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Different kinds of functional components with multiple biological activities in *Cornus officinalis* as food and medicinal resource: a review

Yuhang Liu^a, Lili Cui^{a,b,c}, Wenyi Kang^a, Zhenhua Liu^{a,d,*}, Yan Zhang^{a,e,*}, Changyang Ma^{a,d,*}

^a National R&D Center for Edible Fungus Processing Technology, Henan University, Kaifeng 475004, China

^b Functional Food Engineering Technology Research Center, Kaifeng 475004, China

^c Joint International Research Laboratory of Food & Medicine Resource Function, Kaifeng 475004, China

^d College of Agriculture, Henan University, Kaifeng 475004, China

^e Hebei Food Inspection and Research Institute, Shijiazhuang 050091, China

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ABSTRACT

Cornus officinalis Sieb. et Zucc., a valuable Chinese medicine resource, has a long clinic utilization history. In recent years, more research focus on the chemical composition and pharmacological activity of *C. officinalis* which was used as health foods and drugs. This paper summarized the active ingredients, pharmacological activities and molecular mechanisms of *C. officinalis* in recent 5 years to provide reference for the development and utilization of *C. officinalis*. A total of 149 active constituents of *C. officinalis* were summarized, including iridoids (64), flavonoids (18), lignin (17), tannins (16), organic acids and phenolic acids (14), triterpenes (11) and others (9), which were further subdivided according to their pharmacological effects. It was found that the pharmacological effects of *C. officinalis* were very extensive, mainly including antioxidant, anti-inflammatory, anti-tumor, neuroprotective and other biological activities. Among these activities, the anti-inflammatory and hypoglycemic mechanisms showed multi-pathway and multi-target characteristics, which were elaborated systematically. However, there are still many compounds in *C. officinalis* that have not been studied for biological activity, which means that it still has potential pharmacological activity to be further studied. *C. officinalis* not only has high medicinal value, but also has a potential edible resource. However, limited by people's understanding of the nutritional value of *C. officinalis*, few product types and incomplete processing technology, people's acceptance of the edible value of *C. officinalis* is not high, and it needs to be further developed and utilized.

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1. Introduction

Cornus officinalis belonging to Cornaceae family, whose mature flesh serves as a traditional Chinese medicine, was first included in the Sheng Nong's herbal classic^[1], widely distributed in Tianmu

Mountain, Funiu Mountain, and Qinling Bashan Mountain in China, as well as in Japan and South Korea^[2]. Its nature and flavour are tepefaction, sour and astringent, and its channel tropism is in liver and kidney, often used to tonify the liver and kidney, and arrest the loss of essence^[3]. *C. officinalis* is used to treat dizziness, tinnitus, lower back and knee pain, impotence and ejaculation, frequent urination and urination, vaginal discharge, sweating collapse, internal heat and thirst quenching. It is also present in many well-known prescriptions, such as Liu Wei Di Huang Wan, which is used to treat various liver and kidney diseases^[4]. In addition to having extremely high medicinal

* Corresponding authors at: National R&D Center for Edible Fungus Processing Technology, Henan University, Kaifeng 475004, China.

E-mail address: liuzhenhua@vip.henu.edu.cn (Z.H. Liu); snowwingli@126.com (Y. Zhang); macaya1024@sina.com (C.Y. Ma)

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value, *C. officinalis* is also a highly potential edible resource. In 2023, it was collected into the “Regulations on the Management of the Catalogue of Substances that are traditionally both food and Chinese Medicinal Materials” authorized by the National Health Commission of the People’s Republic of China. In Chinese food processing, it is mainly applied in traditional food industries, such as fruit wine, vinegar, jam, etc., but the application is not yet in-depth. Because people’s understanding of the nutritional value of *C. officinalis* is not comprehensive, the developed products have fewer types of products compared to the same type on the market, and their competitiveness is insufficient^[5]. At the same time, the processing technology of *C. officinalis* food is not yet perfect, leading to a low level of acceptance by people. Thus, it is necessary to summarize the basic research of *C. officinalis*, such as the active ingredients, their bioactivities as well as the mechanisms, which is helpful for its further development and utilization.

C. officinalis contained a variety of bioactive components, and about 300 compounds have been isolated and identified from *C. officinalis*, mainly including iridoids, triterpenes, flavonoids, tannins, organic acids, etc.^[3,6–10]. In recent years, new compounds have been identified constantly from *C. officinalis*. Feng et al.^[11] found a novel iridoid (cornusglucoside I) and a new natural product, methyl 4-(3',4'-dihydroxyphenyl)-4-oxobutanoate, in *C. officinalis*. Wang et al.^[12] isolated 5 new iridoid glycosides, cornusphenosides E–I, from the ethanol extract of fruit of *C. officinalis*, among which cornusphenosides I showed neuroprotective effects on H₂O₂-induced SH-SY5Y cell damage. Peng et al.^[13] isolated 20 structurally diverse compounds from fructus of *C. officinalis*, which included 2 new lignans (officinalignans A–B) and 2 new iridoids, loganin-(4'-O-7'')- α -morroniside and 2'-O-*p*-coumaroyl-kingiside. It was found that officinalignans A and 2'-O-*p*-coumaroyl-kingiside had antioxidant activity, loganin-(4'-O-7'')- α -morroniside and 2'-O-*p*-coumaroyl-kingiside showed strong anti-inflammatory activity. Peng et al.^[14] previously isolated 6 novel iridoid dimers (cornusdiridoid A–F) from *C. officinalis* and evaluated their α -glucosidase, anti-inflammatory and antioxidant activities. Lee et al.^[15] isolated a novel secoiridoid (demethoxy-cornuside) from *C. officinalis* and found that it had the effect of enhancing the activity of progesterone. *C. officinalis* is also rich in pharmacological activities, including anti-oxidant^[16–17], anti-inflammatory^[16], anti-diabetes^[14,18], anti-osteoporosis^[19], immune regulation^[17], neuroprotection^[20], hepatoprotective^[21] and other pharmacological effects. In this paper, the active components and biological mechanisms of *C. officinalis* were reviewed. It was found that there were still many compounds whose activities were not clear, and a considerable part of the activities were superficial and needed further study.

2. Active ingredients in *C. officinalis*

One hundred and forty nine active constituents of *C. officinalis* were summarized, including iridoids (64), accounting for 42.95%; flavonoids (18), accounting for 12.08%; lignin (17), accounting for 11.41%; tannins (16), accounting for 10.73%; organic acids and phenolic acids (14), accounting for 9.40%; triterpenes (11) accounting for 7.38%; others (9) accounting for 6.04% (Fig. 1A). The biological activities of 149 chemical constituents mainly focus on anti-inflammatory, anti-diabetic, anti-oxidation and anti-tumor activities (Fig. 1B).

It is found that iridoids and flavonoids were the main active components of *C. officinalis* by the review. The relationship between

the biological activity and the number of compounds with such activity of *C. officinalis* were summarized. They included anti-inflammatory (89), anti-diabetic (67), anti-oxidant (66), anti-tumor (37), anti-microbial (25), neuroprotection (25), hepatoprotection (21), anti-Alzheimer’s disease (AD) (21), cardioprotection (17), enzyme inhibitor (17), anti-viral (13), anti-obesity (9), cytotoxicity (9), anti-osteoarthritis (8), lung protection (7), renal protection (7), anti-osteoporosis (7), anti-piroplasma (7), bone protection (6), hypolipidemic (5), anti-allergy (5), anti-parkinsonian (5), anti-depressant (5), osteogenesis (4), anti-hypertensive (4), vascular protection (4), potentiate progesterone (4), skin sparing (3), inhibiting melanin production (3), intestinal protection (2), anti-coagulation (2), anti-aging (2), benign prostatic hypertrophy (2), sedation (2), analgesic (2), endometriosis (2), leukemia (1), emphysema (1), hypercholesterolemia (1), testicular disruption (1), muscle dysfunction (1), spinal cord injury (SCI) (1), contact hypersensitivity (1), anxiolytic (1), anti-leishmanial (1), anti-asthma (1), anti-fungal (1), immunosuppressive (1), septic (1), embryo protection (1), moisturizing (1), ischemic stroke (1), wound healing (1), anti-gastric ulcer (1), protective probiotics (1), anti-metabolic syndrome (1) activities.

2.1 Iridoids

Iridoids are the main bioactive component of *C. officinalis*. There are 64 iridoids with a variety of biological activities from *C. officinalis* (1–64). Their structural skeletons include cyclopentane iridoids, secoiridoids and iridoid dimer. Their pharmacological effects include anti-inflammatory (35), anti-diabetic (30), anti-oxidant (13), neuroprotection (10), anti-microbial (5), anti-tumor (4), hepatoprotective (3), anti-AD (3), enzyme inhibitor (3), anti-osteoporosis (3), cardioprotection (3), lung protection (2), anti-allergy (1), hypolipidemic (1), bone protection (1), vascular protection (1), anti-obesity (1) and sedation (1) (Fig. 2A). Among them, anti-inflammatory and anti-diabetic activities are the main biological activity of iridoids. In addition, the relationship network between iridoids and biological activities is established (Fig. 2B).

There were 35 iridoids with anti-inflammatory activity in *C. officinalis*, among which compounds **1**, **2**, **32**, **39**, **40** and **41** showed obvious inhibitory activity in enzyme (cyclooxygenases-2/1) inhibitors screening assay^[28]. Compounds **12**, **13–15**, **17–20**, **31**, **32**, **39**, **42**, **44–56**, **58–60**, **62** and **64** in RAW264.7 cells^[13–14,48,61], BRIN-BD11 and H4IIE cells^[25], HepG2 cells^[29,58], FLS^[69] and HUVECs^[72–73] displayed anti-inflammatory activity by affecting mitogen-activated protein kinases (MAPKs), nuclear factor kappa-B (NF- κ B), janus kinase (JAK), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways. In addition, it has been documented that compound **1** has an inhibitory effect on mice with ulcerative colitis (UC) induced by sodium dextran sulfate sodium (DSS)^[26], and can also improve cartilage degeneration and the development of osteoarthritis in mouse models of osteoarthritis, further confirming its anti-inflammatory activity and good effect *in vivo*^[27]. Some studies had shown that the anti-inflammatory activity of iridoids were also related to the double bond, C-11 substituents and the bonding mode after ring-opening on cyclopentane^[78–79].

There are a total of 30 iridoids with anti-diabetic activity in *C. officinalis* (Table 1), among which compounds **1–2**, **12**, **21–30**, **36–37**, **40–41**, **57**, and **59–62** showed obvious activity in α -glucosidase

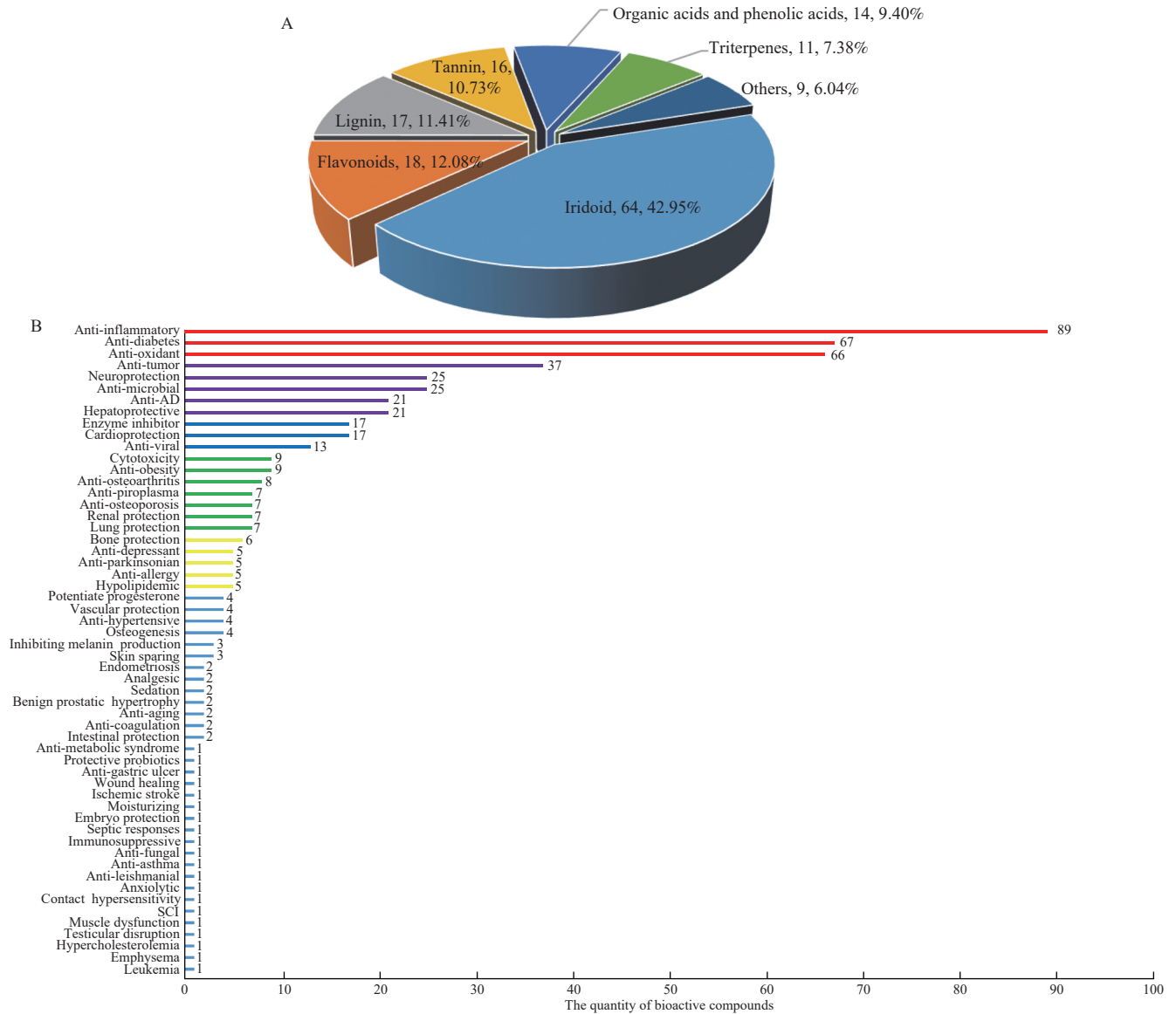


Fig. 1 Active compounds and biological activities in *C. officinalis*. (A) The number and proportion of active compounds; (B) Biological activity and number of compounds with such activity.

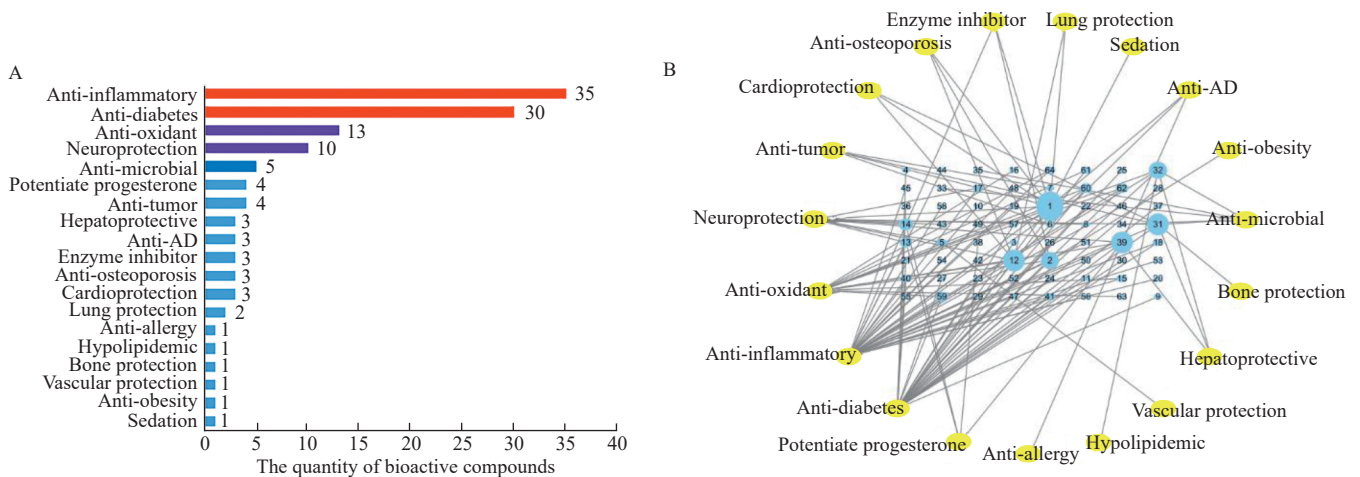


Fig. 2 (A) The bioactivities of iridoids. The length of the column bar represents the number of compounds with this biological activity; (B) The relationship network between iridoids and biological activity. The blue number represents iridoids, the size of the circle represents the number of bioactivities of the compound, the yellow circle represents bioactivity, and each edge line represents the bioactivity of the compound.

Table 1
Bioactive iridoids from *C. officinalis*.

