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RECENT UPDATE ON PHARMACOLOGY AND PHYTOCHEMISTRY OF *DILLENIA INDICA*

Pushpander Kumar[1], Sunil Kumar[*1] and Vipin Kumar[2]

[1]Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, Haryana

[2]Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Ajmer 305801, Rajasthan, India

***Corresponding Author Email: sunilmaduban@yahoo.com**

ABSTRACT

Dillenia indica (D.Indica) (Dilleniaceae) is an Indian medicinal plant commonly known "Elephant apple" in English and "Karambel" in Hindi. It is widely used medicinal plant all over the world. It is very popular in various systems of medicine like ayurvedic, homeopathic and siddha. Whole plant is used in treatment of disease and ailments. Plant is traditionally used in blood cancer, diabetes, diarrhea, gall bladder stone, asthma, stomachache, hairfall, dysentery, abscess, insect repellant and in stomach problem. Various researchers have investigated that D. indica possesses a wide range of pharmacological activity like anticancer, anti-inflammation, antidiabetic, wound healing, antineoceptive, hair waving, antimicrobial, antioxidant, analgesic, dysentery, anxiolytic, anthelmintic, antiarthritic, mucoadhesive, analgesic, hepatoprotective properties etc. In the present review, we are going to discuss about detailed pharmacology, toxicology, chemical constituents, ethnobotany along with traditional uses of D. indica.

KEY WORDS

Dillenia indica, Dilleniaceae, antidiabetic, anticancer, inflammation.

1. INTRODUCTION

Dillenia indica plant belongs to family Dilleniaceae (Figure 1). *Dilenia indica* Linn is a evergreen tree, 30-80 feet in height and 6-8 feet in girth, with a dense rounded crown, which bears large and hard fruit of 3-5 inches in diameter. The plant is locally known as Karambel or Karmal in Marathi, Chalta in Hindi, and Ramphal in Nepal. It grows in moist and evergreen forests of sub-Himalayan tract, from Kumaon and Garhwal eastwards to Assam and Bengal, and southwards to central and southern India. The tree flowers during May-August and fruits ripen during September-February. Leaf is oblong-lanceolate, 8-14 inches long and 2-4 inches broad, with pointed apex and toothed margin; the upper part of the leaf as well as the veins beneath are covered with hairs. Flower is 5-8 inches in diameter, hard consisting of 5 closely fitting imbricate sepals enclosing numerous seeds embedded in a glutinous pulp. Seed are small, compressed reniform with hairy margins [1-3].

Figure 1: *Dillenia indica* [A] Whole plant; [B] leaves

2. Traditional uses

Dillenia indica is used traditionally from a long time in the Asia due to its pharmacological values. The mixed juices of leaves, bark and fruits are given orally (5-15ml, 2-5 times daily) for the treatment of cancer and diarrhea in the Mizoram [3]. Traditionally, fresh leaves and fruit are cut in the pieces and then sun dried then plants is used is also used for treatment of diabetes. As the plant is used traditionally, Kumar et al 2011 provide evidence that the plant is potentially used in the treatment of diabetes with the facilitation of animal models of streptozotocin and alloxan induced diabetes [4]. Unripe fruit decoction in the Manipur is applied on to the scalp for curing dandruff and fall of hair. In the Northern Bangladesh, the fruit mucilage is mixed with the turmeric in the ratio 2:1 used for hair growth [5-7]. Tender shoot of plant is used in asthma in the Imphal valley. And plant is known as *Heigri* as the local name [8]. In the Barak Valley, Assam, leaves are used as insect repellent. Leaves are admixed with the rice to avoid infection in the crop [9]. By Local Kabiraj, filtrate of bark paste is mixed with sugar in a glass of water and kept overnight taken in the morning regularly in empty stomach for blood cancer [10]. Fruits of the plant are given in the fever and in the severe cough to reduce dryness of throat by the Padam, Nyishi and Iidu tribes of Aruanchal Pradesh [11]. Fruit is used to improve appetite, cough and mouth disease and weakness in the Arunachal Pradesh [12-14]. Fruit juice of *Dillenia indica* and root juice of *Mimosa pudica* mixed with few drops of honey is taken once daily to cure dysentery [15]. Fleshy calyx with little salt is taken as a remedy for stomachache [16]. Fruit is used in the treatment of diarrhoea [17]. Calyx is boiled and takes as vegetable to relieve cough and fever; jelly substance of fruit used for washing hair; flowers taken orally for treating dysentery [18]. Traditionally, In the Assam juice of the fruit is mixed with the *Mimosa pudica* root taken to treat dysentery problem [19]. Stem bark and fruit of plant is used for stomachache. Paste of the stem bark is taken with one glass of water in the Eastern Himalayan Andhra Pradesh [20-22]. Fruits and leaves are cut into small pieces and properly sun dried. It is then powdered and regularly taken with water to cure diabetes [23]. Calyx of the plant is used in the Koch Bihar, West Bengal for the treatment of Digestion [24]. Leaves of the plant used traditionally with *Abroma augusta* taken orally in the West Bengal for treatment of the gall bladder stone [25]. Fruit and bark were used in the treatment of abscess in the Similipal bioreserve, Orrisa [26-27]. Fruit is used as decoction in the Mizoram for stomach problem [28]. In the Arunachal Pradesh, dried fruit is chewed to relief the severe cough, weakness and fever [29].

