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# BIOLOGICALLY ACTIVE NATURAL PRODUCTS OF THE GENUS CALLICARPA<sup>1</sup>

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### **Abstract**

About 20 species from *Callicarpa* have reported ethnobotanical and ethnomedical uses, and several members of this genus are well known in the traditional medical systems of China and South Asia. Ethnomedical reports indicate their use in the treatment of hepatitis, rheumatism, fever, headache, indigestion, and other ailments. Several species of *Callicarpa* have been reported to be used against cancer (e.g., *Callicarpa americana* root to treat skin cancer and *Callicarpa rubella* bark to treat tumors of the large intestine). Extracts from about 14 species in this genus have been evaluated for biological activity, including antibacterial, antifungal, anti-insect growth, cytotoxic, and phytotoxic activities. In addition to amino acids, benzenoids, simple carbohydrates, and lipids, numerous diterpenes, flavonoids, phenylpropanoids, phytosterols, sesquiterpenes, and triterpenes have been detected in or isolated from the genus *Callicarpa*. The essential oils of *Callicarpa americana* have recently been reported to have antialgal and phytotoxic activities, and several isolates from this species (and *C. japonica*) were identified as contributing to the mosquito bite-deterrent activity that was first indicated by folkloric usage. Recent bioassay-guided investigations of *C. americana* extracts have resulted in the isolation of several active compounds, mainly of the clerodane diterpene structural type.

### **Keywords**

bioassay; cytotoxicity; Callicarpa; diterpenoid; natural products; pharmacognosy

### **INTRODUCTION**

The genus *Callicarpa* is comprised of 40 or more species, many of which have been used by humans in ways suggesting that the genus is a rich source of biologically active natural products. Traditional usage of various parts of members of *Callicarpa* includes preparations used as fish poisons, insect deterrents, and medicinally. Phytochemical and biological studies of extracts from *Callicarpa* lend support to these previous uses, and suggest that this genus may offer a rich supply of bioactive secondary metabolites. The fruits are a striking feature of the genus; hence the genus name "*Callicarpa*", meaning "handsome fruit", and the common

<sup>&</sup>lt;sup>1</sup>The material presented here is adapted from the Ph.D. dissertation of one of the authors (W.J.) entitled "A Pharmacognostic Investigation of *Callicarpa americana* for Potential Anticancer Agents", completed at the University of Illinois at Chicago, Chicago, IL, 2006.

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name "beautyberry". The fruits of at least one species (*C. americana* L.) are commonly consumed by birds and small mammals and white-tailed deer [54], and occasionally by humans (see below).

### TAXONOMY OF CALLICARPA

Traditionally, *Callicarpa* has been included in the family Verbenaceae, but some current botanical authorities have concluded that it is more appropriately included among the Lamiaceae, with both of these families being grouped in the order Lamiales [10,91]. The plant family Lamiaceae (classically called the Labiatae) is the source of numerous natural products and traditional medicines [27]. The predominant phytochemical characteristic of the family is the presence in many of its species of biologically active terpenoid principles, including monoterpenoids and diterpenoids. The genus *Callicarpa* was described by Harley and coworkers [27] as being comprised primarily of small trees and shrubs with fruits typified as drupaceous with a fleshy exocarp and a hard endocarp, and containing four stony pyrenes.

Two representatives of *Callicarpa* are native or naturalized to the southeastern United States, namely, *C. americana* L. and *C. dichotoma* (Lour.) K. Koch (= *C. purpurea* Juss., an ornamental escapee). Radford and colleagues [63] described these members of the genus as shrubs, 1–2.5 m tall, with pubescent twigs, simple, more or less opposite, leaves, and flowers forming cymes. The fruit is a two-lobed and four-seeded drupe, purple (or rarely white). The genus *Callicarpa* and the species *C. americana* were first described by Carl Linnaeus in 1741, but not published validly until some years later, in 1753 [5]. Thus, these two specimens are the type specimens (isolectotypes) of the species *C. americana* L. and the genus *Callicarpa*.

### ETHNOBOTANICAL AND ETHNOMEDICAL USES OF CALLICARPA SPECIES

The genus Callicarpa has a rich history of ethnobotanical usage, mainly in Asia (Table 1). Several species of the genus Callicarpa have documented ethnobotanical uses as traditional and ethnomedicines and as fish poisons. For example, C. arborea Roxb. has been used in India to treat skin diseases [68], and C. candicans (Burm. f.) Hochr. leaves are reported to be used in Palau and the Philippines to stupefy fish [38,39]. C. formosana Rolfe is used in Taiwanese folk medicine to treat rheumatism and disorders of the digestive tract (oral infections and unspecified stomach disorders and intestinal complaints) [15]. The bark of C. lanata L. has been used in the East Indies as a betel leaf substitute [30]. C. macrophylla Vahl is used extensively in Indian and Chinese systems of traditional medicine. In India, the seeds of C. macrophylla are used to treat oral infections and "intestinal complaints" [1], the leaf extract is used to treat rheumatism [79], the juice of the fruit is used to treat fever [51], and an aromatic oil from the roots is used to treat "disordered stomach" [79]. In Traditional Chinese Medicine, C. macrophylla and two other species (C. pedunculata R.Br. and C. cathayana Chang) have been used to stop internal and external bleeding and to treat burns [6]. C. macrophylla is used also in combination with other herbs in a preparation to treat diarrhea, dysentery, intestinal worms, and skin disorders and to "purify the blood" and eliminate toxins [41].

