Mini-Review:

Phytochemistry and Biological Activities of *Curcuma aeruginosa* (Roxb.)

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Abstract: Curcuma aeruginosa *Roxb. is a stemless, aromatic rhizomatous plant, generally characterized by red corolla lobes, purple calyx, dark purple leaf sheath, purple-brown midrib, and greenish-blue rhizome. This species is usually blooming during the wet and rainy seasons, while the rhizome and leaves have an aromatic odor indicating the presence of volatile constituents. This plant has been used in many traditional medicines as a disinfectant, expectorant, and tonic, including treatment for the wound, diarrhea, dysmenorrhea, fever, coughs, and asthma. This paper aims to provide* C. aeruginosa *Roxb., summarized data regarding traditional uses, ethnopharmacology, phytochemistry, and pharmacological activities. From 1987 to 2021, about 34 phytochemicals have been isolated, and up to 223 compounds have been detected using Gas Chromatography-Mass Spectrometry. These metabolites differ from flavonoids, terpenoids, steroids, phenanthrenes, and so forth. Furthermore, various investigations demonstrated that the extracts and compounds obtained from the plant possess several pharmacological activities such as anticancer, antioxidant, antimicrobial, anti-dengue, immunostimulant, anthelmintic, anti-inflammatory, antiandrogenic, anti-nociceptive, and antipyretic, as well as uterine relaxant effect.* Curcuma aeruginosa *Roxb. is a promising medicinal herb and is usually used as oriental traditional medicine by local folks. Therefore, the result supports this plant as a potential source for therapeutic applications and drug development prospects.*

Keywords: Curcuma aeruginosa *Roxb.; phytochemistry; biological activities; Zingiberaceae*

■ INTRODUCTION

Zingiberaceae, one of the largest families in the order Zingiberales, consists of 53 genera and more than 1200 different species known to have an aromatic rhizome due to high volatile constituents' presence [1-2]. Several prominent genera from this family are *Curcuma, Kaempferia* and *Zingiber* [1]. *Curcuma aeruginosa* Roxb. is one of the widely distributed *Curcuma* species in tropical and subtropical regions such as Indonesia [1,3-4], Japan [5], Thailand [6-7], Bangladesh [8-9], India [10-11], Vietnam [12-13], Malaysia [14-15], Myanmar, Cambodia [16-17], and China [18] (Fig. 1). *C. aeruginosa* Roxb. is used in many traditional medicines [6]. It also has a pungent odor and hot, bitter taste because the essential oil constituent is rich in camphor and starch [19].

Over the past 34 years, *C. aeruginosa* has become a public interest in terms of medicinal and food uses. The plant is rich in essential oil and volatile constituents, known to possess potent antioxidant activity and antimicrobial properties utilized in food preservation and flavoring, pharmaceutical, and natural therapies [10,14]. In the previous study, the essential oil of *C. aeruginosa* has proven to contain high levels of sesquiterpenoid, making it have higher antimicrobial activity than other species in the Zingiberaceae family [14]. In addition, the essential oil has bioactive constituents

Fig 1. The distribution of *C. aeruginosa* worldwide (http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:796418-1)

that are crucial in pharmacological and therapeutic uses.

Since 1987, up to 34 compounds and 223 volatile compounds have been discovered containing 70% terpenoids, 1.9% flavonoids, 1.1% diarylheptanoids, 3.5% steroids, 2.3% aromatics, 1.9% amines, and 19.3% other compounds. Furthermore, these isolated metabolites showed extensive biological activity such as anticancer, antioxidant, antimicrobial, anti-dengue, anthelmintic, anti-inflammatory, antiandrogenic, immunostimulating, anti-nociceptive, antipyretic activity, and uterine relaxant effect. Research on the exploration of metabolites and bioactivities of *C. aeruginosa* is still going on; however, no systematic review of *C. aeruginosa* Roxb. has been published. This study reported in chemical and biological activities studies of the extracts, fractions, and isolated secondary metabolites from this plant species. Consequently, this paper summarizes the traditional use, phytochemistry, and biological aspects of *C. aeruginosa* Roxb. All databases with the keyword "*Curcuma aeruginosa*" from search engines such as Scopus, Scifinder, PubMed, and Google Scholar were collected from 1987 to 2021. This study is expected to be helpful in further studies for future development perspectives of the plant and new drug discovery.

■ TAXONOMY

The *C. aeruginosa* Roxb. is a stemless, rhizomatous and aromatic plant that belongs to the family Zingiberaceae and *Curcuma* genus [20]. The generic name was first established by a Swedish botanist, zoologist, and physician Carl Linnaeus in 1753 [21]. Carl Linnaeus is called a father of taxonomy who formalized binomial nomenclature, and most of the descriptions are in Latin. The *C. aeruginosa* is the Lattin botanical name, and several articles also mentioned *C. aeruginosa* Roxb. or *C. aeruginosa* Roxburgh as the generic name provided by William Roxburgh, who discovered this plant species in 1810 [8,22]. Here, the abbreviations "Roxb" are the standard author abbreviations used in botany to indicate "Roxburgh" as the authority of this nomenclature system.

■ MORPHOLOGY

C. aeruginosa is an oriental plant with 30–40 cm height, and the leaves are elliptic or elliptic-oblong, while the leaf sheath and midrib have a reddish-purple color. Its inflorescences appear at the rhizome's apex and usually bloom during the wet or rainy seasons [23-24]. This plant is also characterized by red corolla lobes,

purple calyx, dark purple leaf sheath, purple-brown midrib, and greenish-blue or bluish-black rhizome [10,13,17]. The rhizome and leaves are aromatic, which indicates the presence of volatile constituents [10].

Vernacular Name

C. aeruginosa is widely distributed in tropical and subtropical regions, especially Asia. Due to this condition, *C. aeruginosa* has many vernacular names, a common informal name given by each origin where the plant grows. *C. aeruginosa* Roxb is usually known as Temu Hitam [25-26], Temu ireng [27], Kathali holud [9], Kha-min-dam [6], Wanmahamek [6,24], Pink and blue ginger [7], Mahamek [28], Black Tumeric [29], Gajutsu [5], Kajeawdang [30], and Kali haldi [8,10].

Traditional Uses

Medicinal plants have attracted many scholars because of their pharmacological properties. One of them, *C. aeruginosa* Roxb. is usually used as oriental traditional medicine by local folks. *C. aeruginosa* has been used as a disinfectant, expectorant, anthelmintic, antifungal, anti-inflammatory, tonic [1], and urine remedies for diarrhea and fungal infections [6-7]. The applications also include treatment for gastrointestinal problems, wounds [28], rheumatic diseases [9], hemorrhoids, leprosy, menstrual disorder, aphrodisiac [19], dysentery, gastritis, dyspepsia, flatulence [31], and decreasing dysmenorrhea [32]. In addition, *C. aeruginosa* extract is used to treat fever, coughs, and asthma [33]. In Thailand, the rhizome macerated with alcohol treats uterine pain and inflammation and postpartum uterine and perimenopausal bleeding [7].

■ PHYTOCHEMISTRY

Based on literature collected from 1987 to 2021, a total of 34 phytochemicals have been isolated from *C. aeruginosa* Roxb. rhizome, including 5 flavonoids (Fig. 2), 26 terpenoids (Fig. 3), and 3 diarylheptanoids (Fig. 4), but none from its leaves yet. The isolated and identified phytochemicals are summarized in Table 1. Out of all the isolated compounds, germacrone (**20**) was found to be the most active compound for antiandrogenic activity and was successfully formulated to treat androgenic alopecia disease.

Table 1. Compounds isolated from *C. aeruginosa* Roxb.

Type	Compounds	Source	Ref.
Flavonoid	Flavone (1)	Rhizome	[35]
	3-(5-ethyl-2-methoxy-phenyl)-6-methoxy-chroman-4-one (2)	Rhizome	[47]
	3-(3-ethyl-2-methoxy-phenyl)- 6-methoxy-chromate-4-one (3)	Rhizome	[47]
	6-hydroxy-5- methoxy-2-(2-methoxy-phenyl)-chroman-4-one (4)	Rhizome	[47]
	8-hydroxy-5-methoxy-3-(2-methoxy-phenyl)-chroman-4-on (5)	Rhizome	[47]
Terpenoid	Difurocumenone (6)	Rhizome	[53]
	Aerugidiol (7)	Rhizome	[36]
	Zedoalactone A (8)	Rhizome	[5]
	Zedoalactone B (9)	Rhizome	[5]
	Zedoarondiol (10)	Rhizome	[5,7]
	Curzerenone (11)	Rhizome	[15,55]
	Furanodienone (12)	Rhizome	[15]
	Furanogermenone (13)	Rhizome	[15]
	Zedoarol (14)	Rhizome	[4,15]
	Curcumenol (15)	Rhizome	[3-4,7,58]
	Isocurcumenol (16)	Rhizome	[4,7]
	Aeruginolactone (17)	Rhizome	[54]
	Aeruginone (18)	Rhizome	[54]
	Furanodiene (19)	Rhizome	[6]
	Germacrone (20)	Rhizome	[7,9,45]
	Zederone (21)	Rhizome	[7]
	Dehydrocurdione (22)	Rhizome	[7]

Table 1. Compounds isolated from *C. aeruginosa* Roxb. (*Continued*)

Type	Compounds	Source	Ref.
Terpenoid	Dehydrocurdione (22)	Rhizome	[1]
	Aeruginon (23)	Rhizome	[1,3]
	Curcumenon (24)	Rhizome	[55]
	Pyrocurzerenone (25)	Rhizome	[55]
	Dehydrochromolaenin (26)	Rhizome	[55]
	Curzeone (27)	Rhizome	[55]
	Linderazulene (28)	Rhizome	[55]
	8,12-epoxy-1(10),4(15),7,11-germacratetraen-6-one (29)	Rhizome	[3]
	1(10),4(5)-diepoxygermacrone (30)	Rhizome	[3]
	Isoaromadendrene epoxide (31)		
Diarylheptanoid	Curcumin (32)	Rhizome	[56]
	Demethoxycurcumin (33)	Rhizome	[56]
	Bisdemethoxycurcumin (34)	Rhizome	[56]

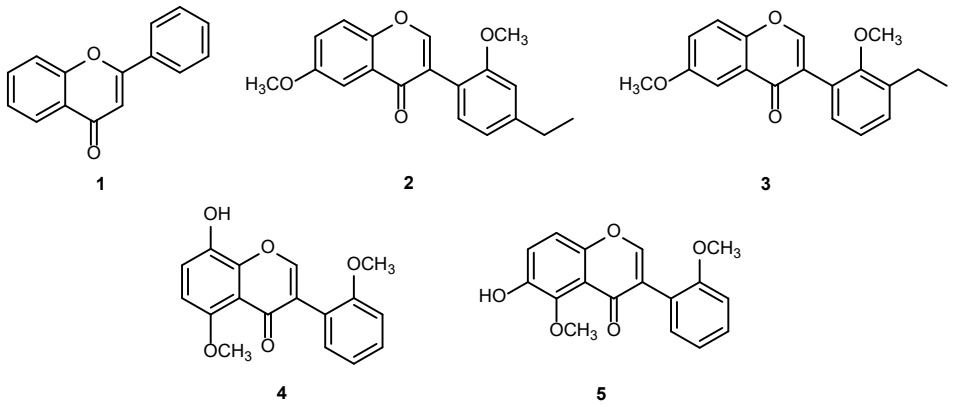

Fig 2. Flavonoid isolated from *C. aeruginosa* Roxb.

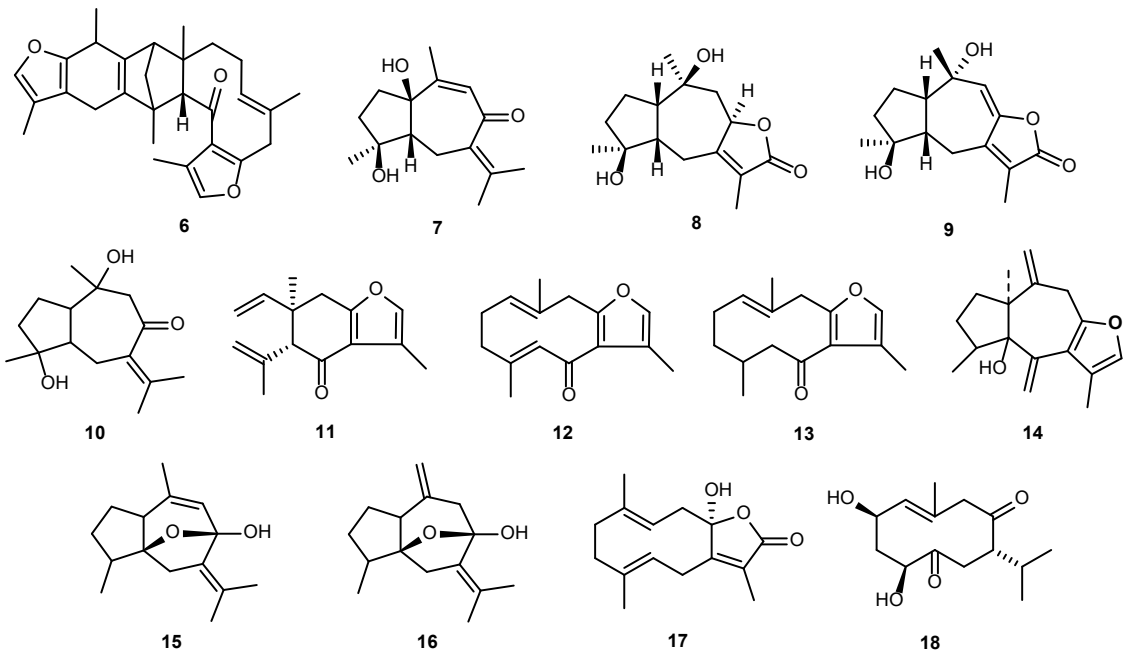

Fig 3. Terpenoid isolated from *C. aeruginosa* Roxb.

