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A comprehensive review on phytopharmacological perspectives of *Pithecellobium dulce* (Roxb.) Benth.

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Abstract

Pithecellobium dulce (Roxb.) Benth, is a resourceful medicinal plant with a wide range of medicinal virtues that has availed widespread consideration recently. Almost all parts of the plant have immense nutritional value. The active constituents of the plant include the rich presence of flavonoids, sterols, tannins, and triterpenoids. Due to its healing characteristics, *P. dulce* has been used by ancient peoples to treat a variety of diseases and disease-preventing attributes, namely; antioxidant, antifungal, antiviral, antibacterial, antidiabetic, antispasmodic, diuretic, anthelmintic, anti-inflammatory, antipyretic, sedative action, and hypoglycemic activity, which has been further confirmed by modern scientific study. The literature was explored *via* reliable search engines such as PubMed and Science Direct. In terms of leaves, stems, roots, and fruits, the data revealed consistent medicinal use. This review goes into detail about *P. dulce*, covering its phytochemistry, nutritional value, and important medicinal significance.

1. Introduction

1.1 Plant description/etymology

Pithecellobium dulce (Roxb.) Benth., often referred to as the Manila tamarind, is one of the important species of Pithecellobium (Hiwale *et al*., 2015; Camachile *et al*., 2020; Grin *et al*., 2010). It is endemic to Mexico's pacific coast, as well as central and southern parts of America. It is a medium-sized evergreen thorny tree, growing up to 18 meters on the Indian plains and in the Andaman Islands.

The species name "dulce" relates to the delicious pod, which has a curly appearance similar to ape earrings. It is the lone species in a genus with 100-200 species and it has spread considerably outside of its native range (Duke and Wain, 1981).

1.2 Morphological description

The bark of *P. dulce* is grey in color, becomes rougher, and begins to peel when mature. The size of the leaves is 2-2.5 × 1-2 cm, with kidney-shaped lobules and a pair of two leaves.

Each leaf has a 2-15 mm slender spine at the root. Hairy crown blooms and little whiteheads with a diameter of 1 cm can be seen in *P. dulce*. The calyx of a joint tube surrounds 50 sparse stamens in the flower. When ripe, each pod is 10-15 × 1.0 cm long, which is spiral in shape and reddish brown in colour (Orwa *et al*., 2009 ; Srinivas *et al*., 2018)

The vernacular names of *P. dulce* are given in (Table 1).

Table 1: Vernacular names of *P. dulce*

Vernacular names	
Arab: Showkat Madras	Kannada: Seemehunase
Bengal: Dekhani babul	Philippines: Camachile
China: Niutidou	Sanskrit: Kodukkaapuli
English: Quamachil, Madras Thorn, Manila tamarind	Spanish: Guamuchil, Guama Americano
French: Campeche, Cassie de Manille,	Tamil: Kodukkaapuli
German: Camambilarinde	Thai: Makham-khong,makham-tha
Greek: Pithekosellobion	Vietnamese: Me Keo, Keo Tay, Me nuoc
Hindi: Vilayati babul, Jangle jalebi	Javanese: Asemlondo, Asambelanda
Japanese: Huamuche, Guamuche	Brazil: Ingarana
Costa Rica: Michiguiste	Cuba: Inga dulce; Tamarindo chino
Guatemala: Jaguay; madre de flecha; tsuiche	Guyana: Bread-and-cheese
Indonesia: Asamkoranji	Malaysia: Asamkranji; Asamtjina
Myanmar: Kway-tanyeng	Sri Lanka: Katugaja; Kodukapuli

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The aerial parts of *P. dulce* have been shown in (Figure 1).

Figure 1: Aerial parts of *P. dulce*.

Species of *P. dulce* are given in (Table 2).

