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A review update on *Dillenia indica*, its morphology, phytochemistry and pharmacological activity with reference to its anticancer activity

Abstract

Dillenia indica, commonly known as elephant apple and locally known as *ou tenga,* is an evergreen tree grows in the moist forest of sub-Himalayan region to Assam. It is an important medicinal plant and has been prevalently used in Indian traditional and ayurvedic medicine for curing plethora of ailments such as digestive, respiratory and central nervous system disorders. Traditionally different parts of *Dillenia indica* are used for the relief of indigestion, asthma, influenza, dysentery, jaundice, promeho, weakness and rheumatic pain, but recent studies reported the extractives showed significant cytotoxic, CNS depressant and free radical scavenging activity. A review on this plant was published in the year 2011.[1] Hence the present review encompasses mainly the research works reported post 2011. Many new phytocompounds and pharmacological activities are reported already. Major chemical compounds betulin (pentacyclic triterpenoid) and betulinic acid show wide spectrum of pharmacological activities like anti-HIV, anti-inflammatory, anti-cancer, anti-malarial etc. Furthermore, *Dillenia indica* possesses analgesic, anti-diabetic, anti-microbial, anti-bacterial, anti-diabetic, anti-oxidant, anti-proliferation, anti-diarrhoeal, anti-implantation, cytotoxic, wound healing and hair waving activity. Numerous research works have proven its uses beyond the ethno medicinal ones, in experimental studies as well. There are many *Dillenia* species but only a few are proven scientifically. *Dillenia indica* is a well-known medicinal plant of this genus for their therapeutic potential in pre-clinical studies. The present review approaches for phytochemical investigations, pharmacological activities and therapeutic importance of the plant.

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Introduction

The use of medicinal plants is always useful to the mankind from prehistoric times. Plants are considered to be the backbone of life on Earth and vital resource for humans as well as animals. Now a day's assurance of the safety, quality, and efficacy of the authenticated medicinal plants and herbal products that are used by the people has become a key issue in industrialized and developing countries. Plants produce several chemical compounds that have biological functions. Therapeutic properties of medicinal plants are conditioned by the presence of active substances such as glycosides, vitamins, flavonoids, alkaloids, tannins and coumarin compounds which are biologically active with the causative agents of the diseases in our body.

Dillenia indica (Figure 1 & Figure 2) is an evergreen large shrub or small to medium-sized, an important medicinal plant found in Assam North-east India. The plant has been blessed with numerous medicinal properties with edible constituents as well. The fruit is the main yield of the plant. The plant grows abundantly in Assam. But due to lack of knowledge and not knowing its medicinal values, most of the fruits of this plant and other parts are wasted. The leaf, bark and fruit of the plant are used in the indigenous system of medicine. It has many medicinal properties like relieving pain and regulating the body heat.[2] It is also used as cooling beverage in the treatment of fever.[3] It tones up the nervous system and removes fatigue. Traditionally they are used as laxative and carminative. It also helps in relieving fatulence.[4] Fruit juice is also used as cardio tonic. Barks and leaves of the plant are used as laxative and astringent. Due to its various biological activities including anti-diabetic and anticancer properties the plant is gaining importance as a valuable medicinal plant.[5,6] In this review emphasise is given on detailed exploration on the traditional claims, pharmacological activity and phytochemical compounds of *Dillenia indica*.

Figure 1 A young *Dillenia indica*.

Figure 2 Fruit of ***Dillenia indica.***

Synonyms of Dillenia indica (Figure 3)

Figure 3 Cross sectional view of the fruit of ***Dillenia indica.***

Dillenia elliptica Thunb, *Dillenia elongate* Miq, *Dillenia speciosa* Thunb. **Figure 4 & Figure 5**

Figure 4 Global distribution of ***Dillenia indica*** (blue dots indicate the availability of the species).

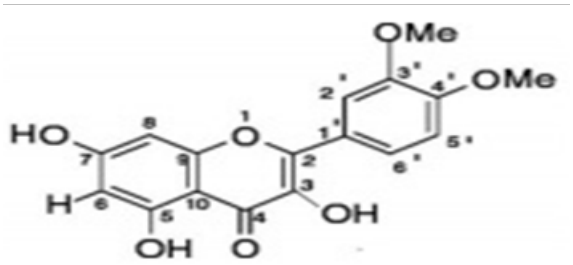

Figure 5 Structure of Dillenetin (Quercetin-3',4'-dimethyl ether).

Common names

Assamese: *Ou-tenga*, Pascol-solta, Panchkol.

Eng: Elephant apple

English: Indian Catmon, Elephant Apple

Hindi: Chalta, Girnar, Karmabel

Indain Languages: Uvaa, Uvaa thekku, Chalita, Ugaa kai, Akku, Mota- Karmal, Punna, Sylita.

Kannada: Bettadakanigala, Kaadu kanigala

Karbi: Pumplung

Khasi: Dieng-soh-karbam

Malayalam: Vazchpunna, Pinnay, Punna

Marathi: Mota karmal, karambel

Miri: Sompa

Mishing: Sampa

Naga: Dhong-phang

Nepali: Thulo Tatri, Ram Phal, Paanca Phal, Panca Kule

Sanskrit: Avartaki, Bhavyam

Tamil: Ugakkay, Kattaral

Bodo: Thaigir

Others: Syalita, Pedakalinga, Ugaa kai, Large-flowered Delinia, Uvaa thekku, Uva Oitenga (Ass.), Betta Kanigal, Ma-tad, Mota-Karmal, Elephant apple (Eng.), Chalita, Chalta, Aasam, Karambel, Uvaa, Punna, Indian Catmon, Bharija, Akku, Dillenia, Hondapara Tree, Elephant Apple, Gimar Or Hondapara Tree

Taxonomical classification of *Dillenia indica*

Kingdom: Plantae

Division: Magnoliophyta

Subdivision: Angiospermae

Class: Magnoliopsida

Subclass: Dilleniidae

Order: Dilleniales

Family: Dilleniaceae

Genus: *Dillenia*

Species: *indica* Linnaeus

Botanical description

It is an evergreen large shrub which grows 6-15m tall, with spreading branches and thick bark.