No.	Compounds	Activities	Methods	Dosage effects	Reference
1	Loganin	Anti-diabetes	Establishment of INS-1 cell line with high expression of forkhead box O1 (FOXO1)		[22]
			Rat mesangial cell line (RMC) HBZY-1		[23]
			HepG2 cells, streptozotocin (STZ)-induced diabetic mice, α -glucosidase inhibitory assay	(3.54 $\pm$ 0.33) mg/mL (half maximal inhibitory concentration, IC ₅₀)	[24]
			BRIN-BD11 and H4IIE cells		[25]
		Anti-inflammatory	DSS-induced UC in male BALB/c mice		[26]
			Destabilization of the medial meniscus (DMM)-induced osteoarthritis (OA) in C57BL/6 male mice		[27]
			Enzyme (cyclooxygenases-2/1) inhibitors screening assay		[28]
			Interleukin-6 (IL-6)-induced signal transducer and activator of transcription 3 (STAT3) in HepG2 cells		[29]
		Anti-oxidant	Reactive oxygen species (ROS) scavenging activity assay		[24]
		Neuroprotection	Scopolamine induced rats		[30]
		Anti-tumor	5 Human cancer cell lines MCF-7, PA-1, WRL-68, COLO-320 and CaCo2		[31]
		Cardioprotection	H9C2 and RLE-6TN cells, male C57BL/6 mice		[32]
		Anti-osteoporosis	MC3T3-E1 cells		[33]
		Enzyme inhibitor	Tyrosinase inhibition assay		[34]
		Lung protection	Lipopolysaccharide (LPS)-induced mice and RAW264.7 and RLE-6TN cells, bleomycin induced pulmonary fibrosis in mice		[35]
		Sedation	Pentobarbital-induced sleep test and insomnia mice models induced by caffeine and <i>p</i> -chlorophenylalanine (PCPA)		[36]
		Anti-AD	3xTg-AD mice		[37]
		Anti-diabetes	α -Glucose inhibition assay	(13.19 $\pm$ 0.47) μ mol/L (IC ₅₀)	[38]
		Anti-inflammatory	Enzyme (cyclooxygenases-2/1) inhibitors screening assay		[28]
		Anti-oxidant	Carbonyl/oxidative stress markers in plasma and leukocytes, antioxidant enzymes assays		[39]
2	Loganic acid	Anti-osteoporosis	Ovariectomy (OVX)-induced osteoporosis mice and mouse preosteoblast MC3T3-E1 cells		[40]
		Enzyme inhibitor	Tyrosinase inhibition assay		[34]
		Anti-obesity	3T3-L1 preadipocytes and ovariectomized mice		[41]
3	Logmalicids A	Anti-diabetes	RMC HBZY-1		[23]
4	Logmalicids B	Anti-diabetes	RMC HBZY-1		[23]
5	Cornin	Neuroprotection	Oxygen glucose deprivation (OGD) treatment of human neuroblastoma (SH-SY5Y) cells		[42]
		Vascular protection	3T3-L1 preadipocytes and ovariectomized mice		[43]
6	Cornifins B	Anti-tumor	Human myeloid leukemia HL-60, lung cancer A-549, and breast cancer SK-BR-3		[44]
7	Luzonoid B	Anti-tumor	HeLa S3 cancer		[45]
8	Cornusfural B	Neuroprotection	Corticosterone-induced PC12 neuronal	(68.23 $\pm$ 2.26)% (viability)	[46]
9	7-Epiloganin	Anti-diabetes	Insulin-induced HepG2 cells	0.742 μ mol/L (half maximal effective concentration, EC ₅₀)	[47]
10	8-Epiloganin	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	(22.9 $\pm$ 4.6) μ mol/L (IC ₅₀)	[29]
11	Neocornuside A	Anti-diabetes	Insulin-induced HepG2 cells	0.582 μ mol/L (EC ₅₀)	[47]
		Anti-diabetes	HepG2 cells, STZ-induced diabetic mice, α -glucosidase inhibitory assay	(2.77 $\pm$ 0.19) mg/mL (IC ₅₀)	[24]
		Anti-inflammatory	RAW264.7 cells (LPS-induced)		[48]
			IL-6-induced STAT3 in HepG2 cells		[29]
		Anti-oxidant	Assessment of intracellular ROS production lipid peroxidation assay		[49]
			ROS scavenging activity assay		[24]
		Neuroprotection	Middle cerebral artery occlusion (MCAO) mice		[50]
			H ₂ O ₂ -induced SH-SY5Y cell	(85.20 $\pm$ 0.01)% (viability)	[51]
		Anti-osteoporosis	β -Glycerophosphate induced MC3T3-E1 cells and primary osteoblasts, OVX-induced mouse		[52]
			MC3T3-E1 cells		[33]
12	Morrionside	Cardioprotection	Rat model of acute myocardial infarction (AMI). OGD treatment of rat coronary artery endothelial cell		[53]
		Lung protection	LPS-induced mice and RAW264.7 and RLE-6TN cells, bleomycin induced pulmonary fibrosis in mice		[35]
		Anti-AD	PC12 cells treated with hydrogen peroxide (H ₂ O ₂) or amyloid beta 1-42 (A β 1-42)		[54]

Table 1 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
13	7- β -O-Methyl morroniside	Neuroprotection	H ₂ O ₂ -induced SH-SY5Y cell	(79.8 $\pm$ 0.033)% (viability)	[51]
		Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	(24.8 $\pm$ 4.5) μ mol/L (IC ₅₀)	[29]
		Potentiate progesterone	Progesterone response element/luciferase (PRE/Luc) assay		[15]
14	7- α -O-Methyl morroniside	Neuroprotection	H ₂ O ₂ -induced SH-SY5Y cell	(78.60 $\pm$ 0.06)% (viability)	[51]
		Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	(32.5 $\pm$ 3.0) μ mol/L (IC ₅₀)	[29]
		Enzyme inhibitor	Tyrosinase inhibition assay		[34]
15	7- β -O-Ethylmorroniside	Potentiate progesterone	PRE/Luc assay		[15]
		Anti-oxidant	1,1-Diphenyl-2-picrylhydrazyl (DPPH) and ferric reducing ability of plasma (FRAP) assays	(64.12 $\pm$ 0.98)% (DPPH) (0.32 $\pm$ 0.03) mmol/L (FRAP)	[55]
		Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	(67.0 $\pm$ 5.1) μ mol/L (IC ₅₀)	[29]
16	7- α -O-Ethylmorroniside	Anti-oxidant	DPPH and FRAP assays	(62.46 $\pm$ 0.31)% (DPPH) (0.29 $\pm$ 0.04) mmol/L (FRAP)	[55]
17	7(S)- <i>n</i> -Butyl morroniside	Anti-inflammatory	<i>N</i> -Formyl-methionylleucyl-phenylalanine (fMLP)-induced human polymorphonuclear neutrophils (PMNs)		[56]
		Neuroprotection	Glutamate-induced HT22 hippocampal cells		[57]
18	7(R)- <i>n</i> -Butyl morroniside	Anti-diabetes	BRIN-BD11 and H4IIE Cells		[25]
		Anti-inflammatory	BRIN-BD11 and H4IIE Cells		
19	Cornusglucoside A	Anti-inflammatory	HepG2 cells		[58]
20	Cornusglucoside B	Anti-inflammatory	HepG2 cells		
21	Cornusdiglycosides A	Anti-diabetes	α -Glucosidase inhibitory assay	(101.20 $\pm$ 1.29) μ mol/L (IC ₅₀)	[59]
22	Cornusdiglycosides B	Anti-diabetes	α -Glucosidase inhibitory assay	(78.90 $\pm$ 4.09) μ mol/L (IC ₅₀)	
23	Cornusdiglycosides C	Anti-diabetes	α -Glucosidase inhibitory assay	(99.10 $\pm$ 3.01) μ mol/L (IC ₅₀)	
24	Cornusdiglycosides D	Anti-diabetes	α -Glucosidase inhibitory assay	(116.70 $\pm$ 5.91) μ mol/L (IC ₅₀)	
25	Cornusdiglycosides E	Anti-diabetes	α -Glucosidase inhibitory assay	(89.50 $\pm$ 3.44) μ mol/L (IC ₅₀)	
26	Cornusdiglycosides F	Anti-diabetes	α -Glucosidase inhibitory assay	(106.30 $\pm$ 7.02) μ mol/L (IC ₅₀)	
27	Cornusdiglycosides G	Anti-diabetes	α -Glucosidase inhibitory assay	(102.70 $\pm$ 0.05) μ mol/L (IC ₅₀)	
28	Cornusdiglycosides H	Anti-diabetes	α -Glucosidase inhibitory assay	(117.50 $\pm$ 4.25) μ mol/L (IC ₅₀)	
29	Cornusdiglycosides I	Anti-diabetes	α -Glucosidase inhibitory assay	(149.50 $\pm$ 1.84) μ mol/L (IC ₅₀)	
30	Cornusdiglycosides J	Anti-diabetes	α -Glucosidase inhibitory assay	(162.20 $\pm$ 9.17) μ mol/L (IC ₅₀)	
31	Sweroside	Anti-diabetes	HL1C rat hepatoma cells		[60]
		Anti-diabetes	α -Glucose inhibition assay	(7.83 $\pm$ 0.29) μ mol/L (IC ₅₀)	[38]
		Anti-inflammatory	RAW264.7 cells (LPS-induced)		[61]
		Neuroprotection	IL-6-induced STAT3 in HepG2 cells		[29]
		Neuroprotection	Scopolamine-induced zebrafish (<i>Danio rerio</i>)		[62]
		Anti-tumor	Human leukemia cell lines, HL-60 (CCL-240TM), U937 (CRL1593.2 TM), K562 (CCL-243TM) and THP-1 (TIB-202TM), and human normal lung cell line of BEAS-2 B (CRL-9609TM)		[63]
		Anti-microbial	<i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Citrobacter freundii</i> and <i>Escherichia coli</i>		[64]
		Bone protection	Bone marrow mesenchymal stem cells (BMSCs) from C57BL/6 mice, OVX-induced osteoporosis mice		[65]
		Cardioprotection	Aconitine-induced H9C2 cardiomyoblast cell line		[66]
		Hepatoprotective	Primary hepatocytes of male C57BL/6 mice were treated with the reconstituted bile acid mixture C57BL/6J mice induced by alpha-naphthylisothiocyanate (ANIT)		[67]
32	Swertimarin	Anti-diabetes	Nicotinamide (NA)-STZ diabetic rats		[68]
		Anti-diabetes	α -Glucose inhibition assay	(11.40 $\pm$ 1.22) μ mol/L (IC ₅₀)	[38]
		Anti-inflammatory	IL-1b induced fibroblast-like synoviocytes (FLS)		[69]
		Anti-inflammatory	Enzyme (cyclooxygenases-2/1) inhibitors screening assay		[28]
		Anti-oxidant	The estimation of catalase (CAT), superoxide dismutase (SOD), thiobarbituric acid reactive substances and glutathione (GSH)		[70]
		Anti-microbial	<i>B. cereus</i> , <i>B. subtilis</i> , <i>C. freundii</i> and <i>E. coli</i>		[64]
		Hepatoprotective	<i>D</i> -Galactosamine induced in rats		[70]
33	8-(R)-Hydroxy-10-hydrosweoside	Hypolipidemic	OA induced HepG2 cells		[68]
		Anti-microbial	<i>B. cereus</i> , <i>B. subtilis</i> and <i>Staphylococcus aureus</i>		[71]
		Anti-microbial	<i>B. cereus</i> , <i>B. subtilis</i> and <i>S. aureus</i>		
34	8-(S)-Hydroxy-10-hydrosweoside	Anti-microbial	<i>B. cereus</i> , <i>B. subtilis</i> and <i>S. aureus</i>		
35	Officinaloside A	Anti-microbial	<i>B. cereus</i> , <i>B. subtilis</i> and <i>S. aureus</i>		

Table 1 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
36	Secoxyloganin	Anti-diabetes	α -Glucose inhibition assay	$(5.27 \pm 0.93) \mu\text{mol/L (IC}_{50})$	[38]
37	Secologanin	Anti-diabetes	α -Glucose inhibition assay	$(6.19 \pm 0.27) \mu\text{mol/L (IC}_{50})$	
38	Demethoxy-cornuside	Potentiate progesterone	PRE/Luc assay		[15]
		Anti-diabetes	BRIN-BD11 and H4IIE cells		[25]
			Human umbilical vein endothelial cells (HUVECs)		[72]
			Activating HUVECs and mice with LPS		[73]
		Anti-inflammatory	Enzyme (cyclooxygenases-2/1) inhibitors screening assay		[28]
			RAW264.7 cells (LPS-induced)	$(36.39 \pm 1.05) \mu\text{mol/L (IC}_{50})$	[14]
39	Cornuside	Anti-AD	3xTg-AD mice		[74]
		Anti-oxidant	Activating HUVECs and mice with LPS		[73]
		Neuroprotection	Rat induced by glucose oxygen deprivation		[75]
		Potentiate progesterone	PRE/Luc assay		[15]
		Hepatoprotective	CCl ₄ -treated rats		[76]
		Anti-allergy	Passive cutaneous anaphylaxis model rats		[77]
		Anti-diabetes	α -Glucose inhibition assay	$(9.53 \pm 0.72) \mu\text{mol/L (IC}_{50})$	[38]
40	Kingside	Anti-inflammatory	Enzyme (cyclooxygenases-2/1) inhibitors screening assay		[28]
		Anti-diabetes	α -Glucose inhibition assay	$(4.91 \pm 1.09) \mu\text{mol/L (IC}_{50})$	[38]
41	8-Epikingside	Anti-inflammatory	Enzyme (cyclooxygenases-2/1) inhibitors screening assay		[28]
42	2'-O- <i>p</i> -Coumaroyl-kingside	Anti-inflammatory	RAW264.7 cells	$(26.77 \pm 1.99) \mu\text{mol/L (IC}_{50})$	[13]
43	Cornusphenosides I	Neuroprotection	H ₂ O ₂ -induced SH-SY5Y cell		[12]
44	3'',5''-Dehydroxycornuside	Anti-inflammatory	RAW264.7 cells (LPS-induced)	$(38.75 \pm 1.27) \mu\text{mol/L (IC}_{50})$	[14]
45	Cornusides C	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(11.9 \pm 2.5) \mu\text{mol/L (IC}_{50})$	[29]
46	Cornusides D	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(79.1 \pm 28.2) \mu\text{mol/L (IC}_{50})$	
47	Cornusides E	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(47.0 \pm 1.2) \mu\text{mol/L (IC}_{50})$	
48	Cornusides F	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(29.7 \pm 6.8) \mu\text{mol/L (IC}_{50})$	
49	Cornusides G	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(27.6 \pm 7.7) \mu\text{mol/L (IC}_{50})$	
50	Cornusides H	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(19.4 \pm 1.5) \mu\text{mol/L (IC}_{50})$	
51	Cornusides I	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(21.9 \pm 3.6) \mu\text{mol/L (IC}_{50})$	
52	Cornusides J	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(43.0 \pm 7.2) \mu\text{mol/L (IC}_{50})$	
53	Cornusides L	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(12.2 \pm 2.3) \mu\text{mol/L (IC}_{50})$	
54	Cornusides M	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(40.5 \pm 10.9) \mu\text{mol/L (IC}_{50})$	
55	Cornusides N	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(52.6 \pm 2.3) \mu\text{mol/L (IC}_{50})$	
56	Cornusides O	Anti-inflammatory	IL-6-induced STAT3 in HepG2 cells	$(71.9 \pm 8.9) \mu\text{mol/L (IC}_{50})$	
57	Neocornuside C	Anti-diabetes	Insulin-induced HepG2 Cells	$1.275 \mu\text{mol/L (EC}_{50})$	[47]
58	Loganin-(4'-O-7'')- α -morroneiside	Anti-inflammatory	RAW264.7 cells (LPS-induced)	$(23.02 \pm 0.29) \mu\text{mol/L (IC}_{50})$	[13]
		Anti-diabetes	α -Gucosidase inhibitory activity	$(243.5 \pm 8.9) \mu\text{mol/L (IC}_{50})$	
59	Cornusdiridoid A	Anti-inflammatory	RAW264.7 cells (LPS-induced)	$(28.87 \pm 1.62) \mu\text{mol/L (IC}_{50})$	
		Anti-oxidant	DPPH and ABTS assays	79.24 ± 3.23 (ABTS)	
		Anti-diabetes	α -Gucosidase inhibitory activity	$(251.9 \pm 2.8) \mu\text{mol/L (IC}_{50})$	
60	Cornusdiridoid B	Anti-inflammatory	RAW264.7 cells (LPS-induced)	$(29.52 \pm 0.32) \mu\text{mol/L (IC}_{50})$	
		Anti-oxidant	DPPH and ABTS assays	78.25 ± 4.12 (DPPH) 44.16 ± 1.53 (ABTS)	
61	Cornusdiridoid C	Anti-diabetes	α -Gucosidase inhibitory activity	$(267.1 \pm 8.1) \mu\text{mol/L (IC}_{50})$	[14]
		Anti-oxidant	DPPH and ABTS assays	$(44.89 \pm 1.80)\%$ (DPPH)	
		Anti-oxidant	DPPH and ABTS assays	$(24.59 \pm 0.47)\%$ (ABTS)	
62	Cornusdiridoid D	Anti-diabetes	α -Gucosidase inhibitory activity	$(516.3 \pm 11.5) \mu\text{mol/L (IC}_{50})$	
		Anti-inflammatory	RAW264.7 cells (LPS-induced)	$(34.12 \pm 1.65) \mu\text{mol/L (IC}_{50})$	
63	Cornusdiridoid E	Anti-oxidant	DPPH and ABTS assays	$(36.60 \pm 1.64)\%$ (DPPH) $(48.99 \pm 0.51)\%$ (ABTS)	
		Anti-oxidant	DPPH and ABTS assays	$(60.17 \pm 5.63)\%$ (DPPH) $(17.10 \pm 0.19)\%$ (ABTS)	
64	Cornusdiridoid F	Anti-inflammatory	RAW264.7 cells (LPS-induced)	$(26.84 \pm 1.24) \mu\text{mol/L (IC}_{50})$	

inhibition experiments^[14,24,38,59]. It has been reported that secoiridoids glycosides have a better inhibitory effect on α -glucosidase than other iridoid glycosides, because the presence of methoxy group on C-7 or double bond on C-6/C-7 significantly reduces the inhibitory effect^[38]. Studies had also shown that the parent ring of iridoid glycosides with a pyran ring, and C-4 carboxyl substitution, unsaturated bond between C-3 and C-4, and C-8 hydroxymethyl had influence on its hypoglycemic effect^[79]. Compounds **1**, **3–4**, **9**, **11**, **12**, **18**, **31**, **39**, and **57** exhibit anti-diabetic effects on INS-1 cell line, rat mesangial cells HBZY, HepG2, BRIN-BD11 and H4IIE cells, and HL1C rat hepatoma cells by protecting insulin secretion function^[22–25,47,60]. Compounds **1**, **12**, and **32** showed significant anti-diabetic activity in STZ induced rats and mice^[24,68].

