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***Calophyllum inophyllum*: A Medical Plant with Multiple Curative Values.**

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ABSTRACT

Calophyllum inophyllum Linn. (Clusiaceae) is a medicinal plant, distributed in many countries of the tropics and subtropics. It has an otablenumber of medicinal properties with high curative value. *C. inophyllum* is very important for its medicinal value. Various parts of this plant such as the leaves, bark, flowers, fruits and seeds were used for the treatment of different ailments in the indigenous system of medicine such as skin diseases, wounds, ulsers, vaginal discharge and the passing of blood after child birth, gonorrhoea, chronic bronchitis, phthisis, sore eyes, heatstroke, migraine and vertigo, and are being employed as antiseptics, astringents, expectorants, diuretics and purgatives particularly in South Asia. Hence, this review focuses on the detailed medicinal uses, phytochemical composition, along with pharmacological properties of this multipurpose *C. Inophyllum* tree.

Keywords: *Calophyllum inophyllum*, pharmacological properties, indigenous medicine, medicinal plant

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INTRODUCTION

In traditional folk medicine various medicinal plants were eaten to treat numerous types of ailments and to improve the health condition. In recent times, these medicinal plants are used based on ethnobotanical evidence available from traditional healers. Hence, the compilation of the ethnobotanical evidence and recent scientific finding of traditional medicinal plants play an important role in the development of modern drug from ancient natural remedies. Therefore, current review focuses on the detailed medicinal uses, phytochemical composition, along with pharmacological properties of this multipurpose *C. inophyllum*.

BOTANY

Scientific name: *Calophyllum inophyllum* Linn (Figure 1).

Common names: Known as Alexandrian Laurel, Laurel Wood, Tamanu, Pannay Tree, Sweet Scented Calophyllum, Beach Calophyllum, and Borneo Mahogany in English. It is known as Bitag in Tropical Asia.

Synonyms: *Calophyllum bintagor* Roxb., *Mesua ferrea* Linn, *Balsamaria inophyllum* Lour., *Calophyllum apetalum* Blanco [Illegitimate], *Calophyllum bintagor* Roxb., *Calophyllum blumei* Wight, *C. inophyllum* var. *blumei* (Wight) Hassk., *C. inophyllum* forma *oblongata* Miq., *C. inophyllum* forma *obovata* Miq., *C. inophyllum* var. *takamaka* Fosberg, *C. inophyllum* var. *wakamatsui* (Kaneh.) Fosberg & Sachet, *Calophyllum ovatifolium* Norona *Calophyllum spurium* Choisy, *Calophyllum wakamatsui* Kanehira.



Figure 1: The *C. inophyllum* tree (A) , flowers (B) , leaf (C) and fruits (D)

Classification

Kingdom	Plantae
Subkingdom	Tracheobionta
Phylum	Tracheophyta
Class	Magnoliopsida
Subclass	Dilleniidae
Order	Theales
Family	Clusiaceae-Guttiferae
Subfamily	Kielmeyeroideae
Tribe	Calophylleae
Genus	Calophyllum
Species	<i>C. inophyllum</i> L.

Distribution

The native of *C. inophyllum* is East Africa, through southern coastal India to Malesia, northern Australia and the Pacific islands which further extended to Philippines, Taiwan, and the Marianas through Southeast Asia [1]. The geographical distribution of this species also includes

The coastal region of Polynesia and Madagascar [2]. During the early migrations of Polynesian settlers, Tamanu has been introduced in Hawai'i from the south Pacific islands [1]. This species was also brought and successfully cultivated in southern China. The habitat of this species is mainly in the coral sands and on the sea shores while some samples may be established in valleys and low land forests [3].

Botanical description

The *C. inophyllum* is a slow growing, medium to large sized tree reaching a height of about 8 to 20 m. The canopy of the tree is widely spread to an irregular crown shape. It has a thick, fissured and grey trunk with a rough and cracked texture of bark. Its sap is milky white.

Leaves of *C. inophyllum* are opposite with largely elliptical or oval lamina of 10 to 20 cm long by 6 to 9 cm wide. The blunt ended leaves are tough and deep shiny green in colour with intimately positioned thin parallel veins organized perpendicularly from a prominently elevated yellowish green midrib to the rounded leaf boundary.

C. inophyllum bears pleasantly scented white flowers in clusters of 4 to 15 flowers each with 4 to 8 delicate oblong petals. Flowers are usually bisexual with a puff of golden yellowish stamens and a pink pistil with a thin, long style and a superior ovary. The flowers are 2.5 cm across and 8 to 14 mm long on long sturdy stalks in leaf axils. The flowering is heaviest in late spring or early summer.