Table 2: Species of *P. dulce*

Acacia obliquifolia M.Martens and Galeotti
Inga javanica DC
Albizia dulcis (Roxb.) F.Muell.
Inga leucantha C. Presl
Feuilleea dulcis (Roxb.) Kuntze
Inga pungens Willd.
Inga camatchili Perr.
Mimosa dulcis Roxb.
Inga dulcis Mart.
Mimosa edulis Gagnep.
Inga dulcis (Roxb.) Willd.
Mimosa pungens (Willd.) Poir.
Inga javana DC.
Mimosa unguis-cati Blanco
Pithecellobium littorale Record
Zygiadulcis (Roxb) Lyons
Pithecollobium dulce (Roxb.) Benth.

2. Distribution

The plant is indigenous to Brazil, Bolivia, Colombia and Argentina. *P. dulce* is one of the species that has to unfold broadly. It is one of the 18 species of this genus. It has been extensively available in India, Huawei, tropical Africa, and specifically coastal areas (Orwa *et al*., 2009). The distribution map of various species of *P. dulce* is shown in Figure 2.

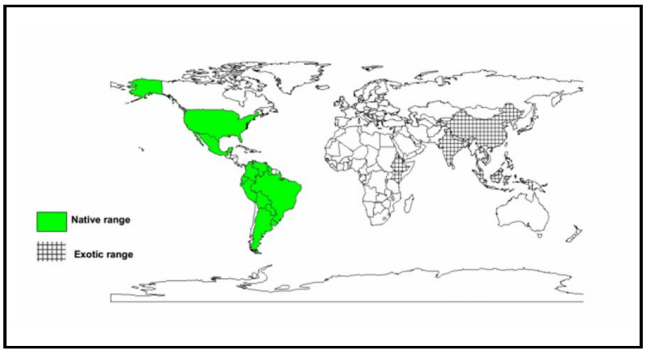

Figure 2: Global geographical distribution of *P. dulce*.

To summarize the traditional therapeutic usage and its pharmacological qualities, an exhaustive literature search was conducted, using material from reputable publications and traditional authentic literature. Utilizing the terms *P. dulce*, traditional medicine and pharmacological characteristics, a literature search was conducted using reputable search engines to obtain data from Google Scholar, PubMed, Springer, and Science Direct. The PICOS model has been used to conduct the inclusion principles of the studies and study design.

All the *in vitro* and *in vivo* researches, were included in the study design of research publications written in English. A comprehensive literature search was carried out with sources sorted by title and abstract. The whole text of eligible studies were chosen. Papers that were irrelevant or similar were omitted. There were a total of 112 articles found. The literature search, on the other hand, was completed using 60 full-length research articles, books, and websites.

3. Folklore evidence

Leaves are used as plasters; they can be used to alleviate pain and venereal sores. indigestion and abortion are both treated with salted soup. Dysentery, dermatitis, and eye inflammation are all treated with the bark. As a tea, the bark soup is consumed. Earaches, leprosy, toothaches, and larvicidal effect are all treated with a leaf decoction. The bark of the plant has been utilized as an astringent in dysentery. It has also been prevalently used as a febrifuge. Roots are used in the treatment of dysentery and as a febrifuge. Literature analysis shows that the leaves of the plant are traditionally used in the medication of leprosy, intestinal disease, peptic ulcers and toothaches, earaches, emollients, abortion, and larvicides in folk medicine (Srinivas *et al*., 2018). Even venereal sores and convulsion can be relieved by applying the leaves as a plaster. Leaf paste is used externally to treat muscle swelling caused by certain inflammatory conditions. The leaves, along with salt, can treat indigestion and, in higher doses, can also cause miscarriage (Manandhar, 2002; Subhadrabandhu, 2001). For gastric diseases like gastric ulcers, the fruits have also been eaten. Despite the common use of *P. dulce* fruit for stomach complications (Megala and Geetha, 2015). *P. dulce* seeds have proven to be beneficial for diabetes and its complications. Therefore, it has traditionally been used to treat diabetic mellitus patients for this purpose (Nagmoti and Juvekar, 2013). The inhalation of the seed juice into the nostrils

against chest congestion and use of pulverized seeds for internal ulcers, local people in Tamil Nadu, India's northern region, have been using the plant's fruit peel to control diabetes. To regulate blood sugar, some persons chew raw fruit peels or drink a water decoction made from them. Yet, no empirical proof remains. Previous research on the peel of the fruit had only reported on its antibacterial, antioxidant, and wound-healing properties, but it was revealed to be a suitable therapeutic target for diabetes mellitus (Srinivas *et al*., 2018). Scientific research on *P. dulce* root is scarce. However, it has been used for treatment of dysentery condition. The decoctions of root is consumed through oral route in Haiti to treat diarrhoea, and root bark is used as an antipyretic and for dysentery in Guyana **(**Kamatsile, 2014). Root extracts are abortive (Banerjee, 2005).