Several *Callicarpa* species have been used to regulate fertility. The peoples of the Torres Straits (located between Papua New Guinea and Australia) were reported to consume the juice of the chewed leaves of a *Callicarpa* species (local name, "argerarger"; probably *C. thozetii* A. A. Munir) mixed with the leaves of several other shrubs and trees to induce permanent sterility [26]. Members of the Marma tribe in Bangladesh reportedly have used the root juice of *C. lanata* L. [cited as *C. tomentosa* (L.) Murr.] in combination with the root juice of *Streblus asper* Laur. (Moraceae) to "treat irregular menstruation" and to promote delayed menstruation [2], and the leaves are known to be chewed with salt as an anthelmintic [8].

Callicarpa americana L. has a number of documented ethnobotanical uses in North America and the berries have been used occasionally as a food. In the early nineteenth century Rafinesque noted that *C. americana* leaves were used to treat dropsy (apparently by people of European heritage), and the fruits were considered edible, although somewhat acidic and astringent (hence "sourberry", a colloquial name at the time) [64]. On the other hand, M. A. Curtis [18] wrote that "These berries are juicy, slightly aromatic and sweetish, and are sometimes eaten, but are probably not very wholesome." More recently, Fernald and Kinsey stated, "The familiar beauty-berry...has the defoliated branches covered in late autumn and early winter with masses of small currant-like pinkish-purple berries...Their best use is as a table-ornament for which they are almost unequaled [22]." The fruits were also known as a source of purple dye for wool [64].

In a traditional practice of the Alabama Indian tribe in North America, a decoction was prepared from the roots and branches of *C. americana* L. for external use in sweat baths as an antirheumatic, diaphoretic, and febrifuge (against malaria specifically), and the Choctaw tribe used decoctions of various *C. americana* plant parts (including roots and berries) to treat colic [58]. For dysentery, *C. americana* roots mixed with roots of *Rubus* sp. were taken in a decoction [81], and the roots were used to treat dizziness [81]. A root decoction was used by the Koasati tribe to treat stomachache [81]. In North Carolina, *C. americana* bark was used to treat fevers, according to an herbalist informant [17]. Dr. Jonathan L. Hartwell cited one report from the central files of the United States National Cancer Institute of a "cure" of skin cancer achieved with the use of a decoction of the root of *C. americana* in Mississippi (circa 1966), but it is not clear whether this use was based on an ethnomedical tradition, or whether it was a case of "ethnoexperimentation" [28].

### PHYTOCHEMICAL STUDIES OF CALLICARPA

Phytochemical screening of several members of the genus *Callicarpa* has been reported, and the presence of flavonoids, essential oils, and terpenoids has been substantiated by detection or isolation of members of these compound classes. An extract of the leaf and stem of *C. angustifolia* King & Gamble tested positive for alkaloids using Mayer's reagent (i.e., formation of precipitate from an aqueous solution of mercuric chloride and potassium iodide), but, to date, the occurrence of alkaloids in any species of the genus has not been confirmed by phytochemical isolation work. Numerous phytochemicals have been isolated from (or detected in) species in *Callicarpa*, including representatives from the following structural classes: clerodane and phyllocladane diterpenes, fatty acids, flavones, lignans, monoterpenes, phenylpropanoids, phytosterols, sesquiterpenes, and triterpenes. A summary of the phytochemical screening results and specific phytochemicals isolated from members of the genus are provided in Tables 2 and 3, respectively.

Several recent phytochemical studies of members of the genus *Callicarpa* have resulted in the isolation of notable diterpenoid constituents. One such study resulted in the isolation of abieta-8,11,13,15-tetraen-18-oic acid (1), calliphyllin (4), calliterpenone (6), 6α-hydroxynidorellol (17), and isopimaric acid (19), and the authors observed that several of these same compounds have been reported from members of the Lamiaceae, supporting an alliance with the latter plant family [33]. Xu and coworkers [90] reported the isolation of four new clerodane diterpenes [pentandralactone and pentandranoic acids A–C (24 and 25–27, respectively)]. No biological activities were reported for the compounds described in either of these phytochemical reports [33,90].

## BIOLOGICAL EVALUATION OF *CALLICARPA* EXTRACTS AND PURE COMPOUND ISOLATES

Various extracts and other preparations of *Callicarpa americana* L. have been evaluated for biological activity in a number of assay systems, including antiviral potential of the freezedried leaf [85], oviposition inhibition activity of an aqueous leaf extract [83], antialgal activity of the leaf essential oil [82], mosquito bite-deterrent activity of volatile constituents from the leaves [11], and cytotoxicity of a chloroform extract of the combined fruits, leaves and twigs [36]. Ethanolic extracts of *C. arborea* Roxb. var. *oblongifolia*, *C. lanata* L., *C. macrophylla* Roxb., and *C. pilosissima* Maxim. were found to lack cytotoxic activity against KB cells [7, 21,77]. *C. pilosissima* Maxim. extracts were evaluated in mice against colon carcinoma 38, B16 melanoma, and P388 murine leukemia, for which activity was observed only against P388 with a 60% increase in life span in the treated mice relative to control at relatively high doses (stated range of 150 to 600 mg/kg/injection) [77]. Other members of the genus have been evaluated for various biological activities (Table 4). 5,6,7-Trimethoxyflavone (58), a constituent of *C. japonica*, displayed activity against Herpes simplex virus and other viral pathogens [29].

The demonstration of a plant-growth suppression effect of extracts from *C. acuminata* H.B.K. was the impetus for a bioassay-guided investigation that resulted in the isolation of akhdarenol (2), isopimaric acid (19), sandaracopimaradien-19-ol (32), 5-hydroxy-6,7,4'-trimethoxyflavone (50), and  $\alpha$ -amyrin (81) [3]. These isolates lacked activity when tested singly in assays for alleleochemical potential, but further testing in other assays indicated that several of these compounds possess cytotoxic activity against insect and hamster cells, with the strongest cytotoxic activity in mammalian cells being associated with 2 and 19 [3].