Leaves: 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 channelled, sheathing and densely tomentose at the base, 2-4cm.

Flowers: The flowers are large, 15-20cm in diameter, with white petals and numerous yellow stamens. Flowers are terminal, solitary, drooping, bisexual, pedicel 7-8cm, clavate, smooth. Sepals are 4cm long, 2cm broad, orbicular and concave.

Petals: Petals are oblong

Fruit: Fruits are large greenish yellow, have many seeds and are edible. The fruit is 5–12cm in diameter aggregate of 15 carpels, each carpel containing five seeds embedded in an edible but fibrous pulp. The fruit is indehiscent, permanently covered calyx, mucilaginous, 5-l2cm. across.

Seeds: Seeds are numerous, thickened, small, hairy along the edges, reniform.[7,8]

Trunk: Trunk is 30-80 feet in height and 6 feet in girth with dense rounded crown.

Geographical distribution

Dillenia indica grows 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.[9] It is also found in Malaysia, Myanmar, Thailand, Bangladesh, Nepal and Sri Lanka. It is found in tropical and subtropical evergreen or rain forests altitude up to 2500ft.

Cultivation

Dillenia indica grows in areas where annual daytime temperatures are within 30-40°C, but can tolerate 7- 47°C. It prefers a mean annual rainfall in the range 3,000–4,000mm but tolerates 2000–5,500mm. Grows best in a rich, slightly acid soil.[10] Prefers a pH in the range 5.5-7, tolerating–8. The seeds sometimes germinate in the fruit, which is left behind on the bank of a river, often partly filled up with mud which gives a favourable substratum for the germination.[11] It prefers a well-drained sandy loam and sunny weather.[12,13]

Natural history of *Dillenia indica*

Life cycle: Flowering is seen during June-August and fruiting during December-April.

Reproduction: Reproduction takes place in seeds. The flowers are complete, bisexual i.e, with the functional male (androecium) and female (gynoecium) parts, including stamens, ovary and carpels. Pollination is done by insects i.e., entomophilous.

Dispersal: Seeds are dispersed by barochory i.e., gravitational dispersal, zoochory i.e., dispersal by animals, anthropochory i.e., dispersal by humans.

Life expectancy: Perennial.

Growth: Perennial

Ecology

Fruits of Dillenia indica are large and hard which are accessible only to the mega herbivores. Seeds from both old and soft fruits are able to germinate well enabling the persistence of the tree to be independent of the survival of its major mega herbivore disperser.[14]

Culture

The culture of the seed is generally complete in full sun/light shade, moist soil, pH 5.5-7.0.

Propagation

Propagation is done by seeds and cuttings. Seeds are usually collected during October to December. It can be propagated from fresh seeds and cutting can be used for vegetative propagation. Trees are mostly planted as specimen plants. From the seeds the new plants are raised. Compared to traditional propagation in vitro propagation has many credible benefits over the traditional one. Micro propagation may also be utilized in supreme research in production of virus-free planting material.

Taste of the fruit (elephant apple) and its nutritional value

The gelatinous pulp surrounding the sepals is mildly sweet, but acidic inside. It is also known for its crunchy outer petals. The taste of the petals resembles unripe apples. At worst the flavour is mealy, astringent and resinous. Table 1

Table 1 Nutritional value of elephant apple per 100gm of edible flesh.

Sl no.	Content	Percent	Sl no.	Content	Amount
1	Protein	0.8	5	Calcium	16mg
2	Fat	0.20-2.50	6	Phosphorus	26mg
3	Fiber	2.10-2.50	7	Ascorbic acid	04mg
4	Ash	3.54	8	Total calorie	59kcal

Dillenia indica in ancient relics

From pre-historic Vedic era, medicinal treatise of Ayurveda has immense value to humankind. In the Vedas and other ancient relics, the medicinal properties of Bhavya (*Dillenia indica*) are depicted. Table 2

Table 2 Ethno-medicinal uses of *Dillenia indica* L.

Tribe/ Ethnic group	Part used	Etbnomedicinal uses
Bodos	Fruit	Fruit is eaten to cure stomach related disorders.
Manipuri	Fruit	Fruit is used for curing hair fall and dandruff.
Wlikir	Fruit	Fruits are consumed raw to combat weakness.
Rajbongshis	Mucilage	Applied on wounds and burns.
Tai Ahom	Fruit	A decoction of fruit is used as anti-dandruff and applied on head to check frequent hair fail. Fruit is also eaten to combat weakness.
Tai Singfou	Fruit	Decoction of fruit is used to remove dandruff.
Santhal	Leaf	A small piece of Leaf is consumed in the treatment of dysentery.
	Root	Root is used as prophylactic for cholera; it is also one of the ingredients of a paste used in the treatment of burning sensation in the chest.
	Stem bark	It is used as chronic progedient sores and carbuncle and as a prophylactic for cholera.
	Mucilage	Applied on wound.

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Yajur veda: It is cited as an important plant;

Upavarhana samhita: The plant is aphrodisiac and promotes virility.

