Arabian Journal of Chemistry (2023) **16**, 104638

King Saud University

Arabian Journal of Chemistry

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REVIEW ARTICLE

A comprehensive review of phytochemistry, pharmacology and clinical applications of Uncariae Ramulus Cum Uncis

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Received 23 August 2022; accepted 28 January 2023
Available online 03 February 2023

KEYWORDS

Uncariae Ramulus Cum Uncis;
Phytochemistry;
Pharmacology;
Clinical Applications

Abstract *Objectives:* Uncariae Ramulus Cum Uncis (URCU) belonging to the genus *Uncaria* is widely distributed in China and used in folk medicine, which has the effect of clearing heat and calming the liver, extinguishing wind and settling convulsion. So, it is used to treat hypertension and neurological diseases. Herein, we reported a review on botany, phytochemistry, pharmacology and clinical applications reported from 1973 up to 2022. All the information and studies concerning URCU were summarized from the library and digital databases (e.g. Sciencedirect, SciFinder, Medline PubMed, Google Scholar, and CNKI).

Key findings: A total of 190 articles about URCU have been collected. The phytochemical investigations of URCU revealed the presence of more than 371 chemical components, including alkaloids, terpenoids, flavonoids, phenylpropanoids, phytosterols and phenolics. Moreover, the compounds isolated from URCU possessed a wide spectrum of pharmacology such as anti-hypertension, antiinflammation, anticancer, antioxidant, antiviral, anti-epilepsy, anti-depressant, ischemic brain injury, neuroprotection, anti-Alzheimer's disease, anti-Parkinson's disease and antiasthma.

Summary: In this paper, the botany, phytochemistry, pharmacology and clinical applications of URCU were reviewed. As a source of traditional folk medicine, URCU has high medicinal value and are widely used in medicine. Therefore, we hope our review can help URCU get better development and utilization.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.arabjc.2023.104638

1. Introduction

As a country that has been using herbal medicine to treat diseases since ancient times, China has abundant natural drug resources and experience in clinical application. Uncariae Ramulus Cum Uncis (URCU) was a common Traditional Chinese Medcicine (TCM) used to extinguish wind and settle convulsion (Zhao, 2021; Tang, 2020). In Chinese Pharmacopoeia (2020 edition), URCU is stem and hook of five species from the genus *Uncaria* (Chinese Pharmacopoeia Commission, 2020). The plants of URCU, with rich chemical compositions and pharmacological activities, have been used in Traditional Chinese medicines or folk medicines to treat various diseases, which have become a hot spot for phytochemical studies. Currently, more than 371 compounds have been extracted and identified from URCU including alkaloids (Chi, 2017), terpenoids (Wu et al., 2007), flavonoids (Sun et al., 2012c), phenylpropanoids (Shin and Lee, 2013), phytosterols (Zhang, 2013) and phenolics (Yang, 2018). And alkaloids were major compounds. Meanwhile, several studies showed that the compounds and extracts isolated from URCU possessed a wide spectrum of pharmacology in vivo or in vitro such as anti-hypertension (Li et al., 2020), antiinflammation (Kim et al., 2010), anticancer (Kim et al., 2014), antioxidant (Yin et al., 2010), antiviral (Reis et al., 2008), anti-epilepsy (Tang et al., 2017), anti-depressant (Qiao et al., 2021), ischemic brain injury (Xie et al., 2009), neuroprotection (Lee et al., 2003), anti-Alzheimer's disease (Fu et al., 2014), anti-Parkinson's disease (Li et al., 2017b) and antiasthma (Wang et al., 2019). So, it is necessary to review URCU for better research. In this study, we comprehensively summarized research on botany, phytochemistry, pharmacology and clinical application of URCU (Fig. 1). The extant information on these species allows us to provide a scientific basis for future research studies and to explore the potential therapeutic use.

2. Search strategy

Comprehensive research and analysis of previously published literature were conducted for studies on the botany, phytochemistry, pharmacology and clinical application properties of URCU. The search was conducted using databases such as Sciencedirect, SciFinder, Medline PubMed, Google Scholar, Baidu Scholar, and CNKI by using the keywords such as *Uncaria hirsuta*; *Uncaria macrophylla*; *Uncaria rhynchophylla*; *Uncaria sessilifructus*; *Uncaria sinensis*. Furthermore, part of the analyzed studies was got by a manual search of articles in the reference lists of the included studies. The PRISMA template for determining the list of articles is displayed in Fig. 2. The chemical structures were drawn using ChemDraw Professional 20.0.

3. Botany, Description and Distribution

URCU was a common TCM used to extinguish wind and settle convulsion. According to the herbal textual research of scholars, URCU mainly referred to *Uncaria sinensis* (Oliv.) Havil in the Tang Dynasty. In the Song Dynasty, URCU mainly referred to *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. and *U. sinensis*. While, URCU mainly included *U. sinensis*, *U. rhynchophylla* and *Uncaria sessilifructus* Roxb.. in the Ming Dynasty. Now, *Uncaria hirsuta* Havil. and *Uncaria macrophylla* Wall. are also considered as the source of URCU (Huang et al., 2016). In Chinese Pharmacopoeia (2020 edition), URCU was the stem with hook of five species from

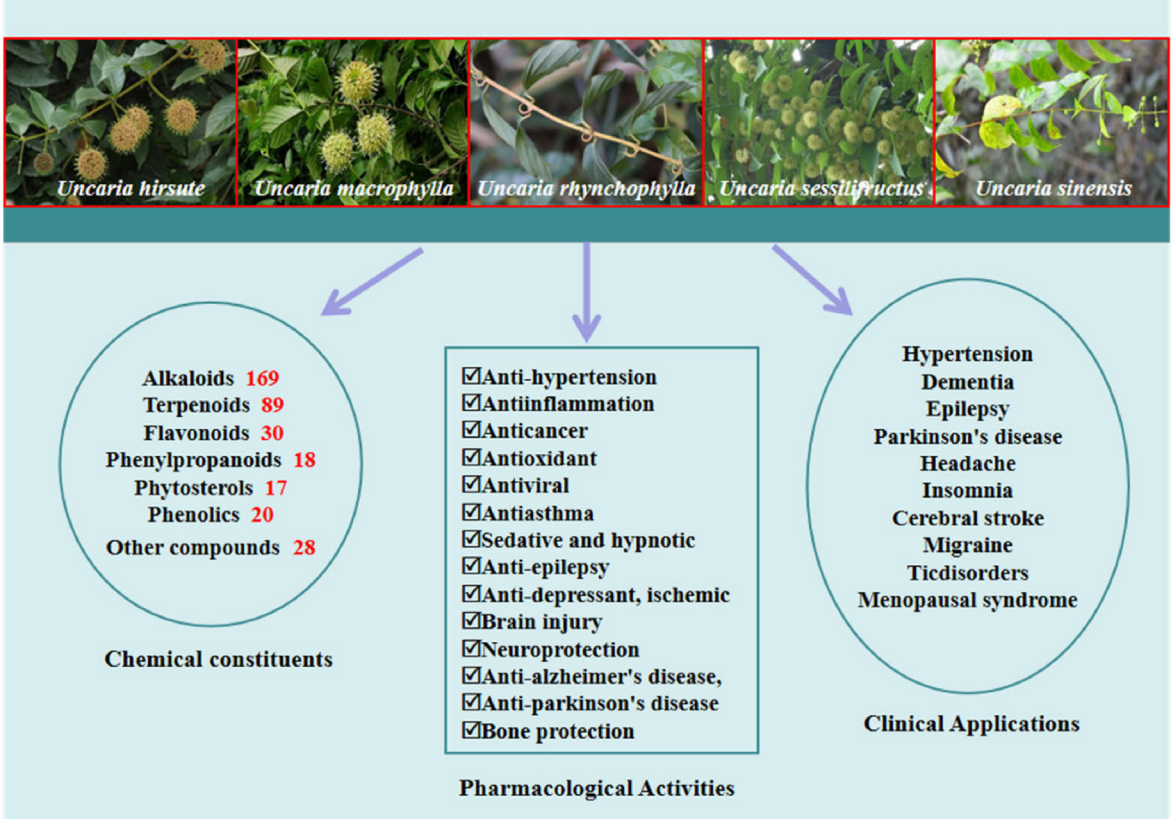

Fig. 1 URCU, chemical constituents, pharmacological activities and clinical applications.

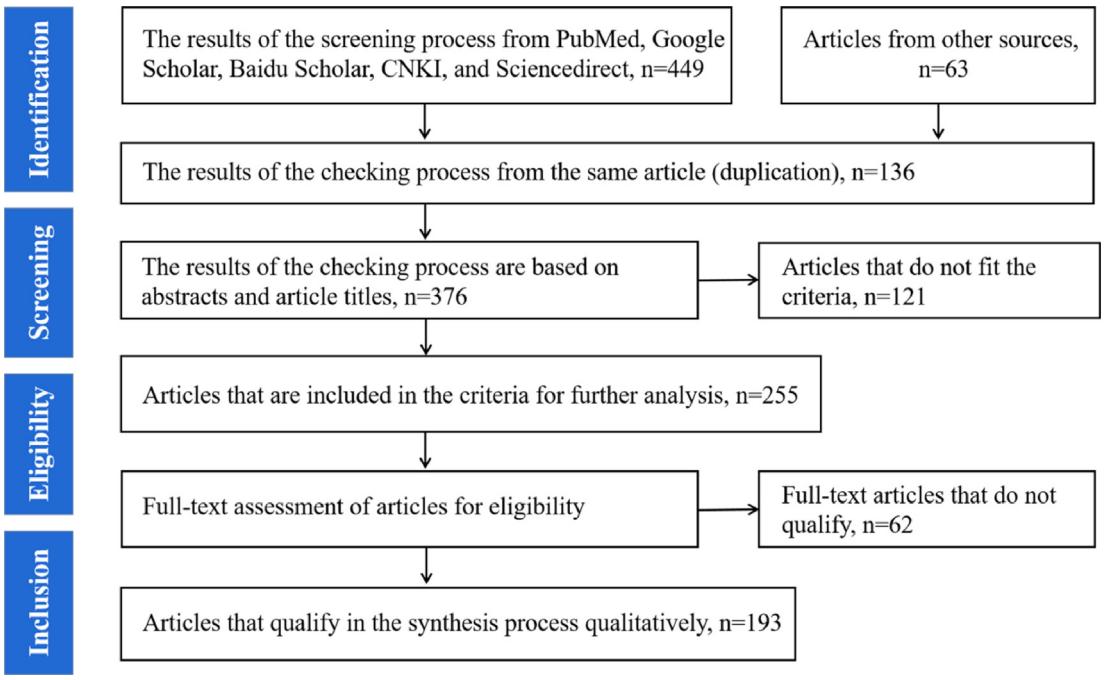

Fig. 2 Research Data Search & Selection Flow.

the genus *Uncaria*, including *U. hirsuta*, *U. macrophylla*, *U. rhynchophylla*, *U. sessilifructus*, *U. sinensis* now (Chinese Pharmacopoeia Commission, 2020).