3. Pharmacological study

In last few years, many researchers have established pharmacological activities experimentally of the plant based on its traditional uses.

3.1. CNS depressant

D. indica methanolic bark extract shows dose dependent CNS depressant activity in cross hole and open field test when screened for CNS depressant

activity at the doses of 100, 200, 400 mg/kg [30]. The activity may be due to alkaloid and flavonoids present in the extract.

3.2. Anticancer activity

Anticancer activity of methanolic extract of *Dillenia indica* L. fruits were studied against healthy human cell lines namely U937, HL60, and K562. The extract showed significant anti-leukemic activity with IC_{50} of 328.80±14.77, 297.69±7.29 and 275.40±8.49 µg/ml against U937, HL60, and K562 cell lines respectively. Furthermore, ethyl acetate fraction prepared from the methanol extract of fruits showed IC_{50} values of 240.0±4.36, 211.80±5.30 and 241.96±8.04 µg/ml. A major active compound betulinic acid was isolated from the ethyl acetate extract by using silica gel column chromatography, showed IC_{50} at concentrations of 13.73±0.89, 12.84±1.23 and 15.27±1.16 µg/ml in U937, HL60 and K562 cell lines [31-32]. The ethyl acetate extract may be a potential source for the anticancer drug. Also, there is great interest in the finding of the exact mechanism of action so that we can explore other potential natural products as an anticancer drug.

3.3. Anti-inflammatory activity

D. indica methanol leaves extract (200,400 and 800 mg/kg) and its fractions (hexane and chloroform; 100 and 200 mg/kg) have been reported to have anti-inflammatory activity in acetic acid induced colitis using female Swiss albino mice (25-30 g). Methanolic leaves (800 mg/kg), Chloroform (200 mg/kg) and hexane (200 mg/kg) showed reduction in macroscopic score, colon myeloperoxidase (MPO), malonaldehyde (MDA) and TNF-α levels and increase in the Colonic catalayse (CAT), Superoxide dismutase (SOD), and glutathione (GSH). The plant extract and its fractions showed significant ($p<0.05$) antiinflammatory [33]. Additionally, Khare *et al.* 2013 also reported anti-inflammatory activity of the leaves plant extract against Carrageenan induced paw edema at the doses of 25, 50, 75 mg/kg p.o. The extract, in dose dependent manner, significantly ($p<0.01$) reduces inflammation [34]. The anti-inflammatory activity may be due to the flavonoids and triterpenes suggested from preliminary phytochemical study.

3.4. Antidiabetic activity

Traditionally, leaves and fruit is used as to cure diabetes in Assam [18]. Recent studies have been performed by the researchers in the order to understand the antidiabetic activity of the plant. Kumar *et al.* 2013 investigated antidiabetic potential of *Dillenia indica* methanolic leaves extract (250-500 mg/kg p.o.) in Streptozotocin, nicotinamide and alloxan induced diabetic Wistar rat. Glibenclamide (10 mg/kg) was used as standard drug. Methanolic extract at the dose 500 mg/kg shows significant ($p<0.001$) antidiabetic activity in alloxan induced diabetic Wistar rat, via stimulation of insulin secretion from pancreatic β-cells. Moreover, I*n vitro* antidiabetic activity ($p<0.05$) of the isolated constituents (Betulinic acid, quercetin, β-sitosterol, stigmasterol) from *D. indica* ethyl acetate extract also has been studied [35-38]. For instance, the antidiabetic activity may be due to the isolated compounds.

