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Systematic Review on Evidence based Therapeutic Potential of *Pithecellobium dulce* for Health Benefits

Mamta Shukla[1], Akanksha Singh[2], Pranabesh Ghosh[3], Sirshendu Chatterjee[4] and Pankaj Singh[5*]

[1]Department of Biotechnology, FoET, Khwaja Moinuddin Chishti Language University, Lucknow - 226013, Uttar Pradesh, India

[2]Department of Microbiology, Babasaheb Bhimrao Ambedkar University, Lucknow - 226025, Uttar Pradesh, India

[3]School of Life Sciences, Seacom Skills University, Santiniketan, Bolpur, Birbhum - 731236, West Bengal, India

[4]Department of Biotechnology, Techno India University, West Bengal, Salt Lake Sector - V, Kolkata - 700091, West Bengal, India

[5]Biotechnology Program, Dr. Rammanohar Lohia Avadh University, Ayodhya - 224001, Uttar Pradesh, India; singhpankaj0984@rediffmail.com

Abstract

Plants are proved as a beneficial source of natural products having therapeutic uses for long back periods. Epidemiological studies suggested that approximately 33% of drugs in developed countries are derived from a plant. *Pithecellobium dulce* is one of the plants which have significant diverse medicinal properties. It is a native fruit of tropical America, and it is cultivated throughout India, especially in Andaman. It is rich in flavonoids, tannins, alkaloids, etc. Experimental studies show that *P. dulce* shows antidiabetic, abortifacient, antitumor, anodyne and larvicidal activities. Furthermore, it shows significant activity against diarrhea, eye inflammation, and anti-venomous as well. It has a specific place in the traditional system of medicine and can be a miraculous part of modern medicine in the future. So, the present review has been designed to explore the pharmaceutical and therapeutic properties of *P. ducle* based on the available scientific literature.

Keywords: Antidiabetic, Antioxidant, Flavonoids, Inflammation, Phytochemicals, Therapeutic

1. Introduction

Plants have been a beneficial source of natural products for maintaining human health and the environment since ancient times. Almost 80% of the population from all over the world uses traditional medicines, which are derived from plants[1]. About 33% of drugs produced in the developed countries alone are derived from plants and 60% of the modern medicinal products are made naturally from ancient plants. These plants have therapeutic properties. *Pithecellobium dulce* (*P. dulce*) is a native plant of tropical America, also originated in America and it is mostly cultivated throughout India and some other countries. The genus *Pithecellobium* has 19 species in which *dulce* species have more pharmacological as well as therapeutic value. It is an evergreen medium-sized plant belonging to the family Fabaceae[2]. They have rich source of vitamins, and minerals and are highly appetizing by taste[3]. It is also known as

**Author for correspondence*

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'vilayati jalebi or 'jangal jalebi' in Hindi and 'kodukkapuli' in Tamil. The different parts of plant extract have antioxidant, anti-inflammatory, antimicrobial, antidiabetic, cardioprotective, antidiarrhoeal, antiulcerogenic, larvicidal, and ovicidal activities due to presence of several bioactive phytocompounds such as flavonoids, saponins, tannins, alkaloids, etc. Natural products discovered so far served as a viable source for new drugs to treat severe diseases[4]. The bark of the plant is described to be used as astringent in dysentery, and febrifuge and is also beneficial in dermatitis and eye inflammation. Roots of *P. dulce* have been reported to possess estrogenic activity and are useful in diarrhea and dysentery infections. Leaves can be used in pain and venereal sores. Also, concoctions of leaves have been reported to be required for indigestion, intestinal disorder, earache, peptic ulcer, venereal diseases, toothache, Leprosy, and larvicide[3,5]. The fruits have been reported to have anti-inflammatory and antimicrobial activity. The seed accommodates triterpene saponins which act as an anti-inflammatory[3]. It also acts as astringent, emollient, abortifacient, antidiabetic, anodyne, and larvicides in folk medicines. Furthermore *P. dulce* also possesses antivenomous activity[1]. Because of its versatile nutraceutical and pharmacological properties *P. dulce* is a highly applaud genus in the traditional system of treatment[4].

