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The composition, pharmacological and economic importance of essential oil of *Litsea cubeba* (Lour.) Pers

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Abstract

Litsea cubeba (Lour.) Pers. is a valuable essential oil-producing plant species. It is a shrub and is mostly found in India, China, Japan, Taiwan, and, Northern Thailand. *L. cubeba* essential oil, which is rich in citral, has been used as a traditional medicine to treat several diseases. The fresh fruits of *L. cubeba* are used for the extraction of essential oil, and the oil is intense yellowish in color, fresh and has a sweet aromatic flavor. The composition of essential oil varies based on the extraction method, cultivar, plant parts, time of sampling and processing. The current manuscript summarizes the composition as well as pharmacological and economic importance of *L. cubeba* essential oil. The literature review revealed that the essential oil of *L. cubeba* exhibited antioxidant, antimicrobial, and antiproliferative activities; also, it can be used as pesticide, repellent and fragrance agent in cosmetics. However, further studies are required to bridge the scientific gap of transferring the scientific findings into commercially valuable products. Also, studies on the potential of *L. cubeba* essential oil in other possible fields like aromatherapy and cognition are desirable.

Keywords: *Litsea cubeba* (Lour.) Pers.; essential oil; antioxidant; antimicrobial; antiproliferative.

Practical Application: The manuscript summarizes the composition, pharmacological and economic importance of essential oil of *L. cubeba*, which helps to develop new valuable food and pharma products.

1 Introduction

Essential oils are volatile secondary metabolites of plants that can be extracted from several parts of plants, such as flowers, seeds, fruits, twigs, leaves, etc. They are the major constituent of perfumes, fragrances, cosmetics and pharmaceutics (Tariq et al., 2019) and are used to treat oral problems (Palombo, 2011). The composition of the oil is responsible for its bioactivity.

Litsea cubeba (Lour.) Pers. is one of the valuable essential oil-producing plant species. It is a shrub mostly found in India, Southeast Asia, China, Japan and Taiwan, and it has been used as a traditional medicine to treat several diseases (Huai & Pei, 2004). *L. cubeba* essential oil is rich in citral, which is an industrially important component used in medicines, flavorings, cosmetics, and insecticides. The fresh fruits of *L. cubeba* are used for the extraction of essential oil, and the oil is intense yellowish in color, fresh and has a sweet aromatic flavor. China is the largest producer of *L. cubeba* essential oil, and U.S.A, Germany, France, England are the top buyers (Chen et al., 2013a, 2016a).

The composition of *L. cubeba* essential oil varies based on the cultivar, geographical factors, and extraction processes, but a major bioactive constituent of the oil is citral. *L. cubeba* essential oil has been reported to exhibit several activities, like anticancer, antioxidant, antimicrobial, anti-inflammatory, pesticidal and insecticide activities (Kamle et al., 2019). The present manuscript summarizes the chemical composition, pharmacological and commercial applications of *L. cubeba* essential oil. A cautious literature survey was conducted to collect information from PubMed, Scopus and Google Scholar, and the collected information was meritoriously compiled.

2 The composition of *L. cubeba* essential oil

The chemical composition of *L. cubeba* essential oil is comparable with the essential oils of *Aloysia triphylla* and *Cymbopogon citratus*. The essential oil is translucent, yellow, sweet and smells like *C. citratus*. Generally, the hydrodistillation method is employed to extract the essential oil from *L. cubeba*. However, the composition of essential oil varies based on the extraction method, cultivar, plant parts, time of sampling and processing. Monoterpenes (citral, limonene, citronellal, etc.) are the major components of *L. cubeba* essential oil that is responsible for the bioactivities of oil (Chen et al., 2013b). The chemical constituents of essential oils isolated from different parts of *L. cubeba* are presented (Tables S1-S5, Supplementary Material).

3 Pharmacological importance

The oil extracted from *L. cubeba* fruits (LFO) was analyzed for antibacterial activity against Gram-positive and Gram-negative pathogens. The minimum bactericidal concentration (MBC) of LFO for *Escherichia coli* was 0.38 µg/mL, whereas the MBC value against *Bacillus subtilis* was 390.6 µg/mL. The MBC values of LFO against the tested pathogens differed. LFO exhibited an LC_{50} (lethal concentration for 50% mortality) value of 31.62 µg/mL in Brine-shrimp lethality assay, and the IC_{50} (50% inhibitory concentration) value in DPPH assay was 1628.85 µg/mL. The results showed that LFO has strong antibacterial and anticarcinogenic activities as well as mild antioxidant property (Bajracharya & Pratigya, 2019).

