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Review Article

Critical Review on *Pongamia Pinnata*: A Versatile Medicinal Plant

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A B S T R A C T

The word herb, as used in herbal medicine, is also known as botanical medicine or as phytotherapy or phytomedicine which means a plant or plant part is used to make medicine to assist in the healing process during illness and disease. So, there are many herbal remedies individually or in combination have been recommended in various medicinal treatises for the cure of different diseases.*Pongamia pinnata* (L.) Pierre is a tree native to Southeast Asia. Recently, interest in *Pongamia pinnata*focused on its potential as a biofuel source as its seeds contain around 40% oil. However, *Pongamia pinnata* has multiple applications beyond biofuel production. *Pongamia pinnata*can also bring socio-economic benefits as its ability to restore degraded and contaminated land provides opportunities for local communities through novel valorisation pathways. These multiple applications have potential to form part of a circular bioeconomy in line with sustainable development goals.*Pongamia pinnata* has a large number of applications, and among those, its medicinal value has been recognised for decades with its roots in Ayurvedic medicine and comprehensive information on *Pongamia pinnata* medicinal uses, phytochemistry, and pharmacology can be found.The literature covering the multiple applications of *Pongamia pinnata*is vast and it is beyond the scope of this study to review it in detail.Therefore, the present review aimed to compile up to date and comprehensive information of *Pongamia pinnata* with special emphasis on its phytochemistry, various scientifically documented pharmacological activities, traditional and folk medicine uses alongwith its role in biofuel industry.

Key words: *Pongamia pinnata* (L.) Pierre, Karanjin, biodiesel, flavonoids, chalcones, phytomedicine.

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INTRODUCTION

Plants have been used for thousands of years to flavour and conserve food, to treat health disorders and to prevent diseases including epidemics. The knowledge of their healing properties has been transmitted over the centuries within and among human communities. Active compounds produced during secondary vegetal metabolism are usually responsible for the biological properties of some plant species used throughout the globe for various purposes, including treatment of infectious diseases. The use of plants for treating diseases is as old as the human species[1]. Popular observations on the use and efficacy of medicinal plants significantly contribute to the disclosure of their therapeutic properties, so that they are frequently prescribed, even if their chemical constituents are not always completely known. All over the globe, especially in South American countries, the use of medicinal plants has significantly supported primary health care. From 250-500 thousand plant species are estimated to exist on the planet, and only between 1 and 10% are used as food by humans and other animals. Brazil has the world's highest biodiversity, accounting for over 20% of the total number of known species. This country presents the most diverse flora, with more than 55 thousand described species, which corresponds to 22% of the global total[2,3].

The 'Pongam Tree' is known as one of the richest and brightest trees of India. The tree is named as '*Pongamia pinnata*' in science. The name 'Pongamia' has derived from

the Tamil name, 'pinnata' that refers to the 'Pinnate leaves'. The tree is a member of the 'leguminosae' family. Its sub family is 'Papilionaceae'. In the Tamil, this is generally known as 'Ponga', 'Dalkaramacha', 'Pongam' and 'Punku'. In both the languages of Hindi and Bengali, the people named it as 'Karanj' or 'Papar' or 'Kanji'. It is called 'Karum Tree' or 'Poonga Oil Tree' in English. It is an Indo-Malaysian species, a medium-sized evergreen tree, common on alluvial and coastal situations from India to Fiji, from sea level to 1200 m. Now found in Australia, Florida, Hawaii, India, Malaysia, Oceania, Phillippines and Seychelles[4-6].

Pongamia pinnata (L.) Pierre (Pongamia) is a tree which traditionally, has been used in India and neighbouring countries as a source of traditional medicines, green manure, wood, animal fodder, fuel, bio-pesticide, and fish poison. *Pongamia pinnata* produces natural chemical compounds, such as karanjin and pongamol, which impart bitter taste to the foliage and other parts of the tree.

