Majalah Obat Tradisional (Trad. Med. J.), May-August 2024
Vol. 29(2), p 121-142
ISSN-p : 1410-5918 ISSN-e : 2406-9086

Submitted : 30-07-2024
Revised : 29-11-2023
Accepted : 06-06-2024

Calophyllum inophyllum: A Comprehensive Analysis of its Ethnobotanical, Phytochemical, and Pharmacological Properties

Sofa Farida[1,2], Riris Istighfari Jenie[3,4], Nanang Fakhrudin[5,6*]

[1] Master of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Sleman 55281, Yogyakarta, Indonesia

[2] Research Center for Pharmaceutical Ingredient and Traditional Medicine, National Agency of Research and Innovation, Cibinong, Bogor 16915, West Java, Indonesia

[3] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, Sleman 55281, Yogyakarta, Indonesia

[4] Cancer Chemoprevention Research Center, Faculty of Pharmacy, Universitas Gadjah Mada, Sleman 55281, Yogyakarta, Indonesia

[5] Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Sleman 55281, Yogyakarta, Indonesia

[6] Medicinal Plants and Natural Products Research Center, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Sleman 55281, Yogyakarta, Indonesia

ABSTRACT

Nyamplung (*Calophyllum inophyllum* L.) is reported to have ethnomedicinal benefits in traditional medicine systems. Leaves, fruit, seeds, flowers, stems, roots and essential oils are the parts that are often used. Previous scientific studies revealed that this plant part is a valuable resource of secondary metabolites and exhibits a wide range of biological activities. The purpose of this review is to deliver thorough and detailed insights into the traditional uses, chemical ingredients, biology, and pharmacological studies as scientific evidence about the useful efficacy of *C. inophyllum* in the development of modern medicine. Traditional use shows *C. inophyllum* is widely used to treat skin diseases, wounds, boils, vaginal discharge, bleeding, gonorrhea, chronic bronchitis, sore eyes, heatstroke, and headaches. *C. inophyllum* is rich in phenols, polyphenols, flavonoids, xanthones, coumarins, and terpenoids. Several research results show that *C. inophyllum* possesses a multitude of pharmacological properties including anti-cancer, anti-inflammatory, antimicrobial, antioxidant, antiplatelet, antiviral, and antidiabetic activities.
Keywords: ethnopharmacology; tamanu; pharmacology; phytochemistry; toxicology.

INTRODUCTION

The concept of developing medicine from nature which is used empirically is the oldest method that has been implemented for decades by traditional societies. Biological natural resources become more attractive when they are recognized by the public and the world because they have extraordinary potential as raw materials for medicine. Living natural resources are also considered important gene libraries in industrial, agricultural, and health development, giving rise to a new projection, namely bioeconomic (Heinrich & Gibbons, 2010; Sukara, 2005). Bioeconomic prioritizes the utilization of using renewable biological resources to produce materials, food, medicine, etc., that is important for the future development of many fields, including industry, agriculture and health. To date, there is a significant rise in the utilization of medicinal plants both in traditional and modern practices. Recently, several medicinal plants have been found to have potent pharmacological activity, including Cubebin from *Piper cubeba* as anti-platelet and *Acmella oleracea* L. as antithrombotic. Other studies show that extracts of some medicinal plants improve the progression of diabetic nephropathy and treat Alzheimer's disease. This proves that medicinal plants which are still rarely studied, have potential pharmacological activity as natural medicines (Ahmad et al., 2022; Herlyanti et al., 2023; Pramiastuti et al., 2023; Putra et al., 2023; Tiaravista et al., 2023). For instance, the utilization of the traditional tea and decoct is still popular among the elderly; and the modern dosage form of phytopharmaceuticals and cosmetic products that are popular among young generation. As stated by the World Health Organization (WHO), more than 80% of developing countries population relies on herbal medicines for medication 'to maintain health (Canter et al., 2005). Numerous research studies have been conducted to scientifically prove the efficacy of medicinal plants. One of them is Nyamplung (*Calophyllum inophyllum* L.).

***Corresponding author : Nanang Fakhrudin**
Email : nanangf@ugm.ac.id

Calophyllum is a large genus in the Calophyllaceae family with about 180-200 species, which are distributed mainly in tropical forests such as South China and Southeast Asia, East Africa, Madagascar, Pacific islands, America, Australia, and Brazil. The *C. inophyllum* tree is a large hardwood growing in mountain forests and coastal swamps. The Calophyllum genus has wood potential and is a folk medicine for various ailments such as vaginal discharge, rheumatism, scabies, boils, and hair growth (Aminudin et al., 2016; Li et al., 2016). Extracts, subfractions, and isolated metabolites of *C. inophyllum* exhibit enhanced antimicrobial, antioxidant, anti-inflammatory, and antimycobacterial activities (Cassien et al., 2021). Calophyllolide is the main compound isolated from *C. inophyllum* seeds which demonstrates anti-inflammatory, wound healing, anticoagulant, anticancer, and antimicrobial, activities (Arora et al., 1962; Yimdjo et al., 2004).

Tamanu oil, which comes from the seeds of *C. inophyllum*, is traditionally used to treat various skin diseases. Most of the bioactive properties of Tamanu oil are resin compounds. They contain bioactive metabolites that are mostly derived from neoflavonoids including pyranetocarin. Several studies have shown that tamanu oil has anti-inflammatory, antioxidant, antimicrobial, and analgesic abilities, as well as being used for wound healing (Pribowo et al., 2021; Raharivelomanana et al., 2018). There are many empirical and scientific studies on the use of *C. inophyllum*, so it is important to dig deeper into the information on the phytochemical compounds and their pharmacological activities. This is useful as scientific evidence in the development and further research to increase its benefits in the medical field.

METHODS

Literature studies of *C. inophyllum* were collected from electronic databases: PubMed, Science Direct, and Google Scholar. The keywords used to search for publications and information include *C. inophyllum*, ethnomedicinal *C. inophyllum,* phytochemistry of *C. inophyllum*, pharmacological *C. inophyllum*, toxicity of *C. inophyllum*. The data presented in this review are from the original article only.

VERNACULAR NAMES

C. inophyllum is known as Tamanu, Alexandrian laurel, Panay tree, and sweet-smelling Calophyllum. In London, commercial logs of *C. inophyllum* are referred to as 'Borneo Mahogany' (Dweck & Meadows, 2002). In various regions in Indonesia, this tree is known as Nyamplung (Javanese, Sundanese), Nyamplung or Camplong (Madura), Punaga (Minangkabau, Dayak, Bali), Kanaga (Dayak), Mantau (Bima), Pantar (Alor), Fitako (Ternate), and Bintangur (Sumatra) (Faisal et al., 2022; Heyne, 1950).

PLANT DESCRIPTION

C. inophyllum Linn. (Calophyllaceae) is a medicinal plant that is spread in various countries in the tropics and subtropics. *C. inophyllum* grows in East Africa, through the south coast of India to Malesia, northern Australia, and the Pacific islands which then extends to the Philippines, Taiwan, and the Mariana Islands to Southeast Asia. The geographical distribution of this species also includes the coastal areas of Polynesia and Madagascar (Dweck & Meadows, 2002; Shanmugrapriya et al., 2016). *C. inophyllum* trees are often found in coastal areas and has the ability to thrive at an elevation ranging from 100 – 350 meters above sea level. *C. inophyllum* is a medium to large, slow-growing tree, reaching a height of about 8 to 20 m. The trunk is up to 1.50 m in diameter with a very short trunk and low branches close to the ground (Shanmugrapriya et al., 2016; Udarno & Tjahyana, 2019).

The *C. inophyllum L.* tree thrives in direct sunlight, although it exhibits slow growth. Trees can be propagated generatively (seeds) and vegetatively (cuttings). However, for plant propagation, it is generally obtained from seeds, because the fruit of *C. inophyllum* is easy to obtain and bears fruit throughout the year. *C. inophyllum* is very well adapted to various types of soil and soil, so it can be found from the lowlands to the highlands (Leksono et al., 2021; Prabakaran & Britto, 2012).

The development of the *C. inophyllum* flower from the bud to the mature bud takes 27 days after initiation. The flowers bloom for 3 days, then 6 days after anthesis, some of the flowers have fallen that only the ovaries remain. Fruiting from small fruit to ripe fruit takes 10-11 weeks after flowers bloom (Hamim et al., 2019).

The fruit is round with a slightly tapered tip, the color is green, the flesh is thin, the seeds are round and inside the seed, there is a core filled with yellow oil. Flowers emerge from stalks, fragrant, white, clustered, and yellow stamens. The leaves are shiny green, the veins are sharply divided, and the veins are pinnate and visible with petioles up to 1.5 cm long. Long oval leaf shape with a blunt tip and a smooth leaf surface (Sulianti et al., 2006).

ETHNOMEDICINAL USES

The tree of *C. inophyllum* has a large number of medicinal properties with high healing potency.

Its bark, fruit, leaf, flower, and seed are used for traditional medicine to treat wounds, skin diseases, boils, bleeding after childbirth, gonorrhea, vaginal discharge, chronic bronchitis, pneumonia, sore eyes, heartburn, migraines, and vertigo, and are used as antiseptic, astringent, expectorant, diuretic, and laxative, especially in South Asia (Shanmugrapriya et al., 2016). A decoction of the root is commonly used traditionally for the treatment of ophthalmia and boils; the bark is used to cure orchitis; the latex is applied to the skin against rheumatism and psoriasis; whereas the decoction of leaves for combating eye infections. *C. inophyllum* is also traditionally used to relieve leprosy and treat rheumatism. The oil of *C. inophyllum* seed oil is an acceptable source of sustainable biodiesel (Dorla et al., 2019; Gupta & Gupta, 2020).

