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***Dillenia Indica* Linn.-A Multipurpose Medicinal Plant of Assam**

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ABSTRACT

Dillenia indica is a well-known medicinal plant which thrives in varied agro-climates. It is native to Northeast India, but is widely distributed throughout the Himalayan range. Various studies on the plant reveals the presence of diverse biologically active chemical compounds associated with curing different ailments such as diabetes, inflammations, diarrhea, cancer, ulcer, microbial diseases, hematic disease, hepatic problems, dental problems, cardiovascular problems, hyperlipidmia and others. Most of the biological activities are contributed by the wide varieties of compounds present in fruit and leaves of *D.indica*. Various scientific investigations have proved that Proanthocyanidins and 3,5,7-Trihydroxy-2-(4'-hydroxybenzyl)-chroman-4-one present in the fruit of *D.indica* are responsible for minimizing the severity of diabetes and diabetic nephropathy. Betulinic acid isolated from *D.indica* has anticancer property. In addition to the therapeutic properties, the mucilage of *D.indica* is used as an important ingredient of various pharmaceutical formulations. Various factors affecting the chemical composition of *D.indica* such as temperature, annual season rainfall, pH, harvest date, climate, land and cultivation methods are discussed in this review. In view of the medicinal and pharmaceutical importance of the plant, it is quite worthy to review the active constituents and clinical effectiveness of *D.indica*.

Keywords: *Dillenia indica*, Biological activity, Chemical constituents, Medicinal plant

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INTRODUCTION

Traditional medicines are the integral part of human civilization to cure various ailments. According to the World Health Organization (WHO), up to 80% of the people of the world are dependent on herbs as traditional remedy to cure various ailments since the beginning of civilization. The bioactive components in fruits and functional food have been used as the therapeutic complement in the treatment of chronic disease [1]. Herbal traditional medicines have gained considerable momentum worldwide during the past decade and play a paramount role in health-care programs especially in developing countries [2]. *Dillenia indica* L. belonging to family *Dilleniaceae* is an evergreen tree found in the moist and evergreen forests of the sub-Himalayan tract, from Kumaon and Garhwal eastwards to Assam, Bengal and Orissa. It is a spreading tree and has large white fragrant flowers with five petals, toothed margin and pointed leaves, and large globose fruits with small brown seeds [3]. Flowering occurs in the plant during May-August and fruits get ripen during September-February. The fruits of the plant are edible. Traditionally the juices of leaves and bark are mixed and given orally for the treatment of cancer and diarrhea in the tribal areas of Mizoram, India [4]. The leaves and bark are reported to have laxative effect and can also be used as an astringent [5]. Traditionally, the fruits, leaves, and barks of *D.indica* are used to treat the diseases such as fever, constipation, diarrhea and stomach pain. [6]. The decoction of fruit has been use to treat hair loss, diabetes and as an immunity enhancer. Juice of *D.indica* mixed with sugar and water can function as a cough syrup with cooling effect. The entire plant is used for medicinal purposes in Asia. Fruits are used in the cuisine [7]. *D.indica* in oral or topical preparations is use to treat abdominal and joint pain, cough, diarrhea, fever, tumours, diabetes, toning up the nervous system and removing fatigue [6-10]. Most traditional uses of *D.indica* in folk medicine are associated with anti-inflammatory purposes [10]. In Brazil the fruits are used in preparations for skin applications to treat inflammation [11, 12]. The leaves and fruits of *D.indica* have been traditionally used to cure diseases like fever, constipation, dysentery, stomachache [13]. Leaves of *D.indica* are used as an astringent. Various dosage form can be made from the leaves like paste, poultice, decoction, powder which can be used in bone fracture, bleeding piles, skin diseases, body ache and breast cancer.[14,15].The fruit is said to possess tonic laxative properties and used for relieving abdominal pain. The bark and leaves are use as astringent [16, 17].

