



The genus *Codonopsis* (Campanulaceae): a review of phytochemistry, bioactivity and quality control

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Abstract *Codonopsis*, in the family Campanulaceae, is a genus containing 42 species of dicotyledonous herbaceous perennial plants, predominantly found in Central, East and South Asia. Several *Codonopsis* species are widely used in traditional medicine and are considered to have multiple medicinal properties. Among the *Codonopsis* species, *Codonopsis pilosula* (Franch.) Nannf. and *C. lanceolata* (Sieb. et Zucc.) Benth. & Hook. f. ex Trautv. are more popular than others according to the findings, especially phytochemical and bioactive studies. Phytochemical research shows that *Codonopsis* species contain mainly polyacetyles, phenylpropanoids, alkaloids, triterpenoids and polysaccharides, which contribute to multiple bioactivities. However, the mechanisms of their bioactivities need to be further elucidated. The less popular *Codonopsis* species remain to be studied and exploited. In addition, although a series of methods for the quality evaluation of *Codonopsis* species have been developed, a feasible and reliable approach to the efficacious and safe use of various *Codonopsis* species is still needed, with considering botanical origin, chemical constituents and bioactive effects. This review aims to provide up-to-date and comprehensive information on the phytochemistry, bioactivity and quality control of medicinal plants in the genus *Codonopsis* and to highlight current gaps in knowledge,

which is useful for the wider development of the *Codonopsis* genus.

Keywords *Codonopsis* · Phytochemistry · Bioactivity · Quality control

Introduction

Codonopsis, which is a dicotyledonous genus of herbaceous perennial plants in the family Campanulaceae, has 42 species predominantly distributed in Central, East and South Asia; 40 *Codonopsis* species can be found in China [1]. However, *Codonopsis pilosula* (Franch.) Nannf., *C. pilosula* Nannf. var. *modesta* (Nannf.) L. D. Shen, *C. tangshen* Oliv. and *C. lanceolata* (Sieb. et Zucc.) Benth. & Hook. f. ex Trautv. are the only species widely used, of which the fresh or dried roots are collectively regarded as famous herbal medicines and have been used in folk medicine for hundreds of years. *Codonopsis Radix* is prescribed as the dried roots of *C. pilosula*, *C. pilosula* var. *modesta* and *C. tangshen* in the Chinese Pharmacopoeia (2010 edition) [2]. It is called “Dangshen” in Chinese and “Tojin” in Japanese, and has been used in traditional Chinese medicine for replenishing *qi* (vital energy) deficiency, strengthening the immune system, improving poor gastrointestinal function, gastric ulcer and appetite, decreasing blood pressure, etc., and is sometimes used as a substitute for Ginseng (*Panax ginseng* C. A. Mey.) [3, 4]. The roots of other *Codonopsis* species, including *C. tubulosa*, *C. subglobosa*, *C. clematidea* and *C. lanceolata*, are reported to be used as substitutes for *Codonopsis Radix* in some regions [3]. *C. lanceolata*, commonly called bonnet bellflower, is a herb with high value in traditional Chinese medicine and its root is also becoming popular as a

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special vegetable in some Asian countries [5]. *C. lanceolata* has been used for the treatment of bronchitis, asthma, cough, tuberculosis, dyspepsia and psychoneurosis [6–8]. Phytochemical researches have revealed that the roots of *Codonopsis* species contained alkaloids, phenylpropanoids, triterpenoids, polyacetylenes, flavones, organic acid, polysaccharides, etc. [9–54]. Among them, polyacetylenes, phenylpropanoids, alkaloids, triterpenoids and polysaccharides are considered to be the major constituents and responsible for most of the activities found in the plants of this genus. The chemical profile varied greatly between species and sample collections may cause these *Codonopsis* species to possess diverse bioactivities. Some compounds belonging to these five chemotypes have been evaluated for potential biological activity and pharmacological mechanisms. However, the pharmacological mechanisms of these *Codonopsis* species related to biological activity and clinical application remain largely unexplained. Additionally, the toxicity of *Codonopsis* has not been reported in the scientific literature.

As many investigations indicated that a variety of chemical constituents contributed to the effects of *Codonopsis* species, the quantitation of bioactive components becomes urgent for ensuring the efficacy of *Codonopsis* species. In the Chinese Pharmacopoeia (2010 edition), only lobetyolin is used as the chemical marker for identification of *Codonopsis Radix*, which seems useless for many *Codonopsis* species involved [2]. Hence, a number of studies have attempted to develop accurate, sensitive and selective analytical methods for qualitative and quantitative evaluation of *Codonopsis* materials.

To provide information benefiting traditional uses and scientific studies, this review summarizes and evaluates the available phytochemical and bioactive properties of *Codonopsis* genus reported by the literature. In addition, for the efficacious and safe uses of *Codonopsis*, the progress of research on quality evaluation of various *Codonopsis* species is also presented.

Chemical constituents of genus *Codonopsis*

Phytochemical studies have been performed on *Codonopsis* species plants over the last 30 years all around the world. Only some of the different *Codonopsis* species plants have been explored for obtaining information on chemo-taxonomical identification, isolation and identification of various important chemicals from this genus and comparison of the chemicals in different plants or species.

C. pilosula, *C. tangshen*, *C. lanceolata* and *C. clematidea* have been widely investigated in their phytochemistry; more than 100 compounds have thereby been isolated and identified. On the other hand, few compounds in *C.*

cordifolioidea, *C. nervosa*, *C. thalictrifolia*, *C. xundianensis* and *C. tubulosa* are reported because they are found only in selected regions. The components in other *Codonopsis* species have not yet been reported since these *Codonopsis* species may be difficult to collect and/or be scarce. To date, polyacetylenes, phenylpropanoids, alkaloids, triterpenoids, etc. have been isolated and characterized from the different parts of these *Codonopsis* species plants. The names of these constituents, the plant and the parts from which they are derived are summarized in Table 1. The structures of the compounds are shown in Figs. 1, 2, 3, 4, 5, 6 and 7.

Alkaloids

The pyrrolidine alkaloids codonopsine (1), codonopsinine (2), codonopsinol (3) and radicamine A (4) were isolated from the aerial parts of *C. clematidea* [9, 10]. Two pyrrolidine alkaloids, codonopyrrolidiums A (5) and B (6), were isolated from the roots of *C. tangshen* [13], and were also found in the roots of *C. pilosula* and *C. pilosula* var. *modesta* [12, 14]. In addition, the pyrrolidine alkaloids codonopsinols A (7), B (8), C (9) and the glycoside, codonopiloside A (10) were obtained from the roots of *C. pilosula* [11]. Codotubulosine B (11) was found in the roots of *C. tubulosa* [15].

Other alkaloids, *n*-9-formyl harman (12), norharman (13), 1-carbomethyl carboline (14), 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid (15) and tryptophan (16), were isolated from the roots of *C. lanceolata* [16, 17, 19]. Tryptophan (16), perlolyrine (17) and nicotinic acid (18) were obtained from the roots of *C. pilosula* [18, 20, 21]. The common compounds uracil (19) and adenosine (20) were found in the roots of *C. pilosula* and the roots of *C. pilosula* and *C. tangshen*, respectively [13, 18, 22].

Phenylpropanoids

The phenylpropanoids tangshenosides I (21), II (22), III (23) and IV (24) were first isolated from *C. tangshen* [23, 25]. Tangshenoside V (25), tangshenoside VI (26) and codonosides A (27) and B (28), considered to be the characteristic components, were isolated from *C. tangshen* [13, 26]. Tangshenoside VI (26) was also isolated from the aerial parts of *C. nervosa* [27]. Recently, tangshenoside VIII (29) has been obtained from the roots of *C. lanceolata* [24]. In addition, 12 phenylpropanoids, cordifoliketones A (30) and B (31), sinapinaldehyde (32), coniferaldehyde (33), coniferoside (34), isoconiferin (35), nervolans B (36) and C (37), dillapiole (38), 1-allyl-2,6-dimethoxy-3,4-methylenedioxybenzene (39), 4-allyl-2-(3-methylbut-2-en-