According to Chinese Flora, the common botanical morphology of URCU is woody vines, tender branches square or cylindrical, glabrous or pubescent, and nutrient laterals often metamorphose into hook prickles. leaves opposite; axils of lateral veins usually have pits; stipules entire or absent, two shallow lobed or two deeply lobed, ventral base or entire surface with mucor hairs. Headlike inflorescences terminal on lateral branches, and sparsely branched as compound umbrella cone inflorescence. Five flowers; the total pedicel has sparse or dense hairs; bracts linear or linear spoon - shaped; calyx tube short, sepal lobes glabrous or densely hairy; corolla disc-shaped or nearly funnel-shaped, glabrous or densely hairy outside, corolla lobes ovately oblong or elliptic; stamens inserted near throat of corolla tube, filaments short; styles extended, stigma spherical or long rod-shaped, verrucous at the top, ovary-two-chambered, placenta at least one third of the upper diaphragm; most ovules. Capsule two-chambered, outer pericarp thick, longitudinally dehiscent, inner pericarp thick bone, dorsally dehiscent; seeds small, mostly, centrally reticulate, with long wings at both ends, two deeply lobed wings below (Uncaria plant in Flora of China @ efloras.org, 2020). The local name, distribution and morphological features of URCU were shown in Table 1.

4. Phytochemistry

To date, about 371 chemical constituents have been isolated from URCU, among which, alkaloids are considered the main constituents. Moreover, other reported secondary metabolites from URCU are terpenoids, flavonoids, phenylpropanoids, phytosterols, phenolics and other compounds.

Table 2 shows all phytochemicals isolated from URCU. The reported phytoconstituents included 169 alkaloids (**1** ∼ **169**), 89 terpenoids (**170** ∼ **258**), 30 flavonoids (**259** ∼ **288**), 18 phenylpropanoids (**287** ∼ **306**), 17 phytosterols (**307** ∼ **323**), 20 phenolics (**324** ∼ **343**), 28 other compounds (**344** ∼ **371**). Each phytochemical has been numbered from (**1** ∼ **371**) and cited in the text. The structures of chemical constituents have been illustrated in Figs. 3-17 according to the chemical classes.

4.1. Alkaloids

Currently, more than 169 alkaloids have been isolated and identified from URCU, among which, indole alkaloids were the main alkaloids. There were 158 indole alkaloids, which included 122 monoterpene indole alkaloids, 13 *β*-carboline alkaloids, 5 cadambine alkaloids, 4 dimeric isoechinulin-type alkaloids and 14 other indole alkaloids. The specific structures of compounds were shown in Figs. 3-9.

4.1.1. Monoterpene indole alkaloids

Monoterpene indole alkaloids are also known as secoiridoid alkaloids, whose basic skeleton is formed by the manish reaction of secologanin and tryptamine. According to the skeleton type and oxidation state, they can be divided into tetracyclic monoterpene indole alkaloids (**1** ∼ **33**), tetracyclic monoterpenes oxidize indoles alkaloids (**34** ∼ **56**), *N*-oxide tetracyclic monoterpene indole alkaloids (**57** ∼ **69**), pentacyclic monoterpene indole alkaloids (**70** ∼ **96**), pentacyclic monoterpenes oxidize indole alkaloids (**97** ∼ **115**), *N*-oxide pentacyclic

Table 1 Local name, distribution and morphological feature of URCU.

Species name	Local name	Distribution	Morphological features
Uncaria hirsuta Havil.	Maogouteng Taiwanfengteng	China (Guangdong, Guangxi, Guizhou, Fujian and Taiwan)	Leaves leathery, densely hard haired below; stipules deeply 2-lobed, lobes ovate; calyx lobes linear oblong, widest near base (Uncaria plant in Flora of China @ efloras.org, 2020).
Uncaria macrophylla Wall.	Dayegouteng	China (Yunnan, Guangxi, Guangdong, Hainan), India, Bhutan, Bangladesh, Myanmar, northern Thailand, Laos and Vietnam	stipules deeply 2-lobed; leaves nearly leathery, ovate or broadly elliptic, 10–16 cm long, 6–12 cm wide (Uncaria plant in Flora of China @ efloras.org, 2020).
Uncaria rhynchophylla (Miq.) Miq. ex Havil.	Gouteng	China (Guangdong, Guangxi, Yunnan, Guizhou, Fujian, Hunan, Hubei and Jiangxi), Japan	corolla ca. 7 mm; reddish brown or dark red under leaves when dry; headed inflorescence regardless of corolla diameter 5–8 mm (Yang et al., 2018).
Uncaria sessilifructus Roxb.	Baigouteng Wubingguogouteng Huaimianwang	China (Guangxi and Yunnan), India, Bangladesh, Bhutan, Myanmar, Nepal, northern Vietnam and Laos	Leaf slightly pink below; calyx lobes oblong, 1 mm long; corolla lobes densely sericeous outside (Chinese Pharmacopoeia Commission, 2020).
Uncaria sinensis (Oliv.) Havil.	Huagouteng	China (Sichuan, Guangxi, Yunnan, Hubei, Guizhou, Hunan, Shaanxi, Gansu)	Stipules entire or absent, broadly triangular or semicircular (Chinese Pharmacopoeia Commission, 2020).

monoterpene indole alkaloids (**116** ~ **122**). The specific structures were shown in Figs. 3-6.

(1) Monoterpene indole alkaloids. 33 tetracyclic monoterpene indole alkaloids (**1** ~ **33**) (Fig. 3) and 27 pentacyclic monoterpene indole alkaloids (**70** ~ **96**) (Fig. 5) were reported from URCU. Tetracyclic monoterpene indole alkaloid's 15-position was mostly α-H and the 20-position mostly had ethylene or ether, which may be related to the secologanin in the synthesis pathway. Pentacyclic monoterpene indole alkaloids mostly formed glycosides at hydroxyl group of 17 or 19-position. Whereas rhynchophylloside J (**93**) formed glycosides at 9-position hydroxyl and rhynchophylloside H (90) formed glycosides at 11 and 17-position hydroxyl groups. In addition, it's worth noting that tetracyclic monoterpene indole alkaloid didn't form glycoside. Uncarrhynchophylline A (**31**) was a monoterpene 22-norindoloquinolizidine alkaloid with a unique ketene unit and uncarrhynchophylline B (**95**) and uncarrhynchophylline C (**96**) were a pair of monoterpene indoloquinolizidinealkaloid epimers possessing an oxygen-bridge between C-3 and C-19 to form an oxazinane ring. Meanwhile, the E-ring is a five-membered lactone ring.

(2) Oxidized monoterpene indole alkaloids. Oxidized monoterpene indole alkaloids are the 2-position oxidation of monoterpene indole alkaloids, which is a typical feature of *Uncaria* alkaloids. At present, 23 tetracyclic monoterpenes oxidize indole alkaloids (**34** ~ **56**) (Fig. 4) and 19 pentacyclic monoterpenes oxidize indole alkaloids (**97** ~ **115**) (Fig. 6) were isolated from URCU. Rhynchophylloside A (**115**) represented a new subtype of oxindole alkaloid with a seven-membered D-ring, rhynchophylloside D (**114**) and E (**112**) were the two oxindole alkaloid diglycosides, which were firstly isolated from the genus *Uncaria*.

(3) N-oxide monoterpene indole alkaloids. *N*-oxide monoterpene indole alkaloids are nitrogen oxides oxidized from N-4 in monoterpene indole alkaloids. 13 *N*-oxide tetracyclic monoterpene indole alkaloids (**57** ~ **69**) and 7 *N*-oxide pentacyclic monoterpene indole alkaloids (**116** ~ **122**) (Fig. 6) were reported in this article.

4.1.2. β-carboline alkaloids

Carboline alkaloid is a kind of alkaloid with a pyridylindole structure, which can be divided into α, β, γ, and δ-carboline according to different cyclization methods. In URCU, all carboline alkaloids were β-carboline alkaloids (**123** ~ **135**) (Fig. 7) and all substitutions occur in C-ring. By observing the structure, we found that most of the substitutions were at 3-position. Meanwhile, some β-carboline alkaloids had secologanin at the 3-position, whose formation might be related to the carbon bond cleavage between the 3 and 21-position of pentacyclic triterpenoids.

4.1.3. Cadambine alkaloids

Cadambine alkaloid is a kind of pentacyclic indole alkaloid, whose D-ring is a heptatomic ring. 5 cadambine alkaloids (**136** ~ **140**) were reported in this article (Fig. 8). Among cadambine alkaloids, the hydroxyl groups at 3 and 21-position of cadambine (**136**) and cadambinic acid (**137**) formed an oxygen bridge.

4.1.4. Dimeric isoechinulin-type alkaloids

(±)-Uncarilin A and (±)-uncarilin B (**141** ~ **144**), two pairs of unusual dimeric isoechinulin-type enantiomers, were isolated from *U. rhynchophylla* (Fig. 8), which contained two characteristic units: indole and diketopiperazine. Geng et al. thought the diketopiperazine core was condensed by "head to tail" cyclization of tryptophan and alanine. Subsequent incorporation of mevalonic acid afforded neoechinulin A, which was transformed to yield compounds **141** ~ **144** via intermolecular [2 + 2] cycloaddition. And, they thought the formation of this kind of compound might be related to the endophytic fungus in *U. rhynchophylla*.

Table 2 Chemical constituents reported from URCU.