Charaka samhita: The fruit is sweet, acidic, astringent, removes bile, phlegm, fetid and flatulence.

Sushruta samhita: The fruit cardiotonic, tasteful, astringent, acidic, removes bile, phlegm, fetid and flatulence.

Rajanighantu: The green fruit is acidic, pungent, hot, removes wind, phlegm, but the ripe fruit is sweet, sour, appetising and beneficial in colic associated with mucous.

Matsya purana: Decoction of this plant can be used as universal antidote for poison.

Agni purana: Spraying water, containing stem extract, in and around the wound by spider bite helps in removing the poison.

Asya shodhana: Cleanses mouth.

Dillenia indica in ayurveda and sidha

Bark, leaves, crushed fruits and juice are drunk for cough, cold, fever, diarrhoea and stomach disease. Dry bark with the seeds of *Sesamum orientale* are made into a paste for applying on blistering boils. Barks and leaves are used as haemostatic. The leaf and bark of the tree are used as both astringent and laxative. The bruised bark is used as a cataplasm in arthritis. The fruit juice is used in cough mixture and also as a cooling beverage for toning up the nervous system. It is considered as a 'vata' suppressant, 'pitta' augmenting drug in Ayurveda. If taken excessively, the fruit is slightly laxative and induce diarrhea. The juice of the fruit, mixed with sugar and water, is used as a cooling beverage and used as a cardio tonic. The plant is aphrodisiac and promotes virility.

Traditional and medicinal uses

a) The fresh juice of the fruit is mixed with honey or sugar and given for treatment against cough and dyspnea.

b) Decoction of the bark of *Dillenia indica* is used in oral thrush and to remove offensive odor from the mouth.

c) The pulp of the fruit is mixed with water to clean the scalp hair.

d) Scabies and skin pigmentation of the skin can be cured by applying the paste of the bark of *Dillenia indica* on the affected areas.

e) The digestive capacity and lack of appetite can be improved by the fresh juice of Bhavya fruit.

f) Fresh juice and cold infusion of *Dillenia indica* is a good hair tonic and applied over the scalp to regenerate in hair fall.

g) The fruit is used in Indian cuisine to prepare various dishes and desserts.

It is also used traditionally in various parts of North-east India; the juices of leaves, bark drunk for the treatment of cancer and diarrhea.[15,16]

Phytochemical constituents

The phytochemical constituent of *Dillenia indica* Linn. crude extract include Glycoside, Flavonoids, Steroids, Saponins and reducing sugar. Table 3 Rich source of flavonoids and triterpenoids are found in leaves.[5] Various chemical constituents like 3, 5, 7-trihydroxy-3', 4'-dimethoxy flavone (dillenetin), betulinic acid Figure 6, β-sitosterol Figure 7 & Figure 8 and stigmasterol are found in *Dillenia indica*.[5,17] (Figure 9 & Figure 10)

Table 3 Phytochemical screening of alcoholic extract of *Dillenia indica* linn.[19]

Chemical constituents	Test	Inference –ve (negative), +ve(positive)
Carbohydrates	Fehling's Test	-ve
Pentose sugars	Pentose sugars	+ve
Hexose sugars	Cobalt chloride Test	+ve
	Non-reducing Sugars	+ve
Non-Reducing Polysaccharides	Iodine Test	-ve
Proteins	Biuret Test	-ve
	Xanthoprotein Test	-ve
Proteins containing Sulphur (Precipitation Tests)	5% CuSo4 Test	-ve
Amino acids	5% Lead acetate	+ve
	5% Ammonium sulphate	-ve
	Ninhydrin Test	-ve
	Cysteine Test	-ve
Steroids	Salkowski Reaction test	+ve
	Liebermann- Burchard Test	+ve
Cardiac Glycosides	Legal's Test	+ve
	Keller-Killiani Test	-ve
Saponin Glycosides	Foam test	+ve
Alkaloids	Dragendorff's Test	+ve
	Wagner's Test	-ve
	Murexide Test	-ve
	Tannic Acid Test	+ve
	Mayer's Test	+ve
Flavonoids	Schinoda Test	-ve
	Sulphuric Acid Test	+ve
	Lead acetate solution Test	+ve
	Zinc+HCl Test	-ve
	NaOH and Acid Test	+ve
Tannins and Phenol Compounds	5% Fecl3 Test	+ve
	1% Lead Acetate	+ve
	1% Potassium Dichromate	+ve
	Dil. Iodine Solution	-ve
	Dil. NH4OH and 1% K2FeCN6	+ve
	Dil. Potassium permanganate Solution.	-ve
	NH4OH and 10% AgNO3	-ve
Triterpenes	Chloroform and H_2SO_4 Test	-ve

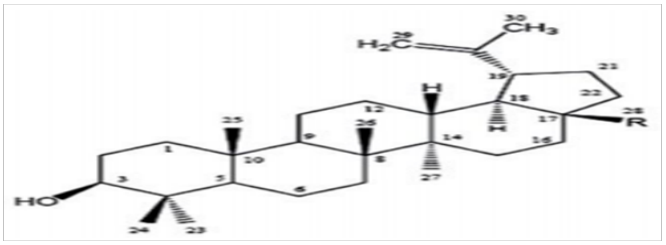


Figure 6 Structure of betulinic acid.

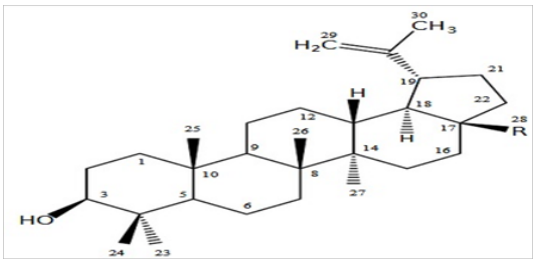


Figure 7 Chemical structure of lupeol (R=-H), betulinaldehyde (R=-CHO) and betulinic acid (R=-COOH).

