Overview of Research on Citral in Lauraceae Plants and Its Biological Activity

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Abstract Citral is a monoterpene aldehyde, which is the main chemical component of essential oils from *Litsea cubeba* and *Cymbopogon citratus*, as well as one of the most important representatives of open-chain monoterpene compounds. The lemon flavor released by citral is very strong, and thus, it is widely used in essence, spices, manufacturing of various foods and beauty and other industries. It has antibacterial, anti-inflammatory, antioxidant, anti-tumor, insecticidal and other biological activity. This paper reviewed citral in Lauraceae plants and its biological activity, in order to provide reference for the development and utilization of citral in Lauraceae plants and its diversified applications.

Key words Lauraceae; Citral; Biological Activity

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Lauraceae, belonging dicotyledoneae, and is a family of Magnoliidae, with 2 000 to 2 500 species in approximately 45 genera worldwide. There are currently about 43 varieties and 5 variants in 423 species of 20 genera. The Lauraceae family has a wide variety and distribution of plants with various utilization value, including *Cinnamomum* with *Cinnamomum cassia* Presl as a representative plant, *Litsea* with *Litsea pungens* Hemsl as a representative plant, *Laurus* with *Laurus nobilis* as a representative plant, *Lindera* with *Lindera glauca* as a representative plant, and *Persea* with *Persea americana* as a representative plant[1]. In addition, other main representative plants include *Cinnamomum burmannii* (Nees et T. Nees) Blume, *Cinnamomum camphora* (L.) Presl, *Cinnamomum camphorach* var. Borneol, *Cinnamomum bodinieri* Lévl., *Cinnamomum subavium* Miq., *Beilschmidia madang*, *etc.* They have functions such as medicinal use, extraction of camphor and camphor wood oil, shipbuilding, furniture making[2], spice making, and antibacterial and antioxidant properties[3]. Lauraceae plants contain more than 60 chemical components including citral (Table 1), cinnamaldehyde, eucalyptol, alkaloids, linalool, camphor, safrole, farnesol, methyleugenol and α-terpineol, borneol, 1,8-cineole, and nerolidol, among which citral is one of the main active ingredients. According to relevant reports, derivatives obtained by structural modification of citral with appropriate methods can improve its volatility, stability, solubility, and antibacterial and antibacterial effects[16], thereby exhibiting biological activity such as anti-tumor, asthma-relieving, antibacterial, mosquito-repelling, spice-making, weeding, and lipid-lowering. In order to better explore the resources of Lauraceae plants and achieve diversified development and utilization of Lauraceae plants, this paper mainly reviewed the research progress of Lauraceae citral and its biological activity.

Table 1 Plants of the Lauraceae family containing citral

Genus	Species	Reference
Cinnamomum Schaeff.	*Cinnamomum glanduliferum Meissn*	[4]
Cinnamomum Schaeff.	*C. bodinieri Levl*	
Cinnamomum Schaeff.	*Cinnamomum parthenoxylon Meissn*	[5]
Cinnamomum Schaeff.	*Cinnamomum molle* H. W. Li, ined.	
Cinnamomum Schaeff.	*Cinnamomum aff. tamala* Nees et Eberm.	[6]
Litsea.	*Litsea cubeba* (Lour.) Pers.	
Litsea.	*L. euosma* W. W. Smith	
Litsea.	*Litrea cubeba* (Lour.) Pers	[7]
Cinnamomum Schaeff.	*Cinnamolmum aff. burmanni Blane*	[8]
Cinnamomum Schaeff.	*Cinnamomum wilsonii*	[9]
Cinnamomum Schaeff.	*C. bodinieri* var. *hupehanum*	
Cinnamomum Schaeff.	*Cinnamomum camphora*	
Litsea.	*Litsea pungens* Hemsl.	[10]
Litsea.	*L. cubeba* (Lour.) Pers.	
Litsea.	*L. rubescens* Lec.	
Litsea.	*L. mollis* Hemsl.	
Litsea.	*L. moupingensis* var. *szechuanensis* (Allen) Yang et P. H. Huang	
Litsea.	*L. populifolia* (Hemsl.) Gamble	
Lindera Thunb.	*Lindra glauca* (Sieb. et Zucc.) Blume	
Litsea.	*Litsea pungens* Hems1.	[11]
Litsea.	*Litsea veitchiana* Gamble	[12]
Litsea.	*Litsea coreana* var. *lanuginosa* (Migo) Yang et P. H. Huang	
Litsea.	*L. rotundifolia* var. *oblongifolia*	[13]
Litsea.	*L. verticillata*	
Cinnamomum Schaeff.	*Cinnamomum micranthum* (Hay.) Hay	[14]
Cinnamomum Schaeff.	*Cinnamomum tenuipilum*	
Cinnamomum Schaeff.	*Cinnamomum tamala*	[15]