The stem of *C. inophyllum* is a hard and strong ornamental plant wood and has been used in construction or shipbuilding. The *C. inophyllum* tree also has the benefit of absorbing pollution with a dust absorption capacity of 0.023-0.025 g/m2 per day. Its oil is traditionally used to cure diabetic wounds, sunburn, psoriasis, and abrasions. In southern Africa, it is useful for treating rheumatism, arthritis, eye inflammation, and herpes as well as for treating scalp and hair problems (Sundur et al., 2014; Sutrisno et al., 2020). In Indonesia, *C. inophyllum* leaves are traditionally used as one of the ingredients used in concoctions to treat cancer, according to Riset Tanaman Obat dan Jamu (National Research on Medicinal Plants and Herbs) (Budiarti & Sholihah, 2018).

PHYTOCHEMISTRY

The leaves of *C. inophyllum* contain many phenolic compounds. The total phenolic content of the water and the methanol extracts was 97 ± 9.2 and 140.28 ± 17.1 mg/g, respectively. While the flavonoid content was 88.94 ± 2.94 and 177.06 ± 5.29 mg/g in the aqueous extract and methanol extract of *C. inophyllum* leaves respectively (Dutta & Ray, 2014). Triterpenoids isolated from stems and leaves this plant were epifriedelanol, canophyllal, 3β, 23-epoxy-friedelan-28-oic acid, oleanolic acid, friedelin, canophyllol, canophyllic acid, and 3-oxofriedelan-28-oic acid (Li et al., 2016). Two tetracyclic dipyranocoumarins, namely isocalophyllic acid and calophyllic acid have been isolated from leaves of *C. inophyllum* (Patil et al., 1993). Inophynone and isoinophynone are epimer pairs that have been isolated from the ethanol extract of fresh leaves of *C. inophyllum* (Ali et al., 1999; Khan et al., 2002). Three novel compounds anti-4-aza-B-homo-5 alphacholestane-3-one), trans2-[2-(trifluoromethyl)phenyl]-10b, 10c-dimethyl-10b, and 10c-dihydropyrene were also identified in the leaves of *C. inophyllum* (Susanto et al., 2019).

The stem bark of *C. inophyllum* contains Inophinnin, inophinone, pyranojacareubin, rheediaxanthone A, macluraxanthone, 4-hydroxyxanthone, caloxanthone C, brasixanthone B and trapezifolixanthone (Mah et al., 2015). Other compound isolates that have been isolated from stem bark are caloxanthone E, 1,5-dihydroxyxanthone friedelan-3-one, and calophynic acid (Iinuma et al., 1995; Yimdjo et al., 2004).

Myricetin and Quercetin are found contained in flower stamens (Subramanian & Nair, 1971). Compounds in the *C. inophyllum* fruit are calophylloid, inophyllum A, C, E, calophynic acid, 1,7-dihydroxy-6-methoxyxanthone, 11,12-anhydroinophyllum A, gallic acid, potocatechuic acid, n-nonacosane, sitosterol-3-O-D-glucopyranoside, and β-sitosterol (Zakaria et al., 2014).

Inocalophyllin A and B were isolated from *C. inophyllum* seeds together with their methyl ester forms (Shen et al., 2003). Meanwhile, the seed coat contains inophyllolide, calustralin, inophyllum C and E (Gupta & Gupta, 2020; Yimdjo et al., 2004). In the root bark, caloxanthone A, brasiliensic acid, and inophylloidic acid are found (Yimdjo et al., 2004).

The oil of *C. inophyllum* oil, as a non-edible oil is a potential source of biofuels with an oil yield of around 70% (Atabani & César, 2014). Calophyllum oil extraction is carried out to extract its natural squalene as a raw material for supplements and cosmetics (Saputra et al., 2014). The oil of *C. inophyllum* oil contains 75.4% of triglycerides with a viscosity of 26.4 mPa/s, density of 0.874 g/cm3, iodine value 98.0 g iodine/100 g, acid value of 46.4 mg KOH/g, water and sediment trace. The resin (viscosity of 4694.8 mPa/s) contains 4.51% total phenolic compound (equivalent to gallic acid), and it also has antioxidant activity 8.82 mg/g (equivalent to ascorbic acid), and an acid value of 126.2 mg KOH/g (Kartika et al., 2021). The composition of methyl ester of the biodiesel of *C. inophyllum* oil analyzed by gas chromatography with mass spectrophotometer was methyl oleate (43.41%), methyl linoleate (23.68%), methyl palmitate (17.05%); metal stearate (11.71%);

Table I. Phytochemicals isolated from *C. inophyllum*

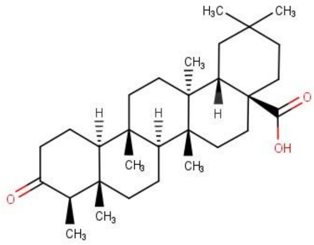
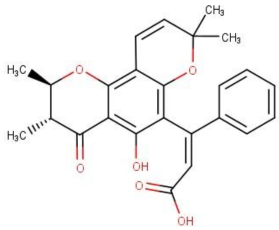
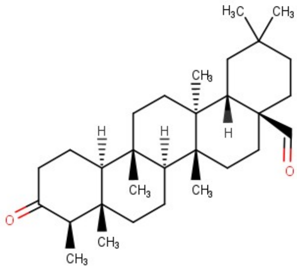
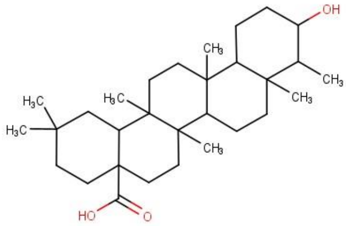
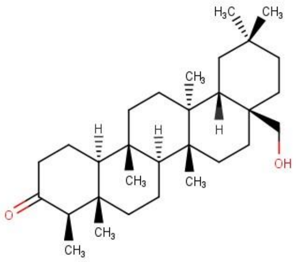
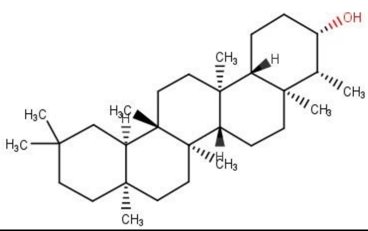
Part of plants	Compound name	Structure	References
	3-oxofriedelan-28-oic acid		(Li et al., 2010)
	Calophyllic acid		(Patil et al., 1993)
	Canophyllal		(Li et al., 2010)
	Canophyllic acid		(Li et al., 2010)
	Canophyllol		(Li et al., 2010)
	Epifriedelanol		(Li et al., 2010)

Table I. (Continued)

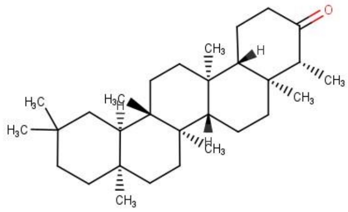
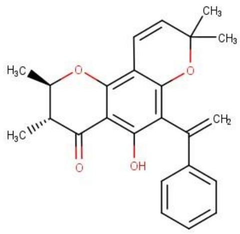
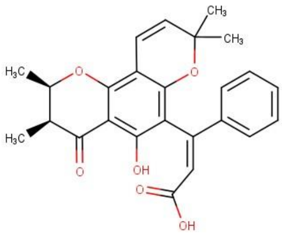
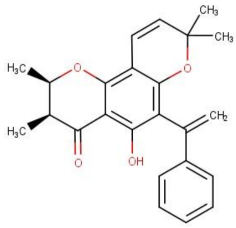
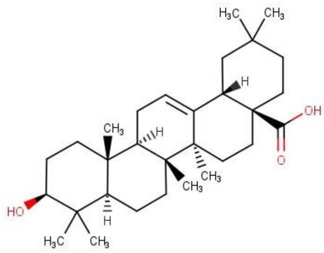
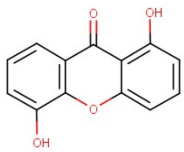
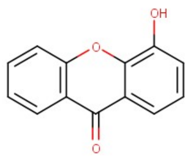
Part of plants	Compound name	Structure	References
Leaves	Friedelin		(Li et al., 2010)
	Inophynone		(Ali et al., 1999; Khan et al., 2002)
	Isocalophyllic acid		(Patil et al., 1993)
	Isoinophynone		(Ali et al., 1999; Khan et al., 2002)
	Oleanolic acid		(Li et al., 2010)
	1,5-dihydroxyxanthone		(Yimdjo et al., 2004)
	4-hydroxyxanthone		(Mah et al., 2015)

Table I. (Continued)

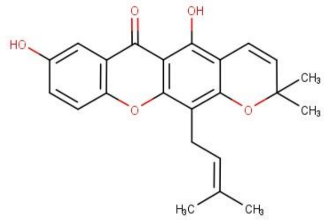
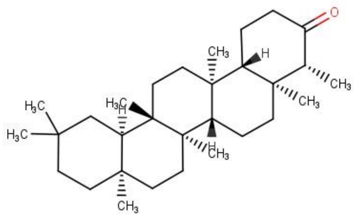
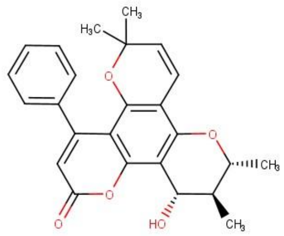
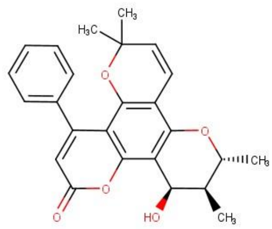
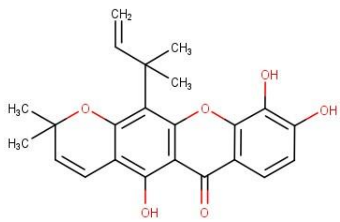
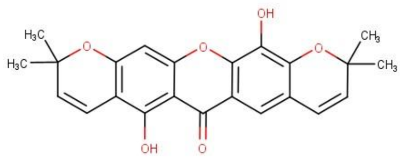
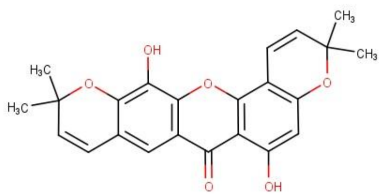
Part of plants	Compound name	Structure	References
	Brasixanthone b		(Mah et al., 2015)
	Friedelan-3-one		(Yimdjo et al., 2004)
	Inophyllum b		(Patil et al., 1993)
	Inophyllum p		(Patil et al., 1993)
	Macluraxanthone		(Mah et al., 2015)
Stem bark	Pyranojacareubin		(Mah et al., 2015)
	Rheediaxanthone a		(Mah et al., 2015)