Observation of the use of fresh *C. americana* leaves as a "folk remedy", used to protect horses and people from mosquito bites, prompted an investigation of the volatile constituents of *C. americana* and *C. japonica* leaves, using biological activity against *Aedes aegypti* and *Anopheles stephensi* to guide chromatographic fractionation, which resulted in the identification of several mosquito bite-deterrent terpenoid components [11]. Of several compounds isolated from *C. americana* essential oil, callicarpenal (5), humulene epoxide II, intermediol, and spathulenol were tested against *A. aegypti* and *A. stephensi*, with callicarpenal (5) displaying the strongest overall activity (mosquito-deterrence effect and knock-down toxicity) [11]. No structure-activity relationship studies were reported with regard to mosquito bite-deterrent activity in this study, but it seems likely that its aldehyde functionality confers potency to this tetranorclerodane diterpene [11].

An investigation of *Callicarpa americana* L. as a potential source of anticancer natural products was carried out using bioassay-guided isolation methodology [36]. The configuration of the isolates, including the absolute configuration of the secondary hydroxy groups was determined using a modified Mosher ester methodology [75,78]. Using this technique, the C-12 hydroxy group in the side chain of the clerodane-type diterpenes isolated was determined as having an *S* absolute configuration [36]. In all, six new compounds and eight known compounds were isolated from the chloroform extract of the combined fruits, leaves, and twigs of *C. americana* L. [36]. The structures of the new compounds were elucidated as 3β,12(*S*)-dihydroxycleroda-4(18),13-dien-15,16-olide (8), 12(*S*),16ξ-dihydroxycleroda-3,13-dien-15,16-olide (10), 12(*S*)-hydroxycleroda-3,13-dien-15,16-olide (12), 12(*S*)-hydroxycleroda-3,13-dien-16,15-olide (13), 12(*S*)-hydroxy-16ξ-methoxycleroda-3,13-dien-15,16-olide (14), and 16ξ-hydroxycleroda-3,11(*E*),13-trien-15,16-olide (16) using a range of spectroscopic techniques, including 1D and 2D NMR and accurate mass measurement [36]. Of several known compounds isolated in this study, three were previously reported to occur in the genus *Callicarpa* [calliterpenone (6), euscaphic acid (88), and 5-hydroxy-6,7,4'-

trimethoxyflavone (**50**)] (see Table 3). Five other known compounds obtained in this same investigation [i.e.,  $3\beta$ ,  $16\xi$ -dihydroxycleroda-4(18), 13-dien-15, 16-olide (**9**), 2-formyl- $16\xi$ -hydroxy-3-A-norcleroda-2, 13-dien-15, 16-olide (**11**), genkwanin (**41**),  $16\xi$ -hydroxycleroda-3, 13-dien-15, 16-olide (**15**), and 5-hydroxy-7, 4'-dimethoxyflavone (**45**)] were not previously known to occur in *Callicarpa* [36].

The isolates obtained from the chloroform-soluble extract of the combined fruits, leaves and twigs of C. americana [36] were tested for cytotoxicity against a panel of human cancer cell lines (Table 5). 12(S),16ξ-Dihydroxycleroda-3,13-dien-15,16-olide (10), 2-formyl-16ξhydroxy-3-A-norcleroda-2,13-dien-15,16-olide (11), genkwanin (41), 12(S)hydroxycleroda-3,13-dien-16,15-olide (13), 16\(\xi\)-hydroxycleroda-3,13-dien-15,16-olide (15), and 16ξ-hydroxycleroda-3,11(E),13-trien-15,16-olide (16) all showed cytotoxic activity with at least one cell line showing activity below 5 µg/mL. By comparison of the relative cytotoxicities of these isolates, a structure-activity relationship trend was suggested [36]. Compounds of the clerodane structure class with a γ-lactone ring in the side chain, and which lacked a free hydroxy group at the 16-position, displayed a slightly less potent cytotoxicity than compounds with a  $\gamma$ -hydroxy group on the  $\alpha$ , $\beta$ -unsaturated  $\gamma$ -lactone ring [36]. One of the new active compounds [12(S),16ξ-dihydroxycleroda-3,13-dien-15,16-olide (10)] isolated and purified from C. americana was tested in an in vivo model of antitumor activity against several cell lines using the hollow fiber assay, in which the human cells are enclosed in selectively permeable polyvinylpyrrolidone fibers and implanted in nude mice [12,57]. The cell lines used in the hollow fiber assay were hormone-dependent prostate cancer (LNCaP), human lung cancer (Lu1), and breast cancer (MCF-7) [36]. Compound 10 was tested in this model at 6.25, 12.5, 25, and 50 mg/kg, administered to the mice via intraperitoneal injection [36].

No cytotoxic activity was observed at either of two physiological sites, even at the highest dose tested (50 mg/kg), and two of the three mice died at each the two highest doses (25 mg/kg and 50 mg/kg) [36]. Despite these negative results, there may be value in continued investigation of members of this genus for anticancer agents, in light of the folkloric evidence for the use of *Callicarpa* species for treatment of cancer, and the promising in vitro results noted in several instances for extracts or isolates.

