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•Review•

Non-volatile constituents and pharmacology of *Chimonanthus*: A review

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[ABSTRACT] *Chimonanthus* plants widely distributed in southern area of China, which have a long history of edibles and medicine. Phytochemical investigations have shown that *Chimonanthus* produced 143 non-volatile constituents, including alkaloids, flavonoids, terpenoids, coumarins and others, which exhibit significant anti-oxidant, anti-bacterial, anti-cancer, anti-inflammatory, antihyperglycemic, antihyperlipidemic and other biological activities. On the basis of systematic reviewing of literatures, this article overviews the non-volatile constituents and pharmacology of *Chimonanthus* from domestic and foreign over the last 30 years (until June 2018), and may provide a useful reference for the further development of *Chimonanthus.*

[KEY WORDS] *Chimonanthus*; Non-volatile constituents; Pharmacology; Review

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Introduction

The genus *Chimonanthus*, a popular garden and ornamental plant, is a member of the family Calycanthaceae endemic to China, which has survived since the tertiary relic period [1]. According to the Flora of China, the genus comprises only six species, *C. praecox*, *C. nitens*, *C. salicifolius*, *C. zhejiangensis*, *C. grammatus* and *C. campanulatus* [2].

Phytochemical studies reveal that *Chimonanthus* contains abundant secondary metabolites, such as alkaloids, flavonoids, coumarins, terpenoids, essential oils and other ingredients. Its roots, leaves, flowers, fruits are popularly applied as folk medicines for treatment of influenza, fever, headache, sore throat, cough relieving, sputum reducing, asthma, epigastric fullness, gastric distention, stomachache, gastric acid, diarrhea, urethritis, traumatic injury, hand-foot-and-mouth disease, rheumatic arthritis etc. Modern pharmacological studies have shown that plants of *Chimonanthus* have anti-bacterial, anti-oxidant, anti-inflammatory, anti-cancer, antihyperglycemic, antihyperlipidemic effects [3-9]. Further more, some species of *Chimonanthus* have been processed into beverages and preparations, like Golden Tea, Xiang-Feng Tea, Shi-Liang Tea, Shanlameiye Granule, Tiekuaizi, Fufangxianlingfengshijiu, Malanganhan Capsule, Piweishu, Huatuo bill ointmentetc.

Methods

All relevant databases were searched for the key words "*Chimonanthus*", the names of its proper constituents include "calycanthine" and "chimonanthine", or the aliases of *Chimonanthus* plants like "Tiekuaizi", "Shiliang Tea", and "Wintersweet". By searching through the foreign language databases like PubMed and SpringerLink, Chinese databases like Blyun and Cintmed, more than 300 Chinese and English articles are selected in total and about 80 literatures are cited in this paper. As there are related literatures [10-11] that have overviewed the studies of *Chimonanthus* volatile oil in detail, this paper would not go into. Instead, in this paper, we aim to highlight non-volatile constituents and pharmacological effects of *Chimonanthus* and to point out several aspects, which should be attended in future research.

Non-volatile constituents

Nowadays the studies of *Chimonanthus* non-volatile constituents are more concentrated on *C. praecox*, *C. nitens*,

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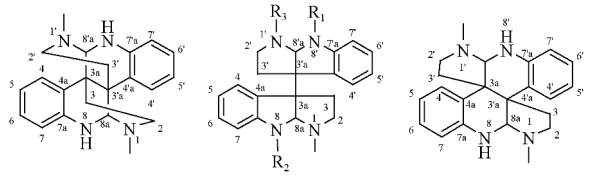
and *C. salicifolius*, only a few literatures reported the studies of *C. grammatus* and *C. zhejiangensis*, and no research about *C. campanulatus* has been found. To date, 143 non-volatile components have been separated and identified from *Chimonanthus*, including 20 alkaloids, 16 flavonoids, 25 coumarins, 39 terpenoids (containing 8 nor-sesquiterpenoids), 6 steroids, 20 organic acids, 17 glycosides and others.

Alkaloids

(+)-Calycanthine (**1**), with a dimeric piperidinoquinoline skeleton, was the first Calycanthaceae alkaloid isolated from the seeds of *C. glaucus* Willd. [12]. With further investigation on *Chimonanthus* alkaloids, researchers have isolated 20 alkaloids (**1**–**20**) from the genus, and they were most distributed in *C. praecox* (especially in seeds), followed by *C. salicifolius* and *C. nitens*.

A number of studies have reported the alkaloids exist in different parts of *C. praecox*. Up to now, more than 15 alkaloids have been founded in *C. praecox*. Yang investigated the alkaloids from the leaves of *C. praecox* anddetermined that the main alkaloid was Chimonanthine, account for 85% [13]. Takayama *et al.* isolated six alkaloids from the seeds of *C. praecox* (**1, 4**–**7, 17**), including two new alkaloids (**7**, **17**), and their absolute configuration were established by biomimetic total synthesis. As a result, the optical rotation of natural chimonamidine (**17**) showed ($[\alpha]_{19}^{D}$ −12.6 (*c* 0.06, EtOH), which was significantly different with (*R*)-(−)-chimonamidine ($[\alpha]_{23}^{D}$ −177.8, *c* 0.17, EtOH) and the enantiomeric (*S*)-(+)-chimonamidine (($[\alpha]_{23}^{D}$ +170.7, *c* 0.18, EtOH)), suggesting that natural chimonamidine was a mixture slightly enriched with the (*R*)-(−)-enantiomer [14]. In 2006, a new pyrrolidinoindoline-type alkaloid, CPC-1 (**18**), and a new tryptamine-derived dimeric alkaloid, CPC-2 (**9**), together with eight known alkaloids (**1**, **3**–**7**, **15**, **16**) were isolated from the seeds and rinds of *C. praecox*. The absolute configuration of CPC-1 was determined by chiral total synthesis [3]. Later, Wang's group obtained four dimeric alkaloids (**1**, **4**–**6**) and one indole glucoside (**14**) from the fruits of *C. praecox* f. concolor [4]. Meanwhile, Morikawa *et al.* found five alkaloids (**1**, **3**–**6**) from flower buds [15]. From seeds of *C. praecox var. concolor*, seven alkaloids (**1**, **4**–**6, 16**, **17**, **20**) were isolated, among which compound **20** is a new alkaloid [16-17]. In 2015, Ma's group investigated five indoline-type (**3**–**5**, **11**, **12**) from the leaves of *C. salicifolius,* including three quinoline-type (**1**, **8**, **10**) dimeric tryptamine-derived alkaloids and two new alkaloids (**11**, **12**) [18]. While the L-isomer of calycanthine (**2**) and berberine (**13**) were only isolated from the leaves of *C. nitens* [19].

Dimeric piperidinoquinoline-type or calycanthine-type (**1**, **2**), and dimeric pyrrolidinoindoline-type or chimonanthine-type (**3**–**7**) were two alkaloids series of *Chimonanthus,* which have been well-reported. While the members of **8**, **9**, whose skeleton are different from these two known types, could be another poentical *Chimonanthus* alkaloids series, namely pyrrolidinoquinoline-type or iso-calycanthine-type. These skeletons both contain the structure of Ph-N-CH-N, which is the simple structure segment of Calycanthaceae alkaloids (see Fig. 1). The same potential biogenetic pathway from *N*-methyltrylptamine of these alkaloids may explain the phenomenon.



piperidinoquinoline-type pyrrolidinoindoline-type pyrrolidinoquinoline-type

Fig. 1 Skeletons of alkaloid from *Chimonanthus*

By analyzing the 20 alkaloids isolated from *Chimonanthus* (see Fig. 2), we can find that the skeletons of these alkaloids have a high similarity and always contain four chiral centers. For example, the compounds **1**–**4**, **8** and **9** are identical in chemical structural formula $C_{22}H_{26}N_4$ but different in stereostructure and optical rotation or malting point performance. Unlike (+)-calycanthine (**1**) and (−)-calycanthine (**2**) enantiomers as well as (−)-iso-calycanthine (**8**) and CPC-2 (**9**), meso-chimonanthine (**3**) and (−)-chimonanthine (**4**), salicifoxazine A (**11**) and salicifoxazine B (**12**) are two groups diastereoisomers at C-3a/C-8a or at C-3a'/C-8a'. Each isomer group has the same skeleton and almost identical in ^{1}H NMR, ^{13}C NMR, and UV spectroscopic data. But the values of optical rotation and malting points or the ion abundances of them show a significant difference (see Table 1), which provided a powerful evidence for structural identification of *Chimonanthus* alkaloids. Since the yield of these novel and bio-active alkaloids is low, the synthesis of these interesting constituents has been a hot topic of interest during the past decades.

Flavonoids

Chemical investigations in *Chimonanthus* revealed that this plant has high content of flavonoids. Quercetin and kaempferol glucosides are two major groups exist in *Chimonanthus*. Some flavonoids (see Fig. 3), such as kaempferol, quercetin, rutin and astragalin are common ingredients for many species. In addition, flavonoids have been considered as standard for the quality control of products of *Chimonanthus* plants, and the content of quercetin and kaempferol are the target flavonoids to be tested. Liu has used four common flavonoids (**21**, **22**, **24**, **27**) as standard substances to establish the HPLC fingerprints of the five *Chimonanthus* species, and find that the contents of them have significant difference. In addition, the harvest time may affect the contents and should be taken into attention for utilization of the chemical compositions of *Chimonanthus* leaves [26].

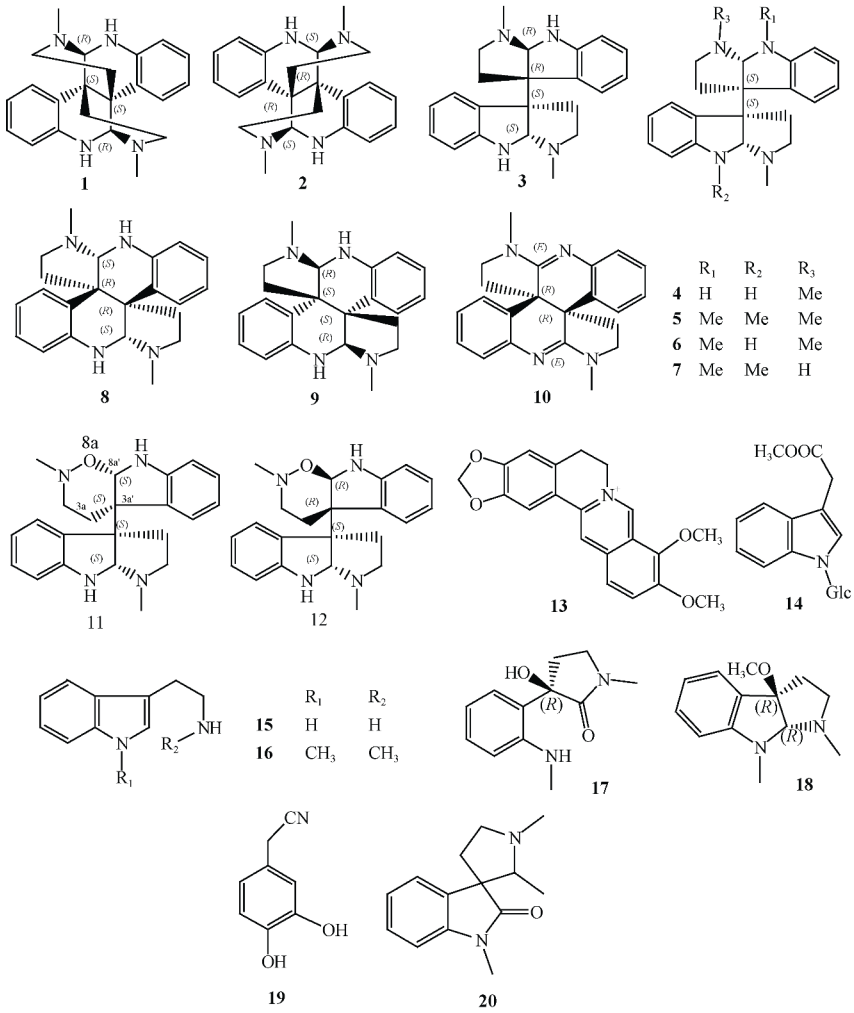


Fig. 2 Structures of alkaloids from *Chimonanthus*

Table 1 Alkaloids from *Chimonanthus*

No.	Name	Formula	Mass	Optical rotation and mp	Origin	Organ
1	(+)-calycanthine	$C_{22}H_{26}N_4$	346	$[\alpha]_{20}^{D}$ +363 (*c* 0.74, MeOH) mp 226–229 °C [7]	*C. nitens* [20-22]	leaf, root
					C. salicifolius [18]	leaf
					C. praecox [3-4, 14-15, 23]	B
					A [16]	seed
2	(−)-calycanthine	$C_{22}H_{26}N_4$	346	$[\alpha]_{20}^{D}$ −489 (*c* 9.0, EtOH) mp 245 °C [25]	*C. nitens* [19]	leaf
3	*meso*-chimonanthine	$C_{22}H_{26}N_4$	346	$[\alpha]_{20}^{D}$ 0 (*c* 1.0, EtOH) mp 176 °C [25]	*C. salicifolius* [18]	leaf
					C. praecox [3, 15]	C
4	(−)-chimonanthine	$C_{22}H_{26}N_4$	346	mp 187–189 °C [20]	*C. nitens* [20]	leaf
					C. salicifolius [18] *C. grammatus* [24]	leaf
					C. praecox [3-4, 14-15, 23]	B
					A [16]	seed
5	(−)-folicanthine	$C_{24}H_{30}N_4$	374	$[\alpha]_{20}^{D}$ −331 (*c* 1.2, EtOH) mp 118–120 °C [7]	*C. salicifolius* [18]	leaf
					C. praecox [3-4, 14-15, 23]	B
					A [16]	seed