2. Plant's Taxonomy

Classification of *P. dulce*[6]:
Domain: Eukaryota
Kingdom: Plantae
Phylum: Spermatophyta
Subphylum: Angiospermae
Class: Dicotyledonae
Order: Fabales
Family: Fabaceae
Genus: *Pithecellobium*
Species: *dulce*

2.1 Habitat

It can grow on dry, brushy, or thinly forested plains or hillsides, often in coastal thickets. It is cultivated at elevations from sea level to 500m.

2.2 Morphology

P. dulce is a medium-sized plant that commonly grows up to 10-15 m, but sometimes ranges from 5-18 m. It has irregular branches length up to 30m across; bole short, up to 1 m thick. The bark is grey in color, rough, furrowed, and eventually peeling. Leaves are bipinnate or bihearted, with two pairs of kidney-shaped leaflets. Each leaflet is 2-2.5 x 1-2 cm in length. New leaf growth concurs with the loss of old leaves, this feature giving the tree an evergreen appearance. At the base of the leaves pairs of thin spines are present and range from 2 to 15 mm in length. The flowers are small in size, whitish green in color, and 1 cm in diameter. Each flower has a hairy corolla and calyx surrounding it into stamens. Stamens are thin, about 50 in number, and united in a tube at the base. Mature pods are 10-15 cm in length and 1.5 cm in width, and spiral in shape. They are green in the starting stage but reddish-brown when they ripen. Each pod contains about 5-10 shiny black seeds up to 2 cm long. The characteristic features of *P. dulce* are its grey bark and tightly coiled seed pods, which make it easy to distinguish[6,7] (Figure 1).

3. Pharmacological Properties of *P. dulce* Plant

The different parts of *P. dulce* plant has many pharmacological properties such as anti-inflammatory, antibacterial, antioxidant, antidiabetic, antiulcer, hepatoprotective, antihyperlipidemic, adulticidal etc. The detail descriptions of each therapeutic property are as follows:

3.1 Antibacterial Effect

Pod pulp of *P. dulce* hasthe ability to restrict the growth of Gram-positive bacteria (*Bacillus subtilis*) and Gram-negative bacteria (*Klebsiella pneumonia*). They have secondary metabolites (flavonoid, saponin, etc.) which are responsible for the inhibition of bacterial growth[6,8]. *P. dulce* yielded a glycoside quercitin. The activity of the flavonol glycoside confirmed, it has anti-inflammatory and antibacterial properties[9]. In previous research, it had proved that aqueous and acetate extracts of *P. dulce* fruit peel inhibits the eight different types of microorganisms *i.e. Staphylococcus epidermis, Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Pseudomonas putida,* and *Proteus vulgaris*. These microorganisms had been isolated from wound infection. It has been found that methanolic extracts also inhibited three bacteria (*K. pneumoniae, S. aureus, and P. putida*)[8,10]. Bark of the plant is used as

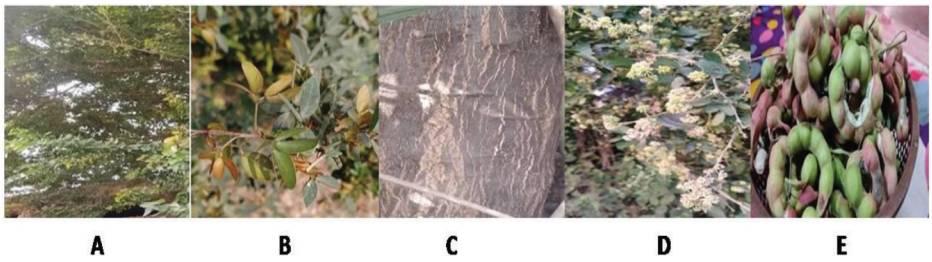


Figure 1. *P. dulce* **(A)** Whole plant **(B)** Leaf **(C)** Stem **(D)** Flower **(E)** Fruit