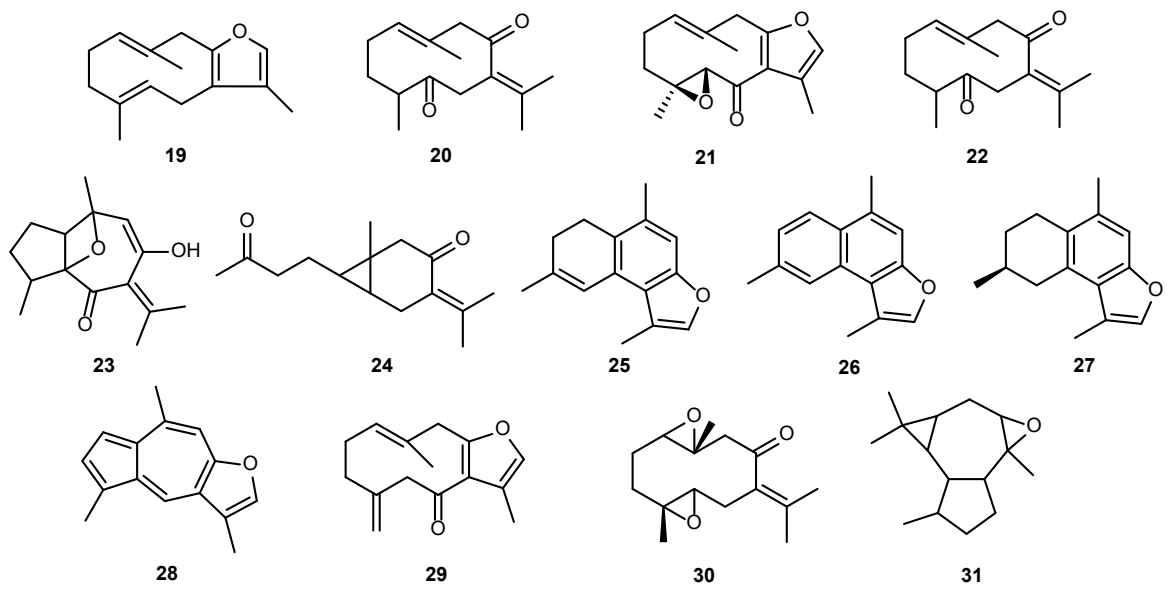

Fig 3. Terpenoid isolated from *C. aeruginosa* Roxb. (*Continued*)

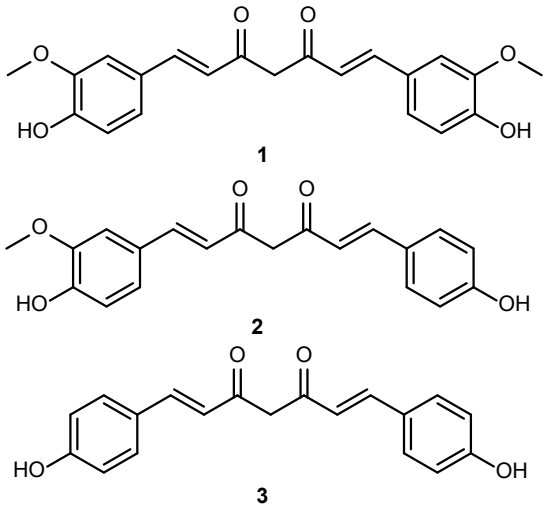

Fig 4. Diarylheptanoids isolated from *C. aeruginosa* Roxb.

The plant is rich in essential oil and volatile constituents. Furthermore, 223 different volatile compounds including 64.5% terpenoids, 4% steroids, 0.45% phenanthrenes, 0.45% dimethyl hopane, 0.45% thiourea derivatives, 4.5% aromatics, 4.5% alcohols, 2.3% amines, 2.3% sugars, and 16.5% others constituent have been detected using Gas Chromatography-Mass Spectroscopy. The extraction method used varies from hydro-distillation, stem-distillation, Soxhlet extraction, and supercritical fluid extraction. Among them, Soxhlet extract was found to contain the greatest variety of secondary metabolites detected by GC-MS analysis. Hence the volatile constituents are summarized in Table 2.

Volatile Constituent

C. aeruginosa Roxb. rhizome and leaves contain 0.32% essential oil [34], with major compounds mostly sesquiterpenes, monoterpenes, esters, and steroids. The oil was extracted from the plant's rhizome and leaves by various methods such as hydro-distillation, steam distillation, and supercritical fluid extraction. These extracts were analyzed using the GC-MS method and were summarized in Table 2.

C. aeruginosa Roxb. essential oil's major constituents that differ by origin have been summarized in Table 3. Camphor, 1,8-cineole, germacrone, curzerenone, and isocurcumenol are the most common compounds found in all essential oil and responsible for many pharmacological activities. However, the major volatile compounds' structures are illustrated in Fig. 5. In addition, essential oil has bioactive constituents that are crucial in pharmacological and therapeutic use. Several articles also mentioned that the essential oil in *C. aeruginosa* Roxb. possesses potent antioxidant activity and antimicrobial properties utilized in food preservation and flavoring and pharmaceutical and natural therapies [10,14].

Table 2. Volatile Constituent from *C. aeruginosa* Roxb.

No.	Compounds	Molecular formula	Plant part	Ref.
Terpenoids				
1.	α-Amorphene	$C_{15}H_{24}$	Rhizome	[13]
2.	α-Atlantol	$C_{15}H_{24}$	Rhizome	[23]
3.	α-Bulnesene	$C_{15}H_{24}$	Rhizome	[14]
4.	α-Copaene	$C_{15}H_{24}$	Rhizome	[13]
5.	α-Curcumene	$C_{15}H_{22}$	Rhizome	[48]
6.	α-Fenchene	$C_{10}H_{16}$	Rhizome	[13]
7.	α-Fenchol	$C_{10}H_{18}O$	Leaf	[11]
8.	α-Humulene	$C_{15}H_{24}$	Leaf, Rhizome	[12,34]
9.	α-Muurolene	$C_{15}H_{24}$	Rhizome	[23]
10.	α-Pinene	$C_{10}H_{16}$	Leaf, Rhizome	[12,48]
11.	α -Selinene	$C_{15}H_{24}$	Leaf	[11]
12.	α-Terpene-4-ol	$C_{10}H_{18}O$	Rhizome	[45]
13.	α-Terpinolene	$C_{10}H_{16}$	Rhizome	[13]
14.	α-Terpineol	$C_{10}H_{18}O$	Rhizome	[11]
15.	α-Thujenal	$C_{11}H_{16}O$	Rhizome	[13]
16.	α-Thujene	$C_{10}H_{16}$	Leaf	[12]
17.	β-Bisabolene	$C_{15}H_{24}$	Rhizome	[19]
18.	β-Caryophyllene	$C_{15}H_{24}$	Leaf	[12]
19.	β-Cubebene	$C_{15}H_{24}$	Leaf	[11,14]
20.	β-Elemene	$C_{15}H_{24}$	Laef, Rhizome	[12,34]
21.	β-Elemenone	$C_{15}H_{22}O$	Leaf	[12]
22.	β-Eudesmol	$C_{15}H_{24}$	Rhizome	[48]
23.	β-Farnesene	$C_{15}H_{24}$	Rhizome	[14]
24.	β-Levantenolide	$C_{20}H_{30}O_3$	Rhizome	[25]
25.	β-Pinene	$C_{10}H_{16}$	Leaf	[12,34]
26.	β-Selinene	$C_{15}H_{24}$	Rhizome	[19]
27.	δ-Cadinene	$C_{15}H_{24}$	Leaf	[12]
28.	δ-Elemene	$C_{15}H_{24}$	Rhizome	[19,57]
29.	γ-Cadinene	$C_{15}H_{24}$	Rhizome	[23]
30.	γ-Elemene	$C_{15}H_{24}$	Leaf, Rhizome	[12,19]
31.	γ-Eudesmol	$C_{15}H_{24}$	Rhizome	[19]
32.	γ-Muurolene	$C_{15}H_{24}$	Rhizome	[23]
33.	γ-Selinene	$C_{15}H_{24}$	Rhizome	[13]
34.	γ-Terpinene	$C_{10}H_{16}$	Leaf	[12]
35.	γ-Terpineol	$C_{10}H_{18}O$	Rhizome	[48]
36.	(+)-2-Bornanone	$C_{10}H_{16}O$	Rhizome	[10]
37.	(+)-epi-Bicyclosesquiphellandrene	$C_{15}H_{24}$	Rhizome	[19]
38.	(E)-β-Famesene	$C_{15}H_{24}$	Leaf	[10-11,61]
39.	(E)-β-Ocimene	$C_{10}H_{16}$	Leaf	[11]
40.	(E)-Nerolidol	$C_{15}H_{26}O$	Rhizome	[13]
41.	(E)-Tagetone	$C_{10}H_{16}O$	Leaf	[11]
42.	(Z)-β-Ocimene	$C_{10}H_{16}$	Leaf	[11]
43.	1,8-Cineole	$C_{10}H_{18}O$	Leaf, Rhizome	[12,34]
44.	1,1,4,7-Tetramethyldecahydro-1H-cyclopropa[E]azulen-4-ol	$C_{15}H_{26}O$	Rhizome	[19]
45.	1H-Cycloprop[e]azulene, decahydro-1,1,7-trimethyl-4-methylene-, (1aR,4aS,7R,7aR,7bS)-(-)-	$C_{15}H_{24}$	Rhizome	[19]
46.	1,1,7-Trimethyl-4-methylenedecahydro-1H-cyclopropa[E]azulen-7-ol	$C_{15}H_{24}O$	Rhizome	[19]

Table 2. Volatile Constituent from *C. aeruginosa* Roxb. (*Continued*)