Table I. (Continued)

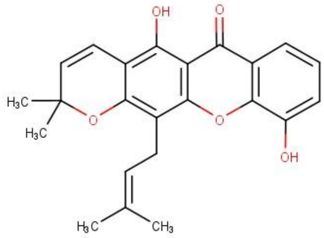
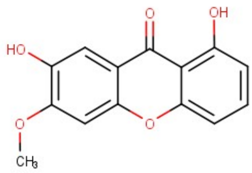
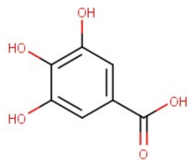
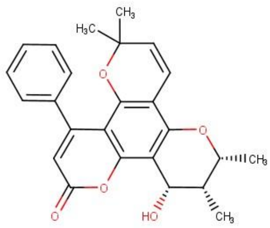
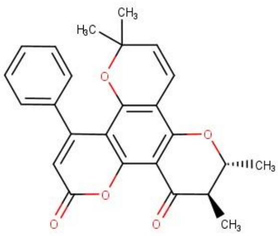
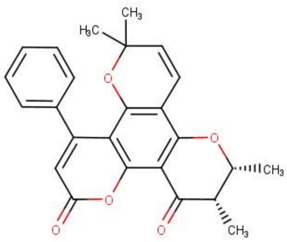
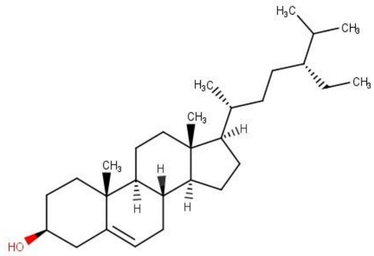
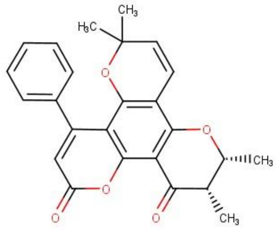
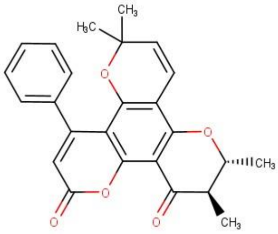
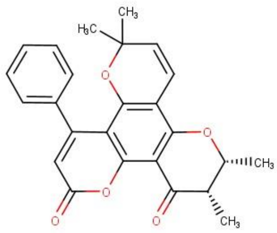
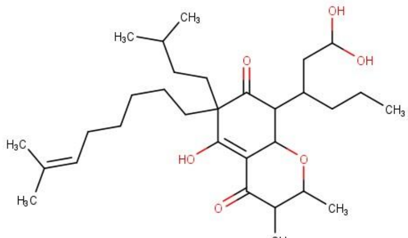
Part of plants	Compound name	Structure	References
	Trapezifolixanthone		(Mah et al., 2015)
	1,7-dihydroxy-6-methoxyxanthone		(Zakaria et al., 2014)
	Gallic acid		(Zakaria et al., 2014)
	Inophyllum a		(Zakaria et al., 2014)
	Inophyllum c		(Zakaria et al., 2014)
	Inophyllum e		(Zakaria et al., 2014)
Flower	Myricetin		(Subramanian & Nair, 1971)
	N-nonacosane		(Zakaria et al., 2014)

Table I. (Continued)

Part of plants	Compound name	Structure	References
	Sitosterol		(Zakaria et al., 2014)
Seed	Inophyllolide		
	Inophyllum c		(Zakaria et al., 2014)
	Inophyllum e		(Zakaria et al., 2014)
Root bark	Brasiliensic acid		(Yimdjo et al., 2004)

methyl arachidate (2.66%); methyl palmitoleate (1.30%), and methyl gondoate (0.20%) (Muderawan et al., 2016). Biofuels are essential for mitigating the impact of climate change because they reduce greenhouse gas emissions of the transportation sector (Yuniastuti et al., 2021).

PHARMACOLOGICAL PROPERTIES

Antiviral activities

Inophyllum compounds can fight the growth of the cultured human immunodeficiency virus type 1 (HIV-1). Inophyllum B and P have demonstrated their efficacy as reverse transcriptase inhibitors, with IC_{50} values of 38 nM and 130 nM, respectively. These compounds exhibit significant potential in the field of antiretroviral therapy. (Patil et al., 1993; Taylor et al., 1994). These two inophyllums were reported to have anti-HIV activity (IC_{50} of 1.4 and 1.6 μM), respectively. Coumarin derivatives, namely castatolide and inophyllum P, are inhibitors of HIV reverse transcriptase enzyme identified in

C. inophyllum extracts. (Spino et al., 1998). Dipyranocoumarin, calophyllolide, inophyllum B, C, G, and P in *C. inophyllum* seeds and leaves demonstrate non-nucleoside reverse transcriptase inhibitory activity that can contribute to the development of new antiviral drugs (Laure et al., 2008).

Anti-inflammatory and immunomodulatory activities

Dehydrocycloguanandin and calophyllin B isolated from *C. inophyllum* leaves showed anti-inflammatory activity *in vivo* through intraperitoneal and oral routes in adrenalectomized rats. The acetone extract of the leaves of *C. inophyllum* showed anti-inflammatory activity in lipopolysaccharide-induced RAW 264.7 macrophage cells. It inhibited nitric oxide production and decreased the expression of NF-κB, iNOS, and COX-2 (Gopalakrishnan et al., 1980; Tsai et al., 2012). Stem barks and leaves ethanol extracts of *C. inophyllum* showed anti-inflammatory activity in Carrageenan-induced paw edema in albino rat (Baig et al., 2014).

C. inophyllum fruit extract at a concentration of 50 g/ml inhibited the activities of cyclooxygenase and lipooxygenase by 77% and 88%, respectively, suggesting its potency as an anti-inflammatory agent (Zakaria et al., 2014). The ethanol extracts obtained from the stem bark and seeds of *C. inophyllum* reduced the volume of leg edema by 28.57 and 36.36%, respectively, in Freund adjuvant-induced arthritis rats. By orally administering 250 mg/kg of bark and seed extracts, the hematological and biochemical parameters of rats with arthritis were restored to normal (Perumal et al., 2017).

Calophyllolide, a major compound in *C. inophyllum* seeds, shows anti-inflammatory activity by upregulating interleukin-6 (a pro-inflammatory cytokine) and downregulating the expression of interleukin-6, tumor necrotic factor-α, and interleukin-1β (pro-inflammatory cytokines) (Nguyen et al., 2017). Inophinnin, a compound of xanthone compound isolated from the stem bark of *C. inophyllum*, demonstrated anti-inflammatory properties by suppressing the production of nitric oxide (Ee et al., 2011). Amentoflavone isolated from the bark and leaves of *C. inophyllum* has an inhibitory effect on 15-lipooxygenase (LOX) (Aminudin et al., 2016).

The presence of friedelin and triterpene compounds from the friedelin group, especially kanofil, kanofilol and kanophilic acid, mesuaxanthone B and calophyllin (Saxena et al., 1982). Anti-inflammatory compounds from *C. inophyllum* fruit are calophynic acid, inophyllum A, C, E, 11,12-anhydroinophyllum A, calophyllolide, tocatechuic acid, gallic acid, beta-sitosterol, nonacosane, and sitosterol-3-O-beta-D-glucophyranoside, 1,7-dihydroxy-6-methoxyxanthone (Zakaria et al., 2014).

Antimicrobial Activities

The antimicrobial and antifungal potential of the ethyl acetate and ethanol extracts of *C. inophyllum* has been identified and studied. The seed oil of *C. inophyllum* shows antimicrobial activity against some Gram-positive bacteria. The activity of ethanol extract is 14 times stronger than that of pure oil (Bhat et al., 1954; Saravanan et al., 2011). Isolation of compounds from stem bark, leaves, and seed oil has confirmed the existence of xanthones, coumarins, and triterpenes with broad biological activity against bacteria and protozoa (Sundur et al., 2014).

The oil of C. inophyllum has an antimicrobial effect on *Staphylococcus aureus* with the largest inhibition diameter of 6.75 mm (Hasibuan et al., 2013). The methanol extract of the *C. inoplyllum* wood showed good antitermitic activity (Kadir et al., 2015). The chloroform extract of the *C. inophyllum* showed larvicidal activity with LC_{50} values of 237.034, 75.492, and 28.783 ppm for 18, 24, and 30 hours of exposure. Petroleum ether extract of *C. inophyllum* leaves was found to be quite active (P<0.01) against eggplant aphids (*Aphis gossypii*) and black bean aphids (*Aphis fabae).* These extracts (at concentrations of 200 and 400μg/disk) inhibited the growth of pathogenic bacteria including (*Staphylococcus aureus, Agrobacterium sp., Shigella dysenteriae, Bacillus cereus, and Escherichia coli*); and they also inhibited (at concentrations of 50 and 200μg/disc) three pathogenic fungi (*Aspergillus niger, Saccharomyces sp., and Candida sp.*) The petroleum ether extract of the leaves of C. inoplyllum showed promising antimicrobial and antifungal activity against *Candida* sp. and *Shigella dysenteriae* (Rana et al., 2017).