No.	Compounds	From	Part	Ref.
1. Alkaloids				
1.1 Indole alkaloids				
1.1.1 Tetracyclic monoterpene indole alkaloids				
1.	hirsutine	U3	*P*1	(Chi, 2017)(Liu, 2021)(Yu et al., 2022)
			*P*2	
		U4	*P*4	
2.	hirsuteine	U3	*P*1	(Guo et al., 2018)(Zhang et al., 2015)(Zhang et al., 2015)
		U5	*P*2	
		U2	*P*6	
3.	*epi*-allo-corynantheine	U3	*P*1	(Zhu et al., 1997)
4.	corynantheidine	U2	*P*4	(Wang et al., 2011a)(Gong, 2021)
		U3	*P*1	
5.	18,19-dihydrocorynantheine dihydrocorynantheine	U2	*P*2	(Liu, 2017)(Wang et al., 2011a)(Yu et al., 2021)(Ma et al., 2009b)(Kong et al., 2017)
			*P*4	
		U3	*P*1	
			*P*2	
			*P*4	
6.	geissoschizine	U3	*P*1	(Gong, 2021)
7.	geissoschizine methyl ether	U3	*P*2	(Liu, 2021)(Chi, 2017)
			*P*1	
			*P*4	(Kong et al., 2017)
8.	villocarine A	U3	*P*2	(Liu, 2021)(Guo et al., 2018)
			*P*1	
9.	corynantheine	U2	*P*2	(Liu, 2017)(Gong, 2021)(Kong et al., 2017)
		U3	*P*1	
			*P*4	
10.	*epi*-allo-corynantheine	U2	*P*2	(Liu, 2017)
	(3-ethenyl-1,2,3,4,6,7,12,12b-octahydro-α-(methoxymethylene)-methyl ester)	U3	*P*1	(Gong, 2021)
11.	uncanidine K	U4	*P*1	(Yu et al., 2022)
12.	17-*O*-ethylhirsutine	U4	*P*1	(Yu et al., 2022)
13.	*Z*-geissoschizine	U3	*P*1	(Yu et al., 2021)
14.	uncarialin A	U3	*P*1	(Liang et al., 2019)
15.	indole [23-a] quinolizine-a-acetic acid	U3	*P*4	(Kong et al., 2017)(Gong, 2021)
			1P1	
16.	*O*-(17)-demethyldihydrocorynantheine 19,20-dihydroisositsirkine	U3	*P*2	(Kong et al., 2017)(Gong, 2021)
			*P*1	
17.	dihydrositsirikine	U3	*P*2	(Liu, 2021)
18.	sitsirikine	U2	*P*2	(Liu, 2017)(Guo et al., 2019)
		U3	*P*1	
19.	uncarialin E	U3	*P*1	(Liang et al., 2019)
20.	uncarialin F	U3	*P*1	(Liang et al., 2019)
21.	uncarialin G	U3	*P*1	(Liang et al., 2019)
22.	uncarialin H	U3	*P*1	(Liang et al., 2019)
23.	uncarialin K	U3	*P*1	(Yu et al., 2021)
24.	17-*O*-methyl-3,4,5,6-tetradehydrogeissoschizine	U3	*P*4	(Kong et al., 2017)
25.	rhynchophyllionium A	U3	*P*1	(Guo et al., 2018)
26.	rhynchophyllionium B	U3	*P*1	(Guo et al., 2018)
27.	rhynchophyllionium C	U3	*P*1	(Guo et al., 2018)
28.	rhynchophyllionium D	U3	*P*1	(Guo et al., 2018)
29.	vallesiachotamine	U3	*P*2	(Aimi et al., 1982)(Kong et al., 2017)
			*P*4	
30.	uncarialin C	U3	*P*1	(Liang et al., 2019)
31.	uncarrhynchophylline A	U3	*P*1	(Li et al., 2021c)
32.	16*R*-E-Isositsirikine	U3	*P*1	(Gong, 2021)
33.	E-geissoschizine methyl ether	U3	*P*1	(Gong, 2021)

(*continued on next page*)

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
1.1.2 Tetracyclic monoterpenes oxidize indoles alkaloids				
34.	rhynchophylline	U2	*P*4	(Wang et al., 2011a)(Phillipson and Hemingway, 1973)(Li et al., 2010)(Liu, 2021)(Liang et al., 2019)(Chi, 2017)(Liu et al., 1993b)(Xin et al., 2008b)
			*P*2	
			*P*6	
		U3	*P*2	
			*P*1	
		U4	*P*1	
		U5	*P*1	
		U1	*P*2	
35.	corynoxinic B	U3	*P*1	(Gong, 2021)
36.	corynoxine B	U2	*P*4	(Wang et al., 2011a)(Phillipson and Hemingway, 1973)
			*P*2	(Gong, 2021)
		U3	*P*1	
37.	corynoxeine	U2	*P*1	(Liu, 2017)(Liu, 2021)(Chi, 2017)(Yu et al., 2021)
			*P*2	
		U3	*P*2	
			*P*1	
38.	9-hydroxy corynoxeine	U3	*P*1	(Xie et al., 2013)
39.	18,19-dehydrocorynoxinic acid	U3	*P*1	(Xie et al., 2013)
40.	isocorynoxeine	U2	*P*2	(Liu, 2017)(Wu et al., 2015)(Aimi et al., 1982)
		U3	*P*1	
			*P*2	
41.	macrophylline A	U2	*P*4	(Wang et al., 2011a)
42.	rhynchophylloside B	U3	*P*1	(Guo et al., 2019)
43.	rhynchophyllic acid	U5	*P*1	(Liu and Feng, 1993)(Gong, 2021)
		U3	*P*1	
44.	isorhynchophylline	U2	*P*2	(Phillipson and Hemingway, 1973)
			*P*4	(Wang et al., 2011a)(Liang et al., 2021)(Li et al., 2010)(Liu, 2021)(Liang et al., 2019)(Liu et al., 1993b)(Xin et al., 2008b)
			*P*3	
			*P*6	
		U3	*P*2	
			*P*1	
		U4	*P*2	
		U1	*P*2	
45.	corynoxine	U2	*P*4	(Wang et al., 2011a)(Liang et al., 2021)
			*P*3	(Phillipson and Hemingway, 1973)(Wu et al., 2007)(Xin et al., 2008b)
		U4	*P*2	
		U3	*P*1	
		U1	*P*2	
46.	isocorynoxine	U2	*P*1	(Zhang et al., 2015)(Zhang et al., 2015)
		U3	*P*2	
47.	9-hydroxy isocorynoxeine	U3	*P*1	(Xie et al., 2013)
48.	18,19-dehydrocorynoxinic acid B	U3	*P*1	(Xie et al., 2013)
49.	22-*O*-demethyl-22-*O*-*β*-D-glucopynosylisocorynoxeine	U3	*P*2	(Ma et al., 2009b)
50.	isorhynchophyllic acid	U3	*P*1	(Chi, 2017)(Liu and Feng, 1993)
		U5	*P*1	
51.	macrophylline B	U2	*P*4	(Wang et al., 2011a)
52.	macrophylline C	U2	*P*3	(Liang et al., 2021)
53.	macrophylline D	U2	*P*3	(Liang et al., 2021)
54.	uncarialin J	U3	*P*1	(Yu et al., 2021)
55.	5-oxo-isorhynchophylline	U3	*P*1	(Yu et al., 2021)
56.	macrophyllianium	U2	*P*4	(Wang et al., 2011a)
1.1.3 *N*-oxide tetracyclic monoterpene indole alkaloids				
57.	hirsuteine *N*-oxide	U3	*P*1	(Guo et al., 2018)
58.	geissoschizine *N*-oxide methylether	U3	*P*2	(Liu, 2021)(Liang et al., 2019)
			*P*1	
59.	uncarialin M	U3	*P*1	(Yu et al., 2021)
60.	uncarialin B	U3	*P*1	(Liang et al., 2019)
61.	hirsutine *N*-oxide	U3	*P*4	(Kong et al., 2017)(Liang et al., 2019)
			*P*1	
62.	uncarrhynchophylline D	U3	*P*1	(Li et al., 2021c)

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
63.	uncarrhynchophylline E	U3	*P*1	(Li et al., 2021c)
64.	uncarialin I	U3	*P*1	(Liang et al., 2019)
65.	16-*epi*-isositsirikine (3*S*,4*S*)-*N*-oxide	U3	*P*1	(Liang et al., 2019)
66.	rhynchophylline *N*-oxide	U3	*P*2	(Ma et al., 2009b)(Liu et al., 1993b)
		U5	*P*1	
67.	corynoxeine *N*-oxide	U3	*P*2	(Liu, 2021)
68.	isorhynchophylline *N*-oxide	U3	*P*2	(Ma et al., 2009b)(Liu et al., 1993b)
		U5	*P*1	
69.	isocorynoxeine *N*-oxide	U3	*P*2	(Ma et al., 2009b)
1.1.4 Pentacyclic monoterpene indole alkaloids				
70.	3-*iso*-19-*epi*-ajmalicine	U1	*P*2	(Xin et al., 2008b)
71.	akuammigine	U3	*P*1	(Guo et al., 2018)
72.	3-isoajmallicine	U1	*P*2	(Xin et al., 2008b)
73.	3*β*-isodihydrocadambine	U5	*P*1	(Zhang et al., 2015)
74.	3-isoajmalicine	U2	*P*2	(Liu, 2017)
75.	rhynchophylloside I	U3	*P*1	(Guo et al., 2019)
76.	tetrahydroalstonine	U4	*P*1	(Yu et al., 2022)
		U3	*P*1	(Liang et al., 2019)(Liu et al., 1993b)
		U5	*P*1	
77.	akuammigine	U4	*P*1	(Yu et al., 2022)(Gong, 2021)
		U3	*P*1	
78.	vincoside lactam (vincosamide)	U3	*P*2	(Liu, 2021)(Xin et al., 2009a)
			*P*1	
79.	rhynchophylloside F	U3	*P*1	(Guo et al., 2019)
80.	rhynchophylloside G	U3	*P*1	(Guo et al., 2019)
81.	2′-*O*-*β*-D-glucopyranosyl-11-hydroxyvincoside lactum	U3	*P*2	(Ma et al., 2009b)
82.	strictosamide	U3	*P*2	(Liu, 2021)(Wu et al., 2015)
			*P*1	
83.	rhynchophine	U3	*P*2	(Aimi et al., 1982)
84.	rubescine	U3	*P*2	(Aimi et al., 1982)
85.	angustine	U3	*P*2	(Zhang et al., 2015)
86.	angustidine	U3	*P*2	(Zhang et al., 2015)
87.	(+)-(19*S*)-angustoline	U3	*P*2	(Zhang et al., 2015)
88.	*β*-yohimbine	U1	*P*2	(Kam et al., 1992)
89.	uncanidine J	U4	*P*1	(Yu et al., 2022)
90.	rhynchophylloside H	U3	*P*1	(Guo et al., 2019)
91.	vincosamide A	U3	*P*2	(Li, 2017)
92.	uncarialin L	U3	*P*1	(Yu et al., 2021)
93.	rhynchophylloside J	U3	*P*1	(Guo et al., 2019)
94.	α-yohimbine	U1	*P*2	(Kam et al., 1992)
95.	uncarrhynchophylline B	U3	*P*1	(Li et al., 2021c)
96.	uncarrhynchophylline C	U3	*P*1	(Li et al., 2021c)
1.1.5 Pentacyclic monoterpenes oxidize indole alkaloids				
97.	uncarine F	U4	*P*2	(Zhang et al., 2015)
98.	uncarine B	U1	*P*2	(Xin et al., 2008b)(Liu, 2017)
		U2	*P*2	
99.	uncarine C (pteropodine)	U5	*P*1	(Liu et al., 1993b)(Gong, 2021)
		U3	*P*1	
100.	pteropodic acid	U5	*P*3	(Liu and Feng, 1993)
101.	mitraphylline	U1	*P*2,	(Xin et al., 2008b)(Zhang, 2013)(Liu et al., 1993b)(Gong, 2021)
		U4	*P*1	
		U5	*P*1	
		U3	*P*1	
102.	mitraphyllic acid	U5	*P*2	(Liu et al., 1993a)(Liu and Feng, 1993)
			*P*1	
103.	mitraphyllic acid (16–1)-*β*-D-glucopyranosylester	U5	*P*2	(Liu et al., 1993a)
104.	uncarine D	U5	*P*2	(Zhang et al., 2015)
105.	uncarine A (isoformosanine)	U1	*P*2	(Xin et al., 2008b)
			*P*1	(Lin et al., 2020)(Liu et al., 1993b)
		U5	*P*1	
106.	isopteropodic acid	U5	*P*1	(Liu and Feng, 1993)
107.	isomitraphylline	U1	*P*2	(Xin et al., 2008b)(Zhang, 2013)(Gong, 2021)
		U4	*P*1	
		U3	*P*1	

