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Review Article

The phytochemistry, pharmacology, and clinical, medicinal, and edible application of the genus *Trollius*: an updated systematic review

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Abstract: The genus *Trollius* includes perennial herbaceous plants from the Ranunculaceae family, which holds a prominent place in the realms of food and medicine. This article presents a thorough review of the chemical components isolated and identified from the genus *Trollius* plants, such as flavonoids, organic acids, volatile oils, and alkaloids, among others. The pharmacological effects of the genus *Trollius* are also addressed, including its anti-inflammatory, anti-viral, anti-oxidant, and anti-tumor properties. Furthermore, this article collates the medicinal and food application status and prospects of the genus *Trollius* plants. Clinically, the genus *Trollius* can be used in Chinese patent medications for ailments such as upper respiratory tract infections, pharyngitis, and tonsillitis. Regarding food, the flowers of the genus *Trollius* can be fashioned into tea which yields benefits like heat-clearing, detoxifying, yin-nourishing, and internal heat-reducing. Flower extracts can also be natural food additives. Additionally, the genus *Trollius* plants show potential and promise in the cigarette flavoring and cosmetics industries.

Keywords: *Trollius*; chemical composition; pharmacological effects; medicine and food homology

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1 Introduction

The genus *Trollius* belongs to the Ranunculaceae family (Fig. 1). Around the world, 30 species of *Trollius* have been identified, primarily found in the temperate regions of the Northern Hemisphere[1]. In China, there are a total of 23 *Trollius* plants, which are widely used in Northern China, Inner Mongolia and many other regions. Among them, the *Trollius* plants that can be used medicinally include *Trollius chinensis* Bunge, *Trollius ledebouri* Rchb, *Trollius macropetalus* Fr, *Trollius buddae* Schipcz, *Trollius japonicus* Miq, *Trollius farreri* Stapf, *Trollius ranunculoides* Hemsl and *Trollius asiaticus* C.A.Mey[2].

The plants of the genus *Trollius* not only possess ornamental value but also exhibit unique appeal in the medicine and food sectors owing to their rich chemical composition and notable pharmacological effects. Modern research indicates that the genus *Trollius* is abundant in numerous components such as flavonoids, organic acids, alkaloids, coumarins, and others. These plants possess pharmacological properties, including anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, and anti-tumor effects[3]. *T. chinensis* Bunge, also known as Jinlianhua, can be amalgamated with various traditional Chinese medicines to create Chinese patent medicine preparations, such as Jinlianhua Tablets, Jinlianhua Capsules, Jinlianhua Sprays, and Jinlianhua Suppositories. These can be used to treat diseases such as upper respiratory tract infections, pharyngitis, tonsillitis, and periodontitis, which are caused by the invasion of wind-heat toxins in the lung or excessive heat toxins in the body[4].

In the culinary world, *T. chinensis* Bunge is often transformed into flower tea. This tea, brewed from the plant, boasts a golden color and an enticing aroma and offers benefits such as heat regulation, detoxification, Yin nourishment, and internal heat reduction. The yellow pigment is a component with high content in plants of the genus *Trollius* and is composed of two parts, xanthophyll epoxide and trollixanthin[10]. This pigment possesses potent antioxidant, stabilizing, antibacterial, and anticancer properties. Existing research indicates that within a specific concentration range, the yellow pigment of *T. buddae* Schipcz shows strong stability. Its maximum scavenging rates for DPPH· and ·OH are 71.7% and 35.7% respectively[40]. Given its high safety

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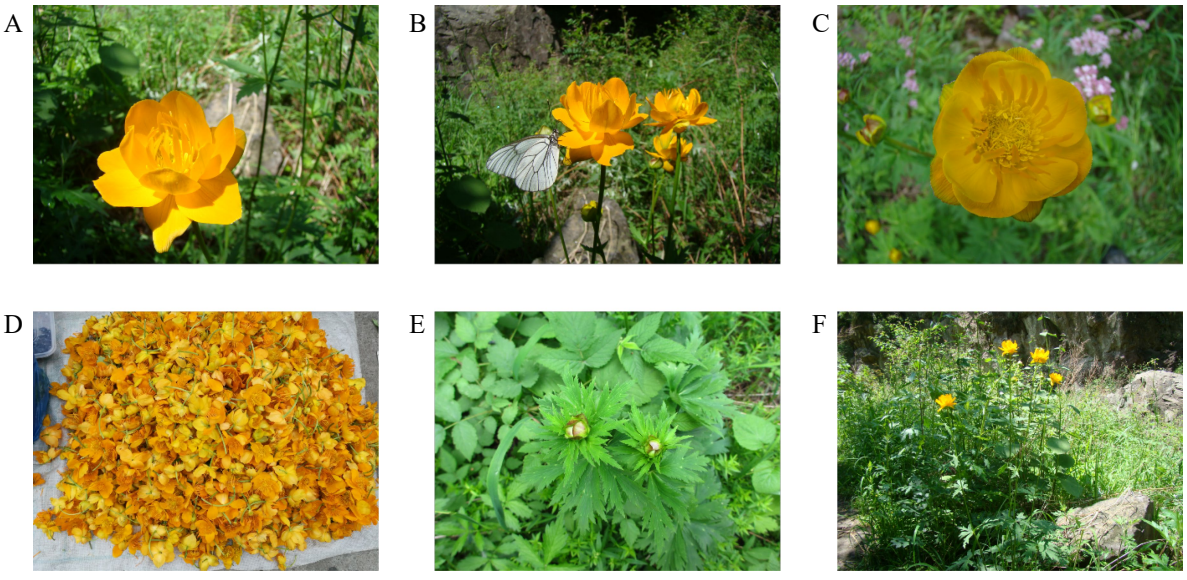


Figure 1 Plant of the genus *Trollius*. (A, B, C, F) Flowers of the genus *Trollius*. (D) The medicinal part after processing. (E) Leaves of the genus *Trollius*.

as a natural pigment, it is frequently utilized as an anticancer health product, colorant, natural food additive, and dye in the food and medicine sectors. Moreover, the genus *Trollius* contains a minute amount of volatile oil components that exhibit antioxidant and anti-bacterial properties. Existing studies have determined that the volatile oil in the plants of the genus *Trollius* has some sun-screening ability and can enhance the aroma and quality of cigarettes[5]. Consequently, the plants of the genus *Trollius* are also employed in cigarette flavoring and cosmetics industry.

As a resource with both medicinal and edible functions, the plants of the genus *Trollius* have broad development prospects and high economic value in the fields of medicine and food. This article elaborates on the chemical composition, pharmacological effects, clinical applications, and application and development prospects in the field of food of the genus *Trollius*. The goal is to highlight the dual-purpose characteristics and important value of the genus *Trollius* as both a medicinal and food resource.

2 Phytochemistry

In recent years, remarkable achievements have been made in the research on plants of the genus *Trollius*. A wide variety of chemical components have been discovered from them. These chemical components mainly cover multiple categories such as flavonoids, organic acids, volatile oils, alkaloids, coumarins, sterols, phenethyl alcohols, ceramides, and monosaccharides. As for flavonoids, the number is quite considerable, up to 102. The main type is flavone C-glycosides, and it also contains a small amount of flavonols, flavonoid glycosides, and dihydroflavones. In terms of organic acids, 61 chemical components have been isolated and identified. Among them, there are 21 phenolic acid compounds and 40 fatty acid compounds.The types of volatile oil components are extremely rich, and the number exceeds 70. It is worth mentioning that among these 70 volatile oil components, there are also 30 fatty acid components. In addition, five alkaloids have been identified in the plants of the genus *Trollius*. Their existence provides a new direction for further in-depth research on the pharmacological effects of plants of the genus *Trollius*.

2.1 Flavonoids

Flavonoids are the main active components in the genus *Trollius* and possess biological activities such as antioxidant, anti-inflammatory, and anti-tumor effects[6]. The flavonoids in the genus *Trollius* are mainly composed of flavone C-glycosides, including vitexin (1), orientin (2), isoswertisin (3), isoswertiajaponin (4), 2"-*O*-*β*-*L*-galactopyranosyl vitexin (16), 2"-*O*-*β*-*D*-glucopyranosyl orientin (23), trollisin I (24), etc. At the same time, they are supplemented with a small amount of flavonols, such as quercetin (56), kaempferol (61), myricetin (62), quercetin-3-*O*-*β*-*L*-rhamnoside (67), quercetin-3-*O*-*β*-*D*-glucopyranoside (68), 3"-*O*-acetylquercetin (90), 2"-*O*-vanilloyl quercetin (43), etc.; they also contain flavonoid glycoside components, such as quercetin 2"-*O*-(*β*-*D*-xyranosyl)-*β*-*D*-glucoside (13), neodiosmin (63), daidzin (81), astragalin (75), glucosylorientin (96), etc., as well as isoflavone components, such as glycitein (84), daidzein (85). In addition, some compounds belong to derivatives of flavonoids, which are formed by connecting different groups on the mother nucleus structure, such as 2"-*O*-(2'"-*O*-methybutyryl)-glucopyranosylisoswertisin (94), 2"-*O*-(6'"-*O*-veratroyl)-galactopyranosyl vitexin (95), 2"-*O*-(2'"-methylbutanoyl) quercetin (34), 2"-*O*-(2"-methylbutanoyl) kaempferol (35), 3"-*O*-veratroyl orientin (41), 3"-*O*-veratroyl vitexin (42), etc.

Modern research shows that the flavone C-glycoside compounds isolated from the plants of the genus *Trollius* have a similar structural framework. Among all the isolated flavone C-glycoside compounds, most sugar molecules are attached to the C-8 position of the flavonoid framework, while the C-5 and C-7 positions of the flavones are usually in an oxidized state[7]. In addition, the structural differences of flavonoid glycosides mainly depend on the presence or absence of hydroxyl or methoxy groups at positions C-7, C-3, C-4, and C-6[8].

Among the flavonoid components in *Trollius* plants, Vitexin and Orientin are the two most important flavonoid components. They are well-known for their antiviral, antibacterial, and antioxidant capabilities. In addition, existing research has shown that vitexin and orientin also have strong inhibitory effects on influenza virus and *Staphylococcus aureus*[9]. For detailed data, refer to Table 1, and Fig. 2.

2.2 Organic acids

Organic acids constitute the second most abundant category of components in the plants of the genus *Trollius*, surpassed only by

flavonoids. They primarily include phenolic acids (103-124) and fatty acids (125-163). Phenolic acid compounds typically include multiple hydroxyl groups on the same benzene ring and are widely present in nature. They principally consist of gallic acid

Table 1 Flavonoid chemical components of the genus *Trollius*.

No.	Compound name	Molecular formula	Source	Reference
1	Vitexin	$C_{21}H_{20}O_{10}$	A, B, C, D, E, F, G	[11, 15, 17, 22]
2	Orientin	$C_{21}H_{20}O_{11}$	A, B, C, D, E, F, G	[12, 14, 16, 17, 21]
3	Isoswertisin	$C_{22}H_{22}O_{10}$	A, H	[19, 22]
4	Isoswertiajaponin	$C_{22}H_{22}O_{11}$	A, B, E, G	[14, 20, 22]
5	Cyanidin 2"-*O*-(*β*-*D*-xyranosyl)-*β*-*D*-glucoside	$C_{26}H_{28}O_{16}$	A, B, C, F	[7, 14, 22]
6	Cyanidin 2"-*O*-(*β*-*D*-pyranosyl)-*β*-*D*-glucoside	$C_{26}H_{27}O_{15}N$	E, G	[7, 21, 22]
7	Cyanidin 2-prime-*O*-*β*-pyranosyl-arabinoside	$C_{26}H_{28}O_{16}$	A	[7]
8	Cyanidin 2"-*O*-*β*-*L*-rhamnoside	$C_{27}H_{30}O_{16}$	A	[7, 14, 20, 22]
9	Cyanidin 3-*O*-*β*-*D*-glucoside-6"-*O*-*α*-*L*-rhamnoside	$C_{26}H_{27}O_{15}N$	A, B, D	[14, 17, 22]
10	6"-*O*-Acetylcyanidin	$C_{32}H_{27}O_{11}N_3$	A, B, D	[11, 14, 17]
11	3"-*O*-Acetylcyanidin	$C_{32}H_{27}O_{11}N$	A, B, C, F, G	[14, 21, 22]
12	2"-*O*-Acetylcyanidin	$C_{32}H_{27}O_{11}N_3$	A, B, F	[14, 22]
13	Quercetin 2"-*O*-(*β*-*D*-xyranosyl)-*β*-*D*-glucoside	$C_{26}H_{28}O_{15}$	E, G	[14, 22]
14	Quercetin 2"-*O*-(*β*-*D*-arabinopyranoside)	$C_{26}H_{28}O_{15}$	A	[14]
15	2"-O-*β*-*L*-Galactopyranosyl vitexin	$C_{27}H_{30}O_{16}$	A, B, F, G	[7, 14]
16	Kaempferol 2"-*O*-*β*-*D*-glucopyranoside	$C_{27}H_{30}O_{15}$	A	[7]
17	Kaempferol-6"-*O*-glucopyranoside	$C_{26}H_{27}O_{14}N$	A B	[14, 17, 22]
18	6"-*O*-Acetylkaempferol	$C_{32}H_{27}O_{10}N_3$	A, B, D	[22]
19	3"-*O*-Acetylkaempferol	$C_{32}H_{27}O_{10}N_3$	A, B	[22]
20	2"-*O*-Acetylkaempferol	$C_{32}H_{27}O_{10}N_3$	A, B	[22]
21	Genistein-7-*O*-*β*-*D*-pyranosylglucoside	$C_{22}H_{22}O_{10}$	A	[23]
22	2"-*O*-*β*-*L*-Galactopyranosyl orientin	$C_{27}H_{31}O_{17}$	A	[7]
23	2"-*O*-*β*-*D*-Glucopyranosyl orientin	$C_{27}H_{31}O_{17}$	A	[7]
24	Trollisin I	$C_{27}H_{30}O_{12}$	A	[7]
25	3"-*O*-(2"'-Methyibutanoyl) resveratrol	$C_{26}H_{28}O_{12}$	A	[21]
26	3"-*O*-(2"'-Methyibutanoyl) quercetin	$C_{27}H_{30}O_{11}$	A B	[13, 12, 22, 24, 32]
27	3"-*O*-(2"'-Methyibutanoyl) luteolin	$C_{26}H_{28}O_{11}$	A	[7, 24]
28	3"-*O*-(2"'-Methyibutanoyl) chrysoeriol	$C_{27}H_{30}O_{12}$	A, B	[7, 24]
29	2"-*O*-Feruloylharpagoside	$C_{24}H_{31}O_{18}$	A, C, F, G	[14, 29]
30	2"-*O*-Feruloylverbascoside	$C_{31}H_{27}O_{14}$	A, B, E, F, G	[14, 29]
31	2"-*O*-Feruloylisovitexin	$C_{31}H_{27}O_{11}$	A	[21, 22]
32	2"-*O*-(3"'-Methoxycaffeoyl) luteolin	$C_{30}H_{26}O_{13}$	A	[17, 22]
33	2"-*O*-Feruloylgenistin	$C_{32}H_{30}O_{13}$	A	[21, 25]
34	2"-*O*-(2"'-Methylbutanoyl) quercetin	$C_{26}H_{28}O_{11}$	A	[14, 32]
35	2"-*O*-(2"-Methylbutanoyl) kaempferol	$C_{26}H_{28}O_{12}$	A B D E F G	[14, 32]
36	4'-Methoxy-2"-*O*-(2"'-methylbutanoyl) luteolin	$C_{32}H_{30}O_{13}$	A, B, D	[32, 33]
37	4'-Methoxy-2"-*O*-(2"'-methylbutanoyl) apigenin	$C_{32}H_{30}O_{14}$	A, B, D	[32, 34]
38	2"-*O*-(2"'-Methylbutanoyl) isogenistin	$C_{20}H_{33}O_{17}$	A, B, E, F, G	[32, 35]
39	2"-*O*-(2"'-Methylbutanoyl) isokanamycin A	$C_{27}H_{29}O_{11}$	A, B, E, F, G	[32, 34]
40	2"-*O*-Isopropylbenzoyl-isokanamycin A	$C_{32}H_{31}O_{14}$	A	[35]
41	3"-*O*-Veratroyl orientin	$C_{29}H_{26}O_{14}$	A	[32, 33]
42	3"-*O*-Veratroyl vitexin	$C_{31}H_{28}O_{13}$	A	[32, 33]
43	2"-*O*-Vanilloyl quercetin	$C_{29}H_{26}O_{14}$	A	[32, 33]
44	2"-*O*-(3"',4"'-Dimethoxybenzoyl) isorhamnetin	$C_{31}H_{30}O_{14}$	A, E, F, G	[14, 32]
45	2"-*O*-(3"',4"'-Dimethoxybenzoyl) isoswertisin	$C_{31}H_{30}O_{13}$	A, B, E, F, G	[14, 32]
46	2"-*O*-(3"',4"'-Dimethoxybenzoyl) isodaidzein	$C_{30}H_{28}O_{13}$	A, B, D, E, F, G	[17, 32]
47	2"-*O*-(3"',4"'-Dimethoxybenzoyl) quercetin	$C_{30}H_{28}O_{14}$	A, B, D, E, F, G	[17, 32]
48	2"-*O*-Vanilloylisorhamnetin	$C_{30}H_{28}O_{13}$	A	[32, 27]
49	2"-*O*-Vanilloylquercetin	$C_{29}H_{26}O_{13}$	A	[14, 32]
50	Salvigenin	$C_{18}H_{16}O_6$	A, B	[7, 27]
51	Acacetin	$C_{16}H_{12}O_5$	A, B	[7]