Fruits also grow in clusters, each with a diameter of 2 to 5 cm. The ball shaped light green fruit has a thin compact outer layer with a smooth texture. When the fruit ripe, the skin turns yellow to brown and the smooth texture becomes wrinkled. The fruit holds a large brown seed with a diameter of 2 to 4 cm which contains a pale yellow kernel. The trees usually bear fruits twice a year which falls from April to June and October to December.

Propagation

C. inophyllum are usually propagated through seeds which are the easy sources. However, the germination of the seed is initially slow. Cracking the shells or shelling the seeds entirely will eventually germinate the seeds faster where a study established a fully shelled seed germinate in 22 days, seeds in a cracked a shell took 38 days to germinate, and 57 days for seeds still in their shells. [4] and [5].

ETHNO MEDICINAL USES

C. inophyllum is a well-known ornamental plant species in which its leaves, bark, flowers, fruits and seeds are diversely used in traditional practices. The high medicinal properties of all parts of this plant have also been employed as antiseptics, astringents, expectorants, diuretics and purgatives [6]. Traditionally, its emetic and purgative gum extracted from the wounded bark of the plant has been recorded to be used for treatment of wounds and ulcers. In Asia mainly in India and Indo-china, the astringent bark which contains tannins and its purgative juices are widely used for vaginal discharge and the passing of blood after child birth and also for gonorrhoea [7]. In addition, antineuralgic, diuretic, antiseptic and disinfectant properties of the bark are also well known and act as an expectorant when taken internally which is useful in chronic bronchitis, and phthisis [4]. The resin is helpful in unrelieved catarrh while the infusion of gum, bark and leaves are drawn on for sore eyes. In Fiji and Linga, the leaves soaked in water are applied to inflamed eyes. The leaf infusion have been reported to be useful for the treatment of heatstroke when taken internally and it is also been prescribed as an inhalation for migraine and vertigo in Cambodia. In Philippines, macerated leaves are also used as astringent for haemorrhoids (piles). In Madagascar, Polynesia and Malaysia, bark is crushed into powder to be used for orchitis while the gum resin is a remedial, resolvent and antiseptic. The seed oil is also utilized against psoriasis and antirheumatic [4]. The blond nut kernel in the fruits of *C. inophyllum* is responsible for the dark green, rich and pleasant smelling oil which is impressively readily and completely absorbed when applied to skin, leaving no residue. It is widely been used for treating skin diseases.

PHARMACOLOGICAL ACTIVITIES

The pharmacological properties include antibacterial, anticancer, antiplatelet, anti-inflammatory, antiviral, UV protection activity, antioxidant activity and wound healing activity [8].

Anti-viral activity

Fractionation of *C. inophyllum* extract yielded several active compounds which play an important role against human immunodeficiency virus type 1 (HIV-1). Inophyllum B and P were isolated from the methanol chloride extract of *C. inophyllum* which showed strong activity against HIV-1 by inhibiting the HIV reverse transcriptase with an IC₅₀ value of 38 and 130 nM, respectively [9]. These compounds are also reported to exhibit anti-HIV properties against cell culture with an IC₅₀ value of 1.4 and 1.6 μM, respectively. Coumarin derivatives isolated from *C. inophyllum* extract such as castatolide and inophyllum P are potent HIV reverse transcriptase non-nucleoside inhibitors [10]. Studies reported that inophyllums has a novel mechanism of interaction with reverse transcriptase and has potential to play a role in combination therapy.

Anti-cancer activity

Primary screening of ten 4- phenylcoumarins isolated from *Calophyllum inophyllum* was conducted by Itoigawa and colleagues in the search for anti-tumor-promoting agents and reported that calocoumarin-A displayed a significant inhibitory effect on Epstein—Barr virus early antigen (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate in Raji cells which was further confirmed by an in vivo two stage carcinogenesis test on mouse skin tumor promotion [11]. Although methanol extraction of *C. inophyllum* leaves exhibited a weak anti-cancer activity against MCF-7 and HT-29 cell lines with 31.25% and 22.56% inhibition at 200 μg/ml tested dose, it is believed to show a higher cancer cell death with the identification and isolation of the potent active chemical constituent present in the extract [12].