(*continued on next page*)

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
108.	isomitraphyllic acid	U5	*P*2	(Liu et al., 1993a)(Xin et al., 2008b)
		U1	*P*2	
109.	uncaric acid A	U1	*P*2	(Xin et al., 2008c)
110.	isomitraphyllic acid (16–1)-*β*-D-glucopyranosyl ester	U5	*P*2	(Liu et al., 1993a)
111.	uncarine E	U3	*P*1	(Gong, 2021)(Liu et al., 1993b)
	(isopteropodine)	U5	*P*1	
112.	rhynchophylloside E	U3	*P*1	(Guo et al., 2019)
113.	rhynchophylloside C	U3	*P*1	(Guo et al., 2019)
114.	rhynchophylloside D	U3	*P*1	(Guo et al., 2019)
115.	rhynchophylloside A	U3	*P*1	(Guo et al., 2019)
1.1.6 *N*-oxide pentacyclic monoterpene indole alkaloids				
116.	uncarine D *N*-oxide	U5	*P*2	(Zhang et al., 2015)
117.	uncarine E *N*-oxide	U5	*P*2	(Zhang et al., 2015)
118.	isomitraphylline *N*-oxide	U1	*P*2	(Zhang et al., 2015)(Zhang, 2013)
		U4	*P*1	
119.	uncarine B *N*-oxide	U1	*P*1	(Pan et al., 2017)
120.	uncarine F *N*-oxide	U5	*P*2	(Zhang et al., 2015)
121.	mitraphylline *N*-oxide	U1	*P*2	(Zhang et al., 2015)
		U4	*P*2	(Zhang et al., 2015)(Liu et al., 1993b)
		U5	*P*1	
122.	uncarine C *N*-oxide	U5	*P*2	(Zhang et al., 2015)(Liu et al., 1993b)
			*P*1	
1.1.7 *β*-carboline alkaloids				
123.	bahienoside A	U1	*P*2	(Xin et al., 2011)
124.	bahienoside B	U1	*P*2	(Xin et al., 2011)
125.	hirsutaside D	U1	*P*2	(Xin et al., 2011)
126.	neonaucleoside B	U1	*P*2	(Xin et al., 2011)
127.	vincoside	U3	*P*2	(Aimi et al., 1982)
128.	strictosidine	U3	*P*2	(Ma et al., 2009b)
129.	hirsutaside A	U1	*P*2	(Xin et al., 2008c)
130.	5*β*-carboxystrictosidine	U1	*P*1	(Lin et al., 2020)
131.	indol[2,3-*a*]quinolizidine	U3	*P*2	(Liu, 2021)
132.	1,2,3,4-tetrahydro-1-oxo-*β*-carboline (*β*-carboline alkaloid)	U3	*P*1	(Cai et al., 2019)
133.	harmane	U1	*P*2	(Xin et al., 2008b)(Chi, 2017)
		U3	*P*1	
134.	croceaine B	U3	*P*2	(Liu, 2021)
135.	4*β*-hydroxyisodolichantoside	U3	*P*2	(Liu, 2021)
1.1.8 Cadambine alkaloids				
136.	cadambine	U3	*P*1	(Chi, 2017)(Endo et al., 1983)
		U5	*P*1	
137.	cadambinic acid	U3	*P*2	(Liu, 2021)
138.	3*α*-dihydrocadambine	U3	*P*1	(Wu et al., 2015)(Endo et al., 1983)
		U5	*P*1	
139.	3*β*-dihydrocadambine	U5	*P*1	(Endo et al., 1983)
140.	3*β*-isodihydrocadambine	U5	*P*1	(Endo et al., 1983)
1.1.9 Dimeric isoechinulin-type alkaloids				
141.	(+)-uncarilin A	U3	*P*1	(Geng et al., 2017)
142.	(+)-uncarilin B	U3	*P*1	(Geng et al., 2017)
143.	(-)-uncarilin B	U3	*P*1	(Geng et al., 2017)
144.	(-)-uncarilin A	U3	*P*1	(Geng et al., 2017)
1.1.10 Other indole alkaloids				
145.	(+)-(7*R*)-3-oxo-7-hydroxy-3,7-seco-dihydrorhynchohylline	U3	*P*1	(Cai et al., 2019)
146.	(+)-(7*S*)-3-oxo-7-hydroxy-3,7-seco-dihydrorhyncho-hylline	U3	*P*1	(Cai et al., 2019)
147.	(+)-(7*R*)-3-oxo-7-hydroxy-3,7-seco-rhynchohylline	U3	*P*1	(Cai et al., 2019)
148.	(+)-(7*S*)-3-oxo-7-hydroxy-3,7-seco-rhynchohylline	U3	*P*1	(Cai et al., 2019)
149.	hirsutanine D	U1	*P*1	(Pan et al., 2017)
150.	hirsutanine E	U1	*P*1	(Pan et al., 2017)
151.	rhynchine A	U3	*P*1	(Zhou et al., 2021)
152.	rhynchine B	U3	*P*1	(Zhou et al., 2021)
153.	rhynchine C	U3	*P*1	(Zhou et al., 2021)
154.	rhynchine D	U3	*P*1	(Zhou et al., 2021)
155.	rhynchine E	U3	*P*1	(Zhou et al., 2021)
156.	salacin	U5	*P*2	(Zhang et al., 2015)

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
157.	uncarialin D	U3	*P*1	(Liang et al., 2019)
158.	uncanidine A	U3	*P*1	(Zhang et al., 2020)
1.2 Other alkaloids				
159.	hirsutanine A	U1	*P*4	(Jia et al., 2014)
160.	hirsutanine B	U1	*P*4	(Jia et al., 2014)
161.	hirsutanine C	U1	*P*4	(Jia et al., 2014)
162.	hirsutanine F	U1	*P*1	(Pan et al., 2017)
163.	protopine	U3	*P*1	(Wu et al., 2015)
164.	venoterpine	U3	*P*1	(Yuan, 2022)
165.	(-)-*N*-methylcytisine	U3	*P*1	(Yuan, 2022)
166.	rhynchophylloside K	U3	*P*1	(Guo et al., 2019)
167.	rhynchophylloside L	U3	*P*1	(Guo et al., 2019)
168.	uncarrhynchoside A	U3	*P*1	(Li et al., 2021c)
169.	uncarrhynchoside B	U3	*P*1	(Li et al., 2021c)
2. Terpenoids				
2.1 Triterpenoids				
2.1.1 Ursane type triterpenoids				
170.	ursolic acid	U2	*P*1	(Wu et al., 2007)(Yang, 2018)(Li et al., 2010)(Liu, 2021)
			*P*3	(Chi, 2017)(Zhang, 2013)(Chen et al., 2014b)
			*P*6	
		U3	*P*2	
			*P*1	
		U4	*P*1	
		U5	*P*1	
171.	ursolic aldehyde	U5	*P*1	(Liu et al., 2011)
172.	α-amyrin acetate	U2	*P*1	(Wu et al., 2007)
173.	6*β*-hydroxyursolic acid	U3	*P*2	(Ma et al., 2009a)
174.	3*β*,6*β*,23-trihydroxyurs-12-en-28-oic acid	U2	*P*1	(Wei et al., 2015)(Ma et al., 2009a)
		U3	*P*2	
175.	3*β*-hydroxyurs-12-en-27,28-diolic acid	U3	*P*1	(Deng et al., 2009)(Wu et al., 2007)
		U2	*P*1	
176.	uncarinic acid C	U3	*P*1	(Yoshioka et al., 2016)
177.	uncarinic acid D	U3	*P*1	(Lee et al., 2000)
178.	quinovic acid	U1	*P*2	(Xin et al., 2009b)(Wei et al., 2015)(Zhang, 2013)(Chen et al., 2014b)
		U2	*P*3	
		U4	*P*1	
		U5	*P*1	
179.	3-*O*-[*β*-D-glucopyranosy1]-quinovic acid	U4	*P*1	(Zhang, 2013)(Wei et al., 2015)
		U2	*P*3	
180.	quinovic acid-3-*O*-*β*-D-fucopyranoside	U5	*P*1	(Chen et al., 2014b)(Wei et al., 2015)
		U2	*P*3	(Fan et al., 2022)(Zhang, 2014)
		U4	*P*3	
			*P*1	
181.	quinovic acid-3-*O*-*β*-D-glucopyranoide (28 → 1)-*β*-D-glucopyranoside	U5	*P*1	(Chen et al., 2014b)
182.	3-*O*-[*β*-D-quinovpyanosyl]-quinovic acid	U4	*P*1	(Zhang, 2013)
183.	3*β*,6*β*-dihydroxy-urs-12-en-28-oic acid	U3	*P*1	(Wei et al., 2015)
184.	3*β*-hydroxy-27-*p*-(*Z*)-coumaroyloxyursan-12-en-28-oic acid	U3	*P*1	(Lee et al., 2000)
185.	3*β*-hydroxy-27-*p*-(*E*)-coumaroyloxyursan-12-en-28-oic acid	U3	*P*1	(Zhang et al., 2014)
186.	3*β*,27-dihydroxy-urs-12-en-28-oic acid	U3	*P*1	(Zhang et al., 2014)
187.	2α-hydroxyursolic acid	U2	*P*3	(Yang, 2018)
188.	quinovic acid-3-*β*-*O*-*β*-6-deoxy-D-rhamnoside	U4	*P*1	(Zhang, 2014)
189.	3*β*,6*β*,19α,23,27-pentahydroxyures-12-en-28-oci acid	U4	*P*1	(Zhang, 2014)
190.	22α-hydroxy-3-oxo-urs-12-en-27,28-diolic acid	U1	*P*2	(Xin et al., 2009b)
191.	6*β*,19α-dihydroxy-3-oxo-urs-12-en-28-oic acid	U3	*P*1	(Deng et al., 2009)(Wei et al., 2015)
		U2	*P*3	
192.	2-oxopomolic acid	U4	*P*1	(Zhang, 2014)
193.	3*β*,6*β*,19α-trihydroxyurs-12-en-28-oic acid	U2	*P*3	(Sun et al., 2012a)(Deng et al., 2009)
		U3	*P*1	
		U4	*P*1	(Zhang, 2013)
194.	3*β*,6*β*,19α-trihydroxy-23-oxo-urs-12-en-28-oic acid	U2	P5	(Sun et al., 2012b)(Zhang et al., 2014)(Zhang, 2013)
		U3	*P*1	
		U4	*P*1	