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The leave and fruit oils were extracted from *L. cubeba* and were assessed for cytotoxic activity against human cancer cells. The fruit oil exhibited anticancer activity against human oral (OEC-M1), liver (J5), and lung (A549) cancer cells in a dose-dependent manner, whereas, the leaf oil did not exhibit antiproliferative activity against tested cancer cells (Ho et al., 2010). LFO exhibited anxiolytic and analgetic activities in mice. The oral supplementation of LFO significantly improved the pentobarbitone-induced mouse sleeping time as well as the time spent and the number of entries of mice in open arm in elevated plus maze assay. The supplementation of 500 mg/kg of body weight of LFO displayed analgetic activity in the tail-flick test. The results suggested that LFO exhibited potent neuroprotective activity (Chen et al., 2012).

The antioxidant and free radical scavenging activities of LFO were assessed. LFO showed IC_{50} of 0.19 and 0.45 mg/mL in hydroxyl and superoxide radical scavenging activities, respectively. LFO effectively suppressed linoleic acid peroxidation. The GC-MS analysis of LFO composition suggested that the presence of a high content of citral had a role in the radical scavenging activity of LFO (Wang et al., 2012).

The vapor of the volatile oil of *L. cubeba* seed (VVO) showed anti-proliferative and apoptotic activities against non-small cell lung carcinoma cells (A549). VVO treatment deactivated Akt (serine/threonine-specific protein kinase) and Mdm2 (E3 ubiquitin-protein ligase), causing overexpression of p53, which in sequence upregulates the expression of p21. Further, the binding of cyclin D1 and p21 was facilitated, which arrested cell cycle progression. The results suggested that VVO treatment induces apoptosis and obstructed cell proliferation in A549 cells (Seal et al., 2012).

Li et al. (2014) reported the antibacterial activity and mechanism of LFO against *E. coli*. The minimum inhibitory concentration (MIC) and MBC of LFO against *E. coli* were 0.125%. At this concentration, the bacterial cell membrane was drastically disturbed and damaged by the LFO, which caused bacterial cell death. GC-MC analysis suggested that aldehydes of LFO were attributed to the bacterial cell damage and lethality.

The essential oils extracted from the fruits, leaves, stem, root, and bark of *L. cubeba* exhibited cytotoxic activity against brine shrimp larvae (LC_{50}: 25.1-30.9 μL/mL) and antimicrobial activity against bacteria, fungi and yeast. There was no antagonistic activity against Gram-negative bacteria, such as *E. coli* and *Pseudomonas aeruginosa*. Especially, fruit oil exhibited strong cytotoxic activity against brine shrimp larvae and in antimicrobial assay compared to other oil samples (Hammid & Ahmad 2015). Likewise, Su & Ho (2016) reported the antimicrobial activities of essential oils of different parts of *L. cubeba* through disk diffusion assay. The results showed that essential oils were potent against *E. coli*, *P. aeruginosa, Klebsiella pneumonia, Vibrio parahaemolyticus, Enterobacter aerogenes, Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis* and *Candida albicans*, and the antagonistic activity was concentration-dependent. The fruit and stem oils are superior compared to the leaf and twig oils in terms of antimicrobial activity (JIS L 1902 method). The study supported the assertion that citral is the potent phytocompound responsible for antimicrobial activity.

Neral and geranial were derived from the essential oil of *L. cubeba* fruits by solvent extraction. The bioactivities of neral and geranial were assessed. Neral and geranial treated macrophage expressed lesser levels of IL-6 and TNFα upon lipopolysaccharide (LPS)-induced condition. Moreover, neral suppressed the expression of pro-IL-1β, iNOS, COX-2 and NLRP-3. Both compounds inhibited NLRP-3 inflammasome-mediated IL-1β secretion, but they differed in inhibition on phosphorylation of ERK1/2, JNK1/3, p38, and IκB. The results revealed that neral and geranial are potent anti-inflammatory agents (Liao et al., 2015). Similarly, LFO, which is rich in neral and geranial, exhibited a strong immunosuppressive effect in isolated bone marrow-derived dendritic cells (DCs). In particular, IL-12 and TNFα expressions were suppressed in LFO treated LPS-stimulated DCs. A contact hypersensitivity response study in mice supported that LFO has the potential to suppress immune response, which could be of aid in the treatment of autoimmune and inflammatory diseases (Chen et al., 2016b).

