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REVIEW ARTICLE

A REVIEW UPDATE ON *DILLENIA INDICA* F. ELONGATA (MIQ.)MIQ.

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ABSTRACT

Dillenia indica f. elongata (Miq.) Miq. (Dilleniaceae) commonly known as Elephant apple. The vernacular names include Chalta, Chulta, Karambel, Bhavya and Ramphal.It is found in Bangladesh, Nepal, China, Indonesia and Assam, West Bengal, Orissa, Bihar, Myanmar regions of India. Dillenia indica f. elongata (Miq.) Miq. has been prevalently used in Indian traditional and ayurvedic medicine for curing plethora of ailments such as digestive, respiratory and central nervous systems. The information was put together, with the help of literature surveyed. Traditionally different parts of Dillenia indica f. elongata (Miq.) Miq. have been used for the relief of indigestion, asthma, influenza, dysentery, jaundice, promeho, weakness and rheumatic pain. Moreover, the extractives showed significant cytotoxic, CNS depressant and free radical scavenging activity. Wood obtained from the bark of the plant has been used for preparing rafters, tool-handles, cupboard and house pots. It is interesting to know that bark of Dillenia indica f. elongata (Miq.) Miq.is used for production of charcoal. Microspheres of metformin hydrochloride and novel mucoadhesive buccal tablets of oxytocin were also prepared from Dillenia indica f. elongata (Miq.) Miq. In vitro propagation is practised whereas micropropagation is considered at the time, when large scale plant multiplication is required. Phytochemical studies revealed substantial presence of polyphenols, tannins, alkaloids and flavanoids which are responsible for the various pharmacological activities. Major chemical constituents present in the plant are betulin (pentacyclic triterpenoid) and betulinic acid that show wide spectrum of pharmacological activities which include anti-HIV, anti-inflammatory, anti-cancer, anti-malarial etc. Furthermore, Dillenia indica f. elongata (Miq.) Miq. is found to possess analgesic, anti-diabetic, anti-microbial, anti-bacterial, anti-diabetic, antioxidant, anti-proliferation, anti-diarrhoeal, antiimplantation, cytotoxic, wound healing and hair waving activity.

 $\textbf{Keyword(s)-} \textit{Dillenia indica} \ f. \ \textit{elongata} \ (\textit{Miq.}) \ \textit{Miq.} \ ; \ Phytochemical profile; \ Traditional uses; \ Pharmacological properties.$

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1. INTRODUCTION

India is a diverse five and dime flea market of medicinal and aromatic plants and we have well accomplished local healthcare tradition still prevalent in indigenous healthcare system^{1,2}. In developed countries, the use of traditional medicines is customary in treating diseases³. The isolation of active principles of the medicinal plant is necessary for the benefits of human being. It is interesting to know that more than 500 medicinal plants have been reported to exhibit medicinal properties in India and many other countries ; Dillenia indica f. elongata (Miq.) Miq. is one of them. It is most edible species among them⁴. Dillenia indica f. elongata (Miq.) Miq. belong to family Dilleniaceae. The genus Dillenia has 60 species, some of them are D. pentagyna, D. suffruticosa, D.papuana, D.excelsa, D.serrata, ovata. Phllipinensis, D.pentagyna (Roxb) from which Dillenia indica f. elongata (Miq.) Miq. and D. Suffruticosa has been reported to be used to treat cancerous growth⁵. However, there are only two plants Dillenia indica f. elongata (Miq.) Miq. and Dillenia

pentagyna Roxb. (D. pentagyna) which are found in India⁶. Dillenia indica f. elongata (Miq.) Miq. (Dilleniaceae) exhibits plethora of medicinal properties. The fruit of Dillenia indica f. elongata (Miq.) Miq. is used in treating laxative problems, abdominal pain⁷. And for enhancing the flavour of Assamese cuisine⁸, bark and leaves possess astringent properties ⁷, the alcoholic extract of leaves of Dillenia indica f. elongata (Miq.) Miq. had been reported to impart CNS depressant activities^{7,9}, seeds have been reported to possess antimicrobial activity¹⁰ and fruits of Dillenia indica f. elongata (Miq.) Miq. have been found to be rich in showing anti-oxidant activity¹¹.