From the recent studies, examination of the Indian tree, *D. indica* in search of antidiabetic activity has lead to the isolation of the newly isolated compound Chromane. Singh *et al.* 2016 also evaluated antidiabetic activity with Streptozotocin induced diabetes model against isolated Chromane and ethanol leaves extract of *D. indica.* Reduction in the blood glucose was found to be dose dependent manner. The plant showed insulinomimic activity [39].

3.6. Wound healing activity

Glycolic extract of mature fruits of *Dillenia indica* L. shows significant ($p<0.05$) wound healing properties against lesions on Wistar rats. Wound was surgically induced on the back of the Wistar rat. Animals were randomly divided into the six groups(a)negative control (b)Group receiving microcurrent (c) Group treated with glycolic extract(d) Group treated with emulsion +glycolic extract(e) Group treated with glycolic extract and microcurrent(f) group treated with emulsion, extract and microcurrent. Group treated with microcurrent and glycolic extract with current showed significant wound healing activity. Probably, wound healing activity due to the presence of flavonoids and saponin confirmed from the phytochemical screening [40-42].

3.7. Antidiarroheal activity

Ethanol extract of *Dillenia indica* leaves and fruit extract (200 and 400 mg/kg) were screened for antidirroheal activity by using castor oil induction and charcoal plug method. Loperamide (5mg/kg) was used as a standard drug. The ethanolic leaves extracts was found more effective than aqueous plant extracts against castor oil induced diarrhea. In the charcoal plug method, distance travelled from pylorus to caecum was measured and leaves extract shows more distance travelled in comparison with fruit extract. Additionally,

Rehman et al also performed antidiaaroheal activity with castor oil (0.5 ml) against methanol root extract (500mg/kg) and standard drug Loperamide (50mg/kg). The extract showed 65.28 % antidiarrheal activity whereas, loperamide showed 72.22 % inhibition. The methanolic root extract showed significant ($p<0.01$) antidiarrheal activity [43-45].

3.8. Antinoceptive activity

Antinoceptive activity of root extract (250 mg/kg and 500 mg/Kg) was investigated significantly ($p<0.01$) against acetic acid induced writhing in Swiss albino mice. Diclofenac sodium (25mg/kg) was used as positive control. Plant root extracts produced 48.82% and 55.88% inhibition and Diclofenac showed 60% inhibition of writhing in test animals, respectively. So, the plant is having significant ($p<0.01$) antineoceptive activity [45].

3.9. Antioxidant activity

From the recent studies, methanolic extract of the leaves *D. indica* have been screened for *in-vitro* antioxidant activity by using three model's DPPH, reducing power and phosphomolybedinum radical scavenging activity. In 1,1-Diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging assay the IC_{50} value of the extract was found to be 100.53 µg/mL while ascorbic acid had the IC_{50} value 58.92 µg/mL [46]. A newly isolated chromane from the alcoholic leaves extract by Singh *et al.* 2016 is having potent antioxidant activity. Three model's DPPH, Hydrogen peroxide scavenging, Superoxide radical scavenging and reducing power assay were introduced for the antioxidant study. From DPPH, IC_{50} values of alcoholic extract, Chromane and ascorbic acid were found to be 228.69, 23.06 and 80µg/mL. Hydrogen peroxide, IC_{50} values of alcoholic extract were found to be 228.69µg/mL, and those of alcoholic extract and Chromane were found to be 23.06µg/mL and 80 µg/mL. Superoxide radical scavenging, IC_{50} of ascorbic acid, alcoholic extract and Chromane was found to be 27.96 µg/mL, 75.09 µg/ml and 23.49 µg/ml respectively. From the reducing power assay, EC_{50} was found to be 111 µg/mL for alcoholic extract, 26.95µg/mL for Chromane and 21.42 µg/mL for ascorbic acid [39,47-48]. Huge antioxidant studies have been performed by the researches. Probably, *In vitro* activities may be due to Chromane isolated from the alcoholic extract.

3.10. Antimicrobial activity

Methanolic leaves extract of *D. indica* has been studied for antimicrobial activity against sixteen microbial strains. A wide range of antimicrobial strains were used like 5 gram positive, 8-gram negative organisms, and 3 fungi organisms. Organic solvents fractions (*n*-hexane, carbon tetrachloride and chloroform) of methanolic extracts were screened for antimicrobial activity by using disc diffusion method. Standard drug Kanamycin (30µg/Disc) was used as positive control. Zone of inhibition of the extracts was ranged from 6-8 mm, 7-8mm, 6-7mm at a concentration 400 µg/disc. As we all know that the antibacterial activity is due to the carbonyl group and also the plant contains flavonoid [49-50].

