New Collection of Crude Drugs in *Chinese Pharmacopoeia 2010* I. *Callicarpa* Linn. and Related Items

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Abstract: *Callicarpa* Linn. (beautyberry) is one of the major genera in Verbenaceae, about 20 of which are medicinal plants. Beautyberry, called *Zizhu* in China, is a generic name of those species and largely used as hemostatic medicine. *The Chinese Pharmacopoeia 2010* has admitted three new crude drugs from the genus of *Callicarpa* Linn. including *Callicarpae Macrophyllae Folium*, *Callicarpae Caulis* et *Folium*, and *Callicarpae Formosanae Folium* for the first time since the 1977 version of the *Chinese Pharmacopoeia*. In order to better understand these new crude drugs, we systematically described their bibliography, admission reasons, botanical identification, chemistry, and pharmacology. Several other species, out of national regulations but intensively studied and widely used, are also covered in this review.

Key words: *Callicarpa formosana*; *Callicarpa kwangtungensis*; *Callicarpa* Linn.; *Callicarpa macrophylla*; Chinese patent medicine; *Chinese Pharmacopoeia*; quality assessment

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Introduction

Callicarpa Linn. (beautyberry) is a genus of shrub and small tree in Verbenaceae. About 190 species are accepted by different botanists and about 20 species have been reported as ethnobotanical uses (Flora of China Editorial Committee, 2009; Jones and Kinghorn, 2008). The genus *Callicarpa* Linn. is native to East and Southeast Asia, Australia, and the southeast of North America and Central America. Forty-eight species from *Callicarpa* Linn. have been found in China, 19 species of which are ethno medicines (Flora of China Editorial Committee, 2005; Committee of *Chinese Herbacology*, 2004) and largely distributed in the south of China (Fig. 1). They are used mainly in Asia to stop internal and external bleeding and treat rheumatism and disorders of the digestive tract, oral infections, and intestinal complaints, etc (Jones and Kinghorn, 2008). In China, the popular herbs in the genus are *Callicarpa formosana* Rolfe, *C. macrophylla* Vahl, *C. kwangtungensis* Chun, *C. nudiflroa* Hook. Ex Arn., and so on. In India, *C. arborea* Roxb., *C. macrophylla*, *C. lanata* L., and *C. rubella* Lindl are often used herbs. *C. americana* L. is an ethonal-botanical species in North America. It is generally believed that favones, triterpenes, and phenolic glycosides are pharmaceutical components, which have been reviewed in some papers (Zhong, Xue, and Yao, 2007; Jones and Kinghorn, 2008; Yan, Lu, and Ning, 2008; Wang, Yang, and Gao, 2008).

The Chinese Pharmacopoeia 2010, published in January 2010 and implemented from October 2010 (Qian *et al*, 2010; Pharmacopoeia Committee of P. R. China, 2010), has collected three species of this genus as new crude drugs, i. e. *Callicarpae Macrophyllae Folium* (*C. macrophylla*), *Callicarpae Caulis* et *Folium* (*C. kwangtungensis*), and *Callicarpae Formosanae Folium* (*C. formosana*). In order to let these new items be well understood, the brief history, botanical identification and resource, the reason to be collected, chemical constituents, pharmacological research, and application of *Callicarpae Macrophyllae Folium*, *Callicarpae Caulis* et *Folium*, and *Callicarpae Formosanae Folium* will be comprehensively reviewed.

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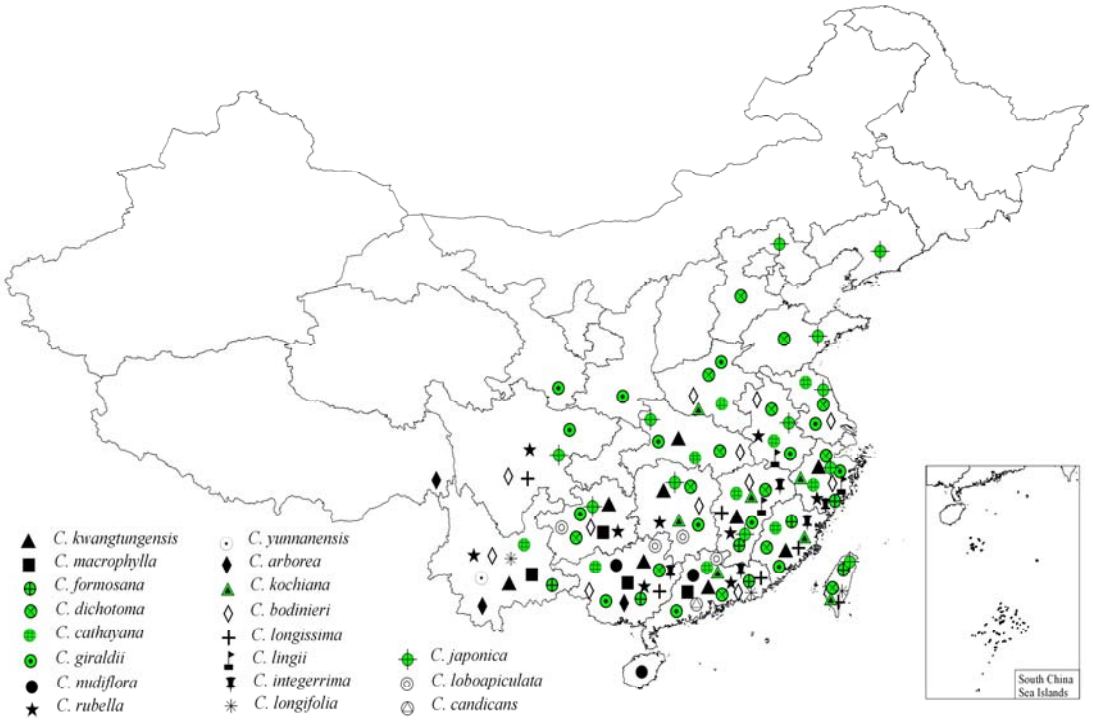


Fig. 1 Distribution of the species of *Callicarpa* Linn. in China

Zizhu bibliography

Botanical description and medicinal species

In China, beautyberry is called *Zizhu* due to its violet berries like pearls, described earliest in *Bencao Shiyi* (*A Supplement to Materia Medica*) by CHEN Cang-qi in B.C. 741 (Kaiyuan 29th, Tang Dynasty). It is described in *Flora of China* (Flora of China Editorial Committee, 2005) as follows: shrubs or trees, erect or rarely climbing; hairs stellate, verticillately branched, dendritic, mealy tomentose, or rarely simple and hooked, branchlets terete or 4-angled; leaves opposite or in 3s; cyme axillary, sessile or pedunculate; bracts linear; calyx campanulate, truncate or minutely 4-dentate, unaltered in fruit; corolla actinomorphic, campanulate or tubular, lobes 4; stamens 4, inserted on corolla tube; filaments slender, often exserted, anthers ovate or oblong, dehiscing by longitudinal slites or circular pores. Ovary imperfectly 2-locular, ovules 2 per locule, attached to middle or distal part of ovary; style usually longer than stamens; stigma usually dilated; fruit a small globose drupe, endocarp bony, mesocarp thin; seeds small, oblong; seed coat membranous; cotyledons fleshy. *Zizhu* is the generic name of those species of the genus *Callicarpa* Linn. for medicinal purpose, however each herb has various folk names in different areas, and *vice versa*, leading to confusion in names. *Chinese Herbacology* (*Zhonghua Bencao*) (1994) covered 15 crude drugs of *Zizhu*, and *Flora of China* (Flora of China Editorial Committee, 2009) embodied seven species for medicinal usage. Table 1 covered all species in China for medicinal usage.

The botanical sources of the three crude drugs are *C. kwangtungensis*, *C. macrophylla*, and *C. formosana*, respectively, belonging to the family Verbenaceae. The genus *Callicarpa* Linn. is grouped into two subgenuses. *Callicarpa* and *Peiantha* Chun et S. L. Chen. Subgen. *Callicarpa* is divided into two sect. of *Tubulosae* (Brig.) P' ei et S. L. Chen and *Callicarpa*. Sections of *Callicarpa* is separated into Ser. *Callicarpae* and Ser. *Verticirimae* (H. T. Chang) P' ei et S. L. Chen. The three species belong to Sect. *Callicarpa* of Subgen. *Callicarpa*: *C. kwangtungensis* is the member of Ser. *Verticirimae*, and *C. macrophylla* and *C. formosanan* are in Ser. *Callicarpae* (Flora of China Editorial Committee, 2009), which coupled with the fact that *C. macrophylla* is the substitute of *C. formosanan* in therapy usage. It also deserves to note that all medicinal species of this genus are involved in Sect. *Callicarpa* except *C. kochiana* Makino; *C. cathayana* H. T. Chang, *C. lingii* Merr., and *C. japonica* Thunb. are included in Ser. *Verticirimae*, while

