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Phytochemistry, bioactivities, and future prospects of *Callicarpa nudiflora*: A review

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Abstract

Callicarpa nudiflora is a regional medicinal herb in China. A typical tropical rainforest medicinal plant, it is processed in China's Hainan province, Guangdong province and Guangxi Zhuang Autonomous Region, as well as India, Vietnam, Malaysia and Singapore. *C. nudiflora* has the functions of clearing away heat, detoxification and dampness. Flavonoids, phenylpropanes, terpenoids and volatile oils as well as phenols and sterols are the main chemical constituents. Modern pharmacology shows that *C. nudiflora* has anti-inflammatory, hemostatic, antibacterial, and hepatoprotective effects, treats breast and colon cancer, and is clinically used to treat tropical bacterial infections, acute infectious hepatitis, and internal and external bleeding. *C. nudiflora* is different from traditional herbal medicines because it has significant anti-inflammatory and hemostatic effects and is widely used as a single prescription medicine. This review evaluates recent advances in fully determining the chemical composition and pharmacological effects of *C. nudiflora*, thereby laying the foundation for future pharmaceutical research.

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Introduction

Callicarpa nudiflora is a Laminae perennial tropical rainforest-bearing herb belonging to the Taoist medicinal herbs found in Hainan Province, China. The 2020 edition of the Chinese Pharmacopoeia[1] indicates the following regarding the medicinal part of *C. nudiflora*: *Callicarpa nudiflora* folium is the dried leaf of *Callicarpa nudiflora Hook. et Arn*. China Flora[2] records the Latin name of *C. nudiflora*: *Callicarpa nudiflora Hook. et Arn*. Synonyms: *Callicarpa reevesii*, *Callicarpa acuminate*, *Callicarpa macrophylla var. sinensis*, and *Callicarpa macro var. sinensis*. The common names include 'deciduous purple bamboo' and 'air-dried firewood'. Nude flowers have the effects of clearing heat, detoxification, and dampness. Flavonoids, phenylpropanoids, terpenes and volatile oils, as well as phenols and sterols, are the main chemical components. *C. nudiflora* has anti-inflammatory, hemostatic, and antibacterial properties, and it has been clinically tested. It is used to treat tropical bacterial infections, acute infectious hepatitis, and internal and external bleeding[3]. In recent investigations, flavonoids from *C. nudiflora* have been demonstrated to have anti-motolity effects on breast cancer cells *in vitro* during the epithelial–mesenchymal transition[4]. *C. nudiflora* extracts have been shown to inhibit breast cancer, affect colon cancer cell proliferation, migration, and invasion, and induce apoptosis sensitivity in nasopharyngeal carcinoma cells from Wuzhishan in Hainan province[5,6]. Currently, *C. nudiflora* has been included in the 1977 edition of the Chinese Pharmacopoeia[7] and the 2020 edition of the Chinese Pharmacopoeia[1].

Much of the research on *C. nudiflora* in recent years has focused on the treatment of tropical diseases, and although there have been some reports on the chemical composition of *C. nudiflora*, new unknown compounds are still being discovered and their physiological effects have not been fully reported. The creation of the *C. nudiflora* quality criteria has been contentious. Therefore, this paper presents a detailed review of the chemical composition of *C. nudiflora* and its pharmacological effects, as well as the development of quality standards to provide a scientific basis for the clinical application and further development of *C. nudiflora*.

Botanical description

C. nudiflora originates from Hainan Province, China, and is a tropical rainforest medicinal plant, divided into wild and cultivated species. Wild species of Hainan Wuzhishan origin are the most efficacious. Recently, Wuzhishan City, with jurisdiction over Baisha and Baoting, has become the home of wild and domestic species[8]. There is also a variety of wild resources distributed throughout various regions of Jiangxi Province. Many varieties of *Callicarpa* are used medicinally around the world and all of the *C. nudiflora* types have similar effects[9]. Commonly used medicinal varieties of *Callicarpa*, include *Callicarpa pedunculata* R. Brown, *Callicarpa dinhotoma* (Lour.) K. koch, *Callicarpa bodinieri* Levi, *Callicarpa bodinieri* Levi. var. *giraldii* Rehd., *Callicarpa kwangtungensis* Chun, *Callicarpa rubella* Lindl., *Callicarpa rubella* Lindl. f. crenata Peih and *Callicarpa cathayana* H. T. Chang.

Morphology

Callicarpa form shrubs to small trees that are up to 7-m tall. Old branches are glabrous and lenticels conspicuous. Branchlets, petioles and inflorescences are densely gray-brown, branched, and velutinous. Leaf blades are ovate-long elliptic to lanceolate, dark green on the surface, turning black when dry, cymes spreading, and bracts linear or lanceolate. The calyxes are cup-shaped, corolla are purple or pink, anthers are elliptic. The plants flower from June to August and tiny, subglobose, red fruit appear from August to December. *C. nudiflora* leaves and fruit turn black when dry and can be used for identification. *C. nudiflora* grows on flatlands to 1,200 m above sea level on mountain slopes, in valleys, in forests by streams or in thickets. Studies have shown that *C. nudiflora* is more efficacious when harvested in spring, during March and April[2].

Cultivation

Soil factors have different effects on the content of different active ingredients in *C. nudiflora*, with fast-acting potassium being the dominant factor, followed by effective sulphur, effective phosphorus and organic matter[10]. *C. nudiflora* is usually grown from seed, cuttings and plants. It should be grown in the understory, with minimal shade and suitable light intensities of 10,100 lx, 22,000 lx, and 43,000 lx. Currently, *C. nudiflora* suffers from low and uneven germination, as well as low seedling establishment rates[11]. Therefore, a method for the rapid release of *C. nudiflora* seeds from dormancy, and to increase germination and seedling establishment, is required. At present, *C. nudiflora* is mostly cultivated from the wild in the home, with limited reported pests and diseases. Only locust damage has been reported, which can be controlled with highly effective and mildly toxic insecticides[12].

Chemical constituents

At present, studies have confirmed the following four main chemical components of *C. nudiflora*: flavonoids, phenylpropanoids, terpenoids and volatile oils. The two main components, flavonoids and phenylpropanoids, exert anti-inflammatory and antibacterial effects. The main chemical flavonoid component is lignan, and the main compound contained in lignan is lignoside[13]. Therefore, lignoside was the main component used to determine the flavonoid content of *C. nudiflora*[14]. Flavonoids inhibit breast and colon cancers, especially in tropical regions where patients are exposed to prolonged heat and humidity, and they also have *in vitro* antibacterial and bactericidal effects[15]. Six new compounds isolated from phenylpropanoids were identified as potential compounds for the anti-inflammatory activity of *C. nudiflora* and as the active substances with the greatest anti-inflammatory potential[16]. A study confirmed that six diterpenoids showed the ability to modulate the levels of inflammatory factors *in vitro* and confirmed the anti-cervicitis mechanism of action of *C. nudiflora*[17]. In addition, diterpenoids exert anti-inflammatory effects by inhibiting the production of nitric oxide[18]. Triterpenoids exert antithrombotic effects by inhibiting platelet aggregation, oleanane in pentacyclic triterpenoid compounds has a hepatoprotective activity, and iridoids are cytotoxic to tumor cells[19]. Phenylpropanoid compounds have antioxidant effects and may improve memory function and cognitive dysfunction in patients[20]. Volatile oils promote wound healing. The essential oil extracted from the leaves of *C. nudiflora* has insecticidal properties and is a potent insecticide[21,22]. This also confirms the mechanism of action that occurs when *C. nudiflora* is ground and applied externally to wounds when treating poisonous insect bites in the tropics. In addition, *C. nudiflora* contains small amounts of phenols and sterols[22].

Flavonoids

Flavonoids are the core chemical constituents of *C. nudiflora* and are the main components responsible for *C. nudiflora*'s anti-inflammatory, antibacterial, hemostatic, and carcinogenic actions. Recent studies have shown that in addition to lignans, there is also a nucleoblast component in the flavonoids called apigenin[20–23]. Currently, 32 flavonoid compounds have been isolated and identified in lipid soluble, ethanol, and trichloromethane extracts of the above-ground parts of *C. nudiflora*. Their isolation yielded lignan, lignan-7-O-n-7-glucopyranoside, lignan-3'-O-ide, glucopyranoside, lignan-4'-O-e, glucopyranoside, and others, which were identified using the spectral data method[23]. The chemical structures of the 32 flavonoids isolated from *C. nudiflora* are shown in Table 1 and Fig. 1.