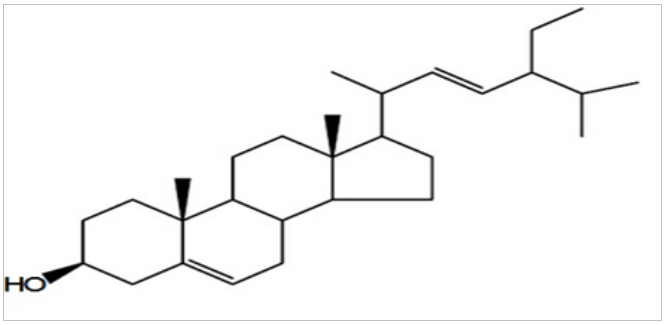


Figure 8 Chemical structure of stigmasterol.

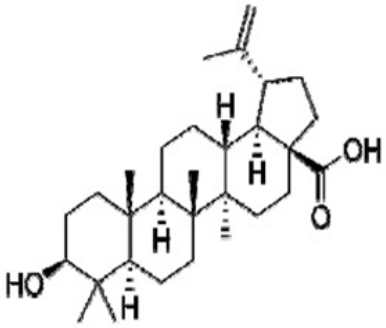


Figure 9 Betulin.

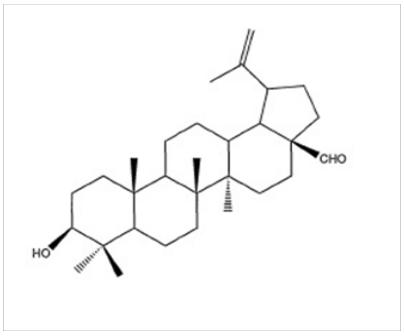


Figure 10 Betulinaldehyde.

Phytochemical compounds from alcoholic extract of *Dillenia indica*

The Phytochemical study shows Alcoholic extracts of *Dillenia indica* L. (Figure 11) contains significant amount of polyphenols which are responsible for the various pharmacological activities like anti-malarial, anti-cancer and anti-inflammatory.[18] Table 4

Carbohydrates, Starch, Proteins containing sulphur, Steroids, Cardiac Glycosides, Saponin Glycosides, Alkaloids, Flavonoids, Tannins and Phenol compounds[19] are present in the alcoholic extract of *Dillenia indica*.[20] From the literature survey, it is seen that different parts of these plants contain many primary and secondary metabolites. The stem bark of *Dillenia indica* contains 10% tannin, dillenetin, betunaldehyde, betulinic acid, dipoloic acid, myricetin, quercetive derivatives (Figure 12).[9]

Table 4 Qualitative phytochemical tests of *D.indica* L. fruit bark and leave.

Phytochemical tests	Fruit extract					Leaves extract method	Bark extract method
	Hexane	DCM	Ethly	Acetone	Methanol		
Alkaloids	-	-	-	-	-	-	-
i. Mayer's test	-	-	-	-	-	-	-
ii. Wagner's test	-	-	-	-	-	-	-
iii. Hanger's test	-	-	-	-	-	-	-
Carbohydrets							
i. Molish's test	-	-	-	-	+	-	-
ii. Fahling's tesi	-	-	-	-	+	-	-
iii. Barfoed's set	-	-	-	-	+	-	-
iv. Benedict's test	-	-	-	-	+	-	-
Saponins test	-	-	-	+	+	-	+

Table Continued

Phytochemical tests	Fruit extract					Leaves extract method	Bark extract method
	Hexane	DCM	Ethly	Acetone	Methanol		
Gums and mucilages test	-	-	-	-	-	-	-
Proteins/Amino acids							
i. biuret test	-	-	-	-	-	-	-
ii. Ninhydrin test	-	-	-	-	-	-	-
Phytosterols							
i. Libermann Burchard's	-	-	-	-	-	-	-
Fixed oils							
i. Spot test	+	-	-	+	+	-	+
ii. Saponification	-	-	-	-	-	-	-
Phenolic compounds							
i. Ferri chloride test	-	-	-	-	-	-	-
ii. Gelatin test	-	-	-	-	-	-	-
iii. Lead aceiate test	-	+	-	+	+	+	+
iv. Alkaline test	-	-	-	+	+	-	+

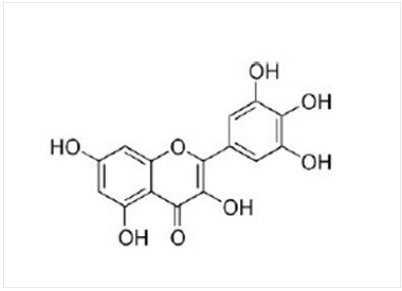


Figure 11 Myricetin.

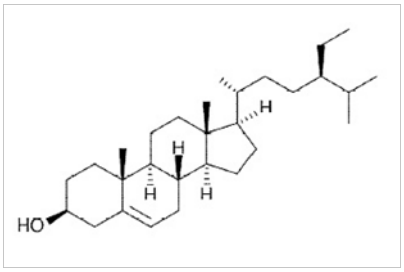


Figure 12 β-Sitosterol.