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Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
195.	3*β*,6*β*,19*α*-trihydroxy-urs-12-en-28-oicacid-24-carboxylicacidmethyl ester	U2	P5	(Sun et al., 2012a)
		U4	*P*3	(Fan et al., 2022)(Zhang, 2014)
			*P*1	
196.	3*β*,6β,19*α*-trihydroxy-23-methoxycarbonyl -urs-12-en-28-oic acid	U3	*P*1	(Zhang et al., 2014)
197.	uncarinic acid H	U3	*P*1	(Zhang et al., 2014)
198.	pomolic acid	U2	*P*3	(Wei et al., 2015)
199.	3*β*,6*β*,19*α*,23-tetrahydroxy-urs-12-en-28-oic acid	U4	*P*1	(Zhang, 2013)(Wei et al., 2015)
		U2	*P*3	
200.	24-dimethoxymethyl-3*β*,6*β*,19*α*-trihydroxy −12-en-28-oic acid	U4	*P*3	(Fan et al., 2022)
201.	3*β*,6*β*,19*α*,24-tetrahydroxyurs-12-en-28-oic acid	U3	*P*1	(Deng et al., 2009)
		U4	*P*1	(Zhang, 2014)
202.	3*β*,19*α*,24-trihydroxyurs-12-en-28-oic acid	U3	*P*1	(Deng et al., 2009)
203.	3*β*,6*β*,19*α*-trihydroxyurs-23-o-12-en-28-oic acid	U3	*P*1	(Deng et al., 2009)
204.	rotundic acid	U4	*P*1	(Zhang, 2014)
205.	uncarinic acid I	U3	*P*1	(Zhang et al., 2014)
206.	uncarisaside A ((3*β*)-3-(*β*-D-glucopyranosyloxy)-12-oxopyroquinovic acid *β*-D-glucopyranosyl ester)	U1	*P*2	(Xin et al., 2009b)
207.	ursolic acid lactone	U3	*P*2	(Li, 2017)
208.	3*β*,6*β*-dihydroxy-urs-12,18-dien-28-oic acid	U2	*P*3	(Wei et al., 2015)
209.	uncargenin D	U2	*P*3	(Wei et al., 2015)
210.	uncarinic acid N	U3	*P*1	(Li et al., 2021b)
211.	uncarinic acid O	U3	*P*1	(Li et al., 2021b)
212.	uncarinic acid P	U3	*P*1	(Li et al., 2021b)
2.1.2 Oleanane type triterpenoids				
213.	oleanoic acid	U2	*P*3	(Yang, 2018)(Chi, 2017)(Chen et al., 2014b)
		U3	*P*1	
		U5	*P*1	
214.	uncarinic acid A	U3	*P*1	(Lee et al., 1999)
215.	uncarinic acid B	U3	*P*1	(Lee et al., 1999)
216.	uncarinic acid E	U3	*P*1	(Lee et al., 2000)
217.	3*β*-hydroxy-27-*p*-(*E*)-coumaroyloxyolean-12-en-28-oic acid	U3	*P*1	(Zhang et al., 2014)
218.	3*β*,6*β*-dihydroxy-olean-12-en-28-oic acid	U2	*P*3	(Wei et al., 2015)
219.	hederagenin	U2	*P*3	(Wei et al., 2015)
		U1	*P*2	(Liu et al., 2021)
220.	3*β*,6*β*,23-trihydroxy-olean-12-en-28-oic acid	U2	*P*3	(Wei et al., 2015)(Zhang, 2014)
		U4	*P*1	
221.	cincholic acid 3*β*-*O*-*β*-D-fucopyranoside	U4	*P*3	(Fan et al., 2022)
			*P*1	(Zhang, 2014)
222.	*β*-amyrin-3-palmitate	U3	*P*2	(Liu, 2021)
223.	*β*-amnyrenol	U3	*P*1	(Chi, 2017)
224.	uncarinic acid F	U3	*P*1	(Zhang et al., 2014)
225.	uncarinic acid G	U3	*P*1	(Zhang et al., 2014)
226.	uncarinic acid J	U3	*P*1	(Zhang et al., 2014)
227.	3*β*,6*β*,19*α*-trihydroxy-olean-12-en-28-oic acid	U2	*P*3	(Wei et al., 2015)
228.	3*β*,6*β*,19*α*,23-tetrahydroxy-olean-12-en-28-oic acid	U2	*P*3	(Wei et al., 2015)
229.	phytolaccoside A	U5	*P*1	(Liu et al., 2011)
230.	sumresinolic acid	U3	*P*1	(Deng et al., 2009)
231.	uncargenin C	U3	*P*1	(Deng et al., 2009)
232.	3-oxo-olean-12-en-28-oic acid	U3	*P*1	(Shin and Lee, 2013)
233.	uncarinic acid M	U3	*P*1	(Li et al., 2021b)
234.	3*β*,19*α*,23-trihydroxy-6-oxo-olean-12-en-28-oic acid	U4	*P*3	(Fan et al., 2022)(Deng et al., 2009)
		U3	*P*1	
235.	uncarilic acid	U4	*P*1	(Zhang, 2013)
236.	uncarinic acid L	U3	*P*1	(Li et al., 2021b)
237.	pyrocincholic acid	U1	*P*2	(Xin et al., 2009b)
238.	pyrocincholic acid ethyl ether	U1	*P*2	(Xin et al., 2009b)
239.	(3*β*)-3-(*β*-D-quinovopyranosyloxy)-pyrocincholic acid-*β*-D-glucopyranosyl ester	U1	*P*2	(Xin et al., 2009b)
240.	(3*β*)-hydroxy-27-norolean-13 (28)-lactone	U1	*P*2	(Xin et al., 2009b)
241.	3*β*,23-dihydroxy-12-oxo-olean-28,13*β*-olide	U2	*P*3	(Wei et al., 2015)

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
242.	secouncarilic acid	U4	*P*1	(Zhang, 2013)
243.	taraxerol	U2	*P*3	(Wei et al., 2015)(Li et al., 2010)
			*P*6	
244.	uncarinic acid K	U3	*P*1	(Li et al., 2021b)
245.	myricadoil	U2	*P*6	(Li et al., 2010)
246.	friedelin	U4	*P*1	(Zhang, 2013)
2.1.3 Lupeol type triterpenoids				
247.	obtusalin	U4	*P*1	(Zhang, 2013)
248.	betulin	U4	*P*1	(Zhang, 2013)
249.	lupenone	U2	*P*3	(Yang, 2018)
2.1.4 Cycloartenone				
250.	24-en-cycloartenone	U4	*P*1	(Zhang, 2013)
2.1.5 Squalene				
251.	squalene	U4	*P*1	(Zhang, 2013)
2.2 Sesquiterpenes				
2.2.1 Megastigmanes				
252.	uncarphyllonone A	U3	*P*1	(Song et al., 2022)
253.	uncarphyllonol A	U3	*P*1	(Song et al., 2022)
254.	uncarphyllonol B	U3	*P*1	(Song et al., 2022)
255.	uncarphabscisic acid A	U3	*P*1	(Song et al., 2022)
256.	uncarphabscisic acid B	U3	*P*1	(Song et al., 2022)
257.	(6*R*,9*R*) −9-hydroxymegastigman-4-en-3-one	U1	*P*2	(Liu et al., 2021)
2.2.2 Azulenoid				
258.	(-)-alloaromadendrene	U4	*P*1	(Zhang, 2013)
2.3 Flavonoids				
2.3.1 Flavonols				
259.	kaempferol	U5	*P*1	(Sun et al., 2012c)(Zhang et al., 2022)(Xin et al., 2008a)
		U3	*P*3	
		U1	*P*2	
260.	quercetin	U5	*P*1	(Sun et al., 2012c)(Chi, 2017)(Liu, 2021)(Liu, 2017)(Xin et al., 2008a)
		U3	*P*1	
			*P*2	
		U2	*P*2	
		U1	*P*2	
261.	trifolin	U3	*P*2	(Aimi et al., 1982)
262.	hyperin (quercetin-3-*O*-*β*-D-galactopyranoside)	U1	*P*1	(Xin et al., 2008a)(Huang et al., 2019)(Chi, 2017)(Sun et al., 2012c)
		U3	*P*2	
			*P*1	
		U5	*P*1	
263.	quercitrin	U1	*P*2	(Xin et al., 2008a)(Li et al., 2017a)
		U3	*P*1	
264.	isoquercitrin	U1	*P*2	(Xin et al., 2008a)
265.	rutin	U1	*P*2	(Xin et al., 2008a)(Li et al., 2017a)(Ma et al., 2009a)(Liu, 2017)
		U3	*P*1	
			*P*2	
		U2	*P*2	
266.	quercetin-3-O-robinobioside	U3	*P*1	(Li et al., 2017a)(Li, 2017)(Sun et al., 2012c)
			*P*2	
		U5	*P*1	
267.	manghaslin	U1	*P*2	(Xin et al., 2008a)
268.	(+)-uncariols C	U3	*P*1	(Li et al., 2017a)
269.	(-)-uncariols C	U3	*P*1	(Li et al., 2017a)
270.	(+)-uncariols D	U3	*P*1	(Li et al., 2017a)
271.	(-)-uncariols D	U3	*P*1	(Li et al., 2017a)
272.	afzelin	U1	*P*2	(Xin et al., 2008a)
273.	kaemferol-3-*O*-*β*-D-galactopyranoside	U3	*P*2	(Ma et al., 2009a)
274.	kaemferol-3-*O*-*β*-D-galactopyranosyl-(6–1)-α-L-rhamnopyranoside	U3	*P*2	(Ma et al., 2009a)
2.3.2 Flavones				
275.	buddleoside (linarin)	U5	*P*1	(Sun et al., 2012c)
2.3.3 Flavan-3-ols				
276.	(+)-catechin	U3	*P*1	(Hou et al., 2005)(Zhang, 2014)
		U4	*P*1	