Botanic description

Pongamia pinnata is a medium-sized evergreen or briefly deciduous, glabrous shrub or tree 15-25m high, with straight or crooked trunk 50-80cm or more in diameter and broad crown of spreading or drooping branches. Bark grey-brown, smooth or faintly vertically fissured. Branchlets hairless with pale stipule scars.Leaves alternate, imparipinnate with long slender leafstalk, hairless, pinkish-red when young, glossy dark green above and dull green with prominent veins beneath when mature. Leaflets 5-9, paired except at end, short-stalked, ovate elliptical or oblong, 5-25 x 2.5-15cm, obtuse-acuminate at apex, rounded to cuneate at base, not toothed at the edges, slightly thickened

Table 1: Vernacular names[7-9]

Language	**Vernacular name**
Telugu	Pungu, Gaanuga
Sanskrit	Ghrtakarauja, Karanjaka, Naktahva, Naktamala
Hindi, Marathi, Guajarati	Karanj, Karanja
English	Indian beech
Tamil	Ponga, Pongam
Kannada	Honge, Hulagilu
Malayalam	Pungu, punnu, Ungu, Unu, Avittal
Oriya	Koranjo
Punjabi	Sukhehein, Karanj, Paphri
Assam	Karchuw
Bengali	Dahara Karanja, Karanja, Natakaranja
Urdu	Karanj

Inflorescence raceme-like, axillary, 6-27cm long, bearing pairs of strongly fragrant flowers; calyx campanulate, 4-5mm long, truncate, finely pubescent. Flower clusters at base of and shorter than leaves, to 15cm long, slender, drooping. Flowers 2-4 together, short-stalked, pea-shaped, 15-18mm long. Calyx campanulate, 4-5mm long, truncate, finely pubescent; corolla white to pink, purple inside, brownish veined outside, 5-toothed, standard rounded obovate 1-2cm long, with basal auricles, often with green central blotch and thin silky hairs on back; wings oblong, oblique, slightly adherent to obtuse keel[1,10,11].

Table 2: Taxonomical classification[12,13]

Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Fabales
Family	Leguminosae
Genus	*Pongamia*
Species	*P. pinnata*
Botanical Name	***Pongamia pinnata* (L.) Pierre**

Pods borne in quantities, smooth, oblique oblong to ellipsoid, 3-8 x 2-3.5 x 1-1.5cm, flattened but slightly swollen, slightly curved with short, curved point (beaked), brown, thick-walled, thick leathery to sub-woody, hard, indehiscent, 1-2 seeded, short stalked. Seed compressed ovoid or elliptical, bean-like, 1.5-2.5 x 1.2-2 x 0.8cm, with a brittle coat long, flattened, dark brown, oily.This species has been placed alone in its genus Pongamia, derived from the Malabar local name (pongam). In 1972, S. R. Bennet, an Indian taxonomist gave the pongam a new name, Derris indica (Lamk.) Bennet, but this change has not been generally adopted. The name Derris, derived from Greek, means 'leather covering or skin'; the specific name 'indica' obviously means of India[14-16].

Biology

In Florida, it sheds its leaves in April and develops new leaves and flowers from May onwards. In India, seed ripens from February to May. Pod production starts 5-7 years after sowing. They do not open naturally, and must decay before seeds can germinate[17].

Documented species distribution

Native: Bangladesh, India, Myanmar, Nepal, Thailand.

Exotic: Australia, China, Egypt, Fiji, Indonesia, Japan, Malaysia, Mauritius, New Zealand, Pakistan, Papua New Guinea, Philippines, Samoa, Seychelles, Solomon Islands, Sri Lanka, Sudan, Tonga, United States of America.

Ecology

P. pinnata is native to humid and sub-tropic environments; common along waterways or seashores, with its roots in fresh or saltwater. It is very tolerant of saline conditions and alkalinity, and occurs naturally in lowland forest on limestone and rocky coral outcrops on the coast, along the edges of mangrove forest and along tidal streams and rivers. It is a shade bearer and can grow under the shade of other trees; it is, however, not a shade demander and grows well even with full overhead light. It is also drought resistant and well adapted to adverse climatic conditions and soil moisture conditions; prolonged drought may however kill seedlings. In its natural habitat, the species tolerates a wide temperature range. Mature trees withstand light frost, waterlogging and tolerate temperatures of up to 50 deg. C. In addition to rain, trees require a dry season of 2-6 months[18].

Biophysical limits

Altitude: 0-1 200m,mean annual temperature: 1-16 to 27-38(50) deg. C, mean annual rainfall: 500-2 500 mm.

Soil type:P. pinnata can grow on most soil types; best growth is found on deep well-drained sandy loams with assured moisture, but it will also grow on sandy soils and heavy swelling clay soils. It does not do well on dry sands, although it tolerates saline conditions, alkalinity and waterlogged soils.