Continued

No.	Name	Formula	Mass	Optical rotation and mp	Origin	Organ
6	(−)-calycanthidine	$C_{23}H_{28}N_4$	360	unknow	*C. praecox* [3-4, 14-15]	D
					A [14, 16]	seed
7	(−)-chimonanthidine	$C_{23}H_{28}N_4$	360	$[\alpha]_{20}^{D}$ −285 (*c* 0.05, EtOH) [14]	*C. praecox* [3, 14]	seed, rind
8	(−)-*iso*-calycanthine	$C_{22}H_{26}N_4$	346	$[\alpha]_{20}^{D}$ −150 (*c* 2.5, EtOH) mp 253 °C [25]	*C. salicifolius* [18]	leaf
9	CPC-2	$C_{22}H_{26}N_4$	346	$[\alpha]_{26}^{D}$ +57 (*c* 0.04, EtOH) [3]	*C. praecox* [3]	seed, rind
10	(3aR, 3'aR, 8-8a, 8'-8'a)-tetradehydroisocalycanthine	$C_{22}H_{22}N_4$	342	$[\alpha]_{20}^{D}$ −449° (*c* 1.0, EtOH) mp 253 °C [21]	*C. salicifolius* [18]	leaf
11	salicifoxazine A	$C_{22}H_{26}N_4O$	362	$[\alpha]_{20}^{D}$ −243.9 (*c* 0.37, MeOH) [18]	*C. salicifolius* [18]	leaf
12	salicifoxazine B	$C_{22}H_{26}N_4O$	362	$[\alpha]_{20}^{D}$ −2.2 (*c* 0.32, MeOH) [18]	*C. salicifolius* [18]	leaf
13	berberine	$C_{20}H_{18}NO_4$	336	/	*C. nitens* [19, 21]	leaf
14	3-methylcarboxymethyl-indole-1-N-*β*-D-glucopyranoside	$C_{17}H_{21}NO_7$	351	$[\alpha]_{20}^{D}$ −12.0 (*c* 0.30, MeOH) [4]	*C. praecox* [4]	fruit
15	tryptamine	$C_{10}H_{12}N_2$	160	/	*C. praecox* [3]	seed, rind
16	Na, Nb-dimethyltryptamine (N_1, N_{10}-dimethyltryptamine)	$C_{12}H_{16}N_2$	188	/	*C. praecox* [3]	seed, rind
					A [17]	seed
17	Chimonamidine	$C_{12}H_{16}N_2O_2$	220	$[\alpha]_{19}^{D}$ −12.6 (*c* 0.06, EtOH) [14]	*C. praecox* [14], A [16]	seed
18	CPC-1	$C_{13}H_{18}N_2O$	218	$[\alpha]_{26}^{D}$ −88 (*c* 0.10, MeOH) [3]	*C. praecox* [3]	seed, rind
19	3, 4-dihydroxybenzonitrile	$C_8H_7NO_2$	149	/	*C. praecox* [23]	leaf, branch
20	chimonanthconin	$C_{14}H_{18}ON_2$	230	/	A [17]	seed

Note: A: *C. praecox* var. concolor; B: seed, fruit, branch, leaf, rind, flower bud; C: flower bud, seed, rind; D: flower bud, seed, rind, fruit, leaf

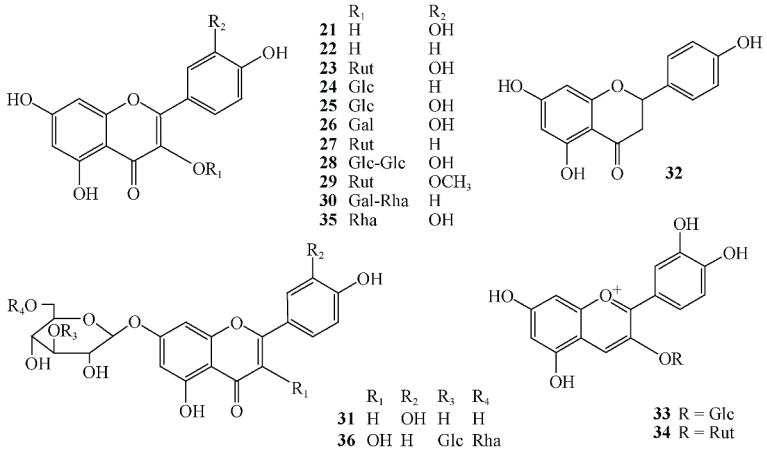


Fig. 3 Structures of flavonoids from *Chimonanthus*

In 2017, a latest study by using GC-MS identified 12 constituents and 8 ingredients (**21**–**26**, **31**, **32**) and they were confirmed by authentic standard from 50% ethanol extracts of *C. nitens* [5]. Another study from the preparation of *C. nitens* leaves also identified four flavonoid glucosides (**23**, **24**, **27**, **30**) [27]. In 2016, a study with high resolution and rapid separation by using UHPLC–QTOF–MS/MS identified 24 flavonoids from *C. praecox* flowers, among which five compounds (**21**–**23**, **26**, **35**) were identified by compared with standard substances [28]. Zhang *et al.* analyzed the main components of 5 species flowers by using HPLC-DAD-ESI/MS analysis, and the results showed that compounds (**21**–**25**, **27**) are six common flavonoids of them [29]. In addition, a new kaempferol triglycoside (**36**) was isolated from the preparation "Shiliang Tea" (*C. salicifolius* leaves) [30].

To date, 16 flavonoids (**21**–**36**) were isolated, and all of them were obtained from the organs of leaves and flowers. Therefore, the leaf and flower could be a better source for isolating flavonoids compared to the others (see Table 2).

Table 2 Flavonoids from *Chimonanthus*

No.	Name	Formula	Mass	Origin	Organ
21	quercetin	$C_{15}H_{10}O_7$	302	A–E [26, 29]	flower, leaf
22	kaempferol	$C_{15}H_{10}O_6$	286	A–E [26, 29]	flower, leaf
23	rutin	$C_{27}H_{30}O_{16}$	610	*C. nitens* [5, 29]	flower; leaf
				A–B, D–E [29]	flower
24	kaempferol-3-*O*-*β*-D-glucoside (astragalin)	$C_{21}H_{20}O_{11}$	448	A–E [26, 29]	leaf, flower
25	isoquercitrin	$C_{21}H_{20}O_{12}$	464	*C. nitens* [5, 29]	flower, leaf
				A–B, D–E [29]	flower
26	hyperin (hyperoside)	$C_{21}H_{20}O_{12}$	464	*C. nitens* [5]	leaf
				C. praecox [28]	flower
27	kaempferol-3-*O*-*β*-D-rutinoside (nicotiflorin)	$C_{27}H_{30}O_{15}$	594	A–E [26, 29]	flower, leaf
28	meratin	$C_{27}H_{30}O_{17}$	626	*C. praecox* [32]	flower
29	isorhamnetin-3-*O*-*β*-D-rutinoside	$C_{28}H_{32}O_{16}$	624	*C. praecox* [15]	flower bud
30	kaempferol-3-*O*-*β*-D-galactose-(6→1)-*α*-L-rhamnoside	$C_{27}H_{30}O_{15}$	594	*C. nitens* [27]	leaf
31	luteoloside	$C_{21}H_{20}O_{11}$	448	*C. nitens* [5]	leaf
32	naringenin	$C_{15}H_{12}O_5$	272	*C. nitens* [5]	leaf
33	cyanidin-3-*O*-*β*-D-glucoside	$C_{21}H_{21}O_{11}^+$	449	*C. praecox* [30]	flower
34	cyanidin-3-*O*-*β*-D-rutinoside	$C_{27}H_{31}O_{15}^+$	595	*C. praecox* [30]	flower
35	quercitrin	$C_{21}H_{20}O_{11}$	448	*C. praecox* [28]	flower
36	kaempferol-7-*O*- *α*-L-rhamnopyranosyl-(1→6)-[*β*-D-glucopyranosyl-(1→3)]-*β*-D-glucopyranoside	$C_{33}H_{40}O_{20}$	756	*C. salicifolius* [31]	leaf

Note: A: *C. praecox*; B: *C. salicifolius*; C: *C. nitens*; D: *C. zhejiangensis*; E: *C. grammatus*

Coumarins

Simple coumarins and coumarin glycosides are mainly constituents in early investigation of *Chimonanthus*, and most of them are 7-OH coumarins (see Fig. 4). In recent years, researchers found a kind of coumarin that substituted in C-3 position of the *α*-pyrone ring. It can be connected by C-C bond directly or via an oxygen atom consist into dimeric or trimeric coumarins, and the connective position always is C_3–$C_{7'}$.

In 2013, Li *et al.* isolated seven coumarins (**38**, **43**, **47**–**51**) from the roots of *C. nitens*, with two new coumarins (**50**, **51**) [22]. In 2016, eight coumarins (**38**–**41**, **52**, **54**–**56**) were investigated from the aerial parts of *C. salicifolius*, including two dimeric coumarins (**55**, **56**) and two coumarinlignan compounds (**52**, **54**) [33]. In the meantime, Wang's group systematically investigated the coumarins of *C. salicifolius* aerial parts, as a result three new compounds (**58**–**60**) and nine known coumarins (**38**–**41**, **52**–**55**, **57**) were obtained and identified. Of them, two C-C connection dimeric coumarins (**55**, **59**), a trimer of coumarin (**60**), and three coumarinlignan coumarins (**52**–**54**) were reported from *Calycanthaceae* for the first time [6]. In 2017, a method based on the modified mass defect filter was firstly developed and validated for comprehensive profiling of coumarins in the different parts of *C. nitens* via UPLC-QTOF/MS. As a result, a total of 42 coumarins, including 27 potential new ones were unambiguously or tentatively identified, which could provide useful information for future utilization of *C. nitens* [34]. Later on, a study on *C. nitens* leaves isolated a 4, 4' position connected dimeric coumarin (**61**) from this genus for the first time [40]. Most of the coumarins were obtained from the aerial parts of *Chimonanthus* (see Table 3).

Terpenoids

To date, 39 terpenoids (**62**–**100**) have been reported in *Chimonanthus* (see Fig. 5). Most of them are bicyclic sesquiterpenoid oxygenated derivatives. Eudesmane-type, clemane-type, oploanane-type, cadinane-type, megastigmane are main types.

Recent studies on *C. praecox* have shown that terpenoids are the most abundant ingredients of these plants. In 2010, Zhang's group identified seven terpenoids from *Radix Chimonanthi pracecocis* (Tiekuaizi in chinese), including two new sesquiterpenoids (**62**, **63**), two megastigmanes (**68**, **69**), and four known sesquiterpenoids (**64**–**67**). But the absolute configuration of the compounds **62**–**65** hasn't been determined yet [35]. Later in 2011, five sesquiterpenoids (**70**–**74**) were isolated from the fruits of *C. praecox,* whereas three sesquiterpenoids (**75**–**77**) and two megastigmane glucosides (**78**, **79**) were isolated from the leaves of *C. praecox* [4]. Another study on the flower buds of *C. praecox* founded 4 sesquiterpenoids (**86**–**89**) as well [15]. In 2013, Zhang *et al.* identified six megastigmanes (**80**–**85**) from the $CHCl_3$ extracts of *C. salicifolius* leaves. Theywere for the first time founded from *Calycanthaceae* family, and the compound **80** was a new natural product [41]. In 2016, two new sesquiterpenoids (**90**, **91**)

and one known sesquiterpenoid (**92**) were obtained from the aerial parts of *C. salicifolius* [33]. In previous studies, the terpenoids of *Chimonanthus* were mainly obtained from *C. praecox* and *C. salicifolius*. In two studies published in 2017, however, Zhang [39] and Huang [40] *et al.* isolated seven terpenoids (**85**, **90**, **91**, **97**–**100**) from *C. nitens* leaves for the first time, while compound **99** and **100** are 1 : 1 mixture of two diastereomers.

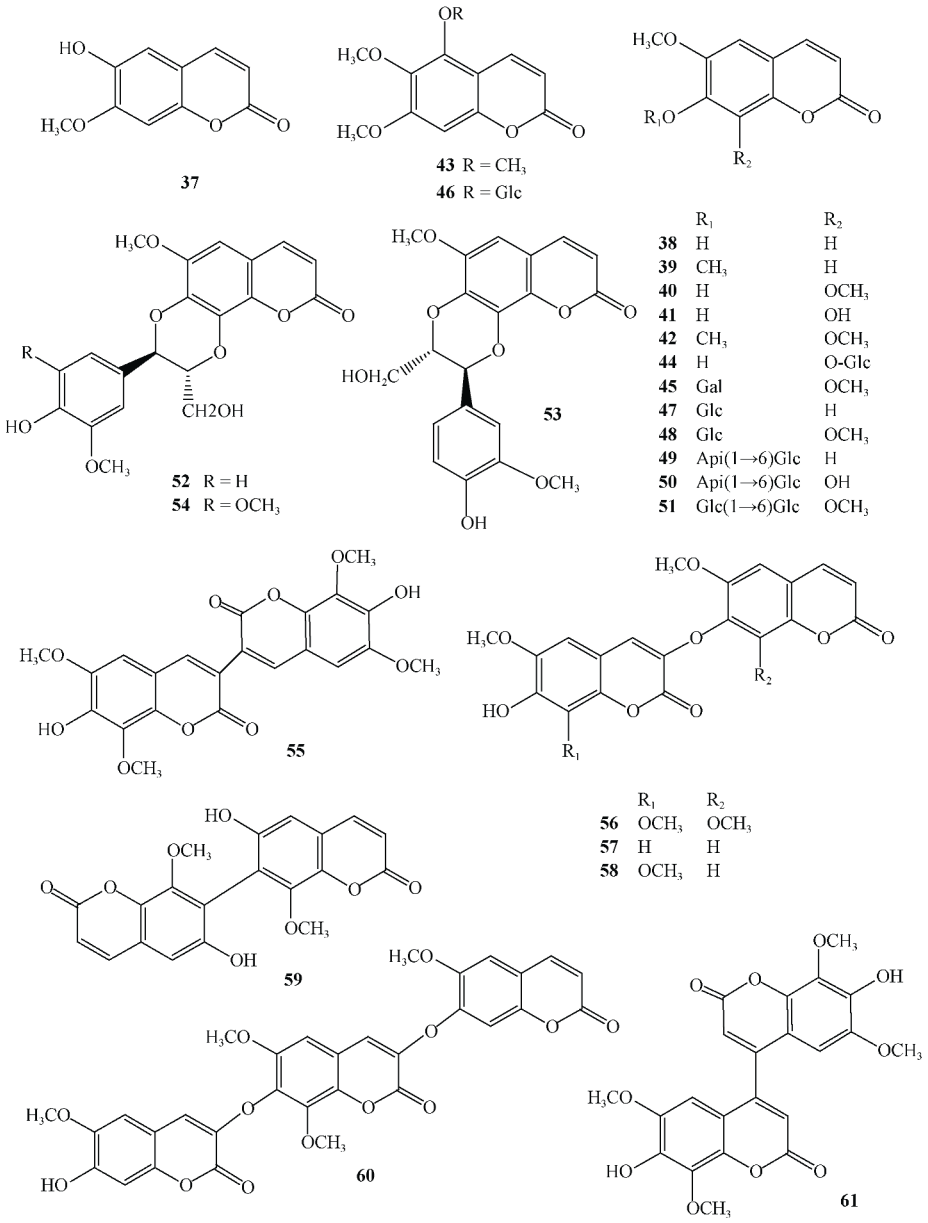


Fig. 4 Structures of coumarins from *Chimonanthus*

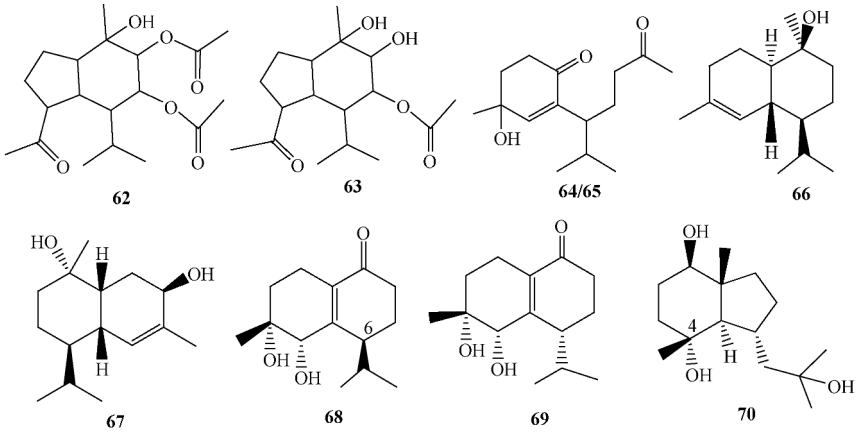
Table 3 Coumarins from *Chimonanthus*

No.	Name	Formula	Mass	Origin	Organ
37	*iso*-scopoletin	$C_{10}H_8O_4$	192	*C. nitens* [19]	leaf
38	scopoletin	$C_{10}H_8O_4$	192	*C. praecox* [15, 35-38]	A
				C. praecox Var. concolor [17]	seed
				C. salicifolius [6, 33]	aerial parts
				C. grammatus [24, 29]	flower, leaf
				C. nitens [20-22, 29]	flower, leaf, root
				C. zhejiangensis [29]	flower