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Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
277.	(-)-epicatechin	U1	*P*2	(Xin et al., 2008a)(Li et al., 2017a)
		U3	*P*1	(Li, 2017)(Yang, 2018)
			*P*2	
		U2	*P*3	
278.	uncariol A	U3	*P*1	(Li et al., 2017a)
279.	uncariol B	U3	*P*1	(Li et al., 2017a)
280.	cinchonain Ia	U3	*P*1	(Li et al., 2017a)
281.	cinchonain Ib	U3	*P*1	(Li et al., 2017a)
282.	cinchonain Ic	U3	*P*1	(Li et al., 2017a)
283.	cinchonain Id	U3	*P*1	(Li et al., 2017a)
2.3.4 Homoisoflavone				
284.	3-(3-hydroxy-4-methoxybenzyl)-5,7-dihydroxychroman-4-one	U2	*P*3	(Yang, 2018)
2.3.5 Chromone				
285.	eugenin	U4	*P*1	(Zhang, 2013)(Liu et al., 2011)
		U5	*P*1	
286.	noreugenin	U3	*P*1	(Deng et al., 2009)
287.	2-methyl-5,7-dihydroxy-chromone-7-*O*-*β*-D-glucopyranoside	U1	*P*2	(Liu et al., 2021)
2.3.6 Flavanone				
288.	neohesperidin	U1	*P*2	(Wu and Chan, 1994)
2.4 Phenylpropanoids				
2.4.1 Simple phenylpropanoids				
289.	*trans*-anethole	U3	*P*1	(Shin and Lee, 2013)
290.	*p*-anisaldehyde	U3	*P*1	(Shin and Lee, 2013)
2.4.2 Coumarins				
291.	umbelliferone (7-hydroxycoumarin)	U1	*P*2	(Wu and Chan, 1994)(Zhang, 2014)(Liu, 2017)
		U4	*P*1	
		U2	*P*2	
292.	scopoletin	U2	*P*3	(Yang, 2018)(Zhang, 2013)(Liu et al., 2011)(Chi, 2017)
		U4	*P*1	
		U5	*P*1	
		U3	*P*1	
293.	5-hydroxy-7-methoxycoumarin	U4	*P*1	(Zhang, 2014)
294.	cleomiscosin B	U3	*P*1	(Deng et al., 2009)
295.	cleomiscosin D	U3	*P*1	(Deng et al., 2009)
2.4.3 Lignans				
296.	(2*R*,3*R*,4*S*)-lyoniresinol-3α-*O*-*β*-D-glucopyra-noside	U5	*P*1	(Sun et al., 2011)
297.	(2*R*,3*S*,4*R*)-lyoniresinol-3α-*O*-*β*-D-glucopyra-noside	U5	*P*1	(Sun et al., 2011)
298.	(2*S*,3*S*,4*R*)-lyoniresinol-3α-*O*-*β*-D-glucopyra-noside	U5	*P*1	(Sun et al., 2011)
299.	(2*S*,3*R*,4*S*)-lyoniresinol-3α-*O*-*β*-D-glucopyra-noside	U5	*P*1	(Sun et al., 2011)
300.	(+)-lyoniresinol	U3	*P*3	(Zhang et al., 2022)
301.	(–)-lyoniresinol	U3	*P*3	(Zhang et al., 2022)
302.	isolariciresinol	U3	*P*3	(Zhang et al., 2022)
Neolignans				
303.	(-)-(7*S*,8*R*)-dihydrodehydrodiconiferyalcohol	U3	*P*1	(Zhang et al., 2010)
304.	leptolepisol D	U3	*P*3	(Zhang et al., 2022)
305.	leptolepisol C	U3	*P*3	(Zhang et al., 2022)
306.	*Threo*-3,3′-dimethoxy-4,8′-oxyneoligna-9,4′,7′,9′-tetraol-7 (8) -ene	U3	*P*3	(Zhang et al., 2022)
2.5 Phytosterols				
2.5.1 Sitosterols				
307.	*β*-sitosterol	U4	*P*1	(Zhang, 2013)(Chi, 2017)(Ma et al., 2009a)(Yang, 2018)
		U3	*P*1	(Liu, 2017)(Wu, 2007)(Li et al., 2010)(Chen et al., 2014b)
			*P*2	
		U2	*P*3	
			*P*2	
			*P*1	
			*P*6	
		U5	*P*1	

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
308.	*β*-daucosterol	U4	*P*1	(Zhang, 2013)(Chi, 2017)(Ma et al., 2009a)(Yang, 2018)
		U3	*P*1	(Wu, 2007)(Chen et al., 2014b)(Xin et al., 2008a)
			*P*2	
		U2	*P*3	
			*P*1	
		U5	*P*1	
		U1	*P*1	
309.	sitost-5-ene-3*β*,7*β*-diol (7*β*-hydroxysitosterol)	U3	*P*1	(Liu et al., 2022)
310.	sitost-5-ene-3*β*,7α-diol (7α-hydroxysitosterol)	U3	*P*1	(Liu et al., 2022)
2.5.2 Stigmasterols				
311.	(24*S*)-stigmast-4-en-3-one	U4	*P*1	(Zhang, 2013)
312.	(24*S*)-stigmasta-4-en-6*β*,7α-diol-3-one	U3	*P*1	(Liu et al., 2022)
313.	stigmasterol	U3	*P*1	(Duan, 2010)
314.	(24*S*)- stigmasta-4-en-3*β*,6*β*-diol	U3	*P*1	(Liu et al., 2022)
315.	(24*S*)- stigmasta-4-en-3*β*,6α-diol	U3	*P*1	(Liu et al., 2022)
316.	(24*S*)-stigmasta-3*β*,6α-diol	U3	*P*1	(Liu et al., 2022)
317.	(24*S*)-stigmasta-3*β*,5α,6*β*-triol	U3	*P*1	(Liu et al., 2022)
		U5	*P*1	(Chen et al., 2014b)
2.5.3 Ergosterols				
318.	(22*E*,24*R*)-ergosta-7,22-diene-3*β*,5α,6*β*-triol	U3	*P*1	(Liu et al., 2022)
319.	(22*E*,24*R*)-6*β*-methoxyergosta-7,22-diene-3*β*,5α-diol	U3	*P*1	(Liu et al., 2022)
320.	(22*E*,24*R*)-ergosta-7,9(11),22-triene-3*β*,5*β*,6α-triol	U3	*P*1	(Liu et al., 2022)
321.	(22*E*,24*R*)-ergosta-7,22-dien-3*β*,5α,6α-triol	U3	*P*1	(Liu et al., 2022)
322.	(22*E*,24*R*)-ergosta-7,22-dien-3*β*,5α- diol-6-one	U3	*P*1	(Liu et al., 2022)
323.	(22*E*,24*R*)-ergosta-7,22-dien-3*β*,5α-diol-6,5-olide	U3	*P*1	(Liu et al., 2022)
2.6 Phenolics				
324.	ethyl 3,4-dihydroxybenzoate	U2	*P*3	(Yang, 2018)(Chi, 2017)
		U3	*P*1	
325.	vanillic acid	U2	*P*3	(Yang, 2018)(Duan, 2010)
		U3	*P*1	
326.	3-hydroxy-5-methoxybenzoic acid	U4	*P*1	(Zhang, 2014)
327.	1,3,5-trimethoxybenzene	U2	*P*3	(Yang, 2018)(Yuan, 2022)
		U3	*P*1	
328.	*p*-hydroxybenzoic acid	U3	*P*2	(Liu, 2021)
329.	syringic acid	U3	*P*2	(Liu, 2021)(Deng et al., 2009)
			*P*1	
330.	*p*-dihydroxyhenzene	U3	*P*1	(Duan, 2010)
331.	protocatechuic acid	U3	*P*2	(Li, 2017)
		U4	*P*1	(Zhang, 2014)
332.	4-methyl-phenol	U4	*P*3	(Fan et al., 2022)
333.	estragole	U3	*P*1	(Shin and Lee, 2013)
334.	1,2,3-trihydroxyphenol	U4	*P*1	(Zhang, 2014)
335.	3,4,5-trimethoxybenzene	U1	*P*1	(Liu et al., 2021)
Phenolic acids				
336.	caffeic acid	U2	*P*2	(Liu, 2017)
337.	ethyl cafficate	U3	*P*1	(Chi, 2017)
338.	*p*-coumaric acid ethyl ester	U3	*P*3	(Zhang et al., 2022)
339.	methyl caffeate	U3	*P*2	(Li, 2017)
340.	methylrosmarinate	U3	*P*1	(Chi, 2017)
341.	chlorogenic acid	U3	*P*2	(Huang, 2019)
		U1	*P*1	(Lin et al., 2020)(Xin et al., 2008a)
			*P*2	
342.	chlorogenic acid ethyl ester	U3	*P*2	(Li, 2017)
343.	1,2-*bis*(4-hydroxy-3-methoxyphenyl)-1,3-propanediol	U3	*P*3	(Zhang et al., 2022)
2.7 Other compounds				
344.	1-methoxyoctadecan-1-ol	U5	*P*1	(Ahn et al., 2014)
345.	vitamin E	U4	*P*1	(Zhang, 2013)
346.	α-tocopherolquinone	U4	*P*1	(Zhang, 2013)
347.	α-tocopherol	U3	*P*2	(Li, 2017)
348.	dihydroactinidiolide	U3	*P*2	(Li, 2017)
349.	palmitic acid	U3	*P*1	(Chi, 2017)
350.	tetracosane	U3	*P*1	(Chi, 2017)
351.	glycerol monopalmtate	U3	*P*1	(Deng et al., 2009)

(*continued on next page*)

Table 2 (*continued*)

No.	Compounds	From	Part	Ref.
352.	*O*-*β*-D-fructofuranosyl-(2 → 6)-α-D-glucopyranosyl-(1 → 6)-*β*-D-fructofuranosyl-(2 → 6)-*β*-D-fructofuranosyl-(2 → 1)-α-D- glucopyranosyl-(6 → 2)-*β*-D- fructofuranoside	U3	*P*2	(Liu, 2021)
353.	2-phenethyl-*O*-α-Lrhamnopyranosyl-(1 → 6)-*β*-D-glucopyranoside	U3	*P*3	(Zhang et al., 2022)
354.	1,2:4,5-di-*O*-isoproylidene-*β*-D-fructopyranose	U2	*P*3	(Yang, 2018)
355.	3,4-dehydrotheaspirone	U3	*P*2	(Li, 2017)
356.	chakyunglupulin A	U3	*P*2	(Li, 2017)
357.	mannitol	U2	*P*3	(Yang, 2018)
358.	sucrose	U3	*P*2	(Liu, 2021)
359.	maackiain	U3	*P*1	(Yuan, 2022)
360.	(-)-(7*S*,8*R*)-dihydrodehydrodiconiferyalcohol	U4	*P*3	(Fan et al., 2022)
361.	vomifoliol	U3	*P*3	(Zhang et al., 2022)
362.	dibutyl phthalate	U3	*P*2	(Liu, 2021)
363.	*bis*(2-ethylhexyl)phthalate	U4	*P*1	(Zhang, 2013)
364.	erythroglaucin	U3	*P*1	(Chi, 2017)
365.	rheochrysidin (physcione)	U3	*P*1	(Chi, 2017)
366.	uncarophyllofolic acid A	U3	*P*1	(Wang et al., 2019b)
367.	uncarophyllofolic acid B	U3	*P*1	(Wang et al., 2019b)
368.	3-diethylamino-5-methoxy-1,2-benzoquinone	U3	*P*1	(Zhang et al., 2016)
369.	3-ethylamino-5-methoxy-1,2-benzoquinone	U3	*P*1	(Zhang et al., 2016)
370.	semiphorone	U3	*P*1	(Gong, 2021)
371.	4-hydorxy-4-methyl-2-pentanone	U3	*P*1	(Gong, 2021)

U1:*Uncaria hirsuta* Havil; U2:*Uncaria macrophylla* Wall; U3:*Uncaria rhynchophylla* (Miq.) Jacks; U4:*Uncaria sessilifructus* Roxb; U5:*Uncaria sinensis* (Oliv.) Havil.
*P*1: stem and hook; *P*2: leaves; *P*3: stem; *P*4: the aerial part; P5: stem bark; *P*6: root.