Chemical Composition

Lauraceae plants contain abundant citral, with the highest content in plant essential oils. Various plants in the genera

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Cinnamomum, *Litsea* and *Lindera* all contain citral, with a content of up to 65% – 80%[14]. Citral with a chemical name of 3, 7-dimethyl-2, 6-octadienal, is a monoterpene aldehyde that can be separated from essential oils. It can be obtained from industrial geraniol (and nerol) through vacuum gas-phase dehydrogenation using copper catalysts, and can also be synthesized from dehydrogenated linalool under vanadium catalysts. Citral has two cis and trans isomers, namely citral a and citral b, respectively. Natural citral is a mixture of two cis and trans isomers (Fig. 1).

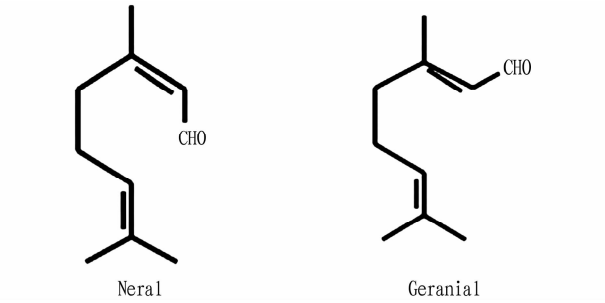

Fig. 1 Structural formulas of citral a and citral b[17]

Citral a

Citral a, also known as geranial and trans-citral, has a structural characteristic, that is the priority groups are on the opposite sides of the carbon atoms of the double bond, forming a two-position double-bond E-isomer, which is a colorless or light yellow liquid with a strong lemon odor, a relative density of 0.889 8, a boiling point of 228 – 229 ℃, easily volatile, insoluble in water, and soluble in ethanol, ether, glycerol, mineral oil, and animal and vegetable oil.

Citral b

Citral b, also known as citral or cis-citral, has a structural characteristic, that is the priority groups are on the same side of the carbon atoms of the double bond, forming a two-position double-bond Z-isomer, Which is a colorless oily transparent sweet liquid with a lemon aroma that is not as sweet as geranial, but slightly sweeter than geranial. It has a relative density of 1.490 0 and a boiling point of 118 – 120 ℃. It is soluble in non-volatile oils, volatile oils, propylene glycol, and ethanol, but insoluble in water and glycerol.