Anti-microbial activity

An investigation revealed the potential anti-microbial activities of methanol and n-hexane extract of *C. inophyllum* fruit peel against *Staphylococcus aureus*, and *Mycobacterium smegmatis* through the disc diffusion method [13]. Methanolic crude extract exhibit higher zone of inhibition in both *S. aureus* and *M. smegmatis* which are 58.1% and 46.9%, respectively whereas the n-hexane crude extract demonstrated a slightly lower zone of inhibition in those microbes which are 53.8% and 37.5%, respectively. Screening of ethanol and ethyl acetate extracts from various parts of *C. inophyllum* such as leaves, fruits, stems, flowers, and roots against *Salmonella typhi*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli* and *Vibrio cholerae* have been studied through the cup-plate method and demonstrated a promising anti-microbial

properties which can be used in the development of novel drugs for the treatment of contagious diseases caused by pathogens [14]. Several compounds have been isolated from the fractionation of the crude extract of the root bark and nut of *C. inophyllum* which were tested against various microorganisms such as *S. aureus*, *V. angillarum*, *E. coli*, and *C. tropicalis* through the classic agar disc dilution method at 20 µg/disk in which compounds such as caloxanthone A, calophynic acid, brasiliensic acid, inophylloidal acid, calophyllolide, inophyllum C and E demonstrated strong inhibitory activity against *S. aureus* [15]. The presence phenolic compounds in *C. inophyllum* which gives an acidic properties is said to be responsible for the antimicrobial activities. Friedelin, canophyllol, canophyllic acid, inophynone which is derivatives of phenolic group in *C. inophyllum* demonstrate significant bactericidal and fungicidal action [16]. The oil of *C. inophyllum* exhibited antibacterial activity in-vitro against Gram negative bacteria. At 20 µg per disc, the *C. inophyllum* extract inhibited the growth of *Staphylococcus aureus* [17].

Anti-inflammatory activity

Anti-inflammatory effect of ethanolic extract of leaf and stem bark of *C. inophyllum* have been studied on albino Wistar rats through carrageenan induced paw edema and cotton pellet granuloma method which consequently demonstrated a strong activity on both acute and chronic models of inflammation directly proportional to the extract dosage [18]. Acetone extract of *C. inophyllum* leaves displayed potential anti-inflammatory effects against lipopolysaccharide-induced RAW 264.7 cells which successfully suppressed the nitric oxide production and also the expression of iNOS, cyclooxygenase (COX-2) and nuclear factor-kappa B (NF-κB) in a dosage reliant behaviour [19]. The Anti-inflammatory activity of *C. inophyllum* is somewhat due to the presence of friedelin and triterpenes of the friedelin group, specifically canophyllal, canophyllol and canophyllic acid, and the heartwood xanthenes being mesuaxanthone B and calophyllin [20]. This inflammatory agent was found to be effective in both intra peritoneal and oral routes demonstrated in adrenalectomised rats [21].

Antioxidant activity

Antioxidant properties of leaf aqueous and methanolic extracts of *C. inophyllum* have been evaluated which demonstrated a significant free radical scavenging activity and reducing power from the methanolic leaf extract in a concentration dependent manner [22]. The strong antioxidant activity of the methanolic leaf extract was related to the high phenol and flavanoid contents which are 140.28±17.1 mg/g and 177.06±5.29 mg/g, respectively [22]. Several bioactive compounds have been isolated from the leaves of *C. inophyllum* and tested for the antioxidant activity in hyperlipidemia model which revealed the compounds such as the combination of calophyllic acid and isocalophyllic acid, triterpene and canophyllic acid to have a strong antioxidant activity at the concentration of 200 µg/ml [23]. Methanolic leaf extract of *C. inophyllum* was analyzed for its antioxidant activity through DPPH and hydrogen peroxide radical scavenging activity and reducing power activity which showed the highest antioxidant activity when the total content of an active compound called Calocoumarin A is high [24]. The oil of *C. inophyllum* comprises xanthenes and coumarins, which gives rise to the antioxidant properties, specifically by inhibiting the lipid peroxidation. The antioxidant agent of *C. inophyllum* protects the skin cell from damaged by reactive oxygen species (ROS). In the presence of free radicals, the antioxidant content of a cell protects the cell from oxidative antagonist [16].

Anti-platelet activity

Numerous compounds isolated from *Calophyllum inophyllum* including 2-(3-methylbut-2-enyl)-1,3,5-trihydroxyxanthone and 2-(3-methylbut-2-enyl)-1,3,5,6-tetrahydroxyxanthone demonstrated a significant inhibitory activity on platelet aggregation in human whole blood induced by arachidonic acid (AA) with an IC₅₀ values of 115.9 and 113.0 µM, respectively while rubraxanthone displayed anti platelet activity against collagen-induced platelet aggregation with an IC₅₀ value of 47.0 µM [25]. Isolated xanthone compound from *C. inophyllum* showed strong inhibitory activity on platelet aggregation, with the inhibitory effect more than 60%. The responsible compound inhibited 3 H-PAF (Platelet Activating Factor) with IC₅₀ value of 44.0µM [26]. The inhibitory action was greater than that of ginkgolide B (BBN-52 021), a well-known natural PAF-antagonist from *Ginkgo biloba* [27].

