

Review

The Extraction of Bioactive Agents from *Calophyllum inophyllum* L., and Their Pharmacological Properties

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Abstract: *Calophyllum inophyllum* L. has been used for many generations by Pacific Islanders because of its numerous health and aesthetic advantages. The leaves, stems, roots, fruits, flowers, and seeds of this plant contain significant phytochemicals, including flavonoids, coumarins, fatty acids, and xanthenes, which have been shown to have wound healing, analgesic, anti-inflammatory, antiaging, anti-arthritis, anti-cancer, anti-proliferative, anti-diabetic, anti-microbial, and anti-HIV effects. The chemical profiles and bioactive potential may vary due to different extraction techniques, plant parts, and geographical origins. Extraction is the essential first step in the analysis of bioactive compounds that leads to further separation, identification, and characterization. Conventional methods like maceration, Soxhlet, and percolation are often used to extract bioactive compounds from *C. inophyllum*. However, little study has been carried out on non-conventional methods such as pressured liquid extraction, supercritical fluid extraction (SFE), and ultrasound-assisted extraction. The SFE method can be used to extract bioactive compounds from *C. inophyllum* to retain their pharmacological properties for application in pharmaceutical and cosmetic products.

Keywords: *Calophyllum inophyllum* L.; extraction technique; traditional uses; bioactive compounds; pharmacological properties



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1. Introduction

Calophyllum inophyllum L. (Calophyllaceae), locally called “Daok” in Guam, is a woody pantropical plant widely distributed in Asia, Africa, and the Pacific regions. It is also known as Tamanu, Beauty leaf, Alexandrian laurel, Indian laurel, Beach Calophyllum, Beach touriga, Kamani, Laurelwood, Honne, etc., in different regions of the world. Daok is a slow-growing medium-to-large tree, up to 20 m in height, with shiny leathery leaves, furrowed bark, fragrant white flowers, spherical brown fruits with large seeds, and a broad spreading crown of irregular branches [1]. In Guam, it grows wildly on shores and forests, and is often planted as an ornamental plant. This tree produces fragrant gums that exuded from its trunk and bark, as well as strong, quality wood that the natives of Guam used to make big canoes, carabao cartwheels, and boat timber [1]. Pacific Islanders have traditionally used different parts of this plant, such as nuts, leaves, roots, bark, and fruits, for their various health and beauty benefits [2]. The oil extracted from *C. inophyllum* nuts contains resinous neoflavanoid and pyranocoumarin compounds beside common fatty acids, which are known to have different medicinal properties [2].

Bioactive compounds in plants are secondary metabolites having pharmacological or toxicological effects on both *humans* and animals. The main chemical groups of bioactive compounds in plants are alkaloids, glycosides, flavonoids, and proanthocyanidins; tannins, mono-, di-, and sesqui-terpenoids; phenylpropanoids, resins, furocoumarins, and naphthodianthrones; and proteins and peptides [3]. The predominant classes of phytoconstituents present in the genus *Calophyllum* are coumarins, xanthenes, chromanones, triterpenes, steroids, and glycosides [4]. Plant bioactive compounds are receiving increased attention due to their huge demand in food, pharmaceutical, and nutraceutical industries.

Extraction is the most crucial initial step that plays an important role in the final result and outcome of analyses for the phytochemicals study. Several conventional and non-conventional methods are employed for the extraction of bioactive compounds. For instance, maceration, Soxhlet extraction, percolation, hydro distillation, and reflux are commonly used as conventional methods, whereas ultrasound-assisted extraction, enzyme-assisted extraction, microwave-assisted extraction, and supercritical fluid extraction are considered non-conventional or modern techniques [5]. Many studies have discussed the extraction, isolation, and characterization of bioactive compounds from different parts of *C. inophyllum* [2,4]. Until now, no single method was regarded as the standard for extracting bioactive compounds from *C. inophyllum*.

The present review focuses on conventional and non-conventional extraction techniques and factors that affect the extraction efficiency of bioactive compounds from *C. inophyllum*. Ethnobotanical uses, major bioactive compounds, and their pharmacological properties are also discussed.

