Recent Trends in BIOCHEMISTRY
Bioactive Molecules from Phyllanthus Niruri and Investigating their effects against Diabetes

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Published Online: June 15, 2020
Ebook: Recent Trends in Biochemistry
Publisher: MedDocs Publishers LLC
Online edition: http://meddocsonline.org/
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Abstract

The use of plant-based medicines, health products, food supplements, and cosmetics is being increased nowadays due to their active and healthy ingredients. Phyllanthus niruri is traditionally used as herbal medicine in Ayurveda, Homeopathy, Naturopathy, Siddha, Unani and Yoga worldwide. They are indigenous plant native to India and are rich in bioactive molecules like Phyllanthin, alkaloids, anthocyanins, chlorogenic acids, coumarins, flavonoids, lignans, phenolic acids, saponins and glycosidic substitutes, tannins and terpenoids. Hence they are used to cure a wide range of diseases and act as a good antidiabetic agent. Presently, many drugs are available to reduce diabetes but they are purely chemicals but Phyllanthin an antidiabetic compound isolated from Phyllanthus niruri effectively reduces blood glucose level. The present review aims to summarize and consolidate the biomedical properties of \textit{Phyllanthus niruri} derivatives on the prevention and control of Diabetics.

Introduction

Phyllanthus sp. is one of the largest genus in the flowering plant belongs to the family Phyllanthaceae. Many trees, herbs and shrubs were described under the genus, approximately more than thousand species were identified and reported in diverse parts of the world including tropical Asia, China, India, Africa, America and Australia [1]. The presence of valuable bioactive components makes the Phyllanthus more popular in the field of pharmacology based on the usage as an herbal drug in Ayurveda, Homeopathy, Naturopathy, Siddha, Unani and Yoga [2]. In recent years, the use of traditional drugs has attained a great advance in the biosynthesis of natural products from the genus Phyllanthus [3]. Simultaneously, an accurate and certified plant should be used as a drug, together with its efficient potency and safety studies is required to create data for the acceptance of herbal medicine in the global market [4]. It has been scientifically proven that each and every part of the plant Phyllanthus including leaves, root, fruit, seeds and stem possess medicinal value. Moreover, it has also been observed that some plants are being toxic to the body and are not safe for consumption. Currently, the use of plant-based medicines, health products, food supplements, and cosmetics is being increased in both developing and developed countries because these natural products are nontoxic with less adverse effect and are available cheaply.

In persistence of the examination for additional potent anti-diabetic remedies from medicinal plants, we assessed the antidiabetic potentials of \textit{P. niruri}. The medicinal plant \textit{Phyllanthus niruri} indigenous to India is rich in enormous bioactive components namely Phyllanthin, alkaloids, anthocyanins, chlorogenic acids, coumarins, flavonoids, lignans, phenolic acids, saponins and glycosidic substitutes, tannins and terpenoids [5]. The same plant parts were widely used in traditional medicine to cure a wide range of ailments including anti-inflammatory [6] cardio protective [7]...
antiviral, antibacterial, anti-cancer [8], anti-hyperglycemic, antispasmodic, antithrombotic, laxative, diuretic, carminative, in the management of diabetes, constipation, fever, malaria, jaundice, hepatitis B, dysentery, gonorrhea, syphilis, tuberculosis, cough, influenza, diarrhea, vaginitis, tumors and kidney stones [9]. Hence, plants are very familiar as they contain several pharmacologically vital biomolecules whose significance is glowingly recognized by several biochemical and pharmacological studies [10].

Intentionally it grows as an annual herb in wild as field weeds throughout the humid, tropical and subtropical regions and attains a height of about 30-60 cm with an angular branched stem and numerous elliptic oblong leaves. As they are monoecious plants the male flowers occur in groups and females present in solitary [2]. Many of the researchers reported the important biological activity of Phyllanthus niruri is its antidiabetic, antiviral, antioxidant, anticancer, and immune modulatory properties [11] isolated a 35 kDa protein from P. niruri exhibits antioxidant property along with cytoprotective activity in hepatocytes. In addition it is considered to be a refurbishment herb since it acts as a starter to boost the body and to overcome stomach upset [10].