(Continued)

No.	Compound name	Molecular formula	Source	Reference
52	Apigenin	$C_{15}H_{10}O_5$	A, B	[7, 27]
53	Pectolinarigenin	$C_{17}H_{14}O_6$	A, B	[7, 19]
54	Cirsimaritin	$C_{17}H_{14}O_6$	A, B	[7, 14, 27, 29]
55	Luteolin	$C_{15}H_{10}O_6$	A, B, G	[7, 27]
56	Quercetin	$C_{15}H_{10}O_7$	A, B	[7, 27]
57	Naringenin	$C_{15}H_{12}O_5$	A	[7]
58	Chrysoeriol	$C_{16}H_{12}O_6$	A, B	[30]
59	Diosmetin	$C_{16}H_{12}O_6$	A, B	[30]
60	Farnisin	$C_{16}H_{12}O_5$	A, B	[30]
61	Kaempferol	$C_{15}H_{10}O_6$	A, B	[30]
62	Myricetin	$C_{15}H_{10}O_8$	A, B	[30]
63	Neodiosmin	$C_{28}H_{32}O_{15}$	A, B, F	[14]
64	8-*C*-*β*-*D*-Pyranosyl catechin	$C_{21}H_{20}O_{10}$	A	[7]
65	7-*O*-Viciafuranosylquercetin	$C_{28}H_{32}O_{14}$	A	[17]
66	7-*O*-Naringeninrutinoside	$C_{28}H_{32}O_{14}$	A	[14]
67	Quercetin-3-*O*-*β*-*L*-rhamnoside	$C_{21}H_{20}O_{11}$	A	[7]
68	Quercetin-3-*O*-*β*-*D*-glucopyranoside	$C_{21}H_{20}O_{11}$	A	[7]
69	5-Hydroxy-4',7,8-trimethoxyflavone	$C_{18}H_{16}O_6$	A	[42]
70	4',5-Dihydroxy-7,8-dimethoxyflavone	$C_{17}H_{14}O_6$	A	[42]
71	6'''-(3-Hydroxy-3-methylbutanoyl)-2''-*O*-*β*-*D*-pyranosyl-hongcaoside	$C_{33}H_{38}O_{20}$	A	[31]
72	6'''-(3-Hydroxy-3-methylbutanoyl)-2''-*O*-*β*-*D*-pyranosylmatrine	$C_{33}H_{38}O_{19}$	A	[31]
73	Hyperoside	$C_{21}H_{20}O_{12}$	A	[17]
74	Naringenin3-(6''-ethylglucuronide)	$C_{23}H_{24}O_{10}$	A	[22]
75	Astragalin	$C_{21}H_{20}O_{11}$	A	[22]
76	2''-*O*-(6'''-*O*-Caffeoyl)-galactopyranosyl vitexin	$C_{36}H_{36}O_{18}$	A	[22]
77	2''-*O*-(6'''-*O*-Feruloyl) galactopyranosyl orientin	$C_{37}H_{38}O_{19}$	A	[22]
78	Trollichinenside A	$C_{36}H_{35}O_{18}$	A	[23]
79	Trollichinenside B	$C_{38}H_{40}O_{20}$	A	[23]
80	Trollichinenside C	$C_{38}H_{40}O_{19}$	A	[23]
81	Daidzin	$C_{21}H_{20}O_9$	A, B	[30]
82	Kaempferol-7-*O*-*β*-*D*-glucoside	$C_{22}H_{22}O_{10}$	A	[28]
83	4,5-Dihydroxy-3,7-dimethoxy isoflavone	$C_{17}H_{14}O_6$	A, B	[30]
84	Glycitein	$C_{16}H_{12}O_5$	A, B	[30]
85	Daidzein	$C_{15}H_{10}O_4$	A, B	[30]
86	Fortunellin	$C_{28}H_{32}O_{14}$	A	[23]
87	Isorhamnetin	$C_{21}H_{20}O_{10}$	A, G	[19]
88	Isoorientin	$C_{21}H_{20}O_{11}$	A, G	[19]
89	2''-*O*-Benzoylisorhamnetin	$C_{29}H_{26}O_{12}$	A	[33]
90	3''-*O*-Acetylquercetin	$C_{31}H_{28}O_{13}$	A	[33]
91	2''-*O*-Veratroylvitexin	$C_{30}H_{28}O_{13}$	A	[22]
92	Isodaphnetin-2''-*O*-(6-*O*-feruloyl)-*β*-*L*-lactoside	$C_{37}H_{38}O_{18}$	A	[11]
93	Eriodictyol	$C_{15}H_{12}O_6$	A	[22]
94	2''-*O*-(2'''-*O*-Methybutyryl)-glucopyranosylisoswertisin	$C_{33}H_{40}O_{16}$	A	[32]
95	2''-*O*-(6'''-*O*-Veratroyl)-galactopyranosyl vitexin	$C_{36}H_{38}O_{18}$	A	[32]
96	Glucosylorientin	$C_{27}H_{30}O_{17}$	A	[22]
97	6''-Malonylcosmosiin	$C_{24}H_{22}O_{13}$	A	[22]
98	(−)-Gallocatechi	$C_{15}H_{14}O_7$	A	[30]
99	Quercetin-2''-*O*-*β*-*L*-arabinopyranoside	$C_{27}H_{30}O_{16}$	A	[30]
100	Apigenin-8-*C*-(2''-*O*-feruloyl)-*β*-*D*-glucoside	$C_{31}H_{28}O_{13}$	A	[28]
101	(2*E*)-2-Methyl-1-*O*-vanilloyl-4-*β*-*D*-glucopyrano-side-2-butene	$C_{19}H_{26}O_{10}$	A, B	[25]
102	Neocarlinoside	$C_{26}H_{28}O_{15}$	A, B	[30]

Note: A. *T. chinensis* Bunge; B. *T. ledebouri* Rchb; C. *T. macropetalus* Fr; D. *T. buddae* Schipcz; E. *T. japonicus* Miq; F. *T. farreri* Stapf; G. *T. altaicus* C.A.Mey.; H. *Trollius europaeus*; I. *T. laxus*. The same below.

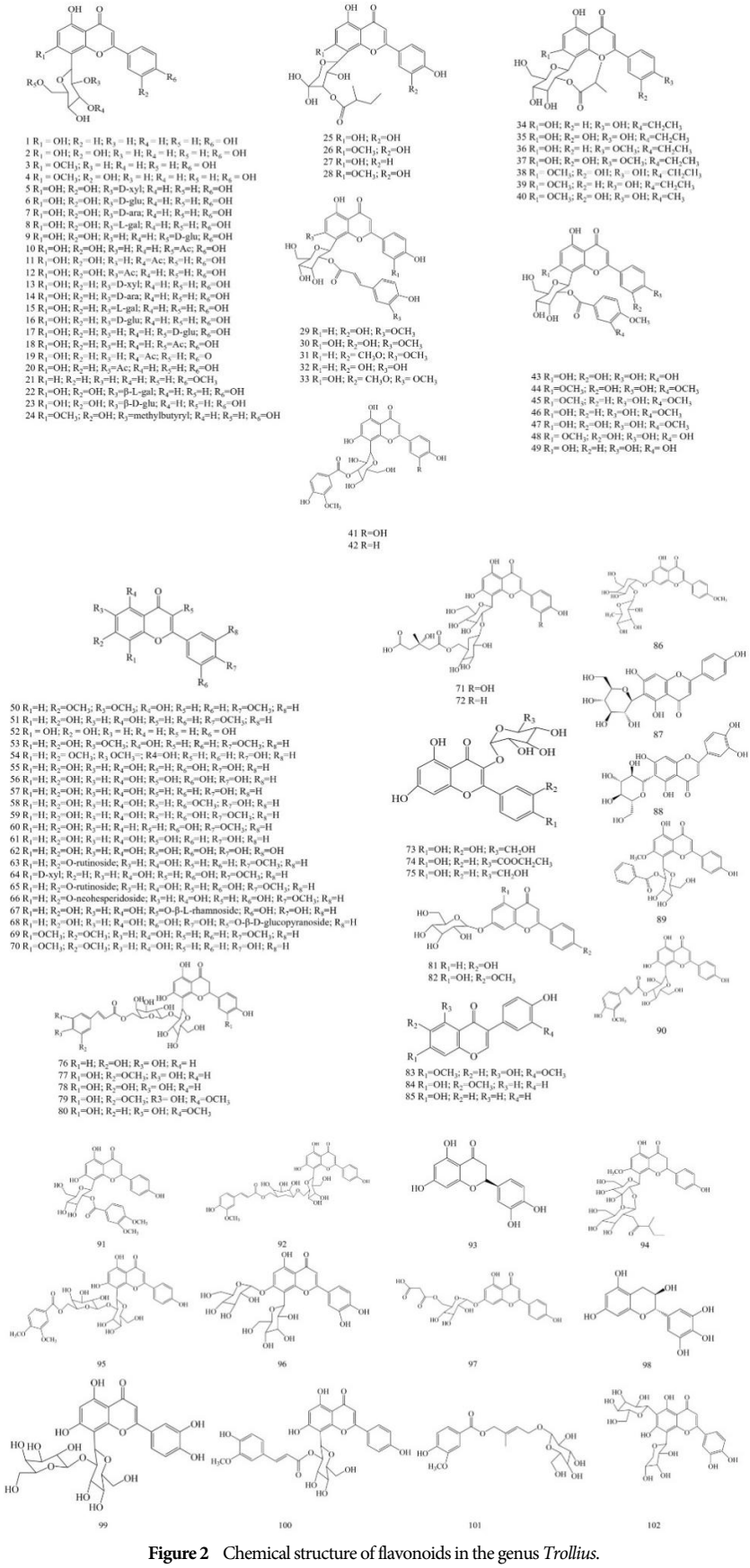


Figure 2 Chemical structure of flavonoids in the genus *Trollius*.

compounds, quinic acid derivatives, benzoic acid derivatives, and phloroglucinol compounds, among others[13]. In the plants of the genus *Trollius*, the phenolic acid compounds mainly occur as benzoic acid derivatives such as veratric acid (121), vanillic acid

(122), 3,4-dihydroxybenzoic acid methylester (116), benzoic acid (120), globeflowery acid (GA) (112), protocatechuic acid (118), 4-hydroxy-2,6-dimethoxybenzaldehyde (124), 4-hydroxybenzoic acid (115) and methyl veratrate (119).