an antimicrobial agent and wound healing agent[11]. The combination of silver nanoparticles with *P. dulce* has shown excellent sensitivity against *E. coli, S. aureus, P. aeruginosa,* and *Candida albicans* because Silver also has antimicrobial properties[4]. Based on scientific reports, natural antioxidants present in plants are promising sources for reducing reactive oxygen species induced diseases than synthetic medicines[10].

3.2 Antioxidant Activity

Aqueous, acetate and methanolic extracts of the *P. dulce* contains high level of total phenolic compound. Phenolic compounds are compounds which are responsible for effective antioxidant activities[11,12]. It reduces the effect of the harmful radicals (unstable radicals cause severe damage to the inner organs, and tissues, and cause various health problems) which are generated through various factors and help in promoting the antioxidant enzymes in our body. It is proved that leaves, seeds, fruits, and barks extract of *P. dulce* have potential activity against free radicals.[2] Antioxidant activity may be supported by its high phenolic contents[13]. *P. dulce* is a potential source of natural antioxidants because of the presence of high phenolic components and flavonoids[14]. Methanolic and 70% acetone extracts of *P. dulce* wood bark and leaves are the probable source of natural antioxidants and medicinal properties. Phenolic compounds are potential plant constituents because their hydroxyl groups and mechanism of action of flavonoids confer scavenging ability. They are helpful in preventing the progress of various oxidative stresses[15].

3.3 Antidiabetic Activity

Diabetes mellitus (DM) is a metabolic disorder caused by either deficiency of the insulin hormone or an increase in insulin resistance, which shows in hyperglycemia. In a previous study, it was proved that repeated administration of *P. dulce* leaves outstandingly reduces the blood glucose level. This experiment was performed on rats[16]. Methanolic extract of *P. dulce* seed possesses significant antihyperglycemic, antihyperlipidemic and antioxidant potential. Because of this, it is proven that they are beneficial in the treatment of diabetes and associated complications[17]. Oral administration of *P. dulce* fruit extract (300 mg/kg b.w. /day) to diabetic rats for 30 days significantly reduced the levels of blood glucose, glycosylated hemoglobin, urea, and creatinine. It indicates that the fruit extract is nontoxic and possesses an antidiabetic nature[18]. Antidiabetic activity may be due to the presence of phytoconstituents like sterols, alkaloids, glycosides, saponins, tannins, carbohydrates, proteins, phenolic compounds, and flavonoids in the alcoholic extract of of *P. dulce* bark[19].

3.4 Hepatoprotective Activity

The liver is the major organ of our body and it is responsible for the metabolism of drugs and toxic chemicals. Thus, it is the primary target organ for nearly all toxic chemicals[20]. Various pharmacological or chemical substances (such as acetaminophen, galactosamine, chloroform, dimethyl nitrosamine, etc.) are responsible for causing hepatic injuries. Ethanolic extract of *P. dulce* has a hepatoprotective effect in paracetamol-induced hepatotoxicity. Ethanolic extract *P. dulce* (EEPD) leaves showed dose-dependent activities on liver and liver function tests revealed that administration of EEPD at a dose of 400mg/kg showed hepatoprotective effect[21]. The Aqueous extract of *P. dulce* fruits (AEPD) could be a useful agent against CCl_4-induced hepatic pathophysiology[22]. In a previous study, it is also proved that ethanolic extract of dog fruit rind at a dose of 100 mg/200 g has hepatoprotective activity against CCl_4 induced liver damage in rats because dog fruit rind encompasses alkaloid, flavonoid, tannin, quinone, and polyphenols. Particularly, flavonoids and polyphenol have antioxidant activity against free radicals[21,23].