Phenylpropanoids

Phenylpropanoids are another major active ingredient of *C. nudiflora* and are the main components of *C. nudiflora* responsible for anti-inflammatory and antibacterial activities. Currently, 20 phenylpropanoids substances have been reported, with lignans, 3-phenylpropanoic acid, and phenylpropanoid glycosides being the most numerous. Verbascoside and forsythoside B are often selected as indicator components when evaluating the quality of *C. nudiflora* using high-performance and ultra-performance liquid chromatography for the detection of multiple active ingredients[24]. The chemical structures of the 20 phenylpropanoids compounds isolated from *C. nudiflora* are shown in Table 1 and Fig. 2.

Terpenoids

To date, as many as 45 species of terpenoids have been identified in *C. nudiflora*, including 20 triterpenes, 17 iridoids, and eight diterpenes, Sixteen of the iridoids are considered to be the main monoterpenoids in *C. nudiflora*[25,26], and diterpenes, mainly callicarpic acid and methylcallicarpate, are the focus of current research on terpenoids in *C. nudiflora* herbs[22]. The triterpenes mainly include oleanane triterpenoid and ursane triterpenoid, and small amounts of lupane triterpenoid have also been identified[27]. In recent years, limited new structures of sesquiterpenes have been isolated from *C. nudiflora*; therefore, they will not be described here. The structures and names of the above confirmed terpenoids are shown in Table 1 and Fig. 3.

Volatile oils

Volatile oils are also a major component of *C. nudiflora*, and 36 components have been isolated and identified in volatile oils, namely monoterpenes and their oxygenated derivatives, as well as alkanes. Although the leaves and flowers of *C. nudiflora* contain volatile oils having different chemical compositions, most of them are terpenoids[26]. In addition, studies have confirmed that the leaves of *C. nudiflora* contain more volatile oils than the flowers. Most of the research on volatile oils has focused on their chemical composition[19,28]. At present, the constituents in volatile oils have not been

Table 1. Chemical constituents from *Callicarpa nudiflora*.

No.	Category	Compound name	Molecular formula	Molecular weight	Ref.
1	Flavonoids	Luteoloside	$C_{21}H_{20}O_{11}$	448.38	[22]
2	Flavonoids	Pigenin-7-*O*-*β*-*D*-glucoside	$C_{21}H_{20}O_{11}$	432.38	[22]
3	Flavonoids	6-hydroxyluteolin-7-O-*β*-*D*- glucopyranoside	$C_{21}H_{20}O_{12}$	464.38	[22]
4	Flavonoids	Luteolin-3′-methoxyl-6-hydroxy-7-*O*-*β*-*D*-glucopyranoside	$C_{22}H_{22}O_{12}$	478.41	[22]
5	Flavonoids	Chrysoeriol-7-*O*-*β*-*D*-glucoside	$C_{22}H_{22}O_{11}$	462.41	[22]
6	Flavonoids	Luteolin-3′-*O*-*β*-*D*-glucopyranoside	$C_{21}H_{20}O_{11}$	448.38	[22]
7	Flavonoids	5,7-dihydroxy -3'- methoxyflavone -4'-O-*β*-*D*- glucoside	$C_{23}H_{24}O_{10}$	460.44	[22]
8	Flavonoids	Lutedin-4′-*O*-*β*-*D*-glucoside	$C_{21}H_{20}O_{11}$	448.38	[22]
9	Flavonoids	Luteolin-3'-O-*β*-*D*-glucoside	$C_{21}H_{20}O_{11}$	448.38	[22]
10	Flavonoids	Querceqin-3'-O-*β*-*D*-glucoside	$C_{21}H_{20}O_{11}$	448.38	[22]
11	Flavonoids	5,4′-dihydroxy-3,7,3′-trimethoxyflavone	$C_{18}H_{16}O_7$	344.32	[22]
12	Flavonoids	5-hydroxy-3,7,3′,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.35	[22]
13	Flavonoids	Luteolin	$C_{15}H_{10}O_6$	286.24	[22]
14	Flavonoids	Apigenin	$C_{15}H_{10}O_5$	270.24	[22]
15	Flavonoids	5,7,4′-trihydroxy-3′-methoxyflavone	$C_{16}H_{12}O_6$	300.27	[22]
16	Flavonoids	Ermanine	$C_{17}H_{14}O_6$	314.08	[22]
17	Flavonoids	Rhamnazin	$C_{17}H_{14}O_7$	330.29	[21]
18	Flavonoids	5-hydroxy-3,7,4′-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	[22]
19	Flavonoids	Querceqin	$C_{15}H_{10}O_7$	302.24	[21]
20	Flavonoids	Isorhamnetin	$C_{16}H_{12}O_7$	316.27	[21]
21	Flavonoids	Ayanin	$C_{18}H_{18}O_7$	346.34	[22]
22	Flavonoids	Rutin	$C_{29}H_{35}O_{15}$	623.58	[22]
23	Flavonoids	Philonotisflavone	$C_{44}H_{44}O_{19}$	876.82	[21]
24	Flavonoids	Luteolin-7-O-(6''-*trans*-cinnamo-yl)-*β*-*D*-glucopyranoside	$C_{30}H_{18}O_{12}$	570.46	[23]
25	Flavonoids	Luteolin-7-*O*-neohesperidoside	$C_{27}H_{30}O_{14}$	578.52	[23]
26	Flavonoids	Luteolin-7-O-(6''-*trans*-caffeoyl)-*β*-*D*-glucopyranoside	$C_{30}H_{26}O_{14}$	610.52	[23]
27	Flavonoids	Rhoifolin	$C_{30}H_{27}NO_{11}$	577.54	[23]
28	Flavonoids	Luteolin-7-O-(6''-*p*-coumaryl)-*β*-*D*-glucopyranoside	$C_{30}H_{27}O_{14}$	611.53	[23]
29	Flavonoids	Luteolin-4′-*O*-(6″-*trans*-caffeoyl)-*β*-*D*-glucopyranoside	$C_{31}H_{28}O_{14}$	624.55	[23]
30	Flavonoids	Luteolin-3'-O-(6''-E-*trans*-caffeoyl)-*β*-*D*-glucopyranoside	$C_{30}H_{26}O_{14}$	610.52	[23]
31	Flavonoids	Luteolin-7-*O*-(6″-*trans*-feruloyl)-*β*-*D*-glucopyranoside	$C_{31}H_{28}O_{14}$	624.55	[23]
32	Flavonoids	Luteolin-7,4′-di-*O*-glucoside	$C_{27}H_{30}O_{16}$	610.52	[23]
33	Penylpropanoids	Forsythoside	$C_{34}H_{44}O_{19}$	756.71	[8]
34	Penylpropanoids	Alyssonoside	$C_{35}H_{46}O_{19}$	770.73	[8]
35	Penylpropanoids	Samioside	$C_{34}H_{44}O_{19}$	756.71	[13]
36	Penylpropanoids	6-*O*-caffeyl-*β*-*D*-glucopyranose	$C_{15}H_{18}O_8$	326.30	[9]
37	Penylpropanoids	6-*O*-caffeyl-*α*-*D*-glucopyranose	$C_{15}H_{18}O_8$	326.30	[9]
38	Penylpropanoids	Isoacteoside	$C_{29}H_{36}O_{15}$	624.59	[15]
39	Penylpropanoids	Isomartynoside	$C_{31}H_{40}O_{15}$	652.65	[7]
40	Penylpropanoids	Martynoside	$C_{31}H_{40}O_{15}$	652.64	[9]
41	Penylpropanoids	Acteoside	$C_{29}H_{36}O_{15}$	624.59	[11]
42	Penylpropanoids	Syringalide A 3'-*α*-*L*-rhamnopyranoside	$C_{29}H_{36}O_{15}$	624.59	[11]
43	Penylpropanoids	Deacylisomartynoside	$C_{21}H_{32}O_{12}$	476.47	[7]
44	Penylpropanoids	Frolic acid	$C_{10}H_{10}O_4$	194.19	[16]
45	Penylpropanoids	4-hydroxy-cinnamic acid	$C_9H_8O_3$	164.16	[6]
46	Penylpropanoids	Caffeic acid	$C_9H_8O_4$	180.16	[17]
47	Penylpropanoids	Aesculetin	$C_9H_6O_4$	178.14	[4]
48	Penylpropanoids	Nudiflorin A	$C_{19}H_{18}O_8$	374.36	[18]
49	Penylpropanoids	Nudiflorin B	$C_{19}H_{18}O_8$	374.34	[18]
50	Penylpropanoids	Nudiflorin C	$C_{19}H_{18}O_8$	374.34	[18]
51	Penylpropanoids	Tortoside F	$C_{26}H_{30}O_{11}$	518.52	[9]
52	Penylpropanoids	Acanthoside B	$C_{28}H_{36}O_{13}$	580.58	[12]
53	Terpenoids	Ursolic acid	$C_{30}H_{48}O_3$	456.71	[25]
54	Terpenoids	2*α*,3*α*- dihydroxy-12-en-28-oic acid	$C_{30}H_{48}O_4$	472.71	[25]
55	Terpenoids	2*α*,3*β*- dihydroxy-12-en-28-oic acid	$C_{30}H_{48}O_4$	472.71	[25]
56	Terpenoids	2*α*,3*α*,19*α*,23-tetrahydroxy-olean-12-en-28-*O*-*β*-*D*-glucoside	$C_{29}H_{46}O_5$	474.33	[25]
57	Terpenoids	2*α*,3*α*,19*α*-trihydroxy-urs-12-en-28-oic acid	$C_{29}H_{46}O_5$	474.68	[25]
58	Terpenoids	2*α*,3*α*,19*α*,23-tetrahydroxy-urs-12-en-28-oic acid	$C_{29}H_{46}O_6$	490.68	[25]
59	Terpenoids	2*α*,3*α*,19*α*,23-tetrahydroxy-urs-12,20(30)-dien-28-oic acid	$C_{30}H_{46}O_6$	502.69	[25]
60	Terpenoids	Oleanolic acid	$C_{30}H_{48}O_3$	456.71	[27]