3.11. Anxiolytic activity

Anxiolytic activity was evaluated against *D. indica* hydroethanolic with the doses of 100, 200 and 400 mg/kg p.o.and Diazepam (2mg/kg). Two models were used to establish anxiolytic activity viz. hole board ($p<0.05$), open field ($p<0.05$). *D. indica* leaves showed significant dose dependent anxiolytic activity [51].

3.12. Anthelmintic activity

Methanoilic extract of stem bark was dissolved in distilled water to give different concentrations 10, 15, 20, 25 mg/mL for anthelmintic activity. Albendazole (10mg/mL) was used as standard drug. Observation was made by paralysis and death time of the earthworm. Methanolic extract showed mild anthelmentic activity as compared to standard drug Albendazole [52].

3.13. Hepatoprotective activity

Ethanolic leaves extract (300 mg/kg p.o.) were used against hepatoprotective activity of *Dillenia indica* in carbon tetrachloride induced hepatotoxicity. Silymarin (25mg/kg) was used as standard drug. From the results, histopathological studies states that the plant showed regeneration from the necrosis in the treated rats with extracts. The extract showed significant ($p<0.001$) hepatoprotective activity against carbon tetrachloride induced hepatic animal model. It is stated that the ethanolic leaves extract possesses hepatoprotective activity [53].

3.14. Antiarthritic activity

Methanolic leaves extract of *D. indica* has been screened for antiarthritic activity. Arthritis was induced by Complete Freund's adjuvant (CFA) induced (0.1 mL) in left hind paw of rat. *Dillenia indica* plant extract with 25, 50, 75 mg/kg and standard cyclophosphamide (100mg/kg) were used for the experiment. The antiarthritic activity was prominent at higher

concentration (75mg/kg). The plant is having significant ($p<0.01$) antiarthritic activity [34].

3.15. Analgesic activity

Methanolic leave extract (100, 200, 400 mg/kg, p.o.) were screened for analgesic activity by using hot plate, tail emerson, acetic acid induced writhing and formalin induced nociception. Methanol extract 400 mg/kg (54.77 %) against formalin induced nociception showed almost same result as compared to Pentazocin (15 mg/kg; 56.51%). Whereas, hot plate and tail immersion method 400 mg/kg showed significant activity and 100 mg/kg and 200 mg/kg showed mild activity [54]. Rony *et al.* 2016 also proved analgesic activity of *D. indica* stem bark extract (100, 200 and 400 mg/kg) against Diclofenace. In the acetic acid induced writhing, stem bark 400 mg/kg showed significant ($p< 0.001$; 46%) analgesic activity whereas Diclofenac showed 78.50 % inhibition. Biological activity was carried out by using tail emerson model and acetic acid induced writhing [30].

3.16. Miscellaneous properties

From D. indica mucilage control release microspheres were prepared, and screened for mucoadhesive properties by Sharma *et al.* 2014 [55].

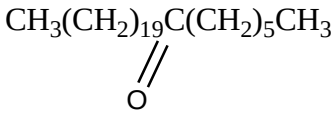
4. Toxicological Study

4.1. Cytotoxic study

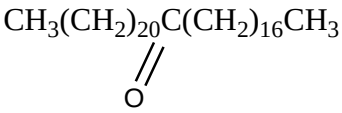
Cytotoxic study of *Dillenia indica* was investigated by various researchers. Methanoic extract was screened for cytotoxic activity by Trialgo *et al.* 2014 using healthy mouse fibroblasts (NIH3T3), healthy monkey kidney (VERO) and four human cancer cell lines (Gastric, AGS; Colon, HT-29; and breast, MCF-7 and MDA-MA-231) using MTT assay [56]. Moghal *et al.* 2013; Rony *et al.* 2016 and Rashid et al 2009 confirmed cytotoxic activity of *D. indica* by using berine shrimp lethality bioassay [30,52,57]. Padhya *et al.* 2008 found out acute toxicity of *Dillenia indica* leaves extract. Suspension of extract in acacia mucilage was administered orally 0.2– 4 g/kg of body weight. The plant extract was found to be safe up to the dose of 2g/kg. Khare *et al.* 2013 also evaluated toxicity study of *D. indica* [34,53]. From the toxic study, it was found that the plant is absolutely safe in every dosage form. And the plant is having almost no side effects on the liver, kidney and pancreas.