Flavonoids like rhamnetin, dihydro-isorhamnetin, (Figure 13) lupeol, myricetin, naringenin, quercetin derivatives and kaempferol glucoside are present in the stem bark of *Dillenia indica*.[21–23]

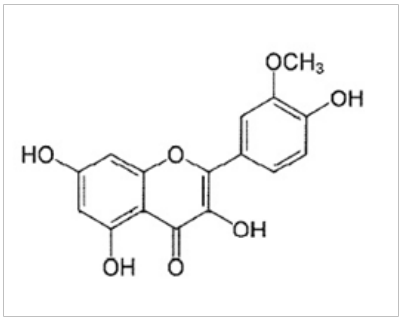


Figure 13 Isorhamnetin.

Phytochemical constituents from ethanolic extract of *Dillenia indica*

Ethanol extract of stem bark of *Dillenia indica* revealed two flavonoids kaempferol glucoside and quercetin (Figure 14) derivative as well as a triterpenoids.[24] **Table 5**

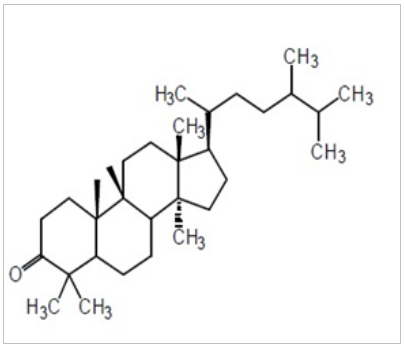


Figure 14 Cycloarteneone.

Phytochemical constituents from methanolic extract of *Dillenia indica*

Methanolic extract of stem after partitioning with n-hexane showed four compounds lupeol, betunaldehyde, betulinic acid and stigmasterol using column chromatographic separation.[25]

Fruits of *Dillenia indica* contain about 34% of total phenolics (Table 6)in methanolic extract and polysaccharide like an arabinogalactan.[26] Presence of fixed oil, colouring matter, sterols, glycosides, saponins, proteins, free amino acids, sugars, free acids and tannins in the seeds are also reported.[27] *D. indica* Linn shows presence of ash, water soluble ash, acid insoluble ash, swelling index, foaming index and organoleptic values. Phytochemical screening shows that alkaloids, terpenoids, glycosides, tannins etc. are present in the plant samples.[28] The fruit also contain cycloartenone and n-hentriacontanol. (Figure 15) Main contents of the fleshy sepals are malic acid, arabinogalactan and glucose. Bark and wood contains myricetinhydroxy-lactone, dihydroisorhamneti and glucosides. Stem bark contains a new hydroxylactone and dihydro-isorrhamnetin[29]

Table 5 Some isolated compounds from different parts of *Dillenia indica.*

Entry	Plant part (s)	Compound name	IUPAC name	MF	MW
1	Bark, fruit, leaf, stem	Betulinaldehyde	(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-prop-1-en-2-yl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta [a] chrysene-3a-carbaldehyde	$C_{30}H_{48}O_2$	440.7
2	Bark, fruit, leaf, stem	Betulinic acid	(3ß)-3-Hydroxy-lup-20(29)-en-28-oic acid	$C_{30}H_{48}O_3$	456.7
3	Bark, sepal	Betulin	Lup-20(29)-ene-3ß,28-diol	$C_{30}H_{50}O_2$	442.72
4	Bark, fruit, leaf, stem	Lupeol	(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a,5a,5b,8,8,11a-hexamethyl-1-prop-1-en-2-yl-1-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13 a,13b-hexadecahydrocyclopenta [a] chrysen-9-o1	$C_{30}H_{50}O$	426.72
5	Leaf,stem	Stigmasterol	(3S,8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-Ethyl-6-methylthept-3-en-2-yl]-10, 13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	$C_{29}H_{48}O$	412.7
6	Bark, fruit, leaf	ß-Sitosterol	17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a] phenanthren-3-ol	$C_{29}H_{50}O$	414.71
7	Bark, fruit, leaf, stem	Dillenetin	3,5,7-trihydroxy-3,4-dimethoxy flavone;2-(3,4-Dimethoxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one	$C_{17}H_{14}O_7$	330.29
8	Fruit,stem	Myricetin	3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl-4H-chromen-4-one	$C_{15}H_{10}O_8$	318.23
9	Fruit,stem	Isorrhamnetin	3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one	$C_{16}H_{12}O_7$	316.26
10	Fruit	Cycloartenone	9ß -9,19-Cyclolanost-2-en-1-one	$C_{30}H_{48}O$	424.7
11	Fruit	n-Hentriacontanol	1-Hentriacontanol	$C_{31}H_{64}O$	452.83

Table 6 Total Phenolic content of various extracts of *D.indica* L. fruit.

Extract	TPC (mgGAE/g)
Hexane	<1
Dichloromethane	13.17±3.09
Ethyl Acetate	17.76±4.92
Acetone	2833±1.17
Methanol	35.45±0.27

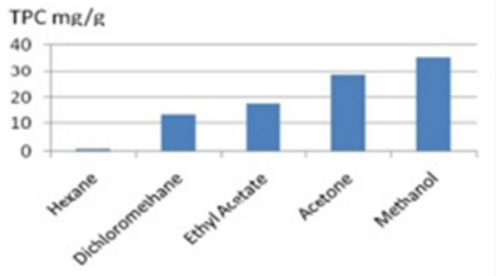


Figure 15 n-Hentriacontanol.