No.	Compounds	Molecular formula	Plant part	Ref.
47.	1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7-trimethyl-4-methylene-, [1a (1aα.,4aα,7β.,7aβ.,7bα.)]	$C_{15}H_{24}O$	Rhizome	[19]
48.	1,5,9-Cyclododecatriene, 1,5,9, trimethyl-	$C_{15}H_{24}$	Rhizome	[19]
49.	1,6-dimethyl-9-(1-methylethylidene)-5,12-dioxatricyclo[9.1.0.0(4,6)]dodecan-8one	$C_{15}H_{22}O_3$	Rhizome	[19]
50.	1,6-Methanonaphthalene, decahydro-1,4,8a-trimethyl-9-methylene-, (1S,4S,4aS,6R,8aS)-(-)	$C_{15}H_{24}$	Rhizome	[19]
51.	1-Isopropyl-7-methyl-4-methylene-1,2,3,4,4a,5,6,8a, octahydronapthalene	$C_{15}H_{24}$	Rhizome	[19]
52.	1-Napthalenol, decahydro-1,4a-dimethyl-7-(1-methylethyldiene)-, [1R-(1α,4aβ,8aα)]	$C_{15}H_{26}O$	Rhizome	[19]
53.	1,2-Naphthalenedione, 6-hydroxy-3,8-dimethyl-5-(1-methylethyl)	$C_{15}H_{16}O_3$	Rhizome	[19]
54.	2-(4A,8-Dimethyl-2,3,4,4a,5,6,7,8-octahydro-2-napthalenyl)-2-propanol	$C_{15}H_{26}O$	Rhizome	[19]
55.	2,4 Diisopropenyl-1-methyl-1-vinylcyclohexane	$C_{15}H_{24}$	Rhizome	[19]
56.	2-Isopropenyl-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronapthalene	$C_{15}H_{24}$	Rhizome	[19]
57.	3-Carene	$C_{10}H_{16}$	Rhizome	[19]
58.	4-epi-cubedol	$C_{15}H_{26}O$	Rhizome	[19]
59.	4-Oxo-α-isodamascol	$C_{13}H_{20}O_2$	Rhizome	[49]
60.	4-Oxo-β-isodamascol	$C_{13}H_{20}O_2$	Rhizome	[25]
61.	5β-Guaia-7(11),10(14)-dien-8α-ol, 5,8 epoxy, (+)	$C_{15}H_{22}O_2$	Rhizome	[19]
62.	5-Azulenemethanol, 1,2,3,4,5,6,7,8-octahydro-α3,8-tetramethyl, [3S-(3α, 5α, 8α)]	$C_{15}H_{26}O$	Rhizome	[19]
63.	6-Isopropenyl-4,8a-dimethyl-1,2,3,5,7,8,8a-octahydro-naphthalen-2-ol	$C_{15}H_{24}O$	Rhizome	[19]
64.	7-Isopropenyl-1,4-dimethyl-1,2,3,4,5,6,7,8-octahydroazulene	$C_{15}H_{24}$	Rhizome	[19]
65.	8,9 b-Dimethyl-4a,9b-dihydrobenzo[b,d]furan-3(4H)-one	$C_{15}H_{22}O$	Rhizome	[25]
66.	10s,11s-Himachala-3(12),4-diene	$C_{15}H_{24}$	Rhizome	[10]
67.	7H-2,4a-Methanonaphthalen-7-one, 1,2,3,4,5,6-hexahydro-1,1,5,5-tetramethyl-, (2S,4aR)-(-)	$C_{15}H_{22}O$	Rhizome	[19]
68.	Albicanol	$C_{15}H_{26}O$	Rhizome	[13]
69.	Allo aromadendrenoxide-(1)	$C_{15}H_{24}O$	Rhizome	[19,61]
70.	Anthiaergostan-5,7,9,22-tetraen-14-ol-15-one	$C_{28}H_{40}O_2$	Rhizome	[25]
71.	Boldenone	$C_{19}H_{26}O_2$	Rhizome	[19]
72.	Borneol	$C_{10}H_{18}O$	Leaf, Rhizome	[12,48]
73.	Camphene	$C_{10}H_{16}$	Leaf, Rhizome	[12,34]
74.	Camphor	$C_{10}H_{16}O$	Leaf, Rhizome	[12,48]
75.	Carvone	$C_{10}H_{14}O$	Leaf	[11]
76.	Caryophyllene	$C_{15}H_{24}$	Rhizome	[19]
77.	Caryophyllene oxide	$C_{15}H_{20}O$	Leaf, Rhizome	[12,19]
78.	*cis*-carveol	$C_{10}H_{16}O$	Leaf	[11]
79.	Curcumanolide A	$C_{15}H_{22}O_2$	Rhizome	[48]
80.	Curcumanolide B	$C_{15}H_{22}O_2$	Rhizome	[48]
81.	Curcumol	$C_{15}H_{24}O_2$	Rhizome	[37]
82.	Curdione	$C_{15}H_{24}O_2$	Rhizome	[27]
83.	Curzerenone	$C_{15}H_{18}O_2$	Leaf	[12]
84.	Curzerene	$C_{15}H_{20}O_2$	Leaf, Rhizome	[12,34]
85.	Cyclohexane, 1-ethenyl-1-methyl-2-(1-methylethenyl)-4-(1-methylethylidene)	$C_{15}H_{24}$	Rhizome	[19]

Table 2. Volatile Constituent from *C. aeruginosa* Roxb. (*Continued*)

No.	Compounds	Molecular formula	Plant part	Ref.
86.	Cycloisolongifolene, 8,9-dehydro-9-formyl	$C_{16}H_{22}O$	Rhizome	[25]
87.	Dehydrocurdione	$C_{15}H_{22}O_2$	Rhizome	[48]
88.	Elemol	$C_{15}H_{26}O$	Rhizome	[13]
89.	*endo*-Borneol	$C_{10}H_{18}O$	Rhizome	[34]
90.	Epi-curzerenone	$C_{10}H_{18}O_2$	Leaf	[11]
91.	Epi-bicyclosesquiphellandrene	$C_{15}H_{24}$	Rhizome	[25]
92.	Eucalyptol	$C_{10}H_{18}O$	Rhizome	[10,19]
93.	Eudesma-4(14),11-diene	$C_{15}H_{24}$	Rhizome	[14]
94.	Furanodienone	$C_{10}H_{18}O_2$	Rhizome, Leaf	[15,11]
95.	Furanoelemene	$C_{15}H_{18}O$	Rhizome	[45]
96.	Furanogermenone	$C_{15}H_{20}O_2$	Rhizome, Leaf	[15,11]
97.	Gajutsulactone A	$C_{15}H_{22}O_2$	Rhizome	[45]
98.	Gajutsulactone B	$C_{15}H_{22}O_2$	Rhizome	[45]
99.	Germacrene A	$C_{15}H_{24}$	Rhizome	[34]
100.	Germacrene B	$C_{15}H_{24}$	Rhizome	[34,61]
101.	Germacrene D	$C_{15}H_{24}$	Rhizome	[45]
102.	Germacrone	$C_{15}H_{22}O$	Leaf, Rhizome	[12,48]
103.	Guaiene	$C_{15}H_{24}$	Rhizome	[19]
104.	Guaiol	$C_{15}H_{26}O$	Rhizome	[45]
105.	Isoborneol	$C_{10}H_{18}O$	Leaf, Rhizome	[12,19]
106.	Isocurcumenol	$C_{15}H_{22}O_2$	Rhizome	[19]
107.	Isofuranodienone	$C_{10}H_{18}O_2$	Leaf	[11]
108.	Isolongidolene, 4,5-dehydro	$C_{15}H_{22}$	Rhizome	[10]
109.	Isospathulenol	$C_{15}H_{24}O$	Rhizome	[19]
110.	Labd-13-en-15-oic acid, 8,12-epoxy-12-hydroxy-γ-lactone	$C_{20}H_{30}O_3$	Rhizome	[25]
111.	Limonene	$C_{10}H_{16}$	Rhizome	[34]
112.	Linalool	$C_{10}H_{18}O$	Leaf	[12]
113.	Methenolone	$C_{20}H_{30}O_2$	Rhizome	[25,57]
114.	Murolan-3,9(11)-diene-10-peroxy	$C_{15}H_{24}O_2$	Rhizome	[19]
115.	Myrcene	$C_{10}H_{16}$	Leaf	[11-12]
116.	Myrtenyl acetate	$C_{12}H_{18}O_2$	Rhizome	[13]
117.	Myrtenal	$C_{10}H_{14}O$	Leaf	[11]
118.	Naphthalene, decahydro-1,4a-dimethyl-2-methylene	$C_{13}H_{22}$	Rhizome	[19]
119.	Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2-(1-methylethenyl)	$C_{15}H_{24}$	Rhizome	[10]
120.	Naphthalene, 1,2,3,5,6,7,8,8a-octahydro-1,a8-dimethyl-7-(1-methylethenyl)	$C_{15}H_{24}$	Rhizome	[10]
121.	Neocurdione	$C_{15}H_{24}O_2$	Rhizome	[13]
122.	Nootkaton-11,12-epoxide	$C_{15}H_{22}O_2$	Rhizome	[19]
123.	*p*-cymene	$C_{10}H_{14}$	Leaf	[11-12]
124.	*p*-Mentha-1,4(8)-diene	$C_{10}H_{16}$	Rhizome	[13]
125.	Phytol	$C_{20}H_{40}O$	Leaf	[11]
126.	Pinocarvone	$C_{10}H_{14}O$	Rhizome	[13]
127.	Pulegone	$C_{10}H_{16}O$	Leaf	[11]
128.	Sabinene	$C_{10}H_{16}$	Leaf	[12]
129.			Rhizome	[48]
130.	Santolinatriene	$C_{10}H_{16}$	Rhizome	[10]
131.	Spathulenol	$C_{15}H_{24}O_2$	Rhizome	[23]
132.	Terpinen-4-ol	$C_{10}H_{18}O$	Leaf, Rhizome	[12,48]

Table 2. Volatile Constituent from *C. aeruginosa* Roxb. (*Continued*)

No.	Compounds	Molecular formula	Plant part	Ref.
133.	*trans*-γ-Bisabolene	$C_{15}H_{24}$	Rhizome	[13]
134.	*trans*-Caryophyllene	$C_{15}H_{24}$	Rhizome	[34]
135.	*trans*-Pinocarveol	$C_{10}H_{16}O$	Leaf	[11]
136.	*trans*-Verbenol	$C_{10}H_{16}O$	Leaf	[11]
137.	Tricyclene	$C_{10}H_{16}$	Rhizome	[48]
138.	Thunbergol	$C_{20}H_{34}O$	Rhizome	[19]
139.	Valerenal	$C_{15}H_{24}O$	Rhizome	[19]
140.	Valerenol	$C_{15}H_{24}O$	Rhizome	[19]
141.	Velleral	$C_{15}H_{20}O_2$	Rhizome	[25,57]
142.	Verbenene	$C_{10}H_{14}$	Rhizome	[13]
143.	Xanthinin	$C_{15}H_{22}O_5$	Rhizome	[14,19]
144.	Zingiberene	$C_{15}H_{24}$	Rhizome	[45]
Steroids				
145.	β-Sitosterol	$C_{29}H_{50}O$	Rhizome	[25,57]
146.	17-Hydroxy-3,20-dioxopregna-1,4,9 (11)-trien-21-yl acetate	$C_{23}H_{28}O_5$	Rhizome	[25]
147.	19-Norpregn-4-en-20-yn-3-one, 17 (TMS) oxy	$C_{23}H_{34}O_2Si$	Rhizome	[25]
148.	4α-Methylandrostanne-2,3-diol-17-dione	$C_{20}H_{30}O_4$	Rhizome	[25]
149.	Androst-5-en 17-one, 3,16-bis [(TMS) oxy)], 0-methyloxime, (3β,16α)	$C_{26}H_{47}NO_5Si$	Rhizome	[25]
150.	Boldenone	$C_{19}H_{26}O_2$	Rhizome	[19]
151.	Cholesta-22,24-dien-5-ol-4,4-dimethyl	$C_{29}H_{48}O$	Rhizome	[25,49]
152	Menthenolone	$C_{20}H_{30}O_2$	Rhizome	[25]
153.	Norethynodrel	$C_{20}H_{26}O_2$	Rhizome	[19]
Phenanthrenes				
154.	5,8-Dihydroxy-4a-methyl-4,4a,4b,5,6,7,8,8a,9,10-decahydro-2(3H)-phenanthrenone	$C_{15}H_{22}O_3$	Rhizome	[19]
Dimethylated Hopanes				
155.	17α,21β-28,30-Bisnorhopane	$C_{28}H_{48}$	Rhizome	[19]
Thiourea derivatives				
156.	N-(4-Hydroxyphenyl)-N,N',N'-Trimethylsulfamide	$C_9H_{14}N_2O_3S$	Rhizome	[19]
Aromatics				
157.	2-(1-(Beta-d-glucopyranosyloxy)-1-methylethyl)-2,3-dihydro-7-oxo-7H-furo(3,2-g)chromene, (R)	$C_{20}H_{24}O_9$	Rhizome	[19]
158.	4,6-dimethyldibenzothiophene	$C_{14}H_{12}S$	Rhizome	[10]
159.	5-isoppropenyl-3,6-dimethyl-6-vinyl-4,5,6,7-tetrahydro-1-benzofuran	$C_{15}H_{20}O$	Rhizome	[19]
160.	Acetophenone	C_8H_8O	Rhizome	[25]
161.	Ethoxybenzene	$C_8H_{10}O$	Rhizome	[10]
162.	Phenol, 3-phenoxy	$C_{12}H_{10}O_2$	Rhizome	[10]
Alcohols				
163.	1-Heptacosanol	$C_{27}H_{56}O$	Rhizome	[19]
164.	1-Hexen-3-ol	$C_6H_{12}O$	Leaf	[11]
165.	2-Heptyl alcohol	$C_7H_{12}O$	Rhizome	[34]
166.	2-Nonanol	$C_9H_{20}O$	Rhizome	[34]
167.	2-Propen-1-ol, 3-(2,6,6-trimethyl-1-cyclohexen-1-yl)	$C_{12}H_{20}O$	Rhizome	[19]
168.	(E)-2-hexenol	$C_6H_{12}O$	Leaf	[11]
169.	(Z)-3-hexenol	$C_6H_{12}O$	Leaf	[11]
170.	Behenic Alcohol	$C_{22}H_{46}O$	Rhizome	[19]
171.	Heptane-2-ol	$C_7H_{16}O$	Rhizome	[48]
172.	Hexanol	$C_6H_{14}O$	Leaf	[11]

Table 2. Volatile Constituent from *C. aeruginosa* Roxb. (*Continued*)