Antioxidant Activity

C. inophyllum seed oil has antioxidant activity and has an IC_{50} value of 3.18 ug/mL using the DPPH radical scavenging method (Safrina & Murtini, 2021). The hexane subfraction of the *C. inophyllum* peel showed moderate antioxidant and anti-diabetic activity with the DPPH test (2,2-diphenyl1-picrylhydrazyl) and inhibition of the α-glucosidase enzyme (Abbas et al., 2021).

Calophyllic acid and isocalophyllic acid in *C. inophyllum* leaves show high antioxidant activity. The methanol extract of the leaves showed better free radical scavenging activity and ferric reduction power than the aqueous extract. This is presumably due to the higher content of phenols and flavonoids in the methanol extract (Dutta & Ray, 2014; Prasad et al., 2012). A mixture of calophyllic acid, isocalophyllic acid, kanophilic acid, and amentoflavone from *C. inophyllum* demonstrated lipid-lowering effect in an *in vivo* hyperlipidemia experiment induced by triton (Prasad et al., 2012).

Anticancer Activities

C. inophyllum fruit extract demonstrated a remarkable antitumor efficacy against MCR-7 cells, exhibiting an IC50 value of 23.59 µg/ml. This effect was achieved by inducing cell cycle arrest in the G0/G1 and G2/M phases and promoting apoptosis. *C. inophyllum* fruit is also capable of suppressing the expression of Bcl2, an anti-apoptotic protein, and induce pro-apoptosis of p53, Bax, and cytochrome C. Fruit extract also affects the mitochondrial apoptotic pathway through activation of caspase-3 and upregulation of intracellular level of reactive oxygen species (Shanmugapriya et al., 2017).

The IC_{50} values of the ethanol extract of the fruit peel and the ethanol extract of *C. inophyllum* seeds in WiDr colon cancer cells were 42.47 µg/mL and 1030.41 µg/mL, respectively. The selectivity indicesof the ethanol extract of the fruit peel and the seed ethanol extract of *C. inophyllum* in WiDr colon cancer cells were 1.50 and 67,982,414.71, respectively. Doxorubicin, a reference drug demonstrated IC_{50} of 3.49 µg/ml and a selectivity index of 764.41 (Fathani & Miladiyah, 2021). Calophyllolide and calustralin from the methanol extract of the seeds of *C. inophyllum* showed cytotoxic activity with IC_{50} of 3.5 µg/ml and IC_{50} of 42.0 µg/ml respectively (Yimdjo et al., 2004).

The oil from *C. inophyllum* seeds is known to be able to induce intrinsic and extrinsic apoptotic pathways in C6 glioma cells with the percentage of apoptotic cells reaching 68.8% after 48 hours and cell proliferation decreasing to 55.6% and 30.3% during 24 and 48 hours. The viability of C6 glioma cells was significantly decreased by treatment with *C. inophyllum* seed oil for 24 and 48 hours with IC_{50} values of 0.22% and 0.082%, respectively (Erdemir, 2021).

The seed oil of *C. inophyllum* contains cytotoxic yellow and green pigments that have been found to inhibit the cell cycle in DLD-1 colon cancer cells, specifically in the G1-S and G2-M phases. The pigment also induced cell death in human \ cell lung cancer cell lines A549 and H1975 with IC_{50} of 0.1206 and 0.0676% in 24 h incubation, respectively. Presence of green pigment has been found to have a synergistic effect on gefitinib, which is a selective inhibitor of the epidermal growth factor receptor. that potentiated cell death in A549 and H1975 cells (Hsieh et al., 2018). However, the cytotoxicity test of *C. inophyllum* seed oil on human skin fibroblast cells showed low cytotoxicity (Ku et al., 2021).

The petroleum ether extract of the leaf *C. inophyllum* L showed cytotoxic activity through the brine shrimp mortality test with LC_{50} of 1413.490, 384.766, and 37.562ppm for 12, 18, and 24 hours of exposure to *A. salina*, respectively (Rana et al., 2017). The presence of 4-phenyl coumarins in *C. inophyllum* leaves was responsible for the inhibition of Epstein-Barr virus (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate in Raji cells. In addition, Calocoumarin-A has demonstrated its protective effects against the formation of mouse skin tumors in carcinogenesis experiments. (Itoigawa et al., 2001).

A mixture of triterpenoids oleanolic acid, canophyllic acid, 3β, 23-epoxy-friedelan-28-oic acid, 3-oxofriedelan-28-oic acid, canophyllol, canophyllal, epifriedelanol, and friedelin, from the stalks and leaves of *C. inophyllum* is known to exert anticancer activity by inhibiting the growth of human leukemic HL-60 cells (Li et al., 2010). Gerontoxanthones and 2-hydroxyxanthones from the ethanolic extract of *C. inophyllum* twigs were reported to have cytotoxic effect against the chronic myelogenous leukemia cell line (K562; IC_{50} of 7.2 and 6.3 µg/mL, respectively) (Xiao et al., 2008). Inophinone, pyranojacareubin, rheediaxanthone A, macluraxanthone, and 4-hydroxyxanthone, a group of xanthones from the stem bark of *C. inophyllum* exhibit antiproliferative action on K562, SNU-1, NCI-H34, HeLa, and Hep G2 (Mah et al., 2015). Caloxanthone O isolated from the ethanolic extract of the twig of *C. inophyllum* is cytotoxic against human gastric cancer cells (SGC-7901) with an IC_{50} of 22.4 µg/mL (Dai et al., 2010).

The roots and seeds of *C. inophyllum* contain several compounds: brasiliensic acid, calophynic acid, calophyllolide, inophylloidic acid, and caloxanthone A. These compounds have demonstrated their inhibitory effects on human epidermoid carcinoma of nasopharyngeal cells with IC_{50} values ranging from 3.5 to 11.0 µg/ml. Their potential in treating this type of cancer is promising and warrants further investigation. (Yimdjo et al., 2004). The presence of Inophyllum A in the roots of *C. inophyllum* has been observed to induce apoptosis in leukemia cells (Jurkat). This process occurs through the generation of ROS and the disruption of mitochondrial

Table II. Bioactive compounds isolated from *C. inophyllum*

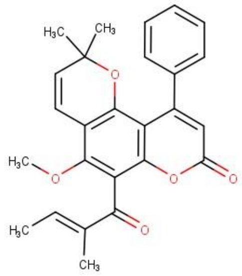
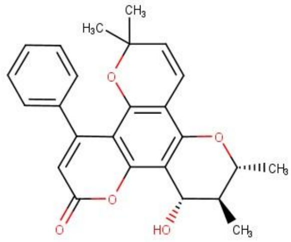
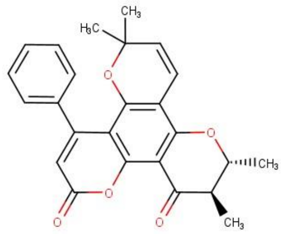
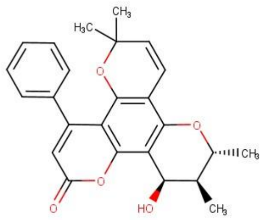
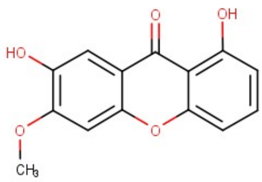
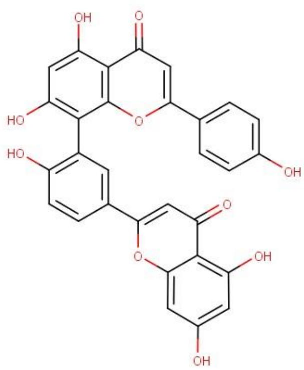
Pharmacological activities	Compound name	Structure	References
	calophyllolide		(Laure et al., 2008)
antiviral	Inophyllum B		(Patil et al., 1993; Taylor et al., 1994)
	inophyllum C		(Laure et al., 2008)
	Inophyllum P		(Laure et al., 2008; Patil et al., 1993; Spino et al., 1998; Taylor et al., 1994)
	1,7-dihydroxy-6-methoxyxanthon e		(Zakaria et al., 2014)
	Amentoflavone		(Aminudin et al., 2016)

Table II. (Continued)

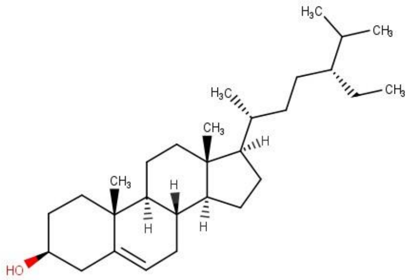
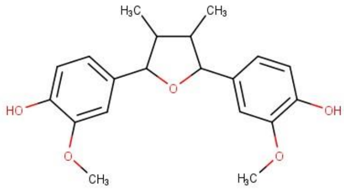
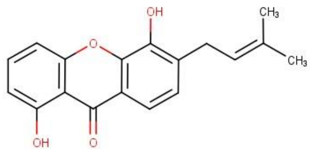
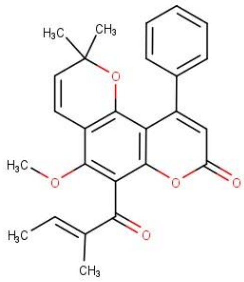
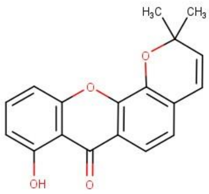
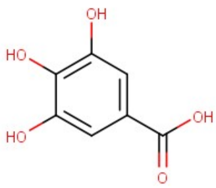
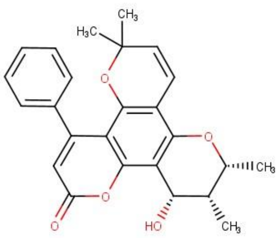
Pharmacological activities	Compound name	Structure	References
	Beta sitosterol		(Zakaria et al., 2014)
	calophyllin		(Saxena et al., 1982
	calophyllin-B		(Gopalakrishnan et al., 1980)
	Calophyllolide		(Nguyen et al., 2017; Zakaria et al., 2014)
Anti-Inflammatory	dehydrocyclogua nandin		(Gopalakrishnan et al., 1980)
	gallic acid		(Zakaria et al., 2014)
	Inophyllum A		(Zakaria et al., 2014)

