

**A REVIEW OF ANTI-DIABETIC ACTIVITY OF TWO MEDICINAL PLANTS USED TRADITIONALLY IN THE MANAGEMENT OF DIABETES MELLITUS FROM THE NORTH EASTERN STATE OF ASSAM, INDIA**

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**ABSTRACT**

Diabetes considered as the epidemic of the century, is one of the most challenging global public health threats the world is facing. And India has emerged as one of the epicenters of the diabetes mellitus epidemic as the number of people with diabetes is around 65.0 million in 2016. Type II diabetes is a complex disease to treat and because of the unique challenges in the management of type II diabetes, a renewed interest is being seen globally in traditional medicine including various local health traditions (LHT). Several of indigenous Indian medicinal plants have been found to be effective in the management of diabetes. *Dillenia indica* and *Phlogacanthus thyrsoiflorus* are two of the traditionally used anti diabetic medicinal plants from north eastern state of Assam, India. The present review explored and consolidated information on the anti diabetic therapeutic potential of *Dillenia indica* and *Phlogacanthus thyrsoiflorus*. Method: An extensive and relevant literature on the anti diabetic activities of *Dillenia indica* and *Phlogacanthus thyrsoiflorus* were gathered through search of electronic databases including Goggle scholar, Pubmed and Medline. Results and conclusion: The review demonstrated that *Dillenia indica* has shown promising effects in controlling hyperglycemia and in control of diabetes-associated complications including diabetic neuropathy and diabetic nephropathy. In case of *Phlogacanthus thyrsoiflorus* only few limited studies are available and these studies have reported good hypoglycemic activities. Considering the results of previous studies *Phlogacanthus* species warrant further studies on its anti diabetic therapeutic potential.

**KEYWORDS:** Diabetes mellitus, medicinal plants, anti diabetic, hypoglycemic.

**INTRODUCTION**

Diabetes has now been considered as the epidemic of the century, one of the most challenging global public health threats.<sup>[1]</sup> The International Diabetes Federation (IDF) 2019 diabetes atlas puts the total number of people living with diabetes worldwide to be about 463 million that is 1 in every 11 adults has diabetes. Diabetes is also responsible for 4.2 million deaths globally. The continuous surge in cases of diabetes worldwide is largely due to an upsurge in type II diabetes cases.<sup>[2]</sup>

Type II diabetes is one of the major leading cause of premature deaths worldwide. In high income countries premature mortality rate due to diabetes decreased from 2000 to 2010, then again resumed upward trend; low middle income countries experienced a persistent increased rate of the same.<sup>[3]</sup> Besides mortality, long

standing diabetes affects all most all the organs in the body. Diabetic individuals have two to three fold increased risk of heart attacks, strokes, kidney failure, neuropathy, foot ulcer, limb infection eventually limb amputation.<sup>[4,5,6]</sup>

The prevalence of diabetes has been increasing rapidly in low middle income countries in comparison to developed nations.<sup>3</sup> And India has emerged as one of the epicenters of the diabetes mellitus epidemic. In India the number of people with diabetes in the year 2016 was a staggering 65.0 million.<sup>[7]</sup>

Considering the fact that type II diabetes is a complex disease to treat and the best approach to manage according to the American Diabetes Association (ADA) is through individualized therapy taking into account the

available treatment options and finalizing the optimal treatment. This further complicates the management of type II diabetes owing to various factors like non availability of glucose lowering agents (GLA) which have low side effect profile, higher rates of drug discontinuation, and cost of treatment on diabetic complications.<sup>[8]</sup>

Because of these unique challenges in the management of type II diabetes, a renewed interest is being seen globally in traditional medicine or complementary and alternative medicine including various local health traditions (LHT) which are shown to be effective in management and prevention of diabetes.<sup>[9]</sup> A review study from nine countries showed that the prevalence of use of traditional medicines to be in the range of 17 to 72% amongst diabetic populations.<sup>[10]</sup> And this is not an exception in Indian context where alternative/AYUSH system of medicine has been an integral part of healthcare system, despite the presence of western medicine. The AYUSH health care system (Ayurveda, Yoga Unani Siddha & Homeopathy) is being practiced in this subcontinent and the traditional/local health practices also play an important role considering the fact that management of chronic disease like diabetes often driven by cost and easy accessibility.<sup>[11]</sup>