5. Phytochemistry

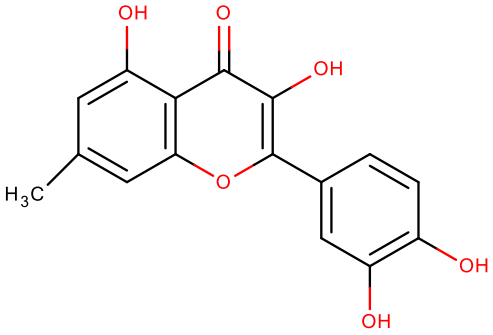
The most important part of phytochemistry is the plant contains flavonoids from the ethyl acetate fraction of the methanol extract of the leaves of *D.indica* (Figure 2). The leaves of the plant contain flavonoids and triterpene. These phytoconstitents are n-heptacosan-7-one (1), n-nonatriacontan-18-one (2), quercetin (3), *β*-sitosterol (4), stigmasterol (5), and stigmasteryl palmitate (6) were isolated from leaves. These phytoconstituent screened for antidiabetic activity and were found to be very potent [35]. Malic acid (7) has been isolated from fruits of *Dillenia indica* [58]. From the leaves of *Dillenia indica* a new chromane 3,5,7, -Trihydroxy-2-(4-hydroxy-benzyl)-chroman-4-one (8) has been isolated and screened for antidiabetic and antioxidant activity [39]. From the stem bark, flavonoids and triterpenes have been evaluated from n-hexane faction of the plant was fractioned by the vacuum liquid chromatography. These phytoconstituents lupeol (9), Betulinic aldehyde (10) and stigmasterol (5) were obtained and from, dichloromethane fraction of the methanol extract betulinic acid (11) was isolated [57]. Stem bark of *D. indica* contains tannin, dillenetin(12), betunaldehyde(9), betulinic acid(11), flavonoids like rhamnetin(13), dihydro-isorhamnetin(14), lupeol(8), myricetin(15), naringenin(16), quercetin(3) derivatives and kaempferol glucoside(17) [58,59,60,61,62]. Wood of the *Dillenia indica* contains betulinic acid (10), lupeol (8), β-sitosterol (4) [63]. Pronthocynadines was elucidated and purified from stem bark of plant [64]. Leaves of *D. indica* found to contain flavonoids, triterpenoids, steroids, tannins, its petroleum ether extract contains cycloartenone (18), n-hentriacontanol (19), sitosterol (4), botulin (20) and chloroform extract contains betulinic acid (12) [65]. Acid hydrolyzed extracts of dried leaves shows presence of kaempferol (17), while fresh leaves contain dihydro-kaempferide (21) and 7 glucosides of naringenin (16) which oxidized to ten corresponding flavonols [66]. Triterpenes and flavonoids were isolated from the methanolic extract of the *D. indica*. Methanolic extract of leaves after bioassay guided fractionation with n-hexane and chloroform also yielded compounds like betulinic acid (12), β-sitosterol (4), stigmasterol (5) as well as dillenetin(11) [67]. Uppaalapati & Rao1980 reported that *D. indica* seed are having fixed oil, colouring matter, sterols, glycosides, saponins, proteins, free amino acids, sugars, free acids and tannins [68].



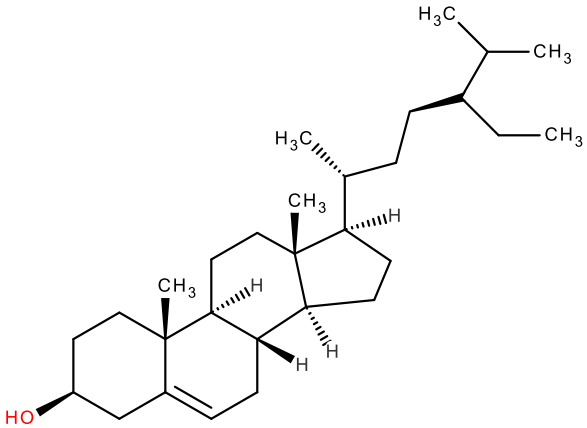
n-heptacosan-7-one (1)