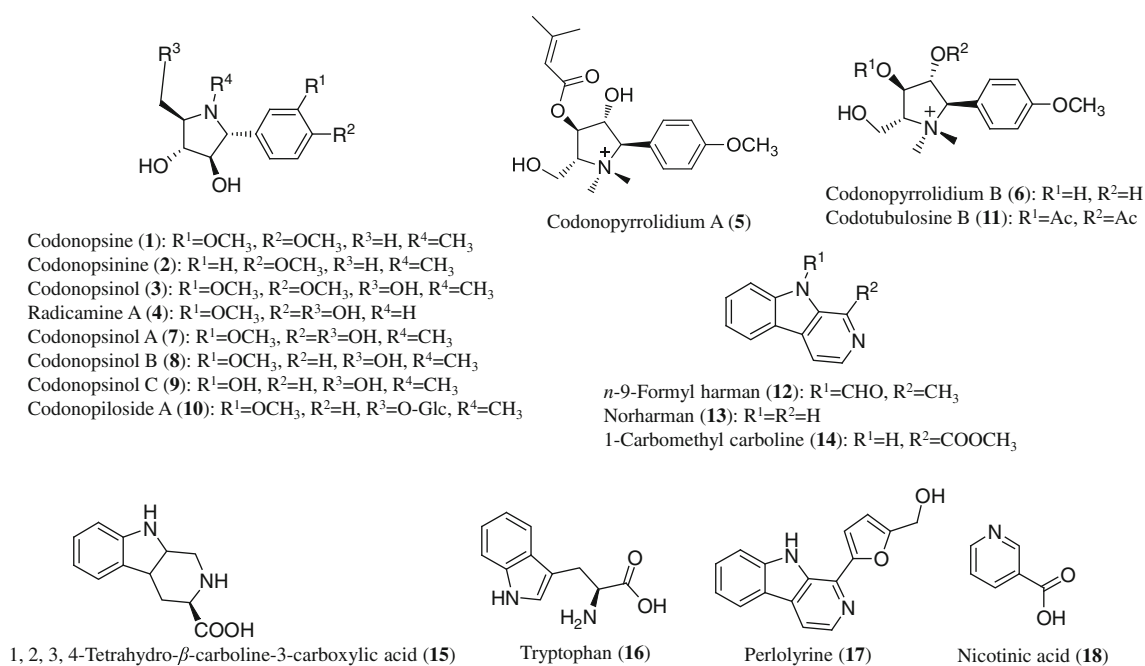


Fig. 1 Structures of alkaloids (1–18) from *Codonopsis* species

1-yl) phenol (40) and sachaliside (41), were isolated from the roots of *C. cordifolioides* [28, 29]. Syringin (42) has been commonly found in 5 *Codonopsis* species [21, 23, 30–32].

Triterpenes

Three new triterpenyl esters, codonopilates A (43), B (44) and C (45), together with seven known triterpenoids, 24-methylenecycloartanyl linolate (46), 24-methylenecycloartan-3-ol (47), friedelin (48), 1-friedelin-3-one (49), stigmast-7-en-3-one (50), taraxerol (51) and stigmast-7-en-3-ol (52), were isolated from the CHCl₃-soluble fraction of the methanol extract of *C. pilosula* [14]. Additionally, α-spinasterol (53) was obtained from *C. pilosula*, *C. tangshen*, *C. lanceolata* and *C. thalictrifolia* [32–35], and taraxeryl acetate (54) was obtained from *C. pilosula*, *C. tangshen* and *C. clematidea* [10, 34, 35]. The oleanan-type bisdesmoside with sugars at C-3 and C-28, codonolaside (55), codonolasides I (56), II (57) and III (58), and their prosapogenins, eclalbasaponin XIII (59) and echinocystic acid 3-*O*-β-D-glucuronopyranoside (60), were isolated from the roots of *C. lanceolata* [36]. The triterpene saponins, lancemasides A (61), B (62), C (63), D (64), E (65), F (66) and G (67), have also been isolated from the roots of *C. lanceolata* cultivated in Korea [19]. Codonolaside IV (68), codonolaside V (69), foetidissimoside A (70), aster saponin Hb (71), oleanolic acid (72), echinocystic acid (73) and stigmasterol (74) were found in the roots of *C. lanceolata*

[19, 30, 34, 37–39]. Foetidissimoside A (70) and rubiprasin B (75) were isolated from the aerial parts of *C. clematidea* [10]. For the aerial parts of *C. thalictrifolia*, isolation of α-spinasterol (53) and β-amyirin acetate (76) was reported [32]. Zeorin (77) and lupeol (78) were isolated from the whole plants of *C. nervosa* [40].

Polyacetylenes

Isolation and identification of lobetyolin (79), lobetyolinin (80) and lobetyol (81) from the roots and aerial parts of plants belonging to the genus *Codonopsis* have also been reported [10, 12, 18, 25, 27, 29, 32, 34, 41, 42]. Three new polyacetylene glucosides, cordifolioidynes A (82), B (83) and C (84), were isolated from a 95 % ethanol extract of the roots of *C. cordifolioides* [29]. Recently, cordifolioidynes B (83) has also been found in *C. pilosula*, *C. pilosula* var. *modesta* and *C. tangshen*, which are the botanical sources of *Codonopsis* Radix [12].

Flavones

Chrysoeriol (85), triclin (86), wogonin (87) and luteolin (88) were isolated from the roots of *C. xundianensis* Wang ZT and Xu GJ, which grows in Yunnan Province, China [43]. Luteolin (88), kaempferol (89), luteolin-5-*O*-β-D-glucopyranoside (90), luteolin-7-*O*-β-D-gentiobioside (91), apigenin-7-*O*-β-D-glucopyranoside (92) and luteolin-7-*O*-

Table 1 Compounds in *Codonopsis* species

No.	Compound names	Species	Part of the plant	References
<i>Alkaloids</i>				
1	Codonopsine	<i>C. clematidea</i>	Aerial parts	[9]
2	Codonopsinine	<i>C. clematidea</i>	Aerial parts	[9]
3	Codonopsinol	<i>C. clematidea</i>	Aerial parts	[10]
4	Radicamine A	<i>C. pilosula</i>	Roots	[11]
5	Codonopyrrolidium A	<i>C. clematidea</i>	Aerial parts	[10]
		<i>C. pilosula</i>	Roots	[12]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[12]
6	Codonopyrrolidium B	<i>C. tangshen</i>	Roots	[13]
		<i>C. pilosula</i>	Roots	[14]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[12]
7	Codonopsinol A	<i>C. tangshen</i>	Roots	[13]
8	Codonopsinol B	<i>C. pilosula</i>	Roots	[11]
9	Codonopsinol C	<i>C. pilosula</i>	Roots	[11]
10	Codonopiloside A	<i>C. pilosula</i>	Roots	[11]
11	Codotubulosine B	<i>C. pilosula</i>	Roots	[11]
12	<i>n</i> -9-Formyl harman	<i>C. tubulosa</i>	Roots	[15]
13	Norharman	<i>C. lanceolata</i>	Roots	[16]
14	1-Carbomethyl carboline	<i>C. lanceolata</i>	Roots	[16]
15	1,2,3,4-Tetrahydro- β -carboline-3-carboxylic acid	<i>C. lanceolata</i>	Roots	[16]
16	Tryptophan	<i>C. lanceolata</i>	Roots	[17]
17	Perlolyrine	<i>C. pilosula</i>	Roots	[18]
		<i>C. lanceolata</i>	Roots	[19]
18	Nicotinic acid	<i>C. pilosula</i>	Roots	[20]
19	Uracil	<i>C. pilosula</i>	Roots	[21]
20	Adenosine	<i>C. pilosula</i>	Roots	[18]
21	Tangshenoside I	<i>C. pilosula</i>	Roots	[22]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[13]
		<i>C. tangshen</i>	Roots	[23]
		<i>C. lanceolata</i>	Roots	[24]
22	Tangshenoside II	<i>C. tangshen</i>	Roots	[23]
		<i>C. lanceolata</i>	Roots	[24]
23	Tangshenoside III	<i>C. tangshen</i>	Roots	[25]
		<i>C. lanceolata</i>	Roots	[24]
24	Tangshenoside IV	<i>C. tangshen</i>	Roots	[25]
		<i>C. lanceolata</i>	Roots	[24]
25	Tangshenoside V	<i>C. tangshen</i>	Roots	[26]
26	Tangshenoside VI	<i>C. tangshen</i>	Roots	[26]
		<i>C. nervosa</i>	Aerial parts	[27]
27	Codonoside A	<i>C. tangshen</i>	Roots	[13]
28	Codonoside B	<i>C. tangshen</i>	Roots	[13]
29	Tangshenoside VIII	<i>C. lanceolata</i>	Roots	[24]
30	Cordifoliketone A	<i>C. cordifolioidea</i>	Roots	[28]