Pharmacological activity of *Dillenia indica*

Antidiabetic activity

Dillenia indica is used in the management of diabetes associated with abnormalities in lipid profiles and transaminase. Antidiabetic effects of *Dillenia indica* methanolic leaves extracts was carried out in streptozotocin induced diabetic Wistar rats. The extract showed significant anti diabetic activity ($p<0.001$). The extract also have effect on reduction in serum cholesterol, triglycerides and serum transaminase levels where as the HDL cholesterol level increases, indicating inhibition of the pathway of cholesterol synthesis by the extract. The methanolic extract enhanced serum insulin level in diabetic rats as compared to the diabetic control group.[29,30] In another study, advanced glycation end products (AGEs) inhibitory activity of alcohol and hydro-alcohol extract (DAE and DHE) of *Dillenia indica* L. were evaluated in the treatment of diabetic nephropathy by targeting markers of oxidative stress. *D. indica* was evaluated for its *in vitro* inhibitory activity against formation of AGEs by using bovine serum albumin. Diabetes was induced in male wistar rats by streptozotocin (65 mg/kg i.p.), 15 min after nicotinamide (230 mg/kg, i.p.) administration; nephroprotective effect was evaluated in diabetic rats with different doses of extracts (100, 200 and 400 mg/kg). Tissue antioxidant enzymes level was measured along with the formation of AGEs in kidney to assess the effect of *D. indica* in ameliorating oxidative stress. *D. indica* showed significant inhibition of AGEs formation *in vitro*. *D. indica* produced significant attenuation in the glycemic status, lipid profile and level of antioxidant enzymes proving efficacy in diabetic nephropathy.[31]

Antioxidant activity

Antioxidant property has been investigated on the fruits of *Dillenia indica*. Methanol, petroleum ether and water extracts of

the shade dried fruits of *Dillenia indica* were obtained and the IC_{50} values of their DPPH, hydroxyl, oxygen and nitric oxide scavenging activities were estimated along with their reductive ability, vitamin C and total phenolic content. Vitamin C is used as the standard reference for the antioxidant scavenging activities. The IC_{50} values for DPPH, hydroxyl, oxygen, nitric oxide and reductive ability of the methanolic extract of *Dillenia indica* were 31.25, 51.82, 51.44, 39.73 and 40.18µg/ml respectively. Higher amount of phenolic content in the methanolic extract of *Dillenia indica* contributed to its superior *in vitro* antioxidant property.[32]

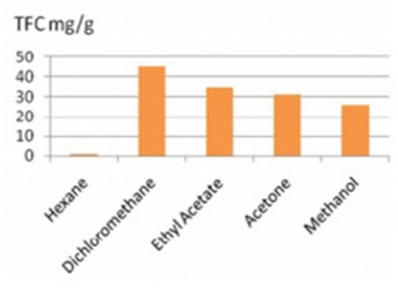
In another study, the decreasing order of antioxidant activity among the *D. indica* fruit extracts found to be methanol extract > ethyl acetate extract > water extract. This order is also similar to the phenolic contents of the extracts that showed the extent of antioxidant activity of the extract is in accordance with the amount of phenolics present in that extract. It is observed that the methanol extract of *D. indica* fruit contains substantial amount of phenolics and it is the extent of phenolics present in this extract responsible for its marked antioxidant activity as assayed through various *in vitro* models.[26]

Anti-inflammatory activity

Ethyl acetate extract of stem bark of *D. indica*, shows *in vivo* anti-inflammatory and analgesic potential in experimental animals. The study shows that the ethyl acetate extracts of *D. indica* (100 and 300mg/kg) in analgesic models (hot plate, tail flick and formalin induced paw licking) along with acute (carrageenan-induced) and chronic (formalin-induced) models of inflammation exhibited good central as well as peripheral analgesic activity as compared with pentazocine and indomethacin (10mg/kg), respectively. The extracts showed significant ($p<0.01$) activity in carrageenan-and formalin induced chronic inflammation models by using indomethacin (8mg/kg) and diclofenac (13.5mg/kg) as standard drugs. Presence of major constituents like flavonoids, tannins and phenols in the ethyl acetate extracts of stem bark of *D. indica* is responsible for its analgesic and anti-inflammatory activity.[33] Table 7

Table 7 Total Flavonoid content of various extracts of *D.indica* L. fruit.

Extract	TFC (mg QE/g)
Hexane	<I
Dichloromethanc	45.04±9.97
Ethyl Acetate	34.63±9.22
Acetone	31.23±3.34
Methanol	26±2.20



Dillenia indica Linn. (Dilleniaceae) is traditionally used to treat skin inflammation. Another study evaluated the healing effect of *Dillenia indica* fruit extracts on induced psoriasis-like wounds in Wistar rats. Extracts were standardized to betulinic acid, including an aqueous ethanolic extract (AEE), ethyl acetate extract (EAE) and petroleum ether extract (PEE). Effects against lipid peroxidation were assessed *in vitro* and wounds were created at the tail of rats. Yields of aqueous ethanolic and ethyl acetate extracts were 4.3 and 0.7%, respectively. Betulinic acid concentrations in AEE and EAE were found to be 4.6 and 107.6mg/g. Extracts neutralized lipid peroxidation *in vitro* at 0.02lg/mL, accelerating healing at 50mg/mL. EAE exhibited activity closer to that of clobetasol. Betulinic acid may be an active constituent for the healing effect.[34]

Anti-diarrhoeal activity

Antidiarrheal potential was investigated in methanolic extract of *Dillenia indica* bark. The extract studied for antidiarrheal property using castor oil and magnesium sulphate induced diarrheal model and charcoal induced gastrointestinal motility as well as PGE_2-induced enterolooping test in mice. Methanolic extract of *Dillenia indica* bark significantly reduced the frequency and severity of diarrhea in test animals throughout the study period at 100 and 200mg/kg body weight of doses 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 intrafluid accumulation. The results obtained in the present study suggest that *Dillenia indica* bark extracts have beneficial effect in controlling the diarrhea in experimental animals. The antidiarrheal property of *Dillenia indica* is mediated through inhibition of hypersecretion, gastrointestinal motility and increase of gastric transit time.[35]