(to be continued)

Table 1. (continued)

No.	Category	Compound name	Molecular formula	Molecular weight	Ref.
61	Terpenoids	2*α*,3*β*,24-trihydroxy-olean-12-en-28-oic acid	$C_{30}H_{50}O_5$	472.71	[25]
62	Terpenoids	Urs-12-en-3*β*-ol	$C_{29}H_{48}O$	490.73	[25]
63	Terpenoids	Arjunglucoside I	$C_{29}H_{50}O_3$	446.71	[27]
64	Terpenoids	2*α*,3*α*,19*α*-trihydroxy-urs -12- en -28-O-*β*-*D*- glucopyranoside	$C_{36}H_{60}O_{10}$	652.87	[25]
65	Terpenoids	2*α*,3*β*,19*α*-trihydroxy-urs -12- en -28-O-*β*-*D*- glucopyranoside	$C_{36}H_{60}O_{10}$	652.87	[25]
66	Terpenoids	2*α*,3*α*,19*α*-trihydroxy-ursane-12-en -28-O-*β*-*D*-glucoside	$C_{35}H_{56}O_{10}$	636.82	[27]
67	Terpenoids	2*α*,3*α*,19*α*-trihydroxy-olean-12-en-28-*O*-*β*-*D*-glucopyranoside	$C_{36}H_{60}O_{10}$	652.87	[25]
68	Terpenoids	2*α*,3*β*,19*α*-trihydroxy-olean-12-en-28-*O*-*β*-*D*-glucoside	$C_{36}H_{60}O_{10}$	652.87	[27]
69	Terpenoids	2*α*,3*α*,24- trihydroxy-ursane -12-en-28-oic acid	$C_{36}H_{60}O_{11}$	668.87	[27]
70	Terpenoids	2*α*,3*α*,24-trihydroxy-olean-12-en-28-oic acid	$C_{36}H_{58}O_{11}$	666.85	[27]
71	Terpenoids	2*α*,3*α*,19*α*,23-tetrahydroxy-ursane-12- en -28-O-*β*-*D*-glucoside	$C_{36}H_{56}O_{11}$	652.82	[27]
72	Terpenoids	2*α*,3*α*,19*α*-trihydroxy-urs-12-en-28-O-*β*-*D*-xylopyranosyl(1→2)-*β*-*D*-glucoside	$C_{41}H_{68}O_{14}$	784.98	[25]
73	Iridoids	Ampicoside	$C_{23}H_{28}O_{13}$	512.46	[25]
74	Iridoids	5''-methoxy-ampicoside	$C_{24}H_{30}O_{14}$	542.49	[25]
75	Iridoids	6-O-vanilloyl-ajugoside	$C_{23}H_{30}O_{12}$	784.98	[25]
76	Iridoids	6-O-syringoyl-ajugol	$C_{23}H_{30}O_{12}$	498.48	[25]
77	Iridoids	3''-methoxy-agnucastoside C	$C_{24}H_{32}O_{13}$	528.51	[20]
78	Iridoids	Agnucastoside C	$C_{34}H_{36}O_{15}$	684.65	[20]
79	Iridoids	6″-*O*-*trans*-caffeoylcatalpol	$C_{24}H_{28}O_{13}$	524.48	[20]
80	Iridoids	6″-*O*-*trans*-feruloylcatalpol	$C_{25}H_{30}O_{13}$	538.50	[20]
81	Iridoids	linearoside	$C_{25}H_{30}O_{12}$	522.50	[20]
82	Iridoids	6-O-*trans*-feruloylcatalpol	$C_{25}H_{30}O_{13}$	538.50	[20]
83	Iridoids	6'-O-caffeoyl-ajugol	$C_{24}H_{30}O_{12}$	510.49	[25]
84	Iridoids	6-O-caffeoyl ajugol	$C_{24}H_{30}O_{12}$	510.49	[25]
85	Iridoids	6-O-vanilloyl-ajugol	$C_{24}H_{32}O_{13}$	528.51	[25]
86	Iridoids	Nudifloside	$C_{24}H_{36}O_{12}$	516.54	[20]
87	Iridoids	Catalpol	$C_{17}H_{26}O_{12}$	510.49	[20]
88	Iridoids	Ajugol	$C_{15}H_{22}O_{10}$	362.33	[20]
89	Iridoids	8-acetyl-harpagide	$C_{15}H_{24}O_9$	348.39	[25]
90	Iridoids	Callicarpic acid	$C_{20}H_{28}O_4$	332.44	[22]
91	Iridoids	Methylcallicarpate	$C_{21}H_{31}O_4$	347.48	[22]
92	Iridoids	Et-3,4-seco-16-hydroxy-12,15-epoxy-4(18),8(17),12,14-labdatetaen-3-oic acid	$C_{20}H_{28}O_4$	332.44	[22]
93	Iridoids	Ent-3,4-seco-14-carbonyl-15,16-epoxy-4(18),8(17),13(14)-labdatrien-3-oic acid	$C_{20}H_{28}O_4$	332.44	[22]
94	Iridoids	Ent-3,4-seco-12*R*,15-epoxy-4(18),8(17),13-labdatrien-3-oic acid	$C_{20}H_{28}O_4$	332.44	[22]
95	Iridoids	3,4-seco-12*R*,13*S*-dihydroxy-4(18),8(17),14(15)-labdatrien-3-oic acid	$C_{20}H_{28}O_4$	336.47	[22]
96	Iridoids	7*α*-hydroxy sandaracopimaric acid	$C_{20}H_{30}O_2$	302.46	[22]
97	Iridoids	16,17-dihydroxy-3-O-phyllocladane	$C_{20}H_{32}O_3$	320.47	[22]
98	Volatile	(1S)-*β*-pinene	$C_{10}H_{16}$	136.24	[27]
99	Volatile	*β*-pinene	$C_{10}H_{16}$	136.24	[25]
100	Volatile	*α*-pinene	$C_{10}H_{16}$	136.24	[25]
101	Volatile	Myrtenol	$C_{10}H_{16}$	136.24	[25]
102	Volatile	*β*-epoxypinane	$C_{10}H_{16}O$	152.24	[27]
103	Volatile	Dihydrocurcumene	$C_{15}H_{24}$	204.36	[25]
104	Volatile	O-cymene	$C_{10}H_{14}$	133.22	[25]
105	Volatile	Benzylalcohol	C_7H_8O	108.14	[27]
106	Volatile	*α*-cedrene	$C_{16}H_{28}$	220.40	[27]
107	Volatile	Viridiflorol	$C_{15}H_{26}O$	222.37	[26]
108	Volatile	Aromadendrene	$C_{14}H_{21}$	189.322	[26]
109	Volatile	Cedrenol	$C_{14}H_{24}O$	220.37	[25]
110	Volatile	(E)-*β*-farnesene	$C_{15}H_{24}$	204.36	[27]
111	Volatile	1-caryophyllene	$C_{15}H_{24}$	204.36	[25]
112	Volatile	Caryophyllene oxide	$C_{15}H_{21}O$	205.32	[25]
113	Volatile	Epoxycaryophyllene	$C_{15}H_{24}O$	220.36	[25]
114	Volatile	*β*-cedrene	$C_{15}H_{24}$	204.36	[27]
115	Volatile	*α*-cedrenol	$C_{15}H_{24}O$	220.37	[25]
116	Volatile	*α*-caryophyllene	$C_{15}H_{24}$	204.36	[26]
117	Volatile	*β*-sesquiphellandrene	$C_{15}H_{24}$	204.36	[27]