Ebani et al. (2018) reported that *L. cubeba* essential oil exhibited antibacterial and antifungal activities against *E. coli* and *Aspergillus fumigatus* with MIC values of 1.106 and 1.770 mg/mL, respectively. Cui et al. (2019) reported that the commercial *L. cubeba* essential oil showed anti-*S. aureus* activity with MIC and MBC values of 0.5 and 1.0 mg/mL, respectively. Further, *L. cubeba* essential oil and dandelion polysaccharide-based nanofibers showed strong stability and controlled release of essential oil without affecting bioactivity, which indicates that nanofibers could be suitable for medical applications.

The commercial *L. cubeba* fruit essential oil showed a strong suppressive effect against *Borrelia burgdorferi*. More specifically, LFO eliminated the stationary phase cells of *B. burgdorferi* at a concentration of 0.1% in the medium. The results of the study suggested that LFO has the potential to eradicate the persistence of *B. burgdorferi* infection (Feng et al., 2018).

The antioxidant, anti-inflammatory and antimicrobial activities as well as the genotoxicity of LFO and *L. cubeba* leaf oil (LLO) were evaluated by Gogoi et al. (2018). Both LFO and LLO exhibited superior DPPH scavenging activity compared to the internal control (ascorbic acid) in terms of IC_{50} values. The reducing power and anti-inflammatory activity of LFO and LLO were comparable with the internal standards of ascorbic acid and diclofenac sodium. Both oils had negligible genotoxicity compared to ethyl methanesulphonate treatment. Both LFO and LLO inhibited the growth of *B. subtilis, B. cereus, S. aureus,* and *S.* Typhimurium, but the MIC values vary. However, the tested fungal and *Candida* spp. showed resistance against the essential oils. Collectively, the results recommended that LFO and LLO have compelling antioxidant and anti-inflammatory activities.

Nguyen et al. (2019) reported the antibacterial activity of LFO against Gram-positive (*B. cereus* ATCC 13061, *B. subtilis* ATCC 11778, *Listeria innocua* ATCC 33090, *S. aureus* ATCC 25923, methicillin-resistant *S. epidermidis* ATCC 35984, methicillin-resistant *S. aureus* ATCC 33591) and Gram-negative (*E. coli* ATCC 25922, *P. aeruginosa* ATCC 9027, *S.* Typhimurium ATCC 14028, *V. parahaemolyticus* ATCC 17802, *Proteus vulgaris* ATCC 49132, *Aeromonas hydrophila* ATCC 35654) species with MIC values of 700-5500 μg/mL. Besides, the addition of erythromycin or vancomycin to LFO improved the antagonistic activity against bacterial pathogens (Table S6).

4 The commercial importance of *L. cubeba* essential oils

4.1 Pesticidal and insecticidal property

The essential oil of *L. cubeba* fruits (LFO) showed toxicity against *Lasioderma serricorne* (LD_{50}: 27.33 μg/adult) and *Liposcelis bostrychophila* (LD_{50}: 71.56 μg/cm^2). Though the fumigant and contact toxicities of LFO were effective against beetle and booklouse, citral showed superior toxic activity. The percentages of repellency after 2 h for LFO against *Lasioderma serricorne* and *Liposcelis bostrychophila* were 76 ± 5 and 84 ± 7 at concentrations of 78.63 and 31.58 nL/cm^2, respectively. The isolated compounds of LFO (citral, d-Limonene, β-pinene, α-pinene) exhibited superior repellency scores compared to oil against both booklouse and cigarette beetle (Yang et al., 2014).

The leaf essential oil of *L. cubeba* (LLO), which is rich in (E)-3, 7-dimethyl-2, 6-octadienal, was tested against *Tenebrio molitor* (mealworm beetle). The contact toxicity of LLO was observed to have an LC_{50} value of 21.2 μg/cm^2, and about 89% of repellency was recorded on the 10th instar of the beetle at 12h of exposure. Similarly, the fumigation toxicities against the 10th instar and adult beetle were recorded to have LC_{50} values of 2.7 and 3.7μl/liter. The results suggested that LLO has potent insecticidal activity against *T. molitor* (Wang et al., 2015).