MATERIALS AND METHOD

To collect the data which support this review we performed an extensive literature survey. A systematic review using Science direct, Scopus, Pubmed, Google and MEDLINE database is performed. All English-language articles published between 2000 and 2018 were searched

using the terms “*Dillenia indica*”. Details regarding the isolation of some active compounds, different plant extracts and their effects on different pharmacological models are captured in this database. Evidence for the support of an extract was assessed from multiple studies.

Anatomy and morphology

It is an evergreen shrub with thick bark and branches which is 6-15m tall. The leaves are generally 15-36cm long, with a conspicuously corrugated surface with impressed veins. Leaves are broadly elliptic– oblong-lanceolate, acuminate, regularly serrate and secondary veins 30-40 paired ending in the serratures, petiole channeled, sheathing and densely tomentose at the base, 2-4cm. The flowers have white petals which is oblong in shape with numerous yellow stamens. Flowers are bisexual, terminal, solitary, pedicel, smooth and clavate. Sepals are orbicular and concave. Fruits are mainly edible which greenish yellow in colour are. The fruit is an aggregation of 15 carpels, each carpel containing five seeds embedded in an edible fibrous pulp. Seeds are numerous, thickened, small, hairy along the edges, reniform. It is an indehiscent fruit, covered by a permanent calyx. The trunk of the shrub is 30-80 feet in height and 6-feet in circumference with dense rounded crown [18, 19]

Taxonomical classification

Dillenia indica L. belongs to the family Dilleniaceae. Its taxonomical classification reported in literature [17] is as given below

Kingdom: Plantae

Division: Magnoliophyta

Subdivision: Angiospermae

Class: Magnoliopsida

Subclass: Dilleniidae

Order: Dilleniales

Family: Dilleniaceae

Genus: *Dillenia*

Species: *indica* Linnaeus

Geographical location and Cultivation factors

D.indica L. occurs in the moist and evergreen forests of the sub Himalayan tract, from Kumaon and Garhwal eastwards to Assam and Bengal, and southwards to central and southern India. It is commonly seen along banks of forest ostreams. The recorded temperatures and rainfall in its natural habitat are 35-65 °F (minimum) to 95-105 °F (maximum) and rainfall of 200-500 cm. The tree is also found in Bangladesh, Nepal, Sri Lanka, Malaysia, Myanmar and Thailand [20]. *D.indica* grows in temperatures within 30-40°C. It prefers a mean annual rainfall in the range 3,000–4,000mm. The plant grows best in a rich, slightly acid soil and prefers a pH in the range 5.5-7. It prefers a well-drained sandy loam and sunny weather [21].

Chemical Constituents

The ethanol extract of stem bark afforded two flavonoids viz., kaempferol glucoside and quercetin derivative as well as a triterpenoids as reported by Srivastava et al 1981[22]. Parvin et al. 2009 reported methanolic extract of stem after partitioning with n-hexane yielded four compounds lupeol, betunaldehyde, betulinic acid and stigmasterol using column chromatographic separation [23]. Leaves of *D. indica* found to contain flavonoids, triterpenoids, steroids, tannins; its petroleum ether extract afforded cycloartenone, n-hentriacontanol, sitosterol, betulin; chloroform extract contains betulinic acid [24]. Methanolic extract of leaves after fractionation with n-hexane and chloroform also yielded compounds like betulinic acid, β -sitosterol, stigmasterol as well as dillenetin [25]. Further 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 [26]. Betulinic acid was isolated and quantified betulinic acid using validated HPLC method from different fractions like methanol, ethyl acetate, n-butanol and water by Kumar *et al.* 2010, amongst which highest concentration was found in ethyl acetate fraction (97.9977.61 mg/g of fraction) [16]. Seven antidiabetic compounds were isolated from the leaves of *D.indica* i.e. betulinic acid, n-heptacosan-7-one, n-nonatriacontan-18-one, quercetin, β sitosterol, stigmasterol, and stigmasteryl palmitate [27]. Pentacyclic triterpene lactone is isolated from the plant [28]. Pavanasivam *et al.* 1975 reported the presence of 3,4, 5,7-tetrahydroxy-3 -methoxyflavanone and 3,5,7-trihydroxy, 4 -dimethoxy-flavone from *D.indica* L [29]. 3, 5,7-Trihydroxy-2-(4'-hydroxy-benzyl)-chroman-4-one was obtained from *D.indica* L. leaves [30].