Citral Extraction Method

The organs of Lauraceae plants that contain citral mainly include leaves and fruits. Currently, the main extraction methods for citral include distillation, supercritical extraction, microwave, and chemical methods[18]. Distillation is the most traditional method for extracting citral. Many small workshops that extract essential oils generally use distillation, but extracting citral using distillation is not environmentally friendly. With the investment and exploration of scientific and technological forces, scholars have further optimized the citral distillation technology and process. Tang *et al.*[19] used molecular distillation to purify citral in *Litsea cubeba* oil, achieving a citral yield of over 80%. Wang *et al.*[20] effectively improved the yield of citral in *L. cubeba* by designing a two-tower vacuum continuous distillation system to separate citral. Zeng *et al.*[21] increased the yield of citral in *L. cubeba* essential oil to 95% through multi-stage continuous vacuum distillation. With technological innovation, supercritical CO_2 extraction is gradually being applied to the field of citral extraction. Supercritical extraction can extract components in sequence based on polarity, boiling point and molecular weight, which determines that the purity of citral obtained by supercritical extraction is relatively low. Research teams of Zhang[22], Sun[23], and Zhao[24] extracted not only citral but also other components with similar molecular weights by supercritical CO_2 fluid technology from *L. cubeba* oil, but the extraction rate of citral in the extracted products was relatively low. Microwave extraction utilizes a microwave reactor to assist in extracting effective components from plant tissues. Liu[25] and Fu[26] respectively used microwave technology and microwave assisted distillation technology to extract citral from *L. cubeba* essential oil. They found that the chemical composition of *L. cubeba* oil might change under microwave conditions, and further systematic research is needed for the specific reasons. In addition to the above extraction methods, there are also chemical methods, phase transfer catalyst methods, *etc.*, but these methods are only in the experimental stage and difficult to be promoted outside the laboratory. The main reason is either high cost or the need for specific environments and harsh experimental conditions. Some extraction processes have a significant impact on the environment. Therefore, with the increasing demand for citral in the market, it is imperative to explore an efficient extraction method and process that is energy-saving, environmentally friendly, and easy to promote, for citral.

Biological Activity

Antibacterial activity

The active components of citral in Lauraceae plants have certain antibacterial activity against bacteria, fungi, microorganisms, *etc.*, including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Aspergillus flavus* and yeast (Table 2). Research has found that citral can disrupt and penetrate the lipid structure of bacterial cell walls, leading to damage to the structure of the cell membrane, changes in integrity and permeability, the flow of cell content, deformation of protein structure, and ultimately cell death, thereby exerting its antibacterial activity[27]. Zhao *et al.*[28] used the steam distillation method to extract essential oil from the fruit of *L. cubeba*. The study found that the essential oil from *L. cubeba* fruit had good inhibitory activity against *S. aureus*, *E. coli*, and *C. albicans*. The minimum concentrations that produced antibacterial effects were 20, 40 and 5, respectively, and the higher the content of the essential oil, the better the antimicrobial effect. Ai *et al.*[29] found that citral had a good antifungal effect on *A. flavus*. Through the combined antimicrobial method, it was found that when the concentration of citral (MIC) and eugenol (MIC) was 17.2 μg/ml + 10.7 μg/ml, they exhibit synergistic antimicrobial effect, and they could completely inhibit mycelial growth, damage the integrity of *A. flavus* cell membrane, decrease the extracellular pH value in sequence, and increase the relative conductivity in sequence, thereby damaging the membrane

inside the *A. flavus* mycelia. This synergistic antimicrobial effect could greatly reduce the amount and cost of natural compounds. Wang *et al.* [30] used the liquid dilution method to determine the minimum inhibitory concentration (MIC) values of *E. coli* and *S. aureus*. The results showed that the minimum inhibitory concentration of citral on *E. coli*, *S. aureus*, *Cryptococcus neoformans* and *Candida krusei* was 1.25 μl/ml, and the minimum inhibitory concentration for both *C. albicans* and Candida dubliniensis was 0.63 μl/ml. In addition, Guo *et al.* [31] found that citral also had certain antibacterial effects on plant pathogens such as *Fusarium oxysporum* f. sp. Niveum and *Pyricularia grisea*, and the antimicrobial effect increased with the increase of citral concentration, so the disease rate of crops such as watermelon and rice could be reduced. Furthermore, the antimicrobial properties of citral can also be applied to the food industry, such as preservation of vegetables and fruits, packaging of meat products, and preservation of dairy products.