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The present review consolidates the fragmented data of the plant which will enlighten the significance of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* and will provide a new oversight for researchers in future.

1.1Taxonomy and Morphology

Dillenia indica f. elongata (Miq.) Miq.is an evergreen large shrub or small to medium-sized tree growing to 30m tall¹². Bark is reddish brown in colour, younger branchlets are brown pubescent, glabrescent and contains leaf scars¹². Microscopically, the stem bark is distinguished by lignified stone cells in the cortex, mucilaginous and tanniniferous cells in the phloem and medullary rays on the contrary, non lignified phloem fires and acicular crystals of calcium oxalate in the cortical and phloem parenchyma cells¹³.

The leaves are 15-36cm long, with a conspicuously corrugated surface along with reticulate and unicostate veins 14 . Veins are close, running into serratures, do not fork at the margins, upper surface and nerves beneath are more or less pubescent. Petiole is narrowly winged,2.5-5 cm long, channeled, sheath in, leaf blade oblong or obovate, oblong,15–40 \times 7–14 cm whereas secondary veins (20–) 30–40(–70)cm on either side, parallel, margin serrate, apex is acute 15 .

Flowering occurs in May-June with large, 15-20cm diameter flowers, 5 white petals and numerous yellow stamens 15-16.

Fruits are aggregate and globose, 10–15 cm in diameter, indehiscent, persistent, pedicellate, bracteate. When ripe, the fruits are greenish yellow in colour, slightly succulent and have a pungent smell. Its characteristic round fruits are large, greenish yellow, have many seeds and are edible. Fruiting occurs in July-August and ripens in November December ¹⁷⁻²⁰. Fruit also contains 1-8 seeds, borne on marginal placenta. Fruits are rich in nutrients and could be processed to commercial products such as beverages and squash ¹⁶.

The seeds are compressed endospermic and develop from anatropous ovules, possess hairy margins and are embedded in a glutinous pulp. The endosperm is composed of rectangular cells containing oil globules and other food reserves¹⁴.

The average specific gravity values of stem-bark and branches are 0.733 and 0.674 respectively. Determination of leaves (dry matter basis) gave dry matter,48.80;crude protein 13.37;NDF,29.06; ADF,47.06; hemicellulose,6.03; cellulose, 20.02; permagnate lignin, 10.06; toal ash,17.09; and silica,7.06% ^{21,22}.









Figure 1: Various parts of Dillenia indica f. elongata (Miq.) Miq

1.2 Scientific Classification

In accordance to botanical scheme of Engler, the plant is classified as follows²³

Kingdom:Plantae

Division:Phanerogamae

Subdivision: Angiosperm

Class: Dicotyledonae Subclass:Polypetalae Order: Dilleniales Family: Dilleniaceae

Genus: Dillenia

Species: Indica f. elongata (Miq.) Miq.

1.3 Distribution and Propagation

Habit and Habitat: *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* is a common evergreen tree that grows widely in tropical forests in western peninsula and evergreen forests of the sub-Himalayan tracts from Uttrakhand to eastwards Assam and southwards to central and southern India ²⁴. Indigenous to Indonesia, it is also found in Bangladesh, Nepal, China, Sri Lanka and Vietnam ²⁵⁻²⁶.

Propagation: Compared to traditional propagation *in vitro* propagation has numerous conceivable benefits over the traditional propagation. For large scale *in vitro* plant production, the integral attributes being quality, cost effectiveness, maintenance of genetic fidelity, and long term storage. Furthermore, micro propagation may be utilized, in supreme research in production of virus-free planting material²⁷.

Micro propagation has also become a trustworthy approach for large scale intense plant multiplication, which is based on plant cell, tissue and organ culture on well-marked tissue culture media under aseptic conditions²⁸⁻²⁹.

2. VERNACULAR NAMES

Dillenia indica f. *elongata (Miq.) Miq.*is known by various vernacular names in distinct geographical regions ³⁰⁻³²(See table 1).