DPPH, ABTS and FRAP assays, peroxy radical-scavenging and reducing capacity assays, hydroxyls, superoxide anions and Reductive power measurement are usually used to investigate the antioxidant activity *in vitro*. Literature^[79] had shown that the

antioxidant activity of iridoids was related to the number of hydroxyl groups, and the higher the number of hydroxyl groups, the better the antioxidant activity, as evidenced by the 13 iridoids identified from *C. officinalis* (Table 1).

At present, there are a total of 10 neuroprotective iridoids in *C. officinalis* (Table 1). It has been reported that substitution of C-7 in iridoid of *C. officinalis* might reduce or eliminate their neuroprotective activity^[12]. It was concluded that compounds **5**, **8**, **12–14**, **17** and **43** could alleviate the damage of SH-SY5Y cells^[12,42,51], HT22 hippocampal cells^[57] and PC12 nerve cells^[46]. At the animal level, compound **1** restored the learning and memory impairment induced by scopolamine in rats^[30], and compound **31** improved the memory impairment induced by scopolamine in zebrafish (*D. rerio*) model^[62].

Iridoids also have a wide range of biological activities. Some compounds, such as compounds **1**, **3**, **12**, **31**, **32**, **39**, have multiple biological activities. The chemical structures and biological activities of iridoids are shown in Fig. 3 and Table 1.

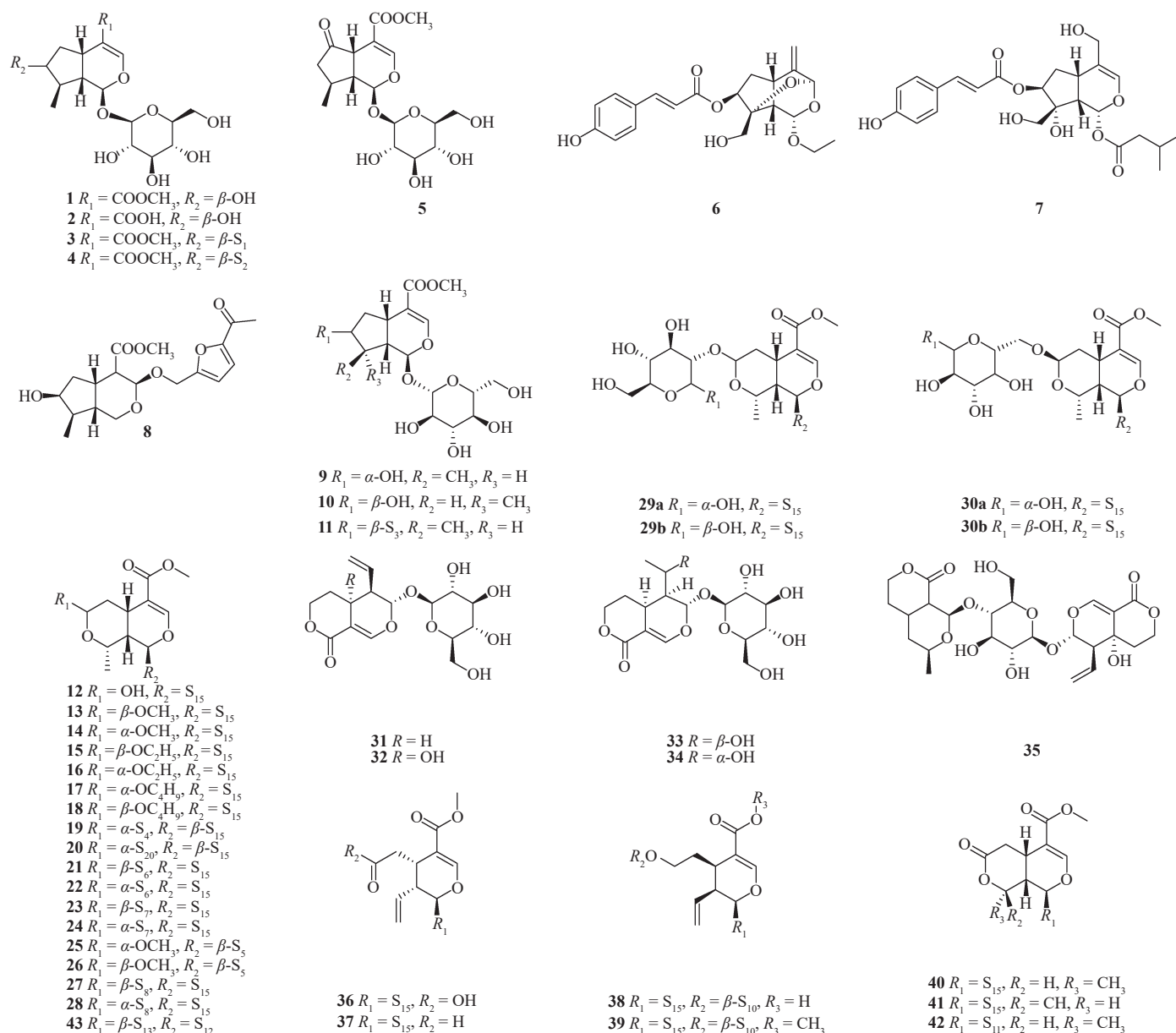


Fig. 3 Active iridoids in *C. officinalis*.

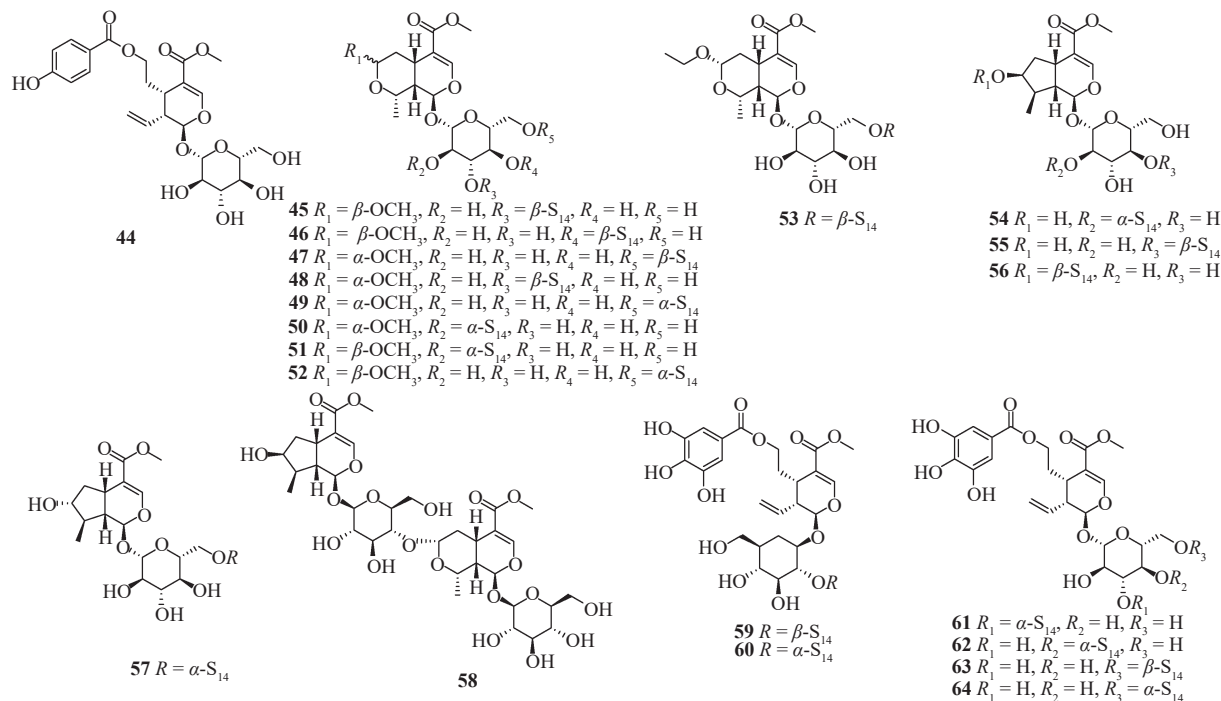


Fig. 3 (Continued)

2.2 Flavonoids

There were 17 active flavonoids in *C. officinalis* (Table 2 and Fig. 4). Their pharmacological effects and the number of compounds with

corresponding effect were like this anti-oxidant (17), anti-inflammatory (14), anti-tumor (14), anti-diabetic (10), cardioprotection (8), neuroprotection (8), hepatoprotective (7), anti-AD (6) etc.. Among them, anti-oxidant, anti-inflammatory, anti-tumor and anti-diabetic activities are the main

Table 2
Bioactive flavonoids from *C. officinalis*.

No.	Compounds	Activities	Methods	Dosage effects	Reference
65	Apigenin	Anti-hypertensive	Angiotensin I-converting enzyme (ACE) inhibitory activity assay		[80]
			SHR and WKY rats		[81]
			FRAP, DPPH, and ABTS assays, high-fat diet-induced injury experiments in rat	0.575 mg/mL (IC ₅₀ , DPPH) 0.344 mg/mL (IC ₅₀ , ABTS)	[82]
		Anti-oxidant	Type 2 diabetes (T2D) rats		[83]
			ABTS assay	0.824 3 μg/mL (IC ₅₀)	[84]
		Cardioprotection	Doxorubicin (DOX) induced rats		[85]
			SHR and WKY rats		[81]
		Anti-inflammatory	T2D rats		[83]
			LPS-induced RAW264.7 cells		[86]
			RAW264.7 cells		[87]
		Hypolipidemic	T2D rats		[83]
			T2D rats		[88]
			Diabetic rats		[83]
		Anti-diabetes	T2D rats		[83]
			Rat lens aldose reductase (RLAR), human recombinant aldose reductase (HRAR), advanced glycation endproducts (AGEs), protein tyrosine phosphatase 1B (PTP1B)		[86]
			RBL-2H3 cells		[87]
		Anti-allergy	HaCaT Cells		[87]
66	Kaempferol	Skin sparing			[87]
		Anti-tumor	H358 xenograft and Lewis lung carcinoma model		[89]
		Hepatoprotective	Hepatic fibrosis was induced by CCl ₄ in Wistar rats		[90]
		Neuroprotection	Hypoxic-ischemic brain injury in neonatal rats		[91]
			Acetylcholinesterase (AChE), butyrylcholinesterase (BChE), beta-site amyloid precursor (APP) cleaving enzyme 1 (BACE1)		[86]
		Anti-AD			[86]
		Anti-piroplasma activity	<i>Babesia caballi</i> and <i>Theileria equi</i>		[92]
					[92]
		Cytotoxicity	HepG2 and human caucasian breast adenocarcinoma cell line (MCF-7)		[93]
		Anti-tumor			[94]
			The human BC cell lines BT474 and MDA-MB-231		[94]

Table 2 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
66	Kaempferol	Cardioprotection	Isoproterenol (ISO)-induced heart failure in diabetic rats		[95]
		Neuroprotection	LPS-Induced striatum injury in mice		[96]
		Anti-diabetes	Rat (NRK-52E) and human renal tubular epithelial cells (RPTEC)		[97]
		Hepatoprotective	D-Galactosamine (D-GalN)/LPS-induced acute liver failure in mice		[98]
		Intestinal protection	LPS-induced epithelial-endothelial co-culture model		[99]
		Anti-depressant	Chronic social defeat stress (CSDS) mouse model		[100]
		Anti-microbial	<i>Candida parapsilosis sensu stricto</i> , <i>C. orthopsilosis</i> , <i>C. metapsilosis</i>		[101]
		Anti-obesity	3T3-L1 cells		[102]
		Osteogenesis	Sarcoma osteogenic-2 (SaOS-2) osteoblasts		[103]
		Lung protection	Mouse silicosis model		[104]
		Anti-inflammatory	DSS induced UC model in mice		[105]
			RAW264.7 cells		[84]
		Anti-oxidant	LPS-induced epithelial-endothelial co-culture model		[99]
			FRAP, DPPH, and ABTS assay	0.850 6 $\mu\text{g/mL}$ (IC_{50} , ABTS) 5.318 $\mu\text{g/mL}$ (IC_{50} , DPPH)	[84]
		Anti-oxidant	DPPH assays	(66.45 $\pm$ 5.79)%	[106]
		Anti-tumor	MCF-7 and osteosarcoma cells (U2-OS)		[107]
		Anti-microbial	Human colon cancer HCT116 cells		[108]
		Anti-microbial	Against 5 bacterial and 2 fungal strains by agar well-diffusion method		[109]
67	Astragalin	Cytotoxicity	CAL27 and MDAMB231 cell lines		[110]
			HepG2 and MCF-7		[93]
		Anti-piroplasma activity	<i>B. caballi</i> and <i>T. equi</i>		[92]
		Anti-inflammatory	LPS-stimulated RAW264.7 cell	(18.42 $\pm$ 2.67) $\mu\text{mol/L}$ (IC_{50})	[111]
		Anti-osteoporosis	Primary human osteoblasts HOb cells		[112]
		Anti-depressant	Chronic unpredictable mild stress (CUMS) mice model		[113]
		Anti-oxidant	ABTS, DPPH and 2-phenyl-4,4,5,5-tetramethylimidazolineoxyl-1-oxyl-3-oxide (PTIO) assay	(12.59 $\pm$ 0.37) $\mu\text{mol/L}$ (IC_{50} , ABTS) (1.85 $\pm$ 0.27) $\mu\text{mol/L}$ (IC_{50} , DPPH) (151.90 $\pm$ 28.35) $\times 10^3$ $\mu\text{mol/L}$ (PTIO)	[114]
			DPPH, ABTS, FRAP and lipid peroxidation inhibition assays		[115]
		Anti-hypertensive	ACE inhibitory activity assay		[80]
		Anti-tumor	NCI-H460 human non-small cell lung cancer (NSCLC) cells		[116]
68	Trifolin	Anti-diabetes	α -Glucosidase inhibitory assay		[117]
		Anti-inflammatory	Rat and mouse models of acetic colitis		[118]
		Anti-piroplasma activity	<i>B. caballi</i> and <i>T. equi</i>		[92]
		Anti-viral	Dengue virus (DENV) protease inhibition assay		[119]
		Anti-tumor	A549 cells		[120]
		Cardioprotection	AMI rats		[121]
			LPS-induced macrophages		[122]
		Anti-oxidant	ABTS, DPPH and PTIO assay	(11.45 $\pm$ 0.78) $\mu\text{mol/L}$ (IC_{50} , ABTS) (8.88 $\pm$ 1.11) $\mu\text{mol/L}$ (IC_{50} , DPPH) (0.66 $\pm$ 0.10) $\times 10^3$ $\mu\text{mol/L}$ (PTIO)	[114]
		Anti-oxidant	Peroxyl radical-scavenging and reducing capacity assays	10.00 $\mu\text{mol/L}$ (IC_{50})	[123]
			DPPH assay, superoxide anion scavenging activity	(21.82 $\pm$ 0.34) $\mu\text{mol/L}$ (IC_{50} , DPPH) (61.37 $\pm$ 1.47) $\mu\text{mol/L}$ (IC_{50} , superoxide anion scavenging activity)	[124]
69	Kaempferol-3-O-rutinoside	Anti-inflammatory	DPPH, ABTS, FRAP and lipid peroxidation inhibition assays		[92]
		Anti-oxidant			
		Anti-oxidant			
		Anti-oxidant			
70	Quercetin	Cardioprotection	Rat model of T2D		[125]
			DPPH and ABTS assay	(8.14 $\pm$ 1.83) $\mu\text{g/mL}$	[126]
		Anti-inflammatory	Rat model of T2D		[125]
			Rat rheumatoid arthritis (RA) model		[127]
		Anti-osteoporosis	RAW264.7 cells		[123]
		Endometriosis	Rat endometriosis model		[128]

Table 2 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
70	Quercetin		Human colon cancer cells		[107]
		Anti-tumor	Human non-tumoral MCF-10A mammary cells, Human breast cancer MCF-7 and MDA-MB-231 cells and Human myocardial AC16 cells		[129]
		Enzyme inhibitor	Recombinant human angiotensin-converting enzyme-2 (RhACE2) activity inhibition assay		[130]
		Cytotoxicity	HepG2 and MCF-7		[93]
		Anti-viral	Hsp70		[131]
			COVID-19		[132]
			Ischemia/reperfusion (I/R) injury in Sprague-Dawley rats		[133]
		Neuroprotection	Male Sprague Dawley rats were fed vincristine		[134]
		Anti-AD	AD mice		[135]
		Cardioprotection	SHR rats		[136]
		Anti-diabetes	STZ-induced diabetes in rats		[137]
		Hepatoprotective	Toosendanin (TSN)-induced hepatotoxicity was diminished in Nrf2 knock-out mice		[138]
		Bone protection	Osteoblast-osteoclast-endothelial cell co-culture		[139]
		Anti-microbial	<i>S. aureus</i> and <i>Pseudomonas aeruginosa</i>		[126]
		Anti-piroplasma activity	<i>B. caballi</i> and <i>T. equi</i>		[92]
71	Quercetin-3- <i>O</i> -glucuronide methyl ester	Anti-oxidant	DPPH assay, superoxide anion scavenging activity	(29.31 ± 0.85) μmol/L (IC ₅₀ , DPPH) (71.06 ± 0.62) μmol/L (IC ₅₀ , superoxide anion scavenging activity)	[124]
		Enzyme inhibitor	Influenza A (H1N1) induced CPE reduction assay in MDCK cell		[140]
		Cytotoxicity	HepG2 and MCF-7		[93]
		Anti-oxidant	DPPH assay	(23.64 ± 1.26) μmol/L (IC ₅₀)	[106]
			Ultraviolet B (UVB) or H ₂ O ₂ -stimulated HaCaT Cells		[140]
		Anti-inflammatory	UVB or H ₂ O ₂ -Stimulated HaCaT Cells		[141]
		Renal protection	HK-2 and NRK-52E tubular cell lines		[142]
		Inhibiting melanin production	α -Melanocyte-stimulating hormone (α -MSH)-induced B16F10 cells		[141]
72	Quercetin-3- <i>O</i> -glucuronide (querciturone)	Moisturizing	Evaluating the moisturizing factor-related genes		
		Anti-tumor	HepG2 cells		[143]
		Bone protection	DBA/2 mice		[144]
		Enzyme inhibitor	rhACE2 activity inhibition assay		[130]
		Anti-viral	HepG2.2.15 cells		[145]
		Anti-piroplasma activity	<i>B. caballi</i> and <i>T. equi</i>		[92]
		Cytotoxicity	HepG2 and MCF-7		[93]
			DPPH assay	(24.08 ± 0.90) μmol/L (IC ₅₀)	[106]
			DPPH assay, ABTS assay, cellular antioxidant activity (CAA) assay (HepG2 cells)	(271.2 ± 9.0) μmol/L (IC ₅₀ , DPPH) (115.9 ± 2.9) μmol/L (IC ₅₀ , ABTS)	[146]
		Anti-oxidant	DPPH, ABTS, FRAP and lipid peroxidation inhibition assays		[115]
			ABTS, DPPH and PTIO assay	(10.37 ± 1.01) μmol/L (IC ₅₀ , ABTS) (8.72 ± 1.53) μmol/L (IC ₅₀ , DPPH) (0.47 ± 0.06) × 10 ³ μmol/L (PTIO)	[114]
			DPPH assays, superoxide anion scavenging activity		[124]
73	Quercetin-3- <i>O</i> - β -D-glucoside		CAL27 and MDAMB231 cell lines		[110]
		Cytotoxicity	HepG2 and MCF-7		[93]
			RhACE2 activity inhibition assay		[130]
		Enzyme inhibitor	H1N1 induced CPE reduction assay in MDCK cell		[140]
		Anti-piroplasma activity	<i>B. caballi</i> and <i>T. equi</i>		[92]