No.	Compounds	Molecular formula	Plant part	Ref.
Aldehydes				
173.	2-[4-methyl-6-(2,6,6)-trimethylcyclohex-1-enyl]hexa-1,3,5-trienyl]cyclohx-1-en-1-carboxaldehyde	$C_{23}H_{32}O$	Rhizome	[19]
Ketone				
174.	(3E)-5-Isopropyliden-6-methyl-3,6,9-decatrien-2-one	$C_{14}H_{20}O$	Rhizome	[19]
175.	Undecane-2one	$C_{11}H_{22}O$	Rhizome	[48]
176.	Tropolone	$C_7H_6O_2$	Rhizome	[37]
Alkanes				
177.	7-Tetradecenal (Z)	$C_{14}H_{26}O$	Rhizome	[19]
178.	(Z)-3-Heptadecene	$C_{17}H_{34}$	Rhizome	[13]
179.	Heneicosane	$C_{21}H_{44}$	Rhizome	[19]
180.	Hexacosane	$C_{26}H_{54}$	Rhizome	[19]
181.	Pentadecene	$C_{15}H_{30}$	Rhizome	[13]
182.	Tetracosane	$C_{24}H_{50}$	Rhizome	[25]
183.	Triacontane	$C_{30}H_{62}$	Rhizome	[25]
184.	Tetratriacontane	$C_{34}H_{70}$	Rhizome	[25]
Esters				
185.	Butanoic acid, 4-[(TMS) oxy]-TMS ester	$C_{10}H_{24}O_3Si_2$	Rhizome	[25]
186.	Butanedioic acid, [(TMS) oxy]-, bis (TMS) ester	$C_{13}H_{30}O_5Si_3$	Rhizome	[25]
187.	Citric acid, ethyl ester, tri-TMS	$C_{17}H_{36}O_7Si_3$	Rhizome	[25]
188.	Glycine, N-(TMS)-, TMS ester	$C_7H_{12}F_3NO_3Si$		
189.	Hexanedioic acid, bis(2-ethylhexyl)ester	$C_{22}H_{42}O_4$	Rhizome	[19]
190.	Hexadecanoid acid, TMS ester	$C_{19}H_{40}O_2Si$	Rhizome	[25]
191.	Malonic acid, bis (TMS) ester	$C_9H_{20}O_4Si_2$	Rhizome	[25]
192.	L-alanine, N-octanyl-ethyl ester	$C_{13}H_{25}NO_3$	Rhizome	[25]
193.	Oxalic acid, bis (TMS) ester	$C_8H_{18}O_4Si_3$	Rhizome	[25]
194.	Stearic acid, TMS ester	$C_{21}H_{44}O_2Si$	Rhizome	[25]
Amines				
195.	4-amino-N-(2-phenylethyl)-1,2,5-oxadiazole-3-carboxamide	$C_{11}H_{12}N_4O_2$	Rhizome	[10]
196.	4,4-Dimethyl-N-(2-phenylethyl)-5α-androst-2-en-17-amine	$C_{29}H_{43}N$	Rhizome	[25]
197.	(*Z*)-9-Octadecenamide	$C_{18}H_{35}NO$	Rhizome	[13]
198.	(*Z*)-13-Docosenamide	$C_{22}H_{43}NO$	Rhizome	[13]
199.	Phenylethanolamine	$C_{17}H_{35}NOSi_3$	Rhizome	[25]
Sugars				
200.	D-Fructose, 1,3,4,5,6-pentakis-O-(TMS)-, O-methyloxime	$C_{22}H_{55}NO_6Si_5$	Rhizome	[25]
201.	D-Glucose, 2,3,4,5,6-pentakis-O-(TMS)-, O-methyloxime	$C_{22}H_{55}NO_6Si_5$	Rhizome	[25]
202.	myo-Inositol, 1,2,3,4,5,6-hexakis-O-(TMS)	$C_{24}H_{60}O_6Si_6$	Rhizome	[25]
203.	α-D Glucopyranoside, 1,3,4,6 tetrakis-O-(TMS)-β-D-fructofuranosyl 2,3,4,6-tetrakis-O-(TMS)-	$C_{36}H_{86}O_{11}Si_8$	Rhizome	[25]
Others				
204.	(-)-Isolongifolol, pentafluoropropionate	$C_{18}H_{25}F_5O_2$	Rhizome	[19]
205.	1,2,3,4-tetrakis (1-methylethylidene)cyclobutane	$C_{16}H_{24}$	Rhizome	[19]
206.	1,2-Dimethyl-5-nitroadamantane	$C_{12}H_{19}NO_2$	Rhizome	[19]
207.	1,7,7-Trimethylbicyclo[2.2.1] Heptan-2-ol	$C_{10}H_{17}ClO$	Rhizome	[19]
208.	1,4-Hexadien-3-one, 5-methyl-1-[2,6,6-trimethyl-2,4,-cyclohexadien-1-yl]	$C_{16}H_{22}O$	Rhizome	[19]
209.	3,7-cyclodecadien-1-one,10-(1-methylethenyl)-,(E,E)	$C_{13}H_{18}O$	Rhizome	[19]
210.	3-Oxatricyclo[20.8.0.0(7,16)]triaconta-1(22), 7(16),9,13,23,29-hexane	$C_{29}H_{42}O$	Rhizome	[19]

Table 2. Volatile Constituent from *C. aeruginosa* Roxb. (*Continued*)

No.	Compounds	Molecular formula	Plant part	Ref.
211.	3-methyl cyclopentane-1-yl-TMS ether	$C_9H_{18}OSi$	Rhizome	[25]
212.	4-isopropyl-7,11-dimethyl-3,7,11-cyclotetradecatrienone	$C_{19}H_{30}O$	Rhizome	[19]
213.	2(3H)-Benzofuranone, 6-ethenylhexahydro-6-methyl-3-methylene-7-(1-methylethenyl)-,[3aS-(3aα,6α,7β,7aβ)	$C_{15}H_{20}O_2$	Rhizome	[19]
214.	4,7-Methanofuro[3,2-c]oxacycloundecin-6(4H)-one, 7,8,9,12-tetrahydro-3,11-dimethyl	$C_{15}H_{18}O_3$	Rhizome	[19]
215.	5aH-3a,12-Methano-1H-cyclopropa[5',6']cyclodecal [1',2':1,5]cyclopenta[1,2-d]dioxol-13-one,1a,2,3,9,12,12a-hexahydro-9-hydr	$C_{23}H_{32}O_5$	Rhizome	[19]
216.	as-Indacen-4(1H)-one, decahydro-, (3a.α,5a.β,8a.β,8b.β.)-	$C_{12}H_{18}O$	Rhizome	[19]
217.	(2E)-2-(4-Methoxybenzylidene) cyclohexanone	$C_{14}H_{16}O_2$	Rhizome	[19]
218.	Bicyclo[3.1.0]hexan-3-one,4-methyl—1-(1-methylethyl)	$C_{10}H_{16}O$	Rhizome	[10]
219.	Bufa-20,22-dienolide, 14,15-epoxy-3,5,16-triihydroxy-(3β, 5β, 15β, 16β)	$C_{28}H_{36}O_8$	Rhizome	[19]
220.	Cyclohexanone, 2-methyl-5-(1-methylethenyl)	$C_{10}H_{16}O$	Rhizome	[10]
221.	Cycloprop[e]indene-1a,2(1H)-dicarboxaldehyde, 3a,4,5,6,6a,6b-hexahydro-5,5,6b-trimethyl-(1a.α, 3a.β, 6a.β, 6b.α)	$C_{15}H_{20}O_2$	Rhizome	[19]
222.	Isocitric Acid	$C_{18}H_{40}O_7Si_4$	Rhizome	[25]
223.	Propolic acid, 3-(1-hydroxy)-2-isopropyl-1,5-methylcyclohexyl)	$C_{13}H_{20}O_3$	Rhizome	[25]

Table 3. Major Volatile Constituents Present (>5%) in *C. aeruginosa* Roxb.

Origin	Plant Part (Method)	Chemical Constituents	Ref.
Bogor, Indonesia	Rhizome (SD)	Tropolone (18.07%), 1,8-cineole (17.90%), curcumol (5.69%), and camphor (5.31%)	[37]
Johor, Malaysia	Rhizome (HD)	Curzerenone (24.6%), 1,8-cineole (11.0%), camphor (10.6%), zedoarol (6.3%), isocurcumenol (5.8%), curcumenol (5.6%), and furanogermenone (5.5%)	[15]
Kuantan, Malaysia	Rhizome (SD)	Cycloisolongifolene, 8,9-dehydro-9-formyl (35.29%), dihydrocostunolide (22.51%), velleral (10%), and germacrone (6.50%)	[14]
Selangor, Malaysia	Rhizome (HD)	Curzerenone (30.4%) and 1,8-cineole (25.2%)	[50]
Pahang, Malaysia	Rhizome (MTBE)	Methenolone (16.54%), cycloisolongifolene, 8,9-dehydro-9-formyl- (15.93%), Labd-13-en-15-oic acid,8,12-epoxy-12-hydroxy-γ-lactone (10.77%), propiolic acid, 3-(1-hydroxy)-2 isopropyl-1,5-methylcyclohexyl) (7.84%), and 4-oxo-β-isodamascol (5.17%)	[25]
	Rhizome (E, methanol)	α-D Glucopyranoside, 1,3,4,6 tetrakis-O-(TMS)-β-D-fructofuranosyl 2,3,4,6-tetrakis-O-(TMS)- (38.08%), D-Glucose, 2,3,4,5,6-pentakis-O-(TMS)-, O-methyloxime (14.61%) and D-Fructose, 1,3,4,5,6-pentakis-O-(TMS)-, O-methyloxime (5.28%)	
	Rhizome (E, chloroform)	Cycloisolongifolene, 8,9-dehydro-9-formyl- (15.7%) and propiolic acid, 3-(1-hydroxy)-2 isopropyl-1,5-methylcyclohexyl) (11.09%)	
Chiang Mai, Thailand	Rhizome (HD)	Camphor (29.39%), germacrone (21.21%), borneol (7.27%), and germacrene B (5.20%)	[34]
Phetchabun, Thailand	Rhizome (HD)	1,8-cineole (22.65%), germacrone (17.7%), furanodiene (11.4%), and β-pinene (8.02%)	[45]
	Rhizome (E, hexane)	Dehydrocurdione (27.64%), curcumenol (15.06%), germacrone (10.15%), and gajutsulactone B (6.30%)	
Ratchaburi, Thailand	Rhizome (HD)	Germacrone (23.49%), curzerenone (11.78%), and 1,8-cineole (10.92%)	[23]
Thailand	Rhizome (SD)	Camphor (16.85%) and curzerenone (16.81%)	[51]
Kerala, India	Rhizome (HD)	Curcumenol (38.7%) and β-pinene (27.5%)	[52]

Table 3. Major Volatile Constituents Present (>5%) in *C. aeruginosa* Roxb. (*Continued*)

Origin	Plant Part (Method)	Chemical Constituents	Ref.
Kerala, India	Rhizome (HD)	Ethoxybenzene (33.44%), santolina triene (7.28%) and eucalyptol (6.44%)	[10]
Kerala, India	Leaf (HD)	l,8-cineole (17.7%), curzerenone (10.5%), furanogermenone (7.8%), camphor (7.5%), (Z)-3-hexenol (5.8%), and furanodienone (5.1%)	[11]
Kerala, India	Rhizome (SCF)	Isocurcumenol (27.09%), 7H-2,4a-methanonaphthalen-7-one, 1,2,3,4,5,6-hexahydro-1,1,5,5-tetramethyl-,(2S,4aR)-(-) (6.31%), and boldenone (5.89%)	[19]
	Rhizome (E, hexane)	Isocurcumenol (13.34%), boldenone (8.5%), Naphthalene, decahydro-1,4a-dimethyl-2-methylene (7.37%), (2E)-2-(4-Methoxybenzylidene) cyclohexanone (6.94%)	
Huế, Vietnam	Leaf (HD)	Curzerene (16.2%), germacrone (13.6%), 1,8-cineole (13.5%) and champor (5.7%)	[12]
Tuyen Quang, Vietnam	Rhizome (HD)	β-pinene (21.9%), neocurdione (16.1%), and curcumol (15.2%)	[13]

*HD = hydro-distillation; SD = steam distillation; E = extract; MTBE = methyl tert-butyl ether, SCF = super critical fluid extraction