Products

Fodder: Opinions vary on the usefulness of *P. pinnata* as a fodder; its value is greatest in arid regions. The leaves can be eaten by cattle and are readily consumed by goats however it is not common. The leaves contain 43% dry matter, 18% crude protein, 62% neutral detergent fibre, and in vitro dry matter digestibility of 50%. The press cake (seed residue) after oil extraction is bitter and unfit for use as a sole animal feed. It is high in protein but possess several toxic factors, particularly karanjin, pongamol and tannin. It is suggested as a short-term substitute for other protein sources but never serving as more than a 75% replacement.

Apiculture: *P. pinnata* flowers are considered a good source of pollen for honeybees in India and they yield adequate nectar.

Fuel: With a calorific value of 4,600kcal/kg, pongam is commonly used as a fuelwood. The seed oil was formerly indispensable as an illuminate in lamps, but has been largely replaced by kerosene.

Fibre: The bark fibre is made into string, twine or rope, and the wood provides paper pulp.

Timber: Wood varies from white to yellowish-grey with no distinct heartwood; beautifully grained and medium to coarse textured. Although it is a moderately strong timber that is relatively easy to saw, turn and finish, the wood is not considered a quality timber because it is not durable, tends to split and warp during seasoning and is susceptible to insect attack. The wood is used for cabinet making, cartwheels, posts, agricultural implements, tool handles and combs.

Tannin or dyestuff: Roots yield a natural pigment, pinnatin, which was synthesized in 1967. The wood ash is employed in dyeing. Oil from the seeds is used for leather dressing in tanning industries.

Lipids: Oil is the most important product of the pongam tree and vast amounts of seeds are collected in India for commercial processing of industrial uses. It has been found that the seed contains 27-40% of a thick, yellow or reddish-brown oil and that 2 kg of mature pods will yield about 1 kg of husked kernels. Extracted oil amounts to 13.4% of the whole seed pod; 26.97% of the kernels. The oil has a bitter taste, a disagreeable aroma and a specific gravity of 0.9371 at 15 deg. C. It is used as a lubricant, varnish, water-paint binder and in soap making. It is one of the few nitrogen-fixing trees to produce seeds containing oil.

Poison: The press cake, when applied to the soil is valued as a pesticide, particularly against nematodes. In rural areas, dried leaves are stored with grain to repel insects. Pounded and roasted seeds used to be utilized as fish poison.

Medicine: The seed oil is rubbed as liniment on skin diseases and rheumatic parts. Internally, it is given as a stomachic and cholagogue in dyspepsia and cases of sluggish liver. A seed powder is given as an expectorant in bronchitis and whooping cough, and is also prescribed as a febrifuge and tonic. Seed paste is spread on sores and rheumatic parts. An infusion of the leaves is used to relieve rheumatism, a decoction is a cough remedy, expressed juice is used on herpes and itches, and when they are crushed, applied as a poultice for the treatment of parasitic skin diseases. The flowers are claimed to have anti-diabetic

action. Fresh stem bark is applied to reduce the enlargement of the spleen. It is astringent and taken internally to relieve bleeding hemorrhoids while a poultice of young leaves is laid on externally. The root bark contains a bitter alkaloid and is employed by the people of Guimaras Island in the Philippines as an abortifacient. The antiseptic root juice is put on sores and ulcers and used to clean teeth[11,19-22].