The commercial *L. cubeba* essential oil showed contact toxicity against *Trichoplusia ni* larvae with an LD_{50} value of 112.5 μg/larva. γ-terpinene of *L. cubeba* essential oil was responsible for most of the toxicity of the oil against *T. ni* larvae (Jiang et al., 2009).

The contact and fumigation toxicities of LFO against *Luciaphorus perniciosus* (Mushroom mite) were LD_{50}: 0.932 and 0.166 μg/cm^3, respectively. Increased toxicity was observed with the addition of 0.01% *L. cubeba* essential oil in citronella grass or black pepper oil. The results indicated that the use of LFO alone or in combination with other oils could control mushroom mites effectively (Pumnuan et al., 2010). The acaricidal activity of LFO against house dust (*Dermatophagoides pteronyssinus* and *D. farinae*) and stored food (*Tyrophagus putrescentiae*) mites were reported by Jeon & Lee (2016). The toxic doses (LD_{50}) of LFO against *D. pteronyssinus, D. farinae,* and *T. putrescentiae* were 1.83, 1.54, and 3.90 μg/cm^2, respectively. The results suggested that LFO could be a potent acaricidal agent against house dust and stored food mites (Jeon & Lee 2016).

The LC_{50} value of *L. cubeba* essential oil against *Callosobruchus chinensis* (L.) was 3.78 μL/L air. Clove/*L. cubeba* oil combination (41:59) yielded a synergistic co-toxicity factor value of 114.15 (Wang et al., 2016). Recently, *L. cubeba* essential oil was reported to exhibit bioactivity against *Saprolegnia parasitica* with MIC of 2.5%, which can be used to control or manage *Saprolegnia* spp. infections in fish farming (Nardoni et al., 2019).

4.2 Fungicidal activity

Litseacubebic acid, monoterpene lactone (6R)-3,7-dimethyl-7-hydroxy-2-octen-6-olide isolate of *L. cubeba* fruit extract, and *L. cubeba* essential oil were tested against phytopathogens. Litseacubebic acid and (6R)-3,7-dimethyl-7-hydroxy-2-octen-6-olide isolate showed antagonistic activity against *Colletotrichum gloeosporioides, Thanatephorus cucumeris, Sclerotinia sclerotiorum*, and *Pseudocer-cospora musae* with lethal concentrations of 588 and 272 μM, respectively. *L. cubeba* essential oil exhibited antifungal activity against *S. sclerotiorum* (IC_{50}: 151.25 μg/mL) and *T. cucumeris* (IC_{50}: 115.58 μg/mL) (Yang et al., 2010).

4.3 As repellent

The mixture of essential oils of *L. cubeba* and *L. salicifolia* was reported to show potent *Aedes aegypti* (L.) repellency. At 0.075% concentration, the mixture of the oils exhibited almost 65.5% escape score in the excito-repellency (contact) test. The synergistic activity (62.7% in non-contact trials) of the mixture of the essential oils against mosquitoes was higher compared to the activities of the individual oils (20-20.3%). The results suggested that the mixture of *L. cubeba* and *L. salicifolia* could be used as an active mosquito repellent (Noosidum et al., 2014). Similarly, Uniyal et al. (2016) reported that the degree of repellency of *Litsea* oil was dose-dependent against *A. aegypti*. Also, *Litsea* oil was a potent active principle compared to N,N-Diethyl-meta-toluamide (DEET) and N, N-diethyl phenylacetamide (DEPA) against *A. aegypti*.

The repellency of *L. cubeba* essential oil against *Monomorium pharaonis* (pharaoh ant) was tested in comparison with turmeric oil. The results showed that turmeric oil exhibits superior repellency against the ant both in the presence and absence of food. *L. cubeba* essential oil showed about 70% minimal repellency against *M. pharaonis* (Wagan et al., 2016).