Fatty acids are divided into saturated and unsaturated fatty acids; these are organic compounds composed of elements like hydrogen, oxygen, and carbon[38]. Among the fatty acid components in *Trollius*, the majority are saturated fatty acid components. Among them, there are two types of short-chain saturated fatty acids: Methyl octanoate and Methyl decanoate. There are 15 medium-and long-chain saturated fatty acids (125-136, 159-163), such as methyl dodecanoate (125), methyl tridecanoate (126), methyl tetradecanoate (127), etc. Five unsaturated fatty acid components have been isolated and identified in *Trollius*. Among them, monounsaturated fatty acids include (*Z*)-9-hexadecenoic acid methylester (149) and (*Z*)-9-octadecenoic acid methylester (150), and polyunsaturated fatty acids are (*Z*,*Z*)-9,12-octadecadienoic acidmethylester (151), (*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid methylester (152) and (*E*)-11-eicosenoic acid methylester (146). In addition, organic acids with special structures have also been isolated and identified in *T. chinensis* Bunge. For example, rhynchophylline (105) is an alkaloid-type organic acid containing a basic group formed by a nitrogen atom. Ascorbic acid (106) contains an enediol structure. Monotropein (104) and tecomin (109) contain glycosides. Ursolic acid (111) has a pentacyclic triterpene structure. 2-Hydroxy benzaldehydeoxime (140) contains an oxime group, and 4-hydroxy-acetophenone (141) contains both a hydroxyl group and a carbonyl group. Some studies have isolated and identified 30 fatty acid components from *T. chinensis* Bunge using the GC/MS method. Among these, 21 are saturated fatty acid components, with a total content of 57.95%. Nine are unsaturated fatty acids, constituting 30.35% of the detected substances. Hexadecanoic acid and tetradecanoic acid are the saturated fatty acid components with the highest abundances, contributing 19.85% and 13.93% respectively to the total content[36]. For detailed data, refer to Table 2 and Fig. 3.

2.3 Volatile components

The volatile oil is a crucial type of active component in the plants of the genus *Trollius*, boasting a variety of biological

Table 2 Organic acid chemical components of the genus *Trollius*.

No.	Compound name	Molecular formula	Source	Reference
103	Trochinenol A	$C_{22}H_{20}O_{11}$	A	[26, 37]
104	Monotropein	$C_{16}H_{22}O_{11}$	A, B	[26, 30]
105	Rhynchophylline	$C_{14}H_6O_8$	A, B	[26, 30]
106	Ascorbic acid	$C_6H_8O_6$	A, B	[26, 30]
107	Salviaflaside	$C_{24}H_{26}O_{13}$	A, B	[26, 30]
108	(2*R*,3*S*)-Piscidic acid	$C_{11}H_{12}O_7$	A, B	[26, 30]
109	Tecomin	$C_{15}H_{20}O_9$	A	[26, 33]
110	Isochlorogenic acid A	$C_{25}H_{24}O_{12}$	A, B	[26, 30]
111	Ursolic acid	$C_{30}H_{48}O_3$	A	[26, 34]
112	Globeflowery acid	$C_{13}H_{16}O_4$	A	[26, 35]
113	3-(6-Hydroxy-7-methoxy-2*H*-1,3-benzodioxol-5-yl) propanoic acid	$C_{11}H_{12}O_6$	A, B	[26, 30]
114	Phlorizin dihydrate	$C_{21}H_{26}O_{11}$	A, B	[26, 30]
115	4-Hydroxybenzoic acid	$C_7H_6O_3$	A	[7, 26]
116	3,4-Dihydroxybenzoicacid methylester	$C_8H_8O_2$	A	[7, 26]
117	Methylparaben	$C_6H_4O_3$	A	[7, 26]
118	Protocatechuic acid	$C_7H_6O_4$	A	[7, 26]
119	Methyl veratrate	$C_{10}H_{12}O_4$	A	[7, 26]
120	Benzoic acid	$C_7H_6O_2$	A	[7, 26]
121	Veratric acid	$C_9H_{10}O_4$	A	[7, 26]
122	Vanillic acid	$C_8H_8O_4$	A	[26, 29]
123	Gallic acid	$C_7H_6O_5$	A, B	[26, 30]
124	4-Hydroxy-2,6 dimethoxybenzaldehyde	$C_9H_{10}O_4$	A, B	[26, 30]
125	Methyl dodecanoate	$C_{13}H_{26}O_2$	A	[26, 36]
126	Methyl tridecanoate	$C_{14}H_{28}O_2$	A	[26, 36]
127	Methyl tetradecanoate	$C_{15}H_{30}O_2$	A	[26, 36]
128	Methyl pentadecanoate	$C_{16}H_{32}O_2$	A	[26, 36]
129	Methyl hexadecanoate	$C_{17}H_{34}O_2$	A	[26, 36]
130	Methyl heptadecanoate	$C_{18}H_{36}O_2$	A	[26, 36]
131	Methyl octadecanoate	$C_{19}H_{38}O_2$	A	[26, 36]
132	Methyl eicosanoate	$C_{21}H_{42}O_2$	A	[26, 36]
133	Methyl docosanoate	$C_{23}H_{46}O_2$	A	[26, 36]
134	Methyl tetracosanoate	$C_{25}H_{50}O_2$	A	[26, 36]
135	Methyl decanoate	$C_{11}H_{22}O_2$	A	[26, 36]

(Continued)

No.	Compound name	Molecular formula	Source	Reference
136	Methyl octanoate	$C_9H_{18}O_2$	A	[26, 36]
137	Dimethyl butanedioate	$C_6H_{10}O_4$	A	[26, 36]
138	Dimethyl octanedioate	$C_{10}H_{18}O_4$	A	[26, 36]
139	Dimethyl nonanedioate	$C_{11}H_{26}O_4$	A	[26, 36]
140	2-Hydroxy benzaldehydeoxime	$C_7H_7NO_2$	A	[26, 36]
141	4-Hydroxy-acetophenone	$C_8H_8O_2$	A	[26, 36]
142	2-Methoxydocosylmethanoate	$C_{25}H_{50}O_3$	A	[26, 36]
143	2,3-Dihydrobenzofuran	C_8H_{8O}	A	[26, 36]
144	4-Phenyl-2-butenoic acid methylester	$C_{11}H_{12}O$	A	[26, 36]
145	9-(Propoxybenzene)-nonanoic acid methylester	$C_{19}H_{30}O_2$	A	[26, 36]
146	(*E*)-11-Eicosenoic acid methylester	$C_{21}H_{40}O_2$	A	[26, 36]
147	(*Z*,*Z*,*Z*)-9,12,15-Ctadecatrien-1-ol	$C_{18}H_{32}O$	A	[26, 36]
148	Methylbenzeneacetate	$_{C9}H_{10}O_2$	A	[26, 36]
149	(*Z*)-9-Hexadecenoic acid methylester	$C_{17}H_{32}O_2$	A	[26, 36]
150	(*Z*)-9-Octadecenoic acid methylester	$C_{19}H_{36}O_2$	A	[26, 36]
151	(*Z*,*Z*)-9,12-Octadecadienoic acidmethylester	$C_{19}H_{32}O_4$	A	[26, 36]
152	(*Z*,*Z*,*Z*)-9,12,15-Octadecatrienoic acid methylester	$C_{19}H_{32}O_2$	A	[26, 36]
153	Trollioside	$C_{19}H_{26}O_9$	A	[26, 36]
154	Proglobellowery acid	$C_7H_6O_2$	A	[26, 36]
155	4-(*D*-Glucopyranosyloxy)-3-(3-methyl-2-butenyl) benzoic acid	$C_{18}H_{24}O_8$	A	[26, 36]
156	3-Phenylprop-2-enoicacid methylester	$C_{11}H_{12}O$	A	[26, 36]
157	3-(4-Hydroxyphenyl) prop-2-enoicacid methylester	$C_{10}H_{10}O_3$	A	[26, 36]
158	(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid methylester	$C_{11}H_{12}O_4$	A	[26, 36]
159	2-Hydroxyhexadecanoic acid methylester	$C_{17}H_{34}O_3$	A	[26, 36]
160	3-Hydroxyhexadecanoic acid methylester	$C_{17}H_{34}O_3$	A	[26, 36]
161	10-Hydroxyhexadecanoic acid methylester	$C_{17}H_{34}O_3$	A	[26, 36]
162	*N*-Hexadecanoic acid	$C_{16}H_{32}O_2$	A	[26, 36]
163	Hexadecanoic acid,10,16-dihydroxy	$C_{16}H_{32}O_4$	A	[26, 36]

activities such as anti-bacterial and anti-oxidant activities. This oil is also widely applied in industries such as cosmetics and cigarette flavoring. To date, over 70 volatile oil components have been identified and isolated from *T. chinensis* Bunge. These mainly include high-grade fatty acids, high-grade alkanes, esters, and alcohols-like decanoic acid, lauric acid, myristic acid, tricosane, pentacosane, dihydroactinidiolide, and *β*-ionone, to name a few[43, 44]. Refer to Table 3, and Fig. 4 for detailed data.

2.4 Alkaloids

Currently, five alkaloids have been isolated and identified from the *Trollius* L. plant family, namely trolline, (*R*)-cyanomethyl-3-hydroxyindole, adenine, integerrimine, and senecionine[26]. Of these, trolline, (*R*)-cyanomethyl-3-hydroxyindole, and adenine are derived from *T. chinensis* Bunge[22, 38], while integerrimine and senecionine are sourced from *Trollius laxus*[8]. Please refer to Table 4 and Fig. 5 for detailed data.

2.5 Other chemical components

Research has shown that the plants of the genus *Trollius* contain coumarin compounds such as 5-*O*-rha-coumarin[15], 6-*O*-rha-8-*O*-glucosyl-coumarin[43], and esculetin[22], as well as sterol compounds including *β*-sitosterol and daucosterol. They also hold phenethyl alcohol compounds like 2-(3,4-dihydroxyphenyl)-ethyl-*O*-*β*-*D*-pyranoglucose, 2-(3,4-dihydroxyphenyl)-ethyl-*O*-*β*-*D*-glucopyranoside, 3,5-dihydroxyphenethyl alcohol-3-*O*-*β*-*D*-glucopyranoside[14], ceramide components such as trolliamide[41], and monosaccharides including *L*-rhamnose, *L*-arabinose, and *D*-galactose[26]. Additionally, some studies have noted that the extraction rate of polysaccharides from *T. chinensis* Bunge has reached 10.43%[42]. For more detailed data, please refer to Table 5 and Fig. 6.

3 Pharmacological effects

The genus *Trollius* has been traditionally used for treating colds, fever, sore throat, and bleeding gums. Recently, some researchers have conducted in-depth studies on the pharmacological effects of related preparations, extracts, or monomeric components of the genus *Trollius*, including antioxidant effects, anticancer effects, antiviral effects, anti-inflammatory effects, and antibacterial effects. In this section, we will summarize and analyze the main pharmacological activities of the genus *Trollius*.

3.1 Anti-oxidant effects

Anti-oxidant effects have been detected in different species of the genus *Trollius*. A variety of anti-oxidant tests (O^{2-}, DPPH, OH^-, R^-, O_2) were applied to the aqueous and alcoholic extracts of the genus *Trollius* to evaluate their anti-oxidant potential. The results suggested that the genus *Trollius* extracts could proficiently neutralize various reactive oxygen species (ROS) and DPPH free radicals under *in vitro* conditions, exhibiting potent anti-oxidant properties[45].

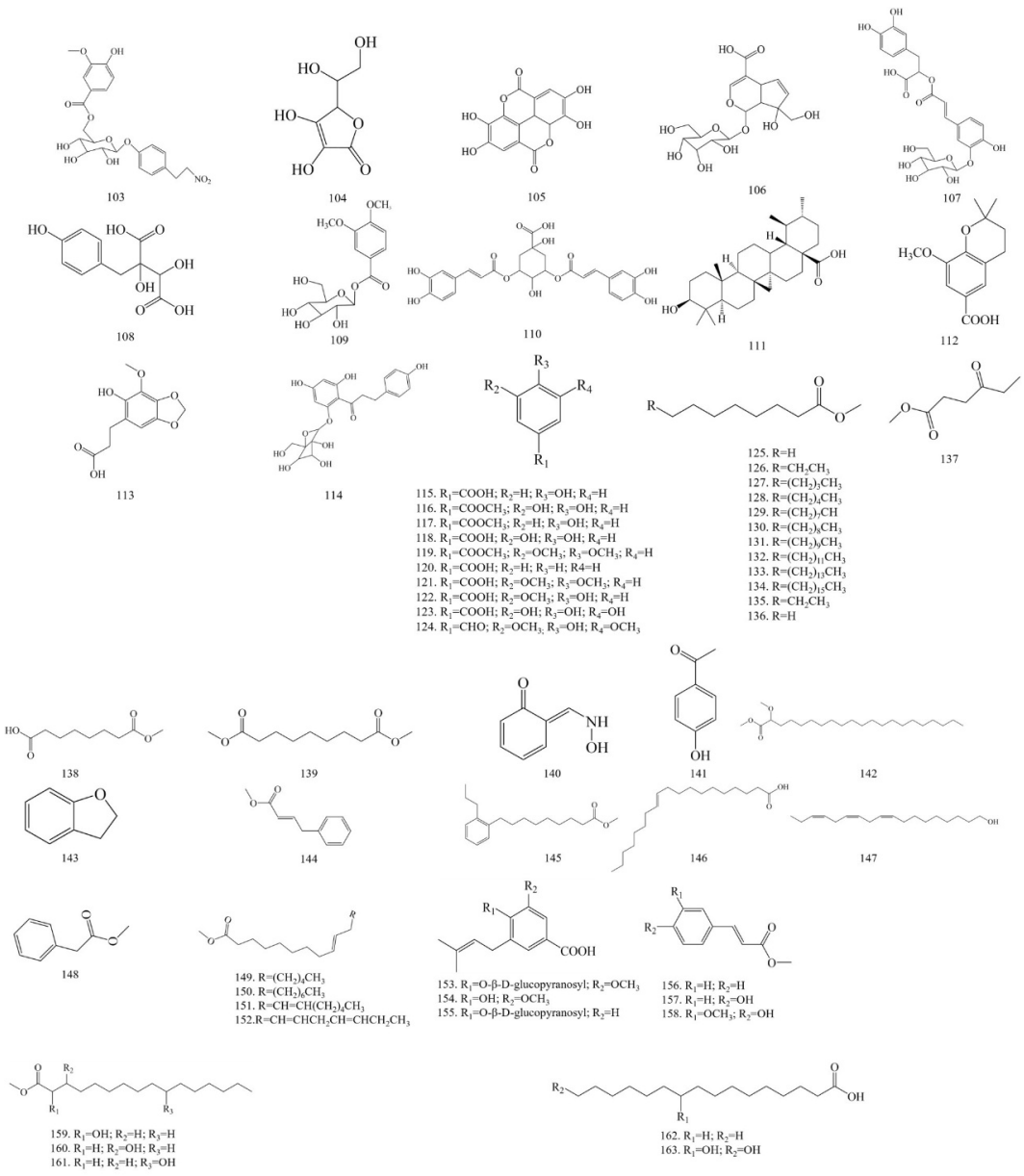


Figure 3 Chemical structure of organic acid components in the genus *Trollius*.