4.1.5. Other indole alkaloids

14 other indole alkaloids (**145** ∼ **158**) (Fig. 8) were reported from URCU. Among other indole alkaloids, compounds **145** ∼ **150** and **156** ∼ **157** were oxindoles, which had carbonyl in 4-position. Notably, hirsutanine D and E (**149** ∼ **150**) were two 3-oxo-3,7-seco-oxindole alkaloids. Moreover, rhynchine A-E (**151** ∼ **155**) were five new indole alkaloids with an unprecedented skeleton. The new skeleton was characterized by an indole moiety and a 2-oxa-8-azatricyclo[6,5,$0^{1,5}$,$0^{1,8}$] tridecane core, forming a unique 6/5/7/5/5 ring system. Rhynchophyllosides K-L (**166** ∼ **167**) were two alkaloids with a quinolone nucleus. Meanwhile, uncanidine A (**158**) was a novel *Uncaria* alkaloid which possessed a 6/5/6/6/6/5 hexacyclic ring system.

4.1.6. Other alkaloids

In addition to indole alkaloids, 11 other alkaloids (**159** ∼ **169**) (Fig. 9) were reported from URCU. Hirsutanine A-C (**159** ∼ **161**) were three monoterpenoid alkaloids, which were isolated from *U. hirsuta*. Notably, hirsutanine C (**161**) was the first dimeric monoterpenoid alkaloid obtained from the genus *Uncaria*. Uncarrhynchoside A and B (**168** ∼ **169**) were rare camptothecin-related monoterpene alkaloids from the *Uncaria* plants. Meanwhile, hirsutanine F (**162**) is the first 3-oxo-3,7-seco-oxindole alkaloid with ring B opened and degraded isolated from the *Uncaria* genus.

4.2. Terpenoids

Terpenoids are compounds derived from mevalonic acid with $(C_5H_8)_n$ general formula. Terpenoids, which were reported from URCU, can be divided into triterpenoids (**170** ∼ **251**) and sesquiterpene (**252**–**258**). 82 triterpenoids included 43 ursane type triterpenoids, 34 oleanane type triterpenoids, 3 lupeol type triterpenoids, 1 cycloartane and 1 squalene. The specific structures were shown in Figs. 10-12.

4.2.1. Ursane type triterpenoids

Ursane type triterpenoids (**170** ∼ **212**) (Fig. 10) are also known as α-aromatic resin, whose basic skeleton is a pentacyclic nucleus of polyhydropinene with a *gem*-dimethyl at 4-position, and a methyl substitution at 19 and 20-position, respectively. According to the number and location of double keys, they can be divided into Δ^{12} ursane type (mostly), Δ^{13} ursane type, $\Delta^{5,12}$ ursane type and $\Delta^{12,18}$ ursane type. Most ursane type triterpenoids from URCU had carboxyl at 17-position and *β*-hydroxyl substitution at 3-position. Compounds **179** ∼ **180**, **182** and **188** formed saponins at the C-3 hydroxyl group with different sugars, respectively. Whereas, compound **181** and uncarisaside A (**206**) formed saponins with glucose at both 3-position hydroxyl group and 17-position carboxyl group. Compound **206** was a special 12-oxo ursane type triterpenoid. Notably, ursolic acid lactone (**207**) formed a pentalactone ring at the 13-position of hydroxyl group and at the 17-position of carboxyl group.

4.2.2. Oleanane type triterpenoids

Oleanane type triterpenoids (**213** ∼ **246**) (Fig. 11) are also known as *β*-aromatic resin, whose basic skeleton is a pentacyclic nucleus of polyhydropinene with a *gem*-dimethyl at 4 and 20-position, respectively. In this article, most oleanane type triterpenoids had carboxyl at 17-position and *β*-hydroxyl substitution at 3-position. According to the number and location of double keys, they also could be divided into

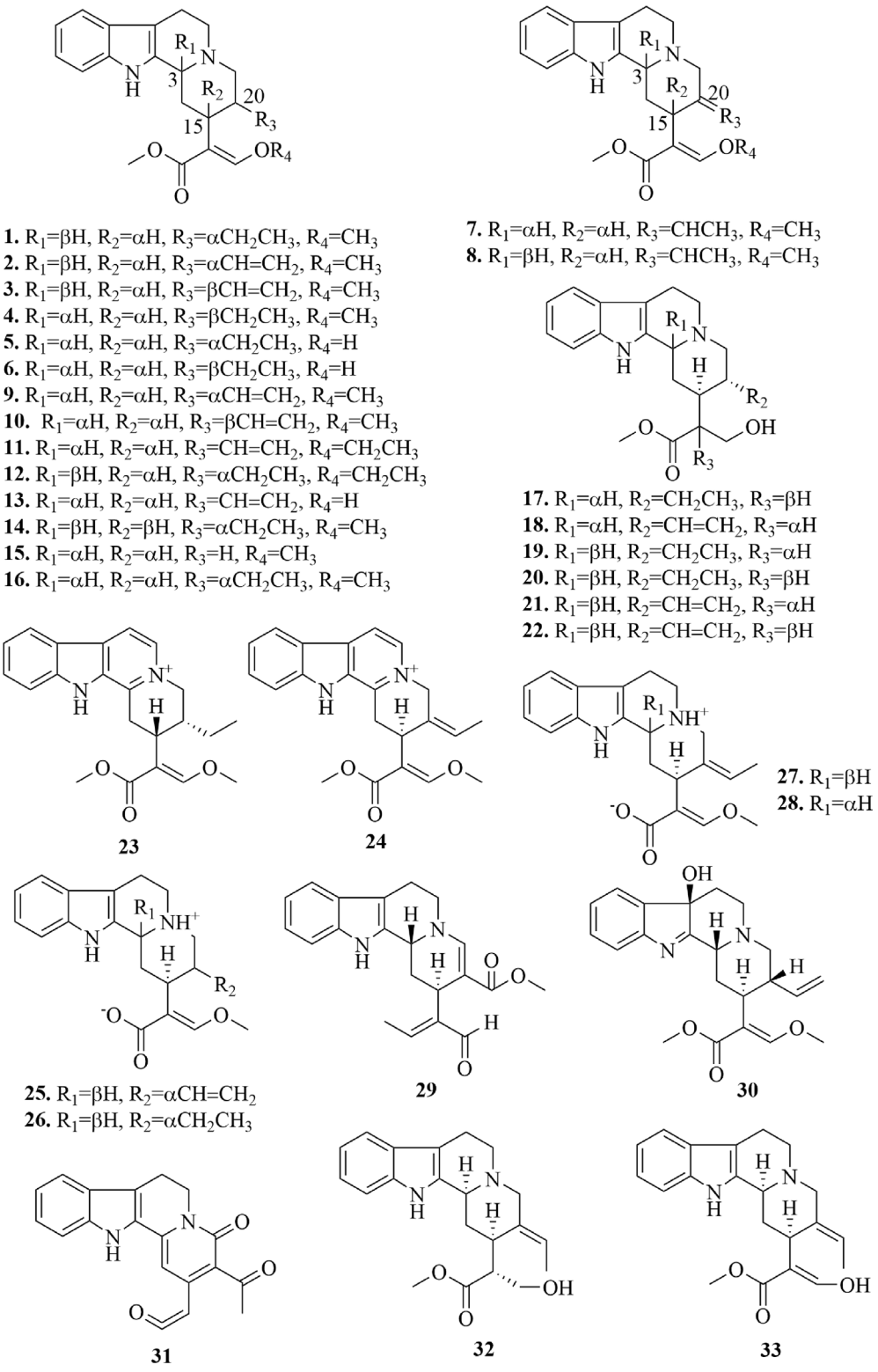


Fig. 3 Structures of tetracyclic monoterpene indole alkaloids in URCU.

Δ^{12} oleanane type (mostly), Δ^{13} oleanane type, Δ^{14} oleanane type and double bond-free oleanane type. In general, oleanane type triterpenoids exist in the form of saponins. But in URCU, only cincholic acid 3-*O*-*β*-D-fucopyranoside (**221**), phytolaccoside A (**229**) and (3*β*)-3-(*β*-D-quinovopyranosyloxy)-pyrocin cholic acid-*β*- D-glucopyranosyl ester (**239**) were saponins. It's worth noting that (3*β*)-hydroxy-27- norolean-13(28)-lactone (**240**) and 3*β*,23-dihydroxy-12-oxo-olean-28,13*β*-olide (**241**) both formed a pentalactone ring by the dehydration condensation reaction of the hydroxyl group at C-13 position and the