Table 2 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
74	Rutin	Enzyme inhibitor	RhACE2 activity inhibition assay		[130]
		Anti-piroplasma activity	<i>B. caballi</i> and <i>T. equi</i>		[92]
			ABTS and PTIO assay	(13.68 ± 0.93) μmol/L (IC ₅₀ , ABTS) (5.91 ± 0.45) × 10 ³ μmol/L (PTIO)	[114]
			DPPH, ABTS, FRAP and lipid peroxidation inhibition assays		[115]
		Anti-oxidant	Rat model of T2D		[125]
			ABTS and DPPH assay	(105.43 ± 0.16) μmol/L (drug concentration eliciting 50% of the maximum stimulation (SC ₅₀), ABTS) (60.25 ± 0.09) μmol/L (SC ₅₀ , DPPH)	[147]
			Rat model of T2D		[125]
		Anti-inflammatory	RAW264.7 cells		[147]
		Neuroprotection	STZ-treated rats		[148]
		Anti-AD	TauP301S mice		[149]
		Anti-viral	Hepatitis C virus		[150]
		Anti-tumor	Mouse breast cancer cells		[151]
		Anti-coagulation	<i>In vivo</i> blood coagulation test		[147]
		Anti-microbial	<i>Streptococcus agalactiae</i>		[152]
		Anti-depressant	Reserpine-induced depression in rats		[153]
		Enzyme inhibitor	RhACE2 activity inhibition assay		[130]
			DPPH assay, superoxide anion scavenging activity		[124]
			DPPH, ABTS, FRAP and lipid peroxidation inhibition assays		[115]
		Anti-oxidant	Rat model of T2D		[125]
			H ₂ O ₂ -stimulated granulosa cells		[154]
75	Hyperoside		Rat model of T2D		[125]
		Anti-inflammatory	12- <i>O</i> -Tetradecanoylphorbol-13-acetate (TPA)-induced ear edema mouse model and LPS-stimulated RAW264.7 cells		[155]
		Anti-osteoarthritis	Murine chondrocytes were stimulated with IL-1β		[156]
		Anti-tumor	MCF-7 and 4T1 cell		[157]
		Renal protection	Renal ischemia models		[158]
		Neuroprotection	6-Hydroxydopamine (6-OHDA)-Induced cytotoxicity in SH-SY5Y cells		[159]
			Murine chondrocytes were stimulated with IL-1β		[156]
		Bone protection	Osteoblastic MC3T3-E1 cells		[160]
		Lung protection	Bleomycin-induced pulmonary fibrosis in mice		[161]
		Anti-diabetes	STZ/high-fat diet-induced diabetic rats		[162]
		Hepatoprotective	Non-alcoholic fatty liver disease (NAFLD) rats		[163]
		Cardioprotection	Mice mode of sepsis by cecal ligation and puncture (CLP) treatment, cell model of myocardial injury by LPS		[164]
			Induced by 1-methyl-4-phenylpyridinium iodide (MPP+) in SH-SY5Y cells		[165]
		Neuroprotection	Transient MCAO in Sprague-Dawley rats		[166]
		Anti-microbial	13 Gram-positive and 44 Gram-negative pathogens		[167]
76	Chrysoeriol	Anti-oxidant	H ₂ O ₂ -treated ARPE-19 cells, H ₂ O ₂ -induced oxidative stress in RPE cells		[168]
		Anti-diabetes	STZ-induced rat		[169]
		Anti-tumor	Estrogen receptor-positive MCF-7 breast cancer cells		[170]
		Enzyme inhibitor	Soluble epoxide hydrolase (sEH)		[171]
			Peroxyl radical-scavenging and reducing capacity assays		[123]
		Anti-oxidant	H ₂ O ₂ -stimulated HUVECs		[172]
77	Luteolin		STZ induced C57BL/6 mice, high glucose (HG) was used to induce H9C2 cells		[173]
		Enzyme inhibitor	RhACE2 activity inhibition assay		[130]
		Anti-osteoporosis	RAW264.7 cells		[123]
		Anti-hypertensive	ACE inhibitory activity assay		[80]

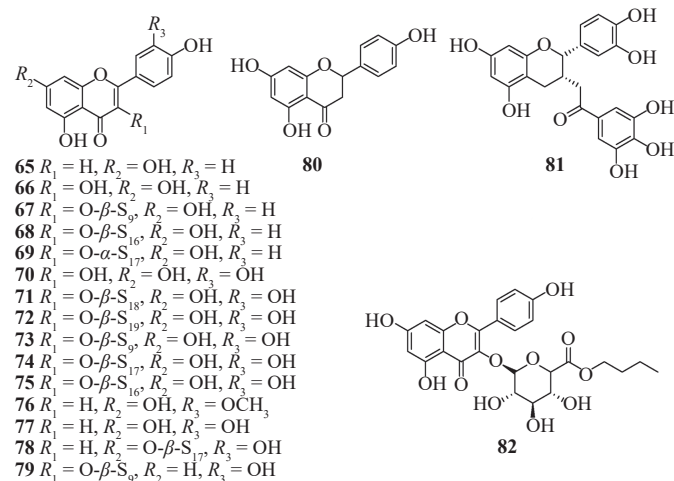
Table 2 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
78	Lonicerin	Anti-osteoarthritis	IL-1 β -stimulated rat chondrocytes and a monosodium iodoacetate (MIA)-induced model of OA		[174]
		Anti-tumor	A375 human melanoma cells		[175]
		Anti-diabetes	I/R model in the isolated rat heart		[176]
			STZ induced C57BL/6 mice, HG was used to induce H9C2 cells		[173]
		Anti-inflammatory	Irinotecan-induced intestinal mucositis		[177]
			STZ induced C57BL/6 mice, HG was used to induce H9C2 cells		[173]
			DOX-induced murine cardiomyocytes		[178]
		Cardioprotection	I/R model in the isolated rat heart		[176]
			STZ induced C57BL/6 mice, HG was used to induce H9C2 cells		[173]
		Bone protection	Glucocorticoid-induced osteoporosis (GIO) rats, MC3T3-E1 cells		[179]
		Ischemic stroke	Human brain microvascular endothelial cells (HBMECs) and tissues		[180]
		Anti-microbial	<i>Trueperella pyogenes</i> strains		[181]
		Hepatoprotective	CCl ₄ Induced rat liver injury model		[182]
		Anti-inflammatory	DSS induced mouse		[183]
		Anti-oxidant	ABTS and DPPH assay	34.97 μ mol/L (SC ₅₀ , ABTS) 30.37 μ mol/L (SC ₅₀ , DPPH)	[184]
		Osteogenesis	Osteoblast-like cell line		[185]
		Cytotoxicity	CAL27 and MDAMB231 cell lines		[110]
		Anti-oxidant	Rat model of T2D		[125]
		Anti-inflammatory	Rat model of T2D		[125]
79	Isoquercitrin	Anti-fungal	<i>C. albicans</i>		[186]
		Anti-viral	Varicella-zoster virus (VZV) and human cytomegalovirus (HCMV)		[187]
		Anti-AD	High fat diet- and amyloid beta-induced mice		[188]
		Anti-tumor	HCC cell		[189]
		Osteogenesis	Bone marrow-derived mesenchymal stem cells		[190]
		Anti-diabetes	STZ induced diabetes in rats		[191]
		Neuroprotection	STZ induced diabetes in rats		[191]
		Anti-parkinsonian	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) acute mouse model		[192]
		Anti-obesity	Adipocyte-specific adipose triglyceride lipase (ATGL) knockout mouse, C3H10T1/2 adipocytes		[193]
		Osteogenesis	Osteoblast-like cell line		[185]
			LPS-stimulated RAW264.7		[111]
		Anti-inflammatory	Arachidonic acid (AA)- and TPA-induced ear edema		[194]
			T2D rats		[83]
		Anti-oxidant	T2D rats		[83]
		Hypolipidemic	T2D rats		[83]
		Vascular protection	T2D rats		[83]
		Anti-tumor	Triple-negative human breast cancer cells (MDA-MR-231) and an animal model with 7,12-dimethylbenz anthracene (DMBA)-induced breast cancer in female rats		[195]
80	Naringenin		Gestational diabetes mellitus (GDM) mice		[196]
		Anti-diabetes	T2D rats		[83]
			Mouse heterogeneous leptin receptor gene knockout (<i>db/+</i>) model for GDM		[197]
		Anti-AD	AlCl ₃ + D-gal induced AD-like model rats		[198]
		Neuroprotection	LPS-induced dopamine (DA) neuronal loss rats		[199]
		Cardioprotection	Myocardial ischemia-reperfusion (MI/R) surgery rats, H9C2 cell line		[200]
		Hepatoprotective	APAP-induced hepatotoxicity in male Wistar rats		[201]
		Anti-obesity	Human white adipocyte cultures (hADSC) and abdominal subcutaneous adipose tissue (pWAT)		[202]

Table 2 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
80	Naringenin	Anti-allergy	Immunoglobulin E (IgE)-mediated passive cutaneous anaphylaxis.		[194]
		Endometriosis	endometriosis rats		[203]
		Renal protection	Animal model of renovascular hypertension		[204]
		Analgesic	Dorsal root ganglion (DRG) neurons from adult female SD rats		[205]
		Anti-AD	SH-SY5Y human neuroblastoma cells		[206]
		Cytotoxicity	CAL27 and MDAMB231 cell lines		[110]
		Hepatoprotective	CCl ₄ -induced fibrotic rat		[207]
		Anti-tumor	The human prostate cancer cell lines LNCaP and PC-3		[208]
		Cardioprotection	H9C2 rat cardiomyoblasts cells subjected to hypoxia/reoxygenation		[209]
			Langendorff-perfused rat heart		[210]
81	Epicatechin 3-O-gallate	Anti-inflammatory	LPS-induced RAW264.7 macrophages		[211]
			Carrageenan-induced paw edema model		[212]
		Sedation	The acetic acid-induced writhing and hot plate models in mice		[212]
		Anti-viral	grass carp (<i>Ctenopharyngodon idellus</i>) kidney (CIK) cells		[213]
		Anti-diabetes	α -Glucosidase enzyme inhibition assay	(67.8 $\pm$ 1.0) μ mol/L (IC ₅₀)	[214]
		Inhibiting melanin production	B16F10 melanoma cells		[215]
		Anti-oxidant	ABTS and DPPH assay	(102.9 $\pm$ 8.6) μ mol/L (SC ₅₀ , ABTS) (26.4 $\pm$ 2.0) μ mol/L (SC ₅₀ , DPPH)	[216]
82	Quercetin 3-O-(6"-n-butyl glucuronide)	Cytotoxicity	HepG2 and MCF-7		[93]

biological activity of flavonoids. The combined structure and biological activity of flavonoids are shown in Fig. 5A. The established network of relationships between flavonoids and biological activities showed that compounds **66**, **70**, **80** have a variety of biological activities (Fig. 5B).

Fig. 4 Active flavonoids in *C. officinalis*.

It was concluded that most of the flavonoids in *C. officinalis* had antioxidant activity. DPPH, ABTS and FRAP assays were used to investigate the antioxidant activity *in vitro*. The study of antioxidant structure-activity relationship of these flavonoids showed that B-ring 4'-OH and A-ring 7-OH had strong antioxidant activity, and the number of -OH groups in the B-ring or A-ring of flavonoids could greatly improve the anti-oxidant capacity of flavonoids^[111].

There were 14 flavonoids with significant anti-inflammatory activity and anti-tumor activity in *C. officinalis* (Table 2). The compounds with these 2 activities have a certain degree of coincidence.

The results showed that flavonoids **65–67**, **72**, **74–75**, **77** and **80–81** could exert anti-inflammatory effects by inhibiting the release of NO and the production of pro-inflammatory cytokines (IL-6, IL-8 and NF- κ B) in HaCaT, H9C2 and RAW264.7 cells^[84,86–87,89,111,122,141,147,155,173,211]. Compounds **66**, **68**, **70** and **77** also showed good anti-inflammatory effects in colitis mouse model and paw edema model^[83,118,125,127,173,177]. Compounds **65**, **68** and **69** have effects on lung cancer^[89,116,120]. Compounds **67** and **70** significantly inhibit the proliferation of human colon cancer cells^[107–108]. Compounds **66**, **67**, **70**, **74** and **80** have inhibitory effects on human BC cell lines BT474 and MDA-MB-231^[94], MCF-7^[107], mouse breast cancer cells^[151] and other breast cancer cells^[195]. Compounds **72** and **79** can significantly inhibit the proliferation of HepG2 and HCC cells^[143,189]. In addition, compound **81** has an inhibitory effect on prostate cancer cells^[208].

There were 10 flavonoids with significant anti-diabetic activity in *C. officinalis* (Table 2). Among them, compounds **65**, **68** and **81** exerted anti-diabetic effects by inhibiting RLAR, HRAR, AGES, PTP1B^[86] and α -glucosidase^[117,214]. It has been shown that 2,3,4-trihydroxybenzoyl flavonoid analogues have a great effect on the inhibitory activity of α -glucosidase, but the C ring of flavonoid has little effect on it^[217]. Compounds **66** and **77** showed anti-diabetic activity in rat (NRK-52E) and RPTEC^[97], as well as hyperglycemic (HG) induced H9C2 cells^[173]. At the animal level, compounds **65**, **70**, **75–77**, **79** and **80** significantly reduced blood glucose and lipid levels and improved insulin resistance in streptozotocin, high-fat diet-induced diabetic mice^[83,86,88,137,162,169,176,191,196–197].

2.3 Lignans

There are few literatures on lignans in *C. officinalis*, and only 1 reference^[13] has isolated and identified 17 lignans (Fig. 6) in *C. officinalis* and verified the antioxidant and anti-inflammatory activities of these compounds (Table 3). DPPH and ABTS assays were used to investigate the antioxidant activity *in vitro*. Fifteen

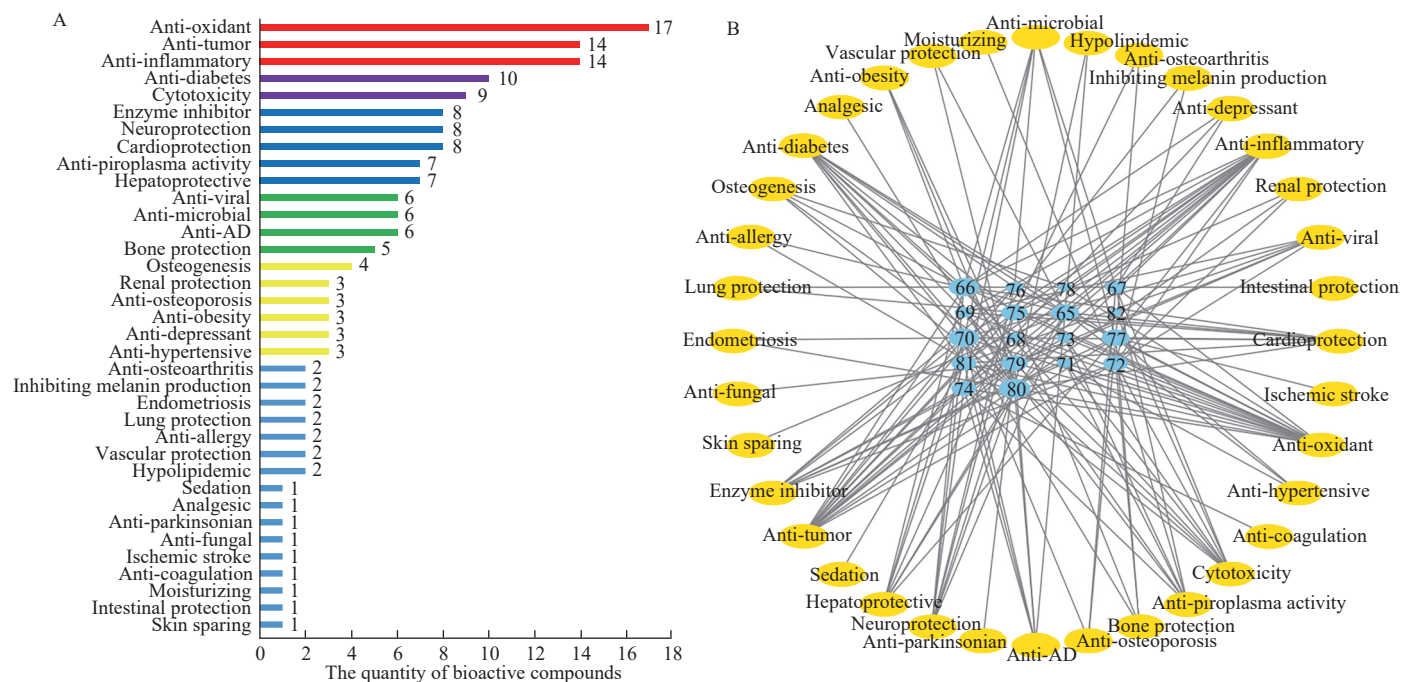


Fig. 5 (A) The bioactivities of flavonoids. The length of the column bar represents the number of compounds with this biological activity. (B) The relationship network between flavonoids and biological activity. The blue number represents flavonoids, the size of the circle represents the number of bioactivity of the compound, the cyan circle represents bioactivity, and each edge line represents the bioactivity of the compound.