Table 1 Medicinal plants used as *Zizhu* and their folk/TCM record*

Plant species	Parts used	Folk name	Nature / Taste
*C. kwangtungensis**	twigs and leaves	a	warm / sour and astringent
*C. macrophylla**	roots and leaves	b	plain / bitter and a bit pungent
*C. formosana**	leaves	c	cold / bitter and astringent
*C. dichotoma**	leaves	d	cold / bitter and astringent
*C. cathayana**	leaves	e	cold / bitter and astringent
*C. giraldii**	leaves	f	cold / bitter and astringent
*C. nudiflora**	leaves	g	plain / astringent, a bit pungent and a bit bitter
*C. rubella**	leaves and young twigs	h	plain or cold / pungent and a bit bitter
	roots	i	plain or cold / pungent and a bit bitter
*C. yunnanensis**	roots and leaves	j	plain / a bit bitter
*C. arborea**	roots and leaves	k	plain / a bit bitter and a bit astringent
*C. kochiana**	roots, twigs and leaves	l	plain / bitter and pungent
*C. bodinieri**	roots, twigs and leaves	m	plain / bitter and a bit pungent
	berries	n	warm / pungent
*C. longissima**	twigs and leaves	o	warm / pungent and a bit bitter
	roots	p	warm / pungent and a bit bitter
C. lingii	leaves		
C. integerrima	leaves		
C. longifolia	leaves		
C. japonica	leaves		
C. loboapiculata	leaves		cold / bitter
C. candicans	leaves		
C. americana	bark		
	leaves		
	roots		
	roots and berries		
	roots and branches		
C. cana			
C. flavida	bark		
C. lanata	leaves		
	fresh roots		

*: from *Chinese Herbacology* (*Zhonghua Bencao*) (1994)

a: *Jindaocai*, *Wannianqing*, *Chouchangshan*, *Layafan*

b: *Dayezizhu*, *Zizhucao*, *Zhixuecao*, *Zhizhu*, *Baibeimu*, *Xipumu*, *Baogouchang*, *Jiadaai*, *Baigufeng*, *Dafengye*, *Yangerduo*, *Zhixuecao*, *Ganfengcai*, *Ziziye*, *Damayi*, *Baifanmu*

c: *Zizhu*, *Duhonghua*, *Cukangzai*, *Yaqueban*, *Zhixuecao*, *Yamucai*, *Pangxiemu*, *Baimaozi*

d: *Zizhu*, *Baitangzishu*, *Xiyaxifan*, *Xiaoyezizhu*

e: *Zizhu*, *Huazizhu*, *Yaquefan*, *Zihongbian*, *Mishaizi*, *Yuxianzi*, *Liyuxianzi*, *Zhenzhucao*, *Xiaoyezhenzhufeng*, *Zhixuecao*, *Chuangshangcao*

f: *Zizhu*, *Laoyahu*, *Ximiyouzhu*, *Banjiuzhan*, *Xiaomituanhua*, *Cukangcao*, *Zhouxiang*, *Houcao*, *Shehuang*, *Boyefan*, *Jimishu*, *Zhenzhuzi*, *Hongpaoguo*

g: *Ganfengcai*, *Jiejiehong*, *Fantangye*, *Zeilayao*, *Dabanjiu*, *Dabanjiumi*, *Baihuacha*

h: *Hongzizhu*, *Xiaohongmiguo*, *Baijinzifeng*, *Shanbawang*, *Yelandian*, *Qidabo*, *Kongqiaoshu*, *Duijieshu*, *Fushengyao*

i: *Duijieshugen*

j: *Yunnanzizhu*, *Miaomaozizhu*, *Diannanzhizhu*

k: *Qiaomuzizhu*, *Nanyangzizhu*

l: *Niushehuang*, *Laolaishizi*, *Changyezizhu*, *Shanpipa*, *Huangzizhu*, *Laoxiemu*

m: *Zhenzhufeng*, *Zhenzhuliu*, *Yuzi*, *Qidabai*, *Zhuzishu*, *Baozhushu*, *Jupanhua*, *Mizi*, *Liyuxiazi*, *Baozhuchai*, *Dayaquefan*, *Dayebanjiumi*, *Baimujiang*

n: *Zhenzhufengzi*

o: *Jianweifeng*, *Qifengshai*, *Ganfengshai*, *Chiyaozi*, *Ganfengchai*, *Heijiefeng*, *Woshoufeng*, *Nianruofeng*, *Chuangufeng*, *Dafengye*, *Lianyufeng*, *Xuetu*, *Niushihuang*, *Yashijiao*, *Fengcao*

p: *Jianweifenggen*

the rest fall into Sect. *Callicarpa*.

The three species can be distinguished principally from the following traits. *C. macrophylla* is the biggest in leaf blade followed by *C. kwangtungensis* and *C. formosana*. *C. kwangtungensis* has sharper leaf blades and is distinct from the other two in blade color and non glandular hairs (Table 2).

Traditional usage

In addition to the *Bencao Shiyi*, the *Bencao Gangmu* (*Compendium of Materia Medica*) (Ni and Li, 2006;

Table 2 Botanical comparison of three new crude drugs used as *Zizhu*

Crude drugs	Plant species	Parts used	Taxonomy	Leaf blade			Nature / Taste
				Shape	Length × width / cm	Color	
Callicarpae Caulis et *Folium*	*C. kwangtungensis*	twigs and leaves	Ser. *Verticirimae*; Sect. *Callicarpa*; Subgen. *Callicarpa*	oblong-lanceolate, narrowly elliptic	big, (10−27) × (3−5)	pale green to light brown	pale / bit bitter and astringent
Callicarpae Macrophylae Folium	*C. macrophylla*	young twigs and leaves	Ser. *Callicarpae*; Sect. *Callicarpa*; Subgen. *Callicarpa*	oblong-lanceolate, narrowly elliptic, ovate-elliptic	biggest, (10−30) × (5−11)	daffodil yellow to sepia	pale / bitter and a bit pungent
Callicarpae Formosanae Folium	*C. formosana*	leaves	Ser. *Callicarpae*; Sect. *Callicarpa*; Subgen. *Callicarpa*	ovate-elliptic, elliptic	small, (4−19) × (2.5−9)	daffodil yellow to sepia	pale / bitter and astringent

Zhong, Xue, and Yao, 2007) described that *Zizhu*, namely *Zijing*, was cool in nature, bitter and astringent in taste, and acted on the liver, lung, and stomach meridians with following functions: 1) to activate blood and promote *Qi* circulation; 2) to relieve swelling and ease pain; and 3) to fight menstrual disorder and anemofrigid cold. In South China, a decoction or powder was prepared from the leaves and twigs of *Zizhu* for oral administration; The mash or powder was spread on the wound. In addition to be used individually, *Zizhu* is compatible with other hemostatic crude drugs for better efficacy, e.g., it mixed with *Platycladi Cacumen*, *Cirsii Japonici Herba*, and *Bletillae Rhizoma* for hemoptysis, haematemesis, and bleeding from five sense organs. Nowadays, *Zizhu* is also one of major ingredients of several Chinese patent medicines (CPMs), five of which are collected in *Chinese Pharmacopoeia 2010* (Table 3) for fighting hemorrhage from respiratory and digestive tracts, gynecological bleeding diseases, and so on.

Callicarpae Caulis et *Folium*, *Callicarpae Macrophyllae Folium*, and *Callicarpae Formosanae Folium* are largely used to fight bleeding in some provinces of South China. They are all directly used internally and externally. However, they are lightly different in *Qi* and *Wei*, and have their specific therapy effects. *Callicarpae Caulis* et *Folium* is used mostly in releasing headache, while *Callicarpae Macrophyllae Folium* in easing rheumatic ache. *Callicarpae Formosanae* is a drug for burn and bite wound from snake and dog, which is similar to *C. americana*, a well studied herb in America.

Establishment of standard for *Zizhu* crude drugs and corresponding CPMs

It has been known that *Callicarpae Caulis* et *Folium*, *Callicarpae Macrophyllae Folium*, and *Callicarpae Formosanae Folium* are largely spread and used in some provinces of South China as the ingredients of several popular CPMs with efficient therapies. For example, CPM II containing *Callicarpae Caulis* et *Folium* showed the curative ratio of over 90%, which has greatly promoted cultivation of this plant in some provinces (Wang, 2008). In order to qualify *Zizhu* crude drugs for clinical practices, local quality regulations have been given.

Callicarpae Caulis et *Folium* was first regulated in *Jiangxi Chinese Materia Medica Standards 1996*. It grows largely at Pingxiang and Yichun Counties, Jiangxi Province, China, and has been used to treat several woman diseases for a long time. It is one of the ingredients of CPM II which is an admission of *Jiangxi Drug Standard 1982*. *Callicarpae Formosanae Folium*, one of the popular Chinese crude drugs named *Zizhuye*, was recognized as the leaves of *C. pedunculata* R. Br. in *Chinese Pharmacopoeia 1977* (Pharmacopoeia Committee of P. R. China, 1977). Since botanists debated for the identity of *C. pedunculata* and *C. formosana*, the latest pharmacopoeia supports that they are different species and *C. formosana* is the only botanical source of *Zizhuye*.