Continued

No.	Name	Formula	Mass	Origin	Organ
39	6, 7-dimethoxycoumarin (scoparone)	$C_{11}H_{10}O_4$	206	*C. salicifolius* [6, 33]	aerial parts
				C. praecox [35-37]	root, stem, leaf
				C. nitens [19-20]	leaf
40	isofraxidin	$C_{11}H_{10}O_5$	222	*C. praecox* [15, 35-36]	flower bud, root, stem
				C. salicifolius [6, 33]	aerial parts
				C. nitens [21]	leaf
41	fraxetin	$C_{10}H_8O_5$	208	*C. salicifolius* [6, 33]	aerial parts
42	6, 7, 8-trimethoxycoumarin	$C_{12}H_{12}O_5$	236	*C. praecox* [35-36]	root, stem
				C. salicifolius [41]	leaf
				C. nitens [39-40]	leaf
43	5, 6, 7-trimethoxycoumarin	$C_{12}H_{12}O_5$	236	*C. nitens* [22]	root
44	fraxin	$C_{16}H_{18}O_{10}$	370	*C. praecox* [32]	flower
45	euoniside	$C_{17}H_{20}O_{10}$	384	*C. praecox* [23]	leaf, branch
46	tomenin	$C_{17}H_{20}O_{10}$	384	*C. praecox* [36]	root, stem
47	scopoletin-7-*O*-*β*-D-glucoside (scopolin)	$C_{16}H_{18}O_9$	354	*C. praecox* [26, 29, 38], *C. nitens* [22, 26, 29]	root, flower, leaf
				B [26, 29]	flower, leaf
48	Calycanthoside (isofraxidin-7-*O*-*β*-D-glucoside)	$C_{17}H_{20}O_{10}$	384	*C. praecox* [35]	root, stem
				C. nitens [22]	root
49	xeroboside	$C_{21}H_{26}O_{13}$	486	*C. nitens* [22]	root
50	nitensoside A	$C_{21}H_{26}O_{14}$	502	*C. nitens* [22]	root
51	nitensoside B	$C_{23}H_{30}O_{15}$	546	*C. nitens* [22]	root
52	cleomiscosin A	$C_{20}H_{18}O_8$	386	*C. salicifolius* [6, 33]	aerial parts
53	cleomiscosin B	$C_{20}H_{18}O_8$	386	*C. salicifolius* [6]	aerial parts
54	cleomiscosin C	$C_{21}H_{20}O_9$	416	*C. salicifolius* [6, 33]	aerial parts
55	3, 3′-biisofraxidin	$C_{22}H_{18}O_{10}$	442	*C. praecox* [23]	leaf, branch
				C. salicifolius [6, 33]	aerial parts
56	arteminorin A	$C_{22}H_{18}O_{10}$	442	*C. salicifolius* [33]	aerial parts
57	hymenain	$C_{20}H_{14}O_8$	382	*C. salicifolius* [6]	aerial parts
58	chimsalicifoliusin A	$C_{21}H_{16}O_9$	412	*C. salicifolius* [6]	aerial parts
59	chimsalicifoliusin B	$C_{20}H_{14}O_8$	382	*C. salicifolius* [6]	aerial parts
60	chimsalicifoliusin C	$C_{31}H_{22}O_{13}$	602	*C. salicifolius* [6]	aerial parts
61	4, 4′-biisofraxidin	$C_{22}H_{18}O_{10}$	442	*C. nitens* [40]	leaf

Note: A: flower bud, root, stem, leaf; B: *C. salicifolius*, *C. zhejiangensis*, *C. grammatus*



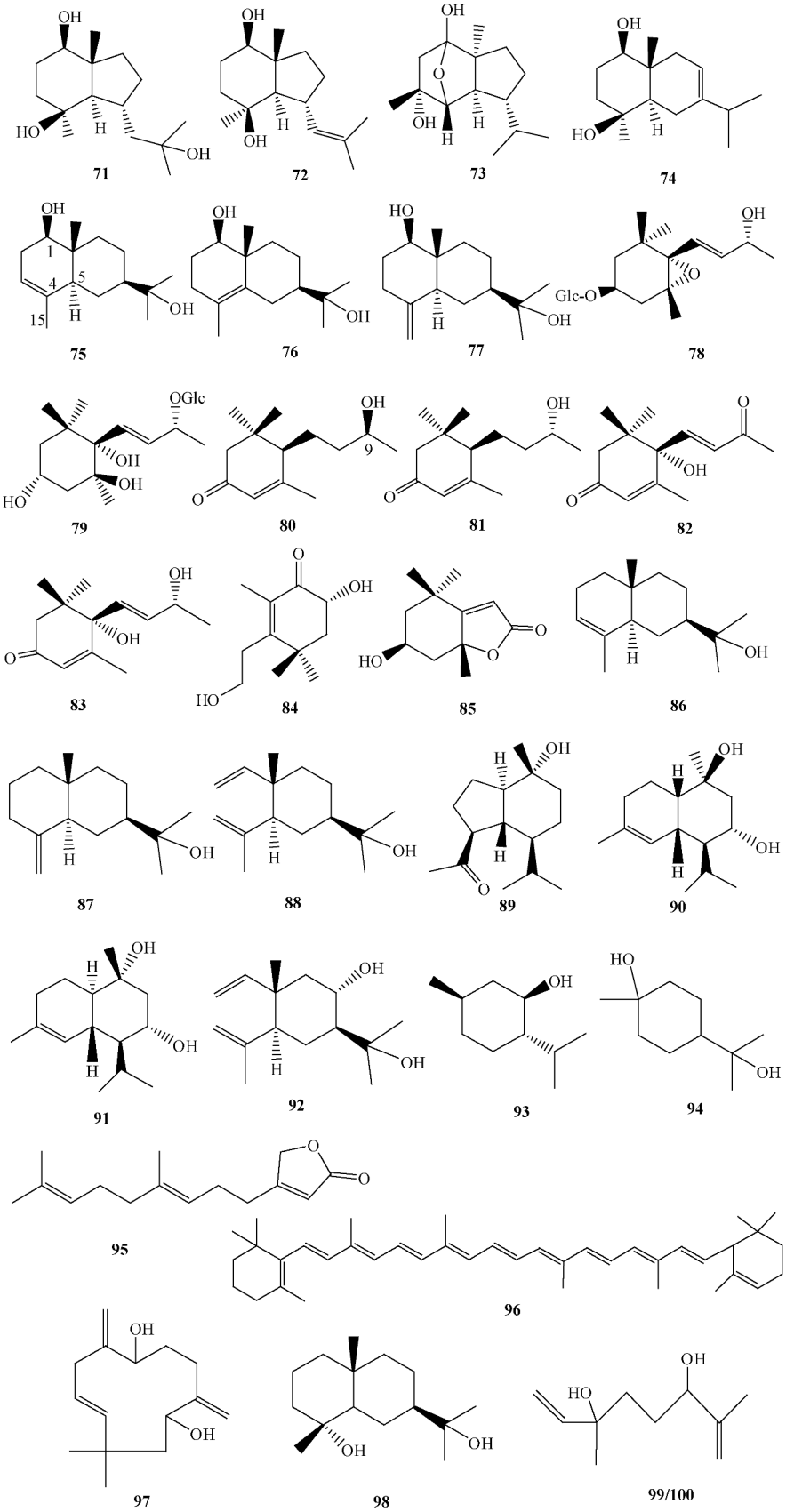


Fig. 5 Structures of terpenoids from *Chimonanthus*

According to the analysis of all terpenoids obtained from the *Chimonanthus* at present, it can be seen that there are many isomers in the plant of *Chimonanthus* (see Table 4). Hydroxyl oxidation, double bond reduction, intramolecular dehydration, different substituent positions, or optical isomers that make terpenoids structural diversely. For example, **82** is the hydroxyl oxidation product of **83**; **71** is the double bond reduction product of **82**; **75**–**77** are three isomers different in double bond between C_4 and C_3, C_4 and C_5 or C_4 and C_{15}; And the **75**, **77**, and **88** are hydroxyl of **86**, **87,** and **92** respectively, while **67**, **90**, **91** both are hydroxyl substituents of compound **66**; In addition, compound **68** (C_6*S) are C-6 epimer of **69** (C_6*R), **70** (C_4*R) are C-4 epimer of **71** (C_4*S), **80** (C_9*S) are C-9 epimer of **81** (C_9*R).

Table 4 Terpenoids from *Chimonanthus*

No.	Name	Formula	Mass	Origin	Organ
62	ZY-9	$C_{19}H_{30}O_6$	354	*C. praecox* [35]	rhizome
63	ZY-16	$C_{17}H_{28}O_5$	312	*C. praecox* [35]	rhizome
64/65	ZY-8/ZY-10	$C_{15}H_{24}O_3$	252	*C. praecox* [35]	rhizome
66	*t*-cadinol	$C_{15}H_{26}O$	222	*C. praecox* [35]	rhizome
67	(1*R*, 3*R*, 6*S*, 7*R*, 10*S*)-7-*iso*propyl-4, 10-dimethylbicyclo [4.4.0]-dec-4-ene-3, 10-diol	$C_{15}H_{26}O_2$	238	*C. praecox* [35]	rhizome
68	oxyphyllenodiol A	$C_{14}H_{22}O_3$	238	*C. praecox* [35]	rhizome
69	oxyphyllenodiol B	$C_{14}H_{22}O_3$	238	*C. praecox* [35]	rhizome
70	4-*epi*-bullatantriol(1*β*, 4*α*, 11-oppositanetriol)	$C_{15}H_{28}O_3$	256	*C. praecox* [4]	fruit
71	bullatantriol	$C_{15}H_{28}O_3$	256	*C. praecox* [4]	fruit
72	homalomenol A	$C_{15}H_{26}O_2$	238	*C. praecox* [4]	fruit
73	homalomenol C	$C_{15}H_{26}O_3$	254	*C. praecox* [4]	fruit
74	oplodiol	$C_{15}H_{26}O_2$	238	*C. praecox* [4]	fruit
75	3-eudesmene-1*β,* 11-diol	$C_{15}H_{26}O_2$	238	*C. praecox* [4]	leaf
76	4-eudesmene-1*β*, 11-diol	$C_{15}H_{26}O_2$	238	*C. praecox* [4]	leaf
77	4 (15)-eudesmen-1*β,* 11-diol(selin-4(15)-en-1*β*, 11-diol)	$C_{15}H_{26}O_2$	238	*C. praecox* [4]	leaf
78	3-hydroxy-5, 6-epoxy-*β*-ionol 3-*O*-*β*-D-glucopyranoside	$C_{19}H_{32}O_8$	388	*C. praecox* [4]	leaf
79	bridelionoside B	$C_{19}H_{34}O_9$	406	*C. praecox* [4]	leaf
80	9-*epi*-blumenol C	$C_{13}H_{22}O_2$	210	*C. salicifolius* [41]	leaf
81	blumenol C	$C_{13}H_{22}O_2$	210	*C. salicifolius* [41]	leaf
82	(+)-dehydrovomifoliol	$C_{13}H_{18}O_3$	222	*C. salicifolius* [41]	leaf
83	(+)-vomifoliol	$C_{13}H_{20}O_3$	224	*C. salicifolius* [41]	leaf
84	robinlin	$C_{11}H_{18}O_3$	198	*C. salicifolius* [41]	leaf
85	(−)-loliolide	$C_{11}H_{16}O_3$	196	*C. salicifolius* [41] *C. nitens* [39]	leaf leaf
86	*α*-eudesmol	$C_{15}H_{26}O$	222	*C. praecox* [15]	flower bud
87	*β*-eudesmol	$C_{15}H_{26}O$	222	*C. praecox* [15]	flower bud
88	*α*-elemol	$C_{15}H_{26}O$	222	*C. praecox* [15]	flower bud
89	oplopanone	$C_{15}H_{26}O_2$	238	*C. praecox* [15]	flower bud
90	8*α*-hydroxy-T-muurolol	$C_{15}H_{26}O_2$	238	*C. salicifolius* [33] *C. nitens* [40]	aerial parts leaf
91	(1*α, 6β, 7β*)-cadinane-4-en-*8α, 10α*-diol	$C_{15}H_{26}O_2$	238	*C. salicifolius* [33] *C. nitens* [40]	aerial parts leaf
92	8*α,* 11-elemodiol	$C_{15}H_{26}O_2$	238	*C. salicifolius* [33]	aerial parts
93	menthol	$C_{10}H_{20}O$	156	*C. nitens* [42]	leaf
94	terpin	$C_{10}H_{20}O_2$	172	*C. nitens* [43]	leaf
95	(*E*)-4-(4, 8-dimethylnona-3, 7-dienyl) furan-2 (5H)-one	$C_{15}H_{22}O_2$	234	*C. grammatus* [24]	leaf
96	*α*-carotene	$C_{40}H_{56}$	536	*C. praecox* [32]	flower
97	2, 6-dihydroxyhumula-3 (12), 7 (13), 9 (*E*)-triene	$C_{15}H_{24}O_2$	236	*C. nitens* [40]	leaf
98	cryptomeridiol	$C_{15}H_{28}O_2$	240	*C. nitens* [40]	leaf
99/100	(3*RS*, 6*RS*)-2, 6-dimethylocta-1, 7-dien-3, 6-diol	$C_{10}H_{18}O_2$	170	*C. nitens* [39]	leaf

The rich and diverse in structural and low contents of terpenoids make stereochemistry determination to be challenging. But the stereochemistry determination can be traced from the phylogenetic relationship of plants genetic relationship aspects, based on the reported *Chimonanthus* terpenoid structures, and combined with the regular of oxidation-reductionredox.