Table 3 Chemical components of volatile oils in the genus *Trollius*.

No.	Compound name	Molecular formula	Source	Reference
164	2,2,6-Trimethyl-cyclohexanone	$C_9H_{16}O$	A	[43]
165	2,6,10-Trimethyltetradecane	$C_{22}H_{46}$	A	[43]
166	6-Methyl-5-hepten-2-ol	$C_8H_{16}O$	A	[43]
167	2,6-Dimethylbenzaldehyde	$C_9H_{10}O$	A	[43]
168	Dodecane	$C_{12}H_{26}$	A	[43]
169	β-Cyclocitral	$C_{10}H_{16}O$	A	[43]
170	Phenylethyl acetate	$C_{10}H_{12}O_2$	A	[43]
171	1-Methylnaphthalene	$C_{11}H_{10}$	A	[43]
172	4-Hydroxy-3-methoxystyrene	$C_9H_{10}O_2$	A	[43]
173	1,2-Dihydro-1,5,8-trimethylnaphthalene	$C_{13}H_{16}$	A	[43]
174	4-{2,2,6-Trimethyl-7-oxabicyclo[4.1.0]hept-1-yl}-3-buten-2-one	$C_{13}H_{20}O_2$	A	[43]
175	Triacontane	$C_{30}H_{62}$	A	[43]
176	2-Methoxyphenol	$C_7H_8O_2$	A	[43]
177	Dihydroactinidiolide	$C_{11}H_{16}O_2$	A	[43]

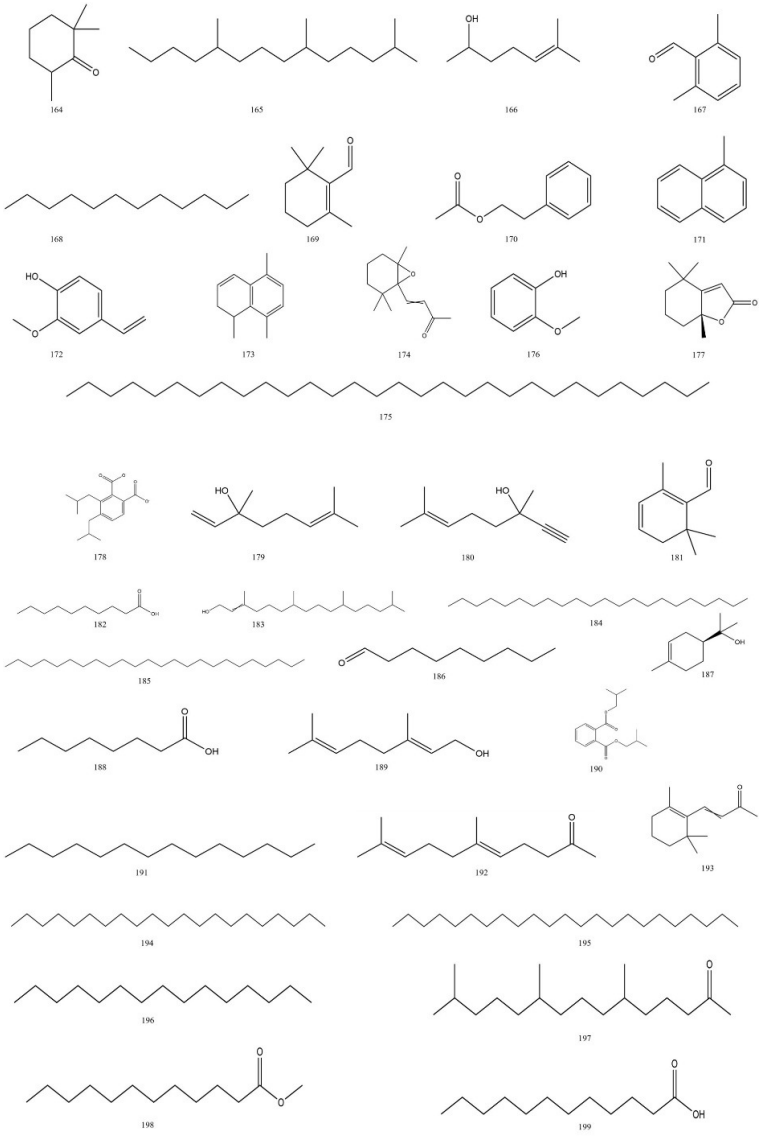
(Continued)

No.	Compound name	Molecular formula	Source	Reference
178	Diisobutylphthalate	$C_{16}H_{22}O_4$	A	[43]
179	Linalool	$C_{10}H_{18}O$	A	[43]
180	Dehydrolinalool	$C_{10}H_{16}O$	A	[43]
181	Safranal	$C_{10}H_{14}O$	A	[43]
182	Decanoic acid	$C_{10}H_{20}O_2$	A	[43]
183	Phytol	$C_{20}H_{40}O$	A	[43]
184	Docosane	$C_{22}H_{46}$	A	[43]
185	Tetracosane	$C_{24}H_{50}$	A	[43]
186	Nonanal	$C_9H_{18}O$	A	[43]
187	*α*-Terpneol	$C_{10}H_{18}O$	A	[43]
188	Octanoic acid	$C_8H_{16}O_2$	A	[43]
189	Lemonol	$C_{10}H_{18}O$	A	[43]
190	Diisobutyl phthalate	$C_{16}H_{22}O_4$	A	[43]
191	Tetradecane	$C_{14}H_{30}$	A	[43]
192	Geranyl acetone	$C_{13}H_{22}O$	A	[43]
193	*β*-Ionone	$C_{13}H_{20}O$	A	[43]
194	Heneicosane	$C_{21}H_{44}$	A	[43]
195	Tricosane	$C_{23}H_{48}$	A	[43]
196	Pentadecane	$C_{15}H_{32}$	A	[43]
197	6,10,14-Trimethyl-2-pentadecanone	$C_{18}H_{36}O$	A	[43]
198	Methyl laurate	$C_{13}H_{26}O_2$	A	[43]
199	Lauric acid	$C_{12}H_{24}O_2$	A	[43]
200	Heptadecane	$C_{17}H_{36}$	A	[43]
201	Octadecane	$C_{18}H_{38}$	A	[43]
202	Methyl myristate	$C_{15}H_{30}O_2$	A	[43]
203	Myristic acid	$C_{14}H_{28}O_2$	A	[43]
204	(−)-Linalool	$C_{10}H_{18}O$	A	[43]
205	1,2,3,5-Tetramethylbenzene	$C_{10}H_{14}$	A	[43]
206	1,2-Dihydro-1,1,6-trimethylnaphthalene	$C_{13}H_{16}$	A	[43]
207	(*E*)-6,10-Dimethyl-5,9-undecadien-2-one	$C_{13}H_{22}O$	A	[43]
208	Phenanthrene	$C_{14}H_{10}$	A	[43]
209	Hexadecanamide	$C_{16}H_{33}NO$	A	[43]
210	Pentatriacontane	$C_{35}H_{70}$	A	[43]
211	Palmitic acid	$C_{16}H_{32}O_2$	A	[43]
212	Palmitic acid ethylester	$C_{18}H_{36}O_2$	A	[43]
213	Methyl palmitate	$C_{17}H_{34}O_2$	A	[43]
214	Linoleic acid	$C_{18}H_{32}O_2$	A	[43]
215	Methyl linolenate	$C_{19}H_{32}O_2$	A	[43]
216	*N*-Eicosane	$C_{20}H_{42}$	A	[43]
217	*N*-Pentacosane	$C_{25}H_{52}$	A	[43]
218	*N*-Heptacosane	$C_{27}H_{56}$	A	[43]
219	*D*-Camphor	$C_{10}H_{16}O$	A	[43]
220	Methyl nonanoate	$C_{10}H_{20}O_2$	A	[43]
221	Tridecanoic acid	$C_{13}H_{26}O_2$	A	[43]
222	Methyl myristate	$C_{15}H_{30}O_2$	A	[43]
223	2-Methoxy-4-vinylphenol	$C_9H_{10}O_2$	A	[43]
224	Palmitoleic acid	$C_{16}H_{30}O_2$	A	[43]
225	Stearic acid	$C_{18}H_{36}O_2$	A	[43]
226	Pentadecanoic acid	$C_{15}H_{30}O_2$	A	[43]
227	Terpineol	$C_{10}H_{18}O$	A	[43]
228	Farnesylacetone	$C_{18}H_{30}O$	A	[43]

(Continued)

No.	Compound name	Molecular formula	Source	Reference
229	Nonanoic acid	$C_9H_{18}O_2$	A	[43]
230	Linolenic acid	$C_{18}H_{30}O_2$	A	[43]
231	Methyl palmitate	$C_{17}H_{34}O_2$	A	[43]
232	Phthalic acid	$C_8H_6O_4$	A	[43]
233	*N*-Hexadecane	$C_{16}H_{34}$	A	[43]
234	2,6-Di-tert-butyl-4-Methylphenol	$C_{15}H_{24}O$	A	[43]
235	Hexacosane	$C_{26}H_{54}$	A	[43]
236	2,6,10,14-Tetramethylnonadecane	$C_{23}H_{48}$	A	[43]
237	Nonadecane	$C_{19}H_{40}$	A	[43]
238	Octacosane	$C_{28}H_{58}$	A	[43]
239	2,6,10-Trimethyldodecane	$C_{15}H_{32}$	A	[43]
240	Dimethyl phthalate	$C_{10}H_{10}O_4$	A	[43]
241	9-Octyl-heptadecane	$C_{25}H_{52}$	A	[43]
242	Ethyl myristate	$C_{16}H_{32}O_2$	A	[43]

In a separate study, Fan *et al.*[46] proceeded to extract *T. ledebouri* Rchb using a series of solvents (petroleum ether, ethyl acetate, 95% ethanol, 60% ethanol, 30% ethanol, and deionized water) to examine the anti-oxidant activity of various parts of



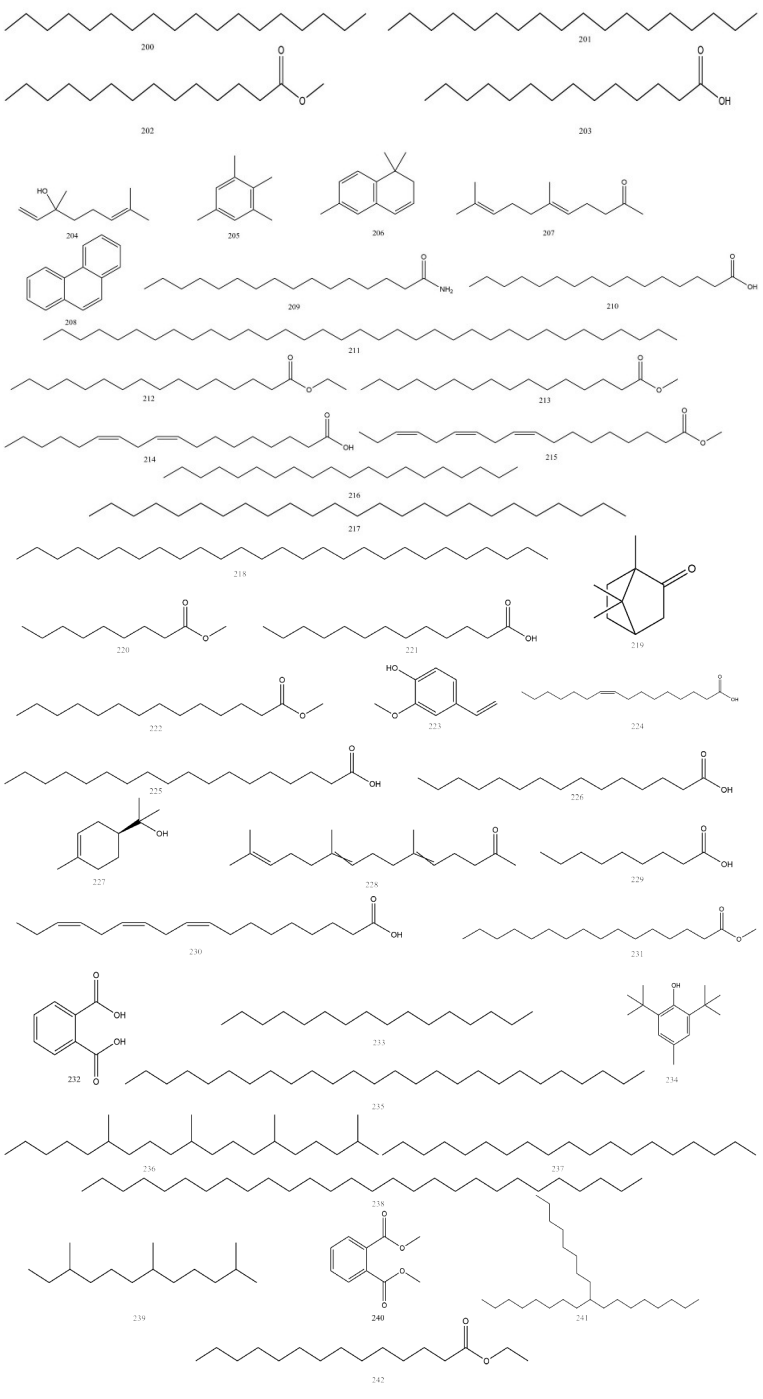


Figure 4 Structure of volatile components in the genus *Trollius*.

Table 4 Alkaloid components in the genus *Trollius*.

