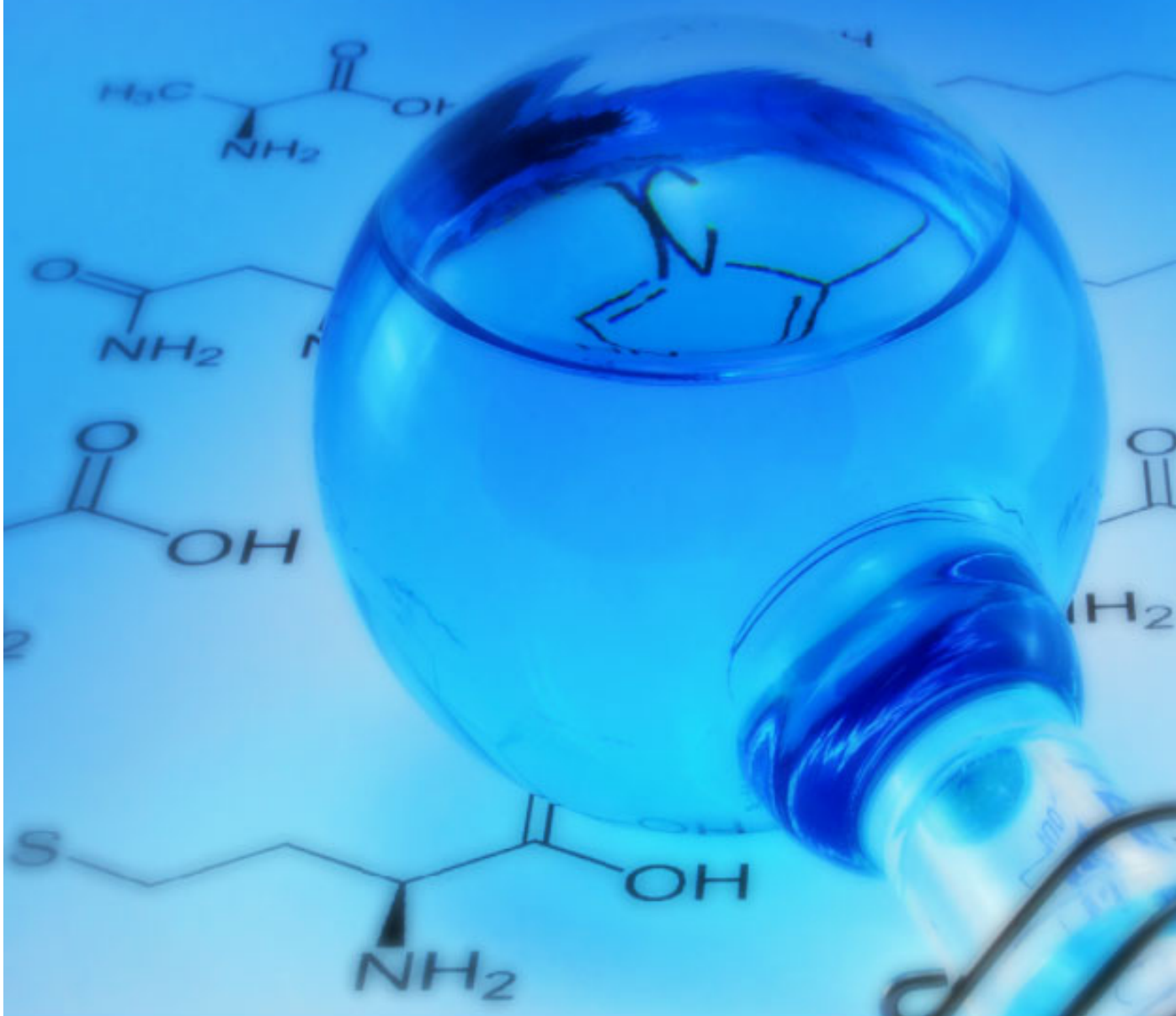


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# Bioactive Molecules from *Phyllanthus Niruri* and Investigating their effects against Diabetes

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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 *Phyllanthus niruri* derivatives on the prevention and control of Diabetics.