Meanwhile, from Fig. 5 and Table 5, we could find sesquiterpenoids is mostly identical to *C. praecox*, while nor-sesquiterpenoids is mostly identical to *C. salicifolius*. Compared to *C. praecox* and *C. salicifolius*, the system investigation about terpenoids in other species is very limited. Is it because there are few terpenoids in other species? According to our recent research on *C. nitens* leaves, it also has abundant (not in content) terpenoids, especially rich in nor-sesquiterpenoids and sesquiterpenoids. Some of these ingredients are actually same with *C. salicifolius*, which could further prove the phylogenetic relationship of plants. So, the systematical phytochemical research on other species is necessary.

Table 5 Steroids from *Chimonanthus*

No.	Name	formula	mass	Origin	organ
101	*β*-sitosterol	$C_{29}H_{50}O$	414	*C. praecox* [35-38]	rhizome, leaf, root
				C. grammatus [24], *C. nitens* [20-21]	leaf
				C. salicifolius [33, 41]	aerial parts
				C. praecox var. concolor [17]	seed
102	*β*-daucosterol	$C_{35}H_{60}O_6$	576	*C. praecox* [36, 38]	rhizome, root
				C. praecox var. concolor [17]	seed
				C. grammatus [24], *C. nitens* [42]	leaf
				C. salicifolius [33]	aerial parts
103	stigmasta-7, 22-diene-3*β*, 5*α*, 6*α*-triol	$C_{28}H_{46}O_3$	430	*C. salicifolius* [33]	aerial parts
104	stigmasterol	$C_{29}H_{48}O$	412	*C. grammatus* [24], *C. nitens* [21], *C. praecox* [37]	leaf
105	stigmast-4-en-3-one	$C_{29}H_{48}O$	412	*C. praecox* [35]	rhizome
	β-sitostenone			*C. salicifolius* [41]	leaf
106	daucoster linoleate	$C_{53}H_{90}O_7$	838	*C. praecox* var. concolor [17]	seed

Steroids

There are only six steroids (**101**–**106**) were reported from *Chimonanthus* (see Fig. 6), and all of them have 10 carbon atoms in C_{17} position, which called phytosterols. The distribution of these compounds in plants is not regular (see Table 5).

Organic acids

The study on total polyphenol content of different polarity fractions of *C. salicifolicus* leaves showed that all fractions exhibited high content of total polyphenol. Due to the different polarity of solvents, the extraction rate and composition of the extracts were greatly affected. The extraction rates of water phase, MeOH, *n*-hexane phase, *n*-butanol phase, CH_2Cl_2 phase and EtOAc phase were 48.80%, 34.84%, 24.47%, 19.99%, 3.01%, and 1.61% respectively; the contents were 175.15 ± 1.06,

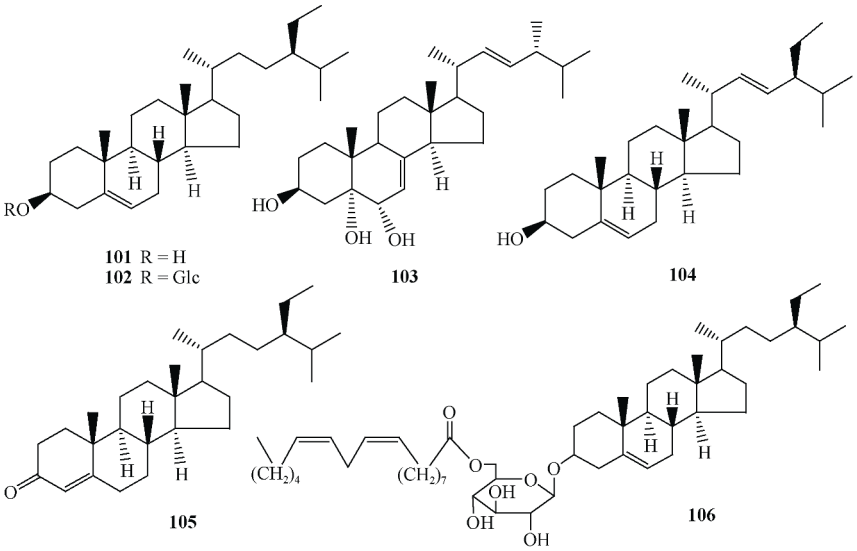


Fig. 6 Structures of sterides from *Chimonanthus*

196.7 ± 4.10, 132.05 ± 4.17, 233.6 ± 3.96, 145.30 ± 1.98 and 309.5 ± 4.81 mg·g^{-1}, respectively. We can find that Ethyl acetate fraction is low in extraction yield but high in content [75].

By using high-speed counter-current chromatography with a stepwise elution mode, five phenylpropanoids (**107**–**109, 113**, **114**) from EtOAc extract of *C. praecox* flowers were obtained. Moreover, the results indicated that this method generated a rapid and efficient pattern for phenolic acids separation and purification, and could be applied to separate and purify other complicated compounds from natural products [44]. In 2017, Zhang [39] and Huang [40] *et al.* isolated another four organic acids (**112**, **124**–**126)** from *C. nitens* leaves for the first time. To date, 20 organic acids have been isolated from *Chimonanthus* in total (see Table 6 and Fig. 7).

Table 6 Organic acids from *Chimonanthus*

No.	name	formula	mass	origin	organ
107	3, 4-dihydroxybenzoic acid	$C_7H_6O_4$	154	*C. praecox* [15, 44]	flower
108	protocatechualdehyde	$C_7H_6O_3$	138	*C. praecox* [44]	flower
109	*p*-hydroxybenzaldehyde	$C_7H_6O_2$	122	*C. praecox* [44]	flower
110	vanillic acid	$C_8H_8O_4$	168	*C. nitens* [19]	leaf
111	*p*-hydroxybenzoic acid	$C_7H_6O_3$	138	*C. nitens* [19]	leaf
112	methyl *β*-hydroxy-benzoate	$C_8H_8O_3$	152	*C. nitens* [40]	leaf
113	*p*-coumaric acid	$C_9H_8O_3$	164	*C. praecox* [44]	flower
114	4-hydorxylcinnamic aldehyde (p-hydorxyleinnamaldehyde)	$C_9H_8O_2$	148	*C. praecox* [44] *C. praecox* var. concolor [17]	flower seed
115	trans-cinnamic acid	$C_9H_8O_2$	148	*C. praecox* [15]	flower
116	caffeic acid	$C_9H_8O_4$	180	*C. nitens* [45]	leaf
117	syringic acid	$C_9H_{10}O_5$	198	*C. praecox* [35]	rhizome
118	prenylated-4-hydroxybenzoic acid	$C_{22}H_{30}O_3$	342	*C. grammatus* [24]	leaf
119	7-hydroxy-6-methoxych roman-2-one	$C_{10}H_{10}O_4$	194	*C. praecox* [35]	rhizome
120	Diisobutylphalate	$C_{16}H_{22}O_4$	278	*C. grammatus* [24]	leaf
121	10-heneicosenoic acid acid	$C_{21}H_{40}O_2$	324	*C. praecox* var. concolor [17]	seed
122	chlorogenic acid	$C_{16}H_{18}O_9$	354	*C. nitens* [45]	leaf
123	*p*-coumaroylquinic acid	$C_{16}H_{18}O_8$	338	*C. nitens* [45]	leaf
124	*p*-hydroxybenzoic acid ethyl ester	$C_9H_{10}O_3$	166	*C. nitens* [39]	leaf
125	*β*-hydroxybenzoyl *p*-coumaric acidanhydribe	$C_{16}H_{12}O_8$	284	*C. nitens* [40]	leaf
126	pyrocat-echol *β*-hydroxybenzoylp-coumaricacidanhydribe	$C_6H_6O_2$	110	*C. nitens* [40]	leaf

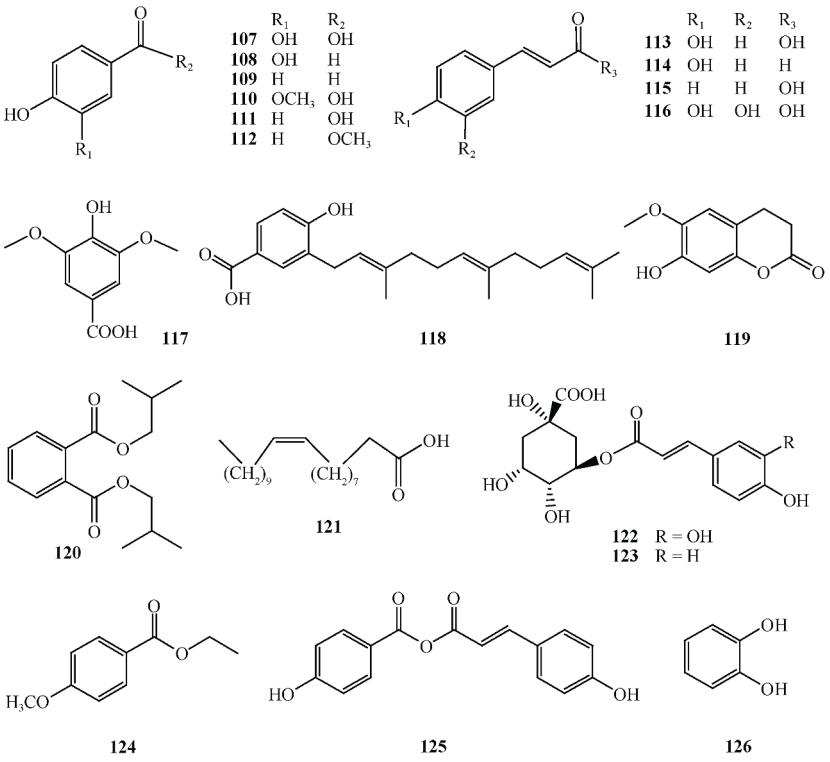


Fig. 7 Structures of organic acids from *Chimonanthus*

Glycosides and others

A number of glycosides have been founded in different parts of *C. praecox* plants (see Table 7 and Fig. 8). From the methanol extract of *C. praecox* flower buds, Morikawa's group obtained a series of glycosides, including four benzyl alcohol glycosides (**129**–**132**), two phenethyl alcohol glycosides (**133**, **134**), and one bisepoxylignan glycoside (**137**) [15]. While Wang and Shi's group obtained another four glucosides, including two phenylpropanoid glucosides (**127**–**128**), one bisepoxylignan glycoside (**136**) and one phenolic glycoside (**135**) from the leaves and branches of *C. praecox* [4, 23]. A new biphenylene lignan was isolated from *C. salicifolius* leaves, and its planar structure was elucidated as compound (**138**) [41]. Researchers also isolated three anthraquinones (**139**–**141**) from the *Chimonanthus* plants, and all of them were emodin-type [29, 33, 46].

Table 7 Glycosides and other compounds from *Chimonanthus*

No.	Name	Formula	Mass	Origin	Organ
	Glycosides				
127	linocinnamarin	$C_{16}H_{20}O_8$	340	*C. praecox* [4]	fruit
128	methyl 4-*β*-D-glucopyranosyl-ferulate	$C_{17}H_{22}O_9$	370	*C. praecox* [4]	fruit
129	benzylalcohol *α*-L-arabinofuranosyl (1→6)-*β*-D-glucopyranoside	$C_{18}H_{26}O_{10}$	402	*C. praecox* [15]	flower bud
130	benzylalcohol *β*-D-xylopyranosyl (1→6)-*β*-D-glucopyranoside (benzyl *β*-primeveroside)	$C_{18}H_{26}O_{10}$	402	*C. praecox* [4, 15]	flower bud, leaf
131	benzylalcohol *α*-L-rhamnopyranosyl (1→6)-*β*-D-glucopyranoside	$C_{19}H_{28}O_{10}$	416	*C. praecox* [15]	flower bud
132	benzylalcohol *β*-D-glucopyranosyl (1→6)-*β*-D-glucopyranoside	$C_{19}H_{28}O_{11}$	432	*C. praecox* [15]	flower bud
133	phenethylalcohol-*β*-D-xylopyranosyl (1→6)-*β*-D-glucopyranoside	$C_{19}H_{28}O_{10}$	416	*C. praecox* [15]	flower bud
134	4-hydroxyphenethylalcohol *β*-D-xylopyranosyl (1→6)-*β*-D-glucopyranoside	$C_{19}H_{28}O_{11}$	432	*C. praecox* [15]	flower bud
135	di-*O*-methylcrenatin	$C_{15}H_{22}O_9$	346	*C. praecox* [23]	leaf, branch
	Lignans				
136	acanthoside B	$C_{28}H_{36}O_{13}$	580	*C. praecox* [23]	leaf, branch
137	(−)-pinoresinol 4, 4'-di-*O*-*β*-D-glucopyranoside	$C_{32}H_{42}O_{16}$	682	*C. praecox* [15]	flower bud
138	2, 6, 2', 6'-tetra-methoxy-4, 4'-bis (2, 3-epoxy-1-hydroxyl-propyl)-biphenyl	$C_{22}H_{26}O_3$	418	*C. salicifolius* [41]	leaf
	Anthraquinones				
139	emodin	$C_{15}H_{10}O_5$	270	A–E [29]	flower
140	emodin-8-*O*-*β*-D-glucopyranoside	$C_{21}H_{20}O_{10}$	432	*C. salicifolius* [46]	leaf
141	physcion	$C_{16}H_{12}O_5$	284	*C. salicifolius* [33]	aerial parts
	Others				
142	*n*-tetratriacontane	$C_{34}H_{70}$	478	*C. praecox* [36]	rhizome
143	scyllitol	$C_6H_{12}O_6$	180	*C. nitens* [42]	leaf

Note: (1) A: *C. praecox*, B: *C. salicifolius,* C: *C. nitens,* D: *C. zhejiangensis,* E: *C. grammatus*

Nutrition

A study showed that the nutrients of *C. salicifolius* mainly contained protein (27.86%), crude fat (31.2%), crude fiber (11.7%), total soluble sugar (7.2%), vitamin B1 (0.1001 mg/100 g), vitamin B2 (1.302 mg/100g), vitamin C (33.6 mg/100g), free amino acids (1.12%), essential amino acids (0.179%), and Ca, Mg, Fe, Zn, Se elements *et al.* [47]. Another study reported that *C. nitens* had eighteen amino acids, seven vitamins, twelve trace elements, among which the contents of Vc, Fe and Se were highest [48]. Moreover, Morikawa *et al.* isolated an essential amino acid, L-tryptophan from the flower buds of C. praecox [15].