3. TRADITIONAL USES

The leaf, bark and fruit of this plant are used as traditional medicine and are well known for their significant characters. The juice of *Dillenia indica* f. *elongata* (Miq.)Miq.leaves; bark and fruits are mixed and given orally (5-15ml, two to five times daily) in the treatment of cancer and diarrhea^{33,34}. When mixed with sugar and water, it is used as a cooling beverage in fever and cough remedies along with leukemic and cardio tonic effect^{14,35}. The leaves and bark are used as laxative, tonic and astringents^{9,36,37}. Bruised bark is applied as a cataplasm for patients with arthritis¹⁴The alcoholic extract of leaves is reported to have CNS depressant activity and also exhibits antioxidant activity due to presence of phenolics constituents and

used in curing abdominal pain ^{4,7,8}. Green leaves, wood and timber have economic importance as well³⁸. The methanolic leaves extract of plant shows antidiabetic activity ³⁹⁻⁴¹. Native communities in Mizoram have used the fruit of the plant as a remedy for jaundice⁴².

Table 1: Vernacular names of *Dillenia indica* f. *elongata* (Miq.) Miq.

Vernacular names	Region/language/system of medicine
Elephant apple	English
Chalita	Assam
Chaalta, Chulta	Bengal
Karambel, Karmal	Gujarat
Chaalta, Chulta	Hindi
Betta kanigala, Bettakanagale	Kannada
Kadukanagala	Konkani
Chalita, Punna	Mal
Karambel, Karmal	Marathi
Uvu, Rai, Oao	Orissa
Oovamaram, Uva	Tamil
Peddakalinga, Uva	Telugu
Bhavya	Sanskrit
Ramphal	Nepal

4. AYURVEDIC USES AND PHARMACEUTICAL FORMULATIONS

Medicinal practices in the form of Ayurvedic, Unani, homeopathy and folk medicinal system co-exist side by side in India and many other countries also. Moreover, among the various systems, folk medicinal system is possibly the least complicated and practiced the most. Dillenia indica f. elongata (Miq.) Miq. also exhibits ayurvedic uses. It is used in treatment of gastrointestinal disorders including diarrhea, indigestion, colic, acidity, constipation, bloating, anorexia, stomachache and Respiratory tract disorders including asthma, bronchitis, pneumonia, cold, influenza. mucus. tonsillitis and sore throat⁴³.

The various parts of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* used in curing ailments are as following:

Leaf:

Hydrocele and contraceptive: A handful of root is tied around the waist for hydrocele.

For contraceptive uses, 1 young leaf of the plant is mixed with 1 handful of rice and soaked in water overnight. In the morning, rice and leaf is macerated and pithas (flattened and steamed food item) are made of the mixture and they are taken on empty stomach.

Dysentery, promeho: One cup of juice obtained from squeezed young leaves is taken twice daily for 7 days 44,45

Juice of leaves and decoction are used in curing fever, cough, constipation, chest pain and for women having breast cancer⁴⁶.It is also used in defeating malaria or malaria like symptoms⁴⁷.

Seed: To enhance digestion: 1 teaspoonful of dried and powdered seed is taken to ensure better digestion⁴⁸.

Fruit: The fruit of *Dillenia indica* f. *elongata* (*Miq.*) *Miq* is beneficial for assessing better appetite, to tackle weakness and rheumatic pain and used for garnish in indigenous ayurvedic medicine for nervousness^{29,49}. In addition to this, it is also used as a cosmetic for preventing dandruff⁵⁰.

Bark: Paste is applied on skin for dealing with dermatological problems. On the other hand bark is also used for production of charcoal⁴⁰.

Controlled release microspheres of metformin hydrochloride (MetH) were developed biodegradableand biocompatible material i.e. from natural sources. Metformin hydrochloride is used in the treatment of noninsulin dependent diabetes mellitus. The microspheres were prepared by the emulsion solvent diffusion technique. Moreover, the prepared microspheres showed mucoadhesive properties⁵¹, swelling properties in intestinal pH52 and controlled release of metformin hydrochloride .The controlled release behavior and colonic delivery of drugs may be attributed to pectous polysaccharides in the extract of Dillenia indica f. elongata (Miq.) Miq.It is used as taste masking agents for bitter drugs, helps to improve pediatric formulations and in encapsulating drugs which are sensitive to gastric pH⁵³⁻⁵⁶.