4. Phytochemical review

Various lucrative phytoconstituents have been isolated from the various parts of plant owing to the medicinal effects. Bioactive fractions of plants and their medicinal importance are mentioned below.

4.1 Leaves

P. dulce extract from leaves mainly contain the following like cyclitol, dulcitol, octacosanol, α-spinasterol, kaempferol-3-rhamnoside, quercetin and afzelin (Zapesochnaya *et al*., 1980).

4.2 Fruit

P. dulce fruits have nutritional and medicinal value which have been found to contain 2, 5, 6-trimethyl 1, 3-oxathiane, trans-3-methyl-2-N-propylthiophane, 2-carboxaldehyde-5-hydroxymethyl, methyl-2-hydroxyicosanoate, D-pinitol, heptacosanoic acid, hexadecanoic acid, tetracosanol, 22-tricosenoic acid and stigmasterol. Fruits also contain ellagic acid, gallic acid, mandelic acid, ferulic acid, vanillic acid, coumaric acid, rutin, naringin and daidzein (Preethi and Saral Mary, 2014).

4.3 Seeds

Pithedulosides, dulcin, hederagenin, oleanolic acid and echinocystic acid were identified. Some pithedulosides were saponins while others were found to be triterpenoidal glycosides (Rao *et al*., 2018).

4.4 Peel

It contains stigmasterol, sitosterol , quercetin and pinitol (Preethi and Saral Mary, 2014).

5. Pharmacological attributes

5.1 Antimicrobial activity

Antimicrobial activity was analyzed for hexane, ethanol, benzene and ethyl acetate extract of the plant on *Enterobacter aerogenes, Klebsiella pneumonia,* and *Acetobacter aceti* by disc diffusion method. The pod pulp extract was found to be efficient against gram-positive, *bacillus subtilis* and gram-negative, *Klebsiella pneumonia* bacteria. Other gram-positive bacteria have a smaller clearance diameter than *B. subtilis* (Megala and Geetha, 2012 ; Pradeepa *et al*., 2014).

5.2 Analgesic and anti-inflammatory effect

The methanolic extract of the leaves was tested against analgesia using the hotplate test and inflammatory action was evaluated at doses of 200 and 400 mg per kg body weight. A significant anti-analgesic effect was detected. The anti-inflammatory response attained after 3 hours was maximal with extract doses of 200 and 400 mg per kg. These results implied that with respect to standard, methanolic extract had significant analgesic and anti-inflammatory effect (Selvan and Muthukumaran, 2011).

5.3 Antioxidant activity

The antioxidant potential of aqueous and methanolic extracts of *P. dulce* was investigated utilizing several *in vitro* assays such as DPPH inhibition, nitric oxide inhibition, hydroxyl inhibition, superoxide anion inhibition, and lipid peroxidation inhibition. Standard phytochemical reaction techniques were used to evaluate the total phenolic content. This antioxidant activity may be attributed to high phenolic contents. Both extracts demonstrated good dose-dependent free radical scavenging efficacy (Nagmoti *et al*., 2012).

5.4 Anticonvulsant activities

The anticonvulsant potential of ethanol and an aqueous extract of *P. dulce* bark were investigated through the maximal electric shock-induced seizure in rats. At the studied dose level, both extracts demonstrated considerable anticonvulsant effectiveness by lowering the duration of the prolonged period. The water extract outperformed the ethanol extract and was comparable to phenytoin sodium, a commonly used antiepileptic medication. The effects of aqueous and ethanolic extracts of *P. dulce* leaves, was studied for parameters including spontaneous motor activity and motor coordination. The results of this study indicate that the extract has significant pharmacological effects in the CNS (Mule *et al*., 2011).