L. cubeba essential oil rich in 9,12-octadecadienoic acid (Z, Z) showed repellency against the crop insect pest *Nephotettix cincticeps* in laboratory and glasshouse assays. The repellency of *L. cubeba* oil was higher in the choice assay than in the no-choice assay, and *L. cubeba* oil showed acetylcholinesterase activity. The results indicated that *L. cubeba* oil is a potent *N. cincticeps* control agent (Chakira et al., 2017).

4.4 Cosmetic application

Huang et al. (2013) reported the potential cosmeceutical properties of *L. cubeba* essential oil. The major component of the essential oil was citral. The whole oil showed tyrosinase inhibitory activity (IC_{50}: 100 μg/mL), free radical scavenging activity (IC_{50}: 17.75 and 10.2 mg/mL for $ABTS^+$ and O_2^-, respectively), UV-TiO_2-NO_2^- -induced protein oxidation, and tyrosine nitration protective activity (0.01, and 0.1 mg/mL, respectively) based on *in vitro* assays. The individual compounds showed inferior activities in all the tests, which indicated that the bioactivity of *L. cubeba* essential oil was a synergistic effect of several bioactive constituents. The results claimed that *L. cubeba* oil could be a promising natural skin-whitening agent (Huang et al., 2013).

5 Bioactivities of *L. cubeba* extracts and isolates

Apart from essential oils, *L. cubeba* extracts exhibited several bioactivities *in vitro* and *in vivo*. Isoquinoline alkaloids isolated from the bark of *L. cubeba* and ethanolic extract showed antimicrobial activity against *S. aureus, Alternaria alternate* and *Colletotrichum nicotianae*, but not all the tested alkaloids exhibited bioactivity. Interestingly, all the samples exhibited cytotoxic activity against cancer cells (BGC-823, HepG2, MCF-7, SGC-7901, SK-MEL-2, SK-OV-3) with different degree of activity (Zhang et al., 2012). Cubelin (a diterpene isolated from the methanol extract of fruits of *L. cubeba*) exhibited cytotoxic activity against HeLa cell. Cubelin induces apoptosis in cancer cells via caspases (Trisonthi et al., 2014). The chloroform extract of heartwood and fruits of *L. cubeba* treated HeLa exhibited a significant reduction in the expression of *PI3KCA, Akt-1* and *Akt-2*, which are involved in cancer cell proliferation (Dalimunthe et al., 2019). n-hexane, ethyl acetate, and ethanol extracts of heartwood and fruits of *L. cubeba* were tested for antiproliferative activity against breast cancer cells. The results showed that all tested extracts arrested the progress of the cancer cell cycle with different degrees of IC_{50} values, ranging from 63-162 μg/mL (Dalimunthe et al., 2017). The results suggested that *L. cubeba* extracts inhibit the proliferation of cancer cells.

Ethanol and water extracts of the root of *L. cubeba* were reported for their protective activity against arthritis in the rodent model. The extracts reduced the arthritic score, thymus index, and paw swelling in Freund's complete adjuvant-mediated arthritis rat model, which was evidenced by the histopathological scores on joint architecture. Further, extract treated animals exhibited a significant suppression in COX-2 (cyclooxygenase-2) and 5-LOX (5-lipoxygenase) expressions as well as in IL-6, IL-1β, and TNF-α productions. However, IL-10 expression was raised in the extract-treated groups. The results suggested that *L. cubeba* root extracts are potent enough to treat the consequences of human arthritis (Lin et al., 2013). Likewise, boldine, an isolate of *L. cubeba*, suppressed the osteoprotegerin/receptor activator of nuclear factor-κB/ receptor activator of nuclear factor-κB ligand signaling pathway, thereby improving the bone strength in collagen-induced arthritis rats (Zhao et al., 2017).

L. cubeba fruits were serially extracted with several solvents (hexane, acetone, methanol, ethanol, and water), and the extracts were tested for *in vitro* antidiabetic and antioxidant properties. The methanol extract showed potent α-glucosidase (IC_{50}: 1435.7 μg/mL) and α-amylase (IC_{50}: 514.9 μg/mL) inhibitory activities. Similarly, ethanol and methanol extracts of *L. cubeba* fruits exhibited the highest radical scavenging activity compared to other tested samples (Chakraborty & Mandal, 2018).