Biological activity

Anti diabetic effect

Kaur *et al.* 2018 reported that *D.indica* produced significant attenuation in the glycemic status, lipid profile and level of antioxidant enzymes proving efficacy in diabetic nephropathy [31]. *D.indica* showed significant decrease in the glycemic condition, renal parameter, lipid profile and antioxidant enzymes level proving its efficacy in diabetic nephropathy. As reported by Kumar *et al.* 2011. *D.indica* ethyl acetate fraction shows prominent antidiabetic effect in experimental type-1 and type-2 diabetes models in rats [32]. Daily oral administration of *D.indica* methanol extract (250 and 500 mg/kg body weight) and glibenclamide (10 mg/kg) showed beneficial effects on blood glucose level ($P < 0.001$) as well as improving kidney, liver functions and hyperlipidaemia due to diabetes as reported by Kumar et al. 2011 [33]. Kaur *et al.* 2015 indicated that alcoholic extract of *D. indica* and chromane isolated from the plant possessed antioxidant and antidiabetic activity and could be a therapeutic agent for regulating several pharmacological targets for management of diabetes [30].

Antioxidant Activities

Proanthocyanidins isolated and purified from fruits of *D. indica* showed strong antioxidant activity, which was evidenced by the high oxygen radical scavenging capacity at $1.06 \times 10^4 \mu\text{mol}$ and ferric reducing antioxidant power of $2320 \mu\text{mol}$. [34]. Md. Abdille *et al.* 2005 reported the antioxidant activity of *D.indica* using DPPH method. The total phenolic contents of the fruits extract was found highest in methanol extract (34.1%) as compared to water extract (1.4%) [35]. Deepa *et al.* 2009 reported that *D.indica* have antioxidant activity. Folin-Ciocalteu method was used to determine the total phenolic content and phosphomolybdenum method for the assay of antioxidant activity, radical scavenging activity using α -diphenyl- β -picrylhydrazyl method, hydroxyl radical (OH^\cdot) scavenging activity by deoxyribose method, and superoxide anion ($\text{O}_2^{\cdot-}$) scavenging activity by phenazine methosulphate/NADH-nitroblue tetrazolium system. The extract is found to have equivalent total phenolic content of 54% as tannic acid. The total antioxidant capacity of the extract was found to be 3.12 mmol/g as equivalent to ascorbic acid at 50 ppm concentration. The radical scavenging activity of butylated hydroxyanisole and extract showed 90.9% and 91.0%, respectively at 25 ppm concentration. The OH scavenging activity of the extract was found to be 53.9% at 100 ppm concentration. At a concentration of 50 μg , the $\text{O}_2^{\cdot-}$ scavenging activity of the extract was 31.7% as compared to 47.7% by gallic acid [36].

Anti Inflammatory Activity

The ethyl acetate extracts of *D. indica* (100 and 300 mg/kg) possessed good central as well as peripheral analgesic activity as compared with pentazocine and indomethacin (10 mg/kg) respectively. The extracts showed significant ($P < 0.01$) activity in carrageenan- and formalin-induced chronic inflammation models by using indomethacin (8 mg/kg) and diclofenac (13.5 mg/kg) as standard drugs respectively [34]. The healing effect of *D.indica* fruit extracts was studied by Kwiecinski *et al.* 2017 on induced psoriasis-like wounds in Wistar rats. The ethanol extract shows lipid peroxidation *in vitro* at 0.02 $\mu\text{g/mL}$, accelerating healing at 50 mg/mL. Complete healing in mice treated with ethanol extract occurred 16 days after wound induction. The result was comparable with standard drug clobetasol [37].