Anticancer potential of *Dillenia indica*

From stem

Ethanolic and petroleum ether extracts of *Dillenia indica* stem barks showed cytotoxic effects in brine Shrimp lethality bioassay performed by observing mortality rate of brine shrimp nauplii (*Artemia salina*). The LC_{50} values observed by probit analysis were 574.926 and 334.284µg/ml for ethanolic and petroleum ether extracts.[36]

Bark

Methanolic extract of *Dillenia indica* bark and its n-hexane and ethyl acetate fractions possess potent cytotoxic (Table 8) principles with LC_{50} value17.68µg/ml, 17.68µmg/ml, 15.80µg/ml and LC_{90} value 486.61, 287.66, 148.82µg/ml, respectively, compared with positive control vincristine sulphate (LC_{50} 0.631mg/ml and LC_{90} value 13.51mg/ml).[37]

Table 8 *In vitro* cytotoxic activity of extracts of stem bark of *Dillenia indica* Thunb.[36]

Conc. (µg/ml)	Log C	% Mortality		Prohit		LC_{50} (µg/ml))	
		DIET	DIPE	MET	DIPE	DIET	DIPE
100	2	10	30	3.72	4.48	575	334.284
200	2.3	20	30	4.16	4.48		
300	2.47	20	40	4.16	4.75		
400	2.6	40	50	4.75	5		
500	2.69	30	60	4.48	5.25		
600	2.77	50	60	5	5.25		
700	2.84	60	80	5.25	5.84		
800	2,90	80	100	5.84	5.27		
900	2.95	100	100	5.25	5.25		
1000	3	100	100	5.84	5		

Fruits

Methanolic extract of *Dillenia indica* L. fruits showed significant anti-leukemic activity in human leukemic cell lines U937, HL60 and K562. Fractionation of the methanolic extract, on the basis of polarity showed that ethyl acetate fraction had highest anti-leukemic activity. A major compound, betulinic acid, was isolated from the ethyl acetate fraction by silica gel column chromatography; it was identified and characterized. Betulinic acid could explain the anti-leukemic activity of the methanolic extract and the ethyl acetate fraction.[38] It induces cell death in U937, HL60 and K562 cell lines by inducing apoptosis. The mechanism of anticancer drugs is to destroy the cancer cells by stopping growth or multiplication at some point in their life cycles. The cytotoxicity of plants that down-regulate the anti-apoptotic genes such COX-2, iNOS, TNFα, Bcl-2 and up-regulation of proapoptotic genes such p53, p21, Bax, caspase and cytochrome C.[39]

Std. stands for standard reference drugs Ara-C (for U937 and HL60) and Gleevec (for K562). Represents significant difference as compared to control ($p<0.05$).[39]

Methanolic extract and Ethyl Acetate Fraction inhibited the growth and produced significant cytotoxicity of leukemic cell lines in a concentration-dependent manner (Figure 16 & Figure 17). ME exerted 50% growth inhibition (IC_{50}) of U937, HL60 and K562 cell lines at concentrations of 328.80±14.77, 297.69±7.29 and 275.40±8.49 mg/ml, respectively and EAF showed the IC_{50} at concentrations of 240.074.36, 211.80±5.30 and 241.96±8.04 mg/ml in U937,HL60 and K562.

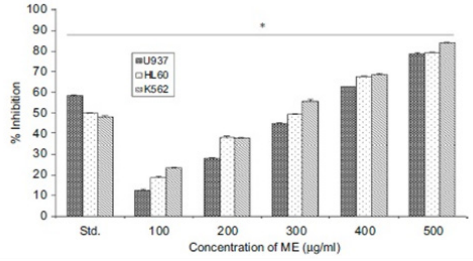


Figure 16 The influence of standard reference drugs and Methanolic Extract on the proliferation of U937, HL60 and K562 cells. The cells were cultured in 10% FBS containing RPMI media and treated with Ara-c(100mg/ml), Gleevec (0.1mg/ml) and ME (100,200,300,400and500mg/ml) for a period of 24h. The percentage growth inhibitions were calculated in comparison to untreated control cells. The number of cells in the control was taken as 100%. Values are expressed as mean±SEM.

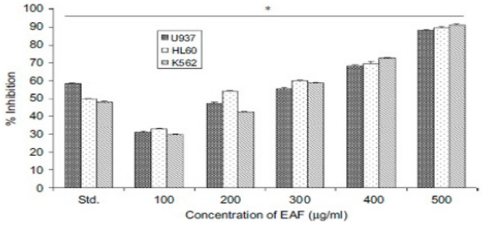


Figure 17 The influence of standard reference drugs and EAF on the proliferation of U937, HL60 and K562 cells. The cells were cultured in 10% FBS containing RPMI media and treated with Ara-c (100mg/ml), Gleevec (0.1mg/ml) and EAF (100,200,300,400 and500mg/ml) for a period of 24h. The percentage growth inhibitions were calculated in comparison to untreated control cells. The number of cells in the control was taken as 100%. Values were expressed as mean±SEM. Std. stands for standard reference drugs Ara C (forU937andHL60) and Gleevec (forK562) represents significant difference as compared to control ($p<0.05$).39

In another study, by Gandhi and Mehta showed, *Dillenia 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.[40]

Chemopreventive potential was evaluated in 8-10 weeks old swiss albino mice by giving a single topical application of initiator-7,12 dimethylbenza(α)anthracene (DMBA) at a concentration of 100µg/100µl acetone and promotion after 14 days by repeated application of croton oil (1% in acetone) thrice weekly for 15 weeks. Oral application of *D.indica* at a dose of 250 mg/kg body weight of mice selected after acute oral toxicity test, showed significant ($p<0.05$) reduction in DMBA induced mice skin papillomagenesis in (i) post-initiation group (oral dose given on the day of promotion) and (ii) pre+post initiation group (oral dose given 7 days before initiation and continued till the end of experiment). There was reduction in the total papilloma count, tumour yield, and tumour burden and tumour incidence when compared with carcinogen control group. Inhibition of tumour formation upto 88.3% was noted following 15 weeks of treatment, which clearly indicates the antitumor property of *Dillenia indica* fruit.

