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Review Article

Medicinal Plants of Sandy Shores: A Short Review on *Calophyllum inophyllum* and *Thespesia populnea*

Mami Kainuma[1], Shigeyuki Baba[1], Hung Tuck Chan[1], Tomomi Inoue[2], Joseph Tangah[3], Eric Wei Chiang Chan[4*]

[1]*Secretariat, International Society for Mangrove Ecosystems, c/o Faculty of Agriculture, University of the Ryukyus, Okinawa 903-0129, Japan*
[2]*Centre for Environmental Biology and Ecosystem Studies, National Institute for Environmental Studies, Onogawa, Tsukuba 305-0053, Japan*
[3]*Forest Research Centre, Sabah Forestry Department, Sandakan 90009, Sabah, Malaysia*
[4]*Faculty of Applied Sciences, UCSI University, Cheras 56000, Kuala Lumpur, Malaysia*

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ABSTRACT
The phytochemistry and pharmacology of two common tree species of sandy shores, namely, *Calophyllum inophyllum* and *Thespesia populnea* have been selected for review. There was global interest in *C. inophyllum* after its leaves were reported to possess anti-human immunodeficiency virus (HIV) properties. Since then, extensive research has been conducted on *Calophyllum* species. Endowed with prenylated xanthones, pyranocoumarins and friedelane triterpenoids, *C. inophyllum* possesses anti-HIV and anticancer properties. Other pharmacological properties include anti-inflammatory, analgesic, anti-dyslipidemic and wound healing activities. Phytochemical constituents of *T. populnea* include sesquiterpene quinones, sesquiterpenoids and flavonoids. Many studies have been conducted on the pharmacological properties of *T. populnea* with major activities of analgesic, anti-inflammatory, anti-diabetic and anti-hyperglycaemic reported in the bark, leaf, fruit and seed. Anticancer properties are reported in the wood. Representing the flora of sandy shores, both *C. inophyllum* and *T. populnea* have promising and exciting medicinal potentials.

Keywords: *Calophyllum inophyllum*, beach calophyllum, *Thespesia populnea*, portia tree, phytochemistry, pharmacology

INTRODUCTION

In an earlier documentation on the phytochemistry and pharmacology of medicinal plants of sandy shores, we reviewed *Vitex trifolia* and *Ipomoea pes-caprae*[1]. In this article, two more sandy shore species, namely, *Calophyllum inophyllum* and *Thespesia populnea* are selected for review based on their ethno-pharmacological importance and availability of relevant information.

Under the genus *Calophyllum*, the Plant List of 2013 has listed 364 species of which 192 are accepted names, including *C. inophyllum*[2]. Two reviews on *Calophyllum* species have highlighted their anticancer, HIV-1 inhibitory, antimalarial, cytoprotective, antinociceptive, molluscicidal and antimicrobial properties that are attributed to chemical constituents of coumarins, xanthones, flavonoids and triterpenes[3,4]. In the Plant List of 2013, the genus *Thespesia* has 35 species of which 11 are accepted names, including *T. populnea*[5].

Currently, there are four reviews on *C. inophyllum*, namely, *C. inophyllum* (tamanu) – the African, Asian, Polynesian and Pacific panacea[6], *C. inophyllum* (kamani)[7], and biology, agroforestry and medicinal value of *C. inophyllum* (Clusiaceae): a review[8], and pharmacological activities and biological importance of *C. inophyllum*[9]. The species has also been documented under the genus of *Calophyllum*[3,4] and as a book chapter[10], including an article on *Calophyllum* seed oil[11]. No reviews are available on the chemical and pharmacological properties of *Thespesia* species. There are three reviews on *T. populnea*, namely, *T. populnea* (milo)[12], phytopharmacological review on *T. populnea*[13], and review on pharmacological studies of *T. populnea*[14]. Nevertheless, this short review is justified as an update and as comparison between the two coastal species.