Diabetes is a chronic common non contagious disease affecting peoples of various countries, deficiency of insulin may result in type 1 diabetes and tissue resistance to insulin results in type 2 diabetes which leads to maximum number of cases. Prevention and control of diabetes is a universal problem and so far, no efficacious medication was discovered. Presently, many drugs are available to reduce diabetes and those drugs primarily reduce the blood glucose and have fewer effects, but drugs obtained from plant sources not only reduce blood glucose but also correlates with pathological aspects of diabetes [12]. Several medicinal plants were used in the treatment of diabetes in human society and one such plant was Phyllanthus niruri. Previously there are reports on Phyllanthus niruri as they exhibit strong α-glucosidase inhibiting ability towards diabetes as compared with other species of Phyllanthus. This antidiabetic property was due to the presence of the bioactive component phyllanthin which is rich in P. niruri. Still now the mechanical action of Phyllanthus niruri in treating diabetes remains unclear [13]. More number of research reports are needed to prove the concept of using plant based medicines and their mechanism of actions in the control and treatment of diabetics. Furthermore, such knowledge is improved only by understanding the biochemical nature of the active principle in the medicinal plants and its respective actions. For the vast range of biochemical properties of Phyllanthus niruri on the effect of various disease alignments, in this review, we need to concentrate on the biomedical properties of Phyllanthus niruri derivatives on the prevention and control of Diabetics.

### Geographical location

Linnaeus in 1973 first defined the genus Phyllanthus and the medicinal plant P. niruri indigenous to India may grow as an annual herb in wild as field weeds throughout the humid, tropical and subtropical regions. It is assumed that about 200 species of plants of this genus are distributed broadly in the Americas, generally in the Caribbean and in Brazil. Similarly it’s common in Asia, India and China which can also grow well in coastal areas. In wild under safe conditions it grows well till the end of rainy season but usually seen during the first showers of monsoon in June and bears nutritious fruits during the month of August [14]. It may attain a height of about 30-60 cm with an angular branched stem and numerous elliptic oblong leaves. As they are monoecious plant the male flowers occur in groups and females present in solitary [2].

### Bio active compounds isolated medicinal plants against diabetics

India the botanical garden of the world is the principal producer of a wide variety of medicinal herbs. Hence, many plants have good sources of medicinal value and are used to cure a wide range of clinical diseases including diabetes. For treating many diseases the plant as a whole is used rather than isolating a particular component [15]. Madhu-meha is the ayurvedic name of diabetics’ which can be cured by ayurvedic formulations from a long century. Different types of ayurvedic plants from India showed efficient antidiabetic effects along with its bioactive principles were reported in literature (Table 1). Among the medicinal plants used for various diseases prevention and control activities in India, P niruri is used to treat several diseases, Rasayana is an Ayurvedic therapy used to treat diabetics with a formulation of combination of drugs from Phyllanthus emblica, Azadirachta indica, Ocium sanctum and Tinosporacordifolia. Recently, using HPLC analysis, scientists stated that the aqueous extract of P. niruri comprises more than 50 biomedical compounds in which the majority of those are isolated using chloroform chemically [16]. Peoples in eastern Nigeria traditionally use Phyllanthus niruri to manage and treat diabetes [2]. Phyllanthus species have coriligin, repandusinic acid A and mallotinin which help to inhibit glucosidase and hence are used to treat diabetes by the peoples of Vietnam [17]. Phyllanthus niruri in the form of pellet was consumed by the peoples of Bangladesh to overcome diabetes [10]. Leaves of Phyllanthus niruri were used as herbal drug to treat diabetes in Malaysia [16]. Various medical plants and its parts showing antidiabetic properties are mentioned in Table 2. This indicates the plant based compounds were used as a biomedicine for lowering the blood glucose levels, however the mechanism behind the efficiency was not explained clearly.