2. Ethnobotany and Ethnomedicinal Uses

C. inophyllum seed oil has been utilized as a traditional medicine to treat skin healing and wound care, pain relief, anti-insect and insect repellent, oral health, joint pain, scar reduction, anti-aging and skincare, hair and scalp care, earaches, and respiratory issues by many cultures throughout its native Southeast Asia and Pacific Islands for generations. In French Polynesia, seed oil has been traditionally used for topical applications on the skin, as well as mucous membrane lesions to cure all kinds of dermal affections (burns, dermatoses, eczema, acne, psoriasis, chilblains, skin cracks, diabetic sores, hemorrhoids, dry skin, etc.) [2]. These trees were considered sacred and planted inside sacred sanctuaries before the Polynesians converted to Christianity. Léguillier et al. [6] confirmed the wound healing and antimicrobial properties of the seed oil collected from Indonesia, Tahiti, Fiji Islands, and New Caledonia, which has been traditionally used topically to treat a wide range of skin injuries [6]. In India, *C. inophyllum*'s roots are used in a decoction to cure ulcers, boils, and ophthalmia, the bark is used to treat orchitis, the latex is applied topically to treat rheumatism and psoriasis, and the leaves are used in a decoction to treat eye infections [4]. In Thai traditional medicine, the mangrove plant *C. inophyllum* is used to treat various ailments such as wound healing, arthritis, and skin diseases [7]. In Madagascar, *C. inophyllum* seeds are used to treat scabies and other skin diseases, and to alleviate the inflammation in case of dental caries [8]. In Vietnam, *C. inophyllum* seed oil has been used as a traditional medicine to treat burns, skin-related and rheumatic diseases, and insomnia [9].

According to Friday and Ogoshi [10], the wood of this plant has been traditionally used for canoe and boat building by the Pacific islanders, while today it is used for cabinet making and furniture, as well as turning and carving. They also reported that leaves have been applied topically to treat wounds and skin diseases, while soaking in water was used to treat eye issues. Seed oil has been used for centuries to treat skin injuries and as a cosmetic such as massage oil and skin moisturizer [10]. Dweck and Meadows [11] reported detailed traditional uses of *C. inophyllum* in Africa, Asia, Polynesia, and the Pacific Islands. For example, (1) the tree is thought to have diuretic properties in Java, but in Samoa, the entire plant is considered toxic; the milky juice can cause blindness and an injection of its sap into the bloodstream is said to result in death; (2) the gum extracted from wounded barks has been used to cure wounds and ulcers; (3) the bark has been used to treat chronic bronchitis, phthisis, internal hemorrhages, and gonorrhea; (4) the decoction of the root has been applied topically to heal ulcers and treat heatstroke; (5) native black communities in Papua New Guinea have traditionally utilized charred leaves as a treatment for acne, rashes, boils, and wounds. These leaves are used by the indigenous people of Samoa and New Caledonia to heal wounds, leg ulcers, and inflammations of the skin. The leaves are applied to irritated eyes by skimming the oily surface of water that has been soaked with leaves in Madagascar, India, and Fiji. (6) Dark-skinned Fijians highly valued the seed oil for treating bruises, arthritis, and joint discomfort. In most South Sea islands, tamanu oil is

utilized as a wound and ulcer remedy [11]. In Guam, nut oil is used for external medicine for an assortment of skin issues, sap from the trunk and bark is used as glue for tools and canoe making, and wood is used for the keel of the canoe.

3. Major Bioactive Compounds of *C. inophyllum* and Their Therapeutic Effects

The major bioactive compounds and their reported biological activities from different parts (fruits, seeds, leaf, stem, root, and flower) of *C. inophyllum* are presented in Table 1. The main bioactive compounds of French Polynesian “tamanu oil” resinous part from the seed are calophyllolide, inopyllums (C, D, E, P), calanolides (A, B, D), and tamanolides [2]. According to Léguillier et al. [6], bioactive fatty acids from the seed oil exhibited accelerated in vitro wound closure, the healing factor being 1.3 to 2.1 higher compared to control, and distinct antibacterial activity against *Staphylococcus aureus* strain involved in skin infections. The authors also reported the lowest and highest cytotoxicity value at LC₅₀ 18.7% and 7.3%, respectively. The bioactive compound (4-(3-methylazetididin-1-yl) pentan-2-ol) of *C. inophyllum* seeds oil demonstrated potent antibacterial activities (17 ± 1.73 to 24 ± 1.15 mm) against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [12]. Nguyen et al. [9] isolated the bioactive calophyllolide compound from seeds and reported their anti-inflammatory and wound-healing activities. Based on their results, calophyllolide reduced fibrosis formation and effectively promoted wound closure in mouse models without causing body weight loss. The “Tamanu oil emulsion” demonstrated evidence of wound healing activity, collagen and glycosaminoglycan synthesis, and cell proliferation in experiments performed on human skin cells (keratinocytes and dermal fibroblasts) [13]. These biological activities could be facilitated by the bioactive neoflavanoid’s molecule present in Tamanu oil emulsion [13]. According to research carried out by Ku et al. [14], *C. inophyllum* seed oils showed the highest UVA (wavelength 320–400 nm) and UVB (wavelength 290–320 nm) absorption efficiencies, making them a potential source of high-efficiency natural screening agents. The results showed maximum inhibition at 250 µg/mL in proteinase inhibition and hemolysis assays, and the LD₅₀ of stem and seed extract was found to be greater than 5000 and 2000 mg/kg/p.o., respectively. One novel chromanone acid derivative, namely inocalophylline C, was identified from the nut oil resin of *C. inophyllum* L., widely distributed in Vietnam [15].