### CONCLUSIONS

The genus *Callicarpa* has a relatively wide geographic distribution, there is considerable ethnobotanical evidence that members of the genus contain pharmacologically active components, and numerous extracts have shown positive results in a range of bioassays relevant to human health. However, to date, relatively few bioassay-guided isolation studies have been carried out to identify active components for drug or agrochemical discovery. A few promising chemical constituents have been obtained with mosquito-deterrent activity [11], cytotoxicity [36], antimicrobial activity [29], among others, but it seems clear that this is just scratching the surface into the elucidation of the potential bioactive natural products from *Callicarpa*, and much more phytochemical prospecting is warranted on this promising genus in the future. In addition, in light of the ongoing debate about the taxonomic position of *Callicarpa*, a thorough evaluation of the chemotaxonomy of this genus as compared to members of Lamiaceae and Verbenaceae would help clarify the relationships among these taxa.

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Diterpenes detected or isolated from *Callicarpa* species.

**Figure 2.** Diterpenes detected or isolated from *Callicarpa* species (continued).

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**Figure 3.** Flavonoids detected or isolated from *Callicarpa* species.

**Figure 4.** Phenylethanoids and phenyl propanoids detected or isolated from *Callicarpa* species (including lignans).

**Figure 5.** Triterpenes and phytosterols detected or isolated from *Callicarpa* species.

Table 1

Ethnobotanical uses of the plants in the genus Callicarpa

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Species Part Used Country Use Reference americana I Bark Jnited States Fever [17] eaves United States Dropsy [64] United States Skin cancer [28] Roots Roots United States Dysentery [81] United States [58] Roots and berries Colic [58] Roots and branches United States Fever, malaria, rheumatism C. arborea Roxb Bark Skin disease [68] India [51] Fever Bark Nepal Bark juice Nepal Indigestion [50] C. bodinieri H.Lév. [56] Leaves China Wounds Papua New Guinea C. cana L [61,88] Not stated Antifertility C. candicans (Burm. f.) Hochr Palau Islands, Philippine Fish poison [55] eaves [24] Malavsia Emmenagogue Leaves cathayana Chang eaves China Wounds [56] [48] flavida Elmer Bark Philippines Toothache [47] formosana Rolfe Entire plant Hepatitis Taiwan Oral infections, intestinal and stomach disorder [15] Not stated Taiwan [56] Wounds Leaves China C. giraldii Hesse ex Rehder Leaves China Wounds [56] C. giraldii Hesse ex Rehder var. lyi (Levl.) C.Y.Wu Leaves China Wounds [56] [56] C. integerrima Champ. ex Benth. eaves China Wounds C. japonica Thunb. eaves China Wounds [56] [32] Japan Fish poison eaves C. kochiana Makino Leaves China Wounds [56] C. lanata L. (C. tomentosa Murr.)<sup>a</sup> India Anthelmintic [8] eaves Fresh roots Bangladesh Fever, malaria [2] lingii Merr. Wounds [56] eaves China C. longifolia Lam. Wounds [56] Leaves China Papua New Guinea **[88]** Not stated Antifertility C. longissima Merr China Wounds [56] Leaves C. macrophylla Vahl Fruit iuice Nepal Fever [53] [56] Leaves China Wounds [84] Leaves (smoked) India Headache Not stated [46] China Fever Fresh roots Fever, mouth ulcers, cough [35] India Nepa Oral infection Roots Root juice Indigestion [49] Nepal [1] Seeds Infections, rheumatism pedunculata R.Br Papua New Guinea [88] Not stated Antifertility China Wounds [56] C. purpurea Juss. (C. dichotoma Raeusch.)a Leaves Wounds [56] . reevesii Wall. (C. nudiflora Hook. et Arn.) Leaves China . rubella Lindl. [25] India Tumors of the large intestine Bark Wounds [56] Leaves China Burns [71] Entire plant China Papua New Guinea Shoulder pain [31] eaves *Callicarpa* sp Not stated Papua New Guinea Body pain [61] Callicarpa sp Papua New Guinea Antifertility [26] *Callicarpa* sp. eaves h Papua New Guinea [20] eaves Antifertility Leaves and twigs Papua New Guinea Antifertility

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<sup>&</sup>lt;sup>a</sup>The botanical binomial in parentheses is listed as a synonym for the preceding species name listed in the "International Plant Names Index" online database.

Only the genus was identified in the cited reference.

 Table 2

 Summary of phytochemical screening of extracts of Callicarpa species

Species	Plant Part	Results	Reference
C. angustifolia King & Gamble	Leaves and twigs	Alkaloids present	[9]
C. bodinieri H.Lév.	Leaves	Flavonoids present	[80]
C. candicans (Burm. f.) Hochr.	Not stated	Alkaloids absent	[24]
	Not stated	Essential oils	[24]
	Not stated	Flavonoids present	[24]
	Not stated	Saponins absent	[24]
	Not stated	Terpenoids present	[24]
C. lanata <sup>a</sup>	Twigs	Alkaloids absent	[62]
	Twigs	Saponins absent	[62]
C. macrophylla Vahl.	Aerial parts	Tannins present (hide test)	[4]
C. tomentosa <sup>a</sup>	Leaves	Flavonoids present	[80]
C. tomentosa <sup>a</sup>	Leaves and twigs	Alkaloids absent	[37]
	Leaves and twigs	Flavonoids absent	[37]
	Leaves and twigs	Saponins absent	[37]
C. reevesii Wall. (C. nudiflora Hook. et A	<sub>rn.)</sub> bNot stated	Tannins present	[71]

 $<sup>\</sup>ensuremath{^{a}}\xspace$  Taxonomic authority not stated in the cited publication.

b The botanical binomial in parentheses is listed as a synonym for the preceding species name listed in the "International Plant Names Index" online database