Biological Activities

Previous pharmacological studies mainly concentrated on the extracts of the *Chimonanthus*, which mainly with the activities on treating colds, coughs, phlegm, asthma, rheumatic arthritis and improving the immune system *etc*. In recent years, with the further studying on individual constituents, a number of individual components have been founded to exhibit significant pharmacological activities in some other respects, such as anti-tumor and anti-oxidant. Thus, these results are well-provided with useful references for the further development of *Chimonanthus*. All related biological activities available for *Chimonanthus* are summarized in Tables 8 and 9.

Anti-bacterial

The evaporate products of Shanlameiye pills have strong inhibition of *Staphylococcus aureus*, the rate of inhibition is 92.35%–93.55% [49]. Studies on different polarity fractions of *C. salicifolicus* leaves inhibited the effects on *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas*

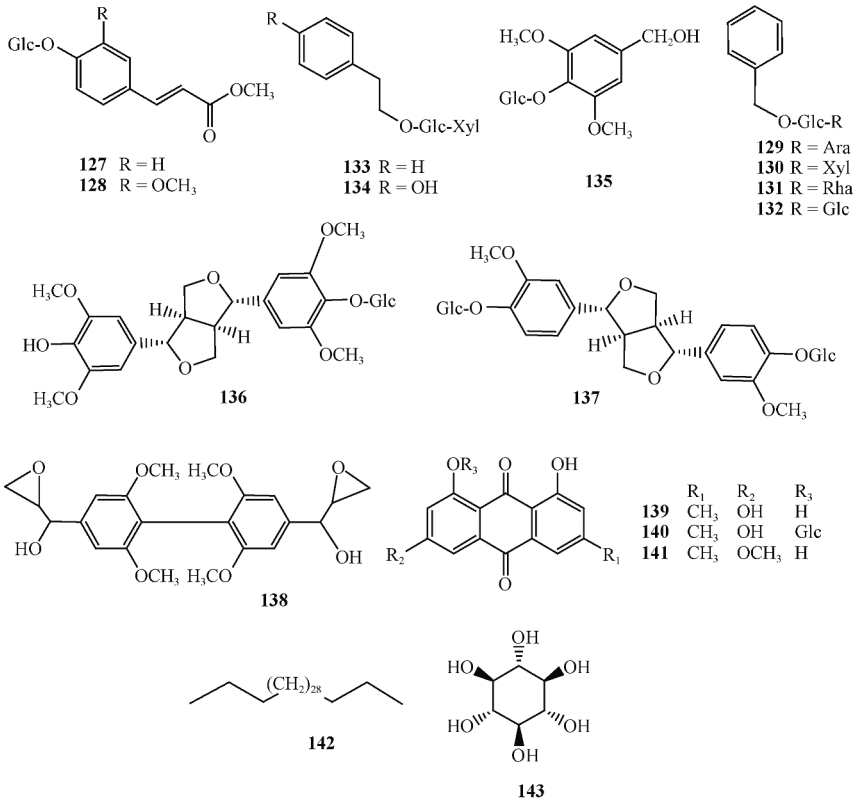


Fig. 8 Structures of glycosides and other compounds from *Chimonanthus*

aeruginosa and showed the dichloromethane fraction (10 mg·mL^{-1}) had the strongest antibacterial activity. The maximum inhibition zone diameters were 11.50 ± 1.05, 11.33 ± 0.82, 11.57 ± 1.62, 11.25 ± 1.04 mm, respectively [75]. Li *et al.* evaluated antimicrobial activities of eight compounds (10 mg·mL^{-1}) that isolated from water extract of *C. nitens* roots by disk diffusion method, using *Staphylococcus aureus*, *Micrococcus luteus*, *Escherichia coli*, *Bacillus subtitles*, *Salmonella typhi*, and *Pseudomonas aeruginosa*. Comparing with gentamicin (0.5 mg·mL^{-1}), compounds **38**, **43**, **48**, and **49** had moderate inhibition activities against *M. luteus*, and their inhibition zone diameters were 24.37 ± 1.73, 9.28 ± 0.62, 10.02 ± 0.54, and 9.80 ± 0.45 mm, respectively [22]. Compounds **38**, **95**, **118** and **120** isolated from the leaves of *C. grammatus* have good antibiotic activity against *Escherichia coli* and *Bacillus subtilis*. A mong them, *E. coli* was most sensitive to **95** (MIC = 1.5 mg·mL^{-1}, MBC = 6 mg·mL^{-1}), while *B. subtilis* most sensitive to **38** (MIC = 0.8 mg·mL^{-1}, MBC = 3 mg·mL^{-1}) [24]. Zhang *et al.* found that D-calycanthine (**1**) and L-folicanthine (**5**) had significant inhibitory activities against five plant pathogenic fungi *Exserohilum turcicum*, *Bipolaris maydis*, *Alternaria solani*, *Sclerotinia sderotiorum*, and *Fusarium oxysportium*, while *B. maydis* was found to be the most susceptible to **1** with an EC_{50} of 29.3 μg·mL^{-1}, followed by *S. sderotiorum* to **5** with an EC_{50} of 61.2 μg·mL^{-1} [7]. Another study also reported that calycanthine had antibacterial activities against *Alternaria brassicicola*, *Botrytis cinerea*, and *Cladosporium fulvum* [50].

Analgesic, antitussive and expectorant effect

Chimonanthines and the intermediates obtained during the synthetic stage were tested on μ-opioid and κ-opioid binding assay. As a result, (–)-chimonanthine and (+)-chimonanthine monourethanes (Ki = 5.7 ± 1.4 nmol·L^{-1}, 4.8 ± 0.6 nmol·L^{-1}) displayed a stronger binding affinity for μ-opioid receptors compared to *meso*-chimonanthine (**3,** Ki = 341 ± 29 nmol·L^{-1}) and (–)-chimonanthine (**4**, Ki = 271 ± 85 nmol·L^{-1}) [51]. By using hot board, body distortion and concentrated ammonia spray methods to study the effects on analgesic, antitussive and expectorant, the alcohol extract of *C. nitens* could be found to significant delay the plant reaction time, to reduce the writhing times of the mice, and to decrease the pain induced by acetic acid methods, whilethe cough was induced by concentrated ammonia, accelerate phlegm displacement in rats [52]. The ethanol extracts of Tiekuaizi could significantly reduce the times of twisting body induced by acetic acid, and greatly improve the pain threshold of hot-plate in mice [53].

Anti-inflammatory

The Shanlamei Ganmao tea can fight against the increase of mice abdominal capillary permeability induced by acetic acid and also can reduce the feet swelling of rats induced by egg white [54]. The water extract from the stem of *C. nitens* could decrease the levels of CRP and IL-8 in lung tissue and serum of COPD rats ($P < 0.05$) [76]. In 2017, a study showed the *C. nitens* extracts had high activities to inhibit the recruitment of neutrophils and the expressions of TNF-α

Table 8 Biological activities of *Chimonanthus* extracts (A)

Species	Fraction	Activity	Description	Ref.
C. nitens leaves	water extract	anti-bacterial	92.35%–93.55% inhibition rate of *Staphylococcus aureus*	49
			57.2% and 52.4% mortality protection rate of HDG (12 g·kg^{-1}), LDG (6 g·kg^{-1}); reduce the mortality of mice infected with *Staphylococcus aureus*	54
			inhibit all kinds of bacteria (3.0–200 mg·L^{-1}), *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Shigella flexneri, Diplococcus pneumoniae, Hemolytic Streptococcus B, Influenza Bacillus*, especially for *Staphylococcus aureus*	54
		antiviral	Inhibit Jingke 68–1 strain, EID_{50} reduced at least 4 times	49
		analgesic	reduce the times of twisting body induced by acetic acid, and greatly improve the pain threshold of hot-plate in mice.	52
		antitussive	reduce cough effect of concentrated ammonia water in mice	52
		expectorant	increase sputum excretion of rats and mice	52
		anti-inflammatory	HDG (12 g·kg^{-1}) and LDG (6 g·kg^{-1}) significantly antagonize the enhancement of capillary permeability induced by acetic acid; reduce the feet swelling of rats induced by egg white	54
		antipyretic	against yeast induced pyrexia	54
	ethanol extract	analgesic	improve the pain threshold of hot-plate in mice, reduce the times of twisting body induced by acetic acid, inhibitory effect on I and II phase pain; L-Arg could reduce but L–NAME could enhance the analgesic action, The analgesic effect may be related to the inhibition of NO production	53
		anti-inflammatory	inhibit the recruitment of neutrophils and the expressions of TNF-α and IL-6 in LPS-stimulated zebrafish and RAW 264.7 cells	8
		anti-depression	increase the content of monoamine neurotransmitters 5-HT and NE; horizontal activity and vertical activity decreased significantly, the immobility time of forced swimming and tail suspension test increased significantly	65
		inhibited fatty acid synthase	Lee's index, fat index, triglyceride, and total cholesterol of HDG (5 g·mL^{-1}) and LDG (1 g·mL^{-1}) decreased by 7.19% and 6.96%, 42.04% and 36.73%, 41.34% and 32.96%, 20.83% and 14.58%, respectively; concentration $\geqslant$ 15 μg·mL^{-1}, the enzyme activity decreased significantly ($P < 0.01$); c = 15 μg·mL^{-1}, the enzyme activity was inhibited by more than 50%; c = 150 μg·mL^{-1}, the enzyme activity was only 6.9% of the blank control group, almost completely inhibited the enzyme activity	57
		anti-depression	improve the behavioral changes of the model mice, and increase the content of monoamine neurotransmitters 5-HT and NE in the brain of the mice, which has certain anti-depression effects. HDG: 50 g·kg^{-1}, LDG: 10 g·kg^{-1}	65
C. nitens leave	50% ethanol extract	against α-glucosidase	IC_{50} 0.376 mg·mL^{-1}, significantly reduced fast blood glucose level and serum triglyceride, total cholesterol, low- density lipoprotein cholesterol, and malondialdehyde as well as malondialdehyde in liver; significantly increased fasting serum insulin and insulin sensitivity index, high-density lipoprotein cholesterol in serum; apparently enhanced total antioxidant capacity activities of superoxide dismutase, glutathione peroxidase, and catalase in serum and liver; decreased liver coefficient, liver transaminase, and alkaline phosphatase. advantageous to regulate glycolipid metabolism and elevate antioxidant capacity in diabetic model mice	9
	Ethyl acetate fraction	AChE inhibitory	IC_{50} 13.27 mg·mL^{-1}	21

Continued

Species	Fraction	Activity	Description	Ref.
C. nitens leave	petroleum ether fraction	lipid-lowering	reducing weight, anti-appetite and reducing fat	58
		AChE inhibitory	In the low concentration range of 0.25 mg·mL^{-1}, the inhibitory activity of petroleum ether extract was higher than ethyl acetate extract.	21
	n-butyl alcohol fraction	lipid-lowering	reducing weight, anti-appetite and reducing fat	58
		AChE inhibitory	IC_{50} 16.12 mg·mL^{-1}	21
	water extract (CCTM) (Monarch hurb)	anti-inflammatory	91.67%total effective rate ($P < 0.05$), treat chronic atrophic gastritis, HP negative conversion rate was 45.83% improving the scores of TCM symptoms	81
			82.50% total effective rate ($P < 0.05$), decrease hs-CRP, IL-6 and TNF-α, improve CCr, ALB improving the scores of TCM symptoms	82
			93.75% total effective rate, improved FEV1, FEV1% pred, PEFR, FEV1/FVC, CD_3^+, CD_4^+, CD_4^+/CD_8^+ improving the scores of TCM symptoms	83
C. nitens stem	water extract	anti-inflammatory	decrease the levels of CRP and IL-8 in lung tissue and serum of COPD rats ($P < 0.05$)	76
C. praecox roots	78% ethanol extract	anti-inflammatory	inhibit the articular swelling of AA rats and decrease the levels of TNF-α and PAF in the serum	55
C. praecox flower	methanol extract	inhibit melanogenesis	demonstrated inhibitory effects on melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells (IC_{50} 2.1 μmol·L^{-1}). and 73.6% inhibition rate in 30 μg·mL^{-1}	15
	water extract	Improve immunity	significantly enhance the rat macrophage phagocytic activity ($P < 0.001$) and humoral immune function ($P < 0.001$)	60
C. salicifolius leaves	water extract	antitumor	inhibit the proliferation, induce apoptosis and G_2/M arrest of Hela cells	62
		against 5-Fluorouracil induced gastrointestinal mucositis	attenuating the subsequent body weight loss, diarrhea, and faecal blood, reducing the hepatic injury, and maintaining both intestinal length and villus structure	66
		antidiarrheal effect	reduce the total number of stools, the rare rate, the level of loose stools and diarrhea index series ($P < 0.01$); Dose: 1.6, 4, and 10 g·kg^{-1}	78
		toxicity, embryotoxicity	had no significant difference in the conception rate, total weight gain during the pregnancy and the number of living, dead and resorbed fetuses ($P > 0.05$), The number of the rib, sternum, the fifth sternum punctated and the parietal bone which were ossified defectively all showed no difference ($P > 0.05$)	69
	chloroform fraction	antitumor	significant inhibitory activity against human colorectal cancer cell line HCT116 and human lung cancer line H1299, with IC_{50} of 56.5 and 26.9 μg·mL^{-1}.	41
	ethyl acetate fraction	reductive power	absorbance value of reducing power is 0.91 ± 0.01 (c = 1.0 mg·mL^{-1})	75
		scavenging DPPH free radicals	Scavenging rate is 91.62% in 1.0 mg·mL^{-1}, IC_{50} 0.48 mg·mL^{-1}	75
		anti-bacterial	inhibit *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*, the maximum inhibition zone diameters were 8.45 ± 0.79, 9.83 ± 0.75, 9.88 ± 0.64, 9.88 ± 1.36 mm, respectively. MIC of 4 mg·mL^{-1} for *B. subtilis* and *P. aeruginosa*, 6 mg·mL^{-1} for *E. coli*, *S. aureus*	75
	n-butanol fraction	reductive power	Absorbance value of reducing power is 0.51 ± 0.04 (c = 1.0 mg·mL^{-1})	75
		scavenging DPPH free radicals	IC_{50} 0.98 mg·mL^{-1}	75
	water fraction	reductive power	Absorbance value of reducing power is 0.46 ± 0.013 (c = 1.0 mg·mL^{-1})	75
		scavenging DPPH free radicals	IC_{50} 1.36 mg·mL^{-1}	75