Table 1. Bioactive compounds and their pharmacological properties from different parts of *C. inophyllum*.

Name of Compound	Pharmacological Property	Plant Part Used	Reference
Palmitic acid, stearic acid, oleic acid and linoleic acid	Wound healing, antimicrobial, and cytotoxic	Seed oil	[6]
Phytol, eugenol, caryophyllene oxide, α-copaene, α-murolene, β-caryophyllene, β-amysin, farnesol, palmitic acid, and cadinene derivatives.	Anti-bacterial	Flowers	[7]
Flavonoids, leucoantocyanins, anthocyanins, phenolic compounds, and tannins	Anti-inflammatory and analgesic	Seed	[8]
Calophyllolide	Anti-inflammatory and wound healing	Seeds	[9]
4- (3-methylazetididin-1-yl) pentan-2-ol	Anti-bacterial	Seeds	[12]
Neoflavanoid	Cell proliferation, glycosaminoglycan and collagen production, and wound healing	Seeds	[13]
Palmitic acid, stearic acid, oleic acid, eicosanoic acid, squalene and linoleic acid.	UV protection	Seeds	[14]
Chromanone acid derivative (inocalophylline C), and calophyllolide	-	Seed (resin)	[15]

Table 1. Cont.

Name of Compound	Pharmacological Property	Plant Part Used	Reference
Xanthones (inophinnin, inophinone, pyranojacareubin, rheediaxanthone A, macluraxanthone and 4-hydroxyxanthone).	Anti-proliferative	Stem bark	[16]
Tannins, saponins, glycosides, flavonoids, steroids, and terpenoids	Antiarthritic	Stem bark and seeds	[17]
Antiarol, syringol, 5-hydroxymethylfurfural, pyrocatechol, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one, and 2-methoxyhydroquinone	Anticancer	Branches	[18]
1,3,6,7-tetrahydroxy-5-methoxy-4-(1',1'-dimethyl-2'-propenyl)-8-(3'',3''-dimethyl-2''-propenyl)-xanthone, (2'S)-7-hydroxy caloxanthone B, caloxanthone B, 7-O-demethyl-mangostanin, caloxanthone A, 7-prenyljacaerubin, pyranojacareubin, daphnifolin, tovoxyrifolin C, 1,3,5-trihydroxyxanthone, 2-hydroxyxanthone, 4-hydroxy-xanthone, caloxanthone C, and macluraxanthone	Cytotoxic	Roots	[19]
Inoxanthone, caloxanthones A, and B, macluraxanthone, 1,5-dihydroxyxanthone, calophynic acid, brasiliensic acid, inophylloidal acid, friedelan-3-one, calaustralin, calophyllolide, inophyllums C, and E	Antimicrobial and cytotoxic	Root bark and nut	[20]
n-Heptane, 1,1-bi(4,4-dimethylhexan-2,6-dione-1-yl), phytol, 2H-Benzo(cd)pyrene-2,6(1, H)-dione, 3,5,7,10-tetrahydroxy-1, caryophyllene, hexadecanoic acid	Anticancer	Leaves	[21]
Flavonoids, tannins, and phenolic compounds,	Anti-inflammatory and anti-arthritis	Leaves	[22]
Pyranocoumarins, calophyllolide, inophyllums B, C, G1, G2 and P	anti-HIV-1	Leaves	[23]
Total phenolic, total flavonoids, bis (2-ethylhexyl) phthalate.	Anti-oxidant	Leaves	[24]
cholestane, and dihydropyrene	-	Leaves	[25]
Polyphenol	Antiaging	Young fruits	[26]
Squalene, coumarin, friedelin, xanthone	-	Leaves	[27]
Inophyllum A, inophyllum C, inophyllum E, calophylloide, calophynic acid, 11,12-anhydroinophyllum A, 1,7-dihydroxy-6-methoxyxanthone, potocatechuic acid, gallic acid, n-nonacosane, β -sitosterol and sitosterol-3-O- β -D-glucopyranoside	Anti-inflammatory	Fruits	[28]
Inocalophyllins A, B, and their methyl esters, calophyllolide	-	Seeds	[29]
Phenolic compounds	Antimicrobial	Fruit peel	[30]
Inophinnin, inophyllin A, macluraxanthone, pyranojacareubin, 4-hydroxyxanthone, friedelin, stigmasterol, and betulinic acid	Anti-inflammatory	Stem bark	[31]