3.5 Cardioprotective Activity

Leaves, seeds, fruits, and wood bark extracts of *P. dulce* were a potentially rich source of antioxidant phytochemicals[10]. Cardioprotective efficacy of ethanol and aqueous fruit extract of *P. dulce* was evaluated in isoproterenol-induced rats. Cardiac toxicity marker enzymes such as Serum Glutamate Oxaloacetate Transaminase (SGPT), Serum Glutamate Pyruvate Transaminase (SGOT), and Creatine Phosphokinase (CPK), And Lactate Dehydrogenase (LDH) were significantly induced with the administration of isoproterenol. Co-administration of extracts along with *P. dulce* extract significantly reversed the cardiac damage induced by isoproterenol[24]. In a previous experiment, myocardial infarction was induced by injecting intraperitoneal isoproterenol (ISO) at dose of 2 mg/kg in one group of experimental rats whereas in other groups of experimental rats, aqueous and ethanolic extract of *P. dulce* fruit peel at a dose of 200 mg/kg was administered intraperitoneally for a period of 14 days followed by injecting intraperitoneal isoproterenol (ISO) at dose of 2 mg/kg. After 14 days of treatment with aqueous and ethanolic extract of *P. dulce* fruit peel in ISO-induced myocardial infarction, rats show positively altered activities of marker enzymes and the biochemical parameters[25].

3.6 Adulticidal Activity

The larvicidal and ovicidal activities of *P. dulce* were proved against *Aedes aegypti, Culex quinquefasciatus, Anopheles stephens* mosquitos. These agents are responsible for dengue, filariasis, malaria, and viral encephalitis like many diseases, which are widely distributed in the tropical and subtropical zones. One of the most efficient strategies for the spreading of dengue virus transmission is to prevent the spreading of disease-carrying mosquitoes. Chemical-based mosquito repellent spray is usually toxic to other beneficiary life forms and may cause severe breathing problems in humans too. So, to reduce the toxic effects of synthetic chemicals, natural or phytochemicals derived repellents can be used to repel the insects. The use of phytochemicals is one of the most important strategy for mosquito control[13,26]. In previous studies, high adult mortality was found in the methanol leaf extract of *P. dulce* against the adults of *A. stephensi* (vector of malaria disease) with the LC_{50} and LC_{90} values were 197.91, 137.33 mg/L respectively[27]. Experimentally, it has been found that seeds extract of this plant has moderate larvicidal and ovicidal effects as compared to leaf. Zero hatchability of *An. stephensi* eggs were attained at the concentration of 400 mg/l for leaf extract and 500 mg/l for seed extract of *P.dulce*[28].

3.7 Antiulcer Activity

Peptic ulcer disease refers to pathological damage that causes ulcers in gastrointestinal tract exposed to acid-activated pepsin. There are three common forms of peptic ulcers: gastric ulcers (inside the stomach), esophageal ulcers (inside the esophagus) duodenal ulcers (inside the duodenum). Treatment of ulcers with ranitidine alcoholic and aqueous extract significantly prevents the number of ulcers, induced by pylorus ligation. Results indicated that 66.6% gastro-protection with ranitidine, 55.56% gastro-protection with alcoholic extract of *P. dulce* at 100 mg/kg, and 61.11% with aqueous extract of *P. dulce* at dose of 100 mg/kg as compared with ulcerated control. The antiulcer activity is probably due to the presence of bioactive compounds like flavonoids- quercetin, rutin, kaempferol, naringin, and daidzein[29]. Cell proliferation was found to be enhanced in drug received animals. The total protein bound carbohydrate to total protein ratio was found to be significantly maintained by hydroalcoholic fruit extract of *P. dulce* (HAEPD). Ulcer score was significantly minimized in HAEPD-administered animals at the dose of 200 mg/kg body weight for 30 days[30].