Continued

Species	Fraction	Activity	Description	Ref.
C. salicifolius leaves	methanol fraction	reductive power	Absorbance value of reducing power is 0.44 ± 0.01 (c = 1.0 mg·mL^{-1})	75
		scavenging DPPH free radicals	IC_{50} 1.24 mg·mL^{-1}	75
		anti-bacterial	inhibit *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*, the maximum inhibition zone diameters were 9.25 ± 0.46, 10.17 ± 0.75, 9.00 ± 0.76, 8.50 ± 1.20 mm, respectively. MIC of 2 mg·mL^{-1}	75
C. salicifolius leaves	dichloromethane fraction	reductive power	Absorbance value of reducing power is 0.31 ± 0.01 (c = 1.0 mg·mL^{-1})	75
		scavenging DPPH free radicals	IC_{50} 0.61 mg·mL^{-1}	75
		anti-bacterial	inhibit *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*, the maximum inhibition zone diameters were 11.50 ± 1.05, 11.33 ± 0.82, 11.57 ± 1.62, 11.25 ± 1.04 mm, respectively. MIC of 2 mg·mL^{-1}	75
	n-hexane fraction	reductive power	Absorbance value of reducing power is 0.29 ± 0.02 (c = 1.0 mg·mL^{-1})	75
		scavenging DPPH free radicals	IC_{50} 1.11 mg·mL^{-1}	75
		anti-bacterial	inhibit *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*, the maximum inhibition zone diameters were 11.00 ± 1.10, 11.17 ± 0.98, 11.38 ± 1.41, 10.50 ± 0.35 mm, respectively. MIC of 2 mg·mL^{-1}	75
	unknown fraction	ameliorate liver injury	ameliorate liver injury induced by alcohol, reduced the levels of ALT and AS, histological damage or inflammatory response (P < 0.05)	67
	unknown fraction	antitumor	inhibit SGC-7901 cells proliferation, the possible mechanism might be related to cell apoptosis, when concentration = 0.8 μg·mL^{-1}, 89.39% ± 0.9% inhibit SGC-7901 cell growth, IC_{50} 0.5 μg·mL^{-1}	63
	C. salicifoliu Enema (CCTM)	anti-inflammatory	100%total effective rate, significantly increased CD_4/CD_8^+, IL-2 of T-lymphocytes, reduced IL-6 and TNF-α; improve the immune function of rats with CPID, regulate the secretion and balance of inflammatory factors,	59
			100% the total effective rate of 72 cases of chronic pelvic inflammatory disease	77
C. grammatus leaves	petroleum extract	AChE inhibitory	IC_{50} 8.153 mg·mL^{-1}, concentration from 0.5–10 mg·mL^{-1}	64
		antitumor	obvious inhibit on A549 when the concentration was 0.5–1 mg·L^{-1}, 74.8% inhibition rate in 1 mg·L^{-1}	64
	Ethyl acetate extract	AChE inhibitory	IC_{50} 4.219 mg·mL^{-1}, concentration from 0.5–10 mg·mL^{-1}	64
		antitumor	have no obvious inhibit on A549 when the concentration was 0.004–1 mg·L^{-1}, 8.49% inhibition rate in 1 mg·L^{-1}	64
	n-butyl alcohol extract	AChE inhibitory	IC_{50} 4.812 mg·mL^{-1}, concentration from 0.5–10 mg·mL^{-1}	64
		antitumor	have no obvious inhibit on A549 when the concentration was 0.004–1 mg·L^{-1}, 19.46% inhibition rate in 1 mg·L^{-1}	64
	water extract	antitumor	c = 0.004–1 mg·L^{-1} obvious inhibit on A549, 37.98% inhibition rate in 0.5 mg·L^{-1}, 14.10% inhibition rate in 1 mg·L^{-1}	64
C. zhejiangensis leaves	water extract	toxicity	had no toxicity, LD_{50} couldn't be measured in 0.3 mL/10 g intragastric administration, and the maximum tolerated dose was 80 g·kg^{-1}	70

Table 9 Biological Activities of Compounds Isolated from the *Chimonanthus* (A)

No.	Compounds	Biological actities	Assays/studys	Dose tested	Results	Ref.
1	*d*-calycanthine	antifungal	mycelial growth inhibitory rate method	0.25 mg·mL^{-1}	Inhibit *Exserohilum turcicum* and *Bipolaris maydis* at a concentration of 250 μg·mL^{-1} with inhibition rates of 76.9%, 81.1%, and with EC_{50} values of 103.1 and 29.3 μg·mL^{-1}, respectively. Inactive in *Sclerotinia sderotiorum*	7
		antibacterial	Growth rate method	0.025–1.0 mg·mL^{-1}	Inhibit *Alternaria brassicicola* and *Cladosporium fulvum* at concentration of 0.5 and 1 mg·mL^{-1} with inhibition rates of 100%, respectively. Maximum inhibition rate of 89.56% at the concentration of 1mg/mL to *Botrytis cinerea*	50
		antioxidant	ABTS cation radical scavenging assay and FRAP assay	5.0 mg·mL^{-1}	IC_{50}/ABTS = 3.24 ± 0.08 mg·L^{-1}, FRAP = 25.71 ± 0.97 μmol·L^{-1}·mg^{-1} (BHT as positive control)	50
		Insecticidal	capillary quantitative drop method and the leaf disk assay	0.25 mg·mL^{-1}	Inactive to third instar larva of *Mythimna separate*	7
		AChE inhibitory	modified Ellman method	/	IC_{50} 24.39 μmol·L^{-1}	21
		anti-convulsant	potassium-induced and spontaneous release of GABA from hippocampal, cerebellar, and cerebral cortical slices	0–300 μmol·L^{-1}	decreased potassium-stimulated GABA release from hippocampal slices by 65% ± 3% (IC_{50} 21.4 ± 2.5 μmol·L^{-1}), from cerebellar by 55% ± 5%; its convulsant action predominantly by inhibiting the release of the inhibitory neurotransmitter GABA as a result of interactions with L-type $Ca2^{+}$ channels and by inhibiting GABA-mediated chloride currents at $GABA_A$ receptors	68
		antihypertensive	*in vivo*	7–10 mg·kg^{-1}	iv 10 mg·kg^{-1} calycanthine role in short-term, iv 7 mg·kg^{-1} total alkaloids, the blood pressure can decrease 40% and lasting more than 0.5 h	56
3	(meso)-chimonanthine	antinociceptive (morphine as positive control)	μ- and κ-opioid binding assay	micromolar range	*u*-opioid (K_i = 341 ± 29 nmol·L^{-1}), *κ*-opioid (K_i = 1447 ± 45 nmol·L^{-1})	51
			tail-flick model	5.0–10.0 mg·kg^{-1}	44% of maximum possible effect at 2890 μmol·kg^{-1} (10 mg·kg^{-1})	
			capsaicin-induced pain model	0.5–5.0 mg·kg^{-1}	144.5 and 722.0 μmol·kg^{-1} (0.5 and 2.5 mg·kg^{-1}) results in 30%–35% inhibition, lose activity at 1445 μmol·kg^{-1} (5.0 mg·kg^{-1}).	
		cytotoxicity	*in vitro*	0–50 μg·mL^{-1}	against SGC-7901, IC_{50} 20.3 μmol·L^{-1}, inactive in HCT-116 and SW-1116 (IC_{50} > 50 μmol·L^{-1})	18
4	(–)-chimonanthine	antinociceptive	μ- and κ-opioid binding assay	micromolar range	μ-opioid (K_i = 341 ± 29 nmol·L^{-1}), κ-opioid (K_i = 1447 ± 45 nmol·L^{-1})	51
			tail-flick model	5.0–10.0 mg·kg^{-1}	40% of maximum possible effect at 2890 μmol·kg^{-1} (10 mg·kg^{-1})	
			capsaicin-induced pain model	0.1–0.5 mg·kg^{-1}	72.2 μmol·kg^{-1} (0.25 mg·kg^{-1}) results in 47% inhibition, and lose activity at 144.5 μmol·kg^{-1} (0.5 mg·kg^{-1}).	
		cytotoxicity	*in vitro* (Fluorouracil control)	0–100 μmol·L^{-1}	against NUGC3, SNU739 and SHSY-5Y cancer cell lines, with IC_{50} values of 19.7 ± 3.8, 10.3 ± 1.5 and 58.2 ± 5.7 μmol·L^{-1}, respectively. Inactive in MCF-7, IC_{50} > 100 μmol·L^{-1}	4
		melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 0.93 μmol·L^{-1}, inhibit both tyrosinase and tyrosine-related protein-1 mRNA expression, showed cytotoxicity at 10 μmol·L^{-1}	15
				0–3 μmol·L^{-1}	inhibit mRNA expression for both tyrosinase and TRP-1 at 3 μmol·L^{-1}	
		against PRRSV	Cytopathic effect method; RT-PCR	50–400 μmol·L^{-1}	IC_{50} 68.9 ± 3.1 μmol·L^{-1}, Ti = 17.9, down regulated the expression of PRRSV NSP9 and ORF 7 gene (Tilmicosin Phosphate as positive control)	23
		cytotoxicity	*in vitro*	0–50 μg·mL^{-1}	against SGC-7901, IC_{50} 20.3 μmol·L^{-1}, inactive in HCT-116 and SW-1116 (IC_{50} > 50 μmol·L^{-1})	18

Continued

No.	Compounds	Biological actities	Assays/studys	Dose tested	Results	Ref.
5	*l*-folicanthine	antifungal	mycelial growth inhibitory rate method	0.25 mg·mL^{-1}	Inhibit *Bipolarismaydis*, *Sclerotinia sderotiorum*, and *Alternaria solani* at a concentration of 250 μg·mL^{-1} with inhibition rates of 78.6%, 82.6%, and 71.3%, and with EC_{50} of 79.6, 61.2, and 125.7 μg·mL^{-1}, respectively	7
		Insecticidal	capillary quantitative drop method and leaf disk assay	0.25 mg·mL^{-1}	Inactive to third instar larva of *Mythimna separate*	7
		cytotoxicity	*in vitro* (Fluorouracil control)	0–100 μmol·L^{-1}	against NUGC3, SNU739 and SHSY-5Y cancer cell lines, with IC_{50} of 13.3 ± 1.5, 17.0 ± 2.8 and 60.1 ± 3.5 μmol·L^{-1}, respectively. Inactive in MCF-7, IC_{50} > 100 μmol·L^{-1}	4
		melanogenesis inhibitory activity	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	significantly inhibited melanogenesis, IC_{50} 1.4 μmol·L^{-1}, showed cytotoxicity at 10 μmol·L^{-1}	15
				0–3 μmol·L^{-1}	Inactive in inhibit tyrosinase, TRP-1, and TRP-2 mRNA expression in B16 4A5 cells	
6	(−)-calycanthidine	cytotoxicity	*in vitro* (Fluorouracil control)	0–100 μmol·L^{-1}	against NUGC3, SNU739 and SHSY-5Y, with IC_{50} values of 17.3 ± 2.3, 18.3 ± 0.7 and 49.5 ± 2.7 μmol·L^{-1}, respectively. Inactive in MCF-7, IC_{50} > 100 μmol·L^{-1}	4
		melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	significantly inhibited melanogenesis, IC_{50} 1.8 μmol·L^{-1}, showed cytotoxicity at 10 μmol·L^{-1}	15
				0–3 μmol·L^{-1}	inhibit TRP-1 mRNA expression at 3 μmol·L^{-1}	
11	salicifoxazine A	cytotoxicity	*in vitro* (Fluorouracil control)	0–50 μg·mL^{-1}	against SW-1116, IC_{50} 26.7 μmol·L^{-1}, inactive in HCT-116 and SGC-7901(IC_{50} > 50 μmol·L^{-1})	18
12	salicifoxazine B	cytotoxicity	*in vitro* (Fluorouracil control)	0–50 μg·mL^{-1}	against SGC-7901, IC_{50} 24.9 μmol·L^{-1}, inactive in HCT-116 and SW-1116 (IC_{50} > 50 μmol·L^{-1})	18
13	berberine	AChE inhibitory	modified Ellman method	0.5–8 mg·mL^{-1}	IC_{50} 9.84 μmol·L^{-1}	21
19	3, 4-dihydroxybenzonitrile	against PRRSV	cytopathic effect method, RT-PCR	50–400 μmol·L^{-1}	IC_{50} 80.5 ± 16.9 μmol·L^{-1}, Ti = 19.9; down regulated the expression of PRRSV NSP9 and ORF 7 gene (Tilmicosin Phosphate as positive control)	23
21	quercetin	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 9.33 × 10^{-3} μmol·L^{-1}	29
			ABTS method	2.0 mg·mL^{-1}	IC_{50} 0.563 mmol·L^{-1} (Trolox as positive control)	46
		α-glucosidase inhibitory	α-glucosidase inhibitory assay	0.05–5.0 mg·mL^{-1}	40 μg·mL^{-1} and 80 μg·mL^{-1} results in 83.2% and 91.7% inhibition, respectively. IC_{50} 66.8 μg·mL^{-1}, K_i = 0.42 ± 0.11 mmol·L^{-1}	5
		melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	inhibit melanogenesis IC_{50} 15.4 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1};	15
				0–100 μmol·L^{-1}	inhibit mushroom tyrosinase IC_{50} 36.2 μmol·L^{-1}	
22	kaempferol	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 44.18 μmol·L^{-1}	29
			ABTS method	2.0 mg·mL^{-1}	IC_{50} 1.53 mmol·L^{-1} (Trolox as positive control)	46
		α-glucosidase inhibitory	α-glucosidase inhibitory assay	0.05–5.0 mg·mL^{-1}	40 and 80 μg·mL^{-1} results in 68.1% and 84.3% inhibition, respectively. IC_{50} 109 μg·mL^{-1}, K_i = 0.78 ± 0.13 mmol·L^{-1}	5
		melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	inhibit melanogenesis IC_{50} 25.4 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1};	15
				0–100 μmol·L^{-1}	inhibit mushroom tyrosinase IC_{50} 14.3 μmol·L^{-1}	
23	rutin	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 1.65 μmol·L^{-1}	29
24	kaempferol-3-*O*-*β*-D-glucoside	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 3.83 μmol·L^{-1}	29
25	isoquercitrin	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 0.017 μmol·L^{-1}	29