5.5 Cardioprotective activity

In relation to cardioprotective effect, isoproterenol induced myocardial infarction in adult male wistar rats was used to test the fruit peel. Intraperitoneal administration of ethanolic extracts of fruit peel was done. The activities of marker enzymes such as SGOT, SGPT, CPK, and LDH were significantly increased (Thangarajan *et al*., 2015).

5.6 Antidiabetic activity

The hydroalcoholic extract of *P. dulce* bark was tested for anti-diabetic efficacy through alloxan-induced rat model. The extract exhibited considerable antidiabetic action (Praveen *et al*., 2010) when compared to the standard glibenclamide, at a dose of 400 mg/kg. The defatted seeds were extracted with methanol and a saponin-enriched fraction was obtained. The fraction was tested against oral toxicity followed by *in vivo* sucrose tolerance test. The fraction inhibited the enzymes significantly and was proven to be safe up to dose of 2000 mg/kg. In an additional study, bark and leaves of the plant were evaluated for α-amylase and α-glucosidase inhibition. By reduction of glucose release from starch and delayed carbohydrate absorption, -amylase and α-glucosidase inhibitors, provide an alternative approach for post-prandial hyperglycemia. The studies confirmed inhibitory action of a methanol and ethanol extract on α-glucosidase and α-amylase (Katekhaye and Nagmoti, 2013).

5.7 Antidiarrhoeal activities

The antidiarrhoeal potential was evaluated through castor oil-induced model. The experiment included a study on aqueous extract of *P. dulce* leaf was investigated for antidiarrheal efficacy. In comparison to the control group, the extracts reduced the frequency and wetness of the faeces (Sugumaran *et al*., 2008). The aqueous extract showed more significant activity than the ethanol extract at the tested dose level.

5.8 Larvicidal activity

The methanolic extract of *P. dulce* had the highest larval mortality in comparison to *Aedes aegypti*. The percentage of hatchability was inversely proportional to the extract concentration (Govindarajan *et al*., 2013). The leaf and seed extracts of *P. dulce* exhibited moderate larvicidal and ovicidal activity.

5.9 Antiulcerogenic activities

An investigation was made for antiulcerogenic effect where the ethanol and cystamine induced gastric and duodenal ulcers in rats were pretreated with hydroalcoholic fruit extract of *P. dulce* for 30 days. The antiulcerogenic effect of the hydroalcoholic fruit extract was determined by quantitative measurement of gastric hydrogen potassium ATPase, Mucin 6 and Mucin 2 expression in the stomach and duodenal tissue using real-time PCR. The gastroprotective effect of *P. dulce* was attained by down-regulating gastric hydrogen potassium ATPase synthesis and up-regulation of mucin secretion in stomach and duodenum (Megala and Devaraju, 2015).

5.10 Antivenom activity

The tannin was extracted from *P. dulce* bark by the method of aqueous extraction. The lethality of the venom was inhibited and the necrotic effect of the venom was minimized by this crude extract. The extract also inhibited 90% of the acetylcholine esterase activity. The plant extract inhibits the nicotinic acetylcholine receptor selectively while precipitating the venom protein non-selectively (Pithayanukul *et al*., 2005).

5.11 Antitubercular activity

The BACTEC 460 TB-Radio-spirometric system was used to test the anti-mycobacterial activity of hexane, chloroform and alcoholic extracts of the leaves. The activity was compared with standard drugs, namely; streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide. The chloroform extract was moderately active. The maximum activity was found in the alcoholic extract at a concentration of 20 mg/ml, which was comparable to that of standard drugs (Shanmugakumaran *et al*., 2006).

5.12 Antiparasite activity

A report on the antiparasitic activity of N-malonyl-(þ) -tryptophan, a compound that was purified from the methanolic extract of *P. dulce* fruit. *In vitro* activity of the methanol extract, its fractions and subtractions against *Hymenolepis nana* was higher than that of the commonly used medicine, praziquantel. Toxicity and ADMET software prediction results suggest that fractions may be safe and effective in treating hymenolepiosis (Gabriela *et al*., 2019).