Previous research studies have shown that scientific investigation of plants traditionally used for their medicinal value is an effective strategy for finding novel therapeutic agents. An example of this is the anti diabetic drug metformin, the active ingredient of which is derived from “guanidine” of the plant *Galega officinalis*, a perennial herb extensively found over most of Europe, Western Asia, New Zeland and United states.<sup>[12]</sup>

The Indian subcontinent with its rich and diverse topography and climate is home to several species of plants and many of these plants have a long history of being used traditionally as medicines for management of various diseases. And several of the indigenous Indian medicinal plants have been found to be effective in the

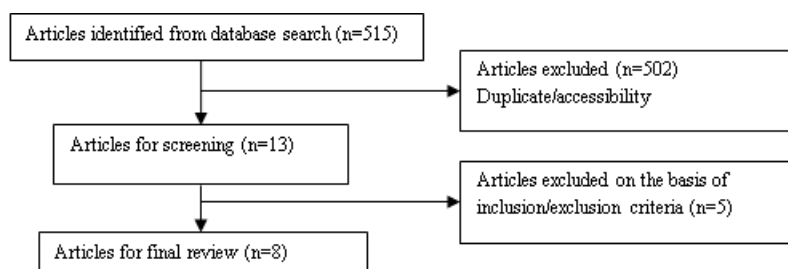
management of diabetes. But systematic studies on the ethno botanical/ethno medicinal use of anti-diabetic medicinal plants from the north eastern part of India which has diverse flora and rich tradition of folk/ethno medicine are limited.<sup>[13]</sup>

*Dillenia indica* and *Phlogacanthus thyrsoiflorus* are two of the traditionally used anti diabetic medicinal plants from north eastern state of Assam, India and these plants are also an integral part of the Assamese culture and cuisine.<sup>[14,15,16,17]</sup> Considering the importance of documenting the traditional medicinal knowledge and in order to provide board overview to future researchers regarding research studies on these plants, the present review makes an attempt to explore the and provide information on anti diabetic studies on *Dillenia indica* and *Phlogacanthus thyrsoiflorus*.

**METHOD:** An extensive and relevant literature on the anti diabetic activities of *Dillenia indica* and *Phlogacanthus thyrsoiflorus* were gathered through search of electronic databases including Goggle scholar, Pubmed and Medline. Reference list of the articles were cross checked. Platform like Researchgate was also used to find out articles that are not readily available on open access format.

The search was conducted using various combinations of MeSH terms with following key words ‘antidiabetic’, ‘medicinal plants’, ‘ethnomedicinal’, ‘traditional medicine’, ‘*Dillenia indica* species’ and same search strategy was repeated for ‘*Phlogacanthus thyrsoiflorus*’. Search was restricted to freely available literature published in English only. Studies with main objective of evaluation of anti-diabetic activity of the above mentioned plants were included. Studies with incomplete or inconclusive information, non-reliable methodology and multiple test ingredients mixing multiple plant/herbs were excluded from this review.

The following flow diagram illustrates the identification, screening, and finalization of articles for review.



**Figure 1: Flow diagram showing identification, screening, and finalization of articles for review.**

### ***Dillenia indica*: Botanical, pharmacognostical, phytochemical description and traditional uses**

*Dillenia* is a genus of about 100 species of flowering plants. It is native to tropical and warm temperature regions and is widely distributed over Southern Asia, Australasia and Indian Ocean Islands. Mostly woody plants, the leaves are simple, wide, well developed and

alternate. The stipules are absent or wing like with bisexual flowers having white or yellow petals. The fruits of some of the species of the genus *Dillenia* are edible and are follicle or berrylike, with enclosed fleshy calyx.<sup>[18,19]</sup>

**Chemical constituents:** *Dillenia indica* is a rich source of triterpenoids, flavonoids, tannins and various other phytoconstituents.<sup>[20,21,22]</sup> The fruit of *Dillenia indica* contain about 34% of total phenolics in methanolic extract and polysaccharide like an arabinogalactan.<sup>[23]</sup> The presence of fixed oil, colouring matter, sterols, glycosides, saponins, proteins, free amino acids, sugars, free acids and tannins in the seeds have also been reported.<sup>[24]</sup>