Table II. (Continued)

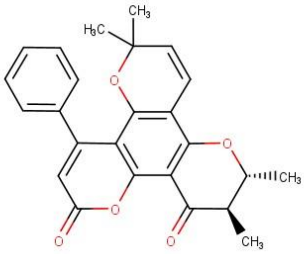
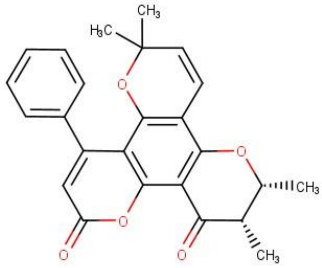
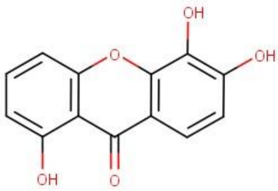
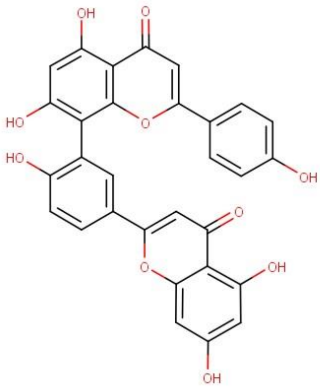
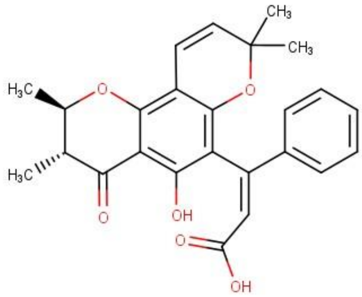
Pharmacological activities	Compound name	Structure	References
	Inophyllum C		(Zakaria et al., 2014)
	Inophyllum E		(Zakaria et al., 2014)
	mesuaxanthone B		(Saxena et al., 1982
	nonacosane		(Zakaria et al., 2014)
	amentoflavone		(Prasad et al., 2012)
Antioxidant	Calophyllic acid		(Prasad et al., 2012)

Table II. (Continued)

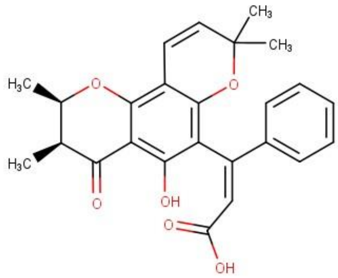
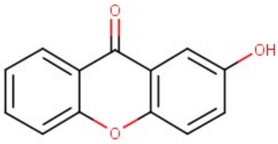
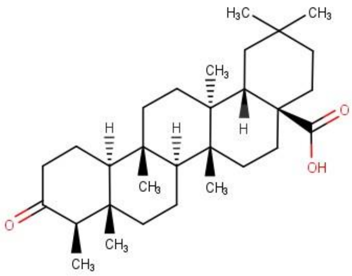
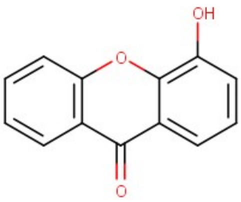
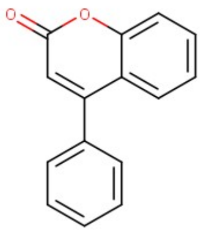
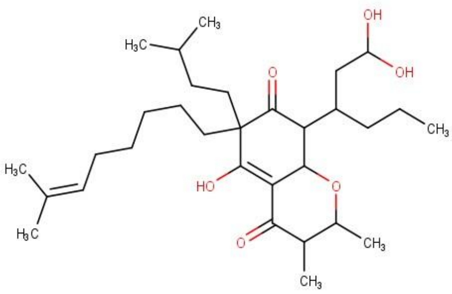
Pharmacological activities	Compound name	Structure	References
	isocalophyllic acid		(Prasad et al., 2012)
	2-hydroxyxanthone		(Xiao et al., 2008)
	3-oxofriedelan-28-oic acid		(Li et al., 2010)
	4-hydroxyxanthone		(Mah et al., 2015)
	4-phenylcoumarin		(Itoigawa et al., 2001)
	brasiliensic acid		(Yimdjo et al., 2004)

Table II. (Continued)

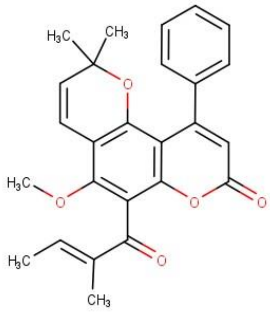
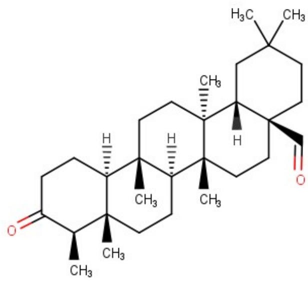
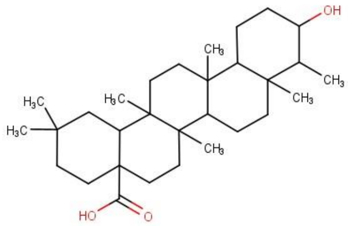
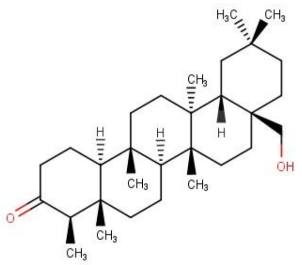
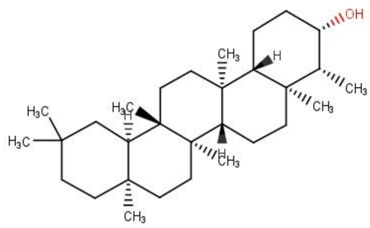
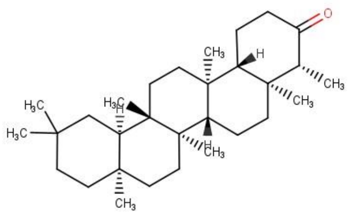
Pharmacological activities	Compound name	Structure	References
Cytotoxic	Calophyllolide		(Yimdjo et al., 2004)
	Canophyllal		(Li et al., 2010)
	canophyllic acid		(Li et al., 2010)
	canophyllol		(Li et al., 2010)
	epifriedelanol		(Li et al., 2010)
	Friedelin		(Li et al., 2010)

Table II. (Continued)

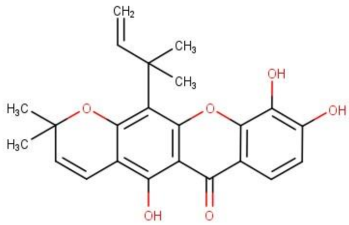
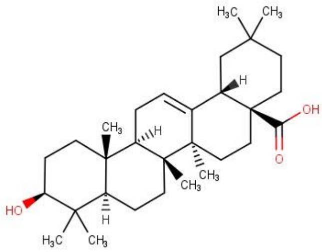
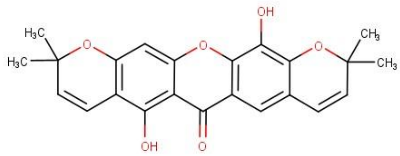
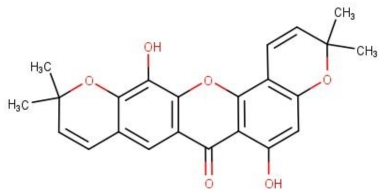
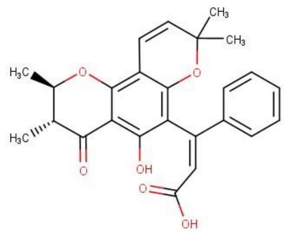
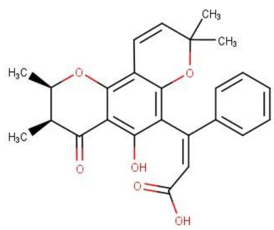
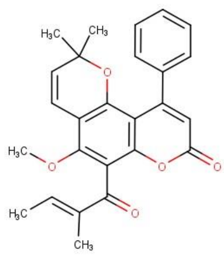
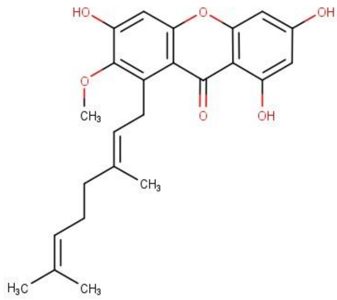
Pharmacological activities	Compound name	Structure	References
	macluraxanthone		(Mah et al., 2015)
	oleanolic acid		(Li et al., 2010)
	pyranojacareubin		(Mah et al., 2015)
	rheediaxanthone A		(Mah et al., 2015)
Antidiabetic	Calophyllic acid		(Jaiswal et al., 2015; Prasad et al., 2012)
	isocalophyllic acid		(Jaiswal et al., 2015; Prasad et al., 2012)
	Calophyllolide		(Arora et al., 1962)

Table II. (Continued)

Pharmacological activities	Compound name	Structure	References
Antiplatelet	Rubraxanthone		(Jantan et al., 2009)

membranes. Additionally, caspase 2, 9, and 3 are simultaneously activated during this process. (Chan et al., 2012).

Antidiabetic Activities

Previous study showed that *C. inophyllum* contains isocalophyllic acid and calophyllic acid. These compounds can activate glucose uptake through PI-3-K-dependent and extracellular signal-regulated kinase 1 and 2 (EKR 1/2) in skeletal muscle cells (Prasad et al., 2013). In skeletal muscle cells, they can inhibit MAPK kinase activation related to reactive oxygen species and increase insulin sensitivity by regulating IRS-1 function (Jaiswal et al., 2015). This shows that both compounds have potential to be developed as drug targeting insulin resistance as well as type 2 diabetes.