Wound healing activity

The oil of *C. inophyllum* has been reported to heal skin wounds or burns caused by corrosive or irritant chemicals, boiling water and exposure to X-ray [4]. Calophyllic acid and lactone was found to be the agent contributing to the oils cicatrising power and reported a significant healing of scar after 6 weeks evidencing *C. inophyllum*'s potential as beneficial natural products [1].

UV protective effect activity

The oil belonging to *C. inophyllum* exhibited significant UV absorption properties. Studies reported that usage of oil at a low concentration (1/10000 v/v) has cytotoxic effect against UV induced DNA damage and oxidative stress. Oil concentrations up to 1% were considered as non-toxic to human epithelial cells, thus unveiled as an important sun protector agent [28].

Antiulcer activity

The xanthones of *C. inophyllum* namely, jacareubin and 6-desoxy jacareubin revealed antiulcer activity in rats [21].

DOSAGE/MODE OF USAGE

The gum extract and the infusion of strips of bark and leaves are used externally for the treatment of wounds and ulcer and also applied for sore eyes. However, for other medicinal purposes, the infusion of bark, root, leaves of *C. inophyllum* are taken internally in decoction form. Scientific information about *C. inophyllum* is not sufficient enough to identify the appropriate range of dosage which is believed to be depends on some factors such as the age and health condition.

TOXOLOGICAL ASSESSMENT

C. inophyllum is reported to have little to no toxicity based on the literature review. Humans consume fruits of *C. inophyllum* even though they are accounted to be faintly toxic [29]. Acute toxicity and lethality test of methanol and chloroform extract of *C. inophyllum* stem bark against albino mice revealed an oral LD₅₀ to be greater than 2000 mg/kg [30] which is characterized as unclassified according to the ranking system of European Economic Community (EEC) for oral acute toxicity (EC Directive 83/467/EEC, 1983). A short term toxicological evaluation of the *C. inophyllum* oil revealed that it has no mortality effect on rats and haematological analysis showed that they are not anaemic [31]. Moderate changes have been observed through the histopathological examination of the sections of heart, liver, kidney and spleen with no deleterious effects recorded. Methanol extract of nut of *C. inophyllum* by column chromatography yielded several active fractions which have been tested for their cytotoxic activity against KB cells in which calophyllolide showed the most significant cytotoxic activity with an IC₅₀ of 3.5 µg/ml while calaustralin showed the least cytotoxic activity with an IC₅₀ of 42.0 µg/ml [15]. Ethanolic extract of twigs of *C. inophyllum* isolated two different chemical constituents namely, gerontoxanthone and 2-hydroxyxanthone which have been reported to exhibit cytotoxicity against chronic myelogenous leukemia cell line (K562) with IC₅₀ values of 7.2 and 6.3 µg ml⁻¹, respectively [32].

PRECAUTIONS/ SAFETY FOR USAGE

Wisdom of our ancestors on the knowledge of medicinal plants should be well utilised with the concern of safety and prospective undesirable effects of the plant. It is important to identify the scientific knowledge of the preparation and application methods of the plants, precautions to be taken, contraindication, and the drug interactions since they are usually self-prescribed. General precautions like washing and cleaning is necessary in order to avoid any presence of pesticide residues on the surface of *C. inophyllum* plant species as well as to wash away the unwanted pollutions. Furthermore, based on several companies material safety data sheet on seed oil of *C. inophyllum*, no hazardous effects have been reported upon ingestion and nor do the health hazard signs or symptoms of exposure [33] and [34]. However, it is important to seek specialized medical guidance from doctors or other certified health care contributor before taking herbs as a medication.

CONCLUSION

Natural products especially plant species are gaining more interest in the drug discovery field due to its traditional medicinal values and the fact that they are rich in valuable compounds which can be extracted to treat diseases. This is a detailed review about the botanical, ethnomedicinal, phytochemistry, pharmacological, and toxicological information on the medicinal herb species called the *C. inophyllum* which have been widely used traditionally as a local medicine. According to the scientific literature on *C. inophyllum*, a broad spectrum of pharmacological properties has been shown by this herb as well as it is reported to be rich in several active bio compounds.

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