Table 1. Cont.

Name of Compound	Pharmacological Property	Plant Part Used	Reference
Apetalic acid, isoapetalic acid, calolongic acid, pinetoric acid I, pinetoric acid II, 2,3-cis calolongic acid, pinetoric acid III, and isopinetic acid	Antimicrobial and cytotoxic	Resins	[32]
Methyl shikimate, (3S,5R,6R,7E,9R)-3,5,6-trihydroxy-β-ionyl-3-O-β-D-glucopyranoside, benzyl-O-α-L-rhamnopyranosyl (1 → 6)-β-D-glucopyranoside, hexyl rutinoid, canophyllol, kaempferol-3-O-α-L-rhamnoside, 27-[(Z)-p-coumaroyloxy] friedelin-28-carboxylic acid, (22E,24R)-24-methyl-5α-cholesta-7,22-diene-3β,5,6β-triol, amentoflavone, and 3-oxo-friedelan-28-oic acid	Anti-inflammatory	Leaves	[33]
Isobornyl isobutanoate, indipone, carvacrol, larixol, rosifoliol and thujaplicinol	Termiticidal	Heartwood	[34]
Caloxanthone A, caloxanthone B, caloxanthone C, macluraxanthone, and pyranojacareubin	Anti-inflammatory, antimicrobial and cytotoxic	Stem bark	[35]
Essential oils	Antidiabetic	All parts	[36]
Phenolic compounds	Anticancer	Fruits	[37]

Flower extracts of *C. inophyllum* were found to be rich in bioactive sesquiterpenoid, triterpenoid, fatty acid, and fatty acid derivatives, which are effective against pathogenic bacteria at different concentrations, especially *Salmonella typhi* [7].

Mah et al. [16] isolated 11 bioactive xanthone compounds from the stem bark of *C. inophyllum* and studied their anti-proliferative effects against the SNU-1 (stomach), HeLa (cervical), NCI-H23 (lung), Hep G2 (liver), and K562 (leukemia) cell lines. Cytotoxicity screening exhibited good inhibitory activities by these isolated xanthone derivatives. The proliferation rate of HeLa cells was strongly inhibited at IC₅₀ values of 2.77, 6.88, 6.95, and 7.57 mM by xanthenes 3, 9, 7, and 11, respectively [16]. Stem bark and seed were found to show significant antiarthritic activity evidenced by clinical, biochemical, histological, and radiological evaluations [17]. Ruangsuriya et al. [18] used patient-derived cells from breast and lung cancer to investigate the anticancer properties of the extract from *C. inophyllum*. Based on their findings, the branches extract contains several bioactive compounds (antiarol, syringol, 5-hydroxymethylfurfural, pyrocatechol, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one, 2-methoxyhydroquinone) which exhibited strong antioxidant activity and no cytotoxicity in the first 24 h of treatment. Nevertheless, it showed notable antiproliferative effects after 72 h [18].

Two new xanthenes, 1,3,6,7-tetrahydroxy-5-methoxy-4-(1',1'-dimethyl-2'-propenyl)-8-(3'',3''-dimethyl-2''-propenyl)-xanthone (1) and (2'S)-7-hydroxy caloxanthone B (2), were isolated from the root of *C. inophyllum* together with twelve known xanthenes, and their cytotoxicity was studied [19]. Among the tested compounds, xanthenes 5 (caloxanthone A) and 14 (macluraxanthone) displayed the most potent and selective cytotoxicity against HCT-116 colon cancers, with the same IC₅₀ values of 3.04 μM [19]. Bioactive xanthone derivatives from the root bark of *C. inophyllum* showed in vitro cytotoxicity against the KB cell line and antibacterial activity against *S. aureus*, *Vibrio. anguillarum*, *Escherichia coli*, and yeast *Candida tropicalis* [20].