No.	Compound name	Molecular formula	Source	Reference
243	Senecionine	$C_{18}H_{25}NO_5$	I	[43]
244	Integerrimine	$C_{18}H_{25}NO_5$	I	[43]
245	Trolline	$C_{12}H_{13}NO_3$	A	[28]
246	(*R*)-Cyanomethyl-3-hydroxyindole	$C_{10}H_7O_2N_2$	A	[28]
247	Adenine	$C_5H_5N_5$	A	[18]

T. ledebouri Rchb. They found that the portions extracted with petroleum ether and 95% ethanol proved to be the most effective anti-oxidant components. The –OH scavenging ability was demonstrated with the maximum –OH scavenging of 30.3% at a concentration of 0.3 mg/mL by aurantium polysaccharide I[47]. In research investigating the anti-oxidant effects of *T. ledebouri* Rchb polysaccharide (TLP) fractions, it was discovered that all four polysaccharide fractions were successful in scavenging DPPH free

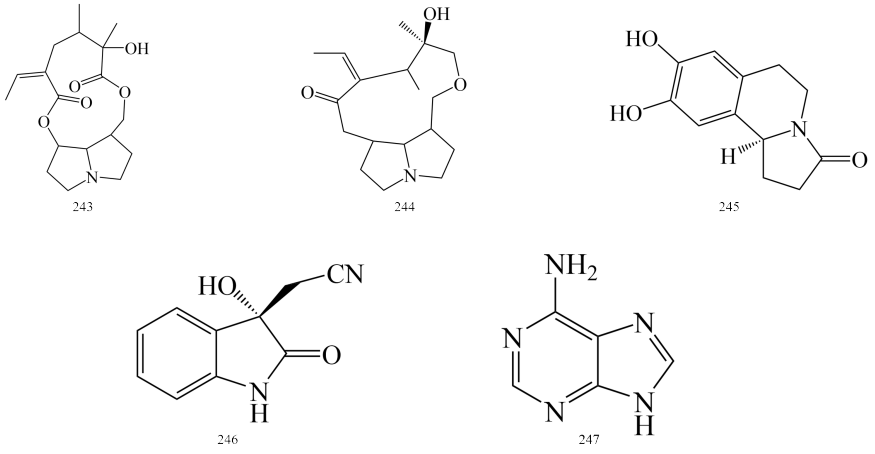


Figure 5 Structure of alkaloid components in the genus *Trollius*.

Table 5 Other components in the genus *Trollius*.

No.	Compound name	Molecular formula	Source	Reference
248	5-*O*-rha-Coumarin	$C_{15}H_{19}O_9$	A	[15]
249	6-*O*-rha-8-*O*-Glueosyl-coumarin	$C_{21}O_{15}H_{28}$	A	[43]
250	Cichoriin	$C_{15}H_{16}O_9$	A	[18]
251	Esculetin	$C_9H_6O_4$	A	[22]
252	Trolliusol A	$C_{17}H_{16}O_6$	A	[12]
253	Trollixanthin	$C_{40}H_{56}N_4$	A	[22]
254	Trolliamide	$C_{42}H_{82}NO_5$	A	[41]
255	Daucosterol	$C_{35}H_{60}O_6$	A	[29]
256	*β*-Sitosterol	$C_{29}H_{50}O$	A	[29]
257	*L*-Rhamnose	$C_6H_{14}O_6$	A	[42]
258	*L*-Arabinose	$C_5H_{10}O_5$	A	[42]
259	*D*-Galactose	$C_6H_{12}O_6$	A	[42]
260	Vanillylamine	$C_8H_{11}NO_2$	A	[30]
261	Homovanillyl alcohol	$C_9H_{12}O_3$	A	[34]
262	Xantho-phyll-epoxyde	$C_{40}H_{56}O_3$	A	[40]
263	2-(3,4-Dihydroxyphenyl)-ethyl-*O*-*β*-*D*-pyranoglucose	$C_8H_{10}O_3$	A	[14]
264	2-(3,4-Dihydroxyphenyl)-ethyl-*O*-*β*-*D*-glucopyranoside	$C_{14}H_{20}O_8$	A	[14]
265	3,5-Dihydroxyphenethyl alcohol-3-*O*-*β*-*D*-glucopyranoside	$C_{14}H_{20}O_8$	A	[14]
266	4-*O*-(6-*O*-Vanilloylajugol-*β*-*D*-glucopyranoyl) phenylethanol	$C_{22}H_{26}O_{10}$	A	[14]

radicals. TLP2 and TLP3, in particular, were effective, with scavenging rates of 35.49% and 23.74% respectively within the concentration range of 0.2–1.2 mg/mL. TLP2 displayed a significant scavenging impact on –OH, achieving 99.3% when its concentration reached 0.30 mg/mL[48]. At that same concentration, the clearance of –OH reached 99.3%[19]. Flavonoid compounds of the genus *Trollius* have been found to possess notable anti-oxidant activity[49]. Total flavonoids of *Trollius altaicus* C.A.Mey (TAF) can augment superoxide dismutase (SOD) and glutathione (GSH) content while reducing malondialdehyde (MDA) and lactate dehydrogenase (LDH) content in cells/serum in human bronchial epithelial cells BEAS-2B's acute injury model, a rat pulmonary fibrosis model, and a rat model of acute injury induced by tracheal drip particulate matter 2.5 (PM2.5) These findings suggest that TAF can effectively sustain the oxidative/antioxidative balance in organisms and curtail damage caused by oxidative stress from PM2.5[49-51]. Research indicates that the Keap1/Nrf2 signaling pathway elevates the expression of anti-oxidants like heme oxygenase-1 (HO-1) and NADH quinone oxidoreductase 1 (NQO1), mitigating *in vivo* oxidative stress levels and thereby reducing pulmonary fibrosis. The total flavonoids of *T. chinensis* Bunge can scavenge superoxide anion radicals, hydroxyl radicals, and DPPH radicals in an A549 lung fibrosis model of human lung cancer cells induced by transforming growth factor-β1 (TGF-β1). They can also enhance SOD expression while reducing MDA and ROS expression, lowering cellular oxidative stress levels. Furthermore, the flavonoids in *T. chinensis* Bunge can act in the classic oxidative stress signaling pathway Keap1/Nrf2, reducing Keap1 expression and enhancing Nrf2, thereby exerting anti-oxidant effects and inhibiting lung fibrosis[52]. Additionally, research has also shown a positive correlation between the ·OH scavenging capacity of *T. ledebouri* Rchb and the yellow pigment content, and between the DPPH scavenging capacity and the flavonoid and polyphenol content[46].

Studies investigating the anti-oxidant components of differing Jinlianhua species have primarily centered on orientin and vitexin. Lipid peroxidation, a byproduct of oxygen free radical-induced cellular damage, is widely considered a key process. MDA, a

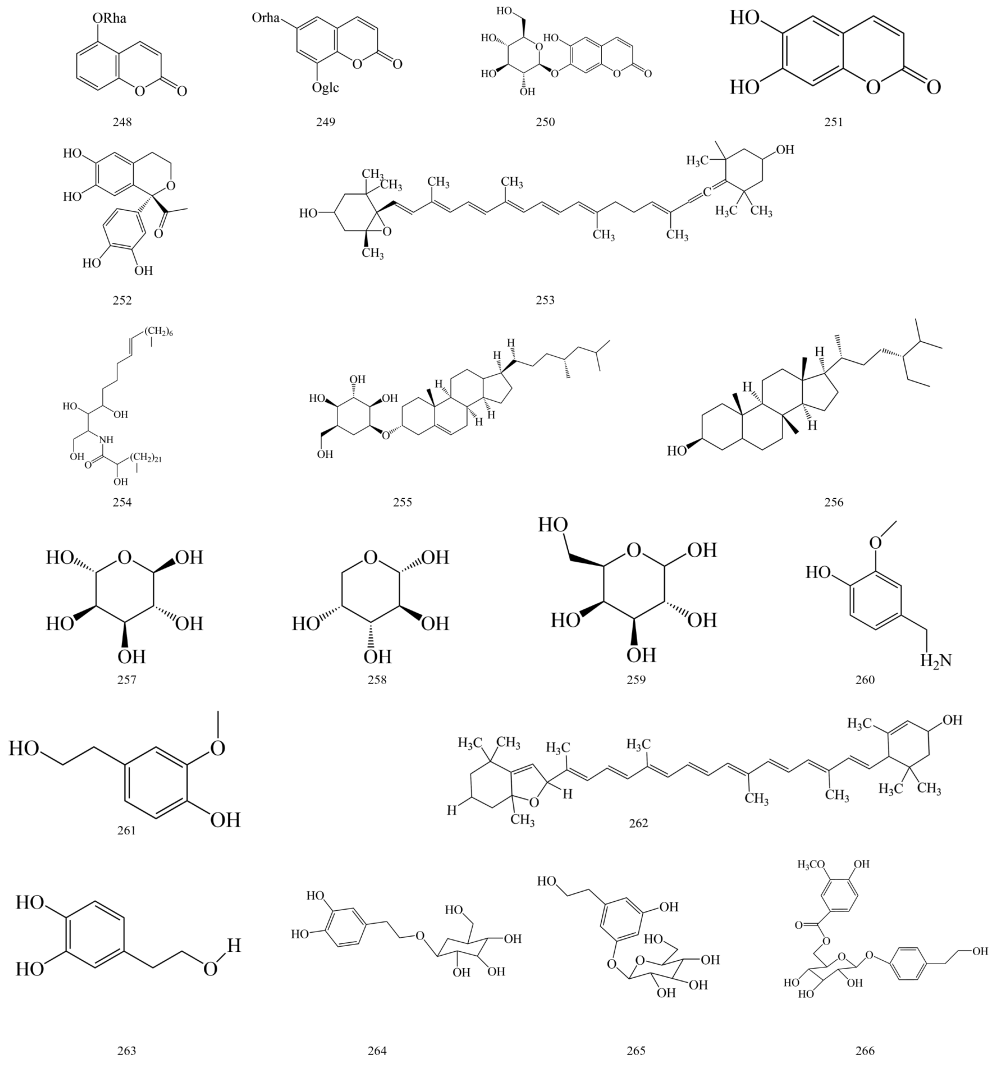


Figure 6 Chemical structure of other components in the genus *Trollius*.

decomposition product of lipid peroxidation, may denature or inactivate cells, consequently reducing tissue elasticity. Lipofuscin, another lipid peroxidation product, is recognized as an aging hallmark. Aging often disrupts Ca^{2+} balance, leading to intracellular Ca^{2+} overload, which may contribute to nervous system aging. Recent research suggests that intracellular Ca^{2+} overload is closely associated with geriatric diseases[53-56]. The activities of Na^{+}-K^{+}-ATPase and Ca^{2+}-Mg^{2+}-ATPase, which dictate Ca^{2+} distribution, are new aging indicators.

Vitexin and Orientin can mitigate the aging effects in *D*-galactose-induced mice through intraperitoneal injection. Their primary mechanism of action is enhancing the activity of anti-oxidant enzymes and scavenging excess oxygen free radicals, thereby reducing cellular and tissue damage, preserving cell membrane stability, and maintaining standard cell structure. This elevation in Na^{+}-K^{+}-ATPase and Ca^{2+}-Mg^{2+}-ATPase activity diminishes free radical damage on cell membranes, maintains Ca^{2+} homeostasis, and decreases MDA and lipofuscin in brain tissues. This process ultimately improves neuronal structure functioning in the hippocampus. It also boosts the activity of SOD, catalase (CAT), and glutathione peroxidase (GSH-Px) in the renal, hepatic, and brain tissues of *D*-galactose-aged mice, diminishing MDA activity[53-56].

Orientin and vitexin also help to scavenge superoxide anions, hydroxyl radicals, and DPPH free radicals, and exert a protective effect on erythrocyte membranes. The anti-oxidant capacity of orientin surpasses that of vitexin[57]. These compounds protect against oxidative damage in *in vitro* erythrocyte models and naturally aging erythrocyte models, with a clear dose dependence. Their mechanism of action primarily involves reducing peroxidation product content, increasing anti-oxidant enzyme vitality and transmembrane ion-transporting enzymes, enhancing cell morphology, and restoring cell membrane structure[58]. Orientin, vitexin, quercetin-3-*O*-naveloside, and quercetin-3-*O*-neohesperidin in *T. ledebouri* Rchb have strong scavenging effects on DPPH, –OH, and O-2, and considerably inhibit H_2O_2-induced oxidative hemolysis of rat erythrocytes[59].

A screening technique using the HPLC-DPPH system, HPLC-Fenton system, HPLC-Riboflavin/EDTA-2Na system, and HPLC-PTIO system has identified 12 substances with anti-oxidant activity in *T. ledebouri* Rchb phenolic acids and flavonoids were found to be important components for anti-oxidant activity in *T. ledebouri* Rchb. Orientin, orientin-2"-*O*-*β*-*L*-galactoside (OGA), veratric acid, vitexin, and artichoke glycoside demonstrated variable anti-oxidant activity degrees[40].

Chlorogenic acid in *T. chinensis* Bunge has appreciable *in vitro* anti-oxidant capacity. Total anti-oxidant activity and scavenging capacity for DPPH radicals and superoxide anion in *T. chinensis* Bunge were measured, indicating a higher total anti-oxidant capacity than vitamin C (VC) at a concentration of 0.8 mg/mL.

The scavenging capacity for superoxide anion and DPPH radicals was 63.7% and 90.0% respectively[59]. The yellow pigment in *T. buddae* Schipcz. also demonstrates scavenging ability for −OH and DPPH radicals, trending upwards with increased pigment concentration. The scavenging effect peaked at 71.7% with a pigment concentration of 25 mg/mL[40].

In conclusion, the genus *Trollius* possesses robust antioxidant properties. Polysaccharides, flavonoids, and phenolic acids within the genus *Trollius* exhibit antioxidant activities to varying extents. Additionally, the yellow pigment in the genus *Trollius* also demonstrates certain antioxidant effects. The genus *Trollius* is capable of activating the classical oxidative stress signaling pathway Keap1/Nrf2, upregulating the expression of antioxidants such as HO-1 and NQO1, enhancing the activity of antioxidant enzymes like SOD and GSH, and scavenging various free radicals such as DPPH, ROS, and ABTS. It is noteworthy that orientin and vitexin in the genus *Trollius* are widely studied as antioxidant active ingredients, and the antioxidant capacity of orientin is stronger than that of vitexin. They can also boost the activity of transmembrane ion transporter enzymes, maintain the transport capacity of cells and the stability of cell membranes, and restore the cytoskeleton structure.