CALOPHYLLUM INOPHYLLUM

Botany and uses

Calophyllum inophyllum L. (beach calophyllum, tamanu or kamani) of the family Clusiaceae is a spreading tree of 10–30 m in height[7,15]. It has a pale grey bark with shallow longitudinal grooves. Stems exude a milky white latex when cut. Leaves are glossy, opposite, dark green above, and characterised by fine and dense parallel veins and a pale midrib. Flowers (2–3 cm in diameter) occurring in clusters are showy, white and fragrant with numerous yellow stamens. Fruits are round, single-seeded berries (3–4 cm in diameter) that hang from a long stalk (Figure 1). Seeds are round and brownish-orange when mature.

Occurring along sandy beaches and non-swampy coastal areas, *C. inophyllum* is distributed from East Africa

*****Author for Correspondence: chanwc@ucsiuniversity.edu.my*

through South and Southeast Asia to Polynesia[7,15]. The species is hardy and thrives well on sandy well-drained sites and is resistant to salt spray. A useful tree for shade, shelter and wind-breaks, *C. inophyllum* is quick to establish and is effective in stabilising coastal dunes.

In the Pacific islands, *C. inophyllum* is an ornamental tree and its timber is widely used for boat building[3]. The beautiful and fragrant flowers are made into leis or garlands. It is a sacred tree with different plant parts used as traditional medicine[4,7,16]. Oil from the seed is used for cosmetics, and for treating skin diseases and wounds. A decoction of leaves and stem resin is used to treat eye infections and ulcers, respectively. In China, the species is used as folk medicine for the treatment of eye ailments, wounds, rheumatism and inflammations[17].

Phytochemistry and pharmacology

There was global interest after leaves of *C. inophyllum* were reported to possess anti-human immunodeficiency virus (HIV) properties[18]. Since then, extensive phytochemical studies on *C. inophyllum* and other *Calophyllum* species have resulted in the isolation of diverse compounds. Major classes of compounds of *C. inophyllum* are xanthones, coumarins and triterpenoids. Xanthones have been reported in twigs and branches[17,19,20]; stems and stem bark[21-25]; roots and root bark[26-30]; and branches and wood[20,31]. Coumarins[18] and triterpenoids[32-34] have been identified in leaves. Coumarins dominate seeds[16,35] and seed oil[36].

Xanthones are a class of heterocyclic compounds containing oxygen with yellow coloration and dibenzo-γ-pyrone basic skeleton[37]. They can be classified into simple xanthones, xanthone glycosides, prenylated xanthones, bisxanthones, xanthonolignoids and other xanthones[38]. Xanthones are important because of their diverse pharmacological and biological properties. In *C. inophyllum*, xanthones of the prenylated-type and they include caloxanthones[17,19,20], gerontoxanthones[19] and pyranoxanthones[21].

Coumarins are a large class of phenolic compounds (more than 1300) with fused benzene and α-pyrone rings[39,40]. They have attracted much research interest because of their anticancer properties. Other pharmacological properties include antioxidant, antimicrobial, anti-inflammatory, anti-hypertensive, anti-tubercular, anti-hyperglycaemic and neuroprotective activities. In *C. inophyllum*, coumarins are of the angular-type (pyranocoumarins). Examples are tamanolides[16], inophyllums[18] and inocalophyllins[35].

Triterpenoids constitute a large and diverse class of plant metabolites that contain 4- or 5-membered ring systems with 30 carbon atoms and six isoprene units[41]. They have a wide spectrum of bioactivities such as bactericidal, fungicidal, antiviral, anticancer, spermicidal, cardiovascular, analgesic and anti-allergic properties[42]. Triterpenoids of the friedelane-type such as friedelin, canophyllol and canophyllic acid have often been reported in *C. inophyllum*[32-34]. Other classes of compounds isolated from *C. inophyllum* include secofriedelane and friedelane acids[32], benzodipyranone derivatives[43], inophynone and isoinophynone epimers[44], and flavonoids[45].

Anti-HIV coumarins of calophyllolide and inophyllums have been isolated from leaves and the seed oil of *C. inophyllum*[18,36]. Of these, inophyllums B and P strongly inhibited HIV reverse transcriptase with IC_{50} values of 38 and 130 nM, and were active against HIV-1 in cell culture with IC_{50} values of 1.4 and 1.6 µM, respectively. The bark of *C. inophyllum* inhibited anti-HIV integrase and protease with IC_{50} values of 5.6 and 16 µg/ml for the aqueous extract, and 9.8 and 64 µg/ml for the ethanol extract[46].