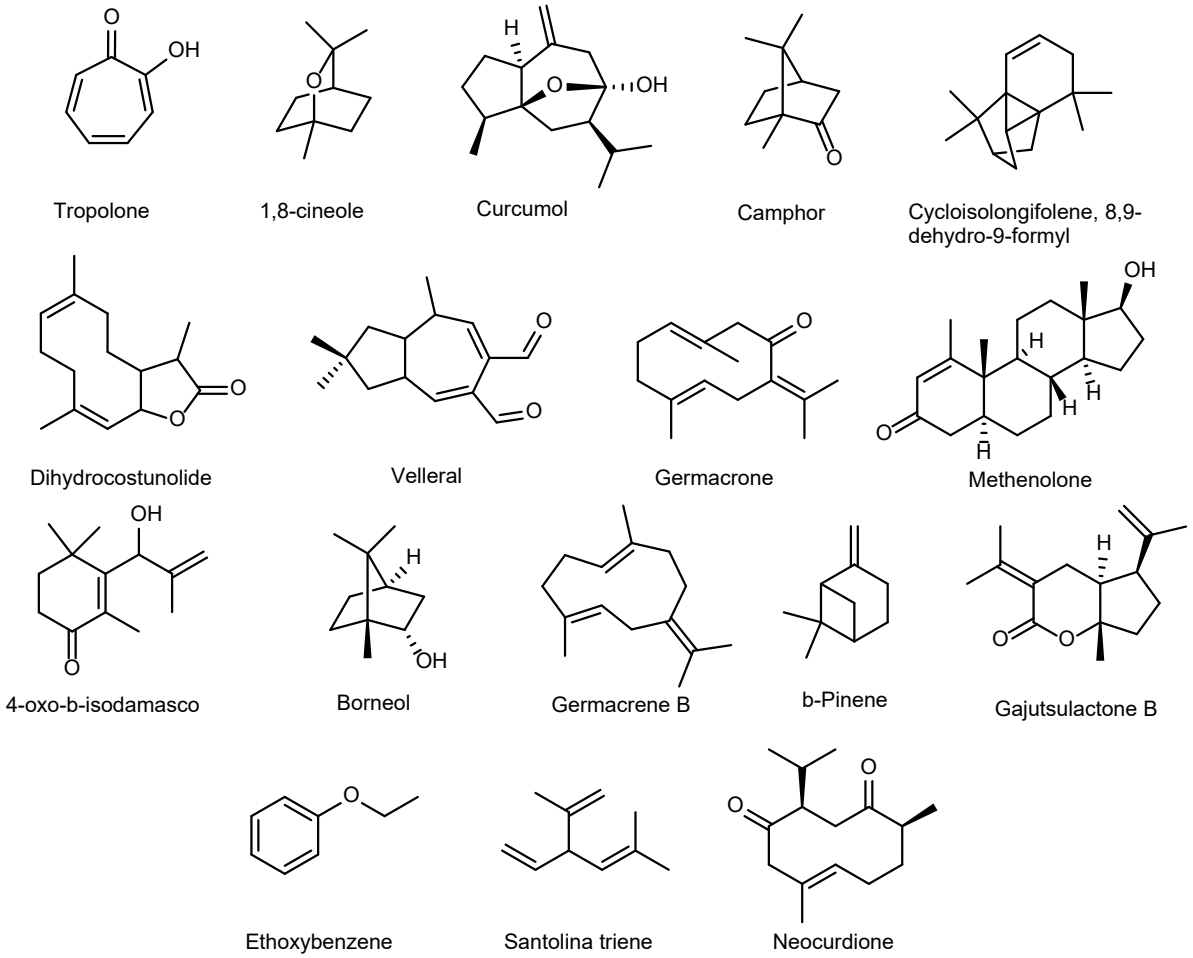

Fig 5. Major volatile compounds of *C. aeruginosa* Roxb.

Flavonoid

One flavone and four isoflavonoids have been isolated from the ethyl acetate (**1**) and petroleum extracts (**2**-**5**) [35,47]. Flavonoid compound isolation from the ethyl acetate extract was firstly carried out by Hastuti et al. [35]. In plants, flavonoids are responsible for the color

and aroma, growth, and development of seedlings, and protect plants from different biotic and abiotic stresses by acting as unique UV filters. Several researchers mentioned flavonoids could prevent injury caused by free radicals and direct scavenging of free radicals. This ability gives flavonoids antioxidant and anti-inflammatory properties [63]. The chemical structures of isolated flavonoids are shown in Fig. 2.

Terpenoid

A total of 26 sesquiterpenes have been isolated from *C. aeruginosa* Roxb. rhizome. Shiba et al. [53] isolated a sesquiterpene dimer called difurocumenone (**6**) from the *n*-hexane fraction of this plant. Masuda et al. [36] isolated aerugidiol (**7**) and determined its absolute configuration using CD spectra data. Four years later, two guaiane-type sesquiterpenes that are zedoalactone A (**8**) and B (**9**), together with zedoarondiol (**10**) was isolated from *n*-butanol extract [5]. These new compounds' structures were characterized using Infra-Red, Mass Spectra, and NMR spectroscopic data to confirm the structure.

Afterwards, Sirat et al. [15] isolated curzerenone (**11**), furanodienone (**12**), furanogermenone (**13**), and zedoarol (**14**). The result showed compound **11** is a major sesquiterpene contained in *C. aeruginosa,* while compounds **12**, **30**, and **14** were reported for the first time. After 9 years, Hj. Sukari et al. [4] isolated zedoarol (**14**), curcumenol (**15**), and isocurcumenol (**16**) from petroleum ether and chloroform extract, which was the first isolated from this species. Giang et al. [54] isolated aeruginolactone (**17**) and aeruginone (**18**) from rhizome of this plant. Srivilai et al. [6] isolated furanodiene (**19**), then Suphrom et al. [7] isolated germacrone (**20**), zederone (**21**), and dehydrocurdione (**22**) as well as compounds **10**, **15**, and **16** from *n*-hexane extract. Later, Atun et al. [1] isolated new sesquiterpenes lactone aeruginon (**23**) and one known compound, curcumenon (**24**), from methanol extract. Following two years, Boutsada et al. [55] isolated pyrocurzerenone (**25**), dehydrochromolaenin (**26**), curzeone (**27**), linderazulene (**28**), 8,12-epoxy-1(10),4(15), and 7,11-germacratetraen-6-one (**29**) from dichloromethane extract of this plant's rhizome.

Recently, Purwantiningsih et al. [3] isolated and characterized 1(10),4(5)-diepoxygermacrone (**30**), isoaromadendrene epoxide (**31**), including **15** and **24** from the *n*-hexane and ethyl acetate extracts. The structures were elucidated through the spectroscopic data from NMR-1D and two-dimensional NMR spectroscopy. The chemical structures of terpenoid isolated from *C. aeruginosa* Roxb. are shown in Fig. 3.

Diarylheptanoid

Diarylheptanoids were characterized by 1,7-diphenylheptane structural skeletons, which are mainly divided into linear or macrocyclic compounds. Diarylheptanoid is usually produced by genus *Curcuma* [63]. Jitoe et al. [56] found the existence of curcumin (**32**), demethoxycurcumin (**33**), bisdemethoxycurcumin (**34**) from the extract of *C. Aeruginosa,* and these structures are shown in Fig. 4.

■ BIOLOGICAL ACTIVITY

C. aeruginosa Roxb. has various pharmacological activities that have been used widely in traditional medicine. This plant's medicinal use has attracted scholars to test its biological activities, including anticancer, antioxidant, antimicrobial, anti-dengue, immunostimulant, anthelmintic, anti-inflammatory, antiandrogenic, anti-nociceptive, and antipyretic, as well as uterine relaxant effect as reported by several papers.

Anticancer Activity

The *in vitro* cytotoxic activities of *C. aeruginosa* Roxb. methanol, *n*-hexane, and chloroform extracts were observed by Atun et al. [1] against MCF-7, Ca Ski, HeLa S3, T-47D, and Vero cell lines using MTT colorimetric assay. The study showed the *n*-hexane and chloroform had potent anticancer activity against MCF-7 with LC_{50} of 69.47 ± 2.16 and 92.60 ± 4.10 µg/mL. In addition, the *n*-hexane showed potent activity against Ca Ski with an LC_{50} value of 66.02 ± 0.45 µg/mL. However, each extract had low activity against HeLa S3, T-47D, and Vero cell lines (LC_{50} > 500 µg/mL).

Subsequently, Fitria et al. [37] observed *in vitro* antiproliferative test of *C. aeruginosa* Roxb. essential oil

against MCF-7 cell lines. The result showed that the cancer cell proliferation decreased as the extract concentration increased. The essential oil at 170 μg/mL concentration exhibited 50.2% inhibition of MCF-7 cancer cell with an IC_{50} value of 161.0 μg/mL. The content of tropolone in essential oils was suspected of prohibiting cancer cells' proliferation by inhibiting Histone Deacetylase (HDAC), an enzyme correlating many biochemical processes. Tropolone is known to inhibit the proliferation of several cancer cells, including HCT-116 (colon cancer), BXPC-3 (pancreatic cancer), and HuT-78 (T-lymphocytes) with a GI_{50} value range from 5 to 30 μM. However, further investigation is needed to test the antiproliferative activity of the isolated compound from this plant.

The essential oil cytotoxic activity evaluated against *Artemia salina* Leach larvae eggs using Brine Shrimp Lethality Test (BSLT) was potent due to its LC_{50} value of 78.2 ± 7.3 μg/mL being lower than 1000 μg/mL [38].

Antioxidant Activity

An antioxidant activity test was performed *in vitro* using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and nitric oxide scavenging assay by George and Britto [10]. Hydro-distillation's essential oil collected from *C. aeruginosa* Roxb. showed a very strong antioxidant activity with IC_{50} and EC_{50} values of 28 μg/mL and 30 μg/mL, respectively. In comparison, the percentage inhibition was 77% at 50 μg/mL compared to the reference compound, ascorbic acid (81% at 50 μg/mL). The total antioxidant activity was determined by phosphomolybdenum assay, and the result showed it had a great percentage close to ascorbic acid (67% at 50 μg/mL), meaning 64.3% at 50 μg/mL with IC_{50} and EC_{50} values of 45 μg/mL and 30 μg/mL. Therefore, the reducing power assay showed a value of 2.54% at 50 μg/mL, lower than ascorbic acid (2.67 μg/mL). In Nitric Oxide (NO) scavenging assay at 50 μg/mL concentration, inhibition was 76.8% for ascorbic acid as a standard and 72.3% for essential oil. These results showed that the essential oil possessed a strong antioxidant activity.

The *in vitro* antioxidant activity test of 70% and 96% ethanolic extracts using 1-diphenyl-2-picrylhydrazyl (DPPH) scavenging was reported by Nurcholis et al. [26]. The result showed that none of the two were more active than ascorbic acid. The 70% extract produced IC_{50} value of 437.07 μg/mL while the value for the 96% was 681.39 μg/mL compared to ascorbic acid (32.91 μg/mL). Therefore, this plant's ethanolic extract showed a very weak antioxidant activity. Besides, more studies are required for antioxidant compounds characterization from *C. aeruginosa* Roxb, recalling the essential oil of this plant possessed a strong antioxidant activity. This result could play a valuable role in food conservation and prevention of oxidative damage related to the pathophysiology of several diseases.

Antimicrobial Activity

The *in vitro* antimicrobial activity assay of the essential oils was evaluated by Tg Kamazeri et al. [14] against some bacteria, namely *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and fungi including *Candida albicans* and *Cryptococcus neoformans* using the disc diffusion and broth microdilution methods. Furthermore, the positive control used was tetracycline (30 μg/mL) or nystatin (100 μg/mL). The essential oil was found to have a moderate activity due to the moderate inhibition showed towards the microorganisms. Its zone of inhibition towards each bacterium was *S. aureus* (7.0 ± 0.0 mm), *B. cereus* (9.3 ± 0.4 mm), *P. aeruginosa* (7.5 ± 0.0 mm), and there was none towards *E. coli*. Moderate inhibition was also performed against the fungi *C. albicans* (8.8 ± 0.4 mm), while the inhibition against *C. neoformans* (7.0 ± 0.0) was weak.

Two years after, Jose and Thomas [17] tested the antibacterial activity towards Gram-positive strains (*S. aureus*, *S. haemolyticus*, and *B. cereus*) and Gram-negative (*S. typhi*, *E. aerogenes*, *V. cholerae*, *P. aeruginosa*, and *S. marcescens*) using the disc diffusion method. At 5 mg/mL concentration, *n*-hexane extract showed high antibacterial activity towards *B. cereus* (21 ± 2.3 mm) and *S. marcescens* (14 ± 1.8 mm) compared to antibiotic streptomycin (3 ± 0.2 mm). The plant's acetone extract (5 mg/mL) also showed high antibacterial activity against *S. aureus* (20 ± 1.8 mm), *B.*

cereus (15 ± 1.6 mm), and *P. aeruginosa* (20 ± 2.3 mm). Methanol extracts (5 mg/mL) were best against *S. typhi* (24 ± 2.1 mm), *V. cholerea* (20 ± 1.3 mm), and *P. aeruginosa* (20 ± 2.1 mm). The chloroform extract was only best at inhibiting *V. cholerae* (20 ± 2.8 mm), while the ethyl acetate and water extract showed no significant inhibition towards all the strains. It suggested the combination of major and minor compounds boosting the synergistic effect for antimicrobial activity [14].

The next year, Theanphong et al. [23] tested the essential oils as an antibacterial agent against *E. coli*, *S. aureus*, *B. subtilis*, and *E. faecalis* using the agar diffusion technique. The result showed a moderate activity against *E. faecalis* (MIC = 6.25 μg/mL) and weak activity against *B. subtilis* (MIC = 50 μg/mL) compared to reference compound, tetracycline (MIC = 0.04 μg/mL). Meanwhile, the essential oil's antimycobacterial activity was also investigated using Green Fluorescent Protein Reporter Microplate Assay (GFPMA) against *Mycobacterium tuberculosis* H32Ra. It was found to possess an inhibitory activity with MIC of 2500 mg/mL, lower than the reference drug, isoniazid (MIC = 0.023-0.046 μg/mL).

The antibacterial activities for the essential oil of *C. aeruginosa* Roxb. fresh rhizome, stem, and leaves have been tested against *S. mutans* by Wahyuni et al. [39] using the micro-dilution method. That fresh rhizome showed potent antibacterial activity towards *S. mutans* with a MIC value of 15.63 μg/mL similar to the reference drug, tetracycline (MIC = 15.63 μg/mL). Nevertheless, the stem and leaves' oil showed no significant antibacterial activity with a MIC > 100 μg/mL.