3.2 Anti-cancer effects

The total flavonoids in *T. chinensis* Bunge exhibit a significant inhibitory effect on various cancer cells. Specifically, these flavonoids markedly inhibit the growth of tumor cells such as K562, HeLaEc-109, and NCIH446, with the inhibitory effect showing a dose-dependent pattern. Additionally, the total flavonoids of *T. chinensis* Bunge also significantly suppress the growth of human gastric cancer cells AGS, human melanoma cells A375SM, and human breast cancer cells MCF-7 and MDA-MB-231. The half inhibitory concentration (IC_{50}) is 143.72, 62.23, 244.50, and 279.06 μg/mL, respectively[39, 60].

The anti-cancer mechanism of *T. chinensis* Bunge primarily resides in its ability to promote cancer cell apoptosis and affect associated pathways. The PARP-1/p53 signaling pathway plays a vital role in cell proliferation, cycle regulation, and apoptosis[63]. *T. chinensis* Bunge can induce apoptosis in human breast cancer MCF-7 cells and hinder their proliferation. Its primary mechanism of action is to suppress the expression of the PARP-1 and p53 proteins in the PARP-1/p53 pathway, reduce the expression of BCL2 and NF-κB, and enhance the expression of caspase 9 and 3[61].

Studies have demonstrated that trefoil factor 3 (TFF3) is significantly overexpressed in papillary thyroid carcinoma. This increase correlates positively with the high expression level of the extracellular signal-regulated kinase (ERK) signaling pathway protein found in papillary thyroid carcinoma tissues. This suggests that TFF3 may contribute to the onset and progression of papillary thyroid carcinoma through the ERK pathway. Therefore, inhibiting TFF3 expression can potentially hinder cancer cell growth. As such, the total flavonoids from *T. chinensis* Bunge have been found to curb the proliferation of human papillary thyroid carcinoma cell K1. This is achieved primarily by repressing the expression of TFF3 and subsequently activating the ERK signaling pathway to induce a pro-apoptotic effect[62].

The total flavonoids of *T. chinensis* Bunge can induce apoptosis in breast cancer MCF-7 cells, human non-small cell lung cancer A549, and HT-29 colon cancer cells. The primary mechanism of action is to inhibit the expression of anti-apoptotic genes Bcl-2 and Bcl-xL in tumor cells, and the expression of NF-κB. These flavonoids up-regulate the expression of pro-apoptotic genes Bax, caspase-9, and caspase-3, which triggers the spontaneous apoptosis of tumor cells and can also down-regulate the expression of the cyclooxygenase 2 (*COX-2*) gene, thus inhibiting the proliferation of tumor cells[63, 64]. Furthermore, the flavonoid monomer components of *T. chinensis* Bunge, including orientin and vitexin, can inhibit the growth of tumor cells. These flavonoids have an inhibitory effect on the growth of the human esophageal cancer cell EC-109 and can induce apoptosis in these cancer cells. By up-regulating the expression of the p53 protein and down-regulating the expression of the BCL-2 protein, these flavonoids promote the apoptosis of the human esophageal cancer cell EC-109 and inhibit its growth[65].

In the genus *Trollius*, total flavonoids and flavonoid compounds exhibit anticancer activity such as orientin and vitexin. The anticancer mechanism is complex and still requires in-depth research. Specifically, it activates cancer cell apoptosis pathways such as PARP-1/p53 and ERK, inhibits the expression of PARP-1, p53 protein and TFF3, suppresses the expression of anti-apoptotic genes such as BCl-2, BCl-xL and NF-κB, upregulates the expression of pro-apoptotic genes such as Bax, caspase 9 and 3, and downregulates the expression of *COX-2* gene, thereby inhibiting tumor proliferation and promoting spontaneous apoptosis of cancer cells.

3.3 Anti-viral effects

Research on the anti-viral properties of the genus *Trollius* primarily focuses on its preparations, extracts, and monomeric components. Both Jinlianhua Capsules and Jinlianhua Decoction have shown significant anti-viral efficacy. Jinlianhua Capsules can inhibit the replication of the human coronavirus OC43 *in vitro* and also suppress the high expression of host cell cytokines like interleukin-1β (*IL-1β*), interleukin-6 (*IL-6*), and interferon-alpha (*IFN-α*) mRNA caused by viral infection[66]. The anti-viral effectiveness rate of Jinlianhua Decoction stands at 75.13%. The disease resistance of any formula without Jinlianhua is notably diminished. IC_{50} values for the 80% Jinlianhua Decoction extract and the secondary 95% Jinlianhua Decoction extract in mouse macrophage RAW264.7 infected with H_1N_1 influenza virus stand at 0.014 and 0.047 mg/mL, respectively[67].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a proteolytic enzyme named 2019-nCoV Mpro. This enzyme cleaves the polyprotein translated by the virus into functional proteins during the virus's replication process, playing a critical role in the life cycle of this novel coronavirus. Hence, screening inhibitors of Mpro can impede the virus's replication and assembly. It is suggested that the Jinlianhua decoction has potential as a treatment for the novel coronavirus. We used molecular docking technology to assess the anti-novel coronavirus activity of the Jinlianhua Decoction. The results indicate that 26 compounds are present in the Jinlianhua. Decoction-including rutin, luteolin-7-*O*-glucoside, kaempferol, and genistin, among others, can bind to the Mpro protein through hydrogen bonds, potentially aiding in the prevention and treatment of the novel coronavirus[66].

It is important to note, however, that the anti-viral activities of different the genus *Trollius* extracts and those obtained with diverse solvents can vary. For instance, the crude extract of *T. ledebouri* Rchb can reduce the lung index and lung pathological damage in mice caused by the H_1N_1 influenza virus[68]. Also, the inhibitory effect of *T. chinensis* Bunge aqueous extract was stronger on Coxsackie virus B3 than on Coxsackie virus A24[69].

The monomeric components of Jinlianhua exhibit significant anti-viral activity. Orientin demonstrates a strong inhibitory effect on Coxsackie virus and parainfluenza virus 3[9], while vitexin displays robust anti-viral activity against parainfluenza virus 3. A flavonoid C-glycoside of Trollius possesses moderate anti-influenza A virus activity[70]. Guava acid, *p*-hydroxybenzoic acid, and acetylorientin all have inhibitory effects on influenza virus type 71[71]. In its anti-influenza virus effect, the genus *Trollius* shows "multi-component-multi-target-multi-pathway" characteristics, primarily exerting anti-influenza impacts through reducing the production of inflammatory factors and activating immune regulatory pathways such as tumor necrosis factor alpha (TNF-*α*), hypoxia-inducible factor-1 (HIF-1), and Toll-like receptors[72]. The anti-viral mechanism of six active Trollius components-vitexin, orientin, vitexin-2"-*O*-*β*-*L*-galactoside, orientin-2"-*O*-*β*-*L*-galactoside, veratric acid, and trolline, was predicted through molecular docking technology. Results indicated that, except trolline, the other five components could impact the TLRs-mediated signaling pathway, with TLR3, 4, and 7 being potential targets for their anti-viral and anti-inflammatory effects. neuraminidase (NA), which plays a crucial role in virus replication and pathogenicity, could be affected by substances that inhibit NA, thus providing potential drugs against the influenza virus. Four flavonoids – vitexin, orientin, vitexin-2"-*O*-*β*-*L*-galactoside, and orientin-2"-*O*-*β*-*L*-galactoside, can target NA, therefore impacting the activity of the influenza virus[73]. Three active *Trollius* components, veratric acid, vitexin, and trolline, combat the H_1N_1 virus by partially down-regulating the TLRs 3 and 7 pathways and up-regulating the TLRs 4 pathway. These components reduce the production of inflammatory factors (including NO, IL-6, and TNF-α) and increase the production of IFN-*β* by dynamically regulating the TLRs 3, 4, and 7 pathways. Hence, they counteract inflammatory damage from excessive production of NO, IL-1, IL-6, and TNF-α due to the virus infection and boost the production of IFN-β to eliminate the virus[74].

In conclusion, series of preparations, extracts and monomeric components in the genus *Trollius* all have antiviral activity. The antiviral effect of the genus *Trollius* shows the characteristics of multi-component-multi-target-multi-pathway synergistic regulation. On the one hand, it can bind to the Mpro protein of the virus and inhibit the replication and assembly of the virus to disrupt the operation of the virus life cycle. On the other hand, it can jointly play an anti-influenza role by reducing the production of inflammatory factors such as TNF-α, HIF-1 and Toll-like receptors and activating the immune regulation pathway of the body.

3.4 Anti-Inflammatory effects

Various species of the genus *Trollius* have demonstrated significant anti-inflammatory efficacy. In clinical applications, preparations derived from the genus *Trollius* are commonly utilized in treating upper respiratory tract diseases.

Jinlianhua soft capsules have a significant therapeutic effect on the exogenous wind-heat syndrome of acute upper respiratory tract infections, particularly in alleviating symptoms such as aversion to wind and fever, runny and clouded nasal discharge, and coughing[75]. The capsules of Jinlianhua effectively treat airway inflammation in ovalbumin-induced allergic asthmatic mice. They significantly reduce the lung weight/body weight ratio in asthmatic mice, improve airway eosinophilic inflammation, and suppress the expression of related inflammatory factors such as IL-5 and IL-13 in lung tissue. Studies have shown that the p38 MAPK signaling pathway is involved in the type 2 immune response of asthma. Following the activation of the p38 MAPK signal, it induces the differentiation and activation of Th2 cells as well as promoting the release of the Th2 cytokines IL-5 and IL-13.

Additionally, the 400 mg/kg group of Jinlianhuan Capsules can inhibit the phosphorylation level of p38 MAPK protein in the lung tissue of asthmatic mice. It is inferred that the anti-allergic asthma airway inflammation action mechanism of Jinlianhua Capsules may be achieved by inhibiting the phosphorylation of p38 MAPK protein in lung tissue[76]. For the treatment of acute respiratory tract infections in children, combining Jinlianhua granules with cefixime granules can shorten the treatment duration and enhance the clinical efficacy[77].

Extracts from various species of the genus *Trollius* possess anti-inflammatory activity. Notably, the 60% ethanol extract of *T. ledebouri* Rchb significantly inhibits ear swelling in mice induced by croton oil with a gavage dose of 1,000 mg/kg[78]. Furthermore, different extraction parts of *T. ledebouri* Rchb can inhibit xylene-induced ear swelling in mice and diminish the number of writhing responses in mice caused by acetic acid[79]. An activity-targeted study on the anti-inflammatory components of *T. chinensis* Bunge led by Zhao *et al.*[80] revealed that flavonoids and phenolic acids are the primary active anti-inflammatory components. The flavonoid components of *T. ledebouri* Rchb can also decrease the ear swelling rate in mice by roughly 70%. Its anti-inflammatory mechanism may be associated with the COX-2 enzyme[78]. TAF can decrease the number of white blood cells in rats with acute lung injury and pulmonary fibrosis caused by tracheal instillation of PM2.5, reduce the levels of inflammatory factors like IL-6, IL-1β, and TNF-α in the serum, diminish lung tissue edema, alveolar morphological damage, and inflammatory cell infiltration, and effectively reduce hydroxyproline (HYP), type I procollagen amino-terminal peptide (PINP), type II procollagen amino-terminal peptide (PIINP) content, and collagen fiber deposition[50, 51]. By combining network pharmacology with *in vivo* and *in vitro* experiments, it was discovered that multi-component-multi-target-multi-pathway characteristics exist between *T. altaicus* C.A.Mey and chronic obstructive pulmonary disease (COPD). Based on the TLR4/NF-κB signaling pathway, TAF can exert a significant anti-inflammatory effect in COPD rats caused by cigarette smoke (CS) combined with lipopolysaccharide (LPS), such as easing lung swelling and reducing pathological lung tissue damage. It also preserves the morphology and cell viability of BEAS-2B cells injured by CS/LPS combined infection and down-regulates inflammatory mediators such as IκB kinase α (IKKα), p65, and IL-1β in the TLR4-NF-κB pathway[81].

The primary anti-inflammatory active components in *T. chinensis* Bunge are orientin, vitexin, and orientin-2"-*O*-pyran galactose. Vitexin exhibits a protective effect on liver injury in mice suffering from ulcerative colitis instigated by dextran sodium sulfate (DSS). The principal mechanism of action involves the inhibition of the TLR4/NF-κB pathway, which reduces the inflammatory response, thereby projecting a liver-protecting effect[82]. Additionally, orientin demonstrates therapeutic effects on RAW264.7 cell inflammation instigated by LPS. The mechanism behind this is linked to the suppression of the NF-κB pathway and the activation of nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome[83]. Similarly, the orientin-2"-*O*-pyran galactose helps mitigate microglial inflammation invoked by LPS. It accomplishes this by inhibiting the production of NO and TNF-*α*, IL-1*β* in microglia driven by LPS, NO synthase

expression, and cyclooxygenase-2, while concurrently inhibiting the activation of the nuclear factor NF-κB and the ERK pathway. This reduces the production of reactive oxygen species activated by LPS, relating to the inhibition of the Nrf2/HO-1 pathway. The OGA affects both the HO-1-mediated NF-κB pathway and the ERK pathway (anti-inflammatory pathway)[84]. Furthermore, OGA significantly reduces the contents of NO, ROS, and MCP-1 in inflammatory RAW264.7 cells induced by LPS, mollifies the secretion of PGE2, TNF-α, and IL-6, inhibits COX-2 activity, and down-regulates the mRNA expression of *TNF-α*, *IL-1β*, and *IL-6*. Its IC_{50} is 5.01 μg/mL[85].

Additionally, the anti-inflammatory active components and mechanisms of action across different species of the genus *Trollius* still require further verification through relevant experiments. Cai *et al.*[4] utilized ultra-high performance liquid chromatography-quadrupole-time-of-flight tandem mass spectrometry (UHPLC-Q-TOF-MS), network pharmacology, and molecular docking verification to investigate the pharmacodynamic substances and mechanisms of the anti-inflammatory effect in *T. chinensis* Bunge. The findings indicated that *T. chinensis* Bunge contains 23 effective active components and carries 13 core targets for anti-inflammation, such as tumor necrosis factor (TNF), RAC-alpha serine/threonine-protein kinase (Akt1), vascular endothelial growth factor A (VEGFA), etc. In summary, *T. chinensis* Bunge may act on core targets including TNF, AKT1, VEGFA, PTGS2, EGFR, SRC through core compounds like salvin, cirsimarin, apigenin, ferulic acid, quercetin, and apigenin, and regulate signaling pathways such as those in cancer, lipid and atherosclerosis, PI3K/Akt, TNF, IL-17, MAPK, AGE-RAGE, and HIF-1. This may subsequently influence biological processes, namely the body's external stimulus-response, MAPK cascade activation, positive regulation of protein phosphorylation, and regulation of the inflammatory response, thereby manifesting an anti-inflammatory effect[75].