**Traditional medicinal uses:** *Dillenia indica* is found to have good therapeutic uses. Different parts of the plant are used to treat various ailments. The fruit (calyx) of the plant are a part of Indian cuisine and is especially popular in the north eastern parts of India. The whole plant of *Dillenia indica* is used to treat fever, as an aphrodisiac and its decoction is an universal antidote.<sup>[25,20,21]</sup> The green unripe fruit of *Dillenia indica* is acidic, sour, bitter, pungent, astringent, removes bile, phlegm and flatulence and is cardiotoxic. The ripe fruit is sweet, sour, appetizing, tasty; dispels fatigue; stops abdominal pains, laxative, beneficial in colic associated with mucous.<sup>[25,22]</sup> The fruits of *Dillenia indica* have been documented to be used as a remedy for diabetes mellitus by the traditional healers in the north east part of India.<sup>[15,16]</sup> The leaves are also used for the treatment of diabetes.<sup>[26,27]</sup>

***Phlogacanthus thyrsoiflorus*: Botanical, pharmacognostical, phytochemical description and traditional uses**

An endemic genus *Phlogacanthus* has 49 species found in South Asian countries viz. Bangladesh, Bhutan, China,

India, Indonesia, Myanmar and Vietnam. The members of the genus *Phlogacanthus* are usually tall herbs, shrubs and small trees. The stem is stout, quadrangular, glabrous, with woody lower portions, puberulous upwards, nodes swollen and flat. The leaves of this genus are opposite decussate, entire, glabrous or obscurely crenate, acuminate at both ends. The flowers of this genus are borne in terminal thyrsoid dense panicles, are showy, orange, red, pink or yellow, imbricate in bud. Amongst all the species of *Phlogacanthus* found in the state of Assam and other north eastern states of India, *Phlogacanthus thyrsoiflorus* is the most commonly found species and *Phlogacanthus curviflorus* is used as dietary supplement and also as medicine by various ethnic groups of these states<sup>28</sup>. The flowers of this plant showed the presence of  $\beta$ -Sitosterol, stigmasterol, 13-labdadien-15,16-olide-19-oic acid (3), 19-hydroxy-8(17),13-labdadien-15,16-olide from the dichloromethane extract and the methanolic extract yielded the compound luteolin.<sup>[29]</sup>

**Medicinal uses:** Different parts of the plant *Phlogacanthus thyrsoiflorus* have been used widely for management of several ailments. The fruits and leaves of this plant are burned and then consumed as a cure for fever by the tribes of Assam.<sup>[30]</sup> As a cure for fever the curry made out of the aerial portion of the plant is given orally with rice.<sup>[31]</sup> Leaf extract of the plant is used orally for cure of gout and rheumatism.<sup>[32]</sup> The flowers of this plant are considered an antidote to pox and are used to treat scabies and jaundice.<sup>[33]</sup> It is also used in curing coughs and cold, chronic bronchitis, asthma and rheumatism.<sup>[34]</sup>



*Dillenia indica* -fruit



*Phlogacanthus thyrsoiflorus* flower

**Figure 2: Images of *Dillenia indica* fruit and *Phlogacanthus thyrsoiflorus* flower.**

## RESULTS

A) *Dillenia indica*-The different parts of the medicinal plant *Dillenia indica* have been studied for their anti diabetic activity. The leaves of the plant have been extensively studied for their antidiabetic activity. The methanolic extracts of the leaves were studied in vivo in alloxan induced diabetic rats by Kumar et al;2011. The extracts were given in the dose of 250 and 500 mg/kg of body weight and serum parameters and histopathological changes were studied. Results showed beneficial effects on blood glucose level ( $P < 0.001$ ) as

well as improved kidney and liver functions. Hyperlipidaemia due to diabetes also showed improvements. The treatment also showed enhanced serum insulin level and favorable effect on the histopathological changes of the pancreas, liver and kidney in alloxan induced diabetic rat.<sup>[35]</sup>