Jaikumar et al. [21] identified 11 bioactive compounds from the *C. inophyllum* leaf extract, where the n-Heptane 1,1-bi(4,4-dimethylhexan-2,6-dione-1-yl) was reported to comprise the highest concentration. Anticancer activity was evaluated using an MTT standard colorimetric assay against MCF-7 cells with IC₅₀ value of 120 μg/mL. They also reported that increased concentration of the leaf extract showed increased cytotoxicity [21].

According to Navyasri et al. [22], fractions 6 and 7 of the leaf extract's bioactive constituents showed moderate-to-strong anti-inflammatory and anti-arthritis activity, confirming the presence of flavonoids, tannins, and phenolic compounds. Various pyranocoumarins, calophyllolide, inophyllums B, C, G1, G2, and P were determined from 136 leaf extracts of *C. inophyllum* of French Polynesia [23]. The results confirmed the geographical distribution of inophyllums and indicate those rich in HIV-1 active (+)-inophyllums [23].

Young fruit extracts of *C. inophyllum* exhibited antiaging properties via upregulating superoxide dismutase and Sirtuin 1 genes, and reduced oxidative stress in *Saccharomyces cerevisiae* BY611 [26]. The presence of phenolic compounds in fruit peel were responsible for the antibacterial activity against *S.aureus* and *Mycobacterium smegmatis* [30]. Shanmugapriya et al. [37] found cytotoxic effects against MCF-7 cells in a dose-dependent manner, with the IC₅₀ for 24 h of 23.59 µg/mL.

4. Factors Affecting the Extraction Efficiency of Bioactive Compounds

There are several factors that affect the extraction efficiency of bioactive components from plants. The major influencing factors include the characteristic of the sample matrix, type of solvents, sample-to-solvent ratio, extraction time and temperature, pressure, and extraction technique. Bioactive compounds are varied not only with the different species of *Calophyllum*, but also different parts of the plant such as the leaves, stem bark, roots, fruit kernel, and heartwood [38]. The selection of solvent polarity is the most significant factor that affects the mass transfer, as well as the solubility of bioactive compounds. Rajendran and Gurunathan [39] examined the ultrasonic-assisted heterogeneous solvent technique to extract seed oil from *C. inophyllum* and found that the equal ratio of diethyl ether and ethanol in assistance with ultrasonic waves yields maximum oil extraction. They also reported the optimal conditions, which included a seed kernel-to-solvent ratio of 1:15 (*w:v*), 45 min, 36 °C temperature, and 54% ultrasonication power, yielding a maximum bio-oil yield of 82.8%. (*w/w*). The effect of solvent polarity levels to separate the bioactive compounds (xanthone and coumarin) from *C. inophyllum* leaf extract were performed using methanol (polar solvent) and hexane (non-polar solvent) with the solvent ratio of 1 [40]. According to the authors, 50% methanol gives the best performance whereby coumarin and xanthenes were separated in the methanol fraction (81.18% recovery) and the hexane fraction (81.91% recovery), respectively [40]. Different extraction methods (conventional and ultrasonic), ethanol concentrations (0%, 30%, 50%, 70%, or 95%), and processing temperatures (drying and freezing) of five Bulgarian medicinal plants were studied to investigate their effects on bioactive compounds [41]. According to the authors, the yield content from dried samples with 70% ethanol using the conventional method was nearly twice that of the ultrasonic extraction method [41].

Temperature and time were reported to affect the extraction efficiency of bioactive compounds from *C. inophyllum*. The total phenolic and flavonoid compounds of *C. inophyllum* leaves were significantly affected by solvent types, the concentration of solvent in water, length of extraction time, and temperature [24]. The optimal conditions for the extraction of the coumarin mixture were 90% ethanol and eight stages of extraction, which contributed to 92.95 ± 3.76% of recovery with the highest DPPH inhibition (57.72 ± 2.70%), with an IC₅₀ value of 305 ppm [24]. The total phenol and flavonoid content of aqueous extracts of *Humulus lupulus* L. was found to increase with increasing temperature from 25 °C to 57.5 °C [42]. However, the concentration of bioactive compounds decreased at temperatures of ≥90 °C due to their denaturation at high temperatures and exposure time [42]. The relative importance of every factor influencing extraction efficiency primarily depends on the particular technique employed. For example, choosing the right solvent is crucial for maceration, but temperature, pressure, solvent concentration, and flow rate are also crucial for supercritical fluid extraction. The essential factors influencing microwave-assisted extraction include the solvent-to-feed ratio, plant sample matrix, extraction temperature and time, solvent composition, microwave power, and energy density [43].