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## 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 *P. niruri*. The medicinal plant *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, antihepatotoxic, laxative, diuretic, carminative, in the management of diabetes, constipation, fever, malaria, jaundice, hepatitis B, dysentery, gonorrhoea, syphilis, tuberculosis, cough, influenza, diarrhoea, 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 k Da 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  $\alpha$ -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 1753 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*, *Ocimum 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 corilagin, repandusinic acid A and mallotin 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 medicinal 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

S. No	Scientific Name	Common Name	Parts used	Bioactive component	Reference
1.	<i>Aeglemarmelos</i>	Wood Apple	Fruits and leaves	Tannins, Marmelosin, Alkaloids and Marmesin	[18]
2.	<i>Allium Sativum</i>	Garlic	Ripe Bulbs	Allicin, Organosulphur and Saponins	[19]
3.	<i>Andrographispaniculata</i>	Green chireta	Whole plant	Diterpene lactones	[20]
4.	<i>Cocciniaindica</i>	Ivy gourd	Leaves	Resins, Alkaloids, Fatty acids, Flavonoids	[21]
5.	<i>Azadirachta indica</i>	Neem	Whole plant	Nimbin, Nimbidinin, Nimbilic acid, Azadirachtin	[15]
6.	<i>Caesalpinia bonducella</i>	Nicker tree	Seed and leaves	Bonducin	[22]

7.	<i>Curcuma longa</i>	Turmeric	Rhizome, leaves	Curcumin	
8.	<i>Enicostemmalittoraleblume</i>	Majmakbooti	Whole plant	Ophelic acid and Tannins	[23]
9.	<i>Gymnesylvestre</i>	Gurmarbooti	Leaves and bark	Saponin, Alkaloids	[24]
10.	<i>Helicterusisora</i>	Screw tree	Roots	Betulic acid, Daucosterol, Sitosterol	
11.	<i>Syzygiumcumini</i>	Jambul	Fruit, seed	Anthocyanins, Glucoside, Ellagic acid, Isoquercetin, Kaempferol, and Myricetin	[25]
12.	<i>Momordicacharantia</i>	Bitter gourd	Fruit	triterpene, proteid, steroid, alkaloid, inorganic, lipid, and phenolic compounds	[26]
13.	<i>Musa Paradisiacal</i>	Banana	Fruit, stem	Polyphenol, Hemicellulose	[27]
14.	<i>Ocimum sanctum</i>	Tulsi	Whole plant	Volatile oil, Triterpenoid, Flavonoids and Saponin	[28]
15.	<i>Polyalthialongifolia</i>	Ashoka tree	Bark	Alkaloids, glycoside, Saponin, polyphenolic compounds, diterpenoids& tannins.	[29]
16.	<i>Tinosporacordifolia</i>	Gaduchi	Stem and leaves	Alkaloids, Diterpenoid Lactones, Glycosides, Steroids, Sesquiterpenoid, Phenolics	[30]
17.	<i>Pterocarpusmarsupium</i>	Indian kino tree	Wood	Marsupin, Epicatechinpterosupin and Liquiritigenin	[31]
18.	<i>Saturejakhuzestanica</i>	Summer savory	Whole plant	Carvacrol, Flavones, Triterpenoid, Steroids, Tannins	[32]
19.	<i>Stevia rabudiana</i>	Candyleaf	Leaf	Stevioside and Rebaudioside	[33]
20.	<i>Salacia reticulate</i>	Koranti	Root, bark and leaves	Salacinol and Kotalanol	[34]