Kaur et al; 2018 studied the effect of alcohol and hydro-alcohol extracts of *Dillenia indica* leaves on diabetic nephropathy in STZ-nicotinamide induced diabetic rats. Diabetic rats were treated with different doses of extracts to analyze their nephroprotective effect and tissue

antioxidant enzymes level and formation of AGEs in kidney was measured. The results of the study showed significant improvement in the glycemic status, renal parameters, lipid profile and produced significant reduction in the formation of AGEs in kidneys. The study concluded that *Dilleniaindica* could be a potential therapeutic agent against diabetic nephropathy.<sup>[36]</sup>

A study by Kaur et al;2017 isolated an active compound “chromane” from *Dillenia indica* leaves which has shown beneficial effect in diabetic neuropathy. In this study, diabetic neuropathy was induced in rats by intraperitoneal administration of STZ and neuropathy development was confirmed from marked hyperalgesia and allodynia and reduced motor nerve conduction velocity (MNCV) was associated with increased formation of AGEs and reactive oxygen species. Alcoholic extract of *Dillenia indica* and chromane were administered orally for 30 days from the 60th day of STZ administration. The study results found that alcoholic extracts of *Dilleniaindica* leaves and chromane reduced hyperglycemia and diabetic neuropathic pain via modulation of oxidative-nitrosative stress and reduction in AGE formation in the experimental diabetic rats.<sup>[37]</sup>

Kumar et al;2013 reported an isolated compound from *Dillenia indica* leaves had antidiabetic effect via inhibition of enzymes Alpha-Amylase and Alpha-Glucosidase. In this study, seven active compounds were isolated and these were administered to streptozotocin-nicotinamide-induced diabetic mice 10 mg/kg body weight dose. The results showed that out of seven compounds four have alpha-amylase and alpha-glucosidase inhibitory activity. The study concluded that the mechanism of antidiabetic activity of *Dillenia indica* is through inhibition of alpha-amylase and alpha-glucosidase activity.<sup>[38]</sup>

Another recent study on the methanolic extracts of *Dillenia indica* fruits, the extracts were studied on

alloxan induced diabetic rats. Anti diabetic study was carried out with doses ranging from 150 to 550 mg/kg body weight for 21 days. Results found that 350 mg/kg body weight dose was the most effective in reduction of blood glucose level and significant reduction in the levels of serum lipids as well as liver marker enzymes were noted. There was significant increase in the activities of antioxidant enzymes in the treated group. And histopathological investigations showed that detrimental effects of oxidative stress were attenuated in the methanolic extract treated group.<sup>[39]</sup>

A study reported by Sahariah et al;2018 evaluated the role of *Dillenia indica* fruits in diabetes-induced oxidative stress. The methanolic fruit extract was administered to mice at a dose range of 150–550 mg/kg body weight. And the study found that 350 mg/kg dose of *Dilleniaindica* extract was most effective in alleviating the blood glucose level as well as in reducing oxidative stress.<sup>[40]</sup>

B) *Phlogacanthus thyrsoiflorus*- Hypoglycemic potential of the stem bark and leaf of the plant *Phlogacanthus thyrsoiflorus* was studied in-vivo in STZ induced diabetic rats. The hypoglycemic effect was assessed by oral glucose tolerance test and the control drug used was Glibenclamide in the dose of 10 mg/kg body weight. The results showed methanolic extract of stem bark and leaf have significant ( $P < 0.05$ ) hypoglycemic activity at a dose of 200mg/kg body weight.<sup>[41]</sup>

Another study reported anti hyperglycemic effect of aqueous extract of the flower of *Phlogacanthus thyrsoiflorus* Nees in streptozotocin induced diabetic mice. The flower extract in doses 100 and 200 mg/kg body weight was administered for 21 days and results showed significant reduction of blood glucose level ( $P < 0.0001$ ), serum cholesterol ( $P < 0.01$ ) and increase in liver glycogen ( $P < 0.0001$ ), indicating good anti hyperglycemic effect.<sup>[42]</sup>