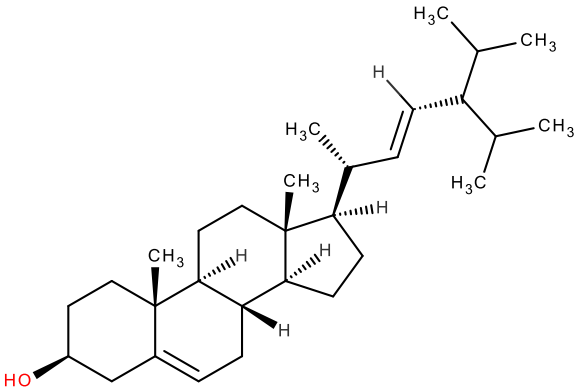
n-nonatriacontan-18-one (2)



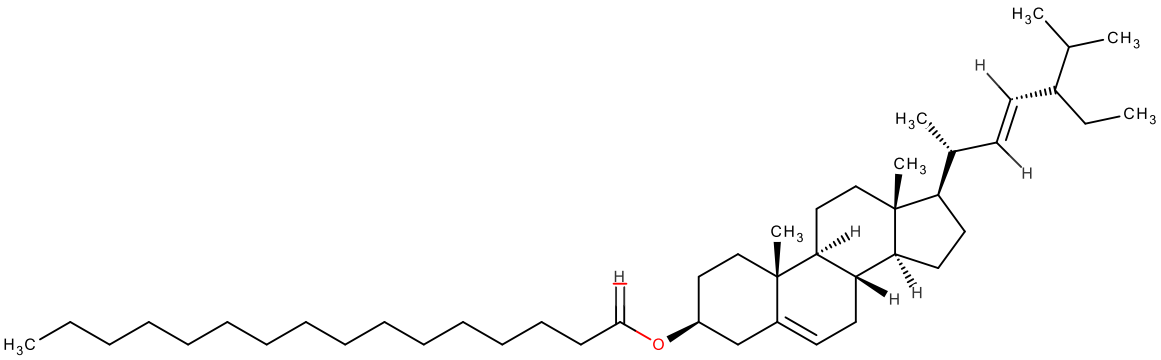
Quercetin (3)



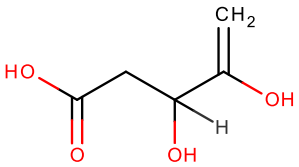
β- Sitosterol (4)



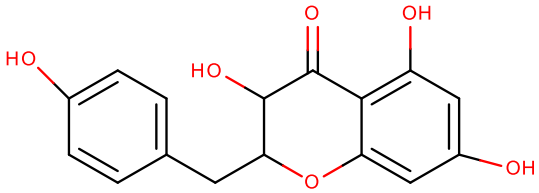
Stigmasterol (5)



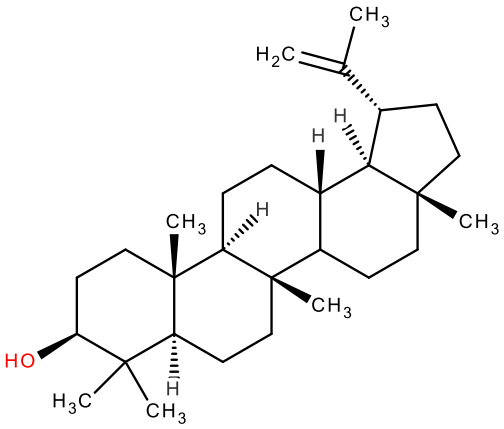
Stigmasteryl palmitate (6)



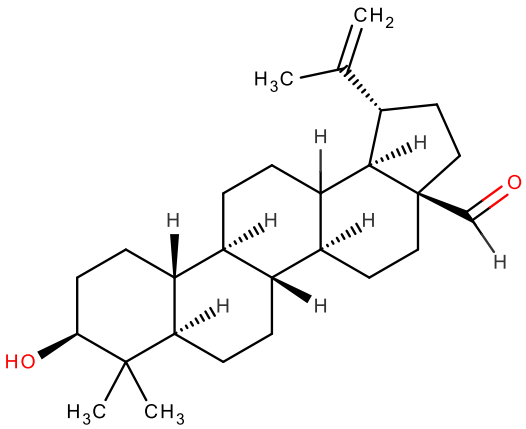
Mallic acid (7)