5. Extraction Technique for Bioactive Compounds

Extraction is the most crucial step in the isolation and purification of bioactive agents from plant tissue. The choice of extraction technique depends on various factors, including the target bioactive compounds of interest, process efficiency, production cost, product quality, available equipment, and environmental impact [44–46]. Extraction can be conducted using conventional and non-conventional techniques, each offering distinct advantages based on the desired compounds and the application. The advantages and disadvantages of using conventional and nonconventional methods for the extraction of bioactive compounds from different plants are described by many authors [5,44–46].

5.1. Conventional Extraction Technique

Several conventional extraction techniques have been employed to extract bioactive compounds from *C. inophyllum* using various solvents, including maceration, percolation, Soxhlet, and dynamic maceration. The common extraction techniques with the extraction conditions and solvents are briefly described in Table 2.

Table 2. Extraction technique, conditions, and solvent used for the extraction of bioactive compounds from *C. inophyllum*.

Extraction Technique	Extraction Conditions	Solvent Used	Target Compound	Reference
Conventional				
Maceration	Sample-to-solvent ratio 1:1; Maceration for five days	Hexane, ethyl acetate, and methanol	Bioactive compounds of flower	[7]
Maceration and percolation	Time = 48 h; Temperature = 30 °C; Solid: solvent = 1: 10 (<i>w/v</i>); Solvent = 80% methanol	Acetone, methanol, ethanol, and n-hexane	Phenolic and flavonoid compounds from leaves	[24]
Maceration	Sample-to-solvent ratio 1:3; Soaked for 72 h	Methanol	Cholestane and dihydropyrene from leaves	[25]
Hydro-distillation	Samples air-dried, pulverized and hydro-distilled for 3 h in a Clevenger-type apparatus	Water	Essential oils from different parts of plants	[36]
Maceration	Moisture 4%, material size 2 mm, submerged in solvent with temperature 50 °C for 4 h under either no stirring or stirring	Hexane, acetone and mixture of hexane, and acetone (3:2, <i>v/v</i>).	Seed oil	[47]
Maceration	Sample-to-solvent ratio; 0.5 kg:3 L; extracted for 72 h	n-Hexane, ethyl acetate, and methanol	Bioactive compounds of fresh fruit shells	[48]
Soxhlet	500 g of sample packed separately in Soxhlet extractor and extracted	Petroleum ether, ethanol, and aqueous	Bioactive compounds of leaves	[22]
Percolation	Sample-to-solvent ratio 1:2.5; Placed in glass percolator at room temperature for 24 h	Ethanol (95%)	Bioactive compounds of leaves	[49]

Table 2. Cont.

Extraction Technique	Extraction Conditions	Solvent Used	Target Compound	Reference
Non-conventional				
Supercritical fluid extraction	Particle size 1–2 mm, pressure 280 bar, temperature 40 °C, flow rate 18 g/min and extraction time 180 min	Carbon dioxide	Seed oil	[50]
Pressurized liquid extraction	Pressure 1500 psi, temperature 120 °C, and time 15 min	Methanol and n-hexane	Phenolic compounds of fruit peel	[30]
Ultrasound-assisted method	Time, temperature, and solvent-to-material ratio ranges of 15–25 min, 35–45 °C, and 14:1–26:1 mL/g, respectively	n-hexane, ethanol, petroleum ether, and ethyl acetate	Seed oil	[51]