### Table 1: Indian Ayurvedic plants with efficient antidiabetic effect

<table>
<thead>
<tr>
<th>S. No</th>
<th>Scientific Name</th>
<th>Common Name</th>
<th>Parts used</th>
<th>Bioactive component</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Aeglemarmelos</td>
<td>Wood Apple</td>
<td>Fruits and leaves</td>
<td>Tannins, Marmelosin, Alkaloids and Marmesin</td>
<td>[18]</td>
</tr>
<tr>
<td>2.</td>
<td>Allium Sativum</td>
<td>Garlic</td>
<td>Ripe Bulbs</td>
<td>Allicin, Organosulphur and Saponins</td>
<td>[19]</td>
</tr>
<tr>
<td>3.</td>
<td>Andrographispaniculata</td>
<td>Green chireta</td>
<td>Whole plant</td>
<td>Diterpene lactones</td>
<td>[20]</td>
</tr>
<tr>
<td>4.</td>
<td>Coccinindica</td>
<td>Ivy gourd</td>
<td>Leaves</td>
<td>Resins, Alkaloids, Fatty acids, Flavonoids</td>
<td>[21]</td>
</tr>
<tr>
<td>5.</td>
<td>Azadirachta indica</td>
<td>Neem</td>
<td>Whole plant</td>
<td>Nimbin, Nimbidinin, Nimblic acid, Azadirachtin</td>
<td>[15]</td>
</tr>
<tr>
<td>6.</td>
<td>Caesalpiniaodoncella</td>
<td>Nicker tree</td>
<td>Seed and leaves</td>
<td>Bonducin</td>
<td>[22]</td>
</tr>
<tr>
<td>S. No</td>
<td>Scientific Name</td>
<td>Common Name</td>
<td>Parts used</td>
<td>Bioactive component</td>
<td>Geographical location</td>
</tr>
<tr>
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<td>-------------------------------</td>
</tr>
<tr>
<td>1.</td>
<td>Achilleasantolina</td>
<td>Santolin yarrow</td>
<td>Leaves</td>
<td>Flavonoids and Sesquiterpenelactones</td>
<td>Jordan</td>
</tr>
<tr>
<td>2.</td>
<td>Ajugaiva</td>
<td>Herb ivy</td>
<td>Aerial parts</td>
<td>Diterpenes, Iridoidglycosides, Flavonoids and Ecdysteroids</td>
<td>Jordan</td>
</tr>
<tr>
<td>3.</td>
<td>Ambrosia maritima</td>
<td>Sea rag wood</td>
<td>Whole plant</td>
<td>Chloro-11,1-Dihydrohymenin, Eicosane, n-Heneicosane and n-Tricosane</td>
<td>Jordan</td>
</tr>
<tr>
<td>4.</td>
<td>Artemisia herba-alba</td>
<td>White wormwood</td>
<td>Aerial parts</td>
<td>Cis-thujone , Trans-thujone , Vanillylalcohol, and Nor-davanone</td>
<td>Iraq and Morocco</td>
</tr>
<tr>
<td>5.</td>
<td>Artemisia vulgaris</td>
<td>Mugwort</td>
<td>Aerial parts, roots and Dried branches</td>
<td>flavonoids, coumarins, sesquiterpen lactones, volatile oils, inulin, and traces of alkaloids</td>
<td>Jordan</td>
</tr>
<tr>
<td>6.</td>
<td>Capparisspinosa</td>
<td>Caper</td>
<td>Seed, Root and Flower bud</td>
<td>Alkaloids, Glycosides, Tannins, Phenolics, Flavonoids, Triterpenoids Steroids, Carbohydrates, Saponins</td>
<td>Jordan</td>
</tr>
<tr>
<td>7.</td>
<td>Ceratoniasiliqua</td>
<td>Carob</td>
<td>Seed</td>
<td>Galactomannan</td>
<td>Israel</td>
</tr>
<tr>
<td>9.</td>
<td>Gynuraprocumbens</td>
<td>SambungNyawa</td>
<td>Leaves</td>
<td>β-sitosterol, Kaempferol,Quercetin ,Isovanillic acid</td>
<td>Malaysia, Thailand, and Indo-China</td>
</tr>
<tr>
<td>10.</td>
<td>Ficusdeltoidea</td>
<td>Mas Cotek</td>
<td>Leaves and Roots</td>
<td>Trans-Furanodinalool oxide, Linalool, cis- Pyranoid Linalool oxide</td>
<td>Malaysia</td>
</tr>
<tr>
<td>11.</td>
<td>Cosmos caudatus</td>
<td>Ulam Raja</td>
<td>Flowers and Leaves</td>
<td>Phenolic acids, Flavonoids, Tannins, Sesquiterpene, Lactones</td>
<td>Malaysia</td>
</tr>
<tr>
<td>12.</td>
<td>Anacardiumoccidentale</td>
<td>PokokGajus</td>
<td>Leaves</td>
<td>Cardanol and Anacardic acid</td>
<td>Brazil</td>
</tr>
<tr>
<td>13.</td>
<td>Averrhoablimbi</td>
<td>BelimbingBuluh</td>
<td>Fruits</td>
<td>Cyanidin-3-o-h-Glucoside, Phenolics, Potassium ion</td>
<td>Indonesia</td>
</tr>
<tr>
<td>14.</td>
<td>Orthosiphonstamineus</td>
<td>MisaiKucing</td>
<td>Leaves</td>
<td>Sinensetin, Eupatorin and Perillene</td>
<td>Australia</td>
</tr>
<tr>
<td>15.</td>
<td>Catharanthusrosea</td>
<td>Periwinkle</td>
<td>Leaves and flowers</td>
<td>Linolenic acid, Ethyl ester , Stearic acid , Phytol and Hexadecanoic acid</td>
<td>Srilanka</td>
</tr>
</tbody>
</table>