3.8 Locomotor Activity

In a previous study on the locomotor activity, aqueous and alcoholic extracts of *P. dulce* leaves showed that both extracts caused significant CNS depression action and hypnotic and skeletal muscle relaxation activity in albino mice. Aqueous and alcoholic extract of leaves of *P. dulce* shows 93.3 percent and 63.3 percent CNS depressant activity at a dose of 100mg/kg respectively[31]. The alcoholic extract of *P. dulce* may increase in the concentration of GABA in brain and has better CNS depressant activity[32].

3.9 Antihyperlipidemic Activity

The excess glucose is usually preserved as glycogen and then fat in our body tissues as storage fuel for the future. It is one of the major risk factors involved in the development of type II diabetes, heart disease, etc[11]. Currently, available hypolipidemic drugs have been associated with a number of side effects compared with allopathic drugs. In previous studies, it is proved that all triton-induced rats displayed

hyperlipidemia as shown by their elevated levels of serum and liver cholesterol, triglyceride (TG), Very Low-Density Lipoprotein (VLDL), Low Density Lipoprotein (LDL), and also the reduction in the High-Density Lipoprotein (HDL) level. *P. dulce* treatment at dose of 200 mg kg-1 was effective in reduction of level of cholesterol, TG, VLDL, LDL, and HDL[33, 34].

3.10 Anti-Inflammatory

Anti-inflammatory effect of a substance may be defined as it has property to reduce inflammatory symptoms such as pain, heat, redness, swelling, and loss of function. Several drugs have been utilized against the inflammation and specific to this the drug aspirin has been utilized by the predominant people all over the world. Long-term use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can cause gastric erosions, which can become stomach ulcers and in extreme cases can cause severe hemorrhage, resulting in death[35]. The methanol extract of leaves of *P. dulce* Benth was screened for analgesic and anti-inflammatory activity at the doses of 200 and 400mg/kg body weight. The maximum anti-inflammatory response was produced at 3 hours with extract doses of 200 and 400 mg/kg[36].

3.11 Antidiarrheal Activity

In diarrhea, variation occurs in bowel movements. We can easily identify this disease by its characteristics such as increase in water level, volume, and repetition of stool. *P. dulce* contains pharmacologically active substances with antidiarrhoeal properties. These attributes may provide the rationale for the use of *P. dulce* in diarrhea management by traditional healers. Ethanolic extract of *P. dulce* at concentration of 400 mg/kg body weight showed approximately 70 percent reductions in diarrhea [37]. Result also showed that with administration of the aqueous extract of *P. dulce* significantly reduced the frequency and has strong antidiarrheal efficacy[4].

3.12 Nephroprotective Activity

Carbon tetrachloride (CCl_4), is widely used antipyretics and as an organic solvent in chemical industries. CCl_4 also works as vermifuge because it is used to treat hookworm infection. It can be absorbed by the skin and inhalation. It can cause serious effects on the liver, brain, kidneys, muscles, and blood. CCl_4 administration caused murine renal dysfunction and cell death by disturbing the status of antioxidant enzyme activities, lipid peroxidation, protein carbonylation followed by the reduction in mitochondrial membrane potential, loss in, unprogrammed cell death and necrosis. The aqueous extract of *P. dulce* fruits protects kidneys against CCl_4-induced oxidative damages in mice model and could be used as an effective protector due to the antioxidative properties, by pathophysiology examination[38]. Phytochemical constituents and pharmacological properties of different parts of *P. dulce* plant are summarised in Table 1.

4. Other Benefits

By the excellent quality nectar and pollen sources, the flowers of *P. dulce* produce high-quality honey**.** Tannin can be extracted from the bark, seeds, and leaves of *P. dulce.* It can help in softening the leather. The tree also produces a reddish-brown, water-soluble exudates gum similar to commercial gum Arabic from Acacia Senegal[39]. The pods are used as a food source by livestock and chickens. The leaves and the young shoots are used for live stock fodder in some areas[40]. Wood is used locally for construction, paneling, boxes, crates, agricultural implements, and cartwheels. Also, wood is used as a domestic fuel in many areas where firewood is in short supply and as fuel for brick kilns in India[41]. A yellow dye is obtained from the bark[42]. The seeds contain about 20% greenish oil, which after refining and bleaching, can be used in the making of soap[43].