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

S. No	Scientific Name	Common Name	Parts used	Bioactive component	Geographical location	Reference
1.	<i>Achilleasantolina</i>	Santolin yarrow	Leaves	Flavonoids and Sesquiterpenelactones	Jordan	[35]
2.	<i>Ajugaiva</i>	Herb ivy	Aerial parts	Diterpenes, Iridoidglycosides, Flavonoids and Ecdysteroids	Jordan	[36]
3.	<i>Ambrosia maritima</i>	Sea rag wood	Whole plant	Chloro-11,1-Dihydrohymenin, Eicosane, n-Heneicosane and n-Tricosane	Jordan	[37]
4.	<i>Artemisia herba-alba</i>	White wormwood	Aerial parts	Cis-thujone , Trans-thujone , Vanillylalcohol, and Nor-davanone	Iraq and Morocco	[38]
5.	<i>Artemisia vulgaris</i>	Mugwort	Aerial parts, roots and Dried branches	flavonoids, coumarins, sesquiterpene lactones, volatile oils, inulin, and traces of alkaloids	Jordan	[39]
6.	<i>Capparisspinosa</i>	Caper	Seed, Root and Flower bud	Alkaloids, Glycosides, Tannins, Phenolics, Flavonoids, Triterpenoids Steroids, Carbohydrates, Saponins	Jordan	[40]
7.	<i>Ceratoniasiliqua</i>	Carob	Seed	Galactomannan	Israel	[41]
8.	<i>Andrographispaniculata</i>	HempeduBumi	Leaves	Diterpenoids, Flavonoids and Polyphenols	Sri Lanka	[16]
9.	<i>Gynuraprocumbens</i>	SambungNyawa	Leaves	$\beta$ -sitosterol, Kaempferol, Quercetin , Isovanillic acid	Malaysia, Thailand, and Indo-China	[16]
10.	<i>Ficusdelto idea</i>	Mas Cotek	Leaves and Roots	Trans-Furanoidlinalool oxide, Linalool, cis- Pyranoid Linalool oxide	Malaysia	[16]
11.	<i>Cosmos caudatus</i>	Ulam Raja	Flowers and Leaves	Phenolic acids, Flavonoids, Tannins, Sesquiterpene, Lactones	Malaysia	[16]
12.	<i>Anacardiumoccidentale</i>	PokokGajus	Leaves	Cardanol and Anacardic acid	Brazil	[16]
13.	<i>Averrhoabilimbi</i>	BelimbingBuluh	Fruits	Cyanidin-3-o-h-Glucoside, Phenolics, Potassium ion	Indonesia	[16]
14.	<i>Orthosiphonstamineus</i>	MisaiKucing	Leaves	Sinensetin, Eupatorin and Perillene	Australia	[16]
15.	<i>Catharanthusrosea</i>	Periwinkle	Leaves and flowers	Linolenic acid, Ethyl ester , Stearic acid , Phytol and Hexadecanoic acid	Srilanka	

### Phyllanthus niruri effects on Diabetes

*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, Protocatechuic acid, Caffeic acid, 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].

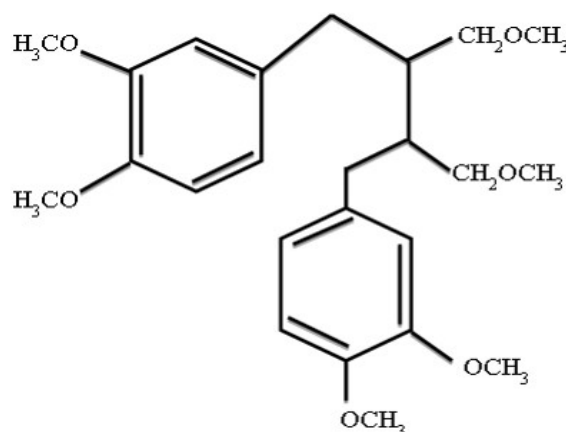
Numerous in vivo experiments were conducted using the extract of *P. niruri* towards rodents and the result shows the extract has the capacity to lower the blood glucose level [14]. Different parts of *Phyllanthus* species have corilagin, repandusinic acid A and melatonin which help to inhibit glucosidase 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 oleifera* was 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  $\beta$  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 Jasmin Bavarva & 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.



**Figure 1:** Phyllanthus niruri



**Figure 2:** Structure of Phyllanthin

## 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 antidiabetic agent 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-[(2S, 3S)-3-[(3, 4-dimethoxyphenyl) methyl]-4-methoxy-2-(methoxymethyl) butyl]-1, 2-dimethoxybenzene with a molecular formula C<sub>24</sub>H<sub>34</sub>O<sub>6</sub> 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<sup>-1</sup> (C–H aliphatic stretch); 1516 and 1464 cm<sup>-1</sup> (C=C ring stretch) and 1141 cm<sup>-1</sup> (C–O–C stretch) 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 K<sub>a</sub> 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], soxhlation [61], and other conventional techniques.

A Phyllanthin-loaded self-micro emulsifying drug conveyance system was developed by a group of scientist which contains Phyllanthin/capryol 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 CCl<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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