Anti-diarrheal activity

Islam *et al.* 2017 studied the antidiarrheal potential of the methanolic extract of *D. indica* bark. At the doses of 100 and 200 mg/kg body weight, methanolic extract significantly reduced the frequency and severity of diarrhea in test animals throughout the study period and also showed a significant ($p < 0.001$; $p < 0.05$) reduction in the gastrointestinal motility in charcoal meal test as well as PGE_2 -induced intra fluid accumulation [38]. The anti-diarrheal activity of aqueous and methanolic extract was evaluated by Yeshwante *et al.* 2009 using Castor oil induced diarrhea model and different parameters such as onset of diarrhea and total number of feces

for the period of 4 hours were observed. The results of test group were compared with Vehicle control group using one way ANOVA followed by Dunnett's Test. The results revealed that both extracts at doses of 200 and 400mg/kg P.O. showed significant ($P<0.01$) prolongation of onset of diarrhea and significant ($P<0.01$) reduction in total number of feces after 2nd hour of treatment while dose of 100mg does not show any activity [39].

Hepatoprotective Activity

Reddy *et al.* 2010 reported the hepatoprotective activity of *D. indica* against CCl_4 induced toxicity and its safety evaluation in Wistar albino rats was done. The different groups of animals were administered with 30% CCl_4 (1 ml kg^{-1} wt) in olive oil intraperitoneally. The seed extract at the dose of 250 and 500 mg kg^{-1} wt were administered to the CCl_4 treated rats. The seed extract produced significant ($p<0.01$) hepatoprotective activity by decreasing the activity of serum enzymes bilirubin, creatinine, urea and lipid peroxidation [40].

Hematoprotective activity

D. indica exhibit *in vitro* and *in vivo* hematoprotective activity when tested as reported by Shukla *et al.* 2015 [41].

Anti-Cancer Activity

Kumar *et al.* isolated betulinic acid from the methanolic extract of *D. indica* L. fruits. The methanolic extract showed significant anti-leukemic activity in human leukemic cell lines U937, HL60 and K562. The isolated betulinic acid showed IC_{50} of values at 13.73, 12.84, 15.27 mg/ml in U937, HL60 and K562 cell lines, respectively [16]. Chowdhury *et al.* 2013 studied cytotoxic activity of the plant using brine shrimp lethality bioassay, where vincristine sulphate was used as a positive control. It was noticed that the methanolic extract and its fractions possess potential cytotoxic principles (with LC_{50} value 17.68 μ g/ml, 17.68 μ g/ml, 15.80 μ g/ml and LC_{90} value 486.61, 287.66, 148.82 μ g/ml respectively) compared with positive control vincristine sulphate (LC_{50} 0.631 μ g/ml and LC_{90} value 13.51 μ g/ml)[42]. Methanolic extract of *D. indica* bark and its n-hexane and ethyl acetate fractions possess potent cytotoxic principles with LC_{50} value 17.68 μ g/ml, 17.68 μ g/ml, 15.80 μ g/ml and LC_{90} value 486.61, 287.66, 148.82 μ g/ml, respectively, compared with positive control vincristine sulphate (LC_{50} 0.631 mg/ml and LC_{90} value 13.51 mg/ml)[16]. In human leukemic cell lines U937, HL60 and K562, the methanolic extract showed significant anti-leukemic activity. Fractionation of the methanolic extract, on the basis of polarity, in which the ethyl acetate fraction showed the highest anti-leukemic activity. From the ethyl acetate fraction a major compound, betulinic acid was isolated, identified and characterized. Betulinic acid could explain the anti-leukemic activity of the methanolic extract and the ethyl acetate fraction [43]. In another study, by Gandhi and Mehta showed, *D. indica* is used as a traditional medicine in cardiovascular diseases and in the treatment of cancer. RP-HPLC method and MTT assay was performed on three

different cell lines HCT-15, DU145 and A-375 which explains the role of betulinic acid in anticancer activity [44]. Betulinic acid derived from birch tree *Betulla* species has shown anti-fibrotic effect by inhibiting NF- κ B signaling pathway; it provides strong evidence towards the molecular mechanism of chemoprevention by *D.indica* due to the presence of betulinic acid by plummeting NF- κ B activation [45].