Novel mucoadhesive buccal tablets (NMBT) of oxytocin were prepared as core in cup fashion so, that the drug is released unidirectionally towards the buccal mucosa. Adhesive cups were prepared with mucilage isolated from edible *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* Oxytocin is used for the induction and augmentation of labor, mid trimester abortion, and the cessation or prevention of postpartum hemorrhage⁵⁷.

5. PHYTOCHEMICAL PROFILE

Plant is found to possess substantial amount of polyphenols, tannins, alkaloids, flavonoids that are responsible for treating wide spectrum of diseases ⁷. Below mentioned are the various chemical constituents that are present in different parts of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.*:

The stem bark on excessive extraction with petroleum ether, chloroform and methanol yielded 10% tannin,

sitosterol, dillenetin, betunaldehyde, betulinic acid, lupeol and stigmasterol^{25,26}. Preet Amol Singh *et al.* 2016, confirmed quantitative presence of betulin (2.510% w/w) in *Dillenia indica* f. elongata (Miq.) Miq. using HPLC ⁷. Flavanoids like kaempferol, rhamnetin, dihydro-isorhamnetin, myricetin, naringenin, quercetin derivatives are also found in *Dillenia indica* f. elongata (Miq.)Miq.^{58,59,60}.

Fruit of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* contains 34 % phenolics, polysaccharide like an arabinogalactan. Fixed oil, colouring matter, sterols, glycosides, saponins, proteins, free amino acids, sugars, free acids, anthraquinone and tannins are also present. The fruits yielded 2 per cent of arabinogalactan. It contained galactose, arabinose, in a molar ratio of 3:2. The main chain of proposed structure consists of β (1 \rightarrow 4) linked D-galactopyranose units to which the non reducing L-arabinose units were attached at 3-position. Physicochemical parameters of the fruit include total ash 4.453%, acid soluble ash 4.150%, tannins 1.2% and reducing sugars 3.44% ^{11,61}.

Apart from this, it has been observed that leaves of twelve species of Dilleniaceae family when extracted successively with petroleum ether and chloroform ascertain the presence of n-hentriacontanol, β -sitosterol, betulin and betulinic acid 62,63,64 . In addition to this, free vitamin C (20.0mg/100g) was found to be present. Carotene was also found in traces 65 . Phytochemical studies has been performed on acid hydrolyzed extracts of dried leaves which showed presence of kaempferol, while fresh leaves contain dihydrokaempferide and 7-glucosides of naringenin which get oxidized to ten corresponding flavonols 63 .

The nutritive value of the vegetable was attributed to the presence of moisture (82.3g),protein (0.8N×6.25g),fat(0.2g),minerals(0.8g),fibre(2.5g),carb ohydrate(13.4g),phosphorous(26mg),iron(nil),energy (59 Kcal) ,calcium (16mg)⁶⁶.

Dealing with phytochemical properties alkaloids, glycosides, steroids, flavanoids, saponins, reducing sugars and tannins are present in *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* ⁶⁷.

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S.No	Name of Phytoconstituent	Structure of phytoconstituent
1.	Betulinic acid	H ₃ C H _{III} H ₃ C H _{III} H ₃ C CH ₃ BETULINIC ACID
2.	Dillenetin	HO OCH ₃ OCH ₃ OCH ₃ OCH ₃ OH ODILLENITIN
3.	Sitosterol	CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃
4.	Lupeol	H_3 C H_3 H_3 C H_3 H_4 C H_3 H_4 C H_3 H_4 C H_4 C H_5 H_5 C
5.	Stigma sterol	H ₃ C _{IIII} H ₃ C _{IIII} H ₃ C _{CH₃} CH ₃ H ₃ C H ₃ C
6.	Quercetin	HO OH O

6. PHARMACOLOGICAL STUDIES

6.1 Anti-inflammatory and analgesic activity

Inflammation is a complex physiological process associated with pain as a secondary process and its hallmarks include swelling, redness, pain and fever⁶⁸. According to the latest research done by Preet Amol Singh et al. 2016, stem bark extract of *Dillenia indica* f. elongata (Miq.) Miq. at dose of 100 and 300 mg/kg possessed good central as well as peripheral analgesic activity. The extracts further showed significant (P<0.01) anti-inflammatory activity in formalin and carrageen an induced inflammation models⁷. Due to presence of flavanoids like kaempferol, rhamnetin, dihydro-isorhamnetin, myricetin, naringenin and quercetin derivatives, *Dillenia indica* f. elongata (Miq.) Miq. favored anti-inflammatory and analgesic activity⁶⁸⁻⁷³.