Callicarpae Macrophyllae Folium, largely used in Guangdong Province, China and one of the ingredients of CMP V, was admitted in appendix of *Guangdong Drug Standard 1987* and *Guangxi Chinese Materia Medica Standards 1990*. Due to similarity in therapy effect and shortage resources of *C. formosana*, *C. macrophylla* has been recognized as the substitute of

Table 3 CPMs containing *Zizhu* as ingredient in China

CPMs	Chinese spelling	Forms	Ingredients	Drug ID
I*	Sanqi Xueshangning Jiaonang	capsule	*Callicarpae Macrophyllae Folium*, *Notoginseng Radix* et *Rhizoma*, *Paridis Rhizoma*, *Aconiti Kusnezoffii Radix Cocta*, *Dioscoreae Rhizoma*, *Borneolum Syntheticum*, *Veratri Japonici Radix* et *Rhizoma*	Z45020612
II *	Kanggongyan Pian	tablet	*Callicarpae Caulis* et *Folium*, *Leonuri Herba*, *Linderae Radix*	Z20023099
III *	Kanggongyan Jiaonang	capsule	*Callicarpae Caulis* et *Folium*, *Leonuri Herba*, *Linderae Radix*	Z20040083 Z19990054
IV *	Zhiyanxiao Keli	granule	*Callicarpae Formosanae Folium*, *Cannabis Semen*, *Sophorae Flos*, *Lonicerae Flos*, *Sanguisorbae Radix*, *Paeoniae Radix Alba*, *Notoginseng Radix* et *Rhizoma*, *Imperatae Rhizoma*, *Artemisiae Scopariae Herba*, *Aurantii Fructus*	Z45021801 Z45020058 Z44022220 Z20027430 Z20023183
V *	Zidi Ningxue San	powder	*Callicarpae Macrophyllae Folium*, *Melastomatis Dodecandri Herba*	Z10900007
VI	Luohua Zizhu Pian	tablet	*Callicarpae Nudiflorae Folium*	Z46020088
VII	Luohua Zizhu Keli	granule	*Callicarpae Nudiflorae Caulis* et *Folium* et *Flos*	Z20060378
VIII	Luohua Zizhu Jiaonang	capsule	*Callicarpae Nudiflorae*	Z20080204 Z20063569 Z20060036 Z20050079
IX	Luohua Zizhu Fensanpian	tablet	*Callicarpae Nudiflorae*	Z20080244 Z20060086
X	Luohua Zizhu Ruanjiaonang	soft capsule	*Callicarpae Nudiflorae*	Z20080270
XI	Fuyanling Jiaonang	capsule	*Callicarpae Formosanae Folium*, *Sophorae Flavescentis Radix*, *Agrimonine Herba*, *Alumen*, *Stemonae Radix*, *Borneolum Syntheticum*, *Cnidii Fructus*, benzalkonium bromide, boric acid, camphor	Z61020453 Z51022274 Z33020435
XII	Baixian Fuyanqing Shuan	suppository	*Callicarpae Cathayanae Folium*, *Sophorae Flavescentis Radix*, *Alumen*, *Stemonae Radix*, *Cnidii Fructus*, *Agrimonine Herba*, borneolum syntheticum, boric acid, camphor	Z20026597
XIII	Zizhu Zhixue Ye	mixture	*Callicarpae Caulis et Folium*	Z52020241

* admission in *Chinese Pharmacopeia 2010*

Callicarpae Formosanae Folium.

Those regulations involved botanical resources and descriptions. However, there was no objective standard for quality control. Although *Callicarpae Nudiflorae Folium* and *Callicarpae Pedunculatae Folium* (corrected to *Callicarpae Formosanae Folium* in *Chinese Pharmacopoeia* 2010) related with *Zizhu* had been described in *Chinese Pharmacopoeia 1977*, they were removed from the successive pharmacopoeias due to inefficient research data. It is necessary to establish a national standard of *Zizhu* crude drugs to meet the requirements of drug manufacturers and pharmaceutical marketing management. Thus, *Zizhu* crude drugs have been recollected to *Chinese Pharmacopoeia 2010* in which the principle quality identification assays were offered. Although *Callicarpae Macrophyllae Folium* is similar with *Callicarpae Formosanae Folium* in therapy effects and characterristics, they are established as two separate crude drugs based on the principle of one botanical source *vs* one Chinese crude drug.

Phytochemistry

Characteristics of chemical composition

Numerous chemical constituents have been isolated or detected from the species of this genus including clerodane, phyllocradane, iridoids, sesqui-

terpenes, triterpenes, flavonoids, liganas, phenyl-propanoids/phenylethanoids, and phytosteroals (Jones and Kinghorn, 2008). The chemical compounds in the species of *Callicarpa* Linn. in China were summarized in Table 4, which indicated that this genus features included rich diterpenes, abundant multi-methoxylated flavonoids, quite abundant phenylethanoid and phenypropanoids, and calliterpenone, a phyllocradane diterpene, which was proposed to be characteristic compound in the species of this genus.

Table 4 Chemical constituents in plants of *Callicarpa* Linn.

	Compounds	Species	References
Sesquiterpenes			
	(1β,6α)-euesm-4(15)-ene-1,6-diol	*C. formosana*	Liu *et al*, 2006
	(−)-clovane-2β,9α-diol	*C. formosana*	Liu *et al*, 2006
	(9β)-caryolane-1,9-diol	*C. formosana*	Liu *et al*, 2006
Diterpenes			
phyllocradane	calliterpenone	*C. formosana*	Hu *et al*, 2001
		C. macrophylla	Singh and Agrawal, 1994
		C. kwangtungensis	Zhou *et al*, 2005
		C. nudiflora	Wang *et al*, 2007
	calliterpenone-17-acetate	*C. macrophylla*	Subramanian, Nair, and Vedantham, 1974
	16α-17-isopropylideno-3-oxo-phyllocladane	*C. macrophylla*	Singh and Agrawal, 1994
abiet	8,11,13,15-Abietetraen-18-oic acid	*C. formosana*	Hu *et al*, 2001
	pedunculatic acid A	*C. formosana*	Liu *et al*, 2006
totaran	pedunculatic acid B	*C. formosana*	Liu *et al*, 2006
	6α-dihydroxy nidorellol	*C. formosana*	Hu *et al*, 2001
isopimarane	calliphyllin	*C. formosana*	Hu *et al*, 2001
		C. macrophylla	Talapatra, Polley, and Talapatra, 1994
	14α-hydroxy-7,15-isopimaradien-18-oic acid	*C. formosana*	Hu *et al*, 2001
	isopimaric acid	*C. formosana*	Hu *et al*, 2002
clerodane	hardwickiic acid	*C. formosana*	Wang *et al*, 2010
	monomethyl kolavate	*C. formosana*	Wang *et al*, 2010
	echinophyllin	*C. formosana*	Wang *et al*, 2010
	clerodermic acid	*C. formosana*	Wang *et al*, 2010
	15,16-dihydro-15-methoxy-16-oxo-hardwickiic acid	*C. formosana*	Wang *et al*, 2010
Triterpenes			
lupane	betulinic acid	*C. formosana*	Hu *et al*, 2001
		C. macrophylla	Pan and Sun, 2006
		C. kwangtungensis	Chen *et al*, 2008
		C. bodinieri	Ren *et al*, 2001b
olean	oleanolic acid	*C. formosana*	Hu *et al*, 2001
		C. macrophylla	Ahmad, Siddiqui and Zaman, 1976
		C. kwangtungensis	Chen *et al*, 2008
		C. nudiflora	Wang *et al*, 2007
		C. cathayana	Zhou, Li, and Xu, 2005
	β-amyrin	*C. formosana*	Hu *et al*, 2001
	2α,3α,24α-trihydroxyoleana-12-en-28-oic acid	*C. bodinieri*	Ren *et al*, 2003
ursane	ursolic acid	*C. formosana*	Hu *et al*, 2001
		C. macrophylla	Pan and Sun, 2006
		C. kwangtungensis	Chen *et al*, 2008
		C. nudiflora	Wang *et al*, 2007; Dong, Liu, and Wang, 2009

(To be continued)

(Continued Table 4)