Anti-HIV coumarins of *Calophyllum* have a phenyl (C_6H_5) group or an alkyl (n-C_3H_7) group at position 4 of the coumarin skeleton[47]. Other characteristics are the methyl groups at C-10 and C-11, and the OH group at C-12[48]. Examples are inophyllums B and P found in *C. inophyllum* (Figure 2). Anti-HIV coumarins have been associated with modes of action such as inhibition of viral adsorption, reverse transcription, protease inhibition and integration in the HIV replication cycle.

In a review on coastal vegetation as an underexplored source of anticancer drugs, *C. inophyllum* was recognised as one of the 16 species[49]. Coumarins, xanthones and triterpenoids isolated from *C. inophyllum* have been reported to be cytotoxic. Coumarins from *C. inophyllum* were screened for inhibition of Epstein-Barr virus (EBV) in TPA-activated Raji cells[50]. Except for inophyllum C and calocoumarin C, all eight coumarins (apetatolide, calocoumarins A and B, calophyllolide, inophyllums A, D and E, and isocalophyllic acid) exhibited inhibitory activity against EBV with calocoumarin A being the most potent. From the root bark and nuts, calophyllolide, caloxanthone A and inophylloidic acid inhibited nasopharynx cancer KB cells with IC50 values of 3.5, 7.4 and 9.7 µg/ml, respectively[30]. Caloxanthone N and gerontoxanthone C from twigs of *C. inophyllum* exhibited cytotoxicity against chronic myelogenous leukaemia K562 cell line with IC_{50} values of 7.2 and 6.3 µg/ml, respectively[19]. Six xanthones from the stem bark of *C. inophyllum* showed anti-proliferative activity against Raji, LS174T, IMR-32 and SK-MEL-28 cancer cell lines[25]. Macluraxanthone and inophinnin displayed broad-spectrum activity. From stems and leaves of *C. inophyllum*, friedelane-type triterpenes (friedelin, epifriedelanol, canophyllal, canophyllol, canophyllic acid, 3-oxo-friedelan-28-oic acid and oleanolic acid) inhibited the growth of human leukaemia HL-60 cells[33]. Of these compounds, 3-oxo-friedelan-28-oic acid was the most effective with an IC50 value of 2.67 µM.

Other pharmacological properties of *C. inophyllum* include anti-inflammatory and analgesic activities of leaves, stem bark and fruits[51-54], anti-dyslipidemic activity of leaves[55], osteogenic activity of fruits[56], acetylcholinesterase enzyme inhibition of the stem bark[57], and wound healing activity of the seed oil[58].

THESPESIA POPULNEA

Botany and uses

Thespesia populnea (L.) Sol. ex Corrêa (portia or milo tree) of the family Malvaceae is a small, evergreen tree, 6–10 m in height with short and often crooked trunk[12,59]. The

Figure 1: Leaves and fruits of *Calophyllum inophyllum*

crown is round, broad, dense and regular. The bark is greyish-brown with lenticels. Leaves are simple, alternate, broadly ovate, pointed at the tip, and heart-shaped. They are fleshy and shiny with palmate veins, turning yellow and red before falling. Flowers are large, solitary and bell-shaped (Figure 3). Petals are five in number, broad, rounded, overlapping and yellow with a maroon heart at the inside base of the corolla, which corresponds to each petal. Flower colour changes from yellow in the morning to pink or red in the evening. Fruits are round capsules, brown to grey when mature and exude a bright yellow resin when cut. Seeds are brown and hairy.

An important tree in the Pacific, the timber of *T. populnea* is used to make small canoes, and the wood is carved into bowls, utensils and figurines[12]. The bark has been used as cordage. In traditional medicine, the ground bark of *T. populnea* is used to treat skin diseases in India, and dysentery and haemorrhoids in Mauritius[60,61]. Leaves are applied to inflamed and swollen joints to reduce inflammation, and the yellow sticky sap of the plant is used to heal ringworm and other skin infections in India. Fruits are used in Ayurveda medicine to treat diabetes[62].