Antiplatelet Activities

Rubraxanthone in *C. inophyllum* showed antiplatelet activity in collagen-induced platelet aggregation (IC_{50}: 47.0 µM); This plant also contains 2-(3-methylbut-2)-enyl)-1,3,5,6-tetrahydroxyxanthone and 2-(3-methylbut-2-enyl)-1,3,5trihydroxyxanthone that showed antiplatelet activity on platelet aggregation induced by arachidonic acid (AA) with IC_{50} values of 113.0 and 115.9 µM, respectively (Jantan et al., 2009). *C. inophyllum* also contains a xanthone compound with strong antiplatelet activity. It potently inhibited platelet aggregation and antagonized Platelet Activating Factor (PAF) with an IC_{50} of 44.0µM (Arora et al., 1962). This activity is stronger than ginkgolide B, a natural antagonist of PAF isolated from *Ginkgo biloba* (Oku et al., 2005). Apart from the antiplatelet activity, calophyllolide, a coumarin from *C. inophyllum* demonstrated anticoagulant effect. The anticoagulant potency is between dicumarol and ethyl biscoumaacetate which represent the long/slow-acting and very fast/short-acting anticoagulant agents (Arora et al., 1962).

Cosmetics

The seed oil of *C. inophyllum* has potential as a cosmetic product. Emulgel and microemulsion forms of the *C. inophyllum* seed oil have good potency to be developed as skin antioxidant agents (Charinrat et al., 2021). Seed hexane extract of *C. inophyllum* showed strong UVA and UVB protection ability (Ku et al., 2021). The seed oil of *C. inophyllum* is recognized for its ability to absorb UV rays, with a maximum absorption at 300 nm, and has an impressive sun protection factor ranging from 18-22. Moreover, when applied at a concentration of 1%, *C. inophyllum* oil demonstrates a remarkable capacity to inhibit UV-induced DNA damage by up to 85%, all without causing any notable irritation or cytotoxicity (Said et al., 2007). The oil extracted from of *C. inophyllum* seed has been formulated into skin protection products, such as face oil and sun screen preparations (Artanti et al., 2020; Lestari et al., 2023).

TOXICOLOGY

Acute toxicity evaluation of *C. inophyllum* showed that the LD_{50} of the methanol extract and the chloroform extract of the stem bark was higher than 2000 mg/kg body weight (Mishra et al., 2010). Meanwhile, the fruit of *C. inophyllum* has low toxicity (Ong et al., 2011). The assessment of the short-term toxicity of *C. inophyllum* seed oil revealed no detrimental impact on the rats' physical characteristics, weight gain, organ weight, or hematological parameters. (Ajayi et al., 2008).

CONCLUSION

Nyamplung (*C. inophyllum*) has a wide range of antiviral, antidiabetic, anti-inflammatory, antibacterial, antioxidant, antiplatelet, and anticancer activities derived from leaves, flowers, fruits, seeds, stems, and roots. The active compounds that generally play a role in pharmacological activity are phenols, flavonoids, xanthones, coumarins, and terpenoids. This review article indicated that *C. inophyllum* contains promising bioactive compounds and is promising to be further explored and developed as a drug source in drug discovery. The research focusing on the molecular mechanism of the bioactive compound would provide a strong scientific basis for further development as a drug.

ACKNOWLEDGEMENT

This work received support from the PPSDMK grant from Kementrian Kesehatan Republik Indonesia.

REFERENCES

Abbas, J., Minarti, M., & Artanti, N. (2021). *Antioxidant and antidiabetes activity from the fruit shell*. 11–16.

Ahmad, N., Lesa, K. N., Sudarmanto, A., Fakhrudin, N., & Ikawati, Z. (2022). The role of Phosphodiesterase-1 and its natural product inhibitors in Alzheimer's disease: A review. *Frontiers in Pharmacology*, *13*(December), 1–16. https://doi.org/10.3389/fphar.2022.1070677

Ali, M. S., Mahmud, S., Perveen, S., Ahmad, V. U., & Rizwani, G. H. (1999). Epimers from the leaves of Calophyllum inophyllum. *Phytochemistry*, *50*(8), 1385–1389. https://doi.org/10.1016/S0031-9422(98)00480-4

Aminudin, N. I., Ahmad, F., Taher, M., & Zulkifli, R. M. (2016). Incrassamarin A–D: Four new 4-substituted coumarins from Calophyllum incrassatum and their biological activities. *Phytochemistry Letters*, *16*(January 2018), 287–293. https://doi.org/10.1016/j.phytol.2016.05.008

Arora, R. B., Mathur, C. N., & Seth, S. D. S. (1962). Calophyllolide, a complex coumarin anticoagulant from Calophyllum inophyllum Linn. *Journal of Pharmacy and Pharmacology*, *14*(1), 534–535. https://doi.org/10.1111/j.2042-7158.1962.tb11133.x

Artanti, A. N., Rahmawati, K. N., Rakhmawati, R., & Prihapsara, F. (2020). Uji Aktivitas Antibakteri dan Antijamur Dari Kombinasi Minyak Nyamplung (*Calophyllum Inophyllum* L .) Dengan Virgin Coconut Oil Dan Pengembangannya Sebagai Face Antibacterial Activities and Anti-Fungus From Combination Of Tamanu Oil (Calophyllum Inophyll. *Jurnal Farmasi Indonesia*, *17*(02), 94–106.

Atabani, A. E., & César, A. D. S. (2014). Calophyllum inophyllum L. - A prospective non-edible biodiesel feedstock. Study of biodiesel production, properties, fatty acid composition, blending and engine performance. *Renewable and Sustainable Energy Reviews*, *37*, 644–655. https://doi.org/10.1016/j.rser.2014.05.037

Baig, mirza danish, Basheeruddin, S., Silpa, S. A., & Reddy, vVenkateshwara a. (2014). Anti-inflammatory Activity of Ethanolic Extracts of Leaf and Stem Bark\nof Calophyllum inophyllum on Albino Wistar Rats. *Internationaljournal of Pharmaceutical Sciences and Drug Research*, *6(2)*(174–177), 174–177.

Bhat, S. G., Kane, J. G., & Sreenivasan, A. (1954). The in vitro evaluation of the antibacterial activity of undi oil (Calophyllum inophyllum Linn.). *Journal of the American Pharmaceutical Association. American Pharmaceutical Association*, *43*(9), 543–546. https://doi.org/10.1002/jps.3030430908

Budiarti, M., & Sholihah, I. Y. M. (2018). Laporan Penelitian Pengembangan Bahan Baku Obat Antimalaria dan Antikanker berdasarkan Hasil Ristoja. In *Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia, Jakarta*.

Canter, P. H., Thomas, H., & Ernst, E. (2005). Bringing medicinal plants into cultivation: Opportunities and challenges for biotechnology. *Trends in Biotechnology*, *23*(4), 180–185. https://doi.org/10.1016/j.tibtech.2005.02.002

Cassien, M., Mercier, A., Thétiot-laurent, S., Culcasi, M., Ricquebourg, E., Asteian, A., Herbette, G., Bianchini, J., Raharivelomanana, P., Pietri, S., Cassien, M., Mercier, A., Thétiot-laurent, S., Culcasi, M., Ricquebourg, E., Cassien, M., Mercier, A., Th, S., Culcasi, M., & Ricquebourg, E. (2021). *Improving the Antioxidant Properties of Calophyllum inophyllum Seed Oil from French Polynesia : Development and Biological Applications of Resinous Ethanol-Soluble Extracts To cite this version : HAL Id : hal-03130041 Improving the Antioxidant Properties* . 0–23.

Chan, K. M., Hamzah, R., Rahaman, A. A., Jong, V. Y. M., Khong, H. Y., Rajab, N. F., Ee, G. C. L., &

Inayat-Hussain, S. H. (2012). The pyranoxanthone inophyllin A induces oxidative stress mediated-apoptosis in Jurkat T lymphoblastic leukemia cells. *Food and Chemical Toxicology*, *50*(8), 2916–2922. https://doi.org/10.1016/j.fct.2012.04.048

Charinrat, S., Jasadee, K., Nattawut, L., & Arpa, P. (2021). *Antioxidant in cosmeceutical products containing Calophyllum inophyllum oil*. 1–9.

Dai, H. F., Zeng, Y. B., Xiao, Q., Han, Z., Zhao, Y. X., & Mei, W. L. (2010). Caloxanthones O and P: Two new prenylated xanthones from calophyllum inophyllum. *Molecules*, *15*(2), 606–612. https://doi.org/10.3390/molecules15020606

Dorla, E., Grondin, I., Hue, T., Clerc, P., Dumas, S., Gauvin-Bialecki, A., & Laurent, P. (2019). Traditional uses, antimicrobial and acaricidal activities of 20 plants selected among Reunion Island's flora. *South African Journal of Botany*, *122*, 447–456. https://doi.org/10.1016/j.sajb.2018.04.014

Dutta, S., & Ray, S. (2014). Evaluation of antioxidant potentials of leaf aqueous and methanolic extracts of Calophyllum inophyllum in relation to total phenol and flavonoid contents. *International Journal of Pharma and Bio Sciences*, *5*(3), 96915111.

Dweck, C., & Meadows, T. (2002). Tamanu (Calophyllum inophyllum) – the African, Asian, Polynesian and Pacific Panacea. *Int J Cosmet Sci*, *24*(6), 341–348.

Ee, G. C. L., Mah, S. H., Rahmani, M., Taufiq-Yap, Y. H., Teh, S. S., & Lim, Y. M. (2011). A new furanoxanthone from the stem bark of Calophyllum inophyllum. *Journal of Asian Natural Products Research*, *13*(10), 956–960. https://doi.org/10.1080/10286020.2011.600248

Erdemir, A. (2021). *Anti-proliferative and apoptosis inducing activity of Calophyllum inophyllum L . oil extracts on C6 glioma cell line*. *30*(1), 1–6.