Table 1 continued

No.	Compound names	Species	Part of the plant	References
31	Cordifoliketone B	<i>C. cordifolioidea</i>	Roots	[28]
32	Coniferaldehyde	<i>C. cordifolioidea</i>	Roots	[29]
33	Sinapinaldehyde	<i>C. cordifolioidea</i>	Roots	[29]
34	Coniferoside	<i>C. cordifolioidea</i>	Roots	[29]
35	Isoconiferin	<i>C. cordifolioidea</i>	Roots	[29]
36	Nervolan B	<i>C. cordifolioidea</i>	Roots	[28]
37	Nervolan C	<i>C. cordifolioidea</i>	Roots	[28]
38	Dillapiole	<i>C. cordifolioidea</i>	Roots	[28]
39	1-Allyl-2,6-dimethoxy-3,4-methylenedioxybenzene	<i>C. cordifolioidea</i>	Roots	[28]
40	4-Allyl-2-(3-methylbut-2-en-1-yl) phenol	<i>C. cordifolioidea</i>	Roots	[28]
41	Sachalaside	<i>C. cordifolioidea</i>	Roots	[29]
42	Syringin	<i>C. pilosula</i>	Roots	[21]
		<i>C. tangshen</i>	Roots	[23]
		<i>C. lanceolata</i>	Roots	[30]
		<i>C. nervosa</i>	Aerial parts	[31]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
<i>Triterpenes</i>				
43	Codonopilate A	<i>C. pilosula</i>	Roots	[14]
44	Codonopilate B	<i>C. pilosula</i>	Roots	[14]
45	Codonopilate C	<i>C. pilosula</i>	Roots	[14]
46	24-Methylenecycloartanyl linolate	<i>C. pilosula</i>	Roots	[14]
47	24-Methylenecycloartan-3-ol	<i>C. pilosula</i>	Roots	[14]
48	Friedelin	<i>C. pilosula</i>	Roots	[14]
		<i>C. tangshen</i>	Roots	[12]
		<i>C. lanceolata</i>	Roots	[33]
49	1-Friedelen-3-one	<i>C. pilosula</i>	Roots	[14]
50	Stigmast-7-en-3-one	<i>C. pilosula</i>	Roots	[14]
51	Taraxerol	<i>C. pilosula</i>	Roots	[14]
		<i>C. tangshen</i>	Roots	[34]
52	Stigmast-7-en-3-ol	<i>C. pilosula</i>	Roots	[14]
53	α -Spinasterol	<i>C. pilosula</i>	Roots	[35]
		<i>C. tangshen</i>	Roots	[34]
		<i>C. lanceolata</i>	Roots	[33]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
54	Taraxeryl acetate	<i>C. pilosula</i>	Roots	[35]
		<i>C. tangshen</i>	Roots	[34]
		<i>C. clematidea</i>	Aerial parts	[10]
55	Codonolaside	<i>C. lanceolata</i>	Roots	[36]
56	Codonolaside I	<i>C. lanceolata</i>	Roots	[36]
57	Codonolaside II	<i>C. lanceolata</i>	Roots	[36]
58	Codonolaside III	<i>C. lanceolata</i>	Roots	[36]
59	Eclalbasaponin XIII	<i>C. lanceolata</i>	Roots	[36]
60	Echinocystic acid-3- <i>O</i> -(6'- <i>O</i> -methyl)- β -D-glucuronopyranoside	<i>C. lanceolata</i>	Roots	[36]
61	Lancemaside A	<i>C. lanceolata</i>	Roots	[19]
62	Lancemaside B	<i>C. lanceolata</i>	Roots	[19]
63	Lancemaside C	<i>C. lanceolata</i>	Roots	[19]
64	Lancemaside D	<i>C. lanceolata</i>	Roots	[19]
65	Lancemaside E	<i>C. lanceolata</i>	Roots	[19]

Table 1 continued

No.	Compound names	Species	Part of the plant	References
66	Lancemaside F	<i>C. lanceolata</i>	Roots	[19]
67	Lancemaside G	<i>C. lanceolata</i>	Roots	[19]
68	Codonolaside IV	<i>C. lanceolata</i>	Roots	[37]
69	Codonolaside V	<i>C. lanceolata</i>	Roots	[38]
70	Foetidissimoside A	<i>C. lanceolata</i>	Roots	[19]
		<i>C. clematidea</i>	Aerial parts	[10]
71	Aster saponin Hb	<i>C. lanceolata</i>	Roots	[39]
72	Oleanolic acid	<i>C. lanceolata</i>	Roots	[30]
73	Echinocystic acid	<i>C. lanceolata</i>	Roots	[30]
74	Stigmasterol	<i>C. tangshen</i>	Roots	[34]
		<i>C. lanceolata</i>	Roots	[33]
75	Rubiprasin B	<i>C. clematidea</i>	Aerial parts	[10]
76	β-Amyrin acetate	<i>C. thalictrifolia</i>	Aerial parts	[32]
77	Zeorin	<i>C. nervosa</i>	Whole plants	[40]
78	Lupeol	<i>C. nervosa</i>	Whole plants	[40]
	<i>Polyacetylenes</i>			
79	Lobetyolin	<i>Codonopsis pilosula</i>	Roots	[18]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[12]
		<i>C. tangshen</i>	Roots	[25]
		<i>C. lanceolata</i>	Roots	[41]
		<i>C. clematidea</i>	Aerial parts	[10]
		<i>C. cordifolioidea</i>	Roots	[29]
		<i>C. nervosa</i>	Whole plants	[27]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
80	Lobetyolinin	<i>C. pilosula</i>	Roots	[18]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[12]
		<i>C. tangshen</i>	Roots	[12]
		<i>C. clematidea</i>	Aerial parts	[10]
81	Lobetyol	<i>C. pilosula</i>	Roots	[42]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[12]
		<i>C. tangshen</i>	Roots	[34]
		<i>C. cordifolioidea</i>	Roots	[29]
82	Cordifolioidyne A	<i>C. cordifolioidea</i>	Roots	[29]
83	Cordifolioidyne B	<i>C. pilosula</i>	Roots	[12]
		<i>C. pilosula</i> var. <i>modesta</i>	Roots	[12]
		<i>C. tangshen</i>	Roots	[12]
		<i>C. cordifolioidea</i>	Roots	[29]
84	Cordifolioidyne C	<i>C. cordifolioidea</i>	Roots	[29]
	<i>Flavones</i>			
85	Chrysoeriol	<i>C. xundianensis</i>	Roots	[43]
86	Tricin	<i>C. xundianensis</i>	Roots	[43]
87	Wogonin	<i>C. xundianensis</i>	Roots	[43]

Table 1 continued

No.	Compound names	Species	Part of the plant	References
88	Luteolin	<i>C. nervosa</i>	Whole plants	[40]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
		<i>C. clematidea</i>	Aerial parts	[10]
		<i>C. xundianensis</i>	Roots	[43]
89	Kaempferol	<i>C. nervosa</i>	Whole plants	[40]
90	Luteolin-5- <i>O</i> - β -D-glucopyranoside	<i>C. nervosa</i>	Aerial parts	[27]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
91	Luteolin-7- <i>O</i> - β -D-gentiobioside	<i>C. nervosa</i>	Aerial parts	[27]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
92	Apigenin-7- <i>O</i> - β -D-glucopyranoside	<i>C. nervosa</i>	Aerial parts	[31]
93	Luteolin-7- <i>O</i> - β -D-glucopyranosyl(1 \rightarrow 6)-[(6''- <i>O</i> -caffeoyl)]- β -D-glucopyranoside	<i>C. nervosa</i>	Whole plants	[40]
		<i>C. clematidea</i>	Aerial parts	[10]
94	Hesperidin	<i>C. pilosula</i>	Roots	[35]
95	Succinic acid	<i>C. pilosula</i>	Roots	[44]
		<i>C. nervosa</i>	Aerial parts	[31]
96	3- <i>O</i> -caffeoylquinic acid	<i>C. nervosa</i>	Aerial parts	[31]
		<i>C. thalictrifolia</i>	Aerial parts	[32]
97	5- <i>O</i> -caffeoylquinic acid	<i>C. nervosa</i>	Aerial parts	[31]
98	4-(β -D-Glucopyranosyl)-benzoic acid	<i>C. nervosa</i>	Aerial parts	[31]
99	Caffeic acid	<i>C. thalictrifolia</i>	Aerial parts	[32]
100	Linoleic acid	<i>C. thalictrifolia</i>	Aerial parts	[32]
101	9,10,13-Trihydroxy-(<i>E</i>)-octadec-11-enoic acid	<i>C. pilosula</i>	Roots	[35]
102	Shikimic acid	<i>C. lanceolata</i>	Roots	[33]
103	Vanillic acid	<i>C. tangshen</i>	Roots	[34]
	<i>Other compounds</i>			
104	Atractylenolide III	<i>C. pilosula</i>	Roots	[21]
105	5-Hydroxymethyl-2-furaldehyde	<i>C. pilosula</i>	Roots	[14]
		<i>C. tangshen</i>	Roots	[34]
106	Angelicin	<i>C. pilosula</i>	Roots	[44]
107	Psoralen	<i>C. pilosula</i>	Roots	[44]
108	Emodin	<i>C. pilosula</i>	Roots	[18]
109	Geniposide	<i>C. pilosula</i>	Roots	[17]
110	Hexyl- β -D-glucopyranoside	<i>C. pilosula</i>	Roots	[18]
111	Butyl- β -D-fructouranoside	<i>C. pilosula</i>	Roots	[18]
112	β -Sitosterol	<i>C. pilosula</i>	Roots	[35]
		<i>C. nervosa</i>	Whole plants	[40]
113	β -Daucosterol	<i>C. pilosula</i>	Roots	[35]
114	Hexyl- β -gentiobioside	<i>C. tangshen</i>	Roots	[25]
115	Hexyl- β -sophoroside	<i>C. tangshen</i>	Roots	[25]
116	(<i>E</i>)-2-hexenyl- β -sophoroside	<i>C. tangshen</i>	Roots	[25]
117	(E)-2-hexenyl- α -L-arabinopyranosyl(1 \rightarrow 6)- β -D-glucopyranoside	<i>C. tangshen</i>	Roots	[25]
		<i>C. clematidea</i>	Aerial parts	[10]
118	Cordifoliflavane A	<i>C. cordifolioidea</i>	Roots	[45]
119	Cordifoliflavane B	<i>C. cordifolioidea</i>	Roots	[45]
120	Lanceolone A	<i>C. lanceolata</i>	Roots	[46]
121	Lanceolone B	<i>C. lanceolata</i>	Roots	[46]
122	Lanceolone C	<i>C. lanceolata</i>	Roots	[46]

Table 1 continued

No.	Compound names	Species	Part of the plant	References
123	Codonocerebroside A	<i>C. lanceolata</i>	Roots	[41]
124	3-Oxo- α -ionol- β -D-glucopyranoside	<i>C. clematidea</i>	Aerial parts	[10]
125	1,6-Hexanediol,3,4-bis(4-hydroxy-3-methoxyphenyl)	<i>C. clematidea</i>	Aerial parts	[10]
126	Sweroside	<i>C. nervosa</i>	Whole plants	[40]

β -D-glucopyranosyl(1 \rightarrow 6)-[(6'''-O-caffeoyl)]- β -D-glucopyranoside (**93**) were obtained from *C. nervosa* [27, 31, 40], and luteolin (**88**), luteolin-5-O- β -D-glucopyranoside (**90**) and luteolin-7-O- β -D-gentiobioside (**91**) were also found in the aerial parts of *C. thalictrifolia* [32]. In addition, luteolin (**88**) and luteolin-7-O- β -D-glucopyranosyl(1 \rightarrow 6)-[(6'''-O-caffeoyl)]- β -D-glucopyranoside (**93**) were isolated from the aerial parts of *C. clematidea* [10]. Hesperidin (**94**) was only isolated from the roots of *C. pilosula* [35].