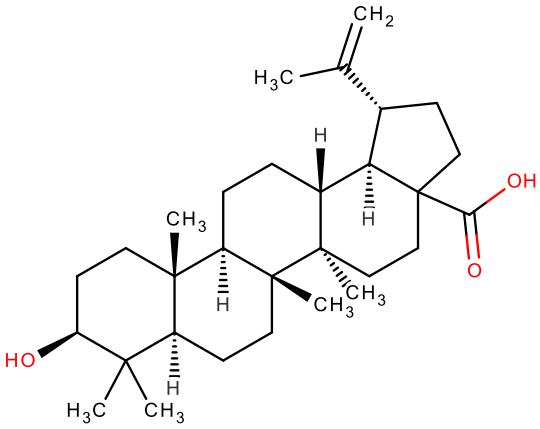
Chromane (8)



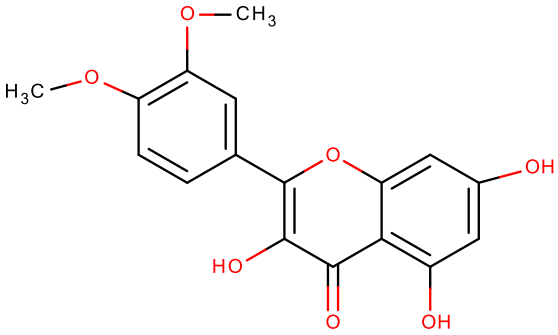
Lupeol (9)



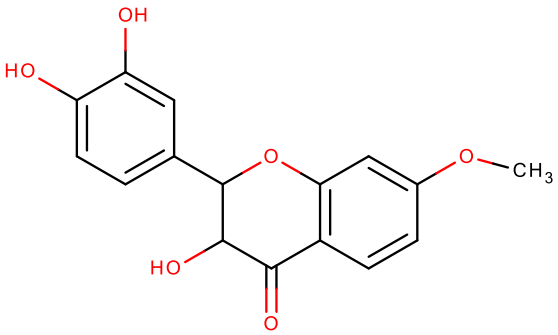
Betulinic aldehyde (10)



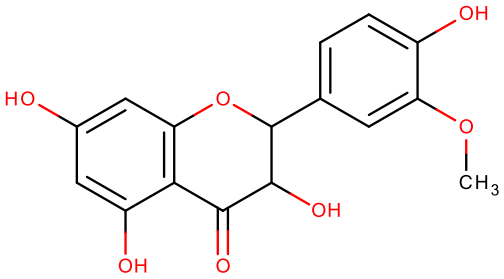
Betulinic acid (11)



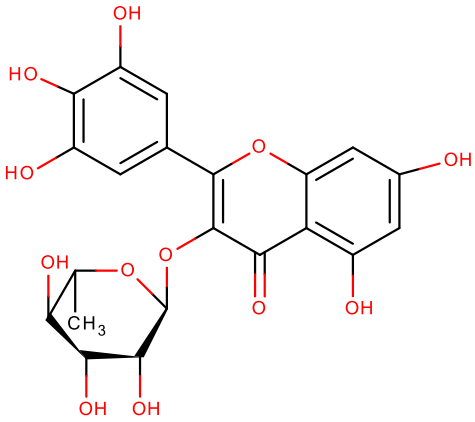
Dillentin(12)



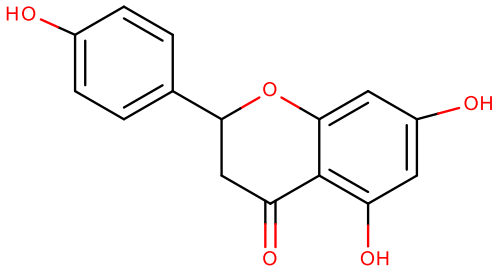
Rhamnetin (13)



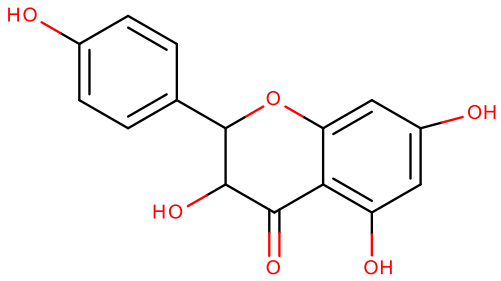
Dihydro-isorhamnetin (14)