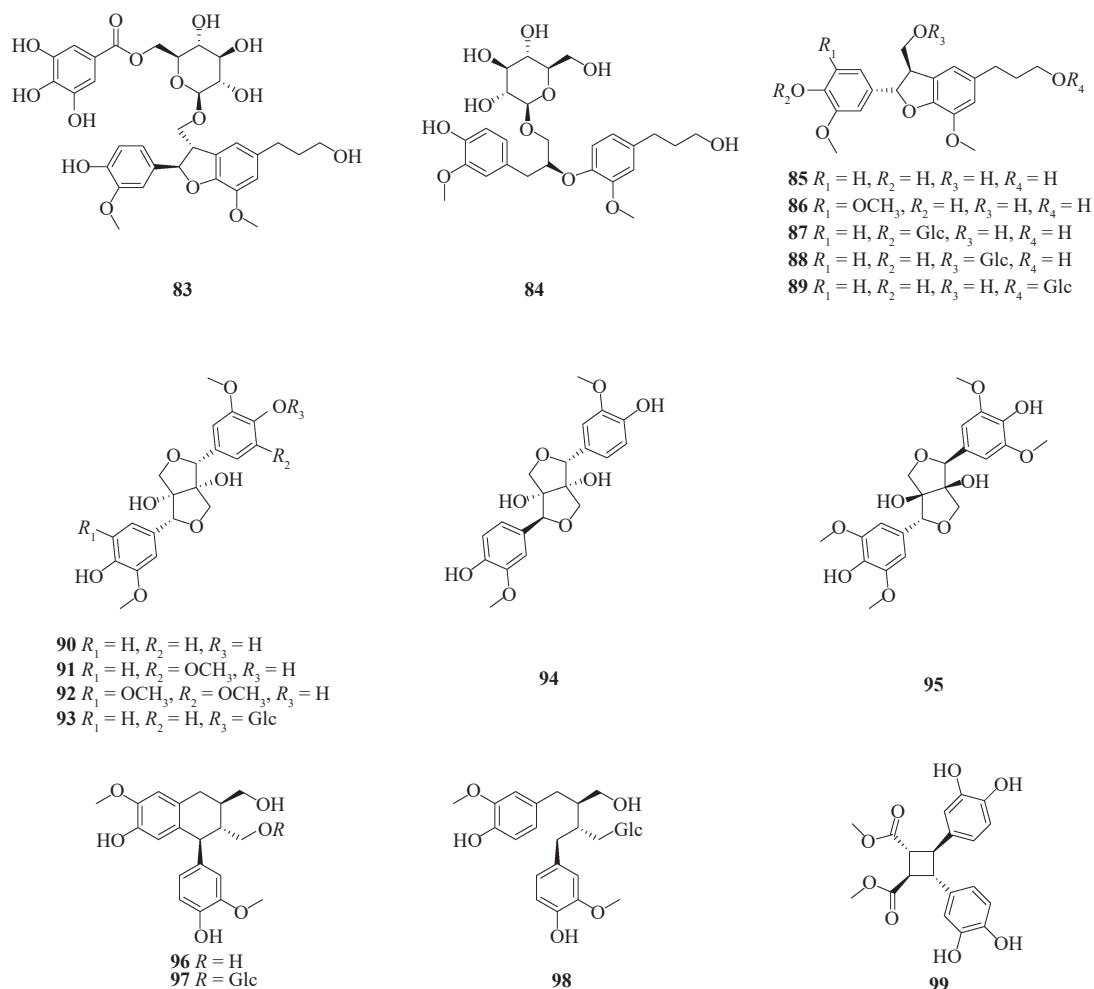


Fig. 6 Active lignans in *C. officinalis*.

Table 3
Lignans with anti-inflammatory and anti-oxidant activity.

No.	Compounds	Methods	Dosage effects	Reference
83	Officialignans A	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(16.75 ± 1.56) μmol/L (IC ₅₀ , DPPH) (37.29 ± 0.83) μmol/L (IC ₅₀ , ABTS) (46.60 ± 1.55) μmol/L (IC ₅₀ , NO inhibition)	
84	Officialignans B	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(44.37 ± 0.22) μmol/L (IC ₅₀ , NO inhibition)	
85	(7S,8R)-Dihydrodehydrodiconiferyl alcohol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(53.97 ± 12.52) μmol/L (IC ₅₀ , DPPH) (47.37 ± 2.30) μmol/L (IC ₅₀ , ABTS) (10.00 ± 1.41) μmol/L (IC ₅₀ , NO inhibition)	
86	(7S,8R)-5-Methoxydihydrodehydroconiferyl alcohol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(21.98 ± 0.18) μmol/L (IC ₅₀ , ABTS) (4.73 ± 0.09) μmol/L (IC ₅₀ , NO inhibition)	
87	(7S,8R)-Urolignoside	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(43.15 ± 2.56) μmol/L (IC ₅₀ , ABTS) (19.09 ± 1.03) μmol/L (IC ₅₀ , NO inhibition)	
88	(7S,8R)-Dihydrodehydrodiconiferyl alcohol-9-β-D-glucopyranoside	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(47.99 ± 2.80) μmol/L (IC ₅₀ , ABTS) (21.08 ± 1.09) μmol/L (IC ₅₀ , NO inhibition)	
89	(7S,8R)-Dihydrodehydrodiconiferyl alcohol-9'-β-D-glucopyranoside	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(55.43 ± 2.56) μmol/L (IC ₅₀ , ABTS) (18.56 ± 1.97) μmol/L (IC ₅₀ , NO inhibition)	
90	D-Pinoresinol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(41.64 ± 6.96) μmol/L (IC ₅₀ , DPPH) (66.43 ± 0.56) μmol/L (IC ₅₀ , ABTS) (93.83 ± 2.87) μmol/L (IC ₅₀ , NO inhibition)	
91	Medioresinol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(51.29 ± 3.61) μmol/L (IC ₅₀ , DPPH) (12.77 ± 0.45) μmol/L (IC ₅₀ , NO inhibition)	[13]
92	Syringaresinol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(41.59 ± 2.17) μmol/L (IC ₅₀ , DPPH) (45.92 ± 2.39) μmol/L (IC ₅₀ , ABTS) (13.96 ± 2.10) μmol/L (IC ₅₀ , NO inhibition)	
93	Pinoresinol O-β-D-glucopyranoside	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(95.63 ± 3.03) μmol/L (IC ₅₀ , ABTS) (55.70 ± 10.68) μmol/L (IC ₅₀ , NO inhibition)	
94	epi-Pinoresinol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(30.80 ± 5.77) μmol/L (IC ₅₀ , DPPH) (54.89 ± 1.95) μmol/L (IC ₅₀ , ABTS) (25.15 ± 0.48) μmol/L (IC ₅₀ , NO inhibition)	
95	epi-Syringaresinol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(81.46 ± 16.31) μmol/L (IC ₅₀ , ABTS) (12.73 ± 2.55) μmol/L (IC ₅₀ , NO inhibition)	
96	(+)-Isolariciresinol	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(19.40 ± 0.26) μmol/L (IC ₅₀ , ABTS) (84.45 ± 1.91) μmol/L (IC ₅₀ , NO inhibition)	
97	Isolariciresinol 9-O-β-D-glucopyranoside	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(25.14 ± 4.30) μmol/L (IC ₅₀ , DPPH) (32.41 ± 1.07) μmol/L (IC ₅₀ , ABTS) (69.32 ± 0.46) μmol/L (IC ₅₀ , NO inhibition)	
98	Secoisolariciresinol 9-O-β-D-glucopyranoside	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(86.08 ± 1.73) μmol/L (IC ₅₀ , NO inhibition)	
99	Dimethyl 3,3',4,4'-tetrahydroxy-δ-truxinate	DPPH and ABTS assay; LPS-stimulated RAW264.7 cells	(76.82 ± 3.56) μmol/L (IC ₅₀ , DPPH) (48.61 ± 2.46) μmol/L (IC ₅₀ , ABTS) (46.16 ± 0.06) μmol/L (IC ₅₀ , NO inhibition)	

lignin compounds showed antioxidant activity, of which compound **83** had the best antioxidant activity. LPS-induced RAW264.7 cells were used to detect the anti-inflammatory activity. The results showed that all lignan compounds had anti-inflammatory activity, among which compounds **85–87**, **89**, **91–92** and **95** showed good anti-inflammatory activity with IC₅₀ values lower than 20 μmol/L.

2.4 Tannins

Tannins are a kind of polyphenolic compounds with complex structure existing in plants, and tannins in *C. officinalis* are abundant. Tannins in *C. officinalis* are hydrolyzable tannins, which can be

divided into gallotannin and ellagotannin according to the different phenolic acids obtained after hydrolysis.

Although most of these compounds have been isolated and identified from *C. officinalis*, there are few reports on the activities of these compounds (Fig. 7), such as compounds **100**, **101**, **104**, **109**, **111**, etc., isolated from *C. officinalis*^[218]. On this basis, this review expanded the scope to find out the research status of these compounds in other plants and integrated the compounds that had been studied to further clarify the role of tannins in *C. officinalis*. A total of 16 tannins compounds in *C. officinalis* were found to have biological activities (Fig. 8). Among them, anti-diabetes and anti-oxidation are the main biological activities of tannin of *C. officinalis*. The combined structures and biological activities of tannins are shown in Table 4.

Table 4 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
101	Cornusiin B	Anti-oxidant	DPPH assay	(6.72 ± 0.16) μmol/L (IC ₅₀)	[220]
			Glucose- and oxalate-induced oxidative stress in NRK-49F cells		
		Anti-inflammatory	LPS-stimulated RAW264.7 cells		
102	Camptothin B	Anti-oxidant	DPPH assay	(5.40 ± 0.16) μmol/L (IC ₅₀)	[106]
		Anti-inflammatory	LPS-stimulated RAW264.7 cells		
		Anti-tumor	Androgen-dependent LNCaP and androgen-insensitive DU145 cell lines		
103	Isoterchebin	Benign prostatic hypertrophy	RWPE-1 cell		[219]
		Anti-AD	AChE, BChE and BACE1 inhibitory assays		[221]
		Anti-viral	Vero cells infected with HSV-1 or HSV-2		[222]
104	Gemin D	Anti-oxidant	DPPH assay, ABTS assay, CAA assay (HepG2 cells)	(80.3 ± 3.4) μmol/L (IC ₅₀ , DPPH) (66.3 ± 1.5) μmol/L (IC ₅₀ , ABTS)	[146]
		Anti-diabetes	Yeast α-glucosidase inhibition assay	(64.19 ± 1.63) μmol/L (IC ₅₀)	[223]
		Anti-tumor	Wild type cell line (MCF-7/wt)		[224]
105	Tellimagrandin I		DPPH assay, ABTS assay, CAA assay (HepG2 cells)	(73.5 ± 2.5) μmol/L (IC ₅₀ , DPPH) (54.5 ± 0.6) μmol/L (IC ₅₀ , ABTS)	[146]
			Glucose- and oxalate-induced oxidative stress in NRK-49F cells		[220]
		Anti-microbial	<i>Helicobacter pylori</i> 's minimum inhibitory concentrations		[225]
106	Tellimagrandin II	Anti-viral	HCV NS3 protease		[226]
		Anti-AD	AChE, BChE and BACE1 inhibitory assays		[221]
		Anti-microbial	<i>H. pylori</i> 's minimum inhibitory concentrations		[225]
107	1,2-di- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-oxidant	DPPH assay, ABTS assay, CAA assay (HepG2 cells)	(50.9 ± 3.3) μmol/L (IC ₅₀ , DPPH) (46.6 ± 1.0) μmol/L (IC ₅₀ , ABTS)	[146]
		Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	(0.90 ± 0.01) μmol/L (IC ₅₀ , AGE formation) (0.90 ± 0.08) μmol/L (IC ₅₀ , RLAR)	[227]
		Anti-viral	HCV NS3 protease		[226]
108	1,2,3-tri- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-AD	AChE, BChE and BACE1 inhibitory assays		[221]
		Anti-microbial	<i>H. pylori</i> 's minimum inhibitory concentrations		[225]
		Anti-tumor	Human cancer K562, HL-60 and HeLa cells		[228]
109	1,2,6-tri- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-tumor	Human cancer K562, HL-60 and HeLa cells		[228]
		Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	(2.81 ± 0.03) μmol/L (IC ₅₀ , AGE formation) (2.35 ± 0.27) μmol/L (IC ₅₀ , RLAR)	[227]
		Anti-AD	AChE, BChE and BACE1 inhibitory assays		[221]
110	1,2,3,6-tetra- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	(1.89 ± 0.24) (IC ₅₀ , AGE formation) (4.01 ± 0.12) μmol/L (IC ₅₀ , RLAR)	[227]
		Anti-oxidant	DPPH assay	20.2 ± 0.6 (SC ₅₀)	[229]
		Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	1.99 ± 0.07 (IC ₅₀ , AGE formation) (0.70 ± 0.12) μmol/L (IC ₅₀ , RLAR)	[227]
111	1,2,3,6-tetra- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-AD	AChE, BChE and BACE1 inhibitory assays		[221]
		Anti-viral	HCV NS3 protease		[226]
		Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	0.80 ± 0.02 (IC ₅₀ , AGE formation) (0.76 ± 0.07) μmol/L (IC ₅₀ , RLAR)	[227]
112	1,2,3,4,6-penta- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-oxidant	DPPH assay, ABTS assay, CAA assay (HepG2 cells)	41.4 ± 3.1 (IC ₅₀ , DPPH) 46.1 ± 5.5 (IC ₅₀ , ABTS)	[146]
			DPPH assay	8.45 ± 1.99 (IC ₅₀)	[106]
		Anti-inflammatory	LPS-stimulated RAW264.7 cells		[106]
112	1,2,3,4,6-penta- <i>O</i> -Galloyl-β- <i>D</i> -glucose	Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	0.80 ± 0.02 (IC ₅₀ , AGE formation) (0.76 ± 0.07) μmol/L (IC ₅₀ , RLAR)	[227]
		Anti-viral	HCV NS3 protease		[226]

Table 4 (Continued)

No.	Compounds	Activities	Methods	Dosage effects	Reference
113	7- <i>O</i> -Galloyl- β - <i>D</i> -sedoheptulose		Assay for inhibition of RLAR, Assay for inhibition of HRAR	296.10 $\pm$ 0.89 (IC ₅₀ , RLAR) (592.0 $\pm$ 23.4) μ mol/L (IC ₅₀ , HRAR)	[230]
		Hepatoprotective	T2D <i>db/db</i> mice		[231]
114	Gallic acid 4- <i>O</i> - β - <i>D</i> -(6'- <i>O</i> -galloyl)-glucosid	Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	42.16 $\pm$ 0.82 (IC ₅₀ , AGE formation) (11.77 $\pm$ 1.23) μ mol/L (IC ₅₀ , RLAR)	[227]
115	Gallic acid 4- <i>O</i> - β - <i>D</i> -glucoside	Anti-diabetes	AGE cross-linking inhibition assay and RLAR inhibition assay	82.74 $\pm$ 8.49 (IC ₅₀ , RLAR)	

The formation of AGEs, increased polyol pathway flux, activation of protein kinase C isoforms, and increased hexosamine pathway flux have been recognized as major factors in the pathogenesis of complications associated with diabetes^[227]. Compounds **104**, **106** and **108–115** showed anti-diabetic effects by inhibiting the formation of yeast α -glucosidase, AGEs and RLAR^[223,227,230], respectively. In addition, tannins in *C. officinalis* also showed good antioxidant activity, among which compounds **100–102**, **104–106**, **109** and **112** were tested by DPPH and ABTS *in vitro*^[106,146,220,229]. At the cellular level, compounds **101**, **104–106** and **112** attenuated antioxidant enzyme activity on NRK-49F cells and HepG2 cells to exert antioxidant activity, respectively^[146,220].

2.5 Organic and phenolic acids

A total of 14 organic acids and phenolic acids of *C. officinalis* have significant biological activities. The main biological activities include anti-inflammatory activity (8), anti-diabetic activity (7), anti-microbial activity (6), anti-AD (6), anti-tumor activity (6),

anti-oxidant activity (5), liver protection (5), neuroprotection (4), cardioprotection (3), renal protection (3), anti-parkinsonian (3), etc.. The relationship between these compounds and biological activities showed that anti-inflammatory, anti-bacterial and anti-diabetic activities were the main biological activities of organic acids and phenolic acids of *C. officinalis*. Compounds **121**, **126**, **127** and **129** exhibited multiple biological activities simultaneously. The chemical structures and biological activities of organic acids are shown in Figs. 9A and 10. A total of 8 compounds with anti-inflammatory activity were identified, which could significantly inhibit the production and release of inflammatory mediators (NO) and pro-inflammatory cytokines (IL-6, IL-8 and NF- κ B) on cultured RAW264.7 cells, IL-1 β -induced human colonic myoblasts, epithelial cells. At the same time, compounds **121**, **128** and **129** showed good anti-inflammatory effects on TNBS induced UC mice, *L*-arginine-induced acute pancreatitis (AP) rat model and DSS induced mouse model^[232–234]. In addition, compounds **119** and **121** can inhibit the activity of cytochrome P450 (CYP450) enzyme and tyrosinase, respectively^[229,235]. Compounds **121** and **126**, when administered, reduced body weight in mice and relieved symptoms in obese mice by lowering insulin levels or activating brown adipose tissue^[236–237].