**Table 2:** Ayurvedic plants with efficient antidiabetic effect from other countries

- **Scientific Name:** Name of the plant in scientific classification.
- **Common Name:** Name by which the plant is commonly known.
- **Parts used:** Parts of the plant used in the study.
- **Bioactive component:** Active components identified in the plant.
- **Geographical location:** Location where the plant is native or studied.
- **Reference:** Reference for the source of the data.
**Phyllanthus niruri** has widespread medicinal possessions from long history to till now in health care system of tropical and subtropical countries. And so that P. niruri can be confidently used as anti-diabetic herb as were tested for their toxicity which show positive results as they are nontoxic in nature [42]. Interestingly, *Phyllanthus niruri* shows a great antidiabetic activity due to the presence of specific bioactive components like phyllanthin, Cyanidin, Malvidin, Flavonols, Flavanone, Lintetralin, ellagic acid constituent of tannin, saponins, Protocatechue acid, Caffeicacid, alkaloids, anthocyanins, chlorogenic acids, coumarins, flavonoids, lignans, phenolic acids, saponins and glycosidic substitutes, tannins and terpenoids [43]. Such kind of bioactive components were widely reported around the world, however its mechanism of actions against the control of blood glucose level are not clearly recorded. The image of P. niruri is given in Figure 1. Many reports showed that P. niruri is used as a folk medicine for the treatment of liver related disorders liver cancer and jaundice and also act as antidiabetic, antidiuretic, anti-inflammatory, antiviral, antitumor and antioxidant [5].

Numerous in vivo experiments were conducted using the extract of P. niruri towards rodents and the result shows the extract has the capacity to lower the blood glucose level [14]. Different parts of Phyllanthus species have corilagin, repandusinic acid A and melatonin which help to inhibit glucosidase and hence are used to treat diabetes by the peoples of Vietnam [17]. Hence, the extraction from the aerial part of the plant increases glucose absorption, mobilization and storage by means of lowering blood glucose mechanism and hence controls diabetes [14]. The boiled leaves decoction is considered to be diuretic for diabetes and everyday oral intake of P. niruri extract resulted not only in decreased blood glucose but also reduces total cholesterol and triglyceride level in both diabetic and normal glycaemic rats [2]. Similarly, the alcoholic extract of P. niruri considerably decreases the blood glucose level in normal and diabetic rats [44]. Reports from histological studies also say methanol extract of P. niruri given to diabetic rats function by, repairing and restoring the integrity and function of damaged pancreas hence stimulating insulin secretion [14]. In addition aqueous extraction of P. niruri leaf medication provides suggestion that intake of this extract might avoid elevation of oxidative stress in the kidney in diabetes [45].