Antimicrobial Activity

The extract of *D.indica* bark was tested against four gram positive and seven gram negative and three pathogenic fungi. N-hexane and Dichloromethane fraction showed remarkable activities against all organisms whereas methanolic crude extract showed highest activity against fungus [46]. Jaiswal *et al.* 2013 studied antibacterial activities of the fruit and bark extracts of *D.indica*. The effect of the extracts like inhibitory concentrations on cell wall, nucleic acid leakage and pathogenic genes of the bacteria was studied. The fruit and bark extracts obtained by 70% aqueous acetone extraction showed minimum inhibitory concentration (using agar dilution method) against different bacteria in the range of 2000–10,000 and 1250–5000 mg, respectively, indicating higher antibacterial activity for bark extract [47].

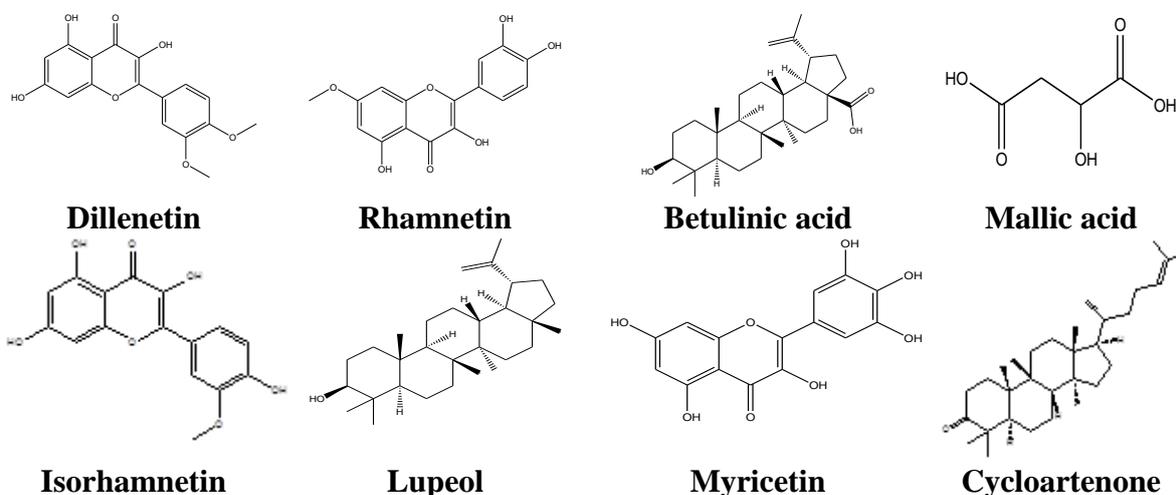
Tyrosinase inhibitory activity

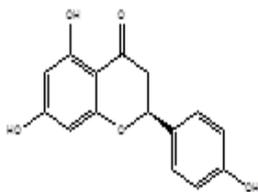
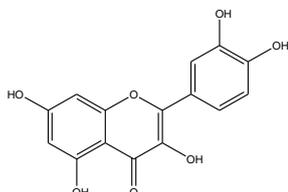
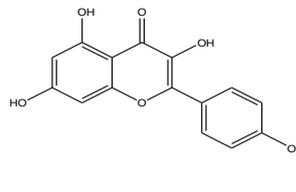
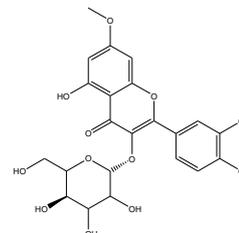
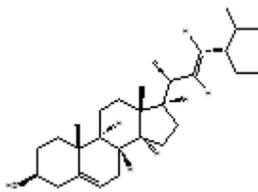
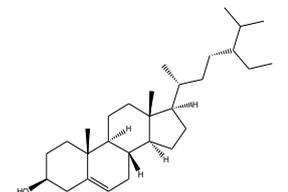
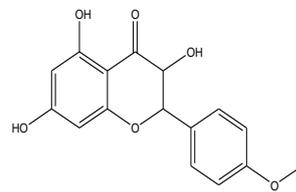
Betulinic acid (BA) isolated from *D.indica* has tyrosinase inhibitory mechanism. Half maximal inhibitory concentration (IC₅₀) of betulinic acid was calculated as 13.93 μ M and 25.66 μ M for diphenolase and monophenolase [48].