(to be continued)

Table 1. (continued)

No.	Category	Compound name	Molecular formula	Molecular weight	Ref.
118	Volatile	Perillaldehyde	$C_{10}H_{14}O$	150.22	[27]
119	Volatile	Cis-carveol	$C_{10}H_{16}O$	152.24	[27]
120	Volatile	L-perillyl alcohol	$C_{10}H_{16}O$	152.24	[27]
121	Volatile	Trans-2-Hexenal	$C_6H_{10}O$	98.15	[27]
122	Volatile	1-Chloroctadecane	$C_{18}H_{37}Cl$	288.94	[27]
123	Volatile	2,6,10,14-tetramethylpentadecane	$C_{19}H_{40}$	152.24	[27]
124	Volatile	Dodecane-3,7-diene	$C_{12}H_{22}$	166.31	[26]
125	Volatile	Octacosane	$C_{28}H_{58}$	394.78	[27]
126	Volatile	Tetradecane	$C_{14}H_{30}$	198.39	[27]
127	Volatile	α-curcumene	$C_{15}H_{24}$	204.36	[27]
128	Volatile	L-Ascorbyl dipalmitate	$C_{38}H_{68}O_8$	652.95	[27]
129	Volatile	β-selinene	$C_{15}H_{24}$	204.36	[27]
130	Volatile	Dimethylbenzylcarbinyl acetate	$C_{12}H_{16}O_2$	192.26	[27]
131	Volatile	β-terpinyl acetate	$C_{12}H_{20}O_2$	196.30	[27]
132	Volatile	Trans-4- thujylalcohol	$C_{10}H_{18}O$	154.25	[25]

considered as markers for qualitative and quantitative examination. The names and structures of the 36 chemical components mentioned above are shown in Table 1 and Fig. 4.

Pharmacological activities

Anti-inflammatory and hemostatic effects are the two main pharmacological actions of *C. nudiflora*[26,28]. *C. nudiflora* also has antibacterial effects, particularly against *Staphylococcus aureus*, and it is considered a potential drug for *S. aureus* infections[29]. There have been studies on the mechanisms by which *C. nudiflora* improves cognitive dysfunction and improves memory in Alzheimer's disease patients[20]. Recent studies have found that *C. nudiflora* inhibits the production of cervical and ovarian cancer cells, as well as the growth of breast and colon cancers, in humans, confirming the anti-tumor effects of *C. nudiflora*[6,15,17,30]. *C. nudiflora* essential oil has a good insecticidal effect and is a potent insecticide[21]. In addition, *C. nudiflora* has recently been found to have antioxidant properties, anti-diabetic and anti-psoriasis effects, and to treat alcoholism[31–33].

The combined pharmacological activity of two or more compounds in *C. nudiflora* is greater than that of individual compounds, with flavonoids and phenylpropanoids dominating, although terpenoids and volatile oils also have some pharmacological activities. Platelet aggregation is inhibited by oleanolic acid and ursolic acid from *C. nudiflora*. Thus, triterpenes appear to have an anti-platelet coagulation effect[27]; therefore, *C. nudiflora* not only has an hemostatic effect but also has an activating effect on removing the phlegm and turbid urine[34–36]. At present, many biologically active compounds have been isolated from *C. nudiflora* by domestic and foreign scholars, but the research has not fully investigated the chemical composition and biological activities of the compounds; therefore, there is still the need for continued exploration.

Anti-inflammatory activity

Chen et al. conducted experiments on *C. nudiflora* treated mice and *C. nudiflora* treated cells. The cell experiments showed that extracts from different parts of *C. nudiflora* produced good anti-inflammatory effects, with those of the flower extracts and flower isolates of *C. nudiflora* being more robust. In mice, exposure to *C. nudiflora* reduced xylene-induced auricular swelling and significantly inhibited auricular swelling and toe swelling, which are indicators of its immune-enhancing effects[36]. In addition, ethanol extracts of *C. nudiflora*: CNE-p, CNE-d, and CNE-b, have the ability to regulate inflammatory factors *in vivo* and *in vitro*, and the strongest anti-inflammatory activity of CNE-p was found in *in vitro* tests[17]. Wang et al. isolated four new compounds from the leaves of *C. nudiflora* using a comprehensive spectroscopic analysis and confirmed the significant inhibitory effects of these compounds, comparable to that of the positive control dexamethasone, on nitric oxide production[37]. The anti-inflammatory effects of Compounds 2–4 from *C. nudiflora* were confirmed through the inhibition of superoxide anion production and elastase release by Lin et al[38]. In addition, *C. nudiflora* cell experiments revealed that diterpene and 5-oxhydryl-3,7,3',4'-tetramethoxyflavone have some anti-inflammatory effects, and 5-oxhydryl-3,7,3',4'-tetramethoxyflavone inhibits inflammatory factors. In addition, nitric oxide production was only slightly inhibited[39]. Wu et al. isolated new compounds from the flowers of *C. nudiflora* that showed anti-inflammatory activities and had significant NLRP3 inflammasome inhibitory activities[40]. In addition, flavonoids and diterpenoids from *C. nudiflora* were found to inhibit lipopolysaccharide-induced nitric oxide production in RAW264.7 cells[41]. These are the most recent studies on the anti-inflammatory effects of *C. nudiflora* available. Chen et al. found that *C. nudiflora* tablets alleviated chronic pelvic inflammatory disease by decreasing inflammatory cytokines, such as IL-1β, MCP-1, and GM-CSF[42].

Hemostatic activity

The two main classes of pharmacological components among the chemical constituents of *C. nudiflora* that exert haemostatic activity are phenylpropanoids and flavonoids. Virtually all parts of *C. nudiflora* can be used and extracts from its roots, stems and leaves have been confirmed to have hemostatic effects[27]. There are two main ways for *C. nudiflora* to exert the hemostatic effect, one is through the intrinsic coagulation pathway, and the other is through both the intrinsic and extrinsic coagulation pathways. *C. nudiflora* extract acts on endogenous coagulation by affecting the timing of prothrombin and fibrinogen content[43,44]. A study about *C.*