Table 2 Study on the antibacterial activity of citral

Citral source	Inhibited microbes	MIC	Reference
Fruit essential oil of	*S. aureus*	20 mg/ml	[28]
L. cubeba (Lour.)	*E. coli*	40 mg/ml	
Pers.	*C. albicans*	5 mg/ml	
Citral and eugenol complex	*A. flavus*	17.2 g/ml +10.7 g/ml	[29]
Fruit essential oil of	*E. coli*	1.25 μl/ml	[30]
L. cubeba	*S. aureus*	1.25 μl/ml	
	C. neoformans	1.25 μl/ml	
	C. krusei	1.25 μl/ml	
	C. albicans	0.63 μl/ml	
	C. dubliniensis	0.63 μl/ml	
Fruit essential oil of	*F. oxysporum*	Antibacterial	[31]
L. cubeba	*P. grisea*	Antibacterial	

Antiinflammatory activity

Citral has a certain degree of anti-inflammatory effect and is effective in treating gallstones, cholecystitis, peritonitis, cholangitis, and inflammation induced by lipopolysaccharide (LPS) in human umbilical vein endothelial cells (HUVEC). In addition, it also has antipyretic effects. Zhang *et al.* [32] found that citral could promote the secretion of bile and reduce the content of total cholesterol, bilirubin, and mucus in bile. Administration of citral by gavage to mice could inhibit the formation of gallstones, and *in-vitro* experiments showed that it could dissolve mixed gallstones and provide anti-inflammatory and analgesic effects. They believe that citral can be used as a new drug for treating cholecystitis, cholangitis, and gallstones. Gogoi *et al.* [33] conducted *in-vitro* anti-inflammatory experiments, and the results showed that the anti-inflammatory activity of 0.20 mg/ml *L. cubeba* fruit on ovalbumin denaturation was 82.21%, and the anti-inflammatory activity of 0.25 mg/ml leaf essential oil on ovalbumin denaturation was 81.49%. The levels of anti-inflammatory activity were both high, only 3.83% and 4.55% lower than the highest anti-inflammatory activity of the standard drug, respectively. Liao *et al.* [34-35] isolated geraniol and neral from the essential oil of *L. cubeba* fruit and found that neral had strong anti-inflammatory activity, which had significant effects in inhibiting LPS-stimulated secretion of cytokines (TNF-α, IL-6 and IL-1β) by macrophages and expression of inflammatory molecules (Pro-IL-1β, NOS, GOX-2, and NLRP-3). In addition, Emílio-Silvaet *et al.* [36] found that citral also had a certain antipyretic effect. When lipopolysaccharide (LPS) was administered to the whole body of rats, it could cause pathological syndrome, and then the administration of citral to rats could slow down the release of plasma cytokines TNF-α, IL-1β and of IL-6 and inhibit prostaglandin E2 (PGE2) production in the hypothalamus, thereby achieving an effective antipyretic effect. Therefore, they believe that citral has good prospects for the development of drug delivery systems.

Insecticidal and repellent effects

Citral has good insecticidal effects. The blood-sucking characteristic of mosquitos makes them a vector for many infectious diseases such as filariasis, yellow fever, malaria, Japanese encephalitis, and dengue fever, thus posing a potential threat to human health. Oyedele *et al.* [37] conducted mosquito repellent experiments using citric acid, and found that citric acid had a significant effect on repelling *Aedes aegypti*. In addition, studies have shown that citral can reduce the ability of *Aedes albopictus* to seek hosts[18]. Citral has a good effect on removing mites. Jeon *et al.* [38] found that the median lethal concentrations of *L. cubeba* essential oil (mainly composed of citral) against dust mites, house dust mites and *Tyrophagus putrescentiae* were 1.54, 1.83, and 3.90 μg/cm^2, respectively, so it had bactericidal activity, and could be used as a high-performance natural mite killer. *Trichomonas vaginitis* is one of the common gynecological diseases caused by *T. vaginalis*. Tu *et al.* [39] used a test tube method to study the effects of *L. cubeba* oil and citral on *T. vaginalis*. The results showed that both could kill all *T. vaginalis* at a concentration of 0.46% within 48 h. Therefore, *L. cubeba* oil and citral has significant effects on killing *T. vaginalis* under *in-vitro* conditions, and are expected to be used as drugs for treating *T. vaginitis*.