Anthelmintic activity

Methanolic extract of barks (25 mg / mL) caused paralysis of the worms at 136 minutes and death at 176.0 minutes while Albendazole (positive control) paralyzed and killed the worms at 17.67 minutes and 48 minutes, respectively [42].

Figure: Structure of various chemical constituents.



**Naringenin****Quercetin****Kaempferol****Rhamnetin-3-glucoside****β-sitosterol****dihydrokaempferide****Stigmasterol**

MISCELLANEOUS

Controlled release metformin hydrochloride microspheres are prepared from mucilage obtained from *D.indica* as reported by Sharma *et al.* 2010 [49]. The microspheres were prepared by spray drying method under different formulation parameters. The prepared microspheres were studied for particle size, drug excipient compatibility, particle shape and surface morphologies, drug entrapment efficiency, mucoadhesivity, and in vitro drug release properties. The prepared microspheres exhibited mucoadhesive properties and demonstrated controlled release of metformin hydrochloride. The microspheres remained adhered up to 3.5 hrs. The study reveals that mucilage of *D.indica* can be used for formulation of controlled release microspheres. The mucilage of *D.indica* was studied by using various analytical techniques as reported by Bal *et al.* 2012 and concluded that mucilage obtained from *D.indica* can be used as a natural mucoadhesive polymer for formulating various drug delivery systems [50].

Table 1: Extract and compounds in *D. indica* with their biological activities

Compounds /Plant extract	Reported biological activities	References
Alcohol and hydro-alcohol extract	Diabetic nephropathy	[31]
Ethyl acetate extract	Antidiabetic	[32]
Methanol extract	Antidiabetic	[33]
Chromane	Antidiabetic	[30]
Proanthocyanidins	Antioxidant	[34]
Methanol extract	Antioxidant	[35]
Aqueous acetone	Antioxidant	[36]
Ethyl acetate extract	Analgesic	[34]
Ethyl acetate extract	Wound Healing	[37]
Methanolic extract	Antidiarrheal	[38]
Aqueous and Methanolic extract	Antidiarrheal	[39]
Hexane extract	Hepatoprotective Activity	[40]
Ethanol extract	Hematoprotective activity	[41]
Betulinic acid	Anticancer activity	[16]
Methanolic extract	Anticancer activity	[42]
Methanolic extract	Anticancer activity	[16]

N-hexane and Dichloromethane extract	Antimicrobial Activity	[46]
Acetone extract	Antimicrobial Activity	[47]
Betulinic acid	Tyrosinase inhibitory activity	[48]
Methanolic extract	Anthelmintic activity	[42]

CONCLUSION

Natural products or their derivatives play a role in disease cure and prevention which is increasing worldwide due to lesser side effect properties. The plant *D.indica* has been use as therapeutic agent and has many traditional values. The people of Assam consumed the fruit of *D.indica* in traditional dishes including meat and fish curries which provides health benefit as the plant is rich in many bioactive constituents. Presence of various biologically active compounds makes *D.indica* as a curing agent for various diseases such as inflammation, cancer, liver diseases, wounds, microbial diseases, skin problems, cardio vascular disorders, constipation, ulcer, free radical related diseases, diabetes, hyperlipidemia etc. Due to its easy availability and fewer side effects *D.indica* the study is going on the plant to develop various formulations. This medicinal plant can be further utilized plant for development of phytopharmaceutical products by setting up food processing industries which will uplift the economic condition of the local people of the region. However detailed studies are required to analyze the therapeutic potentiality and mechanism of action of *D.indica* for treating diseases.

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CONFLICT OF INTERESTS

The authors report no conflict of interest

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