In summary, flavonoids, phenolic acids, and a small number of alkaloid components in the genus *Trollius* all have anti-inflammatory effects. The anti-inflammatory activity of phenolic acid compounds is more prominent. Its anti-inflammatory mechanism mainly plays an anti-inflammatory role by inhibiting the expression of inflammatory factors, inhibiting the immune response caused by the phosphorylation of p38 MAPK protein activated by allergy, and activating related anti-inflammatory pathways such as NF-κB, ERK, Nrf2, and HO-1.

3.5 Anti-bacterial effects

Different species of the genus *Trollius* exhibit a broad anti-bacterial spectrum, and there are abundant research results concerning their anti-bacterial properties. The anti-bacterial activity is evident in various forms, such as oral liquid, tablets, capsules, and granules. Their efficacy against three pathogenic bacteria, in descending order of strength, are *Bacillus subtilis*, *S. aureus*, and *Escherichia coli*. The minimum inhibitory concentration (MIC) of the four Jinlianhua preparations differs against *S. aureus* and *B. subtilis*. When comparing anti-bacterial intensities, from strong to weak, they rank as capsules, oral liquids, tablets, and granules[86]. By assessing the anti-bacterial effect of the genus *Trollius* series preparations (Jinlianhua Oral Liquid, Jinlianhua Tablets, Jinlianhua Granules, and Jinlianhua Capsules) on *E. coli* and *S. aureus*, creating the fingerprint spectrum of the Jinlianhua series preparations, and analyzing their spectrum-effect relationship, it has been found that five chemical components in the Jinlianhua series preparations significantly inhibit *S. aureus*, and two components affect *E. coli*. The establishment of the chemical fingerprint spectrum of the Jinlianhua series preparations, the determination of *in vitro* anti-bacterial activity, and the study of the comprehensive spectrum-effect correlation show that the Jinlianhua oral liquid dosage form exhibits more advantages than the other dosage forms[87].

The research on the four Jinlianhua preparations is currently incomplete. In the follow-up, other techniques like LC-MS should be employed to analyze and identify other chromatographic peaks. Further studies on other strains should also be conducted for a more comprehensive analysis and evaluation.

Various species of the genus *Trollius* exhibit notable anti-bacterial activity. Studies show that the genus *Trollius* can significantly inhibit the growth of *S. aureus*, *Pseudomonas aeruginosa*, *E. coli*, and *Shigella dysenteriae*[88]. Similarly, *T. ledebouri* Rchb is found to have substantial anti-bacterial effects, particularly against *P. aeruginosa* and *Streptococcus pneumoniae*[89]. When comparing the anti-bacterial effects of different 70% ethanol extracts from *T. chinensis* Bunge and *T. ledebouri* Rchb, the results demonstrate that the total extract has the most effective anti-bacterial impact. Furthermore, a dose-dependent relationship is observed when jinlianhua tablets or the 70% ethanol extract of *T. chinensis* Bunge and *T. ledebouri* Rchb, is administered to counter the lethal effect of *S. aureus* introduced intraperitoneally in mice[88].

As for *T. altaicus* C.A.Mey, it has a broad anti-bacterial spectrum and effectively inhibits various Gram-positive and Gram-negative bacteria[89]. The primary research on *T. altaicus* C.A.Mey's anti-bacterial properties focuses on *in vitro* experiments: it measures the anti-bacterial effect using the MIC and minimum bactericidal concentration (MBC) of different solvent extracts, studying several bacteria, including *S. aureus*, *E. coli*, *B. subtilis*, *P. aeruginosa*, *Proteus*, *S. pneumoniae*, *Aerobacter*, and *Streptococcus mutans*, among others[90,91].

Various solvent extracts of the genus *Trollius* have demonstrated inhibitory effects on *S. mutans*, with the 30% ethanol extract exhibiting the most potent anti-bacterial and anti-biofilm effects. The MIC values of the extracts, including water, 30% ethanol, 60% ethanol, and 90% ethanol, are respectively 25, 25, 12.5, and 25 mg/mL, while the MBC value range lies between 12.5 and 50 mg/mL. The primary mechanism of action of these extracts involves inhibiting bacterial growth and reducing the thickness of the bacterial biofilm[92]. Conversely, the ethanol extract of *T. altaicus* C.A.Mey demonstrates a more potent inhibitory effect against *S. mutans* compared to its water and n-butanol extracts. The 30% ethanol extract of *T. altaicus* C.A.Mey can suppress the growth and biofilm formation of *S. mutans*, as well as its acid production. The MIC and MBC are 12.5 and 25 mg/mL, respectively, revealing a certain degree of dose dependence on its anti-bacterial effect[93,94].

In various the genus *Trollius* species, both phenolic acids and flavonoid active components exhibit anti-bacterial effects. More reports have been published on the anti-bacterial effects of phenolic acids. Li *et al.*[12] isolated a novel phenolic compound along with seven known ones from *T. chinensis* Bunge, testing their inhibitory effects on *Candida albicans*, *E. coli*, *B. subtilis*, *P. aeruginosa*, and *S. aureus*. They discovered that these isolates inhibited one fungus and four types of bacteria, with a MIC ranging from 0.04 to 1.44 mg/mL.

Wu *et al.*[35] isolated three phenolic acid components: proglobeflowery acid (PA), GA, and trolloside (TS) from *Trollius*.

PA blocked both *P. aeruginosa* and *S. aureus*, with an MIC between 16 and 200 mg/L. GA inhibited the influenza virus A, with an IC_{50} value of 42.1 μg/mL. TS was effective against *S. aureus*, with an MIC of 128 mg/L. They found that phenolic acid components from *T. chinensis* Bunge (including PA, GA, and TS) may contribute to the treatment of respiratory infections, pharyngitis, tonsillitis, and bronchitis.

Studies by Jiang *et al.*[95] revealed that the total flavonoid extract derived from Trollius altaicus possessed moderate antibacterial activity against Streptococcus mutans. Wu *et al.*[78] first isolated the phenylpropanoid glycoside 2-(3,4-dihydroxyphenyl) ethanol glucoside from *T. ledebouri* Rchb, which demonstrated impressive anti-bacterial activity against *S. aureus*, with a MIC of 64 μg/mL. Peng *et al.*[33] isolated a veratric acid glucoside from *T. chinensis* Bunge, noted for its anti-inflammatory and anti-bacterial properties. Its inhibitory effect on *S. aureus* and *P. aeruginosa* showed MICs of 256 and 128 μg/mL, respectively. The veratric acid glucoside toxicity was lower than that of pure veratric acid. Research conducted by Wang *et al.*[96] revealed that total flavonoids, orientin, and vitexin from *T. macropetalus* Fr strongly inhibited *S. aureus* and *Staphylococcus epidermidis*. Particularly, vitexin demonstrated the strongest anti-bacterial effect. Therefore, the antimicrobial effect of different species of the genus *Trollius* can be studied in terms of the combined effect of multiple chemical components.

All in all, the genus *Trollius* has a wide antibacterial spectrum. Current research is focused on *in vitro* experiments. Multiple chemical components in the genus *Trollius* work together to reduce the thickness of bacterial biofilms, inhibit the formation of bacterial biofilms, and then inhibit the growth of bacteria, thus exerting antibacterial effects. The antibacterial effect of the genus *Trollius* needs more in-depth research and cannot be limited to *in vitro* levels only.

3.6 Others

The flavonoid components in *T. chinensis* Bunge have antipyretic, and analgesic effects, and are capable of protecting myocardial function and improving cerebral ischemia. Research reports suggest that ferroptosis can trigger intracellular redox imbalance, which in turn leads to cell death. More importantly, ferroptosis represents a form of neuron death in the pathology and developmental process of cerebral ischemia. Thus, inhibiting the onset of ferroptosis could, to some extent, alleviate the damage endured by neurons during cerebral ischemia. There might be potential targets in the pathways related to ferroptosis for the regulation of cerebral ischemia.

Excitatory amino acids (EAA) are acidic free amino acids with two carboxyl groups and one amino group, which include glutamic acid (Glu) and aspartic acid (Asp). During the central nervous system development, EAA's influence varies on the same brain region at different stages. They play a neurotrophic role in the early stage of development and later show a "pro-toxic" effect. Glu is the most abundant, widely distributed, and potent excitatory neurotransmitter in the central nervous system. Hence, inhibiting the excitotoxicity caused by Glu is greatly significant for protecting against ischemic brain injury.

Increasing the SOD activity in ischemia-reperfusion model rats can reduce the contents of ROS and MDA, decrease the volume of cerebral infarction, and enhance nerve function. The protective effect on nerves might be tied to the down-regulation of the TLR-4/NF-κB/TNF-α pathway. By inhibiting the TNF-α pathway, it can promote an increase in the expression of glutamate transporters on the astrocyte membranes. This reduces the massive accumulation of glutamate in the synaptic cleft and protects the neurons of the postsynaptic membrane from damage[97,98].

The total flavonoids in *T. chinensis* Bunge can alleviate myocardial fibrosis by reducing angiotensin (AngII)-induced myocardial fibroblasts and migration. The primary mechanism of action may relate to the down-regulation of miR-215-5p expression and the inhibition of the PI3K/AKT signaling pathway[99]. Through examining the spectrum-effect relationship of different solvent extracts of *T. chinensis* Bunge against hypoxia/reoxygenation injury in myocardial cells, the results indicate that nine components in *T. chinensis* Bunge can protect against hypoxia/reoxygenation injury. These are mainly flavonoid compounds, such as orientin, vitexin, OGA, orientin-2"-*O*-*β*-*D*-pyranoside, quercetin-3-*O*-pyranoside, vitexin-2"-*O*-*β*-*L*-galactoside, hyperoside, vitexin-2"-*O*-*β*-*D*-pyranoside, and 2"-*O*-(2"-methylbutyryl)-orientin[100].

The total flavonoids of *T. chinensis* Bunge exhibit significant effects such as relieving cough, eliminating phlegm, and providing analgesia. They specifically prolong the latent cough period, reduce the frequency of the cough, increase the excretion of phenol red, significantly inhibit mouse auricle swelling, reduce the writhing responses in mice triggered by glacial acetic acid, and enhance the pain threshold of mice[101]. Additionally, *T. chinensis* Bunge flavonoids can substantially reduce the rabbit body temperature in the fever model instigated by *E. coli* endotoxin. They also inhibit the production or release of endogenous pyrogens like TNF-*α* and IL-1*β* incited by endotoxin, therefore restraining the production and release of prostaglandin E2. This results in reducing the abnormally heightened body temperature set point, decreasing heat production, enhancing heat dissipation, and returning body temperature to normal[102]. *T. ledebouri* Rchb has the effects of relieving cough and eliminating phlegm, capable of decreasing the number of citric acid spray-induced coughs in guinea pigs, and increasing the excretion of phenol red in mouse tracheas.

T. ledebouri Rchb can relieve coughs and eliminate phlegm. It can decrease the frequency of citric acid spray-induced coughs in guinea pigs and increase the excretion of phenol red in the trachea of mice[103].

In conclusion, flavonoid components in the genus *Trollius* play roles in antipyretic, analgesic, protecting myocardial function and improving cerebral ischemia. The protective mechanism of the genus *Trollius* on cerebral ischemia may be related to down-regulating the TLR-4/NF-κB/TNF-α pathway, and this mechanism needs further study. Flavonoid compounds such as orientin, vitexin and OGA in the genus *Trollius* exert myocardial protection function, mainly manifested in reducing myocardial fibrosis. The mechanism may be related to down-regulating miR-215-5p expression and inhibiting the PI3K/AKT signaling pathway. Total flavonoids of the genus *Trollius* have antipyretic, analgesic, expectorant and cough-relieving effects. The specific mechanism is still unclear, mainly manifested in reducing the number of coughs in mice, reducing the number of writhing responses, inhibiting auricle swelling in mice and inhibiting the production and release of pyrogens in rabbits.

4 Application and development prospects in food and other industries

The genus *Trollius* possesses a wide range of pharmacological effects including antioxidation, antibacterial, and anticancer

activities. It is non-toxic and without side effects, and there are abundant plant resources. Considering these factors, the genus *Trollius* has extremely broad development prospects in other fields such as food, cosmetics, and cigarettes. The flowers of the genus *Trollius* can be utilized as traditional Chinese medicine beverages and health products. The volatile oil can enhance the aroma of cigarettes. Additionally, some polysaccharides and flavonoids have antioxidant effects, and the related extracts can be employed as cosmetics. Finally, the residue of the genus *Trollius* can serve as an additive for animal feed to help improve the immunity of organisms. Figure 7 is the application prospect roadmap of the genus *Trollius* in different industries.

To ensure the safety of different genus *Trollius* varieties within the genus the genus *Trollius* utilized in cosmetics, food, and health product domains, a thorough understanding of their pharmacodynamic material basis, acute and chronic toxicity, genotoxicity, and pharmacokinetics is crucial. Liu *et al.*[104] identified 49 active chemical components in the genus *Trollius*, including phenolic acids, flavonoids, and alkaloids, *via* the UHPLC-MS method. They revealed the primary components get cleaved, mainly losing hydroxyl groups, carboxyl groups, C_2H_4, neutral H_2O molecules, sugar groups, and glycosidic bonds. Further, Ren *et al.*[105] employing the UPLC-Q-TOF-MS method, identified 14 compounds in the extract of *T. ledebouri* Rchb. This offers technical backing for the quality control and prospective clinical application of drugs, food, and cosmetics containing *T. chinensis* Bunge. and sheds light on its pharmacodynamic material basis.

By using the LC-MS technology, Zhao *et al.*[112] studied the pharmacokinetics of *T. chinensis* Bunge under different administration methods (intravenous injection and oral administration), discerning 58 and 42 metabolites, respectively. They found no significant deviation between oral administration and intravenous injection, which aids in a more profound understanding of metabolic pathways of *T. chinensis* Bunge. Different reactions occur among these metabolites, for example, flavonoids like orientin, orientin-2″-*O*-*β*-*L*-galactoside, vitexin, 2″-*O*-(2″-methylbutyryl) vitexin, and isoquercetin undergo reactions such as oxidation, methylation, sulfate ester binding, and glucuronic acid binding[106].