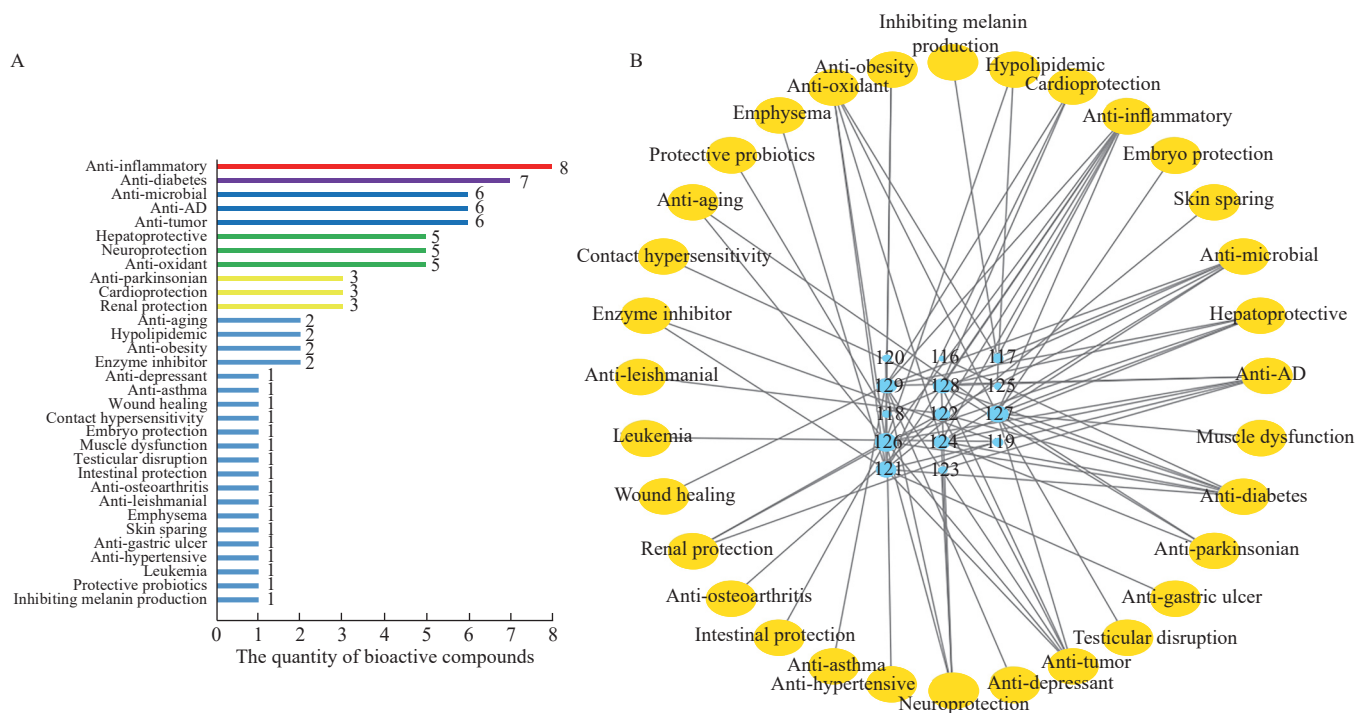


Fig. 9 (A) The bioactivities of organic and phenolic acids. The length of the column bar represents the number of compounds with this biological activity. (B) The relationship network between organic and phenolic acids and biological activity. The blue number represents organic and phenolic acids, the size of the circle represents the number of bioactivity of the compound, the cyan circle represents bioactivity, and each edge line represents the bioactivity of the compound.

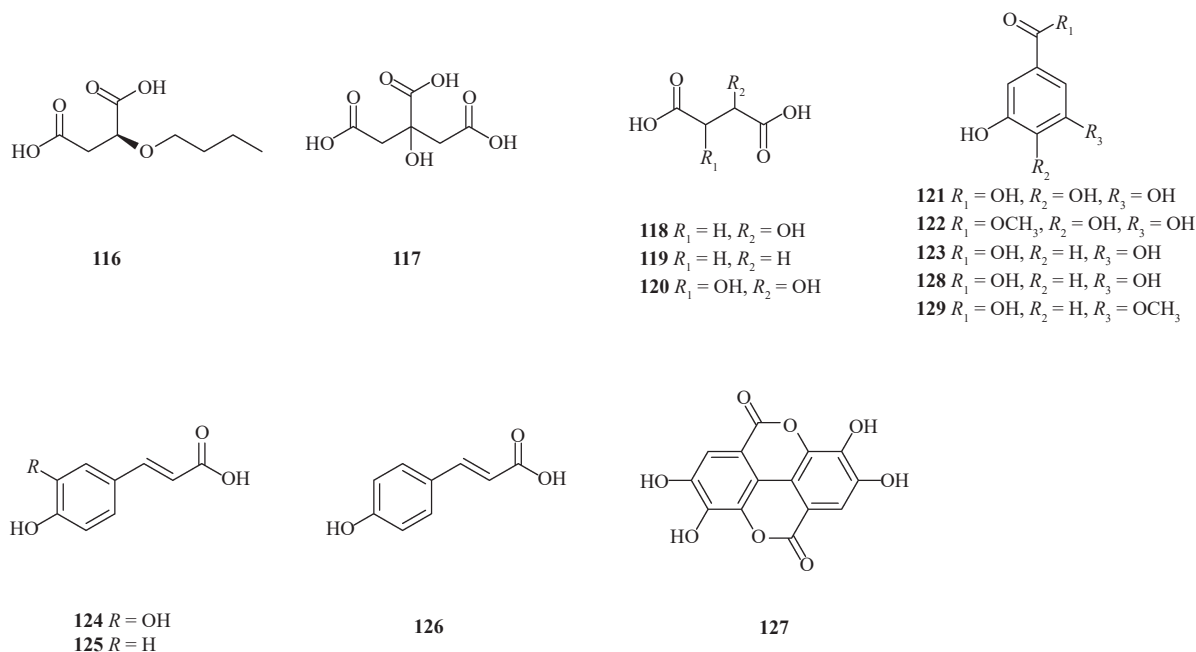
Fig. 10 Active organic and phenolic acids in *C. officinalis*.

Table 5

Bioactive organic and phenolic acids from *C. officinalis*.

No.	Compound	Activities	Methods	Reference
116	2-Butoxy butanedioic acid	Anti-diabetes		[25]
		Anti-microbial	<i>S. aureus</i>	[238]
		Anti-inflammatory	Dairy goats	[239]
117	Citric acid	Inhibiting melanin production	Mouse and human cells	[240]
		Anti-oxidant	Cd tolerance of Dahurian wildrye grass (<i>Elymus dahuricus</i>)	[241]
		Anti-microbial	<i>Alicyclobacillus acidoterrestris</i> and the strain CB1	[242]
118	Malic acid	Protective probiotics	Glycodeoxycholic acid (GDCA) tolerance of <i>Lactocaseibacillus paracasei</i> L9	[243]
		Enzyme inhibitor	CYP450 enzymes	[235]
119	Succinic acid	Leukemia	T-ALL cell lines	[244]
		Renal protection	Renal ischemia/reperfusion (IR) injury in Wistar rats	[245]
120	Tartaric acid	Anti-hypertensive	Hypertensive rats	[246]
121	Gallic acid	Anti-tumor	Lung adenocarcinoma (A549)	[247]
			Human dermal fibroblast cell line (HDF), human non-tumorigenic breast epithelial cell line (MCF10A), breast cancer cell line (MDA-MB-231) and melanoma cancer cell line (A375)	[248]
		Anti-tumor; Anti-oxidant	NSCLC	[249]
			DPPH assay, ABTS assay, CAA assay (HepG2 cells)	[146]
			DPPH assay	[229]
122	Methyl gallate	Anti-oxidant; Anti-diabetes	DPPH radical scavenging activity, LPS-stimulated RAW264.7 cells, androgen-dependent LNCaP and androgen-insensitive DU145 cell lines	[106]
			ABTS and DPPH radical scavenging assay	[216]
			3T3-L1 adipocytes	[250]
		Anti-gastric ulcer	Ethanol-induced gastric ulcer in rats	[251]
		Anti-inflammatory	IL-1 β -induced HIEC-6 cells and TNBS-induced UC in mice	[232]
		Anti-AD	APP/PS1 transgenic mouse	[252]
		Skin sparing	B16F10 melanoma cells and human skin fibroblasts	[253]
		Cardioprotection	Primary cardiomyocyte hypertrophy is stimulated with angiotensin II (Ang II). Cardiac hypertrophic remodeling is induced in mice by transverse aortic constriction (TAC)	[254]
		Anti-obesity	Obese mice	[236]
		Emphysema	COPD-linked lung inflammation/emphysema by utilizing elastase (ET) and cigarette smoke (CS)-induced mice model	[255]

Table 5 (Continued)

No.	Compound	Activities	Reference	Reference
123	3,5-Dihydroxybenzoic acid	Enzyme inhibitor	Tyrosinase inhibitory assay	[229]
		Anti-tumor	Zebrafish xenotransplantation, Hep3B and HepJ5 cells	[256]
		Anti-inflammatory	Swiss mice, RAW264.7 macrophages	[257]
		Anti-diabetes	Posterior limb ischemia in type 1 diabetic rats	[258]
		Anti-leishmanial	<i>Leishmania amazonensis</i>	[259]
		Anti-microbial	<i>Salmonella enterica</i> serovar typhimurium	[260]
		Renal protection	Hyperuricemia nephropathy (HN) mice, LPS-stimulated bone marrow-derived macrophages (BMDMs) and human peripheral blood mononuclear cells (PBMCs)	[261]
		Anti-osteoarthritis	OA in cellular and mice OA model	[262]
		Anti-AD	AChE	[263]
		Neuroprotection	Adult hippocampal neural precursor cells, C57BL/6JRj mice	[264]
124	Caffeic acid	Anti-diabetes	Insulin-resistance HepG2 cell model	[265]
124	Caffeic acid	Neuroprotection	Otenone-induced neurodegeneration in mice	[266]
125	<i>p</i> -Hydroxycinnamic acid	Anti-microbial	<i>Aeromonas veronii</i>	[267]
		Anti-oxidant	Serum antioxidant enzymes	[267]
			DPPH assay	[268]
		Anti-oxidant; Anti-parkinsonian	Model of noise-induced hearing loss	[269]
			Alpha-Synuclein-induced PD models	[270]
		Hepatoprotective	Oxidative stress induced by <i>tert</i> -butyl hydroperoxide (<i>t</i> -BHP) in HepG2 cells	[271]
		Anti-inflammatory	IL-1 β -treated human myofibroblasts of the colon, CCD-18Co, ACE	[272]
		Anti-inflammatory; Anti-AD	Model of noise-induced hearing loss	[269]
			<i>Caenorhabditis elegans</i> models of AD	[273]
		Hypolipidemic	High-fat diet mice	[274]
126	<i>p</i> -Coumaric acid	Anti-oxidant	DPPH, ABTS radical scavenging activity, determination of ferric reducing power, determination of metal-ion chelating activity, the protective effects against oxidative stress in PC12 cells	[275]
		Hypolipidemic	High fat-diet mice model	[275]
		Hepatoprotective	Ethanol induced both L-02 and HepG2 hepatic cells	[276]
		Hepatoprotective	Fipronil induced liver injury	[277]
		Renal protection	DOX-induced nephrotoxicity rats	[278]
		Renal protection	I/R injury rat model	[279]
		Anti-aging	<i>Caenorhabditis elegans</i> models	[280]
		Anti-obesity	Diet-induced obese mice, genetically obese mice, and C3H10T1/2 cells	[237]
		Neuroprotection	LPS induced neuroinflammation in mice	[281]
		Anti-diabetes	STZ-induced diabetic mice, human periodontal ligament fibroblasts (hPLFs) cultured under HG condition	[282]
127	Ellagic acid	Anti-inflammatory	Cigarette smoke extract (CSE)-activated epithelial cells	[283]
		Anti-tumor	Palmitic acid (PA)-induced human hepatoma cell (HepG2)-based hepatocellular injury model	[284]
		Intestinal protection	Ionizing radiation-induced intestinal injury mice	[285]
		Anti-AD	AD rat model induced by aluminum chloride (AlCl ₃)	[286]
		Anti-oxidant	ABTS cation radical scavenging activity and DPPH radical scavenging activity	[287]
		Anti-oxidant	ABTS cation radical scavenging activity and DPPH radical scavenging activity	[288]
		Anti-inflammatory	Heat-induced albumin denaturation	[288]
		Anti-diabetes	HG-induced type 2 diabetes mellitus (T2DM) HepG2 cells	[289]
128	Protocatechuic acid			

Table 5 (Continued)

No.	Compound	Activities	Reference	Reference
128	Protocatechuic acid	Hepatoprotective	Methotrexate (MTX)-treated rats	[290]
		Hepatoprotective	Diclofenac (DCF) treatment rat	[288]
		Anti-tumor	HepG2, SMMC-7721 and HL-7702 cells, xenograft mouse model with inoculated HepG2 cells	[291]
		Testicular disruption	Adjuvant-induced arthritic rats	[292]
		Anti-aging	Aging model was induced by <i>D</i> -galactose (DG)	[293]
		Muscle dysfunction	Incuprizone-induced model of MS	[294]
		Anti-parkinsonian	MPTP-induced PD	[295]
		Embryo protection	<i>D. rerio</i> (zebrafish) embryonic	[296]
		Anti-microbial	Model dental pathogens <i>Enterococcus faecalis</i> and <i>C. albicans</i>	[297]
		Neuroprotection	Arsenic-induced neurotoxicity in mice	[298]
		Hepatoprotective	Rats and <i>SIRT3</i> -knockout mice fed a high-fat diet and in AML-12 cells treated with PA	[299]
		Anti-parkinsonian	Rotenone (rot) induced PC12 cells, MPTP induced PD in male C57BL/6 mice	[300]
		Anti-diabetes	Rat model of high fat diet + high fructose + low dose STZ	[301]
		Anti-AD	A β -induced AD mouse model	[302]
		Anti-inflammatory	Rheumatoid arthritis (RA)-FLSs	[303]
		Anti-inflammatory	<i>L</i> -Arginine induced AP and multiple organs injury (MOI) in rats	[233]
		Anti-tumor	Colon cancer cells	[304]
		Cardioprotection	Mouse model of ISO-induced cardiac hypertrophy	[305]
		Contact hypersensitivity	Mice model induced by 2,4-dinitrofluorobenzene (DNFB)	[306]
129	Syringate	Anti-tumor	HepG2 cells	[307]
		Anti-tumor	Human oral cancer (HOC) SCC131 cells	[308]
		Wound healing	Diabetic wound rats	[309]
		Anti-asthma	Ovalbumin (OVA)-induced asthmatic mice model	[310]
		Cardioprotection	ISO induced myocardial infarction (MI) in rats	[311]
		Cardioprotection	Rat model with myocardial ischemia reperfusion injury	[312]
		Anti-depressant	Glutamate-induced mice	[313]
		Neuroprotection	Glutamate-induced mice	[313]
		Anti-inflammatory	DSS-induced mice	[234]
		Anti-microbial	Methicillin-resistant <i>S. epidermidis</i> strains	[314]
		Anti-AD	Neuron-like cells (SH-SY5Y)	[315]
		Hepatoprotective	Sodium valproate-induced liver injury in rats	[316]

2.6 Triterpenoids

There were 11 active triterpenoids in *C. officinalis* (Fig. 11). These triterpenoids had a wide range of biological activities (Table 6), including anti-inflammatory (8), anti-diabetic (8), anti-tumor (7),

anti-osteoarthritis (5), anti-oxidation (5), liver protection (5), enzyme inhibition (4), anti-bacterial (4), etc.. The main biological activities of triterpenoids in *C. officinalis* were anti-inflammatory, anti-diabetic and anti-tumor (Fig. 12A). Compounds 130, 134–135, and 138–139 have a variety of biological activities (Fig. 12B).

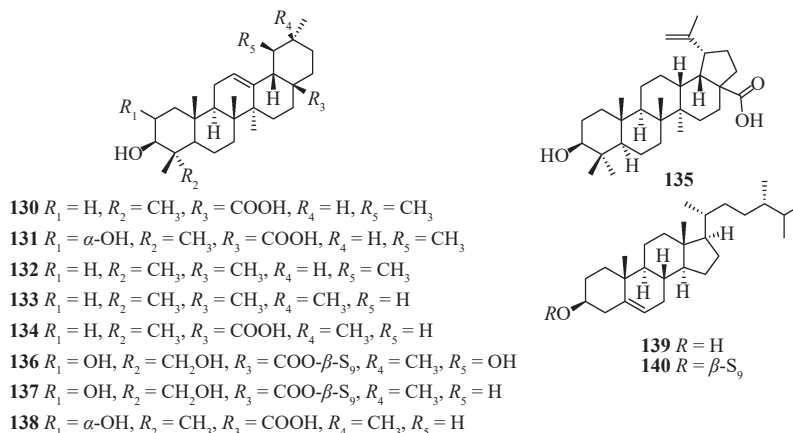
Fig. 11 Active triterpenes in *C. officinalis*.

Table 6Bioactive triterpenes from *C. officinalis*.