Maceration is the most common conventional methods used for the extraction of bioactive compounds from *C. inophyllum*. Mai et al. [47] investigated the maceration extraction process of seeds oil and their antioxidant and antimicrobial activity. The highest oil extraction was obtained at a material size of 2 mm, moisture content of 4%, acetone solvent with a materials/solvent (*w/v*) ratio of 1:30, extraction time of 4 h, and extraction temperature of 50 °C [47]. Total phenolic, flavonoid, and saponin contents were obtained from *C. inophyllum* flower via maceration with sequential extraction using hexane, ethyl acetate, and methanol [7]. The highest yield (58.89%) was obtained with methanol; as the polarity of ethyl acetate and hexane decreased, the yields dropped to 5.68% and 1.64%, respectively. All extracts showed antibacterial activity against pathogenic bacteria [7]. Cholestane and dihydropyrene were isolated and identified from *C. inophyllum* leaves using a crude extract obtained via maceration [25]. According to Abbas et al. [48], extracted and fractionated bioactive compounds from fresh fruit peel exhibited antioxidant and antidiabetic activities. Maceration extraction resulted in the highest crude extracts using methanol (101.387 g) as a solvent, followed by ethyl acetate (66.929 g) and n-hexane (64.215 g). They also reported that the n-hexane sub-fraction contained a high amount of total phenolic (196.57 µg GAE/mg extracts) and flavonoid (38.06 µg QE/mg extracts) content, which showed antioxidant and antidiabetic activity with 6.31% inhibition of DPPH and 16.99% inhibition of α -glucosidase enzyme at 100 µg/mL, respectively [48].

Using the percolation method and optimizing the extraction conditions, Hapsari et al. [24] extracted the highest total phenolic compounds (289.12 mg GAE/g of leaf residue) and total flavonoid compounds (410.4 mg QE/g) using 80% methanol in water at 30 °C for 48 h. Under these conditions, the leaf extracts of *C. inophyllum* show antioxidant activity, with an IC₅₀ value of 0.054 mg/mL [24]. Navyasri et al. [22] reported maximum phytoconstituents, along with flavonoids in ethanolic leaf extracts obtained using the Soxhlet method, which exhibited moderate-to-highly anti-inflammatory and anti-arthritis activity. Soxhlet extraction is the most conventional and reliable technique for seed oil extraction practice as of today. In another study, oil recovery from *C. inophyllum* was compared between the screw press and solvent (n-hexane) extraction techniques. Grated kernel with a 14.4% moisture content produced the highest yield (86.4%) using solvent extraction, while oil yield of 78.0% was achieved using the screw press technique [52].

Essential oils from different parts (leaf, stalk, flower, seed, pod, peel, stem wood, stem bark, root wood, and root bark) of *C. inophyllum* Linn were extracted via hydro-distillation, which yielded (*w/v*) the highest content in the peel (0.560%) and lowest in the roots (0.219%). Among different plant parts, pod essential oils showed strong α -amylase and α -alpha glucosidase inhibition activity compared to the others parts. The high inhibition efficiency must be triggered by the presence of bioactive constituents against postprandial hyperglycemia and other diseases associated with diabetes mellitus [36].

5.2. Non-Conventional Extraction Technique

Very limited research has been conducted for the extraction of bioactive compounds from *C. inophyllum* using non-conventional methods (Table 2). Nguyen and Tran [50] extracted fatty acids and coumarins compounds from the seeds of *C. inophyllum* using supercritical carbon dioxide, and investigated their antibacterial and anti-inflammatory activities using the diffusion method performed on white mouse ears (Swiss albino). The fatty acid content in tamanu oil extracted using sCO₂ (72.62%) was higher than that using the Soxhlet (71.18%) and cold press (71.38%) methods. On the other hand, the coumarin (C₉H₆O₂) content in the tamanu oil extracted using sCO₂ was the highest (169.69 µg/g), being 1.79 and 2.04 times as much as that using the Soxhlet method and commercial oil, respectively [50]. Fruit peels from *C. inophyllum* were extracted using the pressurized liquid extraction method, and the phenolic compounds contained in the peels demonstrated promising antibacterial activity against *Staphylococcus aureus* and *Mycobacterium smegmatis* [30]. Pressurized liquid extraction yielded 9.98% (*w/w*) crude extract, which was more than double compared to Soxhlet extracts (4.18% *w/w*) [30]. Thy et al. [51] reported higher wound healing properties of tamanu oil extracted using the ultrasound-assisted technique when tested on Swiss albino mice and compared with commercial oil. They achieved an optimal yield of 55.15% when extracting at 42 °C with the time of 23 min and solvent-to-material ratio of 26 to 1 (*v/w*) mL/g.