Organic acids

To date, succinic acid (**95**), 3-O-caffeoylquinic acid (**96**), 5-O-caffeoylquinic acid (**97**) and 4-(β -D-glucopyranosyl)-benzoic acid (**98**) have been found in *C. nervosa* [31]. Caffeic acid (**99**), linoleic acid (**100**) and 3-O-caffeoylquinic acid (**96**) were isolated from *C. thalictrifolia* [32]. Succinic acid (**95**) and 9,10,13-trihydroxy-(*E*)-octadec-11-enoic acid (**101**) were isolated from *C. pilosula* [35, 44]. Shikimic acid (**102**) and vanillic acid (**103**) were only obtained from the roots of *C. lanceolata* and *C. tangshen*, respectively [33, 34].

Other compounds

Atractylenolide III (**104**), 5-hydroxymethyl-2-furaldehyde (**105**), angelicin (**106**), psoralen (**107**), emodin (**108**), geniposide (**109**), hexyl- β -D-glucopyranoside (**110**), butyl- β -D-fructouranoside (**111**), β -sitosterol (**112**) and β -daucoesterol (**113**) were isolated from the roots of *C. pilosula* [14, 17, 18, 21, 35, 44]. Hexyl- β -gentiobioside (**114**), hexyl- β -sophoroside (**115**), (*E*)-2-hexenyl- β -sophoroside (**116**), (*E*)-2-hexenyl- α -L-arabinopyranosyl(1 \rightarrow 6)- β -D-glucopyranoside (**117**) and 5-hydroxymethyl-2-furaldehyde (**105**) were isolated from the roots of *C. tangshen* [25, 34]. Cordifoliflavanes A (**118**) and B (**119**) were isolated from the roots of *C. cordifolioidea* [45]. Three new benzofuranylpropanoids, lanceolones A (**120**), B (**121**) and C (**122**), as well as a new cerebroside, codonocerebroside A (**123**), have been isolated from the roots of *C. lanceolata* [41, 46]. (*E*)-2-Hexenyl- α -L-arabinopyranosyl(1 \rightarrow 6)- β -D-

glucopyranoside (**117**), 3-oxo- α -ionol- β -D-glucopyranoside (**124**) and 1,6-hexanediol,3,4-bis(4-hydroxy-3-methoxyphenyl) (**125**) were isolated from the aerial parts of *C. clematidea* [10]. In addition, sweroside (**126**) and β -sitosterol (**112**) were obtained from the whole plants of *C. nervosa* [40]. Nutritive constituents including amino acids and trace elements in *C. pilosula* have been reported [47].

Essential oils

As one of the important compositions, essential oils of several *Codonopsis* species have been reported. In the essential components from *C. pilosula*, 50 of 66 separated components were identified by GC–MS, mainly containing 1,2-benzonedicarboxylic acid dibutyl-ester (12.45 %), heptedecanoic acid (8.10 %) and 2,4,5-triisopropyl styrene (7.62 %) [48]. Using the GC–MS method, 54 peaks were separated and 37 of them were identified in the essential components extracted from *C. clematidea*, in which the most abundant component was methyl hexadecanoate (30.40 %) [49]. The essential oils from the whole plants of *C. thalictrifolia*, as a traditional Tibetan medicine, were analyzed by GC–MS, and 45 of 60 separated components were identified by comparing their mass spectra, in which the main principles were palmitic acid (43.5 %) and linolic acid (18.3 %) [50]. In the essential oils extracted from the fresh and dried roots of *C. cordifolioidea*, 63 compounds were identified by GC–MS analysis, indicating that linolic acid (21.9 %), retene (11.4 %), pentadecane (7.4 %), methyl 9,12,15-octadecatrienoate (6.8 %) and heneicosyl-cyclopentane (3.8 %) were the main components [51].

Polysaccharides

Large-molecule components in *Codonopsis* species were also studied. A water-soluble polysaccharide with a molecular mass of 1.1×10^4 Da was obtained from the roots of *C. pilosula* and its structure investigation revealed that this polysaccharide had a backbone consisting of (1 \rightarrow 3)-linked- β -D-galactopyranosyl, (1 \rightarrow 2, 3)-linked- α -D-galactopyranosyl and (1 \rightarrow 3)-linked- β -D-rhamnopyranosyl residues and were branched with two glycosyl

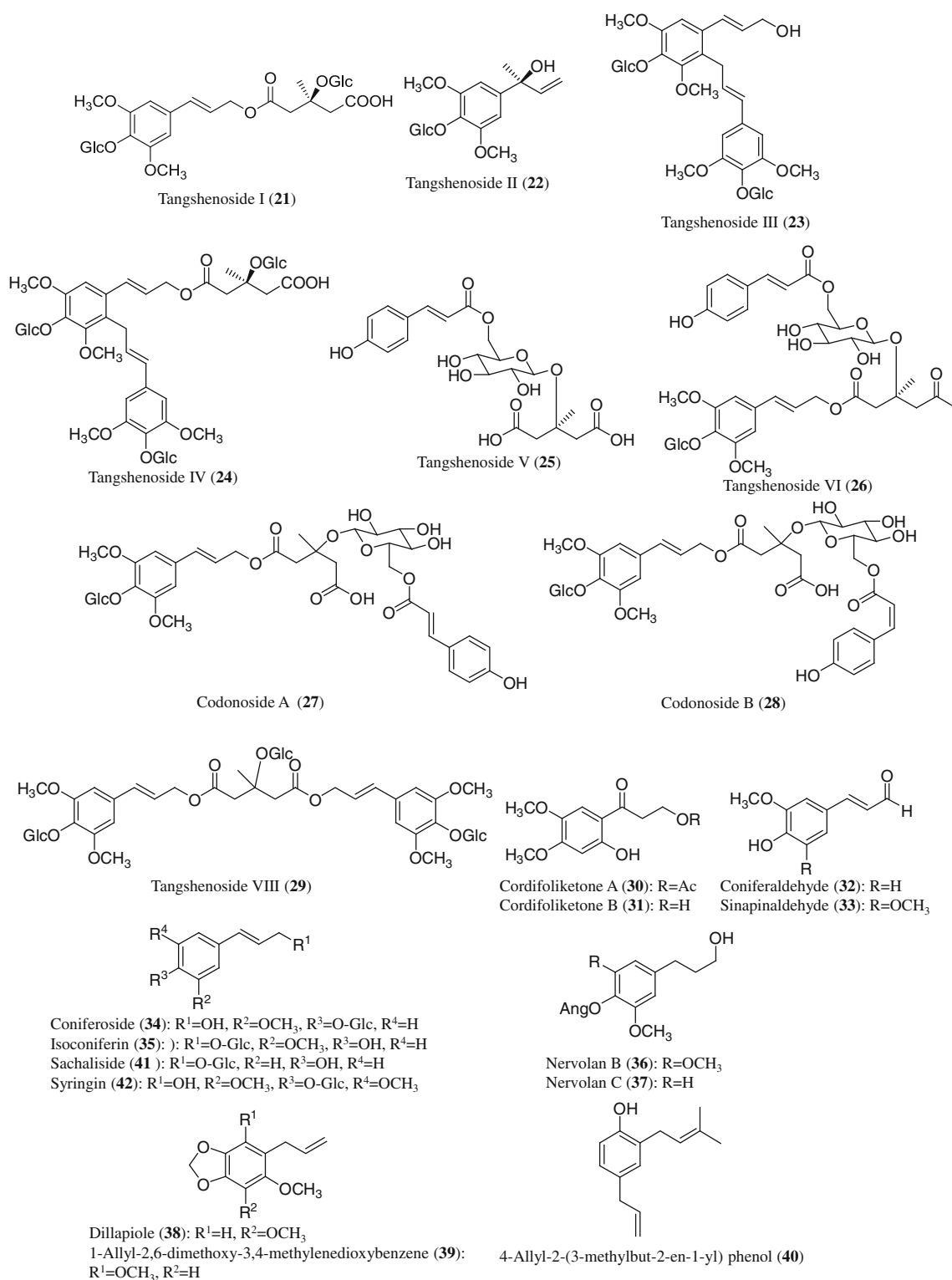


Fig. 2 Structures of phenylpropanoids (21–42) from *Codonopsis* species

residues composed of α -L-arabinose-(1 \rightarrow 5)- α -L-arabinose, whose C-1 linked residues at the O-2 position of galactosyl along the main chain in the ratio of 1:1:2:1:1

[52]. Another polysaccharide with a molecular mass of 7.4×10^4 Da was isolated from *C. pilosula* and its components were galactose, arabinose and rhamnose in the