No.	Compound	Activities	Methods	Reference
130	Ursolic acid	Anti-parkinsonian	MPTP-intoxicated mouse model	[317]
			MPTP-intoxicated mouse model	
		Anti-inflammatory	RAW264.7 line cells, LPS-induced BALB/C mice	[318]
		Anti-tumor	Gemcitabine-resistant pancreatic cancer cells	[319]
		Anti-osteoarthritis	Rat chondrocytes, OA model	[320]
		Lung protection	Mice model of PM2.5-induced chronic obstructive pulmonary disease	[321]
		Cardioprotection	Mice treated with DOX	[322]
		Anti-microbial	Carbapenem-resistant <i>Klebsiella pneumoniae</i> (CRKP)	[323]
		Anti-viral	Epithelioma papulosum cyprini (EPC) cells, rainbow trout	[324]
		Anti-AD	BALB/c mice	[325]
		Hepatoprotective	CCl ₄ -induced liver fibrosis mice	[326]
		Skin sparing	UVB radiation-induced photoaging an <i>in vitro</i> model of human skin dermal fibroblasts	[327]
		Anti-oxidant	2',7'-Dichlorodihydrofluorescein diacetate (H2DCF-DA) and juglone assays as well as osmotic and heat stress assays	[328]
		Anti-depressant	H2DCF-DA and juglone assays as well as osmotic and heat stress assays	[329]
		Hhypercholesterolemia	Hypercholesterolemic hamsters	
			Diabetic rat model	[330]
		Anti-diabetes	HepG2 cells, STZ-induced diabetic mice, α -glucosidase inhibitory assay	[24]
		Anti-allergy	Mast cells were stimulated with IgE	[331]
		Hepatoprotective	Mice induced by high-fat diet and CCl ₄	[332]
131	Corosolic acid		HCT116 xenograft model and AOM/DSS model	[333]
		Anti-tumor	The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure was performed in Sprague-Dawley rats with orthotopic liver cancer	[334]
		Anti-diabetes	α -Glucose inhibition assay	[335]
		Bone protection	Receptor activator of NF- κ B ligand RANKL-induced osteoclastogenesis and hydroxylapatite resorption, LPS-induced mice calvarial osteolysis model	[336]
		Cardioprotection	Dox-induced C57BL/6J mice and AMP-activated protein kinase (AMPK) alpha 2 knockout mice	[337]
		Anti-microbial	KPC-2-positive bacteria	[338]
		Anti-osteoarthritis	OA rat model	[339]
132	α -Amyrin	Anti-obesity	3T3-L1 murine adipocytes	[340]
		Anti-oxidant	DPPH and ABTS assays	[341]
		Enzyme inhibitor	Xanthine oxidase, tyrosinase	[342]
133	β -Amyrin	Anti-inflammatory	LPS and interferone-gamma (IFN- γ) in rat microglial cells	
		Anti-obesity	3T3-L1 murine adipocytes	[340]
		Anti-microbial	<i>C. albicans</i>	[343]
		Renal protection	Glycerol-induced nephrotoxicity in rats	[344]
		Anti-oxidant	DPPH and ABTS assays	[341]
134	Oleanolic acid	Enzyme inhibitor	Xanthine oxidase, tyrosinase	[25]
			BRIN-BD11 and H4IIE cells	
		Anti-inflammatory	<i>Salmonella typhimurium</i> -induced diarrhea and enteritis	[345]
		Anti-tumor	Liver cancer cells	[346]
		SCI	SCI mice	[347]
		Neuroprotection	BV2 microglial cells induced by LPS	[348]
		Anti-microbial	<i>S. aureus</i>	[349]
		Anti-diabetes	α -Glucose inhibition assay	[350]
		Analgesic	Adult zebrafish models of orofacial pain	[351]
		Anti-osteoporosis	RANKL-induced osteoclastogenesis	[352]
		Anti-osteoarthritis	RANKL-induced osteoclastogenesis	
		Anti-allergy	Phorbol-12-myristate 13-acetate plus calcium ionophore A23187 (PMACI)-stimulated human mast cell (HMC)-1, mouse model of compound 48/80-induced anaphylactic shock	[353]
		Hepatoprotective	NAFLD mice	[356]
		Anti-obesity	Diet-induced mouse model of obesity	[357]
135	Betulinic acid	Anti-metabolic syndrome	High-fructose diet-induced metabolic syndrome in rats	[358]
		Anti-oxidant	Cobalt chloride-induced hypoxia stress in retinal pigment epithelial (RPE) cells	[359]
		Vascular protection	LPS-induced rats	[360]
		Anti-diabetes	Alloxane-treated ICR mice	[361]
		Anti-viral	DENV	[362]
		Anti-osteoarthritis	RANKL-induced osteoclastogenesis	[363]
		Lung protection	Bleomycin-induced pulmonary fibrosis in mice	[364]

Table 6 (Continued)

No.	Compound	Activities	Methods	Reference
136	Arjunglucoside I	Anti-oxidant	DPPH radical scavenging assay, lipoxygenase inhibition assay	[365]
		Anti-inflammatory	Inhibition of albumin denaturation	
		Anti-diabetes	α -Glucose inhibition assay	
137	Arjunglucoside II	Enzyme inhibitor	Human kinin-forming enzyme	[366]
138	Maslinic acid	Hepatoprotective	Mice with high-fat-diet-induced obesity, hepatocytes	[367]
		Anti-tumor	Human pancreatic cancer cells	[368]
		Anti-inflammatory	I/R-induced mice	[369]
		Anti-osteoarthritis	IL-1 β -induced chondrocytes, surgically induced mouse OA model	
		Septic responses	HMGB1-activated HUVECs and a CLP-induced sepsis mouse model	[370]
		Cardioprotection	Mice with aortic banding (AB) surgery	[371]
		Lung protection	PM2.5-induced mice	[372]
		Anti-diabetes	STZ-induced diabetic rats	[373]
		Anti-coagulation	Arterial and pulmonary thrombosis mouse model	[374]
			High-fat diet and sucrose-induced type-2 diabetic experimental rats	[375]
139	β -Sitosterol	Anti-diabetes	High-fat diet and sucrose induced type-2 diabetic rats	[376]
			α -Glucose inhibition assay	[265]
		Anti-tumor	HepG2 cells	[377]
			BMDMs, rheumatoid mice	[378]
		Anti-inflammatory	Mouse model of influenza	[379]
		Hepatoprotective	Alcoholic liver injuries rats	[380]
		Anxiolytic	Alpha 5 mutant mouse model	[381]
		Neuroprotection	Cerebral I/R rat model	[382]
140	Daucosterol	Anti-inflammatory	Mouse model of DSS-induced colitis	[383]
		Anti-tumor	A549, NCI-H460, NCI-H23 and L-132 cell lines	[384]
			Human prostate cancer cell lines (PC3 and LNCap)	[385]
		Anti-diabetes	α -Glucose inhibition assay	[265]
		Enzyme inhibitor	α -Amylase assay	[386]

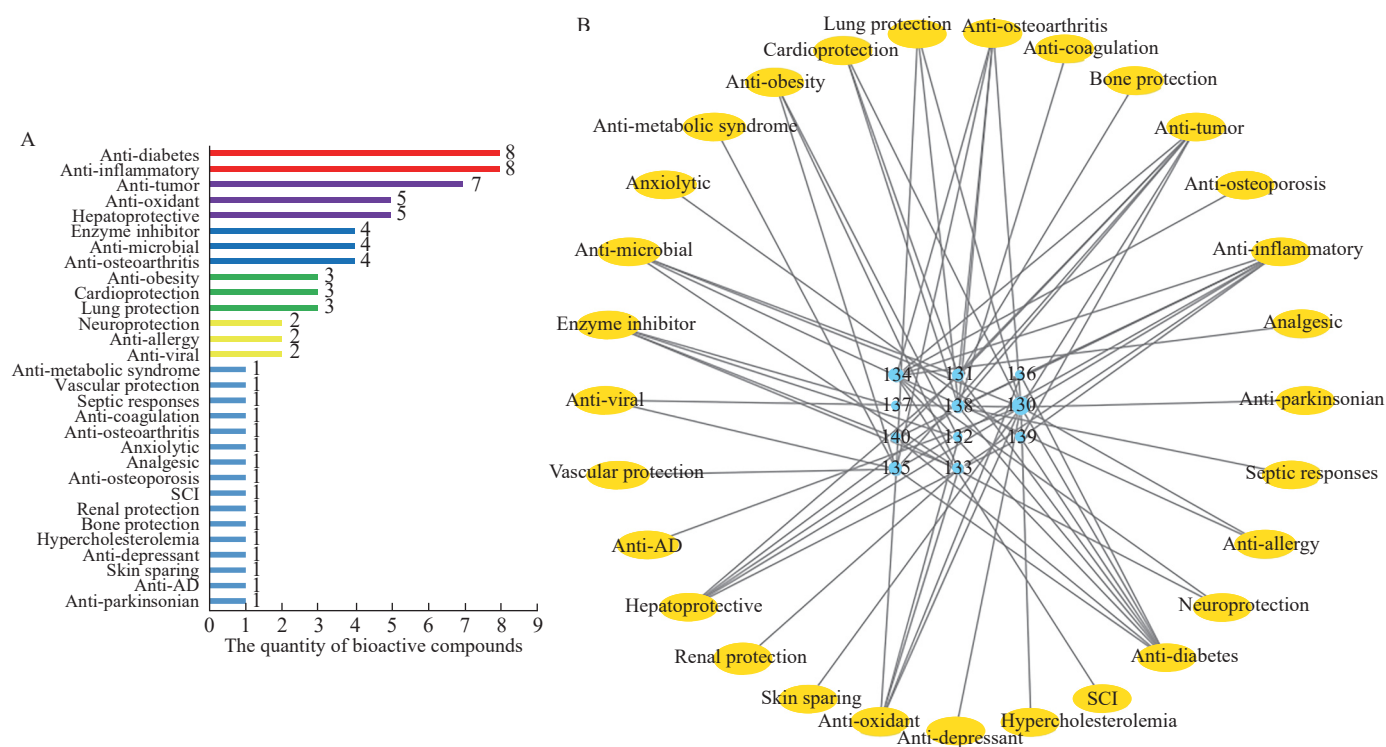


Fig. 12 (A) The bioactivities of triterpenoids. The length of the column bar represents the number of compounds with this biological activity.

(B) The relationship network between triterpenoids and biological activity. The blue number represents triterpenoids, the size of the circle represents the number of bio-activity of the compound, the cyan circle represents bioactivity, and each edge line represents the bioactivity of the compound.

2.7 Other compounds

A total of 9 active compounds (**141–149**) with anti-diabetic (5), anti-oxidant (3), anti-inflammatory (3), anti-microbial (2), anti-tumor (1) and immunosuppressive (1) activities were identified from *C. officinalis* (Fig. 13A). The relationship between these compounds and their biological activities indicates that anti-diabetes, anti-oxidation and anti-inflammatory are the main biological activities. Compounds **142** and **149** had a variety of biological activities (Fig. 13B). Compounds

142, 145–148 exert hypoglycemic effects by inhibiting α -glucosidase activity *in vitro*^[14,18]. In addition, compounds **142–144** showed good anti-oxidant activity in DPPH and ABTS assays^[14]. Compound **142–144** exerts anti-inflammatory effects mainly by inhibiting the production and release of NO, IL-6 and NF- κ B in RAW264.7 cells induced by LPS^[14]. Their chemical structures and biological activities are shown in Fig. 14 and Table 7.

Meanwhile, all substituents of active compounds from *C. officinalis* forementioned in this work are listed in Fig. 15.

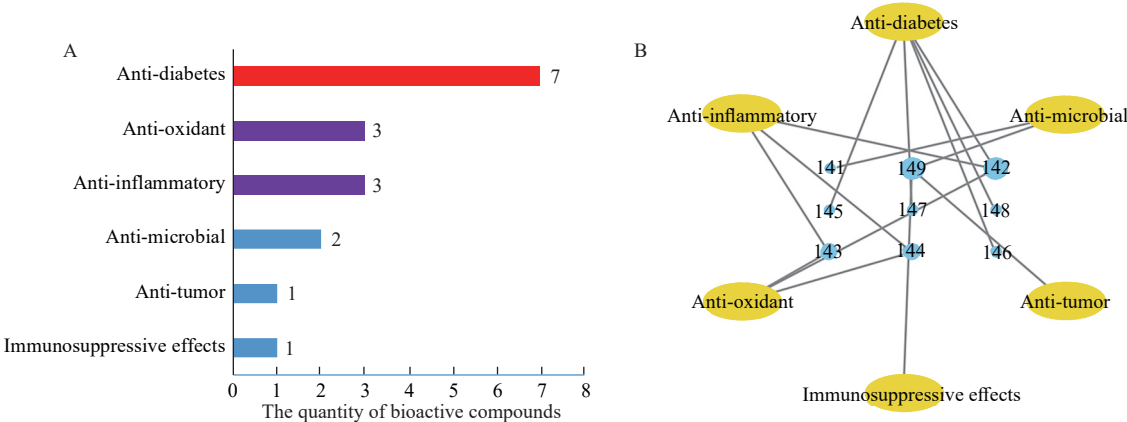


Fig. 13 (A) The bioactivities of other compounds. The length of the column bar represents the number of compounds with this biological activity. (B) The relationship network between other compounds and biological activity. The blue number represents other compounds, the size of the circle represents the number of bio-activity of the compound, the cyan circle represents bioactivity, and each edge line represents the bioactivity of the compound.

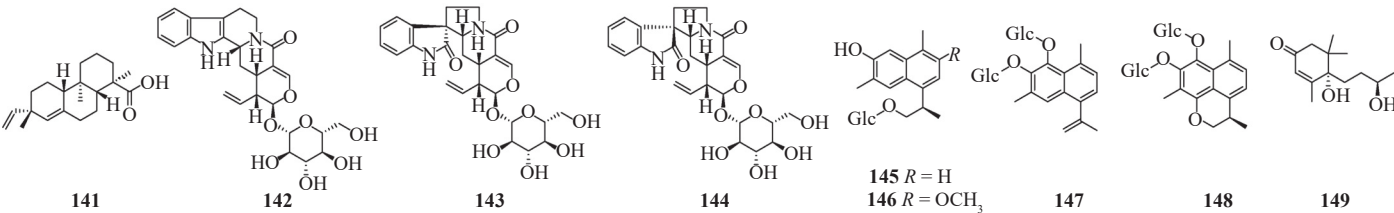


Fig. 14 Other active compounds in *C. officinalis*.

Table 7
Other compounds with biological activities.

No.	Name	Activities	Methods	Reference
141	Pimaric acid	Anti-microbial	<i>Paenibacillus larvae</i>	[387]
		Anti-diabetes	α -Glucose inhibition assay	
142	Vincosamide	Anti-inflammatory	LPS-induced RAW264.7 cells	
		Anti-oxidant	DPPH and ABTS assays	
143	7- <i>epi</i> -Javaniside	Anti-inflammatory	LPS-induced RAW264.7 cells	[14]
		Anti-oxidant	DPPH and ABTS assays	
144	Javaniside	Anti-inflammatory	LPS-induced RAW264.7 cells	
		Anti-oxidant	DPPH and ABTS assays	
145	Cornucadinolide A	Anti-diabetes	α -Glucose inhibition assay	
146	Cornucadinolide B	Anti-diabetes	α -Glucose inhibition assay	
147	Cornucadinolide D	Anti-diabetes	α -Glucose inhibition assay	[18]
148	Cornucadinolide E	Anti-diabetes	α -Glucose inhibition assay	
		Immunosuppressive effects	Jurkat cells	[388]
149	Vomifolol	Anti-tumor	Neuroblastoma SH-SY5Y cells	[389]
		Anti-microbial	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i>	[390]

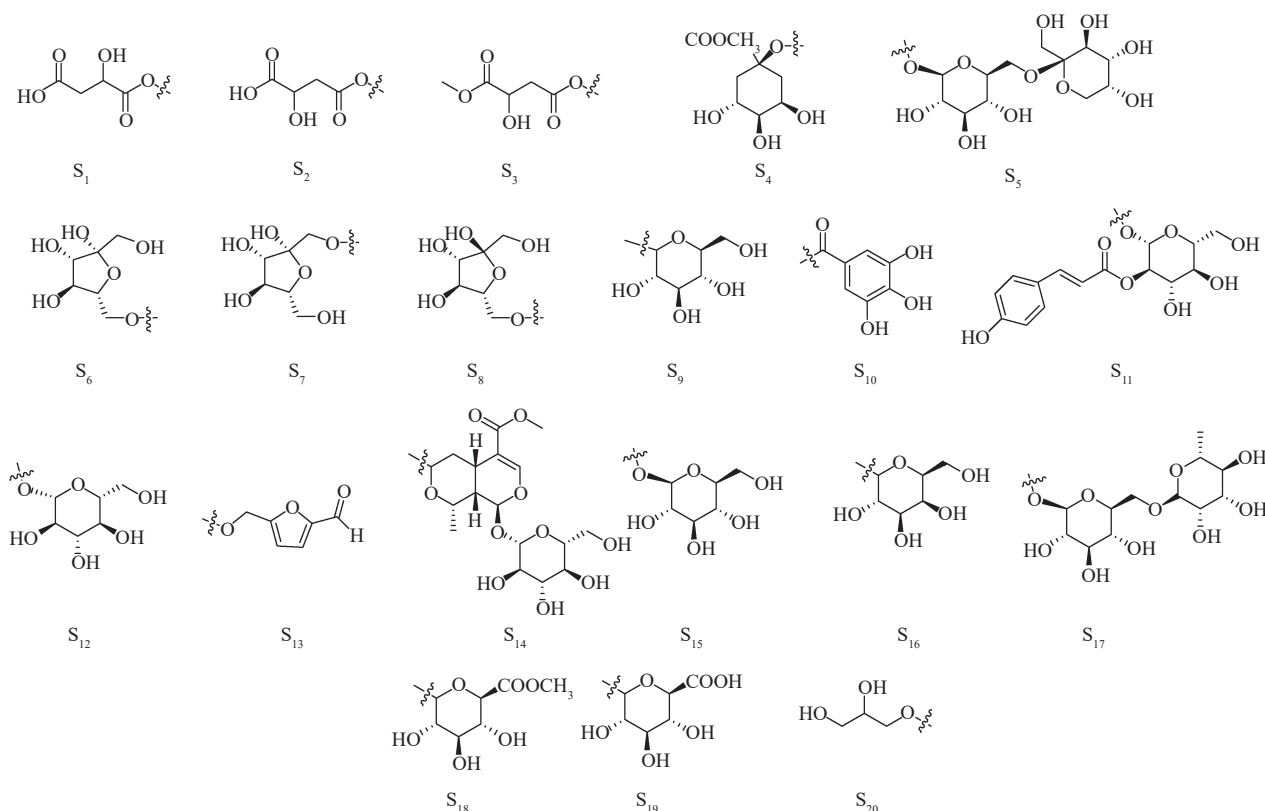


Fig. 15 Substituents of active compounds from *C. officinalis*.