However, the ultrasound-assisted technique, microwave-assisted extraction, enzymatic extraction, and supercritical fluid extraction were recently used besides Soxhlet for the bio-diesel production from the seeds of *C. inophyllum* [53]. Chemical extraction using hexane as a solvent is very effective compared to mechanical extraction using the screw press. Jahirul et al. [54] investigated the oil extraction efficiency between screw press and solvent (n-hexane) extraction, and reported that the percentage yield is higher in solvent extraction (51%) compared to screw press (~25%). Manto et al. [55] reported that the oil yield via ultrasound-assisted extraction with n-hexane and petroleum ether was 60% better compared to 56% and 30% for Soxhlet and traditional solvent extraction by stirring, respectively. A higher oil recovery from the seeds of *C. inophyllum* was found using the microwave hydro-diffusion gravity method (3.25% dry wt basis) when compared with the Soxhlet extraction method (2.28% dwb) [56]. However, a high content of gum in the extracted oil using these methods causes low-quality physical properties of the bio-diesel production. Rajendran and Gurunathan [39] used ultrasonic waves in conjunction with an equal solvent ratio of diethyl ether:ethanol, producing a maximum-yield oil extraction. The highest percentage of bio-oil, i.e., 82.8% (*w/w*), was reported under optimized conditions, which included 45 min, a temperature of 36 °C, a seed kernel-to-solvent ratio of 1:15 (*w:v*), and 54% ultrasonication power. The ultrasound-assisted extraction of oil from *C. inophyllum* Linn seeds was studied, and the effects of the factors (solvent, extraction time, ultrasonic power, extraction temperature, and liquid-to-solid (L/S) ratio) on the oil yield were optimized by Fuad and Don [57]. The highest oil yield (55.44 ± 0.53%) was obtained using n-hexane as a solvent, extraction time of 20 min, ultrasonic power of 210 W, extraction temperature of 40 °C, and L/S ratio of 20 mL/g [57].

6. Future Prospects for Effective Extractions

Since *C. inophyllum* is a rich source of many bioactive compounds (Table 1), it would be difficult to extract all these compounds using an optimized technique or under optimal conditions. Various conventional methods have been employed to extract bioactive compounds from *C. inophyllum*, as discussed in Section 5.1. Several drawbacks of conventional methods, such as lengthy extraction durations, high temperature requirements, poor extraction efficiency, and the thermal destruction of thermolabile chemicals [44,45], have encouraged growing interest, particularly in green and alternative non-conventional extraction technologies such as SFE. There are several key advantages offered by SFE over conventional methods, including higher purity extracts, faster separation, selective fractionation, single-step processing, no residual solvent, and environmentally friendly

procedures [46]. To the best of my knowledge, no research has been published on the use of SFE for extracting bioactive compounds from the leaves, stems, roots, and flowers of *C. inophyllum*. Very limited research has been conducted on the extraction of bioactive compounds from the fruits of *C. inophyllum* using advanced methods (Table 2). In several of our previous studies, we have reported higher bioactivities of compounds extracted via supercritical fluid compared to conventional methods [58–60]. Pereira et al. [61] reported that the combination of supercritical and pressurized fluids extraction methods resulted in better extraction performance and identification of more fatty acids, along with a higher TPC, antioxidant activity, and total carotenoids when compared to conventional extracts of *Butia capitata* fruit pulps. No comprehensive studies have been found for the optimization of extraction parameters (pressure, temperature, flow rate, co-solvent ratio) using SFE and the comparison of their bioactivities among different parts of the plant, influence of geographical location, and harvesting time on the yield quality. Other non-conventional methods, such as microwave-assisted, enzymatic, and ultrasound-assisted methods, could be applied to optimize the extraction technique and conditions to compare the bioactivities of the extracted yield. Mathematical models, such as response surface methodology, could be applied to understand the effect of multiple factors and their interaction on the expected yields. Nevertheless, more research is needed to develop a cost-effective green extraction technology for separating bioactive compounds from the leaves, stems, roots, and fruits of *C. inophyllum*, evaluate their toxicity and other chemical characteristics, and identify their uses as functional components or medicinal agents.

7. Conclusions

This review provides information on ethnobotanical and ethnomedicinal use, and conventional and non-conventional techniques for the extraction of major bioactive compounds and pharmacological activities of *C. inophyllum*. Yield recovery and their bioactivities are primarily influenced by the extraction technique, extraction conditions, and solvent polarity. Maceration is the most common extraction methods used for the phytochemical studies of *C. inophyllum*. Green technology, such as SFE using response surface methodology, could be used to optimize the extraction conditions for obtaining high-quality yields, rich with bioactive compounds, within a short time. Furthermore, extraction conditions for the combination of advanced techniques, such as SFE with UAE, SFE with PLE, and enzyme-based–ultrasound–microwave-assisted extraction, need to be optimized and developed at the pilot scale in order to recover all the potential biologically active compounds from *C. inophyllum* for commercial uses.

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