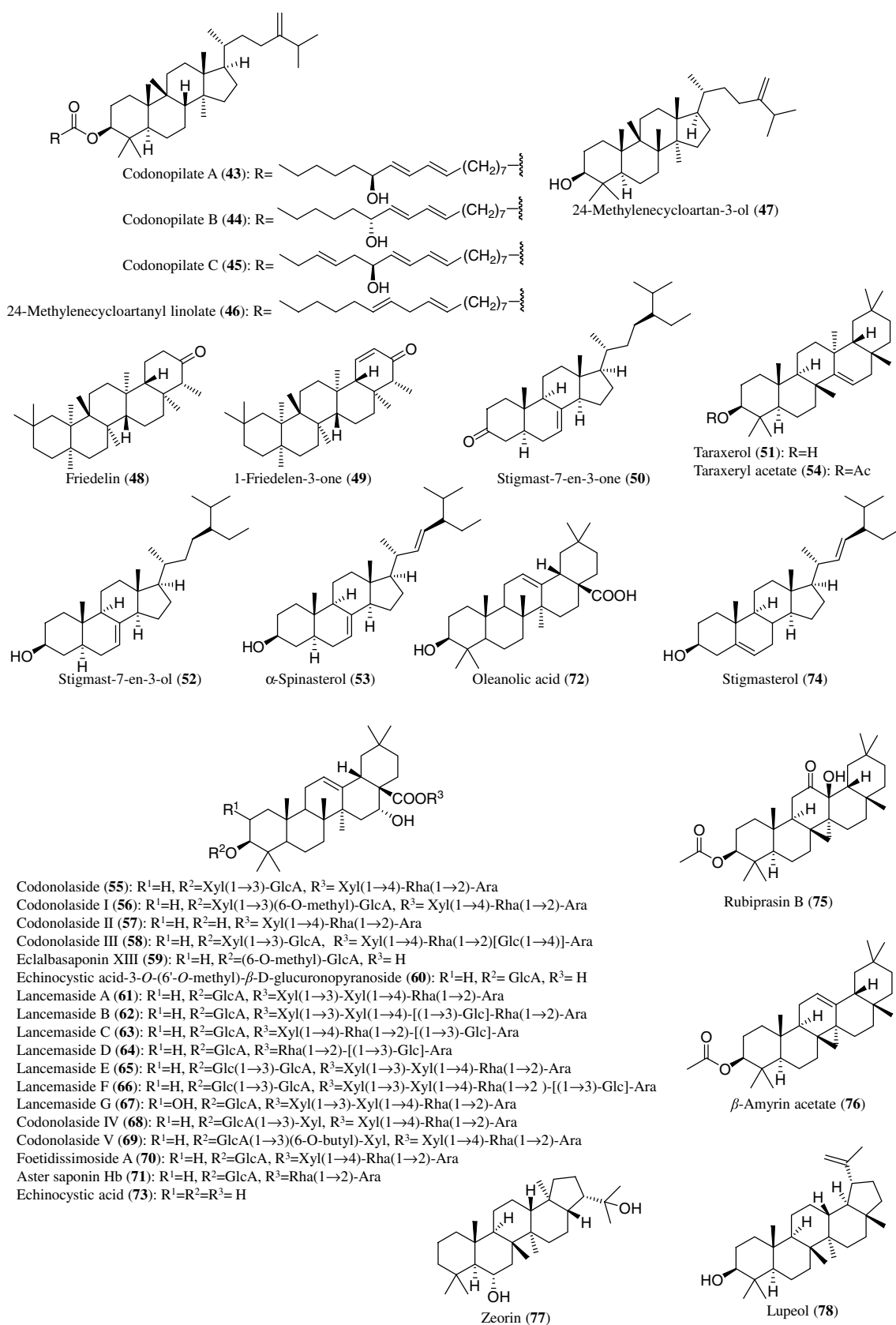
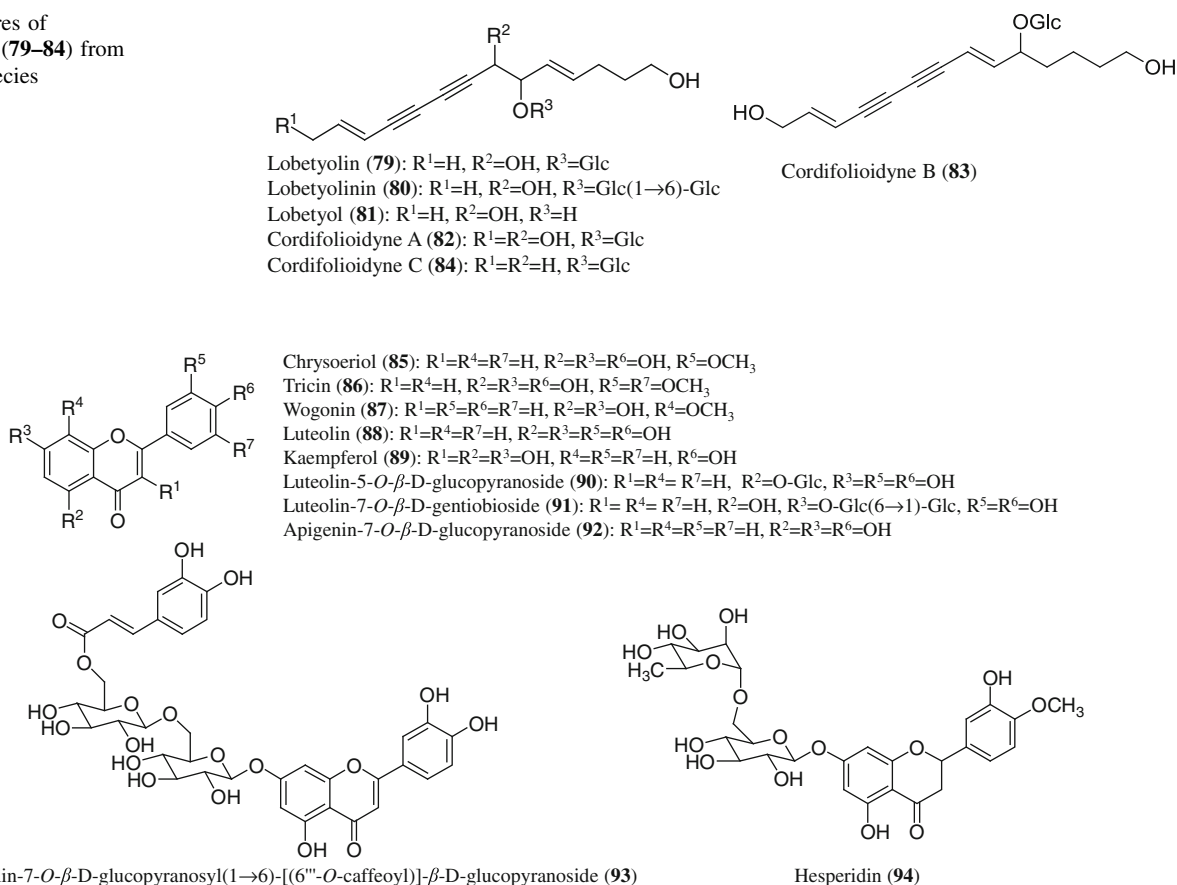


Fig. 3 Structures of triterpenes (43–78) from *Codonopsis* species

Fig. 4 Structures of polyacetylenes (**79–84**) from *Codonopsis* species**Fig. 5** Structures of flavones (**85–94**) from *Codonopsis* species

molar ratio of 1.13:1.12:1. Its main chain was shown to be (1 \rightarrow 3)-linked- β -GalpNAc, (1 \rightarrow 3)-linked- α -Rhap and (1 \rightarrow 2, 3)- β -Galp [53]. Furthermore, a pectic polysaccharide with a molecular mass of 1.45×10^5 Da was at first isolated from *C. pilosula*, and its structural analysis revealed that this polysaccharide is composed of rhamnose, arabinose, galactose and galacturonic acid in the molar ratio of 0.25:0.12:0.13:2.51. Combined with chemical and spectroscopic analyses, its structure was proposed to be 1,4-linked- α -D-GalpA and 1,4-linked- α -D-GalpA6Me interspersed with rare 1,2-linked- β -L-Rhap, 1,2,6-linked- α -D-Galp and terminal α -L-Arap [54].

Bioactivities

Although there is information on the uses of many *Codonopsis* species in traditional medicine, only bioactivity studies on *C. pilosula* and *C. lanceolata* have been reported frequently, which proved their importance as medicinal plants. Bioactivity studies on other *Codonopsis* species such as *C. clematidea* and *C. cordifolioides* were scarce. The studies generally referred to the bioactive

effects of aqueous, methanol and ethanol extracts, as well as their further purified fractions, flavones, saponins and polysaccharides.

Codonopsis pilosula

Anti-tumor activity

The polysaccharide from *C. pilosula* (10 μ g/mL) was able to inhibit the activities of human gastric adenocarcinoma cells and hepatoma carcinoma cells [55]. A pectic polysaccharide (50, 100, 200 and 400 μ g/mL) exhibited marked cytotoxicity to human lung adenocarcinoma A 549 cells, in a dose-dependent manner [54].