3. Main bioactive mechanisms

In the process of our total, we found that the main biological activities of the active compounds in *C. officinalis* are anti-inflammatory and anti-diabetic. Therefore, we tried to summarize these 2 main activities and conclude the main mechanism of these activities in *C. officinalis*.

3.1 Anti-inflammatory activity

Anti-inflammatory activity is one of the main biological activities of the active chemical components in *C. officinalis*. The related mechanisms are mainly the regulation of MAPKs, NF- κ B, JAK, EGFR, VEGF and Nrf2 signaling pathways (Fig. 16).

Compound **1** can up-regulate the mRNA and protein levels of Sirt1 in the colon tissues of UC mice induced by DSS, inhibit the acetylation of NF- κ B-p65 and thus inhibit the mRNA and protein levels of IL-6, TNF- α and IL-1 β in the colon tissues of UC mice, and alleviate the M1-macrophage-mediated inflammatory response^[26]. Similarly, in addition to dose-dependent inhibition of the p65-NF- κ B signaling pathway, reducing the expression of cytokines tumor necrosis factor- α (TNF- α), IL-1 β , and IL-6 in LPS-stimulated RAW264.7 cells, compound **130** also limited inflammation by inhibiting the STAT3 signaling pathway. Compound **76** exhibits significant anti-inflammatory activity by decreasing protein levels of phosphorylated p65 (Ser536), phosphorylated STS3 (Tyr705), iNOS, COX-2, IL-6, IL-1 β , and TNF- α in the NF- κ B and STAT3 signaling pathways. Compound **12** does not directly act on the NF- κ B pathway for anti-inflammatory effects, but inhibits the expression of TLR4 and MyD88 in LPS-stimulated

RAW264.7 cells and prevents the binding of LPS to TLR4, thereby preventing inflammation through the NF- κ B signaling pathway^[48]. Compound **122** exerts anti-inflammatory effects in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced HIEC-6 cells by inhibiting the NF- κ B signaling pathway^[232]. Compound **129** inhibits both NF- κ B and Akt/mTOR signaling pathways to inhibit proliferation, invasion, migration, inflammation, and apoptosis of RA-FLS cells^[303].

There are also compounds in *C. officinalis* that play an anti-inflammatory role through MAPK signaling pathway, among which compound **65** can significantly inhibit the production of NO in RAW264.7 cells, the expression of cytokines IL-1 β , IL-6, COX-2 and iNOS, and the phosphorylation of MAPK signaling molecules. Including extracellular signal-regulated kinase (ERK) and c-Jun N-terminal protein kinase (JNK)^[87]. Some compounds can participate in both MAPK and NF- κ B signaling pathways to exert anti-inflammatory effects, for example, compound **66** exerts anti-inflammatory effects by inhibiting both NF- κ B and MAPK signaling pathways^[87,99,105]. Compound **39** inhibits the expression of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) by inhibiting the NF- κ B signaling pathway, and exerts anti-inflammatory activity on the negative regulation of phosphorylation of ERK1/2, p38 and JNK1/2 of c-Jun^[73]. Compound **72** has anti-inflammatory effects by activating the MAPK/AP-1 pathway and NF- κ B pathway^[141]. Compound **123** inhibits inflammation in yeast, Pam3CSK4, or LPS-stimulated RAW264.7 cells by inhibiting MAPK and NF- κ B signaling pathways^[257].

The remaining compounds exert anti-inflammatory effects through other signaling pathways or by inhibiting the release of related anti-inflammatory factors, among which compounds **10**, **13–15** and **45–56** can inhibit IL-6-induced activation of STAT3 in HepG2 cells, thus producing anti-inflammatory effects^[29]. Compound **17** has

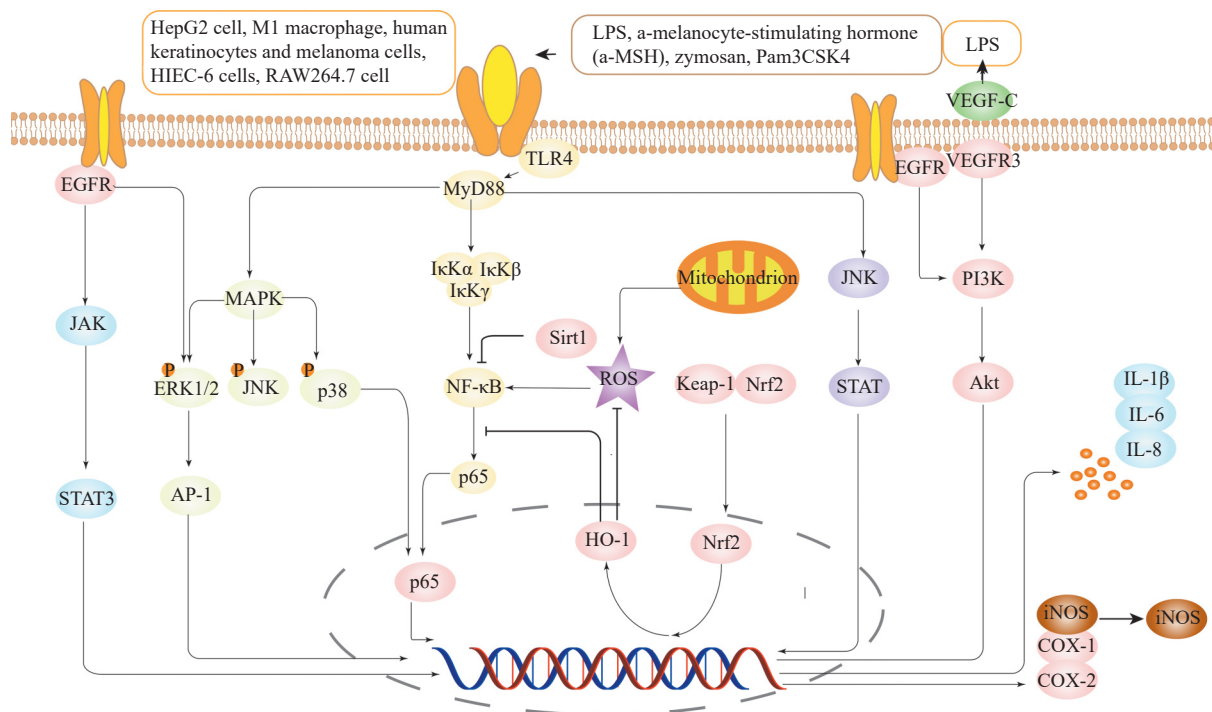


Fig. 16 Anti-inflammatory mechanism of active components in *C. officinalis*.

an inhibitory effect on FMLP-induced superoxide production in human neutrophils *in vitro*, thus reducing the inflammatory response^[56]. Compounds **42**, **58–60** exert anti-inflammatory effects by inhibiting the production of NO and pro-inflammatory cytokines (TNF- α and IL-6)^[13–14]. Compounds **40** and **41** inhibited LPS-induced NO production in RAW264.7 macrophages and COX-2/1 production in zebrafish models, and showed anti-inflammatory effects^[28]. Compounds **65**, **66**, **70** and **77** inhibited NO production in RAW264.7 cells^[84]. The specific binding of compound **69** to exogenous VEGF-C enhanced the secretion of exogenous VEGF-C on the pro-inflammatory cytokines IL-6 and TNF- α , as well as the expression of iNOS and COX-2^[122]. Compound **70** decreased the specific activity of adenosine deaminase (ADA) in joint tissue and down-regulated *ADA* gene expression in rat model of RA, and down-regulated the levels of cytokines IL-1 β , IL-6, TNF- α and other pro-inflammatory factors in RA rats to play anti-inflammatory activities^[127]. Compound **127** reduced IL-8 production in A549 cells stimulated by CSE, producing the same effect as dexamethasone^[283].

3.2 Anti-diabetic activity

The anti-diabetic effect is one of the important pharmacological activities in *C. officinalis*. The active compounds of *C. officinalis* exerted anti-diabetic mechanism mainly through regulating AMPK, PI3K/Akt/mTOR, miR-223/keap1-Nrf2 pathway and increased the expression of peroxisome proliferator-activated receptor γ (PPAR- γ) (Fig. 17).

The previous investigation found that *C. officinalis* has better hypoglycemic activity. For example, the oral administration of *C. officinalis* extract in diabetic rats induced by STZ can significantly reduce the serum blood glucose, triglyceride (TG) levels and urine volume of rats, and alleviate the organ damage of diabetic rats^[391].

It is concluded that PI3K/Akt signaling pathway is an important signaling pathway in the hypoglycemic function of *C. officinalis*. The compounds in *C. officinalis* enable PI3K/Akt signaling pathway to function in the body by either activating or preventing inactivation. Compound **1** can inhibit the subcellular distribution of FOXO1 in islet INS-1 cells through PI3K/Akt signaling pathway, thereby protecting insulin secretion function^[22]. Compound **123** alleviates insulin resistance and regulates glucose uptake in HepG2 cells by blocking the inactivation of the PI3K/Akt pathway and the HG-induced reduction of Glut4 levels^[265]. Compound **129** may play a hypoglycemic role by regulating IRS1/PI3K/Akt2 pathway to improve hepatic insulin resistance^[301].

It was found that *C. officinalis* extract can improve the symptoms of diabetic rats by improving oxidative stress and stimulating PPAR- γ expression^[392]. Further studies found that compound **32** can regulate the PPAR- γ signaling pathway, restore the activities of glucose-6-phosphatase (G6Pase) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and restore the normal transcription levels of genes such as phosphoenolpyruvate carboxykinase (PEPCK), glucokinase (GK), glucose transporter 2 (Glut2), PPAR- γ and Glut4 to produce the effects of lowering blood lipids and increasing insulin sensitivity^[68]. Compound **122** activates CCAAT-enhancer-binding proteins (C/EBPs), increases the expression of PPAR- γ , increases the translocation of Glut4 in 3T3-L1 adipocytes and activates the Akt signaling pathway to improve insulin sensitivity^[250].

The hypoglycemic effect of AMPK signaling pathway is related to Glut4. Compound **80** improves gestational diabetes mellitus (GDM) symptoms by activating AMPK signaling pathway to restore TNF- α -induced insulin resistance^[196]. In the same way as metformin, compound **136** exerts hypoglycemic effects by acting on AMPK pathway. In addition, compound **136** can stimulate *Glut4* mRNA expression and increase glucose uptake^[361]. The current findings suggest that compound **140** exerts a hypoglycemic effect by improving

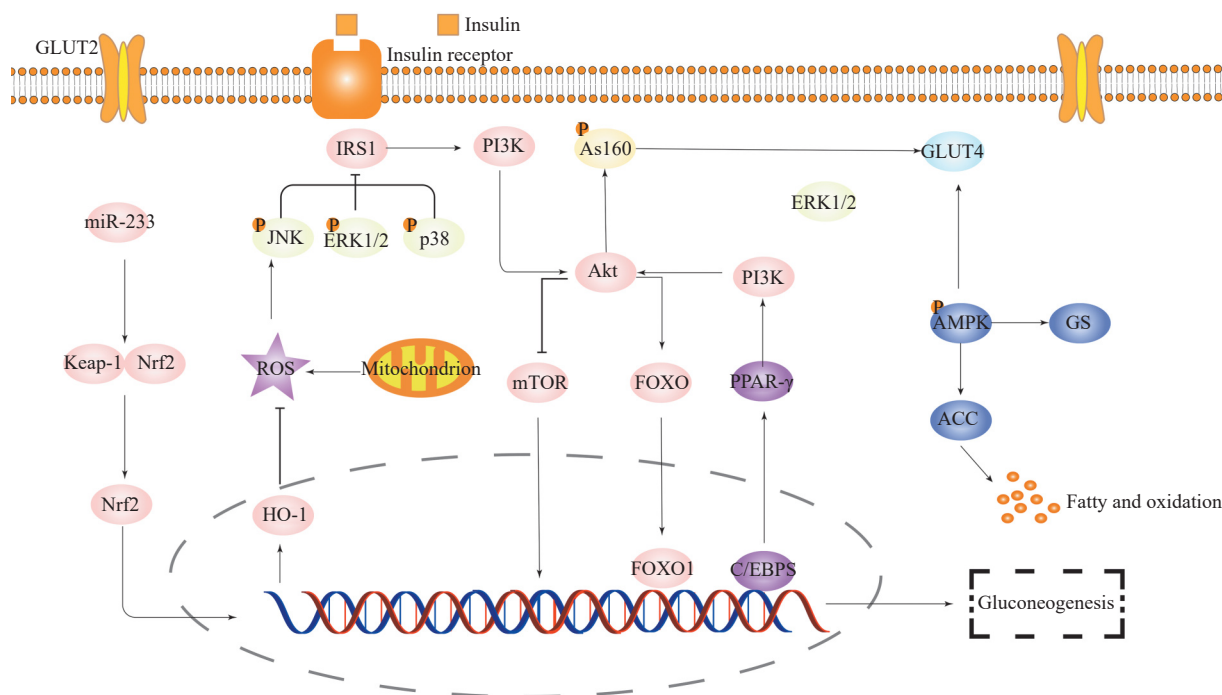


Fig. 17 Anti-diabetic mechanism of active components in *C. officinalis*.

blood glucose control by activating insulin receptors and Glut4 in adipose tissue of high-fat and sucrose-induced rats with T2D^[375-376].

These results showed that some compounds, such as compound **1** and **122**, had both anti-inflammatory and anti-diabetic activities. According to literature review, inflammation may be related to insulin resistance, and the theory of insulin resistance inflammation has attracted much attention^[393-394]. Therefore, it is speculated that there may be compounds that play a hypoglycemic role by inhibiting inflammation in *C. officinalis*, but there are few literatures on this aspect in *C. officinalis*, and further studies are needed.

4. Application value of *C. officinalis*

C. officinalis had important application value. According to its biological active ingredients, nutritional value and ornamental value, its application was mainly divided into four parts: medicinal value, edible value, ornamental value and industrial value.

C. officinalis had important medicinal value for various diseases due to its rich biological activity. According to different diseases, the optimal dosage of *C. officinalis* and the compatibility of traditional Chinese medicine were different, the literature summarized that the dosage of *C. officinalis* in the treatment of diseases was mostly 6.0–74.6 g^[3]. *C. officinalis* was a kind of edible resource, but there were growing concerns about food safety. Deng et al.^[395] pointed out that water extract of *C. officinalis* has no side effects on mice or rats at 100 mg/kg and could inhibit the neurotoxicity of H₂O₂-induced SH-SY5Y cells by reducing oxidative stress.

At present, *C. officinalis* had been made into jelly, jam, fruit wine and other foods according to its nutritional content of *C. officinalis*^[396-397]. And it was reported that *C. officinalis* extract could improve the production performance of ruminants and single-stomach animals^[398], prevent animal body diseases, so *C. officinalis* extract was a potential feed additive. Some studies had shown that *C. officinalis* and its

extract could also be used as a natural tobacco flavor in cigarettes to reduce dryness and irritation^[399]. In addition, *C. officinalis* was a kind of deciduous tree with straight trunk, tall tree shape, cold and drought tolerance, and its leaves, flowers, fruits and shapes had certain ornamental value and could be used as a road tree^[400].

5. Concluding remarks and prospects

C. officinalis is widely distributed in China, which not only has high medicinal value, but also is a potential edible resource. It has been used since it was discovered by the Chinese people 2 000 years ago. In recent years, the chemical composition and pharmacological activity of *C. officinalis* have attracted much attention.

Iridoids, flavonoids, lignins, tannins, organic acids, phenolic acids, triterpenes and other bioactive ingredients in *C. officinalis* have been proved to have pharmacological activities such as anti-inflammatory, anti-diabetes, anti-oxidant, anti-tumor, neuroprotective, anti-bacterial, anti-AD, liver protection and so on. Iridoids and flavonoids are the main bioactive components in *C. officinalis*, which have significant anti-inflammatory, anti-diabetic and anti-oxidant activities, and can be used in the treatment of related diseases. New iridoids have been isolated and identified from *C. officinalis*, but the active mechanism of these compounds remains to be further studied and there are still potential medicinal values waiting to be explored. Similarly, at present, the application of food made of *C. officinalis* is not in-depth, still in a state to be explored, and its real nutritional efficacy, health care value is far from being fully understood. In addition to the processing difficulty of *C. officinalis*, coupled with the mainstream application of *C. officinalis* in China is still in medicine, making the food application of *C. officinalis* is lacking.

Therefore, it is hoped that researchers can take advantage of new scientific technologies to quickly explore the active ingredients and mechanisms of action of *C. officinalis* using techniques such as

GNPS (a molecular network technology), and the bioactive molecules of *C. officinalis* can be further studied in animal and clinical trials to develop drugs to treat related diseases. At the same time, the promotion of food made of *C. officinalis*, and the research and development of deep processing technology and the practice can also make *C. officinalis* better into our lives.

Conflict of interest

Wenyi Kang and Yan Zhang are associate editors, and Changyang Ma is an editorial board member for *Food Science and Human Wellness* and were not involved in the editorial review or the decision to publish this article. All the authors declare no conflict of interest.

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