Faisal, A. P., Nasution, P. R., Wakidi, R. F., & Medan, P. K. (2022). *Aktivitas Antioksidan dari Daun Bintangur (Calophyllum Inophyllum L.) Terhadap Radikal Bebas DPPH. Antioxidant Activity Of Bintangur Leaves (Calophyllum Inophyllum L .) Against DPPH Free Radical, 1 , 1*. *4*(1).

Fathani, I. J., & Miladiyah, I. (2021). Jurnal Kedokteran dan Kesehatan Indonesia. *Indonesian Journal of Medicine and Health*, *12*(2), 166–174. https://doi.org/10.20885/JKKI.Vol12.Iss2art10

Gopalakrishnan, C., Shankaranarayanan, D., & Nazimudeen, S. K. (1980). Anti-inflammatory and C.N.S. depressant activities of xanthones from Calophyllum inophyllum and Mesua ferrea. *Indian Journal of Pharmacology*, *12*(3), 181–191.

Gupta, S., & Gupta, P. (2020). The genus Calophyllum: Review of ethnomedicinal uses, phytochemistry and pharmacology. *Bioactive Natural Products in Drug Discovery*, 215–242. https://doi.org/10.1007/978-981-15-1394-7_5

Hamim, Romadlon, Z., & Dorly. (2019). Perkembangan Morfo-anatomi Bunga , Buah , dan Biji Nyamplung (Calophyllum inophyllum L), Sebagai Tanaman Penghasil Biodisel Morpho-Anatomy Development of Flower , Fruit and Seed of Nyamplung (Calophyllum inophyllum L) as Biodiesel-Producing. *Jurnal Sumberdaya HAYATI*, *5*(1), 1–10.

Hasibuan, S., Sahirman, & Yudawati, N. M. A. (2013). Karakteristik Fisikokimia dan Antibakteri Hasil Purifikasi Minyak Biji Nyamplung (Calophyllum inophyllum L.). *AGRITECH*, *33*(3), 311–319.

Heinrich, M., & Gibbons, S. (2010). Ethnopharmacology in drug discovery: an analysis of its role and potential contribution. *Journal of Pharmacy and Pharmacology*, *53*(4), 425–432. https://doi.org/10.1211/0022357011775712

Herlyanti, K., Fakhrudin, N., Murwanti, R., & Wahyono, A. (2023). Identification of Cubebin from Cubeb (Piper cubeba) as An Antiplatelet Agent. *Tropical Journal of Natural Product Research*, *7*(7), 3392–3397. https://doi.org/10.26538/tjnpr/v7i7.17

Heyne, K. (1950). *Tumbuhan Berguna Indonesia*. Diterjemahkan oleh Badan Litbang Kehutanan Jilid III Cetakan ke `1, 1987. https://doi.org/10.1002/zaac.201300446

Hsieh, C., Lin, Y. W., Chen, C. H., Ku, W., Ma, F., Yu, H., & Chu, C. (2018). Yellow and green pigments from Calophyllum inophyllum L. seed oil induce cell death in colon and lung cancer cells. *Oncology Letters*, *15*(4), 5915–5923. https://doi.org/10.3892/ol.2018.8052

Iinuma, M., Tosa, H., Tanaka, T., & Yonemori, S. (1995). Two xanthones from roots of Calophyllum inophyllum. *Phytochemistry*, *38*(3), 725–728.

https://doi.org/10.1016/0031-9422(94)00733-A

Itoigawa, M., Ito, C., Tan, H. T. W., Kuchide, M., Tokuda, H., Nishino, H., & Furukawa, H. (2001). Cancer chemopreventive agents, 4-phenylcoumarins from Calophyllum inophyllum. *Cancer Letters*, *169*(1), 15–19. https://doi.org/10.1016/S0304-3835(01)00521-3

Jaiswal, N., Gunaganti, N., Maurya, C. K., Narender, T., & Tamrakar, A. K. (2015). Free fatty acid induced impairment of insulin signaling is prevented by the diastereomeric mixture of calophyllic acid and isocalophyllic acid in skeletal muscle cells. *European Journal of Pharmacology*, *746*(January), 70–77. https://doi.org/10.1016/j.ejphar.2014.10.049

Jantan, I., Mohd Yasin, Y. H., Jalil, J., Murad, S., & Idris, M. S. (2009). Antiplatelet aggregation activity of compounds isolated from Guttiferae species in human whole blood. *Pharmaceutical Biology*, *47*(11), 1090–1095. https://doi.org/10.3109/13880200903008641

Kadir, R., Awang, K., Khamaruddin, Z., & Soit, Z. (2015). Chemical compositions and termiticidal activities of the heartwood from Calophyllum inophyllum L. *Anais Da Academia Brasileira de Ciências*, *87*(2), 743–751. https://doi.org/10.1007/978-94-007-1764-0

Kartika, I. A., Cerny, M., & Vandenbossche, V. (2021). *Optimisation of concurrent Calophyllum oil-resin extraction and separation*. *2021*(631), 84–91.

Khan, M. R., Kihara, M., & Omoloso, A. D. (2002). Antimicrobial activity of Calophyllum soulattri. *Fitoterapia*, *73*(7–8), 741–743. https://doi.org/10.1016/S0367-326X(02)00242-3

Ku, W.-J., Lin, C.-J., & Lin, H. (2021). *Protection Performance of Calophyllum inophyllum Seed Extracts : A Natural Ultraviolet Screening Agent*. https://doi.org/10.1177/1934578X20985650

Laure, F., Raharivelomanana, P., Butaud, J. F., Bianchini, J. P., & Gaydou, E. M. (2008). Screening of anti-HIV-1 inophyllums by HPLC-DAD of Calophyllum inophyllum leaf extracts from French Polynesia Islands. *Analytica Chimica Acta*, *624*(1), 147–153. https://doi.org/10.1016/j.aca.2008.06.046

Leksono, B., Sukartiningsih, Windyarini, E., Adinugraha, H. A., Artati, Y., Kwon, J., & Baral, H. (2021). Growth performance of Calophyllum inophyllum at a bioenergy trial plot in Bukit Soeharto Research and Education Forest , East Kalimantan. *IOP Conf. Series: Earth and Environmental Science*, 749 012059. https://doi.org/10.1088/1755-1315/749/1/012059

Lestari, N. W. D. I., Reslely, H., & Dewi, E. (2023). Activity Tests Of Sunscreen Emulgel Preparation of Tamanu Oil (Calophyllum inophyllum L.) Combined With Titanium Dioxide (TiO2). *Indonesian Journal of Pharmaceutical Education (e-Journal)*, *3*(2), 2775–3670. https://doi.org/10.37311/ijpe.v3i2.21225

Li, Y. Z., Li, Z. L., Yin, S. L., Shi, G., Liu, M. S., Jing, Y. K., & Hua, H. M. (2010). Triterpenoids from Calophyllum inophyllum and their growth inhibitory effects on human leukemia HL-60 cells. *Fitoterapia*, *81*(6), 586–589. https://doi.org/10.1016/j.fitote.2010.02.005

Li, Z. L., Li, Y., Qin, N. B., Li, D. H., Liu, Z. G., Liu, Q., & Hua, H. M. (2016). Four new coumarins from the leaves of Calophyllum inophyllum. *Phytochemistry Letters*, *16*, 203–206. https://doi.org/10.1016/j.phytol.2016.04.015

Mah, S. H., Ee, G. C. L., Teh, S. S., & Sukari, M. A. (2015). Antiproliferative xanthone derivatives from Calophyllum inophyllum and Calophyllum soulattri. *Pakistan Journal of Pharmaceutical Sciences*, *28*(2), 425–429.

Muderawan, I. W., Ketut, N., & Daiwataningsih, P. (2016). *(CALOPHYLLUM INOPHYLUM L .) DAN ANALISIS METIL ESTERNYA DENGAN GC-MS*.

Nguyen, V. L., Truong, C. T., Nguyen, B. C. Q., Van Vo, T. N., Dao, T. T., Nguyen, V. D., Thi Trinh, D. T., Huynh, H. K., & Bui, C. B. (2017). Anti-inflammatory and wound healing activities of calophyllolide isolated from Calophyllum inophyllum Linn. *PLoS ONE*, *12*(10), 1–16. https://doi.org/10.1371/journal.pone.0185674

Oku, H., Ueda, Y., Iinuma, M., & Ishiguro, K. (2005). Inhibitory effects of xanthones from Guttiferae plants on PAF-induced hypotension in mice. *Planta Medica*, *71*(1), 90–92. https://doi.org/10.1055/s-2005-837760

Patil, A. D., Freyer, A. J., Eggleston, D. S., Haltiwanger, R. C., Bean, M. F., Taylor, P. B., Caranfa, M. J., Breen, A. L., Bartus, H. R., Johnson, R. K., Hertzberg, R. P., & Westley, J. W. (1993). The Inophyllums, Novel

Inhibitors of HIV-1 Reverse Transcriptase Isolated from the Malaysian Tree, Calophyllum inophyllum Linn. *Journal of Medicinal Chemistry*, *36*(26), 4131–4138. https://doi.org/10.1021/jm00078a001

Perumal, S. S., Ekambaram, S. P., & Dhanam, T. (2017). In vivo antiarthritic activity of the ethanol extracts of stem bark and seeds of calophyllum inophyllum in freund's complete adjuvant induced arthritis. *Pharmaceutical Biology*, *55*(1), 1330–1336. https://doi.org/10.1080/13880209.2016.1226346

Prabakaran, K., & Britto, S. J. (2012). Biology, Agroforestry and Medicinal Value of Calophyllum inophyllum L. (Clusiacaea): A Review. *International Journal of Natural Products Research*, *1*(2), 24–33.