Anti-tumor activity

Citral has a certain degree of anti-tumor activity and minimal toxic side effects. It has a certain protective effect on many cancers, such as colon cancer, breast cancer, cervical cancer and skin cancer. The anti-tumor mechanisms of citral include blocking cell cycle, regulating signaling pathways, and inhibiting the activity of related proteins and enzymes[40]. Suaeyun *et al.* [41] found that lemon grass (the main chemical component of which is citral) could inhibit the formation of DNA adducts in the muscle layer and mucosa of the colon, thereby playing a certain role in rats with colon cancer. Ogata *et al.* [42] first reported in 2000 that citral could induce apoptosis of HL-60 cells. Chaouki *et al.* [43] found that citral could inhibit the growth of breast cancer cells by inducing apoptosis of breast cancer cell lines. In addition, citral has potential therapeutic effects on leukemia. De Martino *et al.* [44] found that citral could activate protease-3, thereby inducing lymphocyte apoptosis in patients with chronic lymphocytic leukemia. The above studies indicate that citral has good anti-tumor effects and is a promising potential anti-tumor drug.

Antioxidant activity

The citral component in Lauraceae plants plays an extremely important role in inhibiting oxidative stress, with strong antioxidant and free radical-scavenging capacities. Mori *et al.* [45] found a significant increase in the activity of total superoxide dismutase (SOD) in the liver and gills of *Centropomus undecimalis* fed with citral (1.76 mg/kg), demonstrating the strong antioxidant ability of citral. Wang *et al.* [46] also found that citral played an indispensable role in antioxidant activity and free radical scavenging. Li *et al.* [47] measured the *in-vitro* antioxidant activity of essential oils from female and male flowers of *L. cubeba*, and found that the IC_{50} value of male flower reducing power was 2.330 mg/ml, while that of female flower was 1.473 mg/ml; and the IC_{50} value of DPPH free radical scavenging in male flowers was 41.62 mg/ml, while in female flowers it was 9.663 mg/ml; and the IC_{50} value of hydroxyl free radical scavenging in male flowers was 56.95 mg/ml, while in female flowers it was 77.98 mg/ml.

Antidiabetic activity

Citral has antidiabetic effect. Subramaniyan *et al.* [48] found that adding citral (30 μm) into hepatocytes (HepG2) could significantly reduce the cytotoxicity of hepatocellular carcinoma (HepG2) cells induced by high glucose (50 mm) and the generation of reactive oxygen species (ROS), DNA damage, lipid peroxidation and antioxidant enzymes, and could also inhibit the expression of extracellular signal-regulated protein kinase-1 (ERK-1), c-Jun N-terminal kinase (JNK) and p38, and protect Hep G2 cells from high glucose-induced damage by inhibiting the expression of mitogen-activated protein kinase (MAPK) signal. Citral can inhibit the adipogenic gene in 3T3-L1 adipocytes. During the differentiation of preadipocytes into adipocytes, citral can inhibit the adipogenesis of 3T3-L1 adipocytes by changing the expression of adipogenic transcription factors and inflammatory biomarkers[49]. Citral inhibits the fat production of 3T3-L1 adipocytes, which makes it have a good development prospect in drug delivery system.

Conclusions and Prospects

Lauraceae plants have a long history and extensive utilization value, and are a natural resource with great development and utilization prospects. Citral, as their main active ingredient, has biological activity such as antioxidant, antibacterial, anti-tumor and anti-inflammatory[50]. In addition, natural insecticides have very broad application prospects. However, the chemical properties of citral in Lauraceae plants are unstable and prone to oxidation-reduction, hydrogenation, and other reactions. Moreover, its biological activity and resource utilization are not yet perfect, and further systematic research and development are needed to produce more citral-related products for wide application in industries such as medicine, beauty, food, and hygiene. These products can better serve human society while enhancing the utilization value of Lauraceae plants.

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