Anti-diabetic activity

After mice were orally administered the polysaccharide from *C. pilosula* for a week, Fu et al. [56] found that three different doses of polysaccharide (100, 200 and 300 mg/kg/day) could effectively decrease fasting blood glucose and insulin in serum, enhance superoxide dismutase (SOD)

Fig. 6 Structures of organic acids (**95–103**) from *Codonopsis* species

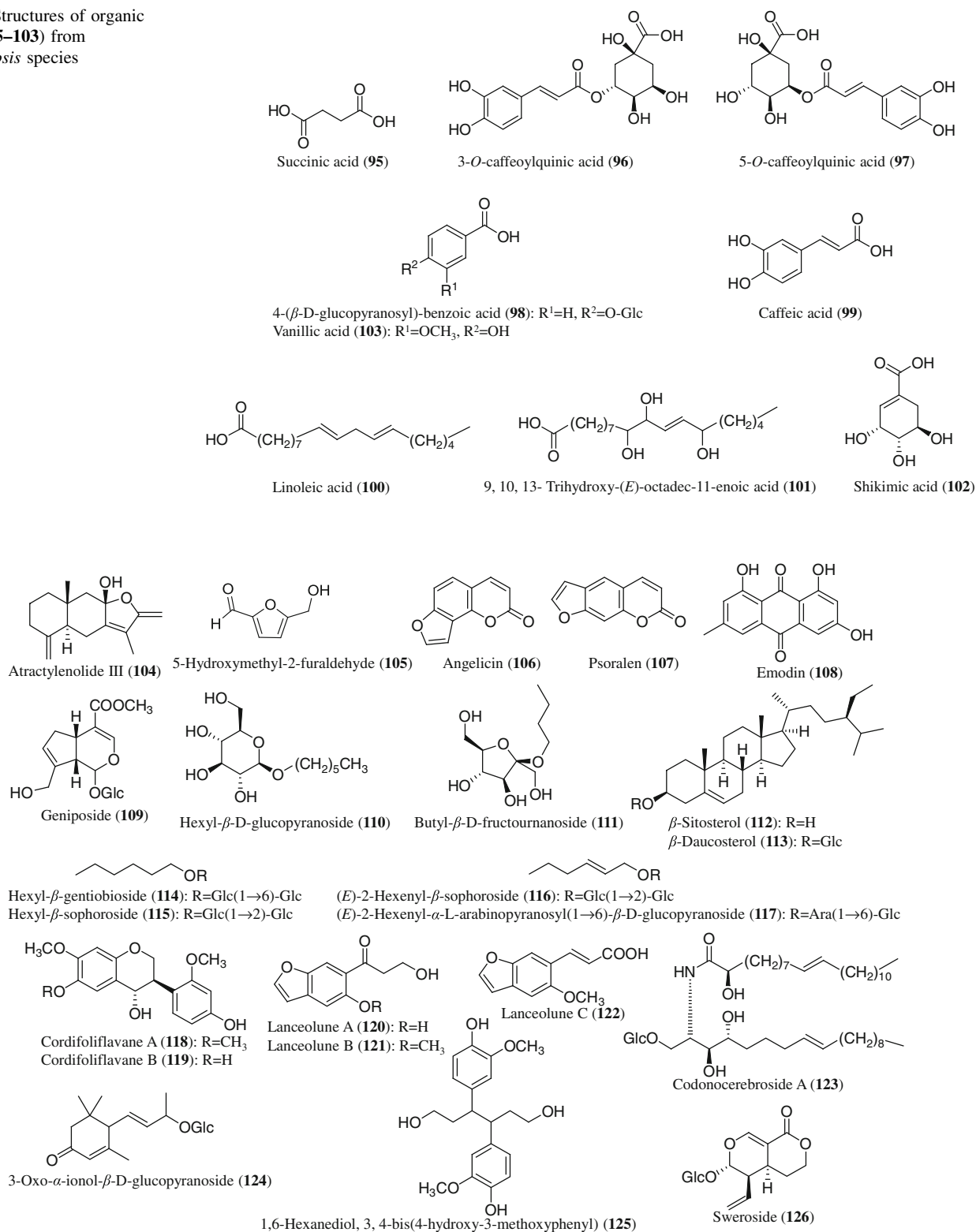


Fig. 7 Structures of other compounds (**104–126**) from *Codonopsis* species

activity and reduce the content of malondialdehyde (MDA) in serum. It was therefore considered to possess a significant hypoglycemic effect in diabetic mice by improving

insulin resistance. He et al. [57] showed that the aqueous extract of the roots of *C. pilosula* (equal to 4.5 g raw material/kg/day) might retard the progression of diabetes

by reducing the blood glucose level and preventing the increase of aldose reductase activity in streptozotocin-induced diabetic mice after 3 days of oral administration.

Anti-aging activity

Xu et al. [58] found that after mice were orally administered the polysaccharide from *C. pilosula* for 8 weeks, the polysaccharide (50 and 150 mg/kg/day) was able to increase the thymus index and spleen index as well as the activities of SOD in serum and liver, glutathione peroxidase and nitric oxide synthase particularly in kidney, while decreasing MDA in serum and liver and lipofuscin in brain. Its postponement of senility might be related to raising immunity, eliminating free radicals and anti-liperoxidation.

Effects on gastric mucosa

Liu et al. [59, 60] found that the water-soluble fraction from the roots of *C. pilosula* (equal to 10 g raw material/kg) had a significant protective effect on gastric mucosal damage caused by alcohol, 0.6 N HCl and 0.2 N NaOH, and suggested that the pharmacological mechanism was related to the synthesis and/or release of prostaglandins in gastric mucosa. To date, Song et al. [61] found that lobetyolin at the oral dose of 1.5 mg/kg had an effect on decreasing the ulcer index and the level of gastrin and increasing the level of 6-keto-prostaglandin F1 α in rats with gastric ulcer induced by ethanol, and suggested that lobetyolin played a protective role in gastric mucosa injury.

Effects on blood system

Aqueous extracts of *C. pilosula* (500 μ g/mL) potently inhibited erythrocyte hemolysis [62]. In addition, after ischemia–reperfusion injury rats received 8 mg/100 g body weight of a solution of saponins via intraperitoneal injection, the results showed that the increase in SOD levels was accompanied by decreases in MDA, serum creatinine and blood urea nitrogen levels; *bcl-2* mRNA and protein levels were raised in transplanted kidneys from treated animals, while *bax* mRNA and protein levels were reduced. The apoptosis index was significantly decreased in transplanted kidneys from treated animals relative to untreated controls. These results clearly demonstrated protective effects on ischemia–reperfusion injury after kidney transplantation, which might be explained by decreasing lipid peroxidation and inhibition of apoptosis [63].

Effects on immunity

Zhang and Wang [64, 65] found that 6 days of oral administration of the polysaccharide from *C. pilosula*

(800 mg/kg/day) had effects on immunosuppressed mice induced by cyclophosphamide, including increasing the thymus and spleen index and the phagocytic activity of peritoneal macrophages and recovering the activity of α -naphthyl-acetate esterase in peripheral lymphocytes. In an immunological study in vitro, a water-soluble polysaccharide (50, 100 and 200 μ g/mL) could stimulate concanavalin A- or lipopolysaccharide (LPS)-induced lymphocyte proliferation in a dose-dependent manner [52]. In addition, the methanol extract of *C. pilosula* (1 mg/mL) inhibited inducible nitric oxide synthase and protein oxidation in LPS-stimulated murine RAW 264.7 macrophage cells [66].

Effects on nervous system

Total alkaloids (30 μ g/mL) caused a significant enhancement of nerve growth factor-induced neurite outgrowth in PC12 cells as well as an increase in the phosphorylation of mitogen-activated protein kinase [67]. Moreover, Pan et al. [68] orally administered alkaloids from *C. pilosula* (1 mg/kg/day) to mice for 4 days after they suffered from amnesia by scopolamine, and found that the alkaloids were effective against the decrease in acetylcholine. Other chemicals, saponins from *Codonopsis Radix*, were reported to have protective effects on the damage to astrocytes induced by hypoxia/hypoglycaemia and reoxygenation, and were able to inhibit the necrosis of astrocytes at three different concentrations (5.2, 52 and 520 μ g/mL) [69]. Additionally, the polysaccharide from *C. pilosula* (1.1 mmol/mL) also had marked protective effect on neural stem cell injury induced by sodium thiosulphate [70].

Other bioactivities

The extract of *C. pilosula* (20, 40 and 60 μ g/mL) significantly attenuated angiotensin II (AngII)-induced insulin-like growth factor II receptor (IGFIIIR) promoter activity. *C. pilosula* also reversed Ca²⁺ influx, mitochondrial outer-membrane permeability and apoptosis increased by AngII plus Leu²⁷-IGFII which was applied to enhance the AngII effect. Molecular markers in the IGFIIIR apoptotic pathway and IGFIIIR-Gaq association were down-regulated by *C. pilosula*. However, p-BadSer136 and Bcl-2 were increased. The results suggested that *C. pilosula* could suppress the AngII plus Leu²⁷-IGFII-induced IGFII/IGFIIIR pathway in myocardial cells [71].

Codonopsis lanceolata

Antioxidant activity

The water-soluble fraction and the *n*-butanol-soluble fraction of ethanol extract of *C. lanceolata* showed

significantly anti-oxidative effects at concentrations of 7.3 and 9.3 mg/mL, respectively. The anti-oxidative effects resulted from the free radical scavenging function, while the former had a much stronger effect [72].