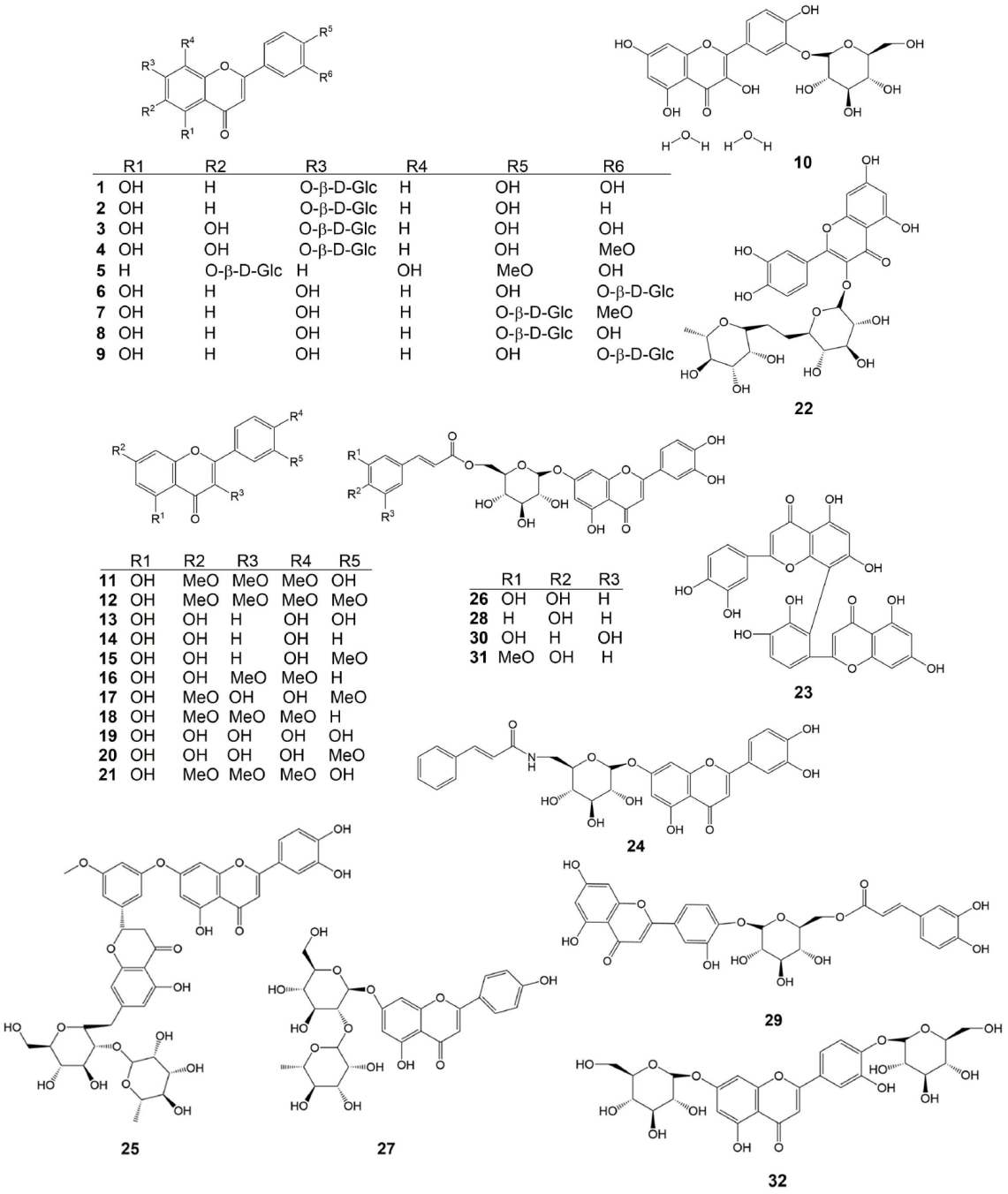


Fig. 1 Structures of flavonoids.

nudiflora acting on the intrinsic and extrinsic coagulation pathways at the same time confirmed that its ethyl acetate and n-butanol extracts could shorten the bleeding and coagulation times and reduce the activated partial thromboplastin time, indicating that it has hemostatic activity; Both can increase the number of platelets and stimulate platelet activation, indicating that it has a hemostatic effect. In addition, it has been found that extraction of *C. nudiflora* with ethyl acetate can significantly enhance the endogenous platelet activating substance adenosine diphosphate, which can promote hemostasis. In *C. nudiflora*, phenylpropanoid glycosides and pentacyclic triterpenoids produce the main hemostatic effect and can reduce the activation time for partial thromboplastin. They are followed by flavonoids, which also have a significant effect on fibrinogen content[44,45]. Wang et al. investigated the mechanism of the haemostatic effects of butanolic extracts of *C. nudiflora* and showed that these extracts had significant haemostatic activities, which may be stimulated by platelet activation, associated with the activation of the PI3K-PKB signaling pathway in platelets[46]. Zhou et al. isolated two new triterpenoids, 2α,3α,19α,23-tetrahydroxyurs-12,20(30)-dien-28-oic acid and 2α,3α,19α-trihydroxyurs-12-en-28-oic acid-28-O-β-D-xylopyranosyl (1→2)-β-D-glucopyranoside, and the anti-platelet aggregation activities of these two compounds *in vitro* indicated their inhibitory effects on adenosine diphosphate-induced platelet aggregation[27]. In the future, researchers will

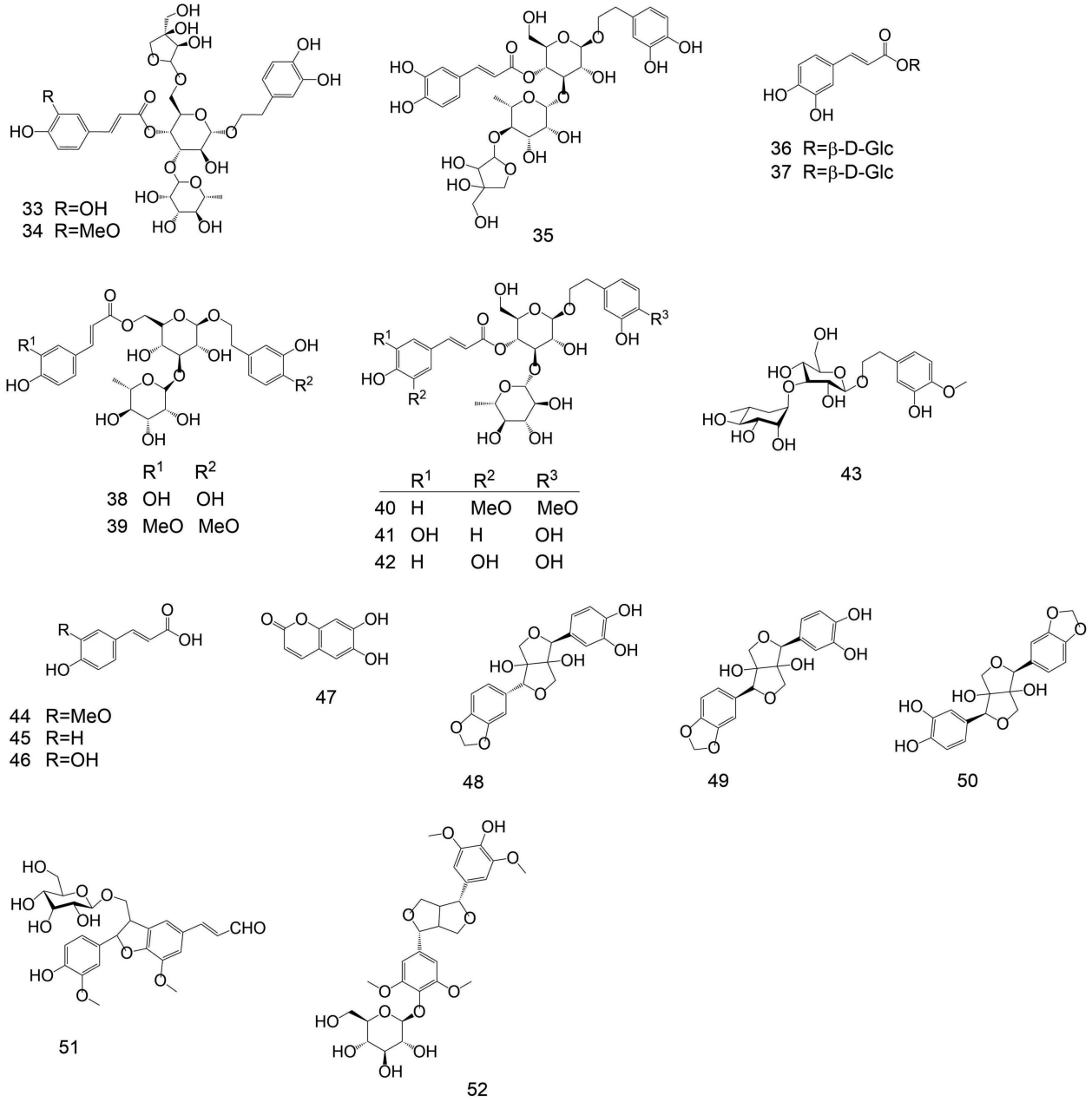


Fig. 2 Structures of penylpropanoids.

likely isolate new compounds from *C. nudiflora* that will reveal new mechanisms by which it exerts hemostatic effects.