Continued

No.	Compounds	Biological actities	Assays/studys	Dose tested	Results	Ref.
27	kaempferol-3-*O*-*β*-D-rutinoside	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 2.21 μmol·L^{-1}	29
38	scopoletin	antimicrobial	disc diffusion method	10 mg·mL^{-1}	Against *Micrococcus luteus*, 24.37 ± 1.73 mm zone inhibition (gentamicin as positive control)	22
		antibiotic	TLC-Bioautography	0.02–40 mg·mL^{-1}	Against *Escherichia coli*, MIC 0.8 mg·mL^{-1}, MBC 3.0 mg·mL^{-1} (huperzine A as positive control)	24
		antioxidant	DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 44.43 μmol·L^{-1}	29
			ABTS method	2.0 mg·mL^{-1}	IC_{50} 8.72 mmol·L^{-1} (Trolox as positive control)	46
		AChE inhibitory	modified Ellman method	0.5–10 mg·mL^{-1}	IC_{50} 18.86 μmol·L^{-1} (huperzine A as positive control)	37
39	6,7-dimethoxycoumarin	AChE inhibitory	modified Ellman method	0.5–10 mg·mL^{-1}	IC_{50} 33.16 μmol·L^{-1} (huperzine A as positive control)	37
		antitumor	MTT method	0–100 μmol·L^{-1}	exhibit weak antitumor activity against cancer cell line HCT116, IC_{50} 81.56 μmol·L^{-1}	41
40	isofraxidin	AChE inhibitory	modified Ellman method	0.5–10mg·mL^{-1}	IC_{50} 23.37 μmol·L^{-1} (huperzine A as positive control)	37
42	6,7,8-trimethoxycoumarin	antitumor	MTT method	0–100 μmol·L^{-1}	exhibit weak antitumor activity against cancer cell line HCT116, IC_{50} 88.26 μmol·L^{-1}	41
43	5,6,7-trimethoxycoumarin	antimicrobial	disc diffusion method	10 mg·mL^{-1}	Against *Micrococcus luteus*, 9.28 ± 0.62 mm zone inhibition (gentamicin as positive control)	22
47	scopolin	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 6.16 μmol·L^{-1}	29
48	calycanthoside	antimicrobial	disc diffusion method	10 mg·mL^{-1}	Against *Micrococcus luteus*, 10.02 ± 0.54 mm zone inhibition (gentamicin as positive control)	22
49	xeroboside	antimicrobial	disc diffusion method	10 mg·mL^{-1}	Against *Micrococcus luteus*, 9.80 ± 0.45 mm zone inhibition (gentamicin as positive control)	22
58	chimsalicifoliusin A	cytotoxicity	MTT assay	0–50 μmol·L^{-1}	against Hela and HL-60 cell lines, with the IC_{50} values of 18.3 and 23.4 μmol·L^{-1}, respectively. Inactive in PC-3 cell lines, IC_{50} > 50 μmol·L^{-1}, (Cisplatin as positive control)	6
59	chimsalicifoliusin B	cytotoxicity	MTT assay	0–50 μmol·L^{-1}	against Hela, HL-60, PC-3 cell lines, with the IC_{50} values of 21.2 and 29.6 μmol·L^{-1}, respectively. Inactive in PC-3 cell lines, IC_{50} > 50 μmol·L^{-1} (Cisplatin as positive control)	6
60	chimsalicifoliusin C	cytotoxicity	MTT assay	0–50 μmol·L^{-1}	against Hela, HL-60, PC-3, with the IC_{50} values of 15.5, 28.6 and 14.2 μmol·L^{-1}, respectively	6
83	(+)-vomifoliol	antitumor	MTT method	0–100 μmol·L^{-1}	exhibit weak antitumor activity against HCT116, IC_{50} 88.26 μmol·L^{-1}	41
86	*α*-eudesmol	melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 4.3 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1}	15
				0–100 μmol·L^{-1}	inactive in L-tyrosine or L-DOPA	
87	*β*-eudesmol	melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 10.0 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1}	15
				0–100 μmol·L^{-1}	inactive in L-tyrosine or L-DOPA	
88	*α*-elemol	melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 6.0 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1}	15
				0–100 μmol·L^{-1}	inactive in L-tyrosine or L-DOPA	

Continued

No.	Compounds	Biological actities	Assays/studys	Dose tested	Results	Ref.
90	8α-hydroxy-T-muurolo	cytotoxicity	MTT assay *in vitro*	1.25–20 μmol·L^{-1}	inactive against human cancer cell lines A549, Hela, and Bel 7402, IC_{50} > 50 μmol·L^{-1}	33
		immuno-modulating	splenocyte proliferation assay	1.25–20 μmol·L^{-1}	inhibited Con A-stimulated mice splenocyte proliferation in a dose-dependent manner	33
91	(1α, 6β, 7β)-cadinane-4-en-8α,10α-diol	cytotoxicity	MTT assay *in vitro*	1.25–20 μmol·L^{-1}	inactive against human cancer cell lines A549, Hela, and Bel 7402, IC_{50} > 50 μmol·L^{-1}	33
		immuno-modulating activity	splenocyte proliferation assay	1.25–20 μmol·L^{-1}	inhibited Con A-stimulated mice splenocyte proliferation in a dose-dependent manner	33
92	8α,11-elemodiol	cytotoxicity	MTT assay *in vitro*	1.25–20 μmol·L^{-1}	inactive against human cancer cell lines A549, Hela, and Bel 7402, IC_{50} > 50 μmol·L^{-1}	33
95	*(E)*-4-(4,8-dimethylnona-3,7-dienyl) furan-2(5H)- one	antibiotic	TLC-Bioautography (huperzine A as positive control)	0.02–40 mg·mL^{-1}	Against *Escherichia coli* and *Bacillus subtilis*, with MIC values of 1.5 and 3.0 mg·mL^{-1}, and MBC values of 6.0 and 12.0 mg·mL^{-1}, respectively	24
118	prenylated-4-hydroxybenzoic acid	antibiotic	TLC-Bioautography (huperzine A as positive control)	0.02–40 mg·mL^{-1}	Against *Escherichia coli* and *Bacillus subtilis*, with MIC values of 2.0 and 1.0 mg·mL^{-1}, and MBC values of 16.0 and 8.0 mg·mL^{-1}, respectively	24
120	diisobutylphalate	antibiotic	TLC-Bioautography (huperzine A as positive control)	0.02–40 mg·mL^{-1}	Against *Escherichia coli* and *Bacillus subtilis*, with MIC values of 2.5 and 10.0 mg·mL^{-1}, and MBC values of 10.0 and 20.0 mg·mL^{-1}, respectively	24
130	benzylalcohol-β-D-xylopyranosyl (1→6)-β-D- glucopyranosid	melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 10.1 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1}	15
				0–100 μmol·L^{-1}	inactive in L-tyrosine or L-DOPA	
132	benzylalcohol-β-*D*- glucopyranosyl (1→6)-β-*D*-glucopyranoside	melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 27.8 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1}	15
				0–100 μmol·L^{-1}	inactive in L-tyrosine or L-DOPA	
137	(–)-pinoresinol 4,4'-di-O-β-D-glucopyranoside	melanogenesis inhibitory	theophylline-stimulated murine B16 melanoma 4A5 cells	0–30 μmol·L^{-1}	IC_{50} 6.8 μmol·L^{-1}, without notable cytotoxic effects at the effective concentrations 30 μmol·L^{-1}	15
				0–100 μmol·L^{-1}	inactive in L-tyrosine or L-DOPA	
139	emodin	antioxidant	Pre-column DPPH assay	40 mg·mL^{-1}	against DPPH radical, IC_{50} 1.93 μmol·L^{-1}	29

and IL-6 in LPS-stimulated zebrafish and RAW 264.7 cells, suggested that the ethanol extracts of *C. nitens* leaves might serve as a source of nutraceutical compounds with anti-inflammatory properties [8]. Clinical observation on the treatment of 48 cases of chronic atrophic gastritis with precancerous lesions by the decoction of *Chimonanthus nitens* leaves implicated the HP negative conversion rate of the cases was 45.83%, and significantly higher than that of the control group (26.19%) ($P < 0.05$). The total effective rate is 91.67% ($P < 0.05$) [81]. Shenqi Shanla Meiye decoction can treat chronic renal failure patients, effective relieve the symptoms of chronic renal failure, nutritional status and renal function. Total effective rate was 82.50% ($P < 0.05$), while decreasing hs-CRP, IL-6 and TNF-α might be one of its mechanisms [82]. Li *et al.* observed the therapeutic effects of Shanla Meiye Jianpi Decoction (SMJD) for AECOPD on serum levels of peripheral T-lymphocyte subpopulations. Results showed that SMJD has significant effects on improving the scores of TCM symptoms, arterial blood gas and lung function of patients with AECOPD. The total effective rate was 93.75% [83].

C. praecox flowers decoctions might significantly enhance the rat macrophage phagocytic activity ($P < 0.001$) and humoral immune function ($P < 0.001$) [60]. The alcohol extract from *C. praecox* could improve the general situation, and effectively inhibit the articular swelling of AA rats. Subsequently, the levels of TNF-α and PAF in the serum were decreased significantly [55].

Yang *et al.* used *C. salicifolius* enema to treat pelvic inflammatory, which was infected by mixed bacteria (*Escherichia coli*, *Staphylococcus aureus*), with gentamicin as a positive control, and found that the CD4/CD8+, IL-2 of T-lymphocytes were increased significantly, and the levels of IL-6 and TNF-α were significantly reduced compared to model group. Results indicated that *C. salicifolius* enema might improve immune function of chronic pelvic inflammation, regulate the balance and secretion of inflammatory factors [59]. Clinical observation on 72 cases of chronic pelvic inflammatory disease treated with *C. salicifolius* enema found that the total effective rate was 100% in the treatment group and 92.31% in the control group. There was a significant difference between the two groups, which indicated that the comprehensive curative effect of *C. salicifolius* enema was better than that of the control drug [77].

Antihypertensive and lipid-lowering

Iv 7 mg·kg^{-1} total alkaloids of Xiang Feng tea (*C. nitens*) in cats and dogs, the blood pressure can be decreased by 40% and lasting more than 0.5 h as well as iv 7 mg·kg^{-1} alkaloid C in cats, while iv alkaloid A and B 10 mg·kg^{-1}, respectively, the blood pressure was decreased only 20% and back to original levels within 5 min [56]. *C. nitens* leaves extract can affect the synthesis of body fat, which probably due to the inhibition of fatty acid synthase and interference in the accumulation of fat. Comparing with normal group, the Lee's index, fat index, triglyceride, and total cholesterol of high-dose of alcohol extract group greatly decreased by 7.19%, 42.04%, 41.34%, and 20.83%, respectively [57]. Another study found that the petroleum ether and n-butyl alcohol extracts in high dosage of *C. nitens* also had the function of reducing weight, anti-appetite and reducing fat [58]. Later Sun suggested that the ethyl linolenate, with the highest content of *C. nitens* petroleum ether, can be one of the material foundations for reducing total cholesterol and triglyceride. Therefore, the medicinal value of *C. nitens* petroleum ether fraction deserves a further investigation [21].

Antioxidant

A large number of experimental studies have shown that flavonoids are one of the main components of antioxidant activity of plants, can be used as a functional additive in the food industry and natural antioxidants. Zhang *et al.* evaluated antioxidant activity of nine main compositions from flowers of five *Chimonanthus* species, the results indicated that flavonoids and coumarins are the two major types of substances with antioxidant capacity in *Chimonanthus* flowers. Rutin, isoquercitrin and quercetin showed most potent antioxidative activity with IC_{50} of 1.65×10^{-3}, 0.017×10^{-3}, and 9.33×10^{-3} μmol·L^{-1}, respectively. Among the five *Chimonanthus* species, *C. praecox* flower is most abundant in secondary metabolites and shows most potent antioxidant activity. *C. praecox* is a good candidate for natural antioxidants industries related to pharmaceutical and functional ingredients [29]. Pan's group use ABTS method to evaluate the free radical scavenging activity of the seven compounds isolated from *C. salicifolius*, compounds (**21**, **22**, **38**) showed higher antioxidant activity than positive control Trolox with IC_{50} values 0.563, 1.53, 8.72 mmol·L^{-1} [46]. Zhang *et al.* use ABTS cation radical scavenging assay and FRAP assay to evaluate the antioxidant activities of alkaloids from *C. praecox* seeds, found (+)-calycanthine (**1**) have strong antioxidant activity with IC_{50} value of (3.24 ± 0.08) mg·L^{-1} against ABTS [50]. Study on the different polarity fractions of *C. salicifolicus* leaves in DPPH radical scavenging ability of the extracts with the concentration at 0.05–1.0 mg·mL^{-1} found that it had strong antioxidant activity in positive dose-dependent relationship. The fraction of ethyl acetate, dichloromethane, *n*-butanol, *n*-hexane, methanol and water had certain scavenging ability on DPPH with IC_{50} of 0.48, 0.61, 0.98, 1.11, 1.24 and 1.36 mg·mL^{-1}, respectively. When the concentration of ethyl acetate extract was 1.0 mg·mL^{-1}, the scavenging rate of DPPH free radical can reach 91.62%. Under the same concentration, the scavenging capacity of VC was 94.20%, which indicated that the antioxidant capacity of ethyl acetate extract was similar to that of VC and had the strongest antioxidant capacity.

Inhibit AChE

Yuan and Sun adopted the improved Ellman method to test the acetylcholinesterase inhibit activity of petroleum ether extract, ethyl acetate extract, *n*-BuOH extract and water extract of *C. praecox* and *C. nitens* leaves, respectively. The

results showed that the four parts had the inhibitory activity, but the ethyl acetate extract showed highest AChE inhibition rate, with the IC_{50} values of 6.809 and 13.27 mg·mL^{-1}, respectively. Meanwhile, by evaluated the acetylcholinesterase inhibit activity of individual compounds, found that compounds **1, 13** of *C. nitens* and **38**–**40** of *C. praecox* exhibit good inhibition effects on AChE activity, the IC_{50} value was 24.39, 9.84, 18.86, 33.16 and 23.37 μmol·L^{-1}, respectively [21, 37]. While another study found the petroleum ether fraction of *C. grammatus* owns certain extent inhibition activity, the inhibition rate of AChE changed very obviously from 1 mg·mL^{-1} to 10 mg·mL^{-1}, IC_{50} value is 8.1 mg·mL^{-1}[61].