	Compounds	Species	References
		C. cathayana	Zhou, Li, and Xu, 2005
		C. bodinieri	Ren *et al*, 2001b
	α-amyrin	*C. macrophylla*	Pan and Sun, 2006
		C. bodinieri	Ren *et al*, 2001c
	2α-hydroxyursolic acid	*C. nudiflora*	Wang *et al*, 2007
	2α,3α-dihydroxyurs-12-en-28-oic acid	*C. formosana*	Chen, Lai,and Wu, 1986
		C. bodinieri	Ren *et al*, 2001a
	2α,3β-dihydroxyurs-12-en-28-oic acid	*C. bodinieri*	Ren *et al*, 2001a
	2α,3α,19α-trihydroxyurs-12-en-28-oic acid	*C. macrophylla*	Pan and Sun, 2006
		C. nudiflora	Wang *et al*, 2007
	2α,3α,19α-trihydroxyurs-12-en-28-oic acid	*C. bodinieri*	Ren *et al*, 2001a
	2α,3α,19α,24-tetrahydroxyurs-12-en-28-oic acid-28-*O*-β-*D*- glucose ester	*C. bodinieri*	Ren *et al*, 2003; 2004
	24-ethylcholesta-7,22-dien-3β-ol	*C. bodinieri*	Ren *et al*, 2003
	urs-12-en-3β-ol	*C. nudiflora*	Dong, Liu, and Wang, 2009
	arjunglucoside I	*C. nudiflora*	Gao *et al*, 2010
acyclic	2,6,14,18,22-pentamethyl-*n*-tetracos-9-en-17α-ol-27-oic acid	*C. macrophylla*	Chung *et al*, 2005
Iridoids			
	6-*O*-benzoylphlorigidoside B	*C. formosana*	Wang *et al*, 2010
	6-*O*-*trans*-cinnamoylphlorigidoside B	*C. formosana*	Wang *et al*, 2010
	6-*O*-*trans*-*p*-coumaroylshanzhiside methyl ester	*C. formosana*	Wang *et al*, 2010
	4'-*O*-*trans*-*p*-coumaroylmussaenoside	*C. formosana*	Wang *et al*, 2010
	6β-hydroxyipolamiide	*C. formosana*	Wang *et al*, 2010
	phlorigidosides	*C. formosana*	Wang *et al*, 2010
	nudifloside	*C. nudiflora*	Mei *et al*, 2009
	linearoside	*C. nudiflora*	Mei *et al*, 2009
Flavonoids			
	5-hydroxy-3,4',7-trimethoxyflavone	*C. formosana*	Hu *et al*, 2001; Chen, Lai, and Wu, 1986
	5-hydroxy-3,6,7,4'-tetramethoxyflavone	*C. bodinieri*	Ren *et al*, 2001bc
	5-hydroxy-3,3',4',7-tetramethoxyflavone	*C. formosana*	Chen, Lai, and Wu, 1986
	5-hydroxy-3,3',4,7-tetramethoxyflavone	*C. nudiflora*	Dong, Liu, and Wang, 2009
	3,5-dimethylkaemphferol (rutin)	*C. formosana*	Hu *et al*, 2001
	3,4',5,7-tetramethoxyflavone	*C. formosana*	Chen, Lai, and Wu, 1986
	3,3',4',5,7-pentamethoxyflavone	*C. formosana*	Chen, Lai, and Wu, 1986
	5,7-dihydroxy-3,3',4'-trimethoxyflavone	*C. nudiflora*	Mei *et al*, 2009
	5,7,4'-trihydroxy-3'-methoxyflavone	*C. nudiflora*	Gao *et al*, 2010
	apigenin	*C. macrophylla*	Subramanian, Nair, and Vedantham, 1974
		C. nudiflora	Gao *et al*, 2010
	apigenin-7-*O*-β-*D*-glucuronide	*C. macrophylla*	Subramanian, Nair, and Vedantham, 1974
	apigenin-7-*O*-β-*D*-glucopyranoside	*C. nudiflora*	Gao *et al*, 2010
	5,4'-dihydroxy-3,7-dimethoxyflavone (kumatakenin)	*C. macrophylla*	Talapatra, Pooley, and Talapatra, 1994
		C. kwangtungensis	Chen *et al*, 2008
	7,4'-dihydroxy-3,5-dimethoxyflavone	*C. formosana*	Hu *et al*, 2001

(To be continued)

(Continued Table 4)

	Compounds	Species	References
	5,7,3,4'-tetremethoxyflavone	*C. formosana*	Chen, Lai, and Wu, 1986
	5,4'-dihydroxy-3,7,3'-trimethoxyflavone	*C. macrophylla*	Talapatra, Polley,and Talapatra, 1994
		C. kwangtungensis	Chen *et al*, 2008
		C. nudiflora	Dong, Liu, and Wang, 2009
	5,7-dihydroxy-3'-methoxyflavone-4'-*O*-glucoside	*C. bodinieri*	Ren *et al*, 2001b
	luteolin	*C. macrophylla*	Subramanian, Nair, and Vedantham, 1974
		C. kwangtungensis	Liu, Cao, and Xing, 2006
		C. nudiflora	Dong, Liu, and Wang, 2009; Gao *et al*, 2010
	luteolin-7-*O*-β-*D*-glucuronide	*C. macrophylla*	Subramanian, Nair, and Vedantham, 1974
	luteolin-7-*O*-β-*D*-glucopyranoside	*C. nudiflora*	Dong, Liu, and Wang, 2009; Gao *et al*, 2010
	luteolin-7-*O*-(6"-*trans*-caffeoyl)-β-*D*-glucopyranoside	*C. nudiflora*	Gao *et al*, 2010
	luteolin-7-*O*-(6"-*trans*-feruloyl)-β-*D*-glucopyranoside	*C. nudiflora*	Gao *et al*, 2010
	luteolin-7-*O*-(6"-*p*-coumaryl)-β-*D*-glucopyranoside	*C. nudiflora*	Gao *et al*, 2010
	luteolin-3'-*O*-β-D-glucopyranoside	*C. nudiflora*	Wang *et al*, 2007; Gao *et al*, 2010
	luteolin-4'-*O*-β-*D*-glucopyranoside	*C. nudiflora*	Wang *et al*, 2007
		C. kwangtungensis	Liu, Cao, and Xing, 2006
		C. bodinieri	Ren *et al*, 2001b
	luteoloside	*C. kwangtungensis*	Liu, Cao, and Xing, 2006
		C. nudiflora	Wang *et al*, 2007
		C. bodinieri	Ren *et al*, 2001b
	rhamnatin (3,5,3',4'-Tetrahydroxy-7-methoxyflavone)	*C. kwangtungensis*	Chen *et al*, 2008
	ermanine (kaempferol-3,4'-dimethylether)	*C. kwangtungensis*	Chen *et al*, 2008
	velutin	*C. kwangtungensis*	Chen *et al*, 2008
	quercetin	*C. kwangtungensis*	Zhou *et al*, 2005
		C. cathayana	Zhou, Li, and Xu, 2005
	quercetin-7-*O*-α-*L*-rhamnopyanoside	*C. cathayana*	Zhou, Li, and Xu, 2005
	quercetin-3-*O*-(6"-β-L-rhamnosy)-β-*D*-glucopyranoside	*C. kwangtungensis*	Zhou *et al*, 2005
Phenylethanoids and phenylpropanoids			
	verbascoside / acteoside	*C. formosana*	Lu and Shen, 2008; Zou *et al*, 2010
		C. macrophylla	Pharmacopoeia Committee of P. R. China, 2010
		C. nudiflora	Mei *et al*, 2009
		C. bodinieri	Ren *et al*, 2004
	forsythoside B	*C. kwangtungensis*	Zhou *et al*, 2008
		C. formosana	Lu and Shen, 2008
		C. kochiana	Lin *et al*, 2010
		C. nudiflora	Gao *et al*, 2010
	poliumoside	*C. kwangtungensis*	Zhou *et al*, 2008
		C. nudiflora	Mei *et al*, 2009
		C. kochiana	Lin *et al*, 2010
	isoverbascoside	*C. formosana*	Lu and Shen, 2008
		C. kochiana	Lin *et al*, 2010
	cistanoside C	*C. kochiana*	Lin *et al*, 2010
	cistanoside D	*C. kochiana*	Lin *et al*, 2010
	lamiophlomioside A	*C. kochiana*	Lin *et al*, 2010
	isomartynoside	*C. nudiflora*	Gao *et al*, 2010
	deacylisomartynoside B	*C. nudiflora*	Gao *et al*, 2010
	arenarioside	*C. formosana*	Lu and Shen, 2008
	(+)-sesamin	*C. bodinieri*	Ren *et al*, 2004
Others			
	β-sitosterol	*C. formosana*	Hu *et al*, 2001
		C. macrophylla	Pan and Sun, 2007

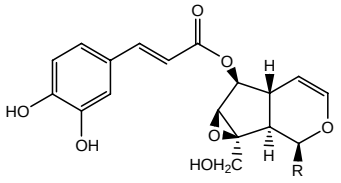
(To be continued)

(Continued Table 4)

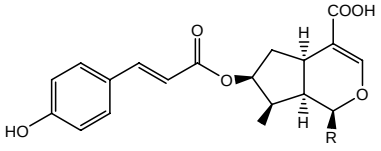
Compounds	Species	References
gallic acid (3,4,5-trihydroxybenzoic acid)	*C. kwangtungensis*	Zhou *et al*, 2005
	C. kwangtungensis	Chen *et al*, 2008
	C. nudiflora	Dong, Liu, and Wang, 2009
	C. cathayana	Zhou, Li, and Xv, 2005
	C. bodinieri	Ren *et al*, 2001b
β-sitosterol-3-*O*-β-*D*-glucoside	*C. macrophylla*	Chung, Upadhyaya, and Ahmad, 2006
myoinositol	*C. formosana*	Hu *et al*, 2001
brassinosteroids	*C. formosana*	Chen, Lai, and Wu, 1986
stigmasterol	*C. formosana*	Chen, Lai, and Wu, 1986
D-glucose	*C. formosana*	Chen, Lai, and Wu, 1986
phytosterols	*C. formosana*	Chen, Lai, and Wu, 1986
sterol glycoside	*C. formosana*	Chen, Lai, and Wu, 1990
linolenic acid	*C. formosana*	Chen, Lai, and Wu, 1990
stearic acid	*C. formosana*	Chen, Lai, and Wu, 1990
myristic acid	*C. formosana*	Chen, Lai, and Wu, 1990
octacosanoic acid	*C. formosana*	Chen, Lai, and Wu, 1990
daucosterol	*C. macrophylla*	Pan and Sun, 2007
	C. kwangtungensis	Chen *et al*, 2008
salicylic acid	*C. kwangtungensis*	Chen *et al*, 2008
syringic acid	*C. kwangtungensis*	Chen *et al*, 2008
isovanillic acid	*C. kwangtungensis*	Chen *et al*, 2008
vanillic acid	*C. nudiflora*	Dong, wang, and Liu, 2010
4-hydroxycinnamic acid	*C. nudiflora*	Dong, wang, and Liu, 2010
daffeic acid	*C. nudiflora*	Dong, wang, and Liu, 2010
ferulic acid	*C. nudiflora*	Dong, wang, and Liu, 2010
protocatechuic acid	*C. nudiflora*	Dong, wang, and Liu, 2010
protocatechuic aldehyde	*C. nudiflora*	Dong, wang, and Liu, 2010
aesculetin	*C. nudiflora*	Dong, wang, and Liu, 2010

Diterpenes

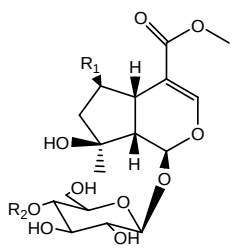
C. formosana is a species richest in terpene diversity including six new iridoids (Fig. 2), three sesquiterpenes (Fig. 3), five triterpenes (Fig. 4), one phyllocradane diterpene, two abiet diterpenes, two totaran diterpenes, three isopimarane diterpenes, and five clerodane diterpenes (Fig. 5), while fewer terpenes were detected in *C. macrophylla* (nine terpenes) and *C. kwangtungensis* (four terpenes), from which no iridoids and sesquiterpenes were isolated.