**Table 1: Studies on *Dillenia indica* and *Phlogacanthus thyrsoiflorus*.**

<i>Dillenia indica</i>				
Author(s);year	Plant part	Type of study	Methodology	Findings
Kumar et al; 2011.	leaves	in vivo	methanolic extracts of the leaves studied in alloxan induced diabetic rats	Significant beneficial effects on blood glucose level; enhanced serum insulin level; favorable effect on the histopathological changes of the pancreas, liver and kidney.
Kaur et al; 2018	leaves	in vivo	alcohol and hydro-alcohol extracts of <i>Dillenia indica</i> leaves on diabetic nephropathy in STZ-nicotinamide induced diabetic rats.	Significant improvement in the glycemic status, renal parameters, lipid profile and produced significant reduction in the formation of ages in kidneys.
Kaur et al;2017	leaves	in vivo	Alcoholic extract of <i>Dillenia indica</i> and isolated active	Significant reduction in hyperglycemia; reduction in

			compound chromane studied in diabetic nephropathy in STZ induced diabetic rats.	diabetic neuropathic pain via modulation of oxidative-nitrosative stress; decrease in AGE formation.
Kumar et al;2013	leaves	in vivo	seven active compounds were isolated and these were administered to streptozotocin-nicotinamide-induced diabetic mice	Out of seven active compounds, four have anti diabetic affect mediating through alpha-amylase and alpha-glucosidase inhibition mechanism.
Sahariah et al;2018	fruit	in vivo	methanolic extracts of <i>Dillenia indica</i> fruits, the extracts were studied in different dosing regimen on alloxan induced diabetic rats.	350 mg/kg body weight dose was the most effective in reduction of blood glucose level and significant reduction in the levels of serum lipids as well as liver marker enzymes were noted; significant increase in the activities of antioxidant enzymes in the treated group; histopathological investigations showed that detrimental effects of oxidative stress were attenuated in the methanolic extract treated group
Sahariah et al;2018	fruit	in vivo	methanolic fruit extract was administered to mice to study diabetes-induced oxidative stress	350 mg/kg dose of <i>Dilleniaindica</i> extract was most effective in alleviating the blood glucose level as well as in reducing oxidative stress
<b><i>Phlogacanthus thyrsoiflorus</i></b>				
Ilham S et al;2012	Stem bark & leaves	in vivo	methanolic extract of stem bark and leaf of the plant <i>Phlogacanthus thyrsoiflorus</i> was studied in-vivo in STZ induced diabetic rats	Significant hypoglycemic activity at a dose of 200mg/kg body weight
Chakravarty S et al;2012	flower	in vivo	aqueous extract of the flower of studied in streptozotocin induced diabetic mice	Significant reduction of blood glucose level (P< 0.0001), serum cholesterol (P< 0.01) and increase in liver glycogen (P< 0.0001),

## CONCLUSION

Diabetes mellitus especially type II diabetes is one of the rapidly growing health challenges of the world. Its treatment with anti diabetic medicinal plants can be of greater benefit as plants contain several compounds which increases the possibility to modify the disease pathophysiology through multiple mechanism of action. In this review article, an attempt has been made to explore the therapeutic use of *Dillenia indica* and *Phlogacanthus thyrsoiflorus*, commonly used anti diabetics in the north eastern states of India . Several scientific studies have proved the traditional use of *Dillenia indica* and *Phlogacanthus thyrsoiflorus* in the treatment of diabetes and its associated complications.

*Dillenia indica* has shown promising effects in

controlling hyperglycemia in various in-vivo studies. In addition to this, it also proved beneficial in the prevention and control of diabetes-associated complications including diabetic neuropathy and diabetic nephropathy. Regardless of these proven anti diabetic effects, no clinical studies were found indicating the need for such studies. Although previous literature looked for probable mechanism of action of *Dillenia indica*, further research and molecular studies are needed to explore several other potential mechanisms.

In case of *Phlogacanthus thyrsoiflorus* only few limited studies are available. These studies have reported good hypoglycemic activities, suggesting biological potential of this medicinal plant. But there remains a huge gap for research such as isolation of pure compounds and therapeutic validation of these pure compounds to

provide evidence for the traditional claim of anti diabetic effect. Thus there is need for more number of in vivo as well as molecular studies to verify the medicinal properties of the plant.

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