Liao *et al.*[107] using the UHPLC-Q-TOF-MS/MS method, determined the metabolites of orientin and paeoniflorin, the genus *Trollius*'s active components, and found that their main metabolic reactions involve oxidation, methylation, acetylation, reduction, loss of glucose groups, and glucuronic acid binding reactions. Phenolic acid components in *T. chinensis* Bunge, such as veratric acid and trollioside, undergo sulfation, methylation, glucuronidation, and amino acid binding reactions[108]. Using the LC-MS method, Zhao *et al.*[109] also studied the serum drug chemistry of *T. chinensis* Bunge extract and discovered that alkaloid components undergo methylation, sulfation, glucuronidation, and acetyl binding reactions in the body, alongside heterocyclic ring cleavage reactions.

Related studies have also revealed the distribution of *T. chinensis* Bunge components in rats, including in bile, urine, feces, and the liver[107]. These discoveries not only enhance our understanding of the active constituents of different the genus *Trollius* varieties in the genus *Trollius* but also highlight the significant guiding role that the application of the genus *Trollius* medicinal materials, their preparations, and health products, play in clinical practice.

4.1 Safety assessment of the genus *Trollius*

So far, studies on the toxicity of various genus *Trollius* species have primarily focused on acute toxicity tests, subacute toxicity tests, genotoxicity tests, and subchronic toxicity tests.

An acute toxicity test reported that each mouse was injected with 0.13 mL of *T. chinensis* Bunge injection through the tail vein. Cui *et al.*[110] administered an extract of *T. ledebouri* Rchb twice to KM mice, at a dosage of 10 g/kg·body weight (BW) and 4 h, observing and recording the results for 14 days. The results demonstrated that the mice showed no signs of poisoning, and no obvious abnormalities were detected in their organs. The oral lethal dose 50 (LD_{50}) of the test mice was determined to be >10.0 g/kg BW. According to GB 15193.1–2003, this is categorized as a non-toxic level. Chen *et al.* conducted a preliminary safety evaluation of *T. altaicus* C.A.Mey extract powder (TAEP) following GB 15193.3–2014 *National Food Safety Standard Acute Oral Toxicity Experiment*, administering 10 g/kg TAEP to SPF-grade KM mice. The results showed that weight

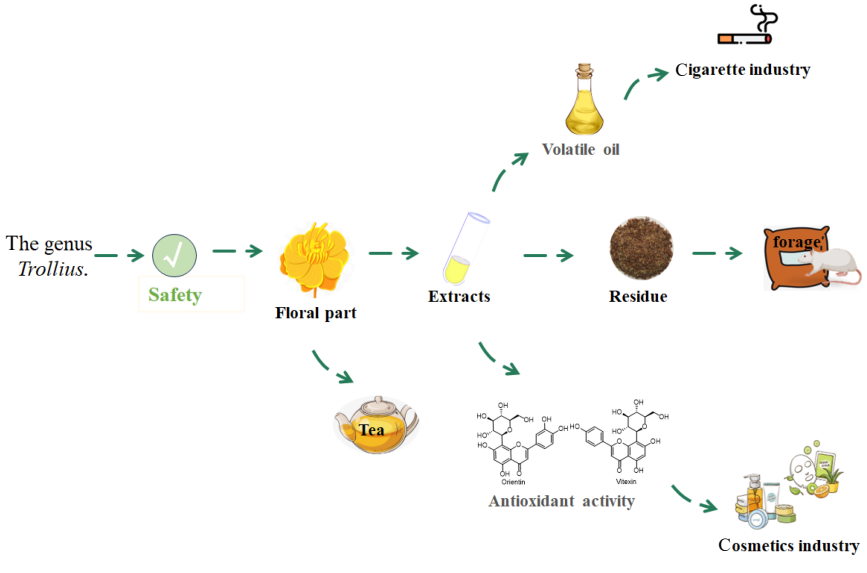


Figure 7 Application prospect roadmap of the genus *Trollius* in different industries.

gain was normal in the mice in the administration group, with no signs of vomiting, drowsiness, or other symptoms of poisoning, and no animals died. Based on these preliminary safety evaluations, it was determined that the acute toxicity grade of TAEP was safe and non-toxic[111]. Zhao *et al.*[112] administered *T. altaicus* C.A.Mey medicine to rats at different dosages (0.2, 0.4, 0.8 g/kg) for 30 days, measured blood biochemical indicators, recorded the rats' weight, their food intake, and the weight of their heart, liver, spleen, and kidney, and calculated the organ coefficient. The results indicated that blood biochemical indicators fell within the normal range in each dosage group, and there were no statistically significant differences in weight, food intake, and organ-body ratio between each group of rats and the control group.

Cui *et al.*[110] evaluated the genotoxicity of *T. ledebouri* Rchb by conducting a bacterial reverse mutation test, a mammalian erythrocyte micronucleus test, and a mouse spermatocyte chromosome aberration test respectively. The results indicated that *T. ledebouri* Rchb did not exhibit a mutagenic effect on TA1535, TA97a, TA98, TA100, and TA1025 histidine-deficient strains of *Salmonella typhimurium*, which was in line with Tang's results[113] from evaluating the genotoxicity of *T. chinensis* Bunge. Also, it did not increase the rate of micronucleated cells in mammalian polychromatic erythrocytes, had no significant impact on the chromosome aberration of mouse spermatocytes, and exhibited neither a teratogenic effect nor cytotoxicity. In addition, Cui *et al.*[110] conducted a teratogenic test. The results showed that pregnant Wistar rats did not display signs of poisoning, did not suffer any effects on their reproductive function, and no fetal skeletal or visceral deformities were observed.

Cui *et al.*[110] incorporated 0.43, 0.85, and 1.70 g/kg BW of *T. ledebouri* Rchb extract into basic feed, based on the standard inclusion rates of Chinese herbal medicine in animal feed (0.25%–1.50% of the diet) and administered the test substance. The dosage for each administration was determined as 8% of the weight of the rat, and the rats were consistently fed this diet for 90 days. The study showed that the SD rats did not exhibit signs of poisoning and showed no deleterious effects on blood routine, blood biochemistry, urine routine, organ weight, organ-body ratio, or other indicators. Given these observations, the researchers concluded *T. ledebouri* Rchb does not cause subchronic toxicity.

Additionally, no adverse reactions were detected in associated *T. chinensis* Bunge preparations. Li *et al.*[114] utilized Meta-analysis to examine the safety of *T. chinensis* Bunge oral liquid in periodontitis treatment. The results demonstrated that there was no statistical significance in the incidence of adverse events between the two patient groups, indicating good safety of the *T. chinensis* Bunge oral liquid. Zheng *et al.*[115] assessed the safety of *T. chinensis* Bunge capsules in treating patients with acute tonsillitis based on the incidence of adverse events and reactions. They evaluated the patients' blood, urine, and stool routine, liver function, kidney function, and electrocardiogram. The results indicated that *T. chinensis* Bunge capsules exhibited no adverse reactions, confirming their good safety.

4.2 Jinlianhua tea

Tea, revered as China's national beverage, boasts a history spanning thousands of years and is widely recognized for its health benefits. Increasingly, tea, as a healthy beverage, is gaining popularity in the marketplace. The genus *Trollius*, renowned for their pleasant aroma, excellent taste, and ornamental value, are now being used to create functional teas. The saying goes, "Drinking two cups of tea is not as good as enjoying three flowers". Concurrently, various types of Trollius are being widely utilized as principal ingredients for health-related beverages, such as the genus *Trollius* Health Beverage, the genus *Trollius* and Licorice Compound Instant Tea, and the genus *Trollius* Throat-soothing Tea Bags, among others.

4.3 The application in the cigarette industry

The genus *Trollius* can also serve as an aroma component in cigarette additives. According to research reports, incorporating 3% of *T. chinensis* Bunge powder into the cigarette tipping adhesive can refine the smoke, decrease impurities, and, to some extent, enhance the aftertaste[116]. In cut tobacco, adding a suitable quantity of *T. chinensis* Bunge volatile oil and *T. chinensis* Bunge glycosides can boost the aroma quality and quantity of CS, while reducing its irritation[44,117,118]. *T. chinensis* Bunge extract enhances and adjusts the smoking taste of single-material tobacco, making the smoke fuller and lessening irritation[119,120].

4.4 The application in the cosmetics industry

Given the toxic hazards posed by synthetic cosmetics to the human body, and their contribution to environmental pollution, attention has shifted toward the utility of Chinese plants. These have been applied both externally and internally for thousands of years and boast numerous records of therapeutic effects, including many verifications of dosage and side effects[121]. Recently, cosmetics containing Chinese herbal medicines experienced a surge in global market demand. Indeed, the National Medical Products Administration revealed in its "Catalog of Cosmetic Raw Materials Already in Use", that out of 8,783 cosmetic raw materials in use, more than 3,000 are derived from Chinese herbal extracts. Well-known brands such as Chando, Winona, Helena Rubinstein, and Chanel, incorporate the anti-oxidant and anti-inflammatory agent, aescin, into their cosmetic formulations[122].

Modern research proposes that Chinese herbal extracts can serve as functional cosmetic raw materials, providing benefits such as acne removal[123], hair blackening, and growth[124], whitening and freckle removal[125], and sun protection[126]. Therefore, developing cosmetics using Chinese herbal components is an increasingly popular trend in both local and international cosmetic research, presenting expansive application prospects and market potential.

To illustrate, Liu *et al.*[127] extracted polysaccharides from *T. chinensis* Bunge flowers and stems and evaluated their moisturizing and anti-oxidant capacities. Findings revealed these polysaccharides to possess a higher moisturizing capability than chitosan and a similar level to sodium hyaluronate, but were less effective than sodium alginate. This moisturizing mechanism hinges on the ability of polar groups in polysaccharides to bind to H_2O in the formation of hydrogen bonds, thus retaining water molecules within the skin.

The anti-oxidant activity of these polysaccharides surpassed other plant-derived polysaccharides such as pumpkin, honeysuckle, and platycodon[127]. Further, *T. altaicus* C.A.Mey, a plant resource from Xinjiang, has seen application in cosmetics for its acne-reducing and soothing effects[128]. An extract from *T. ledebouri* Rchb, as found by Xing *et al.*[129], demonstrated higher DPPH free radical scavenging rates than vitamin E (VE) and could reduce tyrosinase activity in B16-F10 cells, indicating promising applications in whitening and anti-aging cosmetics.

Yang *et al.*[130] developed an anti-aging emollient cream using *T. ledebouri* Rchb as the primary ingredient. The cream's effectiveness was evaluated using a comprehensive method combined with the emollient cream industry standard. Results showed that the home-made cream scored better than matrix cream and commercial cream in short-term moisturizing effect, water-locking effect, anti-aging effect, wrinkle improvement, and sebum thickness increase. This evidence suggests that the genus *Trollius*, as a natural Chinese herbal medicine, possesses the potential to emerge as a future trend in the cosmetics industry.

4.5 Animal feed

Furthermore, the residue from *T. chinensis* Bunge can serve as animal feed. Research indicates that incorporating fermented *T. chinensis* Bunge residue into the feed significantly boosts the body weight and survival rates of broilers, while simultaneously reducing the feed conversion ratio. This effect has a positive correlation with the quantity added. Fermenting *T. chinensis* Bunge residues can also amplify the activity of relevant anti-oxidant enzymes in chicken serum. Moreover, supplementing the feed with fermented *T. chinensis* Bunge residue improves the immune function and disease resilience of non-immunized broilers. Mice that consumed feed with fermented *T. chinensis* Bunge residue exhibited lower mortality rates due to *S. aureus* and *E. coli* infections and showed extended survival times, including under hypoxia. These results suggest that fermented *T. chinensis* Bunge residue can bolster immunity and body resistance[131, 132].

5 Conclusion

Emerging technologies such as molecular biology, bioinformatics, and metabolomics are helping advance phytochemical research on plants from the genus *Trollius* to a more refined and in-depth level. This will allow a more overarching analysis of the genus *Trollius*' chemical constituents, enable the discovery of novel bioactive compounds, and shed light on their biosynthetic pathways and regulatory mechanisms. Moreover, these technologies can provide substantial support for the genus *Trollius*'s pharmacological research, expediting the process of new drug development.

As the mechanisms of the genus *Trollius*'s pharmacological actions continue to be clarified, its clinical applications are poised for further expansion. For instance, in addressing prevalent modern diseases such as inflammatory conditions, infectious diseases, and cardiovascular disorders, the genus *Trollius* or its extracts may exhibit unique therapeutic advantages. Furthermore, with the rise of precision medicine and personalized healthcare concepts, the genus *Trollius*'s application is expected to become more targeted. Tools like genetic sequencing and biomarker detection will aid in offering customized treatment plans for patients.

Regarding medicinal use, the genus *Trollius* can not only serve as a traditional Chinese medicine but can also integrate with modern medications, forming compound formulations or novel drugs. Additionally, its active ingredients can serve as drug precursors or lead compounds, contributing essential resources to the development of new medications. In the culinary realm, the genus *Trollius* can operate as a natural food additive or functional food ingredient, used in the creation of food products that boast anti-oxidant, anti-inflammatory, and immune-boosting properties. Moreover, the genus *Trollius* can be mixed with other ingredients to formulate unique and nutritious food combinations.

Despite the immense potential of the genus *Trollius* in the medical and food industries, its safety and toxicity concerns cannot be overlooked. In the future, it is imperative to reinforce the toxicity assessment and safety research of the genus *Trollius* and its extracts, including experiments on acute toxicity, chronic toxicity, genotoxicity, and reproductive toxicity. Additionally, we must pay attention to the safety and interaction issues of the genus *Trollius* in different populations, such as pregnant women, children, and the elderly. Thorough safety evaluations and toxicological studies will offer a scientific foundation for the rational and safe use of the genus *Trollius*.

In conclusion, the genus *Trollius* holds a promising future boasting diverse applications. By intensifying exploration, fostering technological innovation, expanding clinical applications, personalizing medicine, excavating medicinal and edible benefits, conducting safety and toxicity assessments, as well as promoting industrial development and international collaboration, we can optimize this invaluable resource and notably contribute to the progression of human health.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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