Phytochemistry and pharmacology

From the wood of *T. populnea*, sesquiterpene quinones such as 7-hydroxycadalene, thespesenone, thespesone, and mansonones D–G and M have been isolated[63]. Subsequently, new sesquiterpenoids (populenes A–H), together with mansonones C, D, E, G, H and S, thespesone, gossypol and 6,6'-methoxygossypol have been isolated[64]. Recently, sesquiterpene quinones, anthraquinones and sterols have been identified from the wood[65].

From the other plant parts, sesquiterpene quinones (mansonones C, E, G and H) have been reported in the leaves of *T. populnea*[66]. Cyanidin rutinoside is the main anthocyanin of the flowers[67]. Other compounds isolated from flowers include kaempferol 3-glucoside, quercetin 3-glucoside and rutin[68], and nonacosane, lupenone, myricyl alcohol, lupeol, β-sitosterol and β-sitosterol-β-D-glucoside[69]. From the bark, gossypol has been isolated[70,71]. Major components of the seed oil of *T. populnea* are linoleic acid (39%), palmitic acid (27%) and oleic acid (16%)[72]. Out of 14 fatty acids identified from the seed oil, steric acid methyl ester (47%) and palmitic acid methyl ester (39%) are dominant[73].

Unlike the phytochemistry of *T. populnea* where information is limited, studies on its pharmacological properties are so extensive that they can only be listed in this short review. The pharmacological properties of the bark of *T. populnea* has been most extensively studied with anti-fertility, antioxidant, antimicrobial, anti-lipid peroxidative, hepatoprotective, antinociceptive, anti-inflammatory, anti-hyperglycaemic, antidiabetic, diuretic, anthelmintic, anti-psoriasis, memory enhancing and anti-diarrhoea activities reported.

From leaves of *T. populnea*, antidiabetic, antioxidant, antimicrobial, analgesic, anti-inflammatory, anti-tumour, nephro-protective, alcohol-induced stress reduction, α-amylase inhibition, anti-ulcer, immune-modulatory and wound healing activities have been reported. From fruits, antidiabetic, anti-hyperlipidemic, anti-hyperglycaemic, antioxidant, antibacterial, antipyretic, wound healing, anti-inflammatory and anthelmintic activities have been reported. Flowers possess antioxidant, antibacterial,

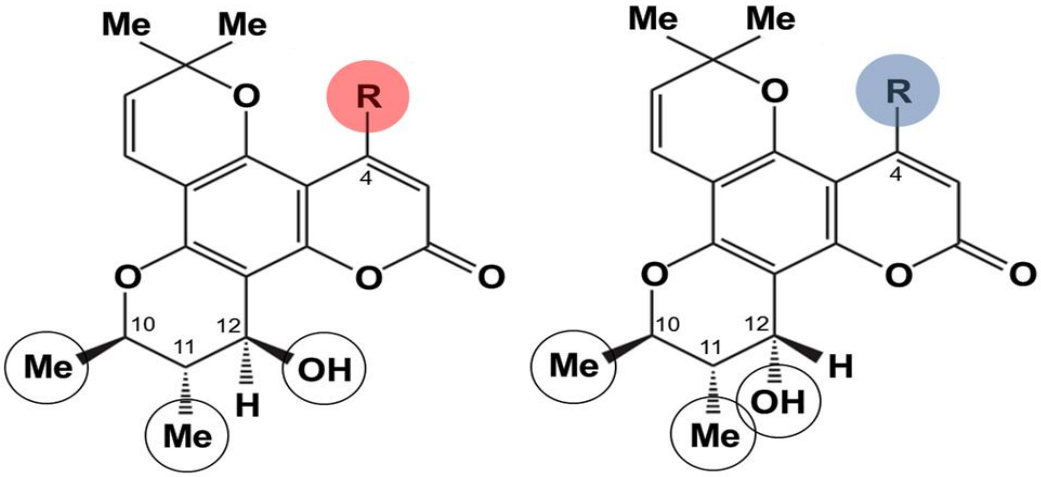

Figure 2: *Calophyllum inophyllum* coumarins with anti-HIV activity
Inophyllum B (left) and inophyllum P (right) with phenyl group (R) at C-4

antiviral, anti-steroidogenic, hepatoprotective and anti-inflammatory activities. Antimicrobial, anti-