Recently, the combination of bio-ethanol extract of P. niruri along with Moringa oleiferawas tested in diabetic albino rats which showed a significant decrease in fasting blood glucose after 2 to 3 hours of administration and this decrease in blood glucose level is due to the stimulation of β cells by the effect of plant extract to secrete insulin which reduce the blood glucose [46]. Furthermore, much scientific research reports proves that the extract from the aerial part of P. niruri inhibits glucose absorption and enhances the storage of glucose and hence reduces the blood glucose level [9]. And also the extract has the ability to develop hepatic glycogen content and increases liver hexokinase activity due to the presence of bioactive components which stimulate the production of insulin by insulin mimicking mechanism [47]. An experiment was conducted using the aqueous and ethanol extract of P. niruri which results in potential decrease of blood glucose and is preferred to be a great significant for type 2 diabetes [48]. Similarly, the extract of P. niruri inhibits the enzymatic pathways of carbohydrate digestion and glucose storage by modifying pancreatic tissue architecture and hence reduces the blood glucose [49]. Most importantly in 1986, a study was conducted by Devi et al (1986) [50] in humans on the diuretic, hypotensive and hypoglycemic effects towards P .niruri, which exhibited a significant diuretic effect. Correspondingly, focused analogous studies in man exposed that P. niruri produced decrease in the systolic blood pressure in non-diabetic hypertensive patients and drop of blood glucose in diabetic patients [51,52]. Further an experiment was conducted by JasminBavarva &Narasimhacharya, (2007) [53] to test the antidiabetic ability of P. niruri among normal and diabetic rats and gave a result as the plasma glucose level was significantly reduced in those experimented animals. Likewise, an antidiabetic study was conducted by Okoliet al., (2010) [14] for 28 days in diabetic rats by feeding them the extract of P. niruri which gave a promising reduction in the blood glucose after the end of the experiment. Moreover, administration of water extract of P niruri to rat as animal models results in decreased blood glucose level (P>0.05) along with decreased triglycerides and hence improves insulin secretion [54]. The above mentioned studies clearly indicate the biomedical values of P. niruri against diabetic patients to reduce the glucose levels in the blood of humans.
Phyllanthin from *P. niruri* for diabetes

Phyllanthin is one of the chief bioactive components of *P. niruri* and it is therapeutically considered as a superior antidiabeticagent who also possesses antidiabetic, antioxidant, hepatoprotective, anticancer, immunosuppressant and anti-inflammatory activities. Phyllanthin was first isolated and reported from Phyllanthus niruri by Ottow in 1891 [55]. Phyllanthin are chemically called 4-[(25, 35)-3-{[3, 4-dimethoxyphenyl]methyl]-4-methoxy-2-(methoxymethyl)butyl]-1, 2-dimethoxybenzene with a molecular formula C24H34O6 and a molecular weight of about 418.51 correspondingly. The structure of Phyllanthin is mentioned in Figure 2. They are synthesized from Phyllanthus niruri in the laboratory using (+) 2, 3-diveratryl succinic acid and resolution was secured through its cinchonine salt [55].

Phyllanthin exhibit extreme UV absorbance at dual wavelengths, 230nm and 280 nm, exposed IR spectrum vibrations at 2999, 2917 and 2868 cm-1 (C–H aliphatic stretch); 1516 and 1464 cm-1 (C=C ring stretch) and 1141 cm-1 (C – O – C vibrations at 2999, 2917 and 2868 cm-1 (C–H aliphatic stretch); 1516 and 1464 cm-1 (C=C ring stretch) and 1141 cm-1 (C – O – C vibration) and exposed molecular ion peak in MS spectrum at 418 m/z and a base peak at 151 m/z. Hence, they exhibit solubility in the array of 7.32–8.57 mg/ml and seem to be pH-independent and it has no p Ka terminating a pH range of 1.12–10.02. The log *P*<sub>ow</sub> value was found to be 3.30±0.05 at pH 7.48 by shake flask method and hence it specifies good permeability through biological membranes [56]. Bearing in mind the significance of Phyllanthin many researchers strained to increase its yield by using numerous advanced techniques. Moreover, plants grown at higher elevation shows rich in Phyllanthin content than that of which grown at lower elevations [57]. According to some research Phyllanthin content of transgenic *P. niruri* (0.3–0.81% w/w) was higher than normal plants (0.09% w/w) which was analysed using HPLC [58]. Various scientists concentrate to raise the yield of Phyllanthin by improving the extraction from plants by means of numerous techniques such as supercritical fluid extraction [59], pressurized liquid extraction [60], Soxhletation [61], and other conventional techniques.