Antibacterial activity

Studies have shown that *C. nudiflora* has antibacterial activity against a wide range of bacteria. Wang et al. used six polar solvents to extract *C. nudiflora* and completed antibacterial tests of *C. nudiflora* against eight bacteria, showing that the ethanol extract of *C. nudiflora* had good antibacterial activity against *Escherichia coli* and *Bacillus subtilis*[47]. A study by Liu et al. showed that *C. nudiflora* has an *in vitro* inhibitory effect on five indicator bacteria: *E. coli*, *Pseudomonas*, *Candida albicans*, *B. subtilis*, and *S. aureus*[48]. In addition, *C. nudiflora* also shows good antibacterial activity against streptomycin-resistant and streptomycin-sensitive mycobacterium tuberculosis, and this study suggests that the antibacterial activity of *C. nudiflora* may be related to protein expression[49]. Three compounds in *C. nudiflora*, alpha-borneol, betulinic acid, and betulin aldehyde, may exhibit specificity activities against specific bacteria through pathways that are absent in the human host, and, therefore, these compounds are referred to as lead compounds. In addition, *C. nudiflora* in combination with vancomycin hydrochloride has a synergistic antibacterial effect against Methicillin-resistant *S. aureus* (MRSA)[50]. Currently, *C. nudiflora* extracts are commercially available as ointment preparations for trauma-related wound healing.

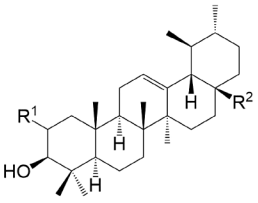
Cytotoxic activity

The cytotoxicity levels of compounds in *C. nudiflora* were evaluated using the MTT assay and revealed that *C. nudiflora* has monomeric proliferative inhibitory activity against Hela, A549, and MCF-7 cell lines, in which the main acting compound

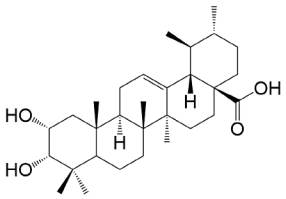
is phenylethanoid. However, no cellular activity was found against cancer cell lines. An extremely subtle cytotoxic activity was also expressed by *C. nudiflora* glycoside[51].

Anti-cancer activity

Several *in vitro* studies have shown that rhoifolin in *C. nudiflora* extracts has antimotility properties against breast



	R1	R2
53	H	COOH
55	OH	COOH
62	H	H



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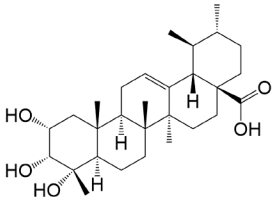

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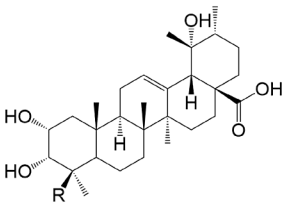
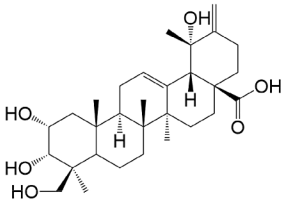


57 R=H
58 R=OH



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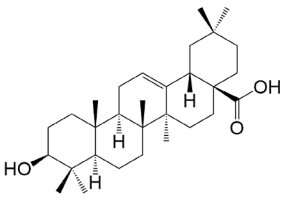
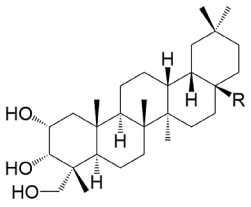
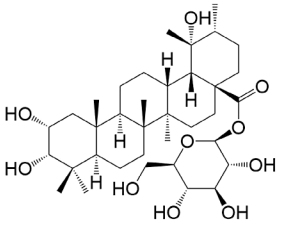


60



61 R=COOH
63 R=H



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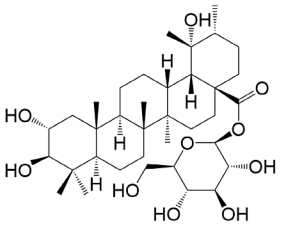

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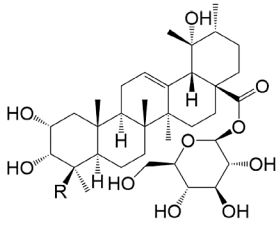
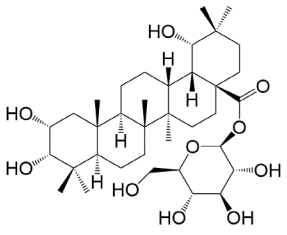


66 R=H
71 R=OH



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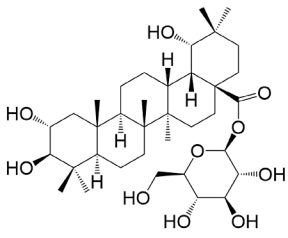

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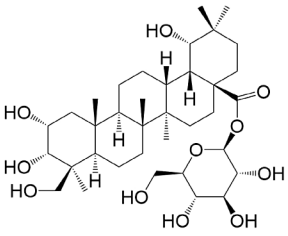

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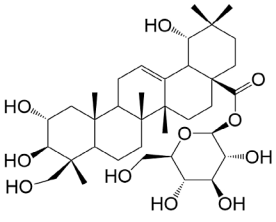

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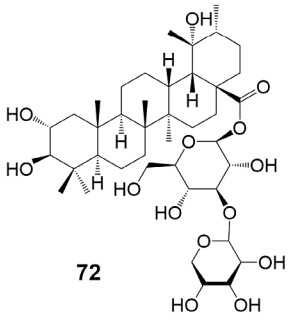

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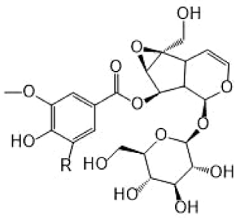
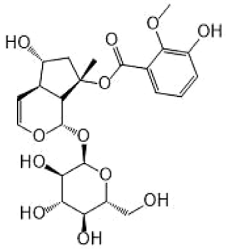


73 R=H
74 R=MeO



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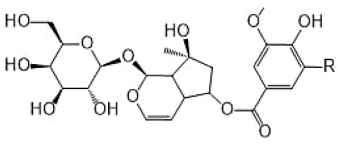
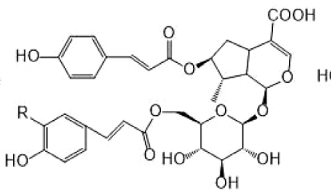
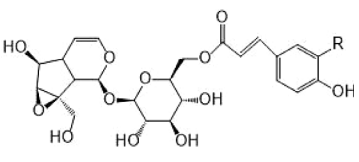