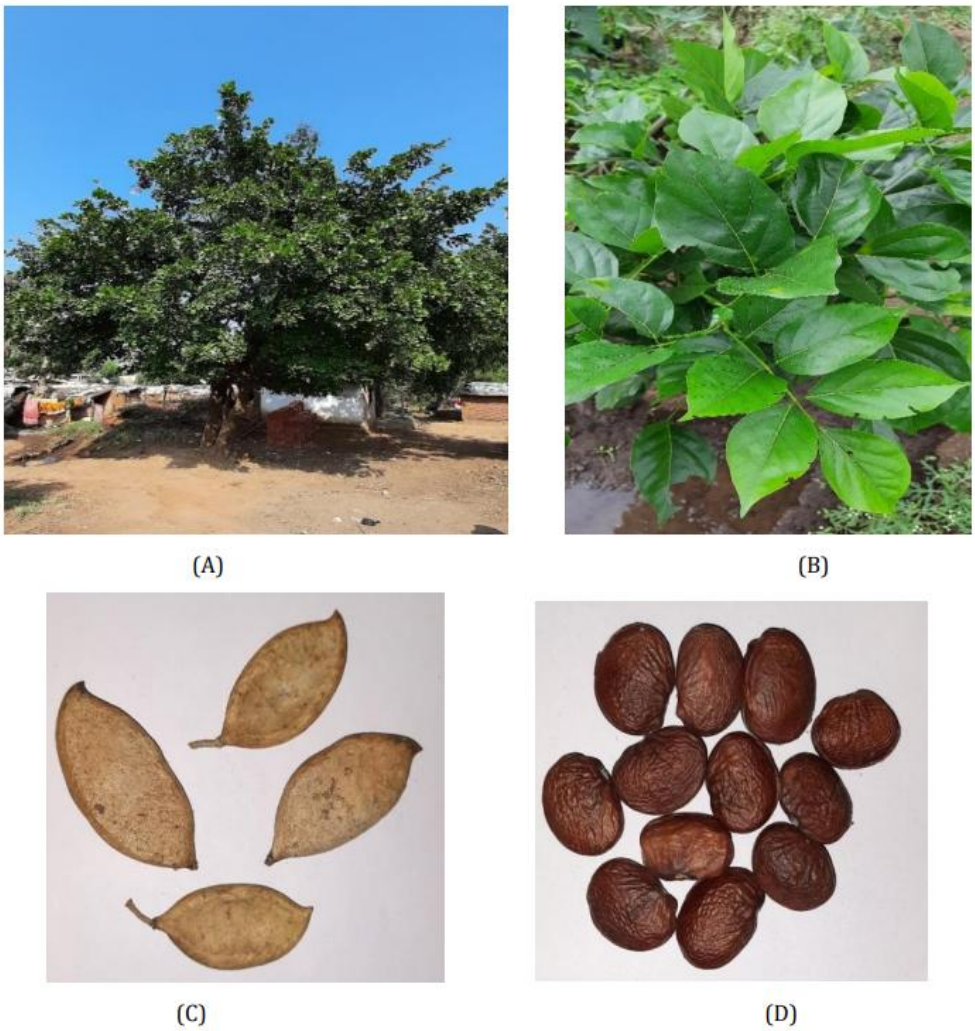

Figure 1: *Pongamia pinnata*: A) The whole plant B) Leaves C) Fruits D) Seeds

Figure 2: *Pongamia pinnata* fluorescence

Table 3: Traditional uses[22-24]

Plant part	Use
Leaves	Whole leaves used as a digestive, laxative and to treat inflammation and wounds. Leaf juice aids in treatment of leprosy, gonorrhea, diarrhea, flatulence, coughs, and colds. Leaf infusions and extracts treats alleviate rheumatism and itches, respectively.
Flowers	Used to treat bleeding hemorrhoids, or piles.
Seed	Extracts can be used to heal scar tissue tumours, treat high blood pressure, and treat anemia. Powder reduces fever and helps in treating bronchitis and whooping cough.
Oil (extracted from seed)	Used as an astringent and to kill parasitic worms. Helpful in treating whooping cough, piles, liver pain, chronic fever, ulcers, and leprosy. Relieves sore joints and muscles and arthritis Used to treat eczema and other skin irritations when mixed with zinc oxide.
Stem	Extracts used to lower or relieve fever and to sedate the central nervous system.
Root	Used as a toothbrush for oral hygiene, used for killing parasitic worms, and used to treat vaginal and skin diseases. Juice used to clean ulcers and to close open sores. Mixed with coconut milk and lime water, juice can treat gonorrhea.
Bark	Relieves coughs and colds, reduces spleen inflammation, and mental disorder. Useful for treatment of bleeding piles.
Fruits	Used as female genital tract infections, ulcers, anti-filarial activity and in abdominal tumours.