Antihyperglycemic and Antihyperlipidemic

Chen *et al*. found that 50% ethanol eluates (EE) of *C. nitens* leaves showed the best inhibitory potency against *α*-glucosidase (IC_{50} 0.376 mg·mL^{-1}). In addition, the experiments of UF-LC–MS guided quercetin and kaempferol as the key factors for 50% EE showing highly inhibitory activity on *α*-glucosidase. Quercetin and kaempferol inhibited yeast *α*-glucosidase in a mixed-type manner with IC_{50} of 66.8 μg·mL^{-1}, 109 μg·mL^{-1} and *Ki* value of 0.42 ± 0.11 mmol·L^{-1}, 0.78 ± 0.13 mmol·L^{-1}. The obtained results suggested *C. nitens* leaves could be used as nutraceutical health supplement for treatment or prevention of T2DM [5]. And in later 2017, A further research investigated the antihyperglycemic and antihyperlipidemic efficacy and antioxidant capacity of *C. nitens* leaf extract (COE) in combination of high-glucose-fat diet-fed and streptozotocin-induced diabetic model mice. Various physiological indexes in diabetic model mice were well improved especially by oral administration of high dose of COE; the results showed that fast blood glucose level and serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, and malondialdehyde as well as malondialdehyde in liver were significantly reduced; fasting serum insulin and insulin sensitivity index were both increased; high-density lipoprotein cholesterol in serum was significantly increased; total antioxidant capacity activities of superoxide dismutase, glutathione peroxidase , and catalase in serum and liver were apparently enhanced; liver coefficient , liver transaminase, and alkaline phosphatase were decreased. Furthermore, pancreas islets and liver in diabetic model mice showed some extend of improvement in morphology and function after 4 weeks of COE treatment. In consequence, COE was advantageous to regulate glycolipid metabolism and elevate antioxidant capacity in diabetic model mice. Thus, the present study will provide a scientific evidence for the use of COE in the management of diabetes and its related complications [9].

Anti-tumor and anti-cancer

In 2009, Chen found *C. salicifolius* water extract could inhibit the proliferation, induce apoptosis and G2/M arrest of Hela cells *in vitro* [62]. *C. salicifolius* extract also has significant inhibitory effects on SGC-7901 cells proliferation, the possible mechanism might be related to cell apoptosis, When the concentration of extract was increased to 0.8 μg·mL^{-1}, the inhibition rate of SGC-7901 cell growth reached 89.39 ± 0.9%, and the IC_{50} was 0.5 μg·mL^{-1} at 24 h [63]. In 2013, Zhang found that the chloroform fraction from the ethanol extract of the leaves of *C. salicifolius* showed significant inhibitory activity against human colorectal cancer cell line HCT116 and human lung cancer line H1299, with IC_{50} of 56.5 and 26.9 μg·mL^{-1}. However, 10 compounds (38–**40, 42, 80**–**85**) that isolated from chloroform fraction were test on against human colorectal cancer cell line HCT116, human ovarian cancer cell line OVCAR3 and human glioma cells line U251, the result showed only nor-sesquiterpene (**83**) and coumarins (**39**, **42**) exhibit weak antitumor activity in Human Colorectal carcinoma cells, with the IC_{50} of 88.26, 81.56 and 88.26 μmol·L^{-1}, respectively. While the rest the IC_{50} were more than 100 μmol·L^{-1} of overall cell lines. Guess the chloroform fraction may still contain active compounds or has the synergy effects of the ingredients [41]. Later in 2016, Wang and coworkers found compounds **58**–**60** showed modest cytotoxicity against Hela and HL-60 cell lines, with IC_{50} values ranging from 14.2 to 29.6 mmol·L^{-1}, while only chimsalicifoliusin C (**60**) had the cytotoxicity against PC-3 cell line. And the positive control Cisplatin with IC_{50} values of 6.8, 8.6, 5.9μmol·L^{-1} for Hela, HL-60, PC-3 respectively [6]. A study showed that three sesquiterpenes (**90**–**92**) were inactive against human cancer cell lines (IC_{50} > 50 μmol·L^{-1}) including A549, Hela, and Bel 7402. Cisplatin was used as a positive control with IC_{50} of 4.71, 6.69, 5.10 μmol·L^{-1}. But compound **90** and **91** significantly inhibited Con A-stimulated mice splenocyte proliferation in a dose-dependent manner [33]. The petroleum ether extract, ethyl acetate extract, and *n*-BuOH extract of *C. grammatus* leaves owns certain inhibitory activity to lung cancer lines A549, while the concentration of the overall extra is between 500 and 1000 μg·mL^{-1}, so it is not obvious that the extracts of *C. grammatus* leaves can strongly inhibit the proliferation of lung cancer cell [64].

A great many of alkaloids from *Chimonanthus* have been reported have the biological activity on anti-tumor and anti-cancer. In 2011, Wang's group evaluated all isolated compounds for their cytotoxicity against a small panel of human cancer cell lines, and only the chimonanthine-type alkaloids (**4**–**6**) were found to have cytotoxic effects against gastric carcinoma NUGC3 and hepatocarcinoma SNU739 cancer cells, with IC_{50} ranging from 10.3 to 19.7 μmol·L^{-1}. 5-Fluorouracil used as positive control, with IC_{50} of 17.5 ± 2.9, 0.4 ± 0.1, 332.3 ± 25.1, 2.1 ± 0.9 μmol·L^{-1} for NUGC3, SHSY-5Y, SNU739, MCF-7 cell lines respectively [4]. In 2014, Toshio Morikawa *et al*. study found the methanol extract of the flower buds of *C. praecox* demonstrated inhibitory effects on melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells (IC_{50} 2.1 μmol·L^{-1}). Among the 23 ingredients, (–)-chimonanthine (**4**, IC_{50} 0.93 μmol·L^{-1}), (–)-folicanthine (**5**, 1.4 μmol·L^{-1}), and (–)-calycanthidine (**6**, 1.8 μmol·L^{-1}) showed potent inhibitory effects. And the most

potent alkaloid (**4**) inhibited both tyrosinase and tyrosine-related protein-1 mRNA expression [15]. Later in 2015, salicifoxazines A–B (**11**–**12**), *meso*- chimonanthine (**3**), (−)-chimonanthine (**4**) were found to show moderate cytotoxic effects against human colorectal carcinoma cells (SW-1116 and HCT-116) and/or gastric carcinoma cells (SGC-7901) comparing to positive control 5-Flurouracil (IC_{50} 5.0, 37.0, 19.6 μmol·L^{-1}, respectively) [18]. Based the current study, lots of *Chimonanthus* alkaloids have been improved exist significant activities on antitumor and anticancer. Thus, the further and systematic research on its photochemical and pharmacology should be going through.

Anti-depression

The ethanol extract of *C. nitens* leaves can significantly improve the behavioral changes of the model mice, and increase the content of monoamine neurotransmitters 5-HT and NE in the brain of the mice, which has certain anti-depression effects. And speculated that its active component may be flavonoids, including rutin, quercetin and kaempferol. However, its anti-depression effect is attributed to a flavonoid component, or a combination of several, which needs further study [65].

Anti-convulsion

(+)-Calycanthine (**1**), the principal alkaloid of the family *Calycanthaceae*, has long been recognized as a central convulsant. It was reported that calycanthine may mediate its convulsant action predominantly by inhibiting the release of the inhibitory neurotransmitter GABA as a result of interactions with L-type Ca^{2+} channels and by inhibiting GABA-mediated chloride currents at $GABA_A$ receptors [68].

Other effects

The aqueous extract of *C. salicifolius* benefits mice (5, 10, and 20 g·kg^{-1}) against 5-Fluorouracil induced gastrointestinal mucositis, attenuating the subsequent body weight loss, diarrhea, and faecal blood, reducing the hepatic injury, and maintaining both intestinal length and villus structure, and the protective effect might be associated with 3 flavonoids (rutin, quercetin and kaempferol) [66]. The extracts of *C. salicifolius* also can ameliorate liver injury induced by alcohol, the levels of ALT and AST reduced significantly compared to model group, and histological damage or inflammatory response were significantly reduced ($P < 0.05$) [67]. (−)-folicanthine (**5**), (−)-chimonanthine (**4**), and aeanthoside B (**136**) also showed a weak effect on Porcine reproductive and respiratory syndrome virus (PRRSV) [23]. The total flavonoids of the *C. praecox* leaves could significantly inhibit ST-segment elevation of ECG, prolong the duration of mouth-opening breathing, increase the number of breathing, inhibit the elevation of CK and LDH in serum, increase SOD activity in myocardium and decrease the content of MDA, can treat acute myocardium induced by isoproterenol in mice [80]. *C. salicifolius* water extract can reduce the total number of stools, the rare rate, the level of loose stools and diarrhea index series, had antidiarrheal effect ($P < 0.01$) [78].

Toxicology

Studying on maternal toxicity, embryotoxicity and teratogenicity of *C. salicifolius* water extract of in SD rats showed there was no significant difference in the conception rate, total weight gain during the pregnancy and the number of living, dead and resorbed fetuses between each dosage groups (3.75, 7.5 and 15.0 g·kg^{-1}) and the control group ($P > 0.05$). The number of the rib, sternum, the fifth sternum punctate and the parietal bone which were ossified defectively all showed no difference among the four groups ($P > 0.05$). The *C. salicifolius* extract had no obvious maternal toxicity, embryotoxicity and teratogenicity in SD rats under this experiment condition [69]. The acute toxicity test of boiling water extracts from the leaves of *C. Zhejiang* in ICR mice drew the same conclusion. It found that LD_{50} couldn't be measured in 0.3 mL/10 g intragastric administration, and the maximum tolerated dose was 80 g·kg^{-1}. And they also analyzed the alkaloids of the extract, only yielded 0. 0048%. Due to the low content (0.0048%) of alkaloids, the *C. Zhejiang* tea had high safety and could be directly consumed [70].

However, Du reported one case of overdosing *C. praecox* root, the patient appeared poison phenomenon with muscle spasms strongly and frequently, and minute traces of urinary protein, red blood cells (++), pus cells 0–2 were detected, indicated the plants has certain damage to kidney, which can cause hematuria [73]. Another data indicated that intravenous injection with chimonanine in mice the LD_{50} was 43.79 ± 1.89 mg·kg^{-1}, and the rats were 17.16 ± 0.82 mg·kg^{-1}. And it was more toxic to rabbits, the LD_{50} was about 10–40 mg·kg^{-1}, could be lethal by intravenous injection and the maximum tolerance was 7.5 mg·kg^{-1} [79].

In the 80–90 century of the last century, there were lots of articles reported that after cattle or goats overate *C. praecox* would induce a series toxicity symptom, especially from April to early May with a high morbidity. Both of them pointed out the poisoning symptoms showed after they mistakenly eat *C. praecox* 1–2 h. The light clinal signs is terrified, hyper pyretic, tachycardia, tachypnea, and anti-feeding, the weight can be recumbency, opisthotonos, tetanic seizures and even cause death. Meanwhile, comparing to overeat *C. praecox* leaves, only a small amount of *C. praecox* seeds can present acute toxicity symptom less in 1 hour if cattle and sheep mistakenly eat, which indicating that the toxicity of the seeds is greater than leaves. Because the toxicity ingredient is alkaloid [74] and the seeds of *C. praecox* (also called "Tubadou" in Chinese) are rich in alkaloids and have a high content of alkaloids (63.41%) [71]. A latest study in 2016, also reported the same accidents, and found the alkaloid calycanthine are mainly toxicity ingredient [72].

Calycanthine is contained within various parts of the plant. But mostly distributed in *C. praecox*. It is a popular garden and ornamental plant, sprouting in March, flourishing

from April to early May and yielding seeds from June to July. During this time, it is easy for animals to mistakenly eat *C. praecox* and produce poisoning, practitioners should be aware of its appearance and clinical signs of toxicity. And when people take them as tea beverage, the seeds which contain the high content of alkaloids especially should be picked out particularly to ensure safety. Meanwhile, more details in clinical research should be taken in *Chimonanthus* alkaloids. In addition, alkaloids as a bioactive ingredient are also toxic components, which should be noted in clinical treatment.

Future Perspectives and Conclusion

The genus *Chimonanthus* plants, a popular garden and ornamental plant, is widely distributed in southern areas of China. It has been used as a traditional Chinese medicine for treatment of cough, influenza, asthma, antitussive, hypertension, dizziness, nausea, stomach ache, fever, rheumatic arthritis, sedative and also used for detoxification. We summarize the active constituents and pharmacological effects, functional mechanisms as well as its clinical applications of *Chimonanthus*. The chemical constituents of this genus *Chimonanthus* are composed of alkaloids, flavonoids, coumarins, sesquiterpene, and other secondary metabolites. Up to date, approximately 143 metabolites and 40 bioactive compounds have been reported from 6 species. Alkaloids, flavonoids and coumarins are three potent bioactives secondary metabolites. d-calycanthine (1), (–)-chimonanthine (3), quercetin (21), kaempferol (22), rutin (23), scopoletin (38), scoparone (39), isofraxidin (40) were most widely observed in *Chimonanthus* species, which may be recommended feature indexes for quality assessment and identification. The bioactivities of *Chimonanthus* plants involved in antibacterial, antifungal, antioxidant, anticarcinogenic, anti-inflammatory, antipyretic-analgesic, weight losing and lipid lowering, gut and gastric modulatory, hepatoprotective, antidiarrheal, anti-AChE, antihypertensive, anti-convulsant, melanogenesis inhibitory, α-glucosidase inhibitory. In clinic, it is used to relieving cough and reducing sputum, treat influenza, fever, headache, sore throat, asthma, epigastric fullness, Gastric distention, stomachache, gastric acid, diarrhea, urethritis, traumatic injury, hand-foot-and-mouth disease, rheumatic arthritis and so on.

The genus plants have abundant bioactive constituents and significant medicinal value, with high potential for development. China possess abundant natural resources of medicinal plants, looking for new active lead compounds has become one of the most important ways to new drug research and development. Based on brief review of *Chimonanthus* and for the further research on *Chimonanthus*, we think the following aspects should be given more attention:

First, *C. praecox*, *C. nitens*, and *C. salicifolius* are three *Chimonanthus* species best-known and most thoroughly phytochemical characterized. However, the chemically and pharmacologically knowledge on other plants is very limited. In addition, some plant extracts were only screened for their preliminary in vitro activities. Given the extracts always have a marked pharmacological activity, so the advanced clinical trial of them deserves to be investigated further. And the isolation of particular constituents responsible for the activities for further process is still necessary.

Second, alkaloids, flavonoids, coumarins and terpenoids are four potent bioactive secondary metabolites. For example, alkaloid is one of the most active ingredients of *Chimonanthus*, and exhibit significant pharmacological activity in antitumor and anticancer especially. Cause the high similarity in structural and low contents of *Chimonanthus* alkaloids have made the isolation, purification and stereochemistry determination challenging, resulting in difficulties to obtain enough amounts for pharmacological assays, especially for *in vivo* testing. Thus, to take full advantage of their anti-tumor and anti-cancer effects, great efforts should be made in chemistry, including synthesis, structural modification, and pharmacological studies. In a word, a detailed study is required to understand the structure–activity relationship of these constituents. In addition, alkaloids are mainly toxicity ingredients of *Chimonanthus* either, the safety of medication should be considered necessary in treatment.

Based upon the above points, researchers should perform a systematic, intensive study on chemical constituents of *Chimonanthus* by using modern pharmacological methods to find active lead compounds, which may provide the scientific basis for the development of new drugs of traditional Chinese medicine andpromote the utilization of the plant resources of *Chimonanthus*.

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