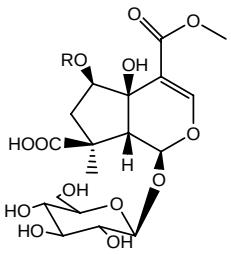
nudifloside R=*O*-β-*D*-glucose



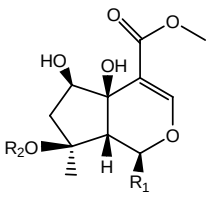
linearoside R=*O*-β-*D*-glucose



6-*O*-*trans*-*p*-coumaroylshanzhiside methyl ester
R_1=*trans*-*p*-coumaroyloxy; R_2=H
4'-*O*-*trans*-*p*-coumaroylmussaenoside
R_1=H; R_2=*trans*-*p*-coumaroyloxy

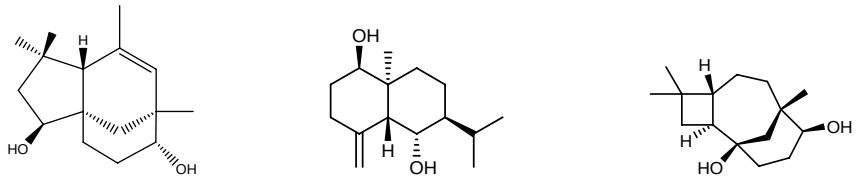


6-*O*-benzoylphlorigidoside B R=benzoyloxy
6-*O*-*trans*-cinnamoylphlorigidoside B
R=*trans*-cinnamoyloxy



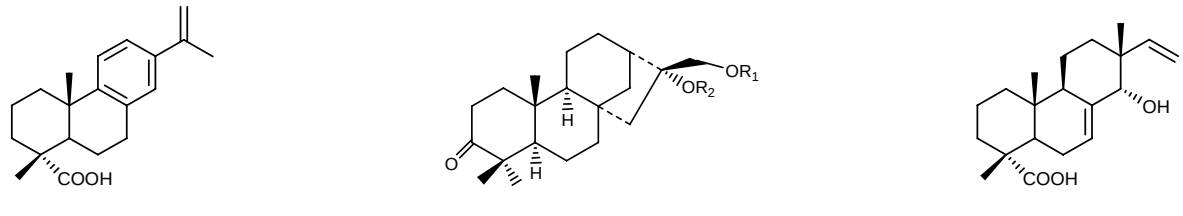
6β-hydroxyipolamiide R_1=*O*-β-*D*-glucose; R_2=H
phlorigidoside B R_1=*O*-β-*D*-glucose; R_2=CH_3COO

Fig. 2 Iridoids isolated from species of *Callicarpa* Linn.

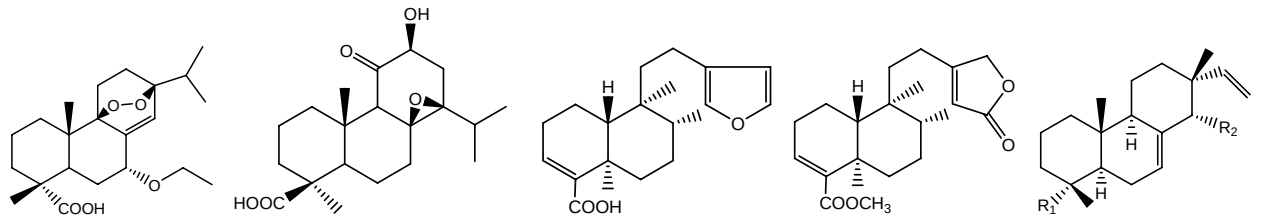


(−)-clovane-2β,9α-diol (1β,6α)-eudesm-4(15)-ene-1,6-diol (9β)-caryolane-1,9-diol

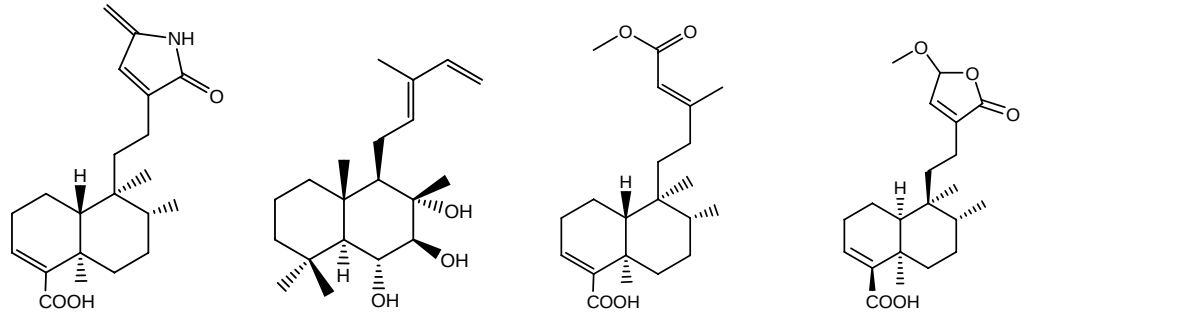
Fig. 3 Sesquiterpenes isolated from species of *Callicarpa* Linn.



8,11,13,15-abietetraen-18-oic acid 16α,17-isopropylideno-3-oxo-phyllocladane R_1=R_2=C(Me)$_2$ 14α-hydroxy-7,15-isopimaradien-18-oic acid
calliterpenone-17-acetate R_1=Ac; R_2=H
calliterpenone R_1=R_2=H



pedunculatic acid A pedunculatic acid B hardwickiic acid clerodermic acid calliphyllin R_1=COOH; R_2=OH
isopimaric acid R_1=COOH; R_2=H



echinophyllin C 6α-hydroxynidorellol monomethyl kolavate 15,16-dihydro-15-methoxy-16-oxo-hardwickiic acid

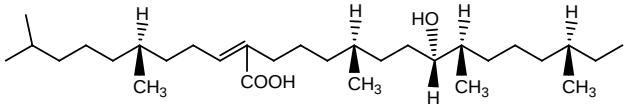
Fig. 4 Diterpenes isolated from species of *Callicarpa* Linn.

Flavonoids

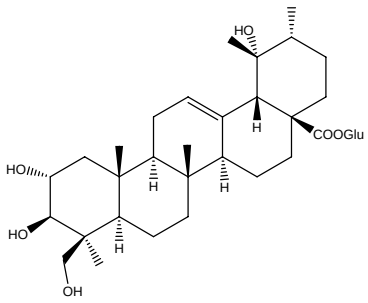
Flavonoid (Fig. 6) is one of the major types of chemical constituents in the plants of *Callicarpa* Linn., e.g., nine in *C. formosana*, six in *C. macrophylla*, and ten in *C. kwangtungensis* (Table 4). It is interesting that all of these flavonoids are flavons, flavonols, and their glycosides. Half of them are highly methoxylated derivatives mainly at C-5, C-7, and C-4' postions, which were mostly found in the plants of *Citrus* L. (Rutaceae) – a genus rich in polymethoxylated flavones (PMFS) (Zhou, Peng, and Du, 2008). However, compared with the plants of *Citrus* L., methoxylated goups are absent from C-6, C-8, C-1', C-4', and C-5' positions in the plants of *Citrus* L.

Phenylethanoids and phenypropanoids

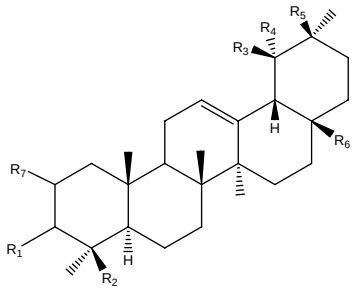
A total of 19 phenylethanoids and phenypropanoids have been isolated from the genus *Callicarpa* Linn. Most of them were isolated from *C. dichotoma* (Lour.) K. Koch, such as 2′-acetyl-verbascoside, brandioside, cistanoside H, echinacoside, forsythoside, isoverbascocide, poliumoside, *E*-tubuloside, *Z*-tubuloside, and verbascoside (Koo *et al*, 2005). Three of them, forsythoside, poliumoside, and verbascoside, were found in all three crude drugs (Table 4). Researchers have also isolated several phenylethanoids and phenypropanoids from other species of this genus.