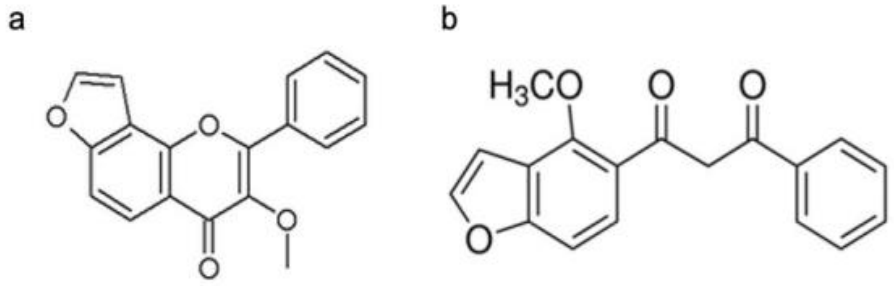

Figure 3: Structure of a) Karanjin b) Pongamol

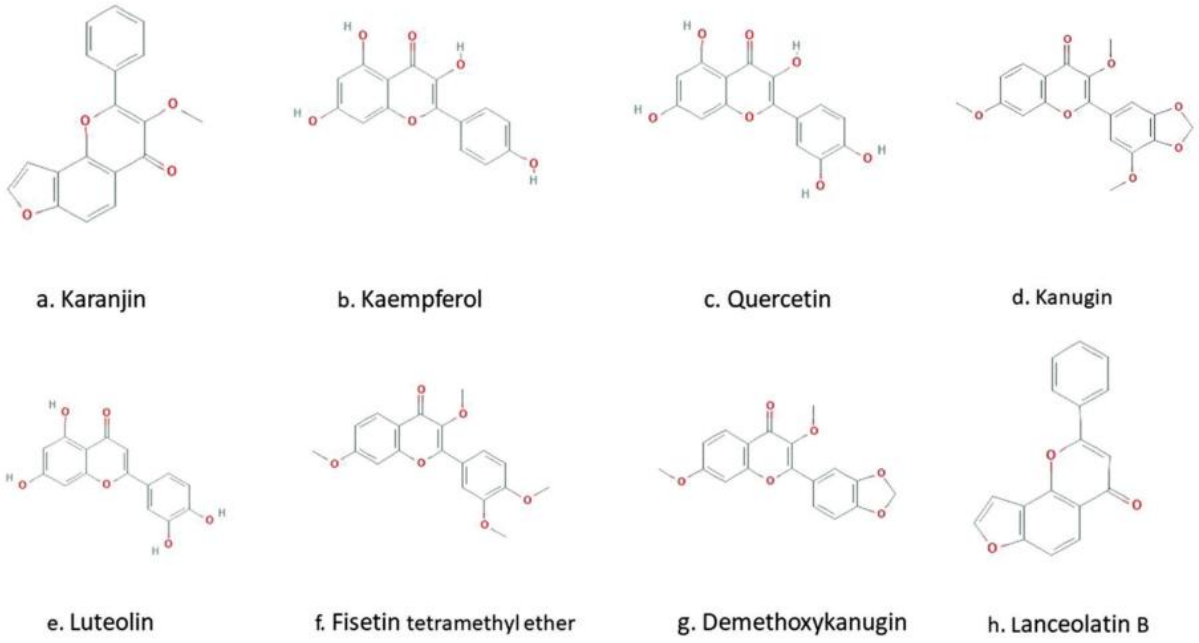

Figure 4: Flavones of *Pongamia pinnata* and their derivatives

Other products: In India, the tree is a host for the useful lac insect. It is also used as a host for the hemi-parasitic sandalwood.

Phytochemistry

There are various chemical constituents isolated from the plant *P. pinnata*. Flavonoid and its derivatives are the most common constituents for isolation. The derivatives of flavonoids are flavones, flavans, and chalcones. Sesquiterpene, diterpene, triterpenes, steroids, amino acids, disaccharides, fatty acids, and ester compounds are also detected in this plant[22,25].

Pharmacology

Several scientific research/studies showed that, this plant consists of various pharmacological activities such as anti-oxidant, anti-microbial, anti-parasite, anti-inflammatory, anti-convulsant, anti-diabetic, anti-hyperammonemia, anti-ulcer, cytotoxicity, anthelminthic, and many others. They are mentioned below:

Anti-inflammatory activity: In acute, subacute and chronic inflammation models, the authors demonstrated the anti-inflammatory efficacy of 70% ethanolic extract of *P. pinnata* leaves in rats. These findings indicate that the extract of *Pongamia pinnata* leaves has substantial anti-inflammatory activity without ulcerative activity, indicating its potential as an anti-inflammatory agent for use in the treatment of various inflammatory diseases[26].

Cardioprotective activity: The authors investigated the cardioprotective activity of *P. pinnata* in diabetic rats with streptozotocin-nicotinamide. The authors researched the effect of *Pongamia pinnata* stem bark petroleum ether extract on cardiomyopathy in diabetic rats[27].

Anti-ulcer activity: Reported studies showed that the methanolic extract of roots of *P. pinnata* tends to decrease acetic acid-induced ulcers. Ulcer protective effect of methanolic extract of *P. pinnata* roots was due to augmentation of mucosal defensive factors such as mucin secretion, the life span of mucosal cells, mucosal cell glycoproteins, and cell proliferation[20,28].