Pramiastuti, O., Wahyuono, S., Fakhrudin, N., & Astuti, P. (2023). Phytochemical and Pharmacological Activities of Curcuma purpurascens Blume, A Review. *Journal of Tropical Biodiversity and Biotechnology*, *8*(1), 1–14. https://doi.org/10.22146/jtbb.75891

Prasad, J., Maurya, C. K., Pandey, J., Jaiswal, N., Madhur, G., Srivastava, A. K., Narender, T., & Tamrakar, A. K. (2013). Diastereomeric mixture of calophyllic acid and isocalophyllic acid stimulates glucose uptake in skeletal muscle cells: Involvement of PI-3-Kinase- and ERK1/2-dependent pathways. *Molecular and Cellular Endocrinology*, *370*(1–2), 11–19. https://doi.org/10.1016/j.mce.2013.02.013

Prasad, J., Shrivastava, A., Khanna, A. K., Bhatia, G., Awasthi, S. K., & Narender, T. (2012). Antidyslipidemic and antioxidant activity of the constituents isolated from the leaves of Calophyllum inophyllum. *Phytomedicine*, *19*(14), 1245–1249. https://doi.org/10.1016/j.phymed.2012.09.001

Pribowo, A., Girish, J., Gustiananda, M., Nandhira, R. G., & Hartrianti, P. (2021). *Potential of Tamanu (Calophyllum inophyllum) Oil for Atopic Dermatitis Treatment*. *2021*.

Putra, I. M. W. A., Fakhrudin, N., Nurrochmad, A., & Wahyuono, S. (2023). A Review of Medicinal Plants with Renoprotective Activity in Diabetic Nephropathy Animal Models. *Life*, *13*(2). https://doi.org/10.3390/life13020560

Raharivelomanana, P., Ansel, J. L., Lupo, E., Mijouin, L., Guillot, S., Butaud, J. F., Ho, R., Lecellier, G., & Pichon, C. (2018). Tamanu oil and skin active properties: From traditional to modern cosmetic uses. *OCL - Oilseeds and Fats, Crops and Lipids*, *25*(5). https://doi.org/10.1051/ocl/2018048

Rana, R., Amin, N. I., Naser, A. A., & Islam, N. (2017). Screening of Calophyllum inophyllum L . leaf extracts for cytotoxic , larvicidal , insect repellent and antimicrobial activities. *Journal of Pharmacognosy and Phytochemistry*, *6*(3), 612–616.

Safrina, U., & Murtini, G. (2021). *Phytochemical Screening And Antioxidant Activity Of Nyamplung Seed Oils (Calophyllum inophyllum L .) Jurusan Farmasi , Poltekkes Kemenkes Jakarta II , Kebayoran Baru , Jakarta Selatan , 12120 Submitted : 3 th August 2020 ; Accepted : 5 th January 2021 SK*. *11*(2), 256–268.

Said, T., Dutot, M., Martin, C., Beaudeux, J. L., Boucher, C., Enee, E., Baudouin, C., Warnet, J. M., & Rat, P. (2007). Cytoprotective effect against UV-induced DNA damage and oxidative stress: Role of new biological UV filter. *European Journal of Pharmaceutical Sciences*, *30*(3–4), 203–210. https://doi.org/10.1016/j.ejps.2006.11.001

Saputra, T., Claratika, A., & Gunawan, S. (2014). Identifikasi kandungan Squalene dari Minyak Nyamplung (calophyllum inophyllum). *Jurnal Teknik Pomits*, *3*(2), 151–153.

Saravanan, R., Dhachinamoorthi, D., Senthilkumar, K., Thamizhvanan, K., Saravanan, R., & Dhachinamoorthi, D. (2011). *Antimicrobial activity of various extracts from various parts of Calophyllum inophyllum L . 01*(03), 102–106.

Saxena, R. C., Nath, R., Palit, G., Nigam, S. K., & Bhargava, K. P. (1982). Effect of calophyllolide, a nonsteroidal anti-inflammatory agent, on capillary permeability. *Planta Medica*, *44*(4), 246–248. https://doi.org/10.1055/s-2007-971459

Shanmugapriya, Chen, Y., Kanwar, J. R., & Sasidharan, S. (2017). Anticancer Activity and Molecular Mechanism of Polyphenol Rich Calophyllum inophyllum Fruit Extract in MCF-7 Breast Cancer Cells. *Nutrition and Cancer*, *69*(8), 1308–1324. https://doi.org/10.1080/01635581.2017.1367944

Shanmugrapriya, Chen, Y., Jothy, S. L., & Sasidharan, S. (2016). Research Journal of Pharmaceutical , Biological and Chemical Sciences Calophyllum inophyllum : A

Medical Plant with Multiple Curative Values. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, *7*(4), 1446–1452.

Shen, Y. C., Hung, M. C., Wang, L. T., & Chen, C. Y. (2003). Inocalophyllins A, B and their methyl esters from the seeds of Calophyllum inophyllum. *Chemical and Pharmaceutical Bulletin*, *51*(7), 802–806. https://doi.org/10.1248/cpb.51.802

Spino, C., Dodier, M., & Sotheeswaran, S. (1998). Anti-HIV coumarins from calophyllum seed oil. *Bioorganic and Medicinal Chemistry Letters*, *8*(24), 3475–3478. https://doi.org/10.1016/S0960-894X(98)00628-3

Subramanian, S. S., & Nair, A. G. R. (1971). Myricetin-7-glucoside from the andraecium of the flowers of Calophyllum inophyllum. *Phytochemistry*, *10*(7), 1679–1680. https://doi.org/10.1016/0031-9422(71)85049-5

Sukara, E. (2005). Keanekaragaman Hayati (Emas Hijau) Alternatif Bagi Indonesia Keluar Dari Krisis Multidimensi. *Berita Biologi*, *7*(6), vii–xx.

Sulianti, S. R. I. B., Kuncari, E. S. R. I., & Chairul, S. M. (2006). *Pemeriksaan Farmakognosi dan Penapisan Fitokimia dari Daun dan Kulit Batang Calophyllum inophyllum dan Calophyllum soulatri Phytopharmaceuticals and phytochemicals evaluation on leaves and bark of*. *7*, 25–29. https://doi.org/10.13057/biodiv/d070108

Sundur, S., Shrivastava, B., Sharma, P., Raj, S. S., & Jayasekhar, V. L. (2014). *A Review Article Of Pharmacological Activities And Biological Importance Of Calophyllum inophyllum*. *2*(12), 599–603.

Susanto, D. F., Aparamarta, H. W., Widjaja, A., Jadid, N., & Gunawan, S. (2019). Heliyon Isolation and identi fi cation of cholestane and dihydropyrene from Calophyllum inophyllum. *Heliyon*, *5*(July), e02893. https://doi.org/10.1016/j.heliyon.2019.e02893

Sutrisno, A. J., Diandasari, G., & Rahmandari, A. V. (2020). Kapasitas Pohon Nyamplung (*Calophyllum Inophyllum* L .) dan Pohon Spathodea (*Spathodea Campanulata*) Dalam Menjerap Debu. *Jurnal Planologi*. *17*(1),88–95. https://doi.org/10.30659/jpsa.v17i1.5197

Taylor, P. B., Culp, J. S., Debouck, C., Johnson, R. K., Patil, A. D., Woolf, D. J., Brooks, I., & Hertzberg, R. P. (1994). Kinetic and mutational analysis of human immunodeficiency virus type 1 reverse transcriptase inhibition by inophyllums, a novel class of non- nucleoside inhibitors. *Journal of Biological Chemistry*, *269*(9), 6325–6331.https://doi.org/10.1016/s0021-9258(17)37375-1

Tiaravista, A. G., Putri, L. W., Nurrochmad, A., Widyarini, S., & Fakhrudin, N. (2023). *Evaluation of the Antithrombotic Activity of Acmella oleracea L . Flower Ethanol Extract*. https://doi.org/10.18196/jfaps.v4i1.19055

Tsai, S. C., Liang, Y. H., Chiang, J. H., Liu, F. C., Lin, W. H., Chang, S. J., Lin, W. Y., Wu, C. H., & Weng, J. R. (2012). Anti-inflammatory effects of Calophyllum inophyllum L. in RAW264.7 cells. *Oncology Reports*, *28*(3), 1096–1102. https://doi.org/10.3892/or.2012.1873

Udarno, L., & Tjahyana, B. E. (2019). MORFOLOGI DAN BUDIDAYA TANAMAN NYAMPLUNG (Calophyllum inophyllum LINN). In *Bunga Rampai Tanaman Industri Potensial Biodesel dan Bioetanol* (pp. 59–64). Balai Penelitian Tanaman Rempah dan Aneka Tanaman Industri.

Xiao, Q., Zeng, Y. B., Mei, W. L., Zhao, Y. X., Deng, Y. Y., & Dai, H. F. (2008). Cytotoxic prenylated xanthones from Calophyllum inophyllum. *Journal of Asian Natural Products Research*, *10*(10), 993–997. https://doi.org/10.1080/10519990802240387

Yimdjo, M. C., Azebaze, A. G., Nkengfack, A. E., Meyer, A. M., Bodo, B., & Fomum, Z. T. (2004). Antimicrobial and cytotoxic agents from Calophyllum inophyllum. *Phytochemistry*, *65*(20), 2789–2795. https://doi.org/10.1016/j.phytochem.2004.08.024

Yuniastuti, E., Anjani, I., Nandariyah, & Delfianti, M. N. I. (2021). Morphological characterization of Calophyllum Inophyllum as a biodiesel Morphological characterization of Calophyllum Inophyllum as a biodiesel. *The 5th International Conference on Climate Change 2020*, 1–8. https://doi.org/10.1088/1755-1315/724/1/012026

Zakaria, M. Bin, Ilham, Z., & Muhamad, N. A. (2014). Anti-inflammatory Activity of Calophyllum Inophyllum Fruits Extracts Anti-Inflammatory Activity of Calophyllum inophyllum Fruits Extracts. *Procedia Chemistry*, *13*(December), 218–220. https://doi.org/10.1016/j.proche.2014.12.031.