyllanthin and β-sitosterol from PD leaves [33]. One phenolic acid, one flavonol-glycoside and three ellagitannins; gallic acid, rutin, corilagin, furosin and geraniin were isolated from the ethyl acetate extract of aerial parts of PD [26]. All these five compounds have shown DPPH scavenging and antioxidant activities [26]. In another study, glochidon, heptadecyl alcohol, montanic acid (from chloroform extract) and β-sitosterol glucoside and debelolactone (from

methanol extract) were isolated from PD whole plant. When these five compounds were subjected to molecular properties prediction and drug-likeness, debelolactone was identified as a compound with good drug-likeness score [35].

Table 1: Compounds isolated from *Phyllanthus debilis* with therapeutic effects

Group	Compound	Therapeutic effect
Phenols	Gallic acid	Antioxidant*, antiulcer, antioxidant
Flavonoids	Rutin	Antioxidant *, anti-inflammatory, radioprotective
Ellagitannins	Corilagin	Antioxidant*, radioprotective, antiviral, antitumor, antihyperalgesic
Ellagitannins	Furosin	Antioxidant*, wound healing
Ellagitannins	Geraniin	Antioxidant*, aldose reductase inhibitory activity, hepatoprotective, antiviral, radioprotective, hepatoprotective, antitumor, antihyperalgesic
Triterpenoids	Glochidon,	Antitumor
Sterol	β-sitosterol	Analgesic, anti-inflammatory
Sterol glucoside	β-sitosterol glucoside	Cholesterol lowering effects
Phenylpropanoids	Debelolactone	Antihepatotoxic*
Phenylpropanoids-Lignins	Phyllanthin**	Hepatoprotective, anticancer, antitumour, antileukemic, antibacterial, antiamnestic, Antiaging, antioxidant, anti-inflammatory, antiapoptotic
Phenylpropanoids-Lignins	Hypohyllanthin**	Hepatoprotective, anti-inflammatory, antiapoptotic

*The effects stated have been demonstrated in the compounds isolated from PD [26,37]. Rest of the effects were demonstrated in the compounds isolated from other species of the *Phyllanthus* genus [1,12,36]. **Some studies have reported the absence of phyllanthin and hypophyllanthin in *P. debilis*.

5. Safety

One study reported that there were no overt signs of hepatotoxicity (in terms of serum ALT and AST levels) and renotoxicity (in terms of serum urea and creatinine levels) upon chronic administration of PD in to mice, suggesting the safety of PD [3]. Antihepatotoxic effects were observed in other studies as well [37]. Antihepatotoxic activity of PD whole plant was revealed and the active compound was isolated and identified as debelalactone, a new oxirano-furanocoumarin [37]. Debelalactone was capable of lowering the elevated liver enzymes aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) from 59% to 86% against CCl_4-induced toxicity in Wistar rats [37]. These biochemical findings were supported by the findings of histopathological investigations of the liver sections. When the whole plant powder of *P. amarus* and *P. debilis* were investigated in another study, *P. debilis* has shown a better efficacy than *P. amarus* against CCl_4 induced rat liver dysfunction [38]. This study has shown the complete restoration of biochemical parameters in plasma and liver. Based on the biochemical parameters, the recovery of the liver from CCl_4 induced damage after treatment with extracts of root, stem and leaf of *P. debilis* were evident with a maximum protective effect with leaf extract [39]. Methanol extracts of PD dried leaves and stems have shown hepatoprotective effects (EC_{50} 74 µg/ml) against *tert*-butyl hydroperoxide induced toxicity in HepG2 cells which was higher than that of *P. amarus*. This protective effect was not observed with aqueous extract of PD [27].

Conclusions

In Sri Lanka *Phyllanthus debilis* is used as a remedy for diabetes mellitus. It is evident that the studies conducted are very limited compared to that of the closely related species *Phyllanthus amarus*. With the limited scientific evidence available there are findings to support the hypoglycemic effects including the effects on inhibiting α-amylase and α-glucosidase enzymes, glycation and glycation induced cross-link inhibitory effects and antioxidant effects of *P. debilis*. All these effects are known to minimize the associated long term complications of diabetes. Additionally, anti-inflammatory effects, anticancer effects, antihepatotoxic effects and limited amount of phytochemicals present in *P. debilis* have been revealed. More investigations on *P. debilis* will be important to identify its true value.

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