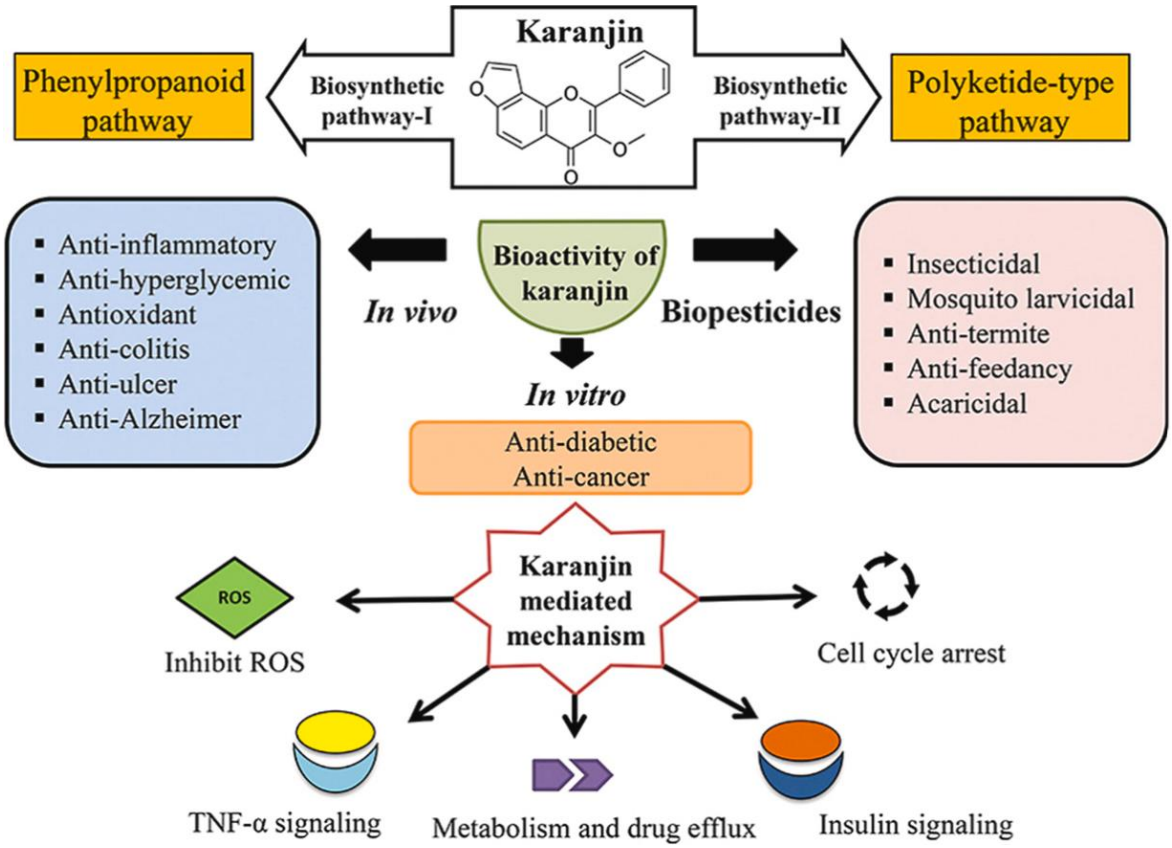

Figure 5: Biological properties of Karanjin

Anti-hyperglycaemic and anti-lipid peroxidative activity: It has been reported that oral administration of ethanolic extract of *Pongamia pinnata* flower shows significant anti-hyperglycemic and anti-lipid peroxidative effect and enhancement in anti-oxidant defense system in alloxan-induced diabetic. These results suggested that the treatment of *Pongamia pinnata* extract could be used as a safe alternative anti-hyperglycemic drug for diabetic patients[29-32].

Anti-bacterial activity: The potential for anti-bacterial properties for this plant is varied depending on the solvent used during the extraction process of phytoconstituents. For instance, the methanol and ethanol extract of the seed of the tree with a dose of 100µg/ml have shown definite anti-bacterial activity on certain pathogens in clinical settings such as *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Micrococcus luteus*. They stated that the strongest zone of inhibition was observed from the seed of the *P. pinnata* and it might be due to the content of the karanjin. Later, the

treatment of karanjin against the bacterial strain of *Staphylococcus aureus* and *Escherichia coli* enterotoxin caused some morphological changes towards the organism. There were shrinking, membrane disruption and break down of the cell wall was observed in the bacterial cells. The researcher concluded that this compound might cause lysis of both organisms due to the significant membrane disruption and interruption of cell wall architectures[12,33,34].