A Phyllanthin-loaded self-micro emulsifying drug conveyance system was developed by a group of scientist who contains Phyllanthin/caprylor 90/cremophor RH 40/transcutol P in ratio of (1.38:39.45:44.38:14.79) w/w gives a tremendous improvement in solubility, in-vitro release and in-vivo oral bioavailability in rats compared with pure Phyllanthin [62]. In addition most of the reports postulate that Phyllanthin and hypophyllanthin from various Phyllanthus species act as the major active components in healing hepatic diseases [63]. Further, an investigation discovered that lignan phyllanthin from *P. niruri* shows radioprotector activity by scavenging free radicals [64]. Accordingly, hexane extract of phyllanthin and hypophyllanthin from Phyllanthus niruri shows a protective action towards CC1<sub>4</sub> and galactosamine which is further induced by cytotoxic hepatocyte cells of rat [63]. On the other hand, action of phyllanthin and hypophyllanthin was tested on P-glycoprotein (P-gp) with multidrug resistance protein 2 (MRP2) by using the in-vitro model of Caco-2 cells. A fluorescence spectroscopy was used to verify its function and the result reveals hypophyllanthin and phyllanthin actively prevent P-gp function, and concluded that phyllanthin and hypophyllanthin have the ability to prevent P-gp function [65].

The antidiabetic phyllanthin was also used in the synthesis of nanoparticles which helps in the formation and stability of those nanoparticles by donating the electrons and interacting with those metal ions [66]. Very recently, a group of scientist works on ethno pharmacological evidence of *P. niruri* in contrast to Type-2 diabetes (T2DM) by means of molecular docking and pharmacophore modelling and found that Phyllanthin took more affinity for aldose reductase and can be used to treat Type-2 diabetes [67]. Correspondingly, the hyperuricemic rats treated with Phyllanthin at 10 mg/kg displayed a major increase in urine output when associated to those of the hyperuricemic control rats even though their water consumption was not affected. However, the deviations in urine output detected with Phyllanthin treated animals were not dose dependent [68]. Anyhow, the bioactive component of *P. niruri* Phyllanthin considerably reversed the plasma uric acid level of hyperuricemic animals to its normal level analogous to that of clinically used drugs [69]. In particular, the uricosuric nature of *P. niruri* lignans Phyllanthin may be of great interest in management of hyperuricemia and gout, considering that in clinical practice about 90% of the gout patients is under excretors of uric acid [70]. Certain studies reveals that among different lignans isolated from *P. niruri*, the phyllanthin significantly decrease the plasma uric acid level of hyperuricemic animals to its ordinary level in a dose-dependent mode, analogous to that of allopurinol, benzbromarone, and probenecid which are used for the medication of hyperuricemia and gout [69].

**Conclusion**

Diabetes is a chronic common non contagious disease affecting a vast range of peoples of various countries. Currently, insulin acts as the only effective drug for ailing diabetic patients.

Worldwide, herbal medicines were used to treat a wide range of infectious, pathogenic and contagious diseases. Enormous collections of herbal plants are used to treat diabetes but only few plants are scientifically proven to cure diabetes due the presence of active phyto components. One such active component was the phyllanthin isolated from *P. niruri*, which was used to cure diabetes in various countries. Phyllanthin is therapeutically considered as a superior antidiabetic agent who also possesses antioxidant, hepatoprotective, anticancer, immunosuppressant and anti-inflammatory activities. Phyllanthus niruri has widespread medicinal possessions from long history to till now in the health care system of tropical and subtropical countries and hence can be confidently used as anti-diabetic herb. Many clinical studies were conducted to prove the effect of phyllanthin towards diabetes which gave positive results. In future, effective research reports are needed to prove the concept of using plant based bio medicines and their mechanism of actions in the control and treatment of diabetes.

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