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 Table 3

 Phytochemical constituents of the genus Callicarpa

Compound Type/Nome	Enosies Studied	Dlant Daut	Doforana
Compound Type/Name Amino Acids	Species Studied	Plant Part	Reference
Alanine	C. japonica Thunb.	Fruits	[60]
Aspartic acid	C. japonica Thunb.	Fruits	[60]
Glycine	C. japonica Thunb.	Fruits	[60]
Serine	C. japonica Thunb.	Fruits	[60]
Threonine	C. japonica Thunb.	Fruits	[60]
Benzenoids			
Salicylic acid	C. integerrima Champ. ex Benth.	Entire plant	[87]
Syringic acid	C. integerrima Champ. ex. Benth		[87]
Vanillic acid	C. integerrima Champ. ex Benth.	Entire plant	[87]
Carbohydrates	G		F 603
D-Glucose	C. japonica Thunb.	Fruits	[60]
myo -Inositol	C. pedunculata R.Br.	Entire plant	[34]
Diterpenenoids [Fig. (1) and Fig. (2)] Abieta-8,11,13,15-tetraen-18-oic acid (1)	C. pedunculata R.Br.	Entire plant	[34]
Abieta-6,11,15,15-tetraen-16-oic acid (1)	C. pedunculata R.Br.	Leaves	[33]
Akhdarenol (2)	C. acuminata H.B.K.	Leaves	[3]
Callicarpone (3)	C. candicans (Burm. f.) Hochr.	Leaves	[40]
Calliphyllin (4)	C. macrophylla Vahl.	Leaves	[79]
	C. pedunculata R.Br.	Leaves	[33]
Callicarpenal (5)	C. americana L.	Leaf essential oil	[11]
	C. japonica Thunb.	Leaf essential oil	[11]
Calliterpenone (6)	C. americana L.	Fruits, leaves, and twigs	[36]
	C. furfuracea Ridl.	Leaves	[70]
	C. longifolia Lam.	Leaves	[76]
	C. macrophylla Vahl.	Aerial parts	[13]
	C. macrophylla Vahl.	Leaves	[72,76]
	C. macrophylla Vahl.	Seeds	[1]
	C. pedunculata R.Br.	Entire plant	[34]
	C. pedunculata R.Br.	Leaves	[33]
Calliterpenone-17-acetate (7)	C. furfuracea Ridl.	Leaves	[70]
	C. longifolia Lam.	Leaves	[76]
	C. macrophylla Vahl.	Aerial parts	[13]
	C. macrophylla Vahl. C. macrophylla Vahl.	Leaves Seeds	[72,76] [1]
3β,12(S)-Dihydroxycleroda-4(18),13-dien-15,16-olide ( <b>8</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
3β,16ξ-Dihydroxycleroda-4(18),13-dien-15,16- olide (9)	C. americana L.	Fruits, leaves, and twigs	[36]
12(S),16\(\xi\)-Dihydroxycleroda-3,13-dien-15,16- olide ( <b>10</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
2-Formyl-16ξ-hydroxy-3-A-norcleroda-2,13-dien-15,16-olide (11)	ì	Fruits, leaves, and twigs	[36]
12(S)-Hydroxycleroda-3,13-dien-15,16-olide ( <b>12</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
12(S)-Hydroxycleroda-3,13-dien-16,15-olide ( <b>13</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
12(S)-Hydroxy-16ξ-methoxycleroda-3,13-dien-15,16-olide ( <b>14</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
16ξ-Hydroxycleroda-3,13-dien-15,16-olide ( <b>15</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
16ξ-Hydroxycleroda-3,11(E),13-trien-15,16-olide ( <b>16</b> )	C. americana L.	Fruits, leaves, and twigs	[36]
6α-Hydroxynidorellol (17)	C. pedunculata R.Br.	Entire plant	[34]
	C. pedunculata R.Br.	Leaves	[33]
3β-Hydroxyphyllocladan-17-oic acid (18)	C. furfuracea	Leaves	[70]
Isopimaric acid (19)		Leaves	[3]
Janainana 1 (20)	C. pedunculata R.Br.	Entire plant	[33]
Isopimarol ( <b>20</b> ) 16α,17-Isopropylideno-3-oxophyllocladane ( <b>21</b> )	C. japonica Thunb. C. macrophylla Vahl.	Leaf essential oil Leaves	[42] [72]
Maingayic acid (22)	C. macrophylia Vani. C. maingayi King & Gamble	Leaves	[59]
17-Norphyllocladane-3,16-dione ( <b>23</b> )	C. furfuracea Ridl.	Leaves	[70]
Pentandralactone (24)	C. pentandra Roxb.	Leaves	[90]
Pentandranoic acid A (25)	C. pentandra Roxb.	Leaves	[90]
Pentandranoic acid B (26)	C. pentandra Roxb.	Leaves	[90]
Pentandranoic acid C (27)	C. pentandra Roxb.	Leaves	[90]
Phylloclad-15-en-3,17-dione ( <b>28</b> )	C. furfuracea Ridl.	Leaves	[70]
3β,16β-Phyllocladane-3,16,17-triol ( <b>29</b> )	C. furfuracea Ridl.	Leaves	[70]
3β,16β-Phyllocladane-3,16,17-triol-17-acetate ( <b>30</b> )	C. furfuracea Ridl.	Leaves	[70]
Phytol (31)	C. japonica Thunb.	Leaves and twigs	[86]
Sandaracopimaradien-19-ol (32)	C. acuminata H.B.K.	Leaves	[3]
16α,17,19-Trihydroxyphyllocladan-3-one (33)	C. furfuracea Ridl.	Leaves	[70]
4,16α,17-Trihydroxy-3,4-secophyllocladan-3-oic acid ( <b>34</b> )	C. furfuracea Ridl.	Leaves	[70]
5β,16α-4,16,17-Trihydroxy-3,4-secophyllocladan-3-oic acid (35)	C. furfuracea Ridl.	Leaves	[70]
Flavonoids [Fig. (3)]	l		