6.2 Anti-diabetic activity

Diabetes mellitus is a metabolic disorder causing from a defect in insulin secretion, insulin action or both. It is found that worldwide total number of people with diabetes is projected to increase from 171 million in 2000 to 366 million in 2030⁷⁴. According to Sunil Kumar et al.2013, \(\beta \) sitosterol, stigmasterol and palmitate stigmasteryl exhibited significant antidiabetic activity in streptozotocin-nicotinamide induced diabetic dose of 10mg/kg. The levels of glucose were found to be decreased upon treating with the extract due to which glycemic control was achieved **Dillenia indica f. elongata (Miq.) Miq. possessed good antidiabetic property as well as improved body weight, liver profile, renal profile and total lipid levels⁴⁰.

6.3 Antimicrobial and Antibacterial activity

According to Haque *et al.*2008, the dried plant extracts were dissolved in 10% DMSO (Dimethyl Sulphoxide) and sterilised by filteration. Standard solutions of Amoxicillin, Kanamcyin (antibacterial agents) and Ketoconozole (antifungal) were prepared. Agar diffusion method was used to perform antimicrobial tests^{79,80}. 100μl of suspension possessing 108 CFU/ml of bacteria, 106 CFU/ml of yeast and 104 spore/ml spread on nutrient agar (NA), subourand dextrose agar (SDA) was used for amendments by Olurinola^{81,82}. The temperature conditions were set at 25°C for 48h. Moreover, the extract that exhibited antimicrobial activity was tested to determine Minimum Inhibitory concentration⁸³.

Acetone and alcoholic extracts of seeds of *Dillenia* indica f. elongata (Miq.) Miq. had shown good antimicrobial activity while chloroform extract was found to have mild activity. The methanolic extract along with some organic soluble fractions of the bark of *Dillenia* indica f. elongata (Miq.) Miq. were tested against four gram-positive, Seven gram-negative bacteria and against three pathogenic fungi. n-Hexane and dichloromethane fractions showed remarkable activities against all the tested bacteria however, n-hexane fraction showed highest activity against

Shigella dysenteriae ^{60,67,84}. Adding on, the antibacterial and antifungal activity of the crude extracts as well as for the isolated pure compounds has been checked using fifteen bacterial strains, which included seven gram-positive and eight gram-negative organisms, and nine fungi. Studies on the antifungal activities revealed that ethyl acetate extract of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* and Grisofulvin have exhibited promising zone of inhibition against the fungi except Candida albicansand Candida krusei^{85,86}.

6.4 Anticancer activity

Cancer, one of the most vulnerable diseases is a leading cause of death in the developed countries and the second leading cause of death in the developing countries ^{87, 88, 89}.

Betulinic acid exhibited an inhibitory activity on the growth of K562 tumor cell line with IC50 value of 6.25 μg/ml and also induced 35% apoptosis at 25 μg/ml. Betulinic acid results in cancer cell death by induction of apoptosis involving caspases. Moreover it was found that betulinic acid was well tolerated in mice up to 500 mg/kg with no toxic effects ⁹⁰⁻⁹³. The fruits of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* using different human cancer cell lines U937, HL60 and K562 have been taken to determine anticancer activity which was performed by Vedasiromoni *et al.*, 2010 ⁸⁸.

6.5 Cytotoxic activity

DMSO (Dimethyl Sulphoxide) solutions of the plant Dillenia indica f. elongata (Miq.) Miq. extractives were layered on Artemia salina for a day in vivo assay. In DMSO (Dimethyl Sulphoxide) 4mg of each of the extracts were dissolved. Solutions of different concentrations were taken, from which lethal concentration LC50 was concluded He crude methanolic extract and dichloromethane soluble fractions were found to be highly toxic to brine shrimp nauplii, with LC of 8.92 μ g/ml and 2.38 μ g/ml, respectively. The crude methanol extract and its n-hexane, Carbon tetrachloride and chloroform soluble fractions were screened against 13 test bacteria and remarkable cytotoxic activity was exhibited by Dillenia indica f. elongata (Miq.) Miq. 58.