More recently, Pangastuti et al. [40] observed *C. aeruginosa* extract's potency against *P. aeruginosa* virulence factor, which was regulated by quorum sensing such as protease LasA, LasB, and biofilm formation. Protease LasA activity was measured using *S. aureus* cell lysis, and that of protease LasB was measured using elastin Congo red assay, while biofilm formation was monitored using PVC biofilm formation assay method. The result showed that the ethyl acetate extract decreased the *P. aeruginosa* virulence of protease LasA, LasB, and biofilm formation by 66.92, 37.80, and 46%, respectively.

Based on those results, *C. aeruginosa* Roxb. rhizome was proposed to have excellent antibacterial activity for therapeutic purposes. However, further studies need to characterize the bioactive antibacterial compound and understand its molecular mechanism of action.

Anti-dengue Effect

Moektiwardoyo et al. [41] conducted an *in vitro* study on the number of thrombocytes, erythrocytes, and hematocrit levels in male Wistar rats (*Rattus norvegicus*) using the Heparin Induction Method. Furthermore, 250 and 500 mg/kg ethanolic extract dosages were administered orally to the rats for seven days continuously. The result showed a significant thrombocyte enhancement with 24.48% and 26.98% values at 250 and 500 mg/kg (α = 0.05), respectively. Meanwhile, the extract (500 mg/kg) enhanced the erythrocytes number up to 10.27% and then hematocrit to 8.19%. The enhancement percentage was below 20%, suggesting the extract is unable to trigger plasma leakage. However, *C. aeruginosa* Roxb. extracts could be developed as an anti-dengue drug, and further investigation is needed to understand their molecular mechanism of action.

Immunostimulating Activity

Anggriani et al. [27] investigated the essential oil's potency as an immunostimulant agent after immune suppression by doxorubicin treatment. In addition, the *in vitro* assay was performed on lymphocyte primary cells, which were isolated from balb/c mice then treated with the essential oil and doxorubicin. The doxorubicin IC_{50} value was 2.68 μM while the essential oil (10, 25, and 50 μg/mL) significantly increased lymphocyte cell viability at the range of 10 to 50 μg/mL after doxorubicin treatment. Flow cytometry analysis also showed that the essential oil at 10 μg/mL concentration increased CD4+ and CD8+ cells percentage in lymphocytes after treating 2 μM doxorubicin. This result showed *C. aeruginosa* Roxb. essential oil acted as an immunostimulant and co-chemotherapy agent after doxorubicin chemotherapy. Furthermore, in molecular docking examination,

curdione, one of the essential oil's major compounds, had a stronger and more stable affinity in binding to CD95 protein with a docking score of -67.2341 compared to native ligand CD95-L with -55.9123. In short, *C. aeruginosa* Roxb. essential oil is promising to be developed as an immunostimulant agent to counter the immune system suppression induced by doxorubicin chemotherapy.

Anthelmintic Activity

In vitro anthelmintic activity of *C. aeruginosa* Roxb. methanol extract was determined by Vanda et al. [29] on *Fasciola gigantica*, a parasitic worm (fluke) that causes fasciolosis. The positive control used was albendazole (0.24 mg/mL), and the negative was PBS (phosphate buffer saline). Three different concentrations from the extract were 10, 25, and 50%. The mortality time was determined under the microscope and observed until the flukes used had no movement. Furthermore, the result showed the average mortality time for concentrations of 10, 20, and 50% were 75 ± 10.6, 57 ± 12.5, and 48 ± 12.5 min longer than the reference drug, albendazole, which killed all the flukes within 30 min. At 50%, the methanol extract had a similar effect compared to albendazole. Hence this extract is a potential anthelmintic agent. Furthermore, it suggested that monoterpenes and sesquiterpenes in the extract are acetylcholine antagonists, which interfere with muscle contraction of flukes and lead to paralysis before finally dead.

A histopathological study stated the extract impacted tegument breakage, an important organ of *F. gigantica*, in respiration and nutrient absorption, leading to the organism's death. The extract also harms the reproductive organs, causing testes disintegration and intestine desquamation. Therefore, more investigation is needed to discover the anthelmintic activity in other extracts of *C. aeruginosa* Roxb. considering its high potential as an anthelmintic drug.

Anti-inflammatory Activity

The first *in vitro* anti-inflammatory test on *C. aeruginosa* Roxb. fresh rhizome extract was conducted by Reanmongkol et al. [32] in Wistar rats using the carrageenan-induced paw edema method. In addition, the rats' right hind paws were measured, and then the chloroform, methanol, and water extracts (100, 200, 400, and 800 mg/kg), as well as aspirin (200 mg/kg) were orally administered 30 min before 0.1 mL of 1% (w/v) carrageenin was injected into the paws. The result showed no significant suppression effect from all the extracts on the paws compared to aspirin's reference drug.

Eight years after, *in vitro* anti-inflammatory test of *C. aeruginosa* Roxb. rhizome 70% ethanolic extract was carried out using inducible-nitric oxide secretion measurement of lipopolysaccharide (LPS)-induced macrophage RAW 264.7 cells. At 25 μg/mL dose, the extract showed a high inhibition percentage of 84.43% at low concentration. The extract's ability as an anti-inflammatory agent tends to be active because of many phenolic and terpenoid compounds that affect its anti-inflammatory activity. Based on this result, the plant's 70% ethanolic extract has potency as an anti-inflammatory agent. This high inhibition percentage might be due to the presence of phenolic and flavonoid compounds [42].

In 2016, Triastuti et al. [43] investigated the *in vivo* anti-inflammatory activity of *C. aeruginosa* Roxb. ethanolic extract using the croton oil-induced ear edema method in male BALB/c mice. The reference drug used was 1% hydrocortisone, while the negative control was 10% croton oil. Furthermore, the concentrations were divided into 40, 80, and 160 mg/ear doses. First, the croton oil (2 μg/μL acetone) was topically applied to the left and right ears. Then all test agents were applied to both after 30 mins. Ear thickness was measured after 4 and 24-h induction. The highest inhibition percentage from ethanolic extract at dose 160 mg/ear on the right ear was 90.35 ± 4.22% ($p < 0.05$) after 24 h injection compared to reference drugs, while 1% hydrocortisone only had 75.06 ± 6.28%. The ethanolic extract at 40 mg/ear dose showed its highest inhibition on the mice's right ear only after 4 h injection with a value of 74.34 ± 3.85% ($p < 0.05$), while at 80 mg/ear, the highest inhibition percentage was 82.50 ± 4.72% ($p < 0.05$) which occurred after 24 h injection on the left ear. Pre-treatment of *C. aeruginosa* has been able to decrease leukocyte migration. *C. aeruginosa* Roxb. extract

demonstrated a potent anti-inflammatory activity, especially for acute topical inflammation compared to the reference drug.

Most recently, Paramita et al. [44] examined the *in vitro* anti-inflammatory activity of *C. aeruginosa* ethanolic extract using an erythrocyte membrane stabilization test. It was followed by *in vivo* anti-inflammatory activity measurement using a carrageenan-induced paw edema method and plethysmo meter. The i*n vitro* anti-inflammatory test showed the extract's EC_{50} value was 47.8 ± 1.6 mg/mL, which was higher than that of the reference drug, indomethacin which was 26.4 ± 2.9 mg/mL. Based on the result, indomethacin still has better anti-inflammatory activity than the extract. In addition, the extract's protective effect on the erythrocyte membrane tended to be mediated by alterations in calcium influx, while *C. aeruginosa* Roxb. membrane-stabilizing ability was possibly caused by the combined effect from bioactive compounds such as flavonoids, terpenoids, and steroids [64]. Based on the Tukey post hoc test ($p < 0.05$), the in vivo anti-inflammatory activity result of the extract showed a significant area under the curve (AUC) value for a 100 mg/kg dose (8.26 ± 0.50) and indomethacin of 10 mg/kg dose (6.50 ± 0.10). The ethanolic extract inhibits the discharge of inflammatory chemical mediators that increase vascular permeability.

In summary, the plant's extracts are potential anti-inflammatory agents. Moreover, a molecular study needs to be conducted to determine *C. aeruginosa* extract and its bioactive compounds' mechanism of action as an anti-inflammatory agent.

Antiandrogenic Activity

Antiandrogenic drugs treat androgen-related diseases such as benign prostatic hyperplasia, acne, hirsutism, and androgenic alopecia [59]. Furanodiene (**19**) *in vitro* antiandrogenic activity was determined against 5α-reductase, an enzyme involved in the development of androgenic alopecia, isolated from male Sprague Dawley (SD) rat's liver [6]. This compound showed significant inhibitory activity of 40.67% at the concentration of 1.0 mg/mL while the *n*-hexane extract showed higher enzymatic inhibition of 72.78% (IC_{50} = 0.22 mg/mL). Compared to the reference drugs, ethynylestradiol that was 47% (IC_{50} = 0.26 mg/mL), *n*-hexane showed a higher potency to be developed as an anti-androgen agent. This higher percentage of *n*-hexane extract than Furanodiene (**19**) indicates that *n*-hexane contains many compounds responsible for the antiandrogenic activity.

In 2012, Suphrom et al. [7] investigated the inhibitory activity of *n*-hexane extract, germacrone (**20**), zederone (2**1**), dehydrocudione (**22**), curcumenol (**15**), zedoarondiol (**10**), and isocurcumenol (**16**) against 5α-reductase isolated from male Sprague Dawley (SD) rats with ethinylestradiol as the positive control. Based on the result, germacrone (**20**) showed the most potent inhibition (65.7%) with an IC_{50} value of 0.42 mg/mL. The *in vivo* anti-androgen activity was also tested using the hamster flank gland. Compound **20** suppressed the flank gland's testosterone-stimulated growth by up to 79–82% inhibition (effective at doses ≤ 3 μg) and weakly suppressed DHT-stimulated growth by up to 27.7% inhibition (100 μg). This fact suggested germacrone (**20**) has a highly potent inhibitory activity on testosterone-stimulated growth of the LNCaP cell model and the *in vivo* anti-androgen activity compared to *in vitro* enzymatic assay. Next, the androgenic receptor binding activity was tested using fluorescent polarization (FP). The result showed that germacrone (**20**) had no interaction with androgen receptor nor associated with androgenic receptor blockage, yet the androgenic activity exhibited was due to 5α-reductase inhibition. Also, the further stability of germacrone (**20**) has been investigated [24].

Srivilai et al. [45] investigated the minoxidil skin penetration effect of the essential oil, *n*-hexane extract, and germacrone (**20**) on Franz diffusion cells using thick human foreskin as membranes. Minoxidil skin penetration with 0.2% and 2% extracts increased the total flux by ~4-fold, germacrone (**20**) by ~10 fold, and essential oil by ~20 fold. In brief, the study showed that the three samples enhance minoxidil absorption through human skin. Pumthong et al. [60] demonstrated the efficacy of the formulation of 5% *C. aeruginosa* hexane extract with 5% minoxidil compared to placebo.

This formulation is not only decreased hair shedding but also stimulated obvious hair growth effectively after 6 months. There is no significant side effect during and after the study means this formulation is safe to use. This potential anti-androgen activity from *C. aeruginosa* essential oil, *n*-hexane extract, and germacrone (**20**) are suspected to be used as a more effective supplement for androgenic alopecia treatment.

Anti-nociceptive Activity

The *in vivo* anti-nociceptive activity of *C. aeruginosa* Roxb. chloroform, methanol, and water extract was first determined by Reanmongkol et al. [32]. They used male Swiss mice and Wistar rats, measured using acetic acid-induced writhing, hot plate, and formalin tests with aspirin (200 mg/kg) as a reference drug. The acetic acid-induced writhing test result showed the chloroform and methanol extracts at 100, 200, and 400 mg/kg doses dependently attenuated the number of writhing induced by a 0.6% acetic acid intraperitoneal injection. Therefore, the number of writhing according to each dose was 35.2 ± 5.8, 21.9 ± 5.2, and 10.7 ± 3.8 mg/kg p.o (aspirin, 9.6 ± 2.6 mg/kg p.o), while methanol alone had 32.8 ± 5.3, 28.2 ± 5.5, and 24.6 ± 3.7 mg/kg p.o (aspirin: 12.7 ± 3.3 mg/kg p.o). However, the water extract did not show any effect on acetic acid-induced writhing response in the mice.

In the hot plate test, the mice were placed on a hot plate maintained at 55 °C ± 1 °C. Then, their nociceptive response was measured every 15 min over 60 min. The result showed that neither of the chloroform, methanol, and water extracts (100, 200, and 400 mg/kg) nor aspirin (200 mg/kg) had any significant protective effects on heat-induced pain in the mice. Moreover, another reference standard, morphine sulfate (10 mg/kg), markedly increased the pain latency.

The formalin test result showed that the chloroform extract at 200 mg/kg dose decreased the licking activity in the late phase of formalin-induced pain with a licking time of 17.50 ± 5.84 sec, similar to aspirin that also suppressed only in the late phase (9.89 ± 16.83 sec). The methanol and water extracts did not affect both in the early and late phases, opposing to morphine sulfate, the reference drug, which significantly reduced the licking activity in both phases with the licking time being 2.8 ± 0.35 ($p < 0.05$) and 0.0 ± 0.0 sec ($p < 0.01$).