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Compound Type/Name	Species Studied	Plant Part	Reference
Apigenin (36)	C. longifolia Lam.	Leaves	[76]
	C. macrophylla Vahl.	Leaves	[76]
Apigenin-7-O -β-D-glucuronide (37)	C. longifolia Lam.	Leaves	[76]
	C. macrophylla Vahl.	Leaves	[76]
Chrysoeriol-4'-O -β-D-glucoside (38)	C. bodinieri H.Lév.	Entire plant	[66]
Cyanidin (39)	C. bodinieri H.Lév.	Fruits	[19]
Cymereside (40)	C. purpurea Juss.	Fruits Entire plant	[19]
Cynaroside (40) 5,4'-Dihydroxy-7-methoxyflavone (Genkwanin) (41)	C. bodinieri H.Lév. C. americana L.	Entire plant Fruits, leaves, and twigs	[66]
5.4'-Dihydroxy-7.7-methoxyffavone (Genkwaiiii) (41)	C. americana L. C. macrophylla Vahl.	Leaves	[79]
7,4'-Dihydroxy-3,5-dimethoxyflavone (43)	C. pedunculata R.Br.	Entire plant	[34]
5.4'-Dihydroxy-3.7.3'-trimethoxyflavone (44)	C. macrophylla Vahl.	Leaves	[14,79]
5-Hydroxy-7,4'-dimethoxyflavone ( <b>45</b> )	C. americana L.	Fruits, leaves, and twigs	
5-Hydroxy-3,6,7,4'-tetramethoxyflavone ( <b>46</b> )	C. bodinieri H.Lév.	Leaves	[67]
5-Hydroxy-3,7,3',4'-tetramethoxyflavone ( <b>47</b> )	C. formosana Rolfe	Leaves	[15]
5-Hydroxy-6,7,3',4'-tetramethoxyflavone ( <b>48</b> )	C. integerrima Champ. ex Benth.	Entire plant	[87]
5-Hydroxy-3,7,4'-trimethoxyflavone (49)	C. formosana Rolfe	Leaves	[15]
	C. pedunculata R.Br.	Entire plant	[34]
5-Hydroxy-6,7,4'-trimethoxyflavone ( <b>50</b> )	C. acuminata H.B.K.	Leaves	[3]
	C. americana L.	Fruits, leaves, and twigs	
Luteolin (51)	C. longifolia Lam.	Leaves	[76]
T (11) (10) (10) (10)	C. macrophylla Vahl.	Leaves	[76]
Luteolin-4'-O -β-D-glucoside (52)	C. bodinieri H.Lév.	Entire plant	[66]
Luteolin-7-O -β-D-glucuronide (53)	C. longifolia Lam. C. macrophylla Vahl.	Leaves	[76] [76]
Paeonidin (54)	C. macrophytta Vant. C. bodinieri H.Lév.	Leaves Fruits	[19]
r acomum (34)	C. purpurea Juss.	Fruits	[19]
3,5,7,3',4'-Pentamethoxyflavone ( <b>55</b> )	C. formosana Rolfe	Leaves	[15]
Petunidin (56)	C. purpurea Juss.	Fruits	[19]
5,7,3',4'-Tetramethoxyflavone ( <b>57</b> )	C. formosana Rolfe	Leaves	[15]
5,6,7-Trimethoxyflavone (58)	C. japonica Thunb.	Not stated	[29,32]
Lignans [Fig. (4)]			
Lariciresinol (59)	C. furfuracea Ridl.	Leaves	[70]
9α-Methoxysesamin-2,2'-diol (60)	C. furfuracea Ridl.	Leaves	[70]
(+)-Sesamin ( <b>61</b> )	C. furfuracea Ridl.	Leaves	[70]
(+)-Sesamin-2-ol ( <b>62</b> )	C. furfuracea Ridl.	Leaves	[70]
Sesamin-2,2'-diol (63)	C. furfuracea Ridl.	Leaves	[70]
<u>Lipids</u>	G : TI I	n :	F.CO.1
Arachidic acid	C. japonica Thunb.	Fruits	[60]
(E)-2-Hexenal Lauric acid	C. americana L. C. japonica Thunb.	Leaf essential oil Fruits	[42,82] [60]
Linoleic acid	C. japonica Thunb.	Fruits	[60]
Myristic acid	C. japonica Thunb.	Fruits	[60]
1-Octen-3-ol	C. americana L.	Leaf essential oil	[42,82]
Oleic acid	C. japonica Thunb.	Fruits	[60]
Palmitic acid	C. japonica Thunb.	Fruits	[60]
Pentatetracontanoic acid	C. bodinieri H.Lév.	Leaves	[67]
N -Pentatriacontane	C. bodinieri H.Lév.	Leaves	[67]
Stearic acid	C. japonica Thunb.	Fruits	[60]
N -Triacontane	C. integerrima Champ. ex Benth.	Entire plant	[87]
Monoterpenoids			
Nopinone	C. americana L.	Leaf essential oil	[82]
α-Pinene	C. americana L.	Leaf essential oil	[42,82]
β-Pinene	C. americana L.	Leaf essential oil	[42,82]
Phenylpropanoids and Phenylethanoids [Fig. (4)] 2'-Acetylverbascoside (2'-acetylacteoside) (64)	C. purpurea Juss. (C. dichotoma	Leaves and twigs	[43]
Brandioside (65)	Raeusch.) <sup>a</sup> C. purpurea Juss. (C. dichotoma Raeusch.) <sup>a</sup>	Leaves and twigs	[43]
Calceolarioside A (66)	C. bodinieri H.Lév.	Leaves	[80]
Cistanoside H (67)	C. purpurea Juss. (C. dichotoma		[43]
` ′	Raeusch.) <sup>a</sup> C. purpurea Juss. (C. dichotoma		
Echinacoside (68)	Raeusch.)a		[43]
Eugenol (69)	C. japonica Thunb.	Leaf essential oil	[42]
Forsythoside B (70)	C. purpurea Juss. (C. dichotoma Raeusch.) <sup>a</sup>		[43]
Isoverbascoside (isoacteoside) (71)	C. bodinieri H.Lév.	Leaves	[80]