76 R=H
85 R=MeO



77 R=MeO
78 R=OH



79 R=OH
80 R=MeO

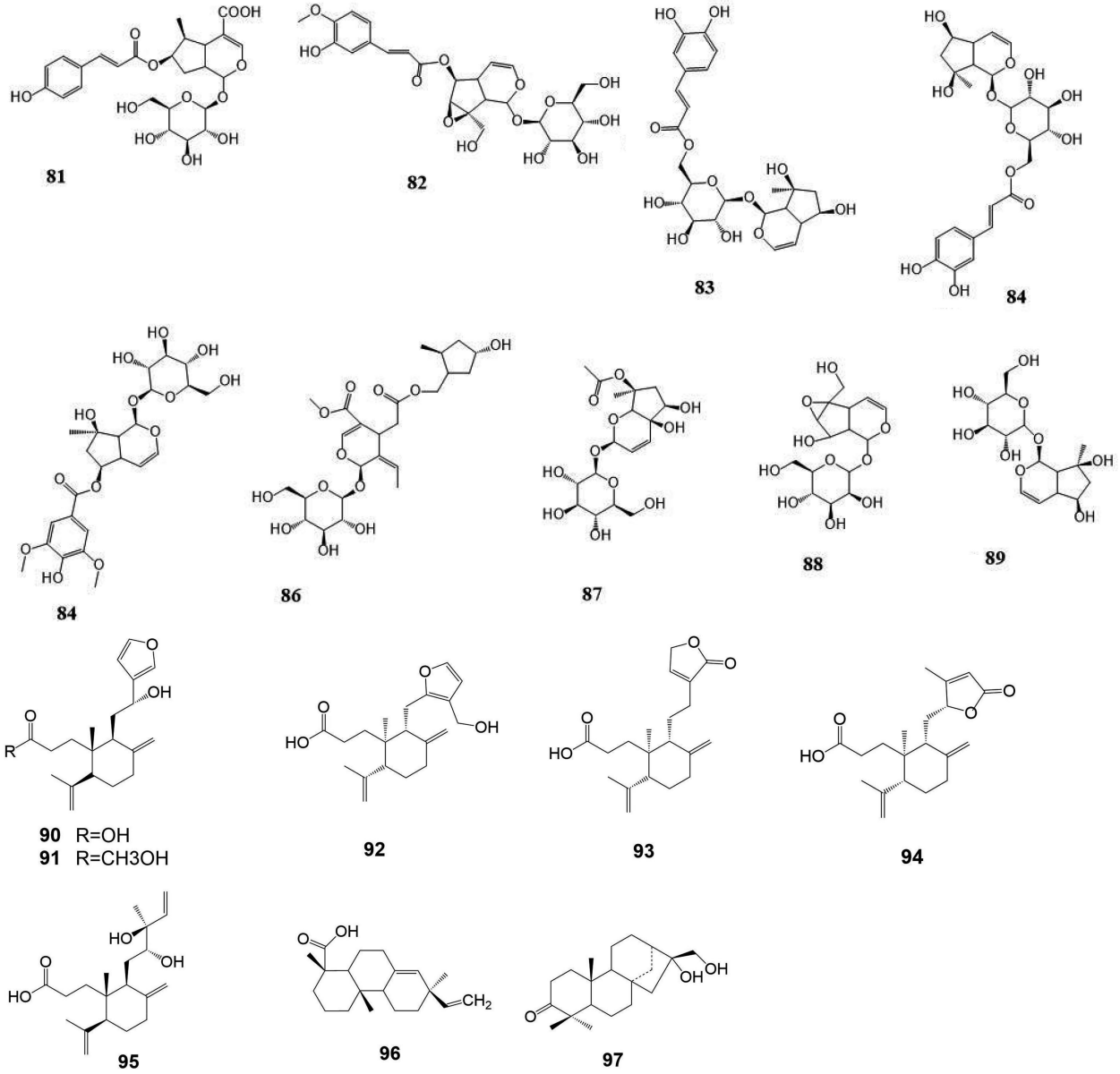


Fig. 3 Structures of Terpenoids.

cancer cells[4,15]. This property is attributed to its downregulation of the podocalyxin–ezrin interaction during the epithelial mesenchymal transition. BALB/c Nu mice experiments have shown that ethyl acetate extracts from *C. nudiflora* significantly inhibit intracellular p-Snail and increase E-cadherin expression in breast cancer cells[52]. Cellular experiments have shown that *C. nudiflora* from Wuzhishan, Hainan Province (China) can inhibit the proliferation and growth of intestinal cancer cells by activating the Wnt/β-catenin signaling pathway[53].*C. nudiflora* affects the epithelial mesenchymal transition, proliferation, and migration of colon cancer cells *in vivo* by inhibiting the activation of the TGF-β1/P38/PAI-1 pathway. *In vitro* experiments have shown that *C. nudiflora* reverses the drug resistance of colon cancer cells *in vitro* by activating the IL-6/STAT3 signaling pathway[6].

Others

Pharmacological studies have shown that *C. nudiflora* has the functions of improving memory, anti- herpes simplex virus-1, and anti-abdominal adhesion after abdominal surgery[54]. Zhou et al. studied the extraction of *C. nudiflora* using three different solvents (petroleum ether, n-butanol, and ethyl acetate) and observed the effects of the three different solvent extracts against herpes simplex virus-1. The ethyl acetate extract was found to be the most effective[55,56]. Ba Li'na determines the anti-psoriasis effect of *C. nudiflora* extract. Sixty KM mice were selected and grouped according to the random number table method. They were given normal saline, *C. nudiflora* extract, and 1 mg/kg methotrexate by gastric perfusion for seven days, respectively. Conclusion showed that the *C. nudiflora* administration group was significantly higher than the other groups. The *C. nudiflora* extract can exert an anti-psoriatic effect by inducing apoptosis[57,58]. The *C. nudiflora* alcohol test reduces mortality and serum alanine aminotransferase and glutamate pyruvic transaminase levels in mice with acute alcoholic liver injury and has a protective effect against alcoholic liver injury[33]. Phenyl ethanol glycosides have

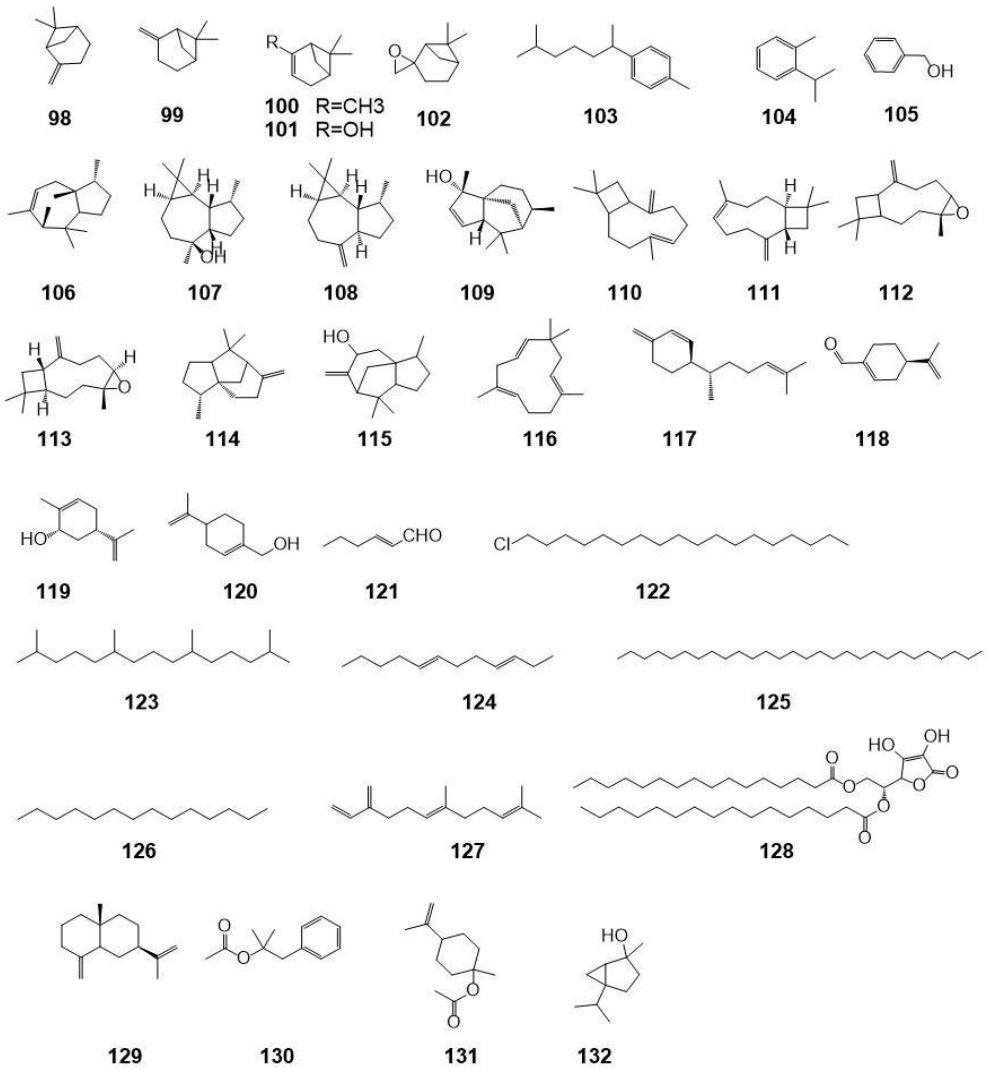


Fig. 4 Structures of volatile oils.

neuroprotective and memory-improving effects; therefore, they have great potential in the treatment of diseases such as Alzheimer's disease[59]. *C. nudiflora* extracts reduce serum insulin, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels. They can improve insulin resistance and reverse liver and pancreatic damage caused by diabetes[60]. In addition, studies have shown that *C. nudiflora* can promote angiogenesis in human microvascular endothelial cells, reduce the body's inflammatory response, and improve urinary bacterial clearance[61,62] (Fig. 5).