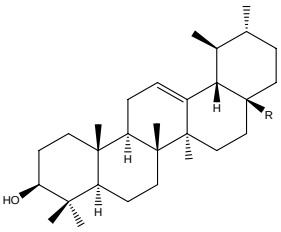
2,6,14,18,22-pentamethyl-*n*-tetracos-9-en-17α-ol-27-oic acid



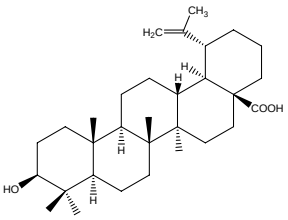
2α,3α,19α,24-tetrahydroxyurs-12-en-28-oic acid-28-*O*-β-*D*-glucose ester



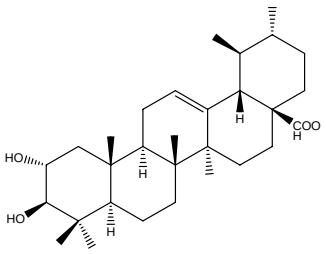
β-amyrin
R_1=β-OH; R_2= CH_3; R_3= R_4=R_5=H; R_6=CH_3; R_7=α-OH; R_7=H
oleanolic acid
R_1=β-OH; R_2= CH_3; R_3= R_4=R_5=H; R_6=COOH; R_7= H
2α,3α,24α-trihydroxyolean-12-en-28-oic acid
R_1=α-OH; R_2=CH_2OH; R_3=R_4=H; R_5=CH_3; R_6=COOH; R_7=α-OH
2α,3α,19α-trihydroxyurs-12-en-28-oic acid
R_1=α-OH; R_2=R_3=CH_3; R_4=OH; R_5=H; R_6=COOH; R_7=α-OH
2α,3α -drihydroxyurs-12-en-28-oic acid
R_1=α-OH; R_2=R_3=CH_3; R_4=R_5=H; R_6=COOH; R_7=α-OH
2α,3β-drihydroxyurs-12-en-28-oic acid
R_1=β-OH; R_2=R_3=CH_3; R_4=R_5=H; R_6=COOH; R_7=α-OH



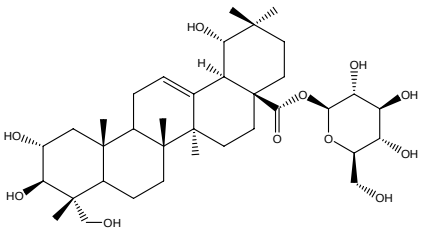
α-amyrin R=CH_3
ursolic acid R=COOH



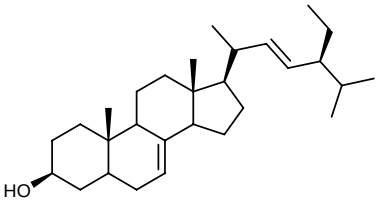
betulinic acid



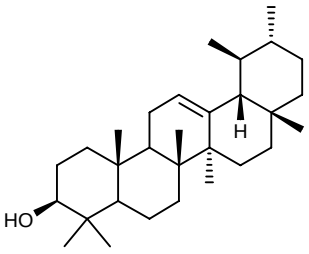
2α-hydroxyursolic acid



arjunglucoside I



24-ethylcholesta-7,22-dien-3β-ol



urs-12-en-3β-ol

Fig. 5 Triterpens isolated from species of *Callicarpa* Linn.

Those compounds isolated from plants of *Callicarpa* spp. in China were showed in Fig. 7.

Calliterpenone, a characteristic compound in the plants of *Callicarpa* Linn.

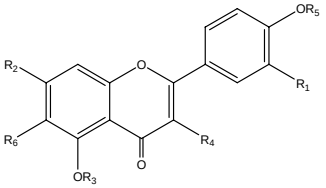
Calliterpenone (Fig. 4), a phyllocradane diterpene, was isolated from several species of this genus, such as *C*. *formosana* (Hu *et al*, 2001), *C. kwangtungensis* (Zhou *et al*, 2005), *C. macrophylla* (Singh and Agrawal, 1994), *C. nudiflora* (Nanjing College of Pharmacy, 1983), *C. americana* (Jones *et al*, 2007), *C. furfuracea* Ridl. (Shao *et al*, 2006), and *C. longifolia* Lamk. (Subramanian *et al*, 1974). However, it has not been discovered from other genera. Thus we propose that it is a characteristic compound for this genus.

Others

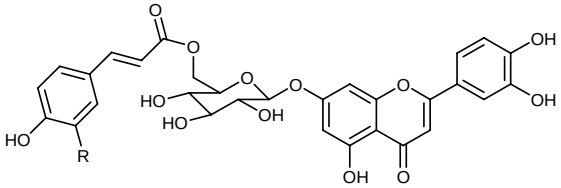
Three triterpene acids, ursolic acid, betulinic acid, and oleanolic acid, commonly spread in many genera, are shared in *C. formosana*, *C. macrophylla*, and *C. kwangtungensis* (Fig. 5). 2,6,14,18,22-Pentamethyl-*n*-tetracos-9-en-17α-ol-27-oic acid, a cyclic triterpene was isolated from *C. macrophylla* (Chung *et al*, 2005) (Fig. 5).

Compounds used for quality control in *Chinese Pharmacopeia 2010*

Of those compounds, only phenylethanoids and phenypropanoids, such as forsythoside B, poliumoside, and verbascoside (Fig. 7), have been used in quality assessment for the three crude drugs in the latest pharmacopeia, where it has been regulated that total



5-hydroxy-3,4',7-trimethoxyflavone
R_1=R_3= R_6=H; R_2=R_4=OCH_3; R_5=CH_3
5-hydroxy-3,3',4,7-tetramethoxyflavone
R_1=R_2=R_4=OCH_3; R_3=R_6=H; R_5=CH_3
5-hydroxy-3,3',4',7-tetramethoxyflavone
R_1= R_2=R_4= OCH_3; R_3=R_6=H; R_5= CH_3
3,4',5,7-tetramethoxyflavone
R_1=R_6=H; R_2=R_4=OCH_3; R_3=R_5=CH_3
3,3',4',5,7-pentamethoxyflavone
R_1=R_2=R_4=OCH_3; R_3=R_5=CH_3; R_6=H
apigenin R_1=R_3=R_4=R_5=R_6=H; R_2=OH
apigenin-7-*O*-β-*D*-glucuronide
R_1=R_3=R_4=R_5=R_6=H;
R_2=*O*-β-*D*-glucuronide
apigenin-7-*O*-β-*D*-glucopyranoside
R_1=R_3=R_4=R_5=R_6=H; R_2=*O*-β-*D*-glc
5,7-dihydroxy-3,3',4'-trimethoxyflavone
R_1= R_4=OCH_3; R_2=OH; R_3=R_6=H; R_5=CH_3
5,4'-dihydroxy-3,7-dimethoxyflavone
R_1=R_3= R_5=R_6=H; R_2=R_4=OCH_3
5,4'-dihydroxy-3,7,3'-trimethoxyflavone
R_1=R_2=R_4=OCH_3; R_3= R_5=R_6=H
5,7-dihydroxy-3'-methoxyflavone-4'-*O*-glucoside
R_1=OCH_3; R_2=OH; R_3=R_4=R_6=H; R_5=*O*-β-*D*-glc
5,7,4'-trihydroxy-3'-methoxyflavone
R_1=OCH_3; R_2= OH; R_3=R_4=R_5=R_6=H
3',5,7-trihydroxyflavone-4'-*O*-glucoside
R_1=R_2=OH; R_3=R_4=R_6=H; R_5=β-*D*-glc
luteolin R_1=R_2=OH; R_3=R_4=R_5=R_6=H
luteolin-7-*O*-β-*D*-glucuronide
R_1=OH; R_2=*O*-β-*D*-glucuronide; R_3=R_4=R_5=R_6=H
luteolin-7-*O*-β-*D*-glucopyranoside
R_1=OH; R_2=*O*-β-*D*-glc; R_3=R_4=R_5=R_6=H
luteolin-3'-*O*-β-*D*-glucopyranoside
R_1=*O*-β-*D*-glc; R_2=OH; R_3=R_4=R_5=R_6=H
luteolin-4'-*O*-β-*D*-glucopyranoside
R_1=R_2=OH; R_3=R_4=R_6=H; R_5=β-*D*-glc
rhamnatin R_1=R_4=OH; R_2=OCH_3; R_3=R_5=R_6=H
ermanine R_1=R_3=R_6=H; R_2=OH; R_4=OCH_3; R_5=CH_3
velutin R_1=CH_3; R_2=OCH_3; R_3=R_4=R_5=R_6=H
quercetin R_1=R_2=R_4=OH; R_3=R_5=R_6=H
quercetin-7-*O*-α-*L*-rhamnopyanoside
R_1=R_4=OH; R_2=*O*-α-*L*- rhamnopyanoside; R_3=R_5=R_6=H
quercetin-3-*O*-(6"-β-L-rhamnosy)-β-*D*-glucopyranoside
R_1=R_2=OH; R_3=R_5=R_6=H;
R_4=O-(6"-*O*-β-*L*-rhamnosyl)-β-*D*-glucopyranosyl
luteoloside R_1=OH; R_2=*O*-β-*D*-glc; R_3=R_4=R_5=R_6=H
5-hydroxy-3,6,7,4'-tetramethoxyflavone
R_1=R_3=H; R_2=R_4=R_6=OCH_3; R_5=CH_3
3,5-dimethylkaemphferol
R_1=R_2=OH; R_3=R_5=H; R_4=*O*-rutinose
7,4'-dihydroxy-3,5-dimethoxyflavone
R_1= R_5=R_6=H; R_2=OH; R_3=CH_3; R_4=OCH_3
5,7,3,4'-tetremethoxyflavone
R_1=R_6=H; R_2=R_4=OCH_3; R_3=R_5=CH_3



luteolin-7-*O*-(6"-*trans*-caffeoyl)-β-*D*-glucopyranoside R=OH
luteolin-7-*O*-(6"-*trans*-feruloyl)-β-*D*-glucopyranoside R=OCH_3
luteolin-7-*O*-(6"-*p*-coumaryl)-β-*D*-glucopyranoside R=H