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Compound Type/Name	Species Studied	Plant Part	Reference
	C. purpurea Juss. (C. dichotoma	Leaves and twigs	[43]
	Raeusch.) <sup>a</sup>		
Poliumoside (72)	C. purpurea Juss. (C. dichotoma Raeusch.) <sup>a</sup>		[43]
E-Tubuloside E ( <b>73</b> )	C. purpurea Juss. (C. dichotoma Raeusch.) <sup>a</sup>	Leaves and twigs	[43]
Z -Tubuloside E ( <b>74</b> )	C. purpurea Juss. (C. dichotoma Raeusch.) <sup>a</sup>	Leaves and twigs	[43]
Verbascoside (acteoside) (75)	C. bodinieri H.Lév.	Leaves	[80]
	C. tomentosa <sup>b</sup>	Leaves	[80]
	C. purpurea Juss. (C. dichotoma Raeusch.) <sup>a</sup>	Leaves and twigs	[43]
Sesquiterpenoids			
Bicyclogermacrene α-Cadinol	C. japonica Thunb. C. americana L.	Leaf essential oil Leaf essential oil	[42] [42,82]
α-cadinoi Camphor (juniper camphor)	C. americana L. C. japonica Thunb.	Leaf essential oil	[42]
Caryophyllene oxide	C. americana L.	Leaf essential oil	[82]
Curcuphenol	C. japonica Thunb.	Leaf essential oil	[42]
β-Elemene	C. japonica Thunb.	Leaf essential oil	[42]
γ-Elemene	C. japonica Thunb.	Leaf essential oil	[42]
δ-Elemene 7-epi -α-Eudesmol	C. japonica Thunb. C. americana L.	Leaf essential oil Leaf essential oil	[42] [42,82]
Germacrene B	C. americana L. C. japonica Thunb.	Leaf essential oil	[42]
Germacrene D	C. japonica Thunb.	Leaf essential oil	[42]
Globulol	C. japonica Thunb.	Leaf essential oil	[42]
α-Guaiene	C. japonica Thunb.	Leaf essential oil	[42]
α-Humulene	C. americana L.	Leaf essential oil	[11,42,82]
	C. japonica Thunb.	Leaf essential oil	[11]
Humulene epoxide II	C. americana L.	Leaf essential oil	[11,42,82]
T-4	C. japonica Thunb.	Leaf essential oil	[11]
Intermediol	C. americana L. C. japonica Thunb.	Leaf essential oil Leaf essential oil	[11]
Khusinol	C. americana L.	Leaf essential oil	[82]
Ledol	C. japonica Thunb.	Leaf essential oil	[42]
Selin-11-en-4-α-ol	C. japonica Thunb.	Leaf essential oil	[42]
α-Selinene	C. americana L.	Leaf essential oil	[42,82]
7- <i>epi</i> -α-Selinene	C. americana L.	Leaf essential oil	[42,82]
Seychellene	C. japonica Thunb.	Leaf essential oil	[42]
Spathulenol Valencene	C. japonica Thunb. C. americana L.	Leaf essential oil Leaf essential oil	[11,42]
Viridiflorol	C. americana L. C. japonica Thunb.	Leaf essential oil	[42,82] [42]
Phytosterols [Fig. (5)]	С. јаронса тнино.	Lear essentiar on	1721
Campesterol (76)	C. japonica Thunb.	Fruits	[60]
β-Sitosterol (77)	C. arborea <sup>b</sup>	Bark	[68]
	C. arborea <sup>b</sup>	Leaves	[14,69]
	C. bodinieri H.Lév.	Entire plant	[66]
	C. formosana Rolfe	Leaves	[15]
	C. integerrima Champ. ex Benth.		[87]
	C. japonica Thunb.	Fruits	[60]
	C. macrophylla Vahl.	Leaves	[79]
β-Sitosterol-d-glucoside (78)	C. pedunculata R.Br. C. formosana Rolfe	Entire plant Leaves	[34]
Stigmasterol (79)	C. bodinieri H.Lév.	Leaves	[67]
Stigmustoror (79)	C. formosana Rolfe	Leaves	[15]
	C. japonica Thunb.	Fruits	[60]
Stigmasterol-D-glucoside (80)	C. formosana Rolfe	Leaves	[15]
Triterpenoids [Fig. (5)]			
<u>α-Amyrin (<b>81</b>)</u>	C. acuminata H.B.K.	Leaves	[3]
R America (82)	C. bodinieri H.Lév.	Leaves	[67]
β-Amyrin ( <b>82</b> )	C. pedunculata R.Br. C. pedunculata R.Br.	Fruits Entire plant	[23]
Bauerenol (83)	C. peauncutata R.Br. C. arborea <sup>b</sup>	Bark	[68]
Betulinic acid (84)	C. arborea <sup>b</sup>	Bark	[68]
	C. arborea C. bodinieri H.Lév.	Entire plant	[66]
	C. macrophylla Vahl.	Leaves	[79]
Corosolic acid (85)	C. bodinieri H.Lév.	Entire plant	[65]
	C. pentandra Roxb.	Leaves	[90]
2α,3α-Dihydroxyurs-12-en-28-oic acid (86)	C. bodinieri H.Lév.	Entire plant	[65]