6 Conclusions and prospects

L. cubeba essential oils are rich in monoterpenes, monoterpene hydrocarbons and sesquiterpenes, especially citral and limonene, and account for bioactivities such as antioxidant and antimicrobial activities. However, these compounds are not the only ones responsible for bioactivities; other minor constituents of essential oil are also involved in synergetic activities. The literature survey suggested that the essential oil of *L. cubeba* has pharmacological (antioxidant, anti-proliferative, antimicrobial, cytotoxicity), commercial and industrial potentials (Figure 1). Nonetheless, further studies are required to transfer

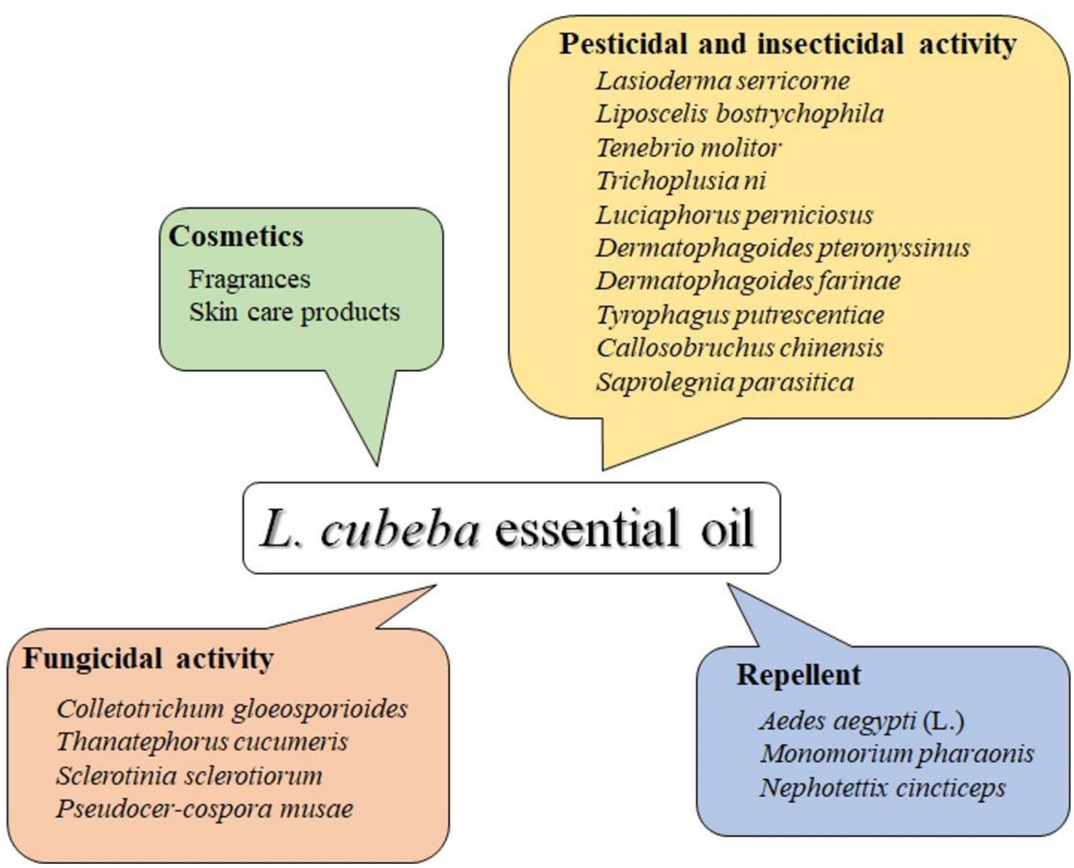

Figure 1. The pharmacological and economical importance of essential oil of *L. cubeba* (Lour.) Pers.

the scientific findings into commercially valuable products. Also, the studies concerning the potential of *L. cubeba* essential oil in aromatherapy and cognitive improvement are possible research leads.

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Supplementary Material

Supplementary material accompanies this paper.

Table S1. The chemical composition of L. cubeba fruit essential oils.

Table S2. The chemical composition of L. cubeba flower essential oils

Table S3. The chemical composition of L. cubeba stem essential oils

Table S4. The chemical composition of L. cubeba leaf essential oils

Table S5. The chemical composition of L. cubeba essential oils isolated from twig, seeds, barks and roots

Table S6. Pharmacological property of essential oil of Litsea cubeba (Lour.) Pers.

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