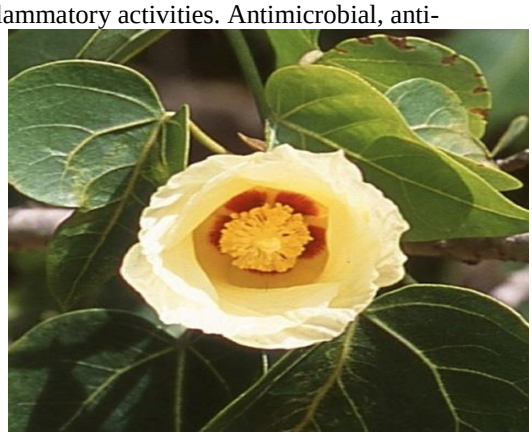

Figure 3: Leaves and flower of *Thespesia populnea*

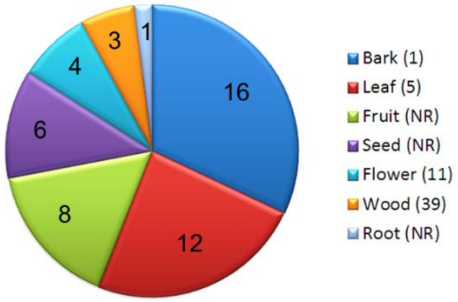

Figure 4: Correlating bioactivities and compounds of *Thespesia populnea*
Figures in sectors: number of bioactivities reported
Figures in brackets: number of compounds isolated
NR: not reported

hyperglycaemic, analgesic, anti-inflammatory, analgesic, antipyretic and anti-fertility activities have been reported in seeds. Among the different plant parts, the wood and roots of *T. populnea* are the least studied. Only cytotoxic and anti-ulcer activities have been reported in the wood, and antimicrobial activity in the roots.

Although a broad spectrum of bioactivities have been reported in *T. populnea*, cytotoxic activity is only reported in the wood. Of the 19 compounds isolated from the wood of *T. populnea*, mansonone E strongly inhibited human cancer cells of MCF-7 and HT-29 with IC_{50} values of 0.05 and 0.18 µg/ml, and gossypol strongly inhibited KB and HeLa cells with IC_{50} values of 0.04 and 0.08 µg/ml, respectively[64]. Thespesilactam (**1**) is a unique sesquiterpenoid alkaloid isolated from the heartwood of *T. populnea*[74]. **1** is small compound ($C_{15}H_{15}NO_3$) containing a benzo-indole scaffold. 3-*O*-Methylthespesilactam (**2**), a methylation product of **1**, was found to possess anticancer activity against A2058 human melanoma cells targeting Janus activated kinase (JAK) and tyrosinase kinase (TYK). **2** inhibited JAK1 and TYK2 most potently with IC50 values of 1.08 and 2.72 mM, respectively.

A simple analysis showed negative correlation between the phytochemistry and pharmacology of *T. populnea* (Figure 4). With only gossypol reported in the bark[70,71], 16 bioactivities have been reported by 18 references. With five mansonones reported in the leaves[66], 12 bioactivities have been reported by 13 references. Conversely, phytochemical studies on the wood of *T. populnea* are most thorough with a variety of sesquiterpene quinones, anthraquinones and sterols isolated[63-65], and yet only antimicrobial, cytotoxic and anti-ulcer activities have been reported by three references. Unaware of the imbalance between knowledge on the phytochemistry and pharmacology of *T. populnea*, scientists continue conducting research on its pharmacological activities, many of which are repetitive. At least six such papers have been published in 2016[75-80].

CONCLUSION

Having xanthones, coumarins and triterpenoids as chemical constituents, *C. inophyllum* possesses anti-HIV and anticancer properties. Through intensive pre-clinical research and clinical trials using identified lead compounds from *C. inophyllum* and other *Calophyllum* species, the prospects of producing drugs with consistent quality, low toxicity and high specificity to treat HIV and cancer are foreseeable. Information on the phytochemistry of *T. populnea* is limited compared to the numerous studies on its pharmacology which continue incessantly with much repetition. Representing the flora of sandy shores, both tree species have promising and exciting medicinal potentials.

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