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Compound Type/Name	Species Studied	Plant Part	Reference
	C. formosana Rolfe	Leaves	[15]
	C. pentandra Roxb.	Leaves	[90]
Epilupeol (87)	C. arborea <sup>b</sup>	Leaves	[69]
Euscaphic acid (88)	C. americana L.	Fruits, leaves, and twigs	[36]
	C. bodinieri H.Lév.	Entire plant	[65]
Oleanolic acid (89)	C. macrophylla Vahl.	Seeds	[1]
Pomolic acid (90)	C. pentandra Roxb.	Leaves	[90]
2α,3α,24-Trihydroxyolean-12-en-28-oic acid ( <b>91</b> )	C. bodinieri H.Lév.	Entire plant	[65]
Ursolic acid (92)	C. arborea <sup>b</sup>	Leaves	[14,69]
	C. bodinieri H.Lév.	Entire plant	[66]
	C. formosana Rolfe	Leaves	[15]
	C. longifolia Lam.	Leaves	[76]
	C. pedunculata R.Br.	Fruits	[23]
	C. pedunculata R.Br.	Entire plant	[34]
	C. pentandra Roxb.	Leaves	[90]

<sup>&</sup>lt;sup>a</sup>The botanical binomial in parentheses is listed as a synonym for the preceding species name listed in the "International Plant Names Index" online database.

 $<sup>\</sup>ensuremath{^b}\xspace$  The taxonomic authority was not stated in the cited publication.

 Table 4

 Biological evaluation of extracts of species of Callicarpa

Species	Part Used	Biological Activity	Reference
C. acuminata H.B.K.	Leaves	Plant growth inhibition	[3]
C. americana L.	Freeze-dried leaves	Inactive against several viruses in plaque-inhibition assays	[85]
	Leaves	Insect oviposition deterrent	[83]
	Fresh leaf essential oil	Antialgal	[82]
	Fresh leaf essential oil	Mosquito bite deterrent	[11]
	Fruits, leaves, and twigs	Cytotoxic activity	[36]
C. arborea Roxb. var. oblongifolia	Aerial parts	Inactive against 9KB cells at 20 Rg/mL	[7]
		Diuretic	[7]
C. cana <sup>a</sup>	Fruits, leaves, and twigs	Fish poison	[74]
C. cana L. (C. erioclona ) <sup>b</sup>	Bark	Antibacterial	[16]
C. formosana Rolfe	Leaves	Insect feeding deterrent	[86]
	Not stated	Monocyte antiproliferation	[44]
	Not stated	Inactive in antiproliferation and no effect on IL-1β and TNF-α levels	[45]
	Twigs	Insect feeding deterrent	[86]
C. furfuracea Ridl.	Bark	Antibacterial	[16]
C. fulvohirsuta Merr.	Bark	Antibacterial	[16]
C. havilandii H.J.Lam	Bark and leaves, separately	Antibacterial	[16]
C. japonica Thunb.	Aerial parts	Antiviral activity	[89]
	Entire plant	Insect feeding deterrent	[86]
	Leaves	Phytotoxic	[42]
C. lanata L.	Aerial parts	Inactive against 9KB cells at 20 µg/mL; LD <sub>50</sub> >1000 mg/kg (i.p., mice)	[21]
C. longifolia Lam.	Leaves	Inactive against Staphylococcus aureus	[16]
C. macrophylla Vahl.	Aerial parts	Inactive against 9KB cells at 20 Rg/mL	[7]
	Leaves	Antibacterial	[73]
		Antifungal	[73]
C. pilosissima Maxim.	Dried entire plant	Inactive against Colon 38 tumor	[77]
		Weakly active against P388 tumor	[77]
		Inactive against melanoma-B16 tumor	[77]
		Inactive against 9KB cells	[77]
C. stapfii H.N. Moldenke	Bark and leaves, separately	Antibacterial	[16]

aTaxonomic authority not stated in the cited publication.

The botanical binomial in parentheses is listed as a synonym for the preceding species name listed in the "International Plant Names Index" online

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Table 5

Cytotoxic activity of compounds isolated from Callicarpa americana  $^{a,b}$ 

				Cell Line <sup>c,d</sup>	$^{\mathrm{c,d}}$	
Compound Code	MCF-7	Lu1	Col2	LNCaP	npound Code MCF-7 Lu1 Col2 LNCaP hTERT-RPE1 HUVE0	HUVEC
10	-	2.4	2.3	4.1	1.9	1.8
11	3.9	2.8	6	4.5	1.9	8.6
13	2.8	2.9	-	3.3	-	-
15	3.5	2.8	-	3.3	-	4.1
16	2.7	2.6	-	2.5	-	1.2
41	-	>20	>20 >20	>20	3.9	>20

 $^a\mathrm{Compounds}~\mathbf{6,8,9,12,14,45,50},$  and  $\mathbf{88}$  were inactive in the cell lines tested.

 $^{\it b}$  Adapted from [36].

<sup>c</sup>Cell lines: MCF-7 = breast cancer; Lu1 = lung cancer; Col2 = colon cancer; LNCaP = hormone-dependent prostate cancer; hTERT-RPE1 = human telomerase reverse-transcriptase retinal pigment epithelium; HUVEC = human umbilical vein epithelial cells.

 $^d\mathrm{ED50}$  values are given in  $\mathrm{\mu g/mL}$  , and values <5  $\mathrm{\mu g/mL}$  are considered to be active.