5.13 Nephroprotective activity

Investigation of the renal protective effect in CCl_4 induced renal pathology was undertaken to assess its role in CCl_4 induced kidney oxidative damage and cell death. It was observed that the aqueous extract had protective role against CCl_4 induced renal oxidative impairments. The plant was proven to have nephroprotective activities (Manna *et al*., 2011).

Bioactive fractions, nutritional value and elemental composition of *P. dulce* are given in (Tables 3,4,5).

Table 3: Bioactive fractions of plants and their medicinal importance

S.No.	Part of the plant	Extraction	Biological activity	Reference
1.	Leaf and seed	Hexane, benzene, chloroform, ethyl acetate and methanol	Adulticidal	Govindarajan and Rajamohan, 2012; Rajeswary and Govindarajan, 2014; Raman *et al*., 2012
2.	Seed	Methanol	Antidiabetic	Raman *et al*., 2012
3.	Seed	Methanol	Hypolipidemic	Nagmoti *et al*., 2015
4.	Wood bark, leaf, fruit	Methanol, acetone aqueous, hydroalcoholic	Antioxidant	Katekhaye and Kale, 2012; Nagmoti *et al*., 2012; Sukantha *et al*., 2014
5.	Fruits	Aqueous, hydroalcoholic	H^+, K^+-ATPase inhibition	Megala and Geetha, 2009
6.	Fruits	Alcoholic	Antiulcer	Megala and Geetha, 2012
7.	Bark	Hexane	Antivenom	Pithayanukul *et al*., 2005
8.	Fruit	Aqueous	Nephroprotective	Murugesan *et al*., 2019
9.	Leaves	Ethanol	Antidiarrheal	Rashid *et al*., 2015
10.	Pod pulp, Fruit peel, Leaves	Ethanol	Antibacterial	Pradeepa *et al*., 2014 Sukantha *et al*., 2014
11.	Leaves, seed	Aqueous, Ethanol	Antifungal	Bautista *et al*., 2005 Shanmugakumar *et al*., 2006
12.	Fruits	Methanolic	Antiparasitic	Dhanisha *et al*., 2021

Table 4: Nutritional value of *P. dulce*

1.	Energy	78 kcal
2.	Water	77.8%
3.	Protein	3%
4.	Fat	0.4%
5.	Carbohydrate	18.2%
6.	Fiber	1.2%
7.	Ash	0.6%
8.	Calcium (1.3% RDI)	13 mg
9.	Phosphorous (4.2% RDI)	42 mg
10.	Iron (2.7% RDI)	0.5 mg
11.	Sodium	19 mg
12.	Potassium (6.3% RDI)	222 mg
13.	Vitamin A	15 mg
14.	Thiamin/B1 (16.6% RDI)	0.24 mg
15.	Riboflavin/B2 (5.8% RDI)	0.10 mg
16.	Niacin/B6 (3% RDI)	0.60 mg
17.	Vitamin C (221% RDI)	133 mg

Table 5: Elemental composition

S. No.	Elements	Concentrations (mg/kg)
1.	Arsenic (As)	17.6
2.	Copper (Cu)	16.25
3.	Cadmium (Cd)	3.48
4.	Iron (Fe)	1.89
5.	Lead (Pb)	0.19
6.	Magnesium (Mg)	15.06
7.	Potassium (K)	26.89
8.	Sodium (Na)	10.19
9.	Zinc (Zn)	26.89

6. Conclusion

P. dulce has been described, examined and validated by modern researchers to have a high potential for health-boosting, disease prevention and life extension qualities. The current analysis suggests that it offers a variety of beneficial health impacts and pharmacological activities. Furthermore, this study promotes the consumption of traditionally used crude drugs against modern life-threatening illness. The review strongly reflects the multifarious potential of *P. dulce* which requires further research on mechanism of action of the plant. Further exploration is recommended with respect to the association between chemical constituents and pharmacological activity.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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