4.1 Agroforestry Uses

Fly Ash (FA) stress caused deadly changes in different leaf attributes like sugar, protein contents, photosynthetic pigments, nitrate content, and nitrate reductase activity in foliar tissues of plants growing at a highly contaminated site in comparison to a low-pollution site. *P. dulce* is a FA pollution-resistant plant species. In FA stress condition observed that reduction in net photosynthetic rate and significant increase was observed in the proline, sulfur and nitrogen contents. In this condition, due to an increase in oxidative stress antioxidant enzymes such as Ascorbate Peroxidase (APX), Catalase (CAT), Peroxidase (POD), and Superoxide Dismutase (SOD) also increase. Hence, this species may be used for remediation of FA dumps and also used as the biomarker and for mitigation of FA pollution around thermal plants. Further, plantation of this tree species would help in pollution control in an urban area. Experimental results also showed that *P. dulce*

Table 1. Phytochemical constituents and pharmacological properties of different parts of *P. dulce* plant

Parts of plant	Phytochemical constituents	Pharmacological Properties	References
Leaves	Cyclitol, dulcitol, octacosanol, α-spinasterol, kaempferol-3-rhmnoside, quercetin and afzelin	Antibacterial, anthelmintic, larvicidal, and ovicidal against mosquito vectors, skeletal muscles relaxant activity, and CNS depressant	[9,19,27]
Fruits	2,5,6-trimethyl 1,3-oxathiane, trans-3-methyl-3-N-propylthiophane, 2- carboxaldehyde-5-(hydroxymethyl), D-pinitol, heptacosanol,22-tricosenoic acid, methyl-2- hydroxy icosanoate and stigmasterol	Antidiabetic, cardioprotective, positively altered the activities of marker enzymes and biochemical parameters, antiulcer, antioxidant potential, and antimicrobial activity	[9,19,46]
Seed	13 free amino acids out of which 5 (valine, hidtithreonine dine, leucine)	Aedesaegypti, control of postprandial hyperglycemia, inhibitory effect on intestinal α-Glucosidase and pancreatic α-Amylase	[9,19,47]
Roots	Sterols and essential amino acids	Good remedy for diarrhea, Guiana and dysentery	[9,19]
Stem	Alkaloids, anthraquinones, tannins, terpenoids, and sterols exhibiting	Antimicrobial activities, reduce eye information, dysentery, diarrhea, and febrifuge	[9,19]

plant has an antioxidant defence system that leads to increase in stress tolerance effect[44].

4.2 Nitrogen Fixation

P. dulce is well known for its tolerance of heat, drought, salinity, and impoverished soils. *P. dulce* forms nodules with rhizobia. Mostly nodulation is common in all types of soils. The indigenous woody legumes and their root nodule bacteria play an important role in the overall nitrogen fixation in soil. These bacteria convert atmospheric free nitrogen into nitrate form and plant use nitrate in their metabolic processes[45].

5. Conclusions

In this review, we have explored and proven the pharmacological abilities of *P. dulce*. It has a strong potential for health-promoting, disease-preventing properties. In this study, we have summarized that due to presence of secondary metabolites in plant extract it has antioxidant, antifungal, anti-inflammatory, and cardioprotective properties, etc. Phytochemicals investigation proves that plant extracts has efficient pharmacological properties. Thus, bioassay-guided isolation and identification of the bioactive components must be developed to reveal the structure-activity relationship of bioactive components. Therefore, *Pithecellobium* species can be used for the treatment of many severe disorders. However, more studies are still required in future to explore its more applications for therapeutic purposes.

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