Fig. 6 Flavonoids isolated from species of *Callicarpa* Linn.

contents of forsythoside B and poliumoside in dried *Callicarpae Caulis* et *Folium* are no less than 0.50%, verbascoside content is no less than 0.15% in dried *Callicarpae Macrophyllae Folium* and 0.50% in dried *Callicarpae Formosanae Folium*, respectively. They are proposed to be pharmacological compounds in the genus of *Callicarpa* Linn. Forsythoside B responsible for antibacteria and poliumoside responsible for anti-oxidant and antihemolysis by Nazemiyeh *et al* (2008) and He *et al* (2000) were isolated from *C. kwangtungensis* during screening hemostasis constituents (Zhou *et al*, 2008). Zhou proposed that they played roles in pharmacological bioactivities in *Callicarpae Caulis* et *Folium*. Since no quality and quantity analysis methods were available upon those compounds, Zhou *et al* (2008) developed an HPLC analysis method for determination which is authorized by the latest pharmacopeia. Verbascoside is a major component of phenolic glycosides largely accumulated in *Callicarpae Formosanae Folium* (> 9.5 mg/g) (Zou *et al*, 2010). Since verbascoside isolated from *Scrophularia ningpoensis* was reported to fight platelet aggregation in rabbits (Huang *et al*, 2004), Zou *et al* (2010) supposed that it is one of compounds contributing to haemostasis and establishing a RP-HPLC analysis method. Recently, Koo *et al* (2006) reported that verbascoside isolated from *C. dichotoma* had significant neuroprotective activity against glutamate-induced neurotoxicity in primary cultured rat cortical cells. It is obvious that verbascoside possesses various pharmacological activities, which is necessary in quality assessment of *Callicarpae Formosanae Folium*. Since *Callicarpae Macrophyllae Folium* is the substitute of *Callicarpae Formosanae Folium*, they shared the same analysis method in the latest pharmacopeia.

Other compounds proposed for quality assessment of *Zizhu* drugs

Certainly some compounds isolated from this genus or other genera have been studied in bioactivities, which are ideally suggested to be chemical assays in quality assessment for *Zizhu* drugs. Besides phenolic glycosides associated with hemostasis, it has been illustrated that some flavones and triterpene acids contribute to analgesia, and several iridoids and clerodane diterpenes show cytotoxic bioactivities as well.

A number of polymethoxylated flavones discovered in this genus showed that *Callicarpa* Linn. is one of the

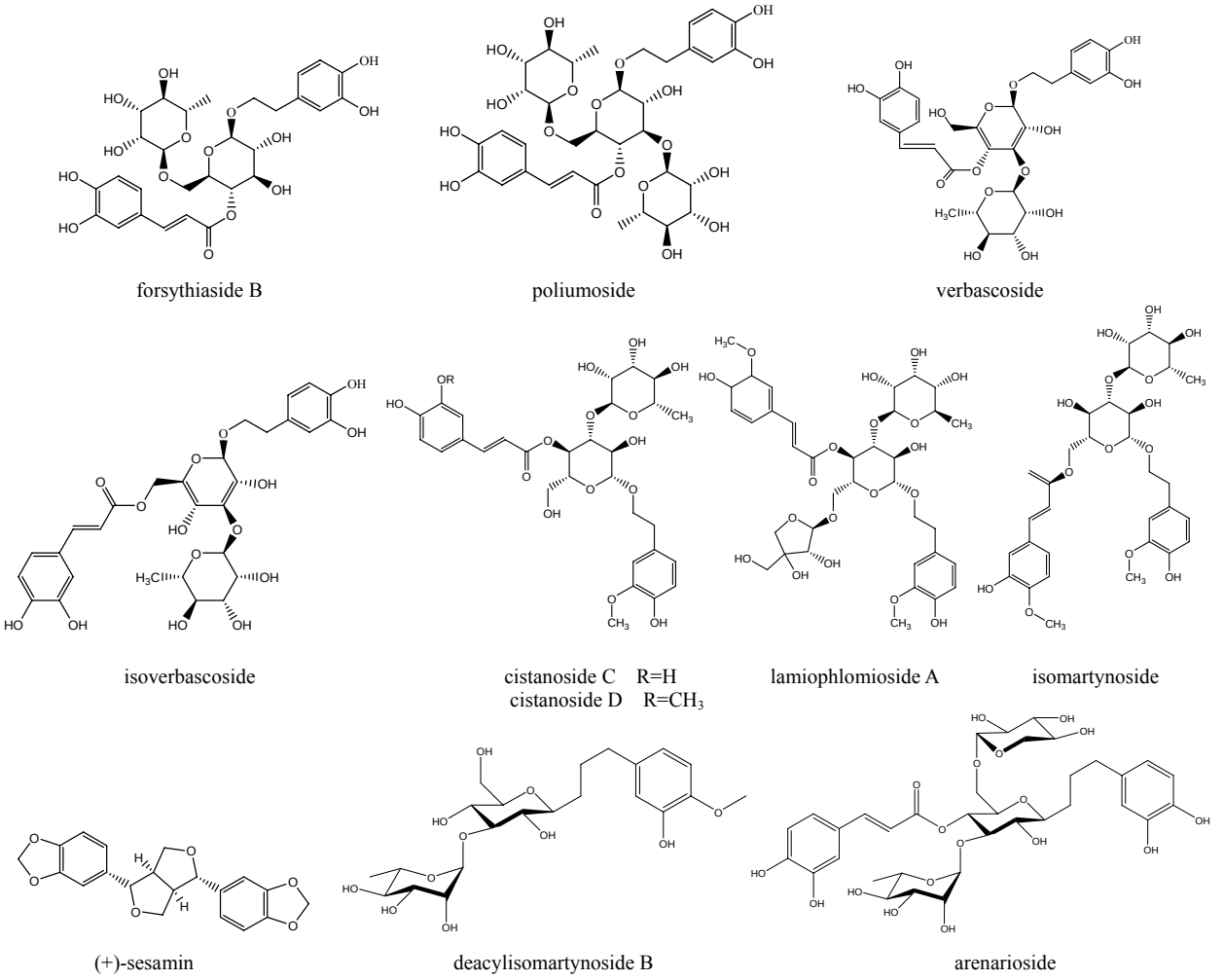


Fig. 7 Phenylethanoid and phenypropanoid isolated from species of *Callicarpa* Linn.

major genera in number of polymethoxylated flavones. There are lots of well-known flavones, such as quecitin, luteolin and their glycosides in bioactivities of antitumor, anti-inflamation, anti-oxidation, and so on. In addition, other bioactivities were found in several species. For example, 4',5,6,7-tetramethoxy-flavone from *C. japonica* Thunb and maingayic acid from *C. maingayi* King et Gamble were found piscicides (Nagai, Izawa, and Mizoguchi, 1973), and hydroxyl polymethoxylated flavones had better anti-inflamation activity than the corresponding polymethoxylated flavones (Zhou, Peng, and Du, 2008). However, a little is known in bio-activities of polymethoxylated flavones from this genus. As far, Ren *et al* (2003) reported that luteolin-4'-*O*-β-*D*-glucopyranoside and 5,7-dihydroxy-3'-methoxyflavone-4'-*O*-glucoside from *C. bodinieri* possessed analgesic effect upon mice. It is necessary to carry out studies on bioactivities of polymethoxylated flavones in this genus.

Several iridoid and clerodane diternens and an acyclic triterpene callicarpenol were found to have cytotoxic bioactivities. Nudifloside and linearoside first isolated from *C. nudiflora* showed cytotoxicity against a K562 cell line with IC_{50} values of 20.7 and 36.0 μg/mL, respectively (Mei *et al*, 2009). Jone *et al* (2007) isolated six new clerodane diternens from *C. americana* and investigated their cytotoxic bioactivities, three of which 12(*S*),16ξ-dihydroxycleroda-3,13-dien-15,16-olide, 16ξ-dihydroxycleroda-3,11(*E*),13-dien-15,16-olide, and 12(*S*),16ξ-dihydroxycleroda-3,13-dien-16,15-olide, together with two known clerodane diternens such as 16ξ-hydroxycleroda-3,13-dien-15,16-olide and 2-formyl-16ξ-hydroxy-3-*A*-norcleroda-2,13-dien-15,16-olide, were active against a panel of human cancer cell lines (ED_{50} < 5 μg/mL). The structure-activity relationship trends suggested that the γ-OH in α,β-unsaturated γ-lactone ring structure was necessary for activity, but the decalin ring system also contributed to the cytotoxic potency.