In 2015, *in vivo* anti-nociceptive activity was also determined in Swiss albino mice using acetic acid induced-writhing and formalin-induced licking tests [9]. The reference drugs used were diclofenac (10 mg/kg) and aspirin (100 mg/kg), while the negative control was 5% carboxymethyl cellulose (CMC) in distilled water (10 mL/kg). Furthermore, the *C. aeruginosa* methanol extract demonstrated significant peripheral anti-nociceptive activity, compared to diclofenac, by reducing the number of acetic acid-induced writhing. Based on the result, prostaglandin biosynthesis inhibition by the extract was suspected. The methanol extract exhibited 37.50% and 45.31% inhibition ($p < 0.001$) at doses of 200 and 400 mg/kg, respectively. An isolated compound from vacuum liquid chromatography (VLC) extract, germacrone (**20**), also showed a potent anti-nociceptive activity that exhibited 22.6, 34.77, and 51.17% inhibition of writhing at 10, 20, and 40 mg/kg doses ($p < 0.001$), respectively. Moreover, germacrone (**20**) is known to have no lethal toxicity in mice up to 750 mg/kg dose [46]. In formalin-induced hind paw licking, the methanol extract showed an anti-nociceptive activity in early and late phases compared to aspirin's reference drug. With the doses of 200 and 400 mg/kg, the extract exhibited 33.27% and 38.13% inhibition ($p < 0.001$) in the early licking phase, while in the late phase, it exhibited 69.72% and 73.71% inhibition ($p < 0.001$), respectively. Germacrone (**20**), also showed a good anti-nociceptive activity that exhibited 30.43% and 37.53% ($p < 0.001$) in the early phase, but 32.7% and 60.96% inhibition ($p < 0.001$) in the late phase at 20 mg/kg and 40 mg/kg doses. Methanol extract and germacrone (**20**) potent activity in both early and late phases' inhibition indicated a significant pain reduction, which tended to be effective as an anti-inflammatory agent. Germacrone (**20**) showed potent activity in the writhing and formalin licking tests indicating the compound as a central and peripheral anti-nociceptive agent from *C. aeruginosa* Roxb. Hence, further investigation is required to establish the molecular mechanism of action by the *in silico* method.

Antipyretic Activity

The investigation of *in vivo* antipyretic activity was reported by Reanmongkol et al. [32] in male Wistar rats using Brewer's yeast-induced fever. The chloroform, methanol, and water extracts concentrations were divided into 100, 200, and 400 mg/kg, while aspirin (200 mg/kg) was a positive control. Twenty percent brewer's yeast suspension (10 mL/kg) was injected into the rats' dorsum, and the body temperature was checked after 17 h. The test agents were orally administered, while the temperature was measured every 1 h until 5 h. The result showed that none of the extracts significantly affected the pyrexia induced by yeast in rats, while aspirin significantly decreased it.

Uterine Relaxant Effect

The *in vivo* uterine relaxant effect of *C. aeruginosa* Roxb. rhizome's chloroform and methanol extracts were investigated by Thaina et al. [30] using isolated uterus strips from estrogen rats. Virgin female Wistar rats were pretreated with diethylstilbestrol (0.1 mg/kg) for 24 h before being sacrificed by cervical dislocation, then isolating the uterine horns. The uterine strips were isolated from the ovarian and cervical segments of the uterine horns. The contractions number were recorded before adding the test agent. The reference drugs used were verapamil (an L-type calcium channel blocker), atropine (antimuscarinic drug), and diclofenac (a non-steroidal anti-inflammatory drug). The study was carried out on non-stimulated, agonist, and KCl-stimulated uteri. Furthermore, the examined non-stimulated uterine contraction began from plant extract (10–400 µg/mL) into bathing solution according to the increase of concentration. The result showed that the methanol and chloroform extracts had no significant effect on the non-stimulated uterus.

The study was continued on oxytocin, $PGF_{2\alpha}$, and KCl-induced uterine contractions. Then, the uterine strips were prepared with oxytocin (1 mU/mL), $PGF_{2\alpha}$ (0.5 µg/mL), or KCl (40 mM) until stable response to the agonist or KCl was achieved. The extracts (10–400 µg/mL), namely verapamil (10^{-9} to 3×10^{-5} M) and diclofenac (0.25–500 µg/mL) were added to the bathing solution. Oxytocin at 1 mU/mL caused rhythmic contraction of the isolated uterus. Based on the result, the chloroform and methanol extracts showed a significant concentration-dependent inhibition induced by oxytocin (1 mU/mL), ACh (3×10^{-4}), $PGF_{2\alpha}$ (0.5 µg/mL), and KCl (40 mM) concentrations with IC_{50} values of 31.4, 56.21, 58.59, and 29.28 µg/mL for chloroform extract, and 57.79, 223.8, 69.3, and 69.19 µg/mL for methanol extract. Meanwhile, the reference drug, verapamil, exhibited a similar inhibition with IC_{50} values of 0.03, 0.25, 0.35, and 0.04 µg/mL. The IC_{50} value of the other reference drug, diclofenac, against $PGF_{2\alpha}$-induced contraction was 31.36 µg/mL and against KCl-induced contraction was 26.79 µg/mL. Besides, the chloroform and methanol extract causes complete inhibition of contraction by oxytocin. The inhibition potency's order was verapamil > chloroform extract > methanol extract. In addition, the two extracts also showed an inhibitory effect against the contraction from $PGF_{2\alpha}$ similar to verapamil and diclofenac with the potency's order being verapamil > diclofenac > chloroform extract and methanol extract. The order of inhibitory potency induced by acetylcholine was atropine > verapamil > chloroform extract > methanol extract. Therefore, it is suspected that the extracts inhibited uterine contraction by interrupting Ca^{2+} influx, probably through voltage-gated L-type calcium channels. The methanol extract is suspected to reduce the contraction caused by oxytocin in Ca^{2+} free EDTA solution, and its action is related to the intracellular mechanism. Also, the extract's inhibitory potency tends to be useful for dysmenorrhea treatment and as a tocolytic agent. Further investigation needs to examine any possible side effects, which harmful to other organs.

■ CONCLUSION

Curcuma aeruginosa Roxb. is distributed in tropical and subtropical regions, especially Asia. The rhizome of *C. aeruginosa* Roxb. has many traditional uses, namely as a disinfectant, expectorant, and tonic, including treatment for the wound, diarrhea, rheumatic dysmenorrhea, fever, coughs, and asthma. Furthermore, the 34 bioactive phytochemicals and 223 compounds

detected in the plant's rhizome and leaves are flavonoids, terpenoids, steroids, phenanthrenes, demethylated hopanes, thiourea derivatives, and aromatic groups. The major bioactive compounds extracted from the rhizome are curzerenone, 1,8-cineole, cycloisolongifolene, 8,9-dehydro-9-formyl, camphor, curcumenol, and germacrone. All these compounds with diverse pharmacological activity make the research of this species more interesting. One exciting compound found is germacrone, which has been proven active as an anti-androgen to treat androgenic alopecia disease.

The extracts provide various bioactivities such as anticancer, antioxidant, antimicrobial, anti-dengue, immunostimulant, anthelmintic, anti-inflammatory, antiandrogenic, anti-nociceptive, and antipyretic activity, as well as uterine relaxant effect. Therefore, these various bioactivities provide strong evidence to support their application in treating many diseases. In addition, the essential oil of *C. aeruginosa* Roxb. showed potent bioactivity that can be used as antibacterial and antioxidant agents, while the methanol extract can be used to treat anthelmintic infections. However, further biological assay studies of these essential oils are needed to determine the action mechanism of minimal bactericidal concentration (MBC), cytoplasmic membrane disruption, and leakage of intracellular components study. Also, more studies like the activity of isolated compounds are still unexplored yet. In conclusion, further intensive investigations are recommended to explore the clinical trials to identify C. *aeruginosa* Roxb. bioactive compounds' molecular mechanism of action, identify and characterize them, also demonstrate their effectiveness as natural medicines for discovering novel drugs.

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■ REFERENCES

[1] Atun, S., Arianingrum, R., Aznam, N., and Ab Malek, S.N., 2016, Isolation of sesquiterpenes lactone from *Curcuma aeruginosa* rhizome and the cytotoxic activity against human cancer cell lines, *Int. J. Pharmacogn. Phytochem. Res*., 8 (7), 1168–1172.

[2] Kress, W.J., Prince, L.M., and Williams, K.J., 2002, The phylogeny and a new classification of the gingers (Zingiberaceae): Evidence from molecular data, *Am. J. Bot*., 89 (1), 1682–1696.

[3] Purwantiningsih, Hartono, Firdaus, S.O., Kurniawanti, Rahayu, D.U., Nurhayati, L., Ilmiawati, A., and Wukirsari, T., 2019, Sesquiterpenes from Indonesian of *Curcuma aeruginosa* rhizome and its antibacterial activities, *Drug Invent. Today*, 11, 386–390.

[4] Hj. Sukari, M.A., Md. Saad, S., Hj. Lajis, N., Rahmani, M., Muse, R., Yusuf, U.K., and Riyanto, S., 2007, Chemical constituents and bioactivity of *Curcuma aeruginosa* Roxb, *Nat. Prod. Sci*., 13 (3), 175–179.

[5] Takano, I., Yasuda, I., Takeya, K., and Itokawa, H., 1995, Guaiane sesquiterpene lactones from *Curcuma aeruginosa*, *Phytochemistry*, 40 (4), 1197–1200.

[6] Srivilai, J., Khorana, N., Waranuch, N., and Ingkaninan, K., 2011, Anti-androgenic activity of furanodiene isolated from *Curcuma aeruginosa* Roxb. extract, *Naresuan Univ. J*., Special Issue, 33–37.

[7] Suphrom, N., Pumthong, G., Khorana, N., Waranuch, N., Limpeanchob, N., and Ingkaninan, K., 2012, Antiandrogenic effect of sesquiterpenes isolated from the rhizomes of *Curcuma aeruginosa* Roxb, *Fitoterapia*, 83 (5), 864–871.

[8] Choudhury, D., Ghosal, M., Das, A.P., and Mandal, P., 2013, Development of single node cutting propagation techniques and evaluation of antioxidant activity of *Curcuma aeruginosa* Roxburgh rhizome, *Int. J. Pharm. Pharm. Sci*., 5 (2), 227–234.

[9] Hossain, C.F., Al-Amin, M., Md. Sayem, A.S., Siragee, I.H., Tunan, A.M., Hassan, F., Kabir, M.M., and Sultana, G.N.N., 2015, Antinociceptive principle from *Curcuma aeruginosa*, *BMC Complementary Altern. Med.*, 15 (1), 191–198.

[10] George, M., and Britto, S.J., 2015. Phytochemical and antioxidant studies on the essential oil of the rhizome of *Curcuma aeruginosa* Roxb, *Int. Res. J. Pharm*., 6 (8), 573–579.

[11] Jirovetz, L., Buchbauer, G., Puschmann, C., Shafi, M.P., and Nambiar, M.K.G., 2000, Essential oil analysis of *Curcuma aeruginosa* Roxb. leaves from South India, *J. Essent. Oil Res.*, 12 (1), 47–49.

[12] Dũng, N.X., Tuyêt, N.T.B., and Leclercq, P.A., 1995, Characterization of the leaf oil of *Curcuma aeruginosa* Roxb. from Vietnam, *J. Essent. Oil Res*., 7 (6), 657–659.

[13] Oanh, P.T., Thanh, N.T., Xuyen, D.T., Huong, L.T., Avoseh, O.N., and Ogunwande, I.A., 2018, The rhizome essential oil of *Curcuma aeruginosa* Roxb. (Zingiberaceae) from Vietnam, *Trends Phytochem. Res.*, 2 (3), 179–184.

[14] Tg Kamazeri, T.S.A., Abd Samah, O., Taher, M., Susanti, D., and Qaralleh, H., 2012, Antimicrobial activity and essential oils of *Curcuma aeruginosa*, *Curcuma mangga*, and *Zingiber cassumunar* from Malaysia, *Asian Pac. J. Trop. Med*., 5 (3), 202–209.

[15] Sirat, H.M., Jamil, S., and Hussain, J., 1998, Essential oil of *Curcuma aeruginosa* Roxb. from Malaysia, *J. Essent. Oil Res*., 10 (4), 453–458.

[16] Burkill, I.H., Birtwistle, W., Foxworthy, F.W., Scrivenor, J.B., and Watson, J.G. 1935, *A Dictionary of the Economic Products of the Malay Peninsula*, Vol. 1, Governments of the Straits Settlements and Federated Malay States by the Crown Agents for the Colonies, Kuala Lumpur, Malaysia

[17] Jose, S., and Thomas, T.D., 2014, Comparative phytochemical and antibacterial studies of two indigenous medicinal plants *Curcuma caesia* Roxb. and *Curcuma aeruginosa* Roxb, *Int. J. Green Pharm.*, 8, 65–71.

[18] Fang, H.J., Yu, J.G., Chen, Y.H., and Hu, Q., 1982, Studies on Chinese curcuma. II. Comparison of the chemical components of essential oils from rhizome of five species medicinal curcuma plants*, Yaoxue Xuebao*, 17 (6), 441–447.