Conclusions and perspectives

The quality control method based on chemical constituents and pharmacological activity of *C. nudiflora* needs to be improved

Current research on *C. nudiflora* focuses on the chemical composition and pharmacological activity of the plant. Its chemical components include flavonoids, phenylpropanoids, terpenes, and volatiles. According to previous studies, flavonoids and phenylpropanoids are the two main components of *C. nudiflora* and the basis for its medicinal effects. Therefore, these two components became the marker compounds for the quality control of *C. nudiflora*. Significant amounts of verbascosides have been found in *C. nudiflora*[63–65], and these compounds can also act as markers for *C. nudiflora* quality standards. The main components of *C. nudiflora* can change owing to various factors, including origin, harvesting, distribution[66,67], storage, and forgery, leading to great variations[68]. In *C. nudiflora* produced in Hainan Province (China), the coefficient of variation exceeded 50% for seven different active ingredients. This data indicates the importance of developing quality standards for *C. nudiflora*. Owing to the complexity and uncertainty of the pharmacological mechanisms of *C. nudiflora*, coupled with the gradual identification of more and more compounds, one or a few markers in *C. nudiflora* may not be enough to set an overall quality standard for the herb. Therefore, some researchers have suggested that in the future, phytofingerprinting technology may be used, because it is already widely accepted as the basis for the effective identification of herbal medicines[69]. *C. nudiflora* samples harvested at different times and under different weather conditions have significant variations and specificities. Researchers have also confirmed this by testing

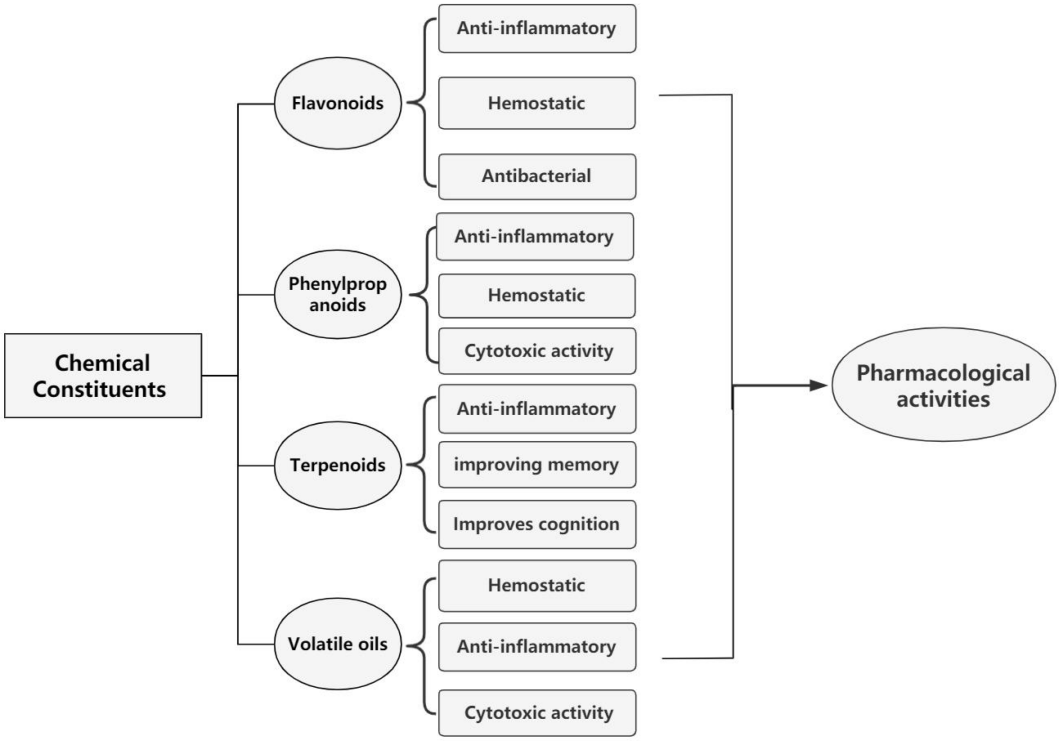


Fig. 5 Major chemical constituents and pharmacological activities in *Callicarpa nudiflora*.

fingerprints with other *Verbenaceae* plants, such as *C. kwangtungensis*, *C. macrophylla*, *C. formosana*, and *C. kochiana*[70]. At present, there is a gap in research on the changes in pharmacological activities caused by the changes in chemical components of *C. nudiflora* plants. Thus, there is a need to strengthen the research on the mechanism of action between the variability in the chemical composition and the pharmacological activities of *C. nudiflora* to improve better clinical applications.

The pharmacological activity of *C. nudiflora* is greater when used clinically in combination

Studies have confirmed the rich pharmacological activity of *C. nudiflora*. *C. nudiflora* tablets have been widely used clinically with good results. However, only a few individual isolates from *C. nudiflora* have been reported in the literature to have good anti-inflammatory activities. Because of the limited formulation development capacity of *C. nudiflora*, only a few pharmaceutical companies are focused on developing *C. nudiflora* raw materials. Soup made from *C. nudiflora* is mostly given to patients in tropical regions, and its efficacy is limited. Recent studies have shown that *C. nudiflora* has better activity when taken together with another herb than when taken alone[71,72]. *C. nudiflora* granules combined with entecavir in the treatment of cirrhosis upper gastro-intestinal bleeding can effectively improve patients' liver function and enhance patients' coagulation function. *C. nudiflora* granules combined with montelukast retention enema in the treatment of chronic radiation colitis can effectively improve clinical symptoms without the occurrence of serious adverse reactions. *C. nudiflora* capsules or tablets combined with antibiotics can effectively relieve symptoms and reduce inflammation in the treatment of pelvic inflammatory disease, sequelae of qi stagnation, and blood stasis[73]. *C. nudiflora* tablets combined with indocin therapy can effectively prevent vaginal bleeding and shorten the time of menstrual return in patients after medication-induced abortions[74,75]. *C. nudiflora* capsules combined with amikacin sulfate injections in the treatment of urinary tract infection can reduce the inflammatory response and improve the clearance of urinary bacteria[62]. Studies have shown that combinations of drugs can be more stable and significant than a single drug and can effectively reduce the adverse effects caused by Western drugs.

C. nudiflora has good development prospects

At present, research on *C. nudiflora* is mainly focused on ethanol extraction, and the compounds isolated are mostly terpenoids, flavonoids, phenylethanol glycosides, and phenylpropanoids. The pharmacological effects, including antisepsis, anti-inflammatory, and hemostasis, possessed by *C. nudiflora* have been tested, and more products are being developed based on these efficacies. A new toothpaste made from an extract of *C. nudiflora* improves the symptoms of gingivitis[76,77]. A new hemostatic disinfectant containing an extract of *C. nudiflora* leaves was developed and tested to be effective[77]. *C. nudiflora* is no longer confined to the treatment of insect and snake bites or trauma in tropical rainforests, it has also been discovered to aid in rheumatic paralysis, tropical diseases, internal injuries, and tumor-based diseases. Preparations of *C. nudiflora* are currently being developed for the market. Anti-uterine inflammatory tablets and capsules containing *C. nudiflora* as well as *C. nudiflora*-containing tablets, dispersible tablets, suppositories, and granules are being developed. Some contain a combination of *C. nudiflora* and other herbs. *C. nudiflora* can act as an insecticide owing to its insecticidal properties[21]. *C. nudiflora* has a variety of pharmacological effects, and there are still many chemical constituents and biological activities to be further studied.

In recent years, a number of additional potent and new medicinal resources have been discovered in the tropics, with 137 different types of plants producing anti-oncogenic medicinal ingredients. In addition, plants required to make a number of drugs that previously had to be imported have been found in Hainan Province (China). These resources need to be developed.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest.

Dates

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