Callicarpone is a fish-killing component from *C. canadicans* (Burm. f.) Hochr. (Kawazu and Mitsui, 1966). 2,6,14,18,22-Pentamethyl-*n*-tetracos-9-en-17α-ol-27-oic acid, an acyclic triterpene callicarpenol showed cytotoxic activity against P388 murine leukemia cells with the IC_{50} value of 9 μg/mL (Chung *et al*, 2005).

Abiet, totaran, and isopimarane diterpenes from the genus *Callicarpa* Linn. have not been known in bioactivities. However, phyllocradane diterpenes, such as calliterpenone and its acetate from *C. macrophylla* were found to be novel plant growth promoters (Goel *et al*, 2007), and 2α,3α,24-trihydroxy-12-oleanene-28-oic acid from *C. bodinieri* possessed analgesic effect upon mice (Ren *et al*, 2003). Those results enriched bioactivities of the genus *Callicarpa* Linn., which might be useful in quality assessment assistant with quality and quantity analysis methods.

So, it is reasonable and possible to add luteolin-4'-*O*-β-*D*-glucopyranoside, 5,7-dihydroxy-3'-methoxyflavone-4'-*O*-glucoside, 2α,3α,24-trihydroxy-12-oleanene-28-oic acid, nudifloside and linearoside, callicarpone, 2,6,14,18,22-pentamethyl-*n*-tetracos-9-en-17α-ol-27-oic acid, and calliterpenone and its acetate as supplemental standard substances for quality control of *Zizhu* crude drugs and related products.

Pharmacology

This genus has been reviewed in pharmacological aspects including homeostasis bioactivities, analgesic bioactivity, antimicrobial, antivirus bioactivities, hepatoprotective bioactivities, and burn treatment (Zhong, Xue, and Yao, 2007; Jones and Kinghorn, 2008; Yan, Lu, and Ning, 2008; Wang, Yang, and Gao, 2008), indicated that this genus has broad bioactivities. Here we only briefly introduced bioassay of extract and juicy of the *Callicarpa* spp. based upon experimental evidences because individual compounds had been described in the previous sections and extracts of the herbs were more employed in pharmacological studies.

Antimicrobial activities

The species of *Callicarpa* Linn. had antibacterial and antivirus bioactivities. Zhou *et al* (2006) described that the 95% EtOH extract of *C. kwangtungensis* had inhibitory activities against *Staphyloccocus aureus* Rosenbach, *Salmonella typhi*, and *Diplococcus pneumonia*, while *C. formosana* and *C. cathayana* H. T. Chang showed negative effects on *Staphyloccocus aureus*, *Salmonella typhi*, *Canidia albicans*, *Salmonella typhi*, and *Shigella spp*. *C.nudiflora* Hook. ex Arn. had a wide spectrum of antibacterial such as *Staphylococcus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Shigella spp.*, and *Salmonella enterica serovar* Typhi.

In volatile oil of *C. japonica* Thunb, 1-octen-3-ol, 2-hexenal, 2,4-hexadienal,2,4-heptadienal, and epiglobulol were responsible for antimicrobial bioactivities, while 5,6,7-trimethylflavone had antivirus activities against HSV-1, human cytomegalo virus, and polionyelitis virus (Cantrell *et al*, 2005).

Homeostasis activities

Zhou *et al* (2006) reported that after oral administration of the EtOH extract of *C. kwangtungensis*, the mice suffered from tail-cutting showed a faster blood clotting than the control. Lu *et al* (1999) found that the aqueous extract of *C. formosana* led to blood clotting and platelet increasing in mice treated by tail-cutting which was a possible mechanism of the haemostasis pharmacology.

Hepatoprotective activities

Hepatoprotective bioactivities were found in aqueous or EtOH extracts of shoots or fruits of *C. cathayana* (Wang and Fang, 1994; Huang, Jiang, and Xu, 1998). It is believed that liver disease is a result of lipid peroxidation induced by free radicals, so Jiang *et al* (1999) investigated six *Callicarpa* species in anti-oxidation including *C. kochiana* Makino, *C. bodinieri*, *C. japonica*, *C. macrophrlla*, C. *cathayana*, and *C. giraldii*. They all showed inhibition of lipid peroxidation (LPO) but *C. giraldii*. The IC_{50} values of H_2O_2-induced red blood cell LPO and hemolysis and brain homogenate LPO were in the following order: the fruit of *C. bodinieri* > the shoot of *C. bodinieri* > the shoot of *C. kochiana*. Large variations in IC_{50} values indicated that other components were responsible for anti-oxidation besides flavonoids.

Remedy for scalded skin syndrome

Xu (2006) demonstrated that juicy of leaves of *C. formosana* could heal the hot water-injured skins of rats. Xie *et al* (1995) reported that aqueous extracts of *C. nudiflora* contributed to wound healing by inhibiting the growth of fibroblast and promoting the synthesis of DNA.

Discussion

Botanical resources of *Zizhu*

Since these three crude drugs are unclear in botanical resources in literatures, we listed them and corresponding botanical resources together in Table 1. The distribution chart of *Zizhu* in China is also given (Fig. 1), which can be used as a basic data for learning botanical resource and distribution.

Proposed chemical constituents for quality control

Although lots of compounds have been isolated from the genus of *Callicarpa* Linn., no bioassays were carried out for hemostasis effect. Therefore, hemostasis components are not clear in this genus. However, researchers have discovered many compounds of various bioactivities and established HPLC analysis methods, which might be helpful in quality assessment. And increasing compounds are discovered, which is the base for deep studies of bioactivities.

Chen *et al* (2008) believed that, besides forsythoside B and poliumoside, two compounds associated with bleeding, gallic acid is one of the constituents responsible for antibleeding in *C. kwangtungensis*. However, HPLC analysis method is not available yet in it. Liu *et al* (2006) established an HPLC method for the determination of luteolin in *C. kwangtungensis*, since luteolin from many plants showed antimicroorganism, anti-inflamatory, antivirus, and antitumor activities. Unfortunately, it has not any specificity either in activity or in distribution. Goel *et al* (2007) and Singh *et al* (2004) discovered that phyllocladdane diterpenes calliterpenone and its acetate, novel plant growth promoters like brassinosteroids, aurines, cytokinins, gibberellins and abscisic acid and antagonists in the growth retardant effect of allelo-chemicals were largely accumulated in *C. macrophylla*. Rapid analytical methods for the two compounds have been established based upon HPLC and HPTLC (Verma *et al*, 2009). Pan *et al* (2008) established a RP-HPLC method for analyzing content of betulinic acid in twigs of *Callicarpae Macrophyllae Folium*, responsible for analgesia, anti-HIV, and anticancer activities. Several HPLC methods were established in quality control of *Callicarpae Nudiflorae Folium*. Since luteolin and its glycosides are abundant in this crude drug, Hu *et al* (2009) developed an HPLC analysis method for luteolin. Zhang *et al* (2009) established a method for quality control of oleanolic acid and ursolic acid in *C. nudiflora* due to their abilities of anti-microbial and anti-inflamation and protecting liver. Those studies might be candidate assays for quality control in updating *National Pharmacopeia*.

Medicinal plants and CPMs

Only seven of 19 medicinal species, *C. kwangtungensis*, *C. macrophylla*, *C. formosana*, *C. nudiflora*, *C. cathayana*, *C. kochiana*, and *C. bodinieri*, were investigated in bioactivities based upon crude extract bioassay as well as in phytochemisty, which basically provided candidate admissions. However, insufficient research data upon them were collected for the *Chinese Pharmacopeia* and so left a large space for further studies upon the other species.

There are several other crude drugs of *Zizhu* used as CPMs ingredient, excluded from the latest pharmacopeia, in Chinese pharmaceutical market, e.g., CPMs VI−XII containing *Callicarpae Nudiflorae Folium* or *Callicarpae Cathayanae Folium*. They are widely used in clinical practices, and intensively studies have been carried out in chemical constituents and pharmacology.

CPMs VI−X are quite popular medicines for fighting inflammation and hemorrhage from respiratory and digestive tracts. Recently, *Callicarpae Nudiflorae Folium*, the major ingredient of those CPMs was studied in chemical constituents (Wang *et al*, 2007; Dong, Liu, and Wang, 2009; Dong, Wang, and Liu, 2010; Gao *et al*, 2010; Mei *et al*, 2009), and its bioactive compounds had been determined by HPLC analysis (Zhang, Hong, and Liu, 2009). CPM VI containing *Callicarpae Nudiflorae Folium* as major ingredient has been found to show good efficacy in clinical practice (Xi, Gao, and Niu, 2010; Yang, Zhou, and Bai, 2010; Su *et al*, 2009), which is valuable for updating *National Pharmacopeia*.

Conclusion

Callicarpa Linn. is one of the major genera in the Verbenaceaeous family. About 20 species are medicinal herbs often used in homeostasis. In China, intensive studies have been carried out in *C. kwangtungensis*, *C. macrophylla*, *C. formosana*, and *C. nudiflroa* which are popularly used in China. The first three, therefore, have been admitted in *Chinese Pharmacopeia 2010*.

Obviously, *Callicarpa* Linn. species resource is rich in China, many of which has not yet been well known in pharmacology and phytochemistry. In addition, compounds isolated should be proved bioactivities by bioassays. Fortunately researchers are providing more findings in this genus, which is helpful for the improvement of national regulations in quality control of Chinese herbs.

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