[19] Dessy, VJ, Sivakumar, S.R., George, M., and Francis, S., 2019, GC-MS analysis of bioactive compounds present in different extracts of rhizome of *Curcuma aeruginosa* Roxb, *J. Drug Delivery Ther*., 9 (2-s), 13–19.

[20] Kaliyadasa, E., and Samarasinghe, BA, 2019, A review on golden species of Zingiberaceae family around the world: Genus Curcuma, *Afr. J. Agric. Res.*, 14 (9), 519–531.

[21] Kanase, V., and Khan, F., 2018, An overview of medicinal value of Curcuma species, *Asian J. Pharm. Clin. Res.*, 11 (2), 40–45.

[22] Roxburgh, W., 1810, *Descriptions of Several of the Monandrous Plants of India: Belonging to the Natural Order, Called Scitamineae by Linnaeus, Cannae by Jussieu, and Drimyrhizae by Ventenat*, 1st Ed., Hindoostanee Press, Calcutta, India.

[23] Theanphong, O., Mingvanish, W., and Kirdmanee, C., 2015, Chemical constituents and biological activities of essential oil from *Curcuma aeruginosa* Roxb. rhizome, *Bull. Health Sci. Technol*., 13 (1), 6–16.

[24] Suphrom, N., Srivilai, J., Pumthong, G., Khorana, N., Waranuch, N., Limpeanchob, N., and Ingkaninan, K., 2014, Stability studies of antiandrogenic compounds in *Curcuma aeruginosa* Roxb. extract, *J. Pharm. Pharmacol*., 66 (9), 1282–1293.

[25] Simoh, S., and Zainal, A., 2015, Chemical profiling of *Curcuma aeruginosa* Roxb. rhizome using different techniques of solvent extraction, *Asian Pac. J. Trop. Biomed*., 5 (5), 412–417.

[26] Nurcholis, W., Khumaida, N., Syukurs, M., Bintang, M., and Ardyani, IDAAC, 2015, Phytochemical screening, antioxidant and cytotoxic activities in extracts of different rhizome parts from *Curcuma aeruginosa* Roxb, *Int. J. Res. Ayurveda Pharm*., 6 (3), 634–637.

[27] Anggriani, L., Yasmin, A., Wulandari, A.R., Leksono, G.M., Ikawati, M., and Meiyanto, E., 2019, extract of temu ireng (*Curcuma aeruginosa* Roxb.) rhizome reduces doxorubicin-induced immunosuppressive effects, *AIP Conf. Proc*., 2099, 020001.

[28] Srivastava, S., Nitin, C., Srivastava, S., Dan, M., Rawat, A.K.S., and Pushpangadan, P., 2006,

Pharmacognostic evaluation of *Curcuma aeurigenosa* Roxb, *Nat. Prod. Sci.*, 12 (3), 162–165.

[29] Vanda, H., Parindra, R., Hambal, M., and Athaillah, F., 2020, Anthelmintic activity of *Curcuma Aeruginosa* Roxb extract on *Fasciola gigantica* in vitro, *E3S Web. Conf.*, 151, 01046.

[30] Thaina, P., Tungcharoen, P., Wongnawa, M., Reanmongkol, W., and Subhadhirasakul, S., 2009, Uterine relaxant effects of *Curcuma aeruginosa* Roxb. rhizome extracts, *J. Ethnopharmacol.*, 121 (3), 433–443.

[31] Neamsuvan, O., Tuwaemaengae, T., Bensulong, F., Asae, A., and Mosamae, K., 2012, A survey of folk remedies for gastrointestinal tract diseases from Thailand's three southern border provinces, *J. Ethnopharmacol.*, 144 (1), 11–21.

[32] Reanmongkol, W., Subhadhirasakul, S., Khaisombat, N., Fuengnawakit, P., Jantasila, S., and Khamjun, A., 2006, investigation the antinociceptive, antipyretic and anti-inflammatory activities of *Curcuma aeruginosa* Roxb. extracts in experimental animals, *Songklanakarin J. Sci. Technol.*, 28 (5), 999–1008.

[33] Kartasapoetra, A.G., 1996, *Budaya Tanaman Berkhasiat Obat*, Rineka Cipta, Jakarta.

[34] Akarchariya, N., Sirilun, S., Julsrigival, J., and Chansakaowa, S., 2017, Chemical profiling and antimicrobial activity of essential oil from *Curcuma aeruginosa* Roxb., *Curcuma glans* K. Larsen & J. Mood and *Curcuma cf. xanthorrhiza* Roxb. collected in Thailand, *Asian Pac. J. Trop. Biomed.*, 7 (10), 881–885.

[35] Hastuti, B., Ibrahim, S., and Efdi, M., 2016, Isolation structure and elucidation of flavone from Temu Hitam rhizome (*Curcuma aeruginosa* Roxb.), *J. Chem. Pharm. Res.*, 8 (5), 302–304.

[36] Masuda. T., Jitoe, A., and Nakatani, N., 1991, structure of aerugidiol, a new bridge-head oxygenated guaiane sesquiterpene, *Chem. Lett.*, 20 (9), 1625–1628.

[37] Fitria, R., Seno, D.S.H., Priosoeryanto, B.P., Hartanti, and Nurcholis, W., 2019, Volatile compound profiles and cytotoxicity in essential oils from rhizome of *Curcuma aeruginosa* and *Curcuma zanthorrhiza*, *Biodiversitas*, 20 (10), 2943–2948.

[38] Meyer, B.N., Ferrigni, N.R., Putnam, J.E., Jacobsen, L.B., Nichols, D.E., McLaughin, J.L., 1982, Brine shrimp: A convenient general bioassay for active plant constituent, *Planta Med.*, 45 (5), 31–34.

[39] Wahyuni, W.T., Batubara, I., and Tambunan, D.Y., 2017, Antibacterial and teeth biofilm degradation activity of *Curcuma aeruginosa* essential oil, *J. Biol. Sci.*, 17 (2), 84–90.

[40] Pangastuti, A., Sari, S.L.A., Nugraheni, E.R., and Astuti, R.T., 2020, Inhibition of *Pseudomonas aeruginosa* virulence factors expression regulated by quorum sensing system using ethyl acetate extract of temu ireng (*Curcuma aeruginosa*), *IOP Conf. Ser.: Mater. Sci. Eng.*, 858, 012031.

[41] Moektiwardoyo, W.M., Tjitraresmi, A., Susilawati, Y., Iskandar, Y., Halimah. E., and Zahryanti, D., 2014, The potential of dewa leaves (*Gynura Pseudochina* (L) DC) and temu ireng rhizomes (*Curcuma aeruginosa* Roxb.) as medicinal herbs for dengue fever treatment, *Procedia Chem.*, 13, 134–141.

[42] Andrina, S., Churiyah, C., and Nuralih, N., 2015, Anti-inflammatory effect of ethanolic extract of *Curcuma aeruginosa* Roxb rhizome, *Morinda Citrifolia* fruit and *Apium graveolens* leaf on lipopplysaccharide-induce RAW 264.7 cell lines, *Indo. J. Cancer Chemoprevention.*, 6 (3), 84–88.

[43] Triastuti, A., Wibowo, A., Astuti, P., 2016, investigation of anti-inflammatory activities of *Curcuma aeruginosa* Roxb. in experimental animals, *Int. J. Pharm. Clin. Res.*, 8 (5), 471–475.

[44] Paramita, S., Ismail, S., Marliana, E., and Moerad, E.B., 2019, Anti-inflammatory activities of *Curcuma aeruginosa* with membrane stabilization and carrageenan-induced paw oedema test, *EurAsian J. Biosci.*, 13, 2389–2394.

[45] Srivilai, J., Waranuch, N., Tangsumranjit, A., Khorana, N., and Ingkaninan, K., 2018, Germacrone and sesquiterpene-enriched extracts from *Curcuma aeruginosa* Roxb. increase skin penetration of minoxidil, a hair growth promoter, *Drug Delivery Transl. Res.*, 8 (1), 140–149.

[46] Melo, M.G.D., Araújo, A.A.S., Rocha, C.P.L., Almeida, E.M.S.A., de Souza Siqueira, R., Bonjardim, L.R., and Quintans-Júnior, L.J., 2008, Purification, physicochemical properties, thermal

analysis and antinociceptive effect of atranorin extracted from *Cladina kalbii*, *Biol. Pharm. Bull.*, 31 (10), 1977–1980.

[47] Nugrahaningtyas, K.D., Matsjeh, S., and Wahyuni, T.D., 2005, Isolation and identification of flavonoid compounds from Curcuma's rhizome (*Curcuma aeruginosa* Roxb.), *Asian J. Nat. Prod. Biochem.*, 3 (1), 32–38.

[48] Zwaving, J.H., and Bos, R., 1992, analysis of the essential oils of five Curcuma species, *Flavour Fragrance J.*, 7 (1), 19–22.

[49] Simoh, S., Shin, S.Y., Abd Rahim, F., Ahmad, M.A., and Zainal, A., 2018, Comparative analysis of metabolites and antioxidant potentials from different plant parts of *Curcuma aeruginosa* Roxb., *Sains Malays.*, 47 (12), 3031–3041.

[50] Jantan, I., Ahmad, A.S., Mohd Ali, N.A., Ahmad, A.R., and Ibrahim, H., 1999, Chemical composition of the rhizome oils of four *Curcuma* species from Malaysia, *J. Essent. Oil Res.*, 11 (6), 719–723.

[51] Aromdee, C., Polrat, S., and Wangsomnuek, P., 2011, Constituents of the rhizome of *Curcuma aeruginosa* and its DNA fingerprint, *Int. J. Phytomed.*, 3, 198–203.

[52] Angel, G.R., Menon, N., Vimala, B., and Nambisan, B., 2014, Essential oil composition of eight starchy Curcuma species, *Ind. Crops Prod.*, 60, 233–238.

[53] Shiba, K., Myata, A., and Kitagawa, I., 1987, Difurocumenone from *Curcuma aeruginosa* as drug, *Jpn. Kokai Tokkyo Koho JP*, 1 (165), 587.

[54] Giang, P.M., Son, P.T., Matsunami, K., and Otsuka, H., 2008, New sesquiterpenoids from *Curcuma* aff. *aeruginosa* Roxb., *Heterocycles*, 74 (1), 977–982.

[55] Boutsada, P., Giang, V.H., Linh, T.M., Mai, N.C., Cham, P.T., Hanh, T.T.H., Phonenavong, K., Sengchanh, S., Cuong, N.X., Lien, L.Q., and Ban, NK, 2018, Sesquiterpenoids from the rhizomes of *Curcuma aeruginosa*, *Vietnam J. Chem.*, 56 (6), 721–725.

[56] Jitoe, A., Masuda, T., Tengah, I.G.P., Suprapta, D.N., Gara, I.W., and Nakatani, N., 1992, Antioxidant activity of tropical ginger extracts and analysis of the contained curcuminoids, *J. Agric. Food Chem.*, 40 (8), 1337–1340.

[57] Simoh, S., Shin, S.Y., Rahim, F.A., Ahmad, M.A, and Zainal, A., 2018, Comparative analysis of metabolites and antioxidant potentials from different plant parts of *Curcuma aeruginosa* Roxb., *Sains Malays.*, 47 (12), 3031–3041.

[58] Rahayu, D.U.C., Hartono, and Sugita, P., 2018, Antibacterial activity of curcumenol from rhizomes of Indonesian *Curcuma aeruginosa* (Zingiberaceae), *Rasayan J. Chem.*, 11 (2), 762–765.

[59] Srivilai, J., Khorana, N., Waranuch, N., Wisuitiprot, W., Suphrom, N., Suksamrarn, A., and Ingkaninan, K., 2016, Germacrene analogs are anti-androgenic on androgen-dependent cells, *Nat. Prod. Commun.*, 11 *(*9), 1225–1228.

[60] Pumthong, G., Asawanonda, P., Varothai, S., Jariyasethavong, V., Triwongwaranat, D., Suthipinittharm, P., Ingkaninan, K., Leelapornpisit, P., and Waranuch, N., 2012, *Curcuma aeruginosa*, a novel botanically derived 5α-reductase inhibitor in the treatment of male-pattern baldness: A multicenter, randomized, double-blind, placebo-controlled study, *J. Dermatol. Treat.*, 23 (5), 385–392.

[61] Santhoshkumar, R., and Yusuf, A., 2019, Chemotaxonomic studies on rhizome extract compositions of twenty *Curcuma* species from South India, *Biochem. Syst. Ecol.*, 84, 21–25.

[62] Panche, A.N., Diwan, AD, and Chandra, S.R., 2016, Flavonoids: An overview, *J. Nutr. Sci.*, 5.

[63] Sun, D.J., Zhu, L.J., Zhao, Y.Q., Zhen, Y.Q., Zhang, L., Lin, C.C., and Chen, L.X., 2020, Diarylheptanoid: A privileged structure in drug discovery, *Fitoterapia*, 142, 104490.

[64] Padmanabhan, P., and Jangle, SN, 2012, Evaluation of *in-vitro* anti-inflammatory activity of herbal preparation, a combination of four medicinal plants, *Int. J. Basic Appl. Med. Sci.*, 2 (1), 109–116.