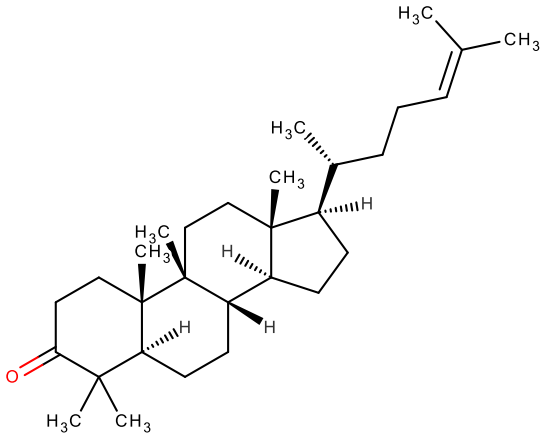
Myricitrin (15)



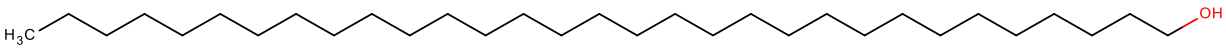
Naringenin (16)



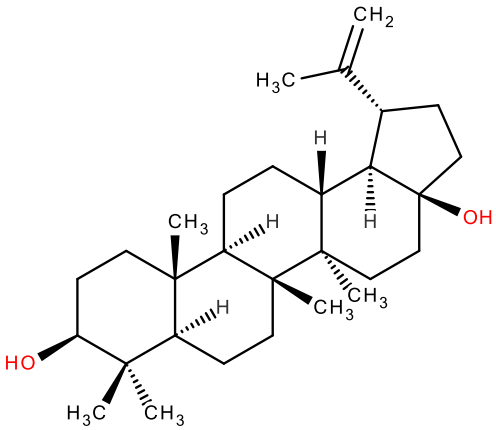
Kaempferol (17)



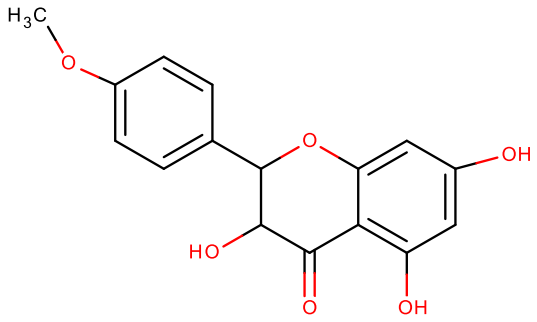
Cyclooctenone (18)



n-hentriacontanol (19)



Betulin(20)



Dihydrokampferide(21)

Figure 2: Structure of bioactive constituent of *D. indica*

6. CONCLUSION

Herbal drug is getting more attention than synthetic drugs. Facts behind hypothesis that herbal drug have thousands of chemical constituents in plant. They make complimentary contribution to each other chemical constituents; they make optimized balance of by products or secondary metabolites. And thus they have almost minimum or no side effect/adverse effects of natural products. On other hand if we use single synthetic product contains huge amount of side effects. *Dillenia indica* is having huge medical properties; it is used traditional in the disease and ailment all over India. Potential pharmacological properties of *D. indica* leaves, fruit, bark, and its isolated compound screened by various researchers is confirmed by research articles published in last few years. *D.indica* is having diverse reported pharmacological activities such as antidiabetic, anticancer, hepatoprotective, anti-inflammatory, antidiarroheal, etc. Flavonoids, triterpenoids, anthocyanidines were isolated from plant. Due to the non-toxicity of plant, it signifies potential uses as remedy in several ailments. In this review we have discussed about detailed pharmacology, toxicology, chemical constituents, ethnobotany along with traditional uses of *D. indica*.

6.1. Future prospective

D. indica has been used traditionally for treatment and management of various diseases. Plant is used all around the world for its medicinal values. The plant is having enormous traditional uses and also so many potentially scientifically proved biological activities. It is very important to discover pharmacological based mechanism of the *D. indica* for diseases and also we can find out receptor-molecular interaction by using Docking studies. There are huge possibilities in the isolation of chemical constituents from the extracts of plant. More biologically active phytoconstituents should be isolated using bioactivity-guided fractionation strategies. In addition to that, *D. indica* should be added in herbal formulation. Overall, from the pre-clinical study, the plant is having wide range of activities. Besides that, it is quite surprising that still the plant is not introduced in to the clinical trials. A formulation of the herbal supplements or nutraceutical should be formulated and used in the clinical trials.

7. CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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***Corresponding Author:**
Sunil Kumar*
Email: **sunilmaduban@yahoo.com**