Anti-Alzheimer's disease activity: *Pongamia pinnata* is traditionally used for the treatment of mental problems and also used as a brain tonic in different parts of India. Previous studies on *Pongamia pinnata* showed antistress, neuroprotective and antianxiety activities. Anti-Alzheimer's activity of karanjin was evaluated through elevated plus maze and Morris water maze (MWM) model on Swiss albino mice. Results of this study showed significant ($P<0.01$) anti-Alzheimer's activity of karanjin (25 and 50mg/kg) and demonstrated improvement in learning, memory and inhibited the symptoms of diazepam induced memory loss in experimental animals. The findings of this study suggested that karanjin may be useful in the treatment of the patients suffering from Alzheimer's disease and memory-related disorders[35].

Pongamia pinnata plant also possess various ethnopharmacological activities like anti-ulcer activity, anti-diarrhoeal activity, anti-oxidant and anti-hyperammonemic activity,anti-plasmodial activity, anti-lice activity, anti-viral activity, anti-protozoal activity, anti-convulsant activity, anthelmintic activity, neuroprotective activity, immune modulatory and anti-cancer activity[1,3,14,36,37].

Other activities: The karanjin may be used to control the mosquito populations. Thekaranjin was produced potent toxicity towards *Culex pipiens*pallens, *Aedes aegypti*, and *Aedes albopictus* larvae. Molecular docking studies of karanjin was carried out with the receptors responsible for psoriasis (IL-17A, IL-17F, IL-23, RORγt, and TLR-7). The docking score result of karanjin was well comparable with methotrexate, a known drug used for treating psoriasis. Overall, the results suggested that Karanjin could be used as a natural and better alternative in curing psoriasis without any side effects[14,37].

Pharmacokinetic and bioavailability of karanjin

Due to the limited research focus on the pharmacokinetic characteristics of karanjin, a complete overview of the absorption, distribution, metabolism and excretion profiles of karanjin is still relatively lacking. To date, there have been only one report on pharmacokinetic studies of karanjin in rats. Pharmacokinetics of karanjin in experimental animals by RP-HPLC method and the parameters were analyzed using non-compartmental model. The absorption of karanjin was rapid in animals with T_{max} of 2.307 ± 0.11 h and $t_{1/2}$ value of 3.78 ± 0.30 h. Further, the pharmacokinetic results designated that the karanjin has been eliminated from systemic circulation at 24 h. Findings of this study recommended that the results would be valid for the future study on karanjin for its different therapeutic uses and also beneficial for justifying the dosage and route of administration from its formulations[14,45].

Seed oil as biofuel

Pongamia pinnata has been widely studied as a potential feedstock for biodiesel fuel, though little is known about its feasibility at a commercial level. *P. pinnata* plant is considered as a source of biodiesel. Oil is extracted from the seeds of the *P. pinnata*. Seed oil is a thick, yellowish, or reddish-brown having calorific value of 40.756MJ/kg. The oil is extracted through expeller and solvent extraction. The seeds of karanja contain at least 27–40% of oil. There are many factors affecting the quality of the oil (biodiesel) such as viscosity, flash point, calorific value, specific gravity, and acid value/free fatty acid content. The free fatty acid content is very high in seed oil of karanja. Biodiesel produced through 2-step transesterification process. The Karanja oil also undergoes in 2 step processes in which acid-esterification done before alkali transesterification. In some supercritical conditions, both the steps can be carried out simultaneously because of the shortage of time.

Microwave and CaO as a heterogeneous catalyst are used to enhance the transesterification process. The transesterification process addresses some issues like high viscosity, same as other vegetable oils. Therefore, the karanja oil is not suitable for direct use in a diesel engine. After addressing these issues by this process, the quality of karanja oil methyl ester (biodiesel) is produced that is also cost-effective. There is a various method for the production of biodiesel from the karanja oil such as pyrolysis, micro-emulsion, and bleeding. In recent years, Karanja oil is considered as a good commercial option over other mineral fuels. The use of various anti-oxidants in the karanja oil improves the oxidation stability, cost-analysis of biodiesel[1,38-39].