6.6 Antioxidant activity

The free radical scavenging capacity of the extracts was accomplished using DPPH i.e. 1-diphenyl-2-picrylhydrazyl on stable radical 1⁹⁵⁻⁹⁷. In this, extract was dissolved in methanol and mixed with serial dilutions (1 to 500 µg) of *Dillenia indica* f. *elongata* (Miq.) Miq. and after 10 min of time period the absorbance was read at 515 nm with the help of spectrophotometer. It is found that the methanol extract of *Dillenia indica* f. *elongata* (Miq.) Miq. fruit contains substantial quantity of phenolics and due this extent of phenolics present in the extract, it is responsible for its marked antioxidant activity ⁹⁸⁻¹⁰⁰.

6.7 Antiproliferation activity

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Anti-proliferation activities of around 12 Thai Lanna medicinal plants were studied on cancer cell lines by

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SRB assay including *Dillenia indica* f. *elongata* (*Miq.*) *Miq.*, which was more effective than doxorubicin compared to other medicinal plants studied by Saowakhon et al, 2008. Anticancer potential of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* can be further explored for treatment. Leaf preparations are recommended in treating breast cancer ^{33,101}.

6.8 Antidiarrheal activity

The methanol extract of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* leaves using castor oil induced diarrhoea model were studied, from which it was concluded, that the inhibition of the diarrhoea and prolongation of onset might be due to inhibition of inflammatory mediator release and phytoconstituents such as flavanoids and tannins might be responsible for the activity ¹⁰²⁻¹⁰⁴.

6.9 Hair waving activity

With reference to the recent research work done by Jyoti Prasad Saika *et al*, 2013 the waste hair collected were directed to purified sap for the time period of 12h and the final results were achieved by using Fourier Transfer Infrared Spectroscopy (FTIS). The experiment was accomplished at room temperature 25°C under dark conditions and good hair waving activity was noticed ¹⁰⁵.

6.10 Wound healing activity

A glycolic extract of *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* prepared from the mature fruits of the plant which showed significant wound healing activity alone or in combination with microcurrent stimulation to skin wounds surgically induced on the back of Wistar rats. Moreover, due to presence of flavanoids *Dillenia indica* f. *elongata* (*Miq.*) *Miq.* works well in healing of wounds as determined by Janick Paull et al, 2008 31,106-108.

6.11 Antiimplantation activity

Biological screening of 50% ethanolic extract of stem bark of *Dillenia indica* f. *elongata* (Miq.) Miq.

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revealed antiimplantation activity in rats. CNS effects were not favoured. LD_{50} of the extract was >1000mg/kg i.p. in mice and significant results for antiimplantation activity was achieved 109 .

6.12 Anti-HIV activity

Dillenia indica f. *elongata (Miq.) Miq.* also possess anti-HIV activity due to presence of betulinic acid as remarked by Theo et al, 2009 ¹¹⁰.

CONCLUSION

In this review, a brief account on the taxonomy and morphology of the plant was studied. Phytochemical profile and its main chemical constituents were also taken into consideration. It was found that the plant has its roots in traditional and as well as Ayurveda system of medicine. There is no reported toxicity available of this plant according to the literature surveyed making the plant further more beneficial in curing various ailments. Dillenia indica f. elongata (Miq.) Miq. can be a natural source pentacyclic triterpenoids (Betulin, betulinic acid etc.) that are abundantly found in the plant and are further responsible for vast pharmacological actions. The present review gives a detailed description of phytochemical profile, traditional uses, pharmaceutical formulations and pharmacological properties of the plant. Understanding the pharmaceutical enrichment of the plant, this concise study will provide a valuable help to the scientists to further screen the plant, so that the plant may find its way in pharmaceutical industries in a more constructive manner.

Conflict of interest

We declare that we have no conflict of interests.

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