DMBA induced skin carcinogenesis in Swiss albino mice model involves two-stages- initiation and promotion, where initiation is accomplished by a single application of sufficiently small dose of carcinogen and promotion requires repeated and prolonged exposure to promoter.[41,42] DMBA is carcinogenic and it has the ability to cause irreversible damage in DNA. It alters endogenous pro-inflammatory cytokines. The molecular mechanism of chemoprevention lies in down regulation of inflammatory mediators such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), ornithine decarboxylase, Interleukin-6 expression and can be mediated directly by reduction of NF-κB activation.[43] Betulinic acid derived from birch tree *Betulla spp* has shown anti-fibrotic effect by inhibiting NF-κB signaling pathway,[44] it provides strong evidence towards the molecular mechanism of chemoprevention by *D. indica* due to the presence of betulinic acid by plummeting NF-κB activation.

D.indica had been used in various ailments for long time but its use as anti-cancerous agent can provide a new insight in the field of cancer prevention. Chemoprevention seeks to eliminate precancerous cells to steer clear of the necessity of chemotherapy. Its ability to scavenge free radicals *in vitro* and its chemo-preventive potential in DMBA induced mice skin papillomagenesis suggests that use of the fruit in our food will help the normal people to keep themselves protected from the onset of cancer to some extent. Nevertheless, extensive study is needed to elucidate the exact mechanism underlying this prevention effect.[45]

In another cytotoxicity screening, dimethyl sulfoxide (DMSO) solutions of the plant extractives were applied against *Artemia salina* in a 1-day *in vivo* assay. For the experiment, 4 mg of each of the extracts was dissolved in DMSO. Solutions of varying concentrations such as 400, 200, 100, 50, 25, 12.5, 6.3, 3.1, 1.6, 0.8µg/mL were obtained by serial dilution technique. The median lethal concentration LC_{50} of the test samples after 24 hours was obtained by a plot of percentage of the shrimps killed against the logarithm of the sample concentration.[46]

Application of *Dillenia indica* as pharmaceutical excipients

The medicinal and nutritive values of *Dillenia indica* influence its

applicability as pharmaceutical excipients. Mucilaginous extract of *Dillenia indica* is used as Pharmaceutical excipients. The advantage of natural pharmaceutical excipients over synthetic pharmaceutical excipients is that natural substances are biodegradable, biocompatible, easily accessible, economic, and nontoxic. The mucilages isolated from the seeds of *Dillenia indica* is a good source of pectin which is a polysaccharide and one of the major constituent of fruits like Apple, Lemon, Banana, *Dillenia indica*, *Abelmoschus esculentus* and used as gelling agents in jam, jellies and major dietary supplements to our body.[47] It is reported that the natural mucilaginous substances isolated from the seeds of *Dillenia indica* have high swelling capacities along with appreciable mucoadhesive strength.[48] Natural mucilages isolated from the fruit of *Dillenia indica* was evaluated for preparing mucoadhesive nasal gels for the delivery of Felodipine.[49] Using excised goat nasal mucosa, it is observed that *Dillenia indica* exhibited favourable mucoadhesive properties that caused their adherence to the nasal mucosa for a long time thereby enhancing the absorption of drugs administered intranasally. Mucilaginous substances isolated from the fruit of *Dillenia indica is* used in preparing ofloxacin mucoadhesive microspheres when tested in vivo and also showed extended drug release.[50] Pantoprazole loaded micro beads were prepared by the mucilaginous extract from the fruit of *Dillenia indica*. The micro beads were found in spherical shape with sufficient swelling, mucoadhesive property, and acid resistance, considered significant for its use in mucoadhesive drug delivery, particularly for controlled release.[51] Evaluation of delivery of low bioavailable drugs to the buccal cavity by natural mucoadhesive substance isolated from the fruit of *Dillenia indica* is also reported.[52] Table 9

Conclusion

The extensive literature survey and recent reports on exploring its activity revealed that *Dillenia indica* is highly regarded as a potential and upcoming candidate in the herbal medicine. Different extracts of this plant and its parts have been reported to contain phytoconstituents like flavonoids, steroids, triterpenoids, phenolics, saponins, responsible for superior pharmacological activities performed on animal models. From the reports it is obvious that it has anticancer activity *in vitro* on different cell lines with inhibitory property and significant cytotoxicity. Betulinic acid plays an important role in exerting anticancer activity. The plant has good therapeutic potential and large-scale, controlled pharmacological study is needed to validate these results. The review overall depicts the importance of *Dillenia indica* as a medicinal plant by its various phytochemical compounds and pharmacological activities. Further evaluation needs to be carried out on this plant to explore the hitherto unknown effects and their practical pharmacological and clinical applications, for the welfare of the mankind.[53]

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Conflicts of Interest

The authors declare that there is no conflict of interests involved in this study.

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