Nutrition for farm animals

Previously in studying nutrition regarding this molecule, karanjin was included in a cake ingredient to make a karanj cake. Solvent extracted karanj cake did not cause any digestion problem to lambs, however, the lambs which were fed with 50% expeller pressed karanj cake showed the lower percent of digestibility of dry matter, organic matter, crude protein, total carbohydrate, neutral detergent fiber and acid detergent fiber. Hence, solvent extracted karanj cake could be given to the lambs without causing any harm for 98 days but not for expeller-pressed karanj cake as it might disrupt nutrient intake and digestibility.

In other studies, the researcher found out that the usage of detoxified karanja cake for farm animals could be added as a replacement of soybean meal, but only at low levels as the higher level of replacement might cause danger. Findings suggested that there was no interruption at total protein levels, including enzymes. In an experiment, the lambs that were given with damage-causing extract cake that was washed by water did not show any adverse effects. After the experiment was done for 196 days, several organs were collected to see the function. It showed normal activities in serum enzymes, no damage features of tissues in the liver, intestine, parathyroid gland and testis. There was no rupture or lesion in the organ. Karanjin infused in the ingredient of the cake as nutrition for the farm animal is an excellent alternative in regards to its quality attributed[40-42].

Toxicity

LD_{50} for Karanjin was found to be 14.32mg/kg and of pongamal 17.14mg/kg body weight. The pure oil did not show lethal effect even at 20ml/kg body weight. Karanja oil is found to be most toxic and it is prepared to have an adverse effect on the body of mice. Karanjin and de-Meo-Karanjin are also reported to be toxic compounds[14].

Food security and socio-economic benefits

While most of the attention on *Pongamia pinnata* in recent years has focused on its potential as a sustainable source of biofuel, and the vast majority of literature refers to *Pongamia pinnata* as a non-edible crop, recently, Terviva® has invested in research and development to cultivate and market *Pongamia pinnata* as a sustainable food source. After ten years of trials in North America, initially using elite trees from Australia, the company has patented technologies to process *Pongamia pinnata* seeds into edible grade protein for both human and animal consumption, and to refine crude Pongamia oil into food-grade vegetable oil. In comparison with other oil and protein crops, except for palm oil, *Pongamia pinnata* yields are higher than most which combined with its ability to grow in marginal land, has huge implications for food-security at a time where sustainable food sources are vital. However, this might reduce *Pongamia pinnata* value as a biofuel feedstock given the debate surrounding the use of land for food vs fuel. It remains to be seen what part *Pongamia pinnata* will play as a sustainable food source and whether in the case of *Pongamia pinnata*, food security and sustainable biofuel production can be complemented. Although *Pongamia pinnata* seed cake, the by-product of the oil extraction process, is rich in protein, is not normally used as a source of animal feed due to the presence of anti-nutritional factors (ANFs) such as phytates, saponins, karanjin and pongamol[43,44].

CONCLUSION

In traditional system of Ayurvedic medicine *Pongamia pinnata* has been widely used as curative agents for variety of ailments. Concentrated fruits or seeds extract can be found in various herbal preparations are widely available in market today. *Pongamia pinnata* preparation oil is widely available and employed by practitioner of natural health for treatment of rheumatism. In the traditional systems of medicines, such as Ayurveda and Unani, the *Pongamia pinnata* plant is used for anti- inflammatory, anti-plasmodial, antinociceptive, anti-hyperglycaemic, anti-lipid peroxidative, anti-diarrhoeal, anti-ulcer, anti-hyperammonic and anti-oxidant, anti-bacterial. Its oil is a source of biodiesel. It has also alternative source of energy, which is renewable, safe and non-pollutant.

This review has provided a comprehensive view about the botanical description, phytochemistry and pharmacology of *Pongamia pinnata*. However, further study on the phytochemistry and the mechanisms of the chemical constituents in exhibiting certain biological activities are required to fully understand the phytochemical profile and the complex pharmacological effects of this species. Furthermore, more clinical studies on the toxicity of all the plant parts extracts and the other compounds isolated from this plant are also crucial to ensure the safety and to assess their eligibility to be used as sources of modern medicines.Research on the multiple applications of *Pongamiapinnata* has grown considerably in the past decade or so and the growing interest in its commercial viability and environmental benefits indicate the potential of this multifaceted, resilient tree to provide benefits to society at a small and large scale.

Author contributions

All authors contributed todata collection, drafting or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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