Hepatoprotective activity

After the alcohol-induced hepatic injury mice were orally administered the ethanol extract of *C. lanceolata* (1 and 2 g/kg/day) for 8 weeks, a protective effect was seen [73]. Zhang et al. suggested that the mechanism might be related to anti-oxidative ability, reduced liver lipid peroxidation, and elimination of free radical and its products [73]. On the other hand, the methanol extract of *C. lanceolata* (182 mg/kg/day) appeared to be associated with adenosine- and adiponectin-mediated regulation of hepatic steatosis and Toll-like receptor-mediated modulation of hepatic proinflammatory responses in mice with alcoholic fatty livers after 8 weeks of oral administration [74]. Kim et al. [75] indicated that a week of oral administration of the saponins from *C. lanceolata* (50 mg/kg/day) could decrease the up-regulated levels of glutamate-oxalacetate transaminase and glutamate-pyruvate transaminase in serum of mice induced by water-immersed stress conditions, and the hepatic protective effect was marked due to radical scavenging actions.

Anti-inflammatory activity

Triterpenoids contributed to the anti-inflammatory activity of the ethanol extract of *C. lanceolata* [76]. Lee et al. [77] have shown that methanol extracts of *C. lanceolata* (100 mg/mL) clearly blocked the production of TNF- α and nitric oxide, the expression of IL-3 and IL-6 as well as the phagocytic uptake in LPS-activated RAW264.7 cells, and suggested that the therapeutic activity of *C. lanceolata* on inflammation-mediated symptoms might be mediated by the modulation of macrophage functions. Lancemaside A (15 and 30 μ M), a triterpenoid isolated from *C. lanceolata*, significantly suppressed the inflammatory functions of LPS-treated RAW264.7 cells by suppressing the production of nitric oxide, the expression of the nitric oxide producing enzyme inducible nitric oxide synthase, the up-regulation of the costimulatory molecule CD80, and the morphological changes induced by LPS exposure. In addition, lancemaside A diminished the phagocytic activity of RAW264.7 cells and boosted the neutralizing capacity of these cells when treated with the radical generator sodium nitroprusside. Interestingly, lancemaside A strongly blocked the adhesion activity of RAW264.7 cells to plastic culture plates, inhibited the cell–cell adhesion of U937 cells that was triggered by treatment with an anti- β 1-integrin antibody, and immobilized cell-fibronectin. These

findings suggested that the anti-inflammatory mechanism of lancemaside A involves the suppression of the cellular responses of macrophages and monocytes by blocking redox activation and the IKK/NF- κ B pathway [78].

Anti-tumor activity

The *n*-butanol soluble fraction of aqueous extract from *C. lanceolata* (50, 100, 150 and 200 μ g/mL) significantly inhibited human colon cancer HT-29 cell growth in a dose- and time-dependent manner by inducing G0/G1 phase arrest and apoptosis [79]. Moreover, the saponins from *C. lanceolata* (100, 150 and 200 μ g/mL) could significantly inhibit the growth of HepG2 cells through up-regulating caspases-8 and caspases-9 and subsequently activating caspase-3 [80]. Lee et al. [81] indicated that β -D-xylopyranosyl(1 \rightarrow 3)- β -D-glucuronopyranosyl echinocystic acid (40 μ M) was a potent inducer of apoptosis and facilitated its activity via Bid cleavage and translocation to mitochondria, Bax reduction in cytosol, release of cytochrome *c* and Smac/DIABLO into the cytosol, and subsequently caspase activation.

Effects on blood system

Byeon et al. [82] found that the *n*-butanol fraction of *C. lanceolata* (200 μ g/mL) not only up-regulated mRNA expression of granulocyte–macrophage-colony stimulating factor (GM-CSF) but also increased the proliferation of splenocytes, and suggested that *C. lanceolata* had an effect on recovering the blood loss via activating relevant signaling cascades, such as NF- κ B and AP-1. Choi et al. [83] showed that oral administration of the aqueous extract of *C. lanceolata* (100, 300 and 900 mg/kg/day) for 6 weeks could significantly decrease the weight of adipose pads and the levels of triglycerides, total cholesterol and low-density-lipoprotein cholesterol in rats with high-calorie/high-fat-diet-induced obesity. Additionally, 3T3-L1 cells treated with the aqueous extract (0.5 and 0.7 μ g/mL) could also inhibit lipid accumulation and expression of C/EBP α and PPAR γ . When rats with Qi-deficiency and blood stasis syndrome were orally administered the ethanol extract of *C. lanceolata* (5 and 10 g/kg/day) for 14 days, Xu et al. [84] found that the ethanol extract could decrease whole blood viscosity, plasma viscosity, aggregation indexes of red blood cells and packed red blood cells, and speed up red blood cell electrodeposition time significantly, and concluded that it had effects on invigorating energy, activating blood flow and resolving blood stasis on rats. In addition, after lipid metabolic disorder rats were orally administered the ethanol extract of *C. lanceolata* (equal to 1.5, 3.0 and 6.0 g raw materials/kg/day) for 8 weeks, the results showed that the ethanol extract could decrease the

ratio of liver weight to body weight, the level of triglyceride and the activity of inducible nitric oxide synthase, and increase nitrogen monoxide, endothelial nitric oxide synthase activity, and the activities of lipases, including total lipase activity in the liver, lipoprotein lipase and hepatic lipase [85]. Han et al. [85] concluded that its mechanism in regulating blood lipids might be by accelerating lipid metabolism and inhibiting the produce of lipid peroxidation.

Effects on nervous system

After 4 days of oral administration of an ethyl-acetate-soluble fraction of 95 % ethanol extract of *C. lanceolata* (50 mg/kg/day) to gerbils, ischemic neuronal loss was potentially reduced by maintaining Cu,Zn-superoxide dismutase and brain-derived neurotrophic factor immunoreactivity in the ischemic hippocampal CA1 region [86].

Other bioactivities

Oleanolic acid isolated from *C. lanceolata* (20, 40 and 80 $\mu\text{g}/\text{mL}$) might protect DNA from damage induced by UV radiation and promote DNA damage repair [87].

Codonopsis clematidea

Chen et al. [88] showed that 15 days of oral administration of polysaccharides from *C. clematidea* (15 and 30 g/kg/day) increased the activities of SOD and reduced the content of MDA in mice brain. Moreover, Han [89] found that 7 days of oral administration of the polysaccharides from *C. clematidea* (100 mg/kg/day) had a significant effect against cancer cachexia in mice and inferred that the possible mechanism might be inhibition of the tumor growth and decrease in the serum content of TNF- α and IL-6. In addition, after the mice were orally administered flavonoids from *C. clematidea* (0.5 and 1.0 mg/kg/day) for 25 days, Wang et al. [90] found that SOD activities were increased in blood and liver, the content of MDA was decreased in blood and liver, swimming time was prolonged, and the content of liver glycogen and muscle glycogen was increased, and therefore inferred that the flavonoids were related to the antioxidant and anti-fatigue effects of *C. clematidea*.

Codonopsis cordifolioidea

Qiu et al. [51] showed that the essential oils from fresh roots of *C. cordifolioidea* were effective against *Staphylococcus aureus* and *Salmonella typhimurium* with a

minimum inhibitory concentration (MIC) of 25 $\mu\text{g}/\text{mL}$, and the essential oils from dried roots of *C. cordifolioidea* were effective against *Staphylococcus aureus*, *Salmonella typhimurium*, and *Shigella flexneri* with a MIC of 50 $\mu\text{g}/\text{mL}$. Gao et al. [45] showed that 4-hydroxyisoflavanes and cordifoliflavanes A and B isolated from *C. cordifolioidea* with minimal cytotoxicity against C8166 cells ($\text{CC}_{50} > 200 \mu\text{g}/\text{mL}$) had weak anti-HIV-1 activities with EC_{50} values of 5.26 and 2.25 $\mu\text{g}/\text{mL}$, respectively, and anti-tobacco mosaic virus activities with inhibition rates of 11.5 and 18.6 %, respectively.

Quality control

Due to the different chemical components, bioactivities and clinical effects of different *Codonopsis* species, the first step in assuring the quality of traditional medicines is correct identification [91].

To authenticate *Codonopsis Radix*, morphological and histological studies have been carried out on the roots of seven *Codonopsis* species [92, 93]. However, their roots could not be identified accurately due to similar morphology. The histological characteristics such as the shape of parenchyma cells of the phloem and xylem, and the percentage value of the diameter of the xylem to that of the root may vary in different growing stages of plants and drying conditions of the roots. On the other hand, *Codonopsis Radix* consisting of at least two species was commonly found in commodities [94]. Therefore, it is difficult to elucidate the botanical sources of *Codonopsis Radix* based on morphological inspection and histological characteristics.

DNA-based markers have now become a popular tool for the identification of plants because the genetic composition is unique for each individual and is less affected by growth period, physiological condition, environmental factors, harvest time, storage and processing conditions [95]. In addition, molecular approaches are widely used not only in plant taxonomy but also in identification of crude drugs [94, 96, 97]. Fu et al. [98] reported that the sequence difference allows effective and reliable differentiation of *Codonopsis* from two related adulterants *Campanumoea javania* and *Platycodon grandiflorus* by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). Recently, He et al. [94] have reported that the sequence of the internal transcribed spacer (ITS) of nuclear ribosomal DNA (nrDNA) as a molecular marker could effectively and accurately identify a number of *C. pilosula*, *C. pilosula* var. *modesta*, *C. tangshen* and *C. lanceolata* specimens and be applied to authentication of *Codonopsis Radix*.

The diverse chemical components make it possible to discriminate *Codonopsis* species and further evaluate the

Table 2 HPLC applications in quantitative analysis for quality control of *Codonopsis* species

Analytes	Species	Extraction methods	Columns	Mobile phases	Analytical time (min)	Detection	References
Adenosine	<i>C. pilosula</i>	Ultrasonic extraction with 15 % (v/v) methanol aqueous solution	C18 (Discovery, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–water (5:95); flow rate: 1.0 mL/min	15	UV 260 nm	[101]
Attractylenolide III	<i>C. pilosula</i>	Ultrasonic extraction with methanol	ODS (Hypersil, 4.6 mm × 250 mm, 5 μm)	Methanol–water (67:33); flow rate: 1.0 mL/min	20	UV 220 nm ELSD (gas flow: 2.2 L/min, nebulizer temperature: 80 °C)	[102]
Attractylenolide III	<i>C. pilosula</i> , <i>C. pilosula</i> var. <i>modesta</i> and <i>C. tangshen</i>	Ultrasonic extraction with ethanol	C18 (Diamonsil, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–water (70:30); flow rate: 1.0 mL/min	8	UV 220 nm	[103]
Codonopyrrolidium B	<i>C. pilosula</i>	Ultrasonic extraction with 75 % (v/v) methanol aqueous solution	C18 (Kromasil, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–0.1 % diethylamine (10:90); flow rate: 1.0 mL/min	15	UV 267 nm	[104]
Ginsenoside	<i>C. lanceolata</i>	Refluxing extraction with methanol	C18 (Diamonsil, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–0.1 % formic acid (33:67); flow rate: 1.0 mL/min	25	UV 207 nm	[105]
Lobetyolin	<i>C. tangshen</i>	Soxhlet extraction with methanol	C18 (Supelco Discovery, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–0.5 % acetic acid (20:80); flow rate: 1.0 mL/min	30	UV 268 nm	[106]
Lobetyolin	<i>C. nervosa</i>	Refluxing extraction with chloroform and then with methanol	CLC-ODS (Shim-pack, 4.6 mm × 150 mm, 5 μm)	Acetonitrile–water (17:83); flow rate: 1.0 mL/min	30	UV 267 nm	[27]
Lobetyolin	<i>C. tubulosa</i>	Ultrasonic extraction with methanol	ODS (Hypersil, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–water (20:80); flow rate: 1.0 mL/min	25	UV 270 nm	[107]

Table 2 continued

Analytes	Species	Extraction methods	Columns	Mobile phases	Analytical time (min)	Detection	References
Lobetyolin	<i>C. pilosula</i> , <i>C. pilosula</i> var. <i>modesta</i> and <i>C. tangshen</i>	Ultrasonic extraction with ethanol	C18 (Diamonsil, 4.6 mm × 200 mm, 5 μm)	Acetonitrile–0.1 % acetic acid (26:74); flow rate: 1.0 mL/min	10	UV 267.3 nm	[103]
Lobetyolin	<i>C. pilosula</i> , <i>C. pilosula</i> var. <i>modesta</i> and <i>C. tangshen</i>	Ultrasonic extraction with ethanol	C18 (Hypersil, 4.6 mm × 200 mm, 5 μm)	Acetonitrile–0.1 % acetic acid (28:72); flow rate: 1.0 mL/min	8	UV 267.3 nm	[108]
Lobetyolin	<i>C. pilosula</i> , <i>C. pilosula</i> var. <i>modesta</i> , <i>C. tangshen</i> , <i>C. tubulosa</i> , <i>C. subglobosa</i> , <i>C. clematidea</i> , <i>C. canescens</i> and <i>C. lanceolata</i>	Refluxing extraction with methanol	XBD-C18 (Agilent ZORBAX, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–water (17:83) with gradient elution; flow rate: 1.0 mL/min	40	UV 267 nm	[109]
Lobetyolin, lobetyol and tangshenoside I	<i>C. pilosula</i>	Ultrasonic extraction with 70 % (v/v) ethanol aqueous solution	C18 (Kromasil, 4.6 mm × 250 mm, 5 μm)	Acetonitrile and 1.0 % aqueous solution of 0.1 M phosphoric acid–water–1.0 % aqueous solution of 0.1 M phosphoric acid (10:90) with gradient elution; flow rate: 1.0 mL/min	60	UV 267 nm	[110]
Lancemasides A, B, C, E, G, foetidissimoside A, and aster saponin Hb	<i>C. lanceolata</i>	Shaken extraction with 50 % (v/v) methanol aqueous solution	Pro-C18 RS (YMC-Pack, 3.0 mm × 100 mm, 3 μm)	Acetonitrile–0.1 % formic acid (33:67); flow rate: 0.2 mL/min	5	MS	[39]
Codonopyrrolidiums A and B, tangshenoside I, cordifoliodyne B, lobetyolimin, lobetyolin and lobetyol	<i>C. pilosula</i> , <i>C. pilosula</i> var. <i>modesta</i> and <i>C. tangshen</i>	Ultrasonic extraction with methanol	Pro-C18 (YMC-Pack, 4.6 mm × 250 mm, 5 μm)	Acetonitrile–0.1 % phosphoric acid (2:98) with gradient elution; flow rate: 1.0 mL/min	65	UV 215 nm	[111]

UV ultraviolet, ELSD evaporating light scattering detector, MS mass spectrometry

quality of *Codonopsis* species. Polysaccharides, polyacet-ylenes, alkaloids and saponins have been proven to contribute to the biological activities of *Codonopsis*. Therefore, quantitative analysis for the quality control of *Codonopsis* has mostly focused on these chemotypes of compounds. To date, a series of analytical methods have been employed and reported to quantify the contents of bioactive components in various *Codonopsis* species. Lu et al. [99] compared the contents of fructose and stigmast-7-en-3-ol to discriminate 5 *Codonopsis* species from each other by thin-layer chromatography (TLC)–ultraviolet spectrum (UV). Tangshenoside I, which was considered as a valuable marker for identification of *Codonopsis Radix* [23], was detected by TLC–UV [100]. High-performance liquid chromatography (HPLC) is an accurate, sensitive and selective technique which has been widely used in quality control of herbal drugs. Currently, HPLC coupled with UV, evaporating light scattering detector (ELSD) and electrospray ionization (ESI)–mass spectrometry (MS) have become the usual analytical techniques for separation and quantification of markers from complicated Chinese medicinal material extracts. HPLC methods for quantitation of specific chemicals in *Codonopsis* are summarized in Table 2 [27, 39, 101–111]. It is found that lobetyolin was mostly used as a marker compound for quantitative analysis of *Codonopsis Radix*. However, Qiao et al. [109] have reported that lobetyolin was widely found not only in the three *Codonopsis* taxa used as *Codonopsis Radix*, but also in other species of the same genus and even in species of other genera from the family Campanulaceae, indicating that it was not characteristic for *Codonopsis* species. Therefore, HPLC methods on the basis of multiple components having potential bioactivities, including polyacet-ylenes, phenylpropanoids, alkaloids and saponins, were used to compare and assess the quality of *Codonopsis* species [39, 110, 111]. In addition, chemical fingerprint analysis, which shows not only the bioactive and characteristic components present but also their relative ratios, is also recognized as a reliable means for the identification and qualification of herbal medicines. GC and HPLC–UV fingerprint methods were devised for comparing different *Codonopsis* species and producing areas of *Codonopsis Radix* and for evaluating the quality of *Codonopsis Radix* [109, 112–114]. Moreover, the alkaloids codotubulosines A and B, adenosine and 5-(hydroxymethyl) furfural were analyzed by ¹H nuclear magnetic resonance (¹H-NMR) in 7 *Codonopsis* species and *Campanumoea javanica* [15]. The combination of near-infrared (NIR) spectroscopy with chemometrics has been reported to discriminate *C. pilosula* from different geographical origins [115].

Codonopsis Radix is one of the herbs commonly processed by sulfur fumigation, and it is often questioned whether sulfur fumigation could affect the chemical

components in the herbs. Ma et al. [116] established a rapid and versatile ultra-high-performance liquid chromatography coupled with ultra-high-resolution quadrupole time-of-flight mass spectrometry (UHPLC UHD Q-TOF MS/MS) method that was able to detect 15 sulfur-containing compounds only in sulfur-fumigated samples, and therefore was successfully applied to discriminate sulfur-fumigated *Codonopsis Radix* among commercial samples.

Conclusion

The importance of the genus *Codonopsis* has been highlighted based on their wide uses in traditional medicine. Combining phytochemical investigation of *C. pilosula*, *C. tangshen* and *C. lanceolata* and their widely known bioactive properties, and especially of the related mechanism to explain their ethnomedicinal uses and support development of pharmaceutical products, will undoubtedly be the key for advanced research in the future. Additionally, more studies are still urgently needed on the development of the less popular *Codonopsis* species. For efficacious and safe use, a series of methods for quality assessment have been developed to ensure the quality of *Codonopsis* species according to morphological, molecular and chemical characteristics. Establishing a feasible and reliable approach to quality evaluation of various *Codonopsis* species thus remains difficult, without considering botanical origin, chemical constituents and bioactive activities.

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