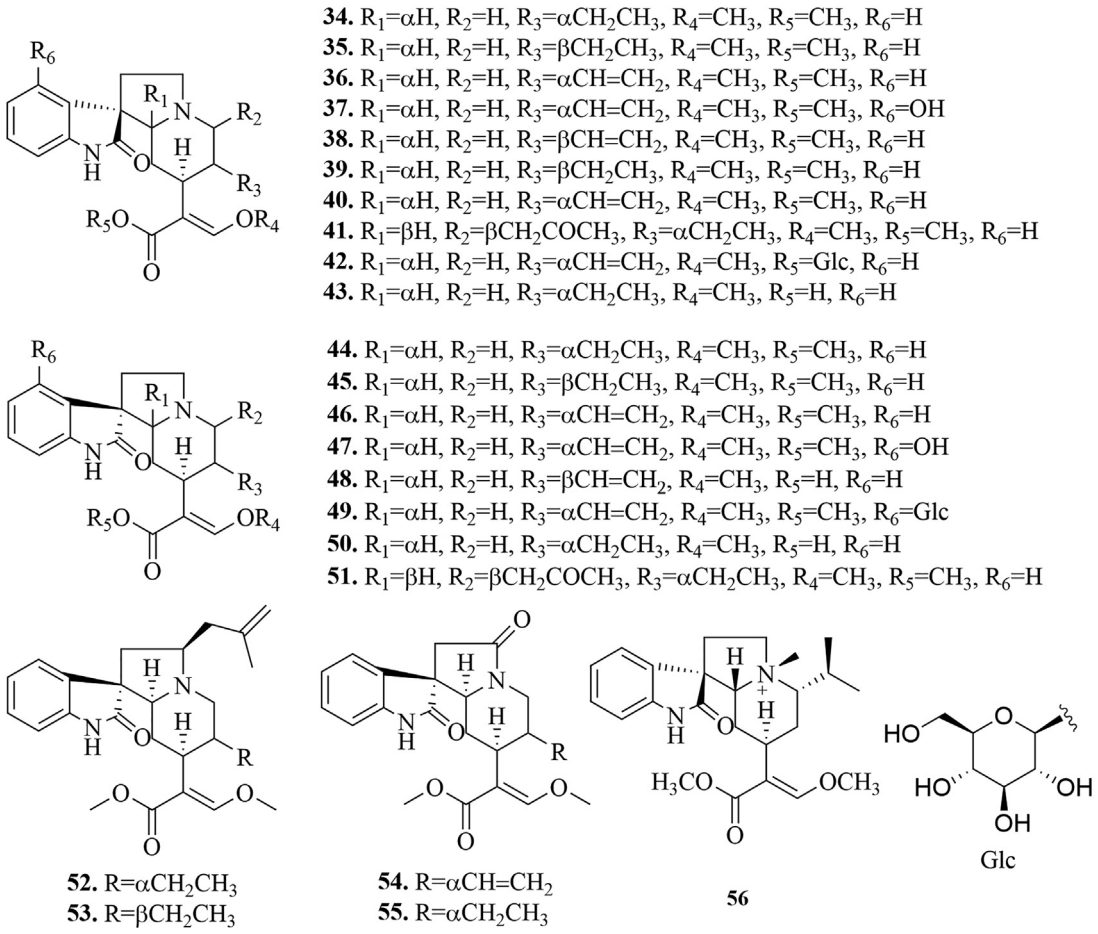


Fig. 4 Structures of tetracyclic monoterpenes oxidize indoles alkaloids in URCU.

carboxyl group at 17-position. In addition, secouncarilic acid (**242**) was the first oleanane-type 5,6-secotriterpenoid, which had a nine-membered lactone ring.

4.2.3. Lupeol type triterpenoids

Lupeol type triterpenoid is a kind of triterpenoid, whose five rings are all *trans*-condensed. Especially, the lupeol type triterpenoid's E-ring is a five-membered ring. Meanwhile, it has an α-isopropyl substitution at the 19-position of the E-ring. At present, three lupeol type triterpenoids were isolated from URCU including obtusalin (**247**), betulin (**248**) and lupenone (**249**) (Fig. 12).

4.2.4. Sesquiterpenes

Sesquiterpenes (**252** ~ **258**) are a class of terpenoids composed of three isoprene units (15 carbons) (Fig. 12). In URCU, 7 sesquiterpenes were reported, which included 6 megastigmanes (**252** ~ **257**) and 1 azulenoid (**258**). Megastigmane, also known as lonone, is a kind of monocyclic sesquiterpene. In general, most megastigmanes have a 1,1-dimethylcyclohexane (alkene) structure and exist in the form of glycoside, whereas all megastigmanes in this article are aglycones. Notably, compounds **252** ~ **254** and **257** lost two carbons in the decarboxylation reaction of source synthesis, so they were special norsesquiterpenoids. Uncarphabscisic acid A (**255**) and uncarphabscisic acid B (**256**) formed a pentalactone ring. In addition, azulenoid is an aromatic derivative synthesized by the parallel synthesis of a five-membered ring and seven-membered ring, and its molecular structure has a high conjugated system. At present, only one azulenoid, (-)-alloaromadendrene (**258**), was isolated from *U. sessilifructus*.

4.3. Flavonoids

According to structures, 30 flavonoids are divided into flavonols (**259** ~ **274**), flavone (**275**), flavan-3-ols (**276** ~ **283**), homoisoflavone (**284**), chromone (**285** ~ **287**) and flavanones (**288**) (Fig. 13). Although the parent nucleus of flavonols and flavone both are 2-phenyl chromone, flavonols connect hydroxyl or other oxygen-containing groups at 3-position. In URCU, most flavonols mostly formed glycosides with various sugars at the 3-position. Notably, two pairs of phenylpropanoid-substituted flavonol enantiomers, (±)-uncariols C and D (**268** ~ **271**), were isolated from the leaves of *U. rhynchophylla,* which had phenylpropanoid substitution at 8-position and two configurations at 9-position.

Flavan-3-ols are also known as catechins, whose parent nucleus is the 3,4-2H-2-phenyl-1-benzopyran ring. And the C-2 and 3 of flavan-3-ol are chiral carbons, which are generally (2*R*, 3*S*) and (2*R*, 3*R*) in plants. Six phenylpropanoid-substituted flavan-3-ols were isolated from the leaves of *U.*

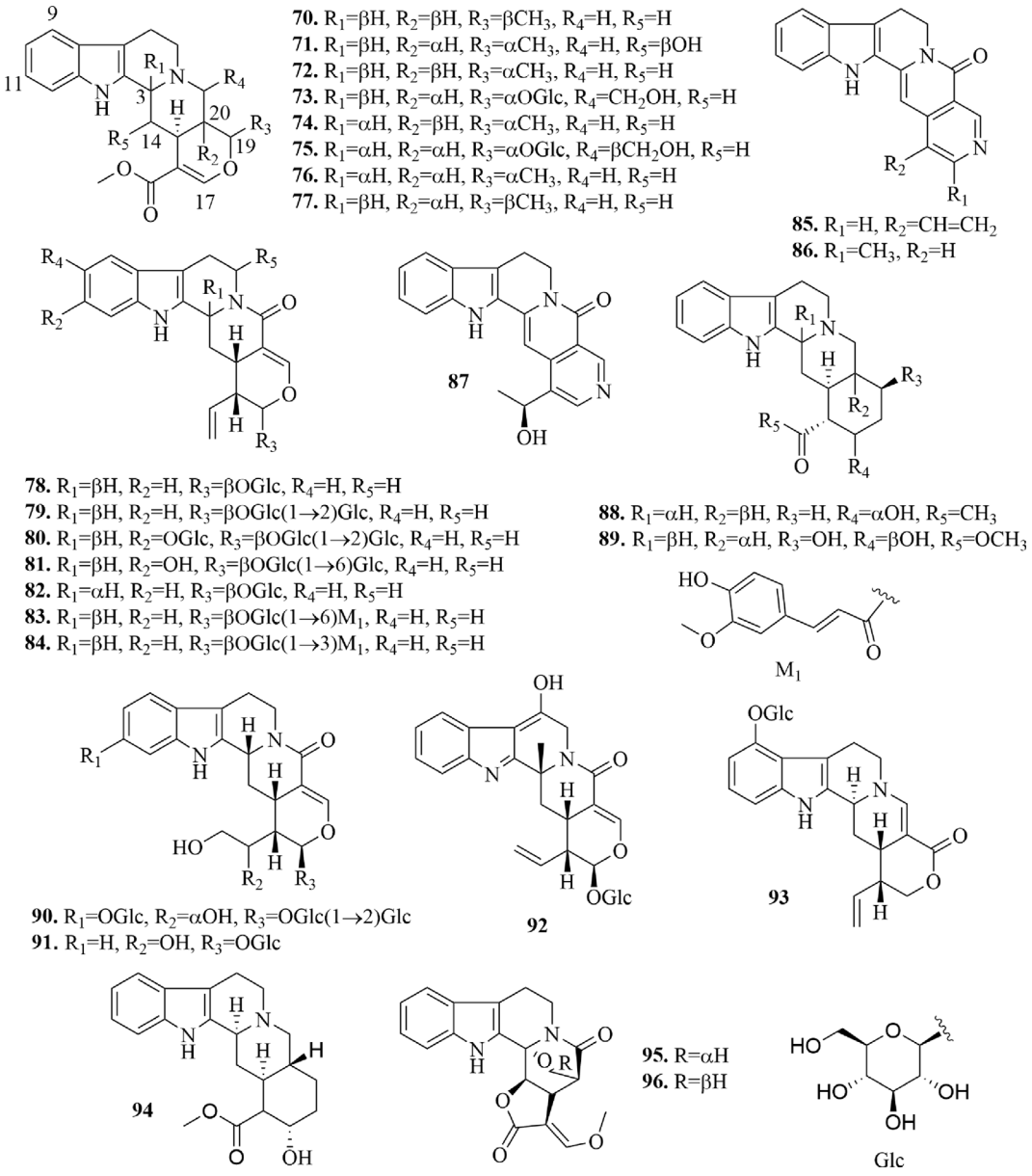


Fig. 5 Structures of pentacyclic monoterpene indole alkaloids in URCU.

rhynchophylla and whose configurations were (2*R*, 3*R*). Uncariol A (**278**), uncariol B (**279**), cinchonain Ia (**280**) and cinchonain Ib (**281**) had phenylpropanoid substitutions at C-8. Whereas, cinchonain Ic (**282**) and cinchonain Id (**283**) had phenylpropanoid substitutions at C-6, which have two configurations at 9-position. It's worth that the phenylpropanoid substituents of compounds **280** ~ **283** formed a six-membered lactone ring with the benzene ring, respectively.

4.4. Phenylpropanoids

Phenylpropanoids, a class of compounds consisting of a benzene ring linked to three carbons (C6-C3), can be divided into simple phenylpropanoids (**289** ~ **290**), coumarins (**291** ~ **295**) and lignans (**296** ~ **306**) (Fig. 14). The parent nucleus of coumarins is pyranone nucleus, which is formed by dehydration cyclization of *cis*-hydroxycinnamic acid. And most coumarins have hydroxyl substitution at the 7- position. It is noteworthy that phenylpropanoid substitutions of cleomiscosin B (**294**) and cleomiscosin D (**295**) both form dioxane with the hydroxyl groups of 7 and 8-position. Lignans are natural compounds synthesized from two C6-C3 units. And most of the lignans in URCU were arylnaphthalenes, and there were two configurations at 2, 3 and 4-position, respectively. Neolignans are compounds formed by linking the aliphatic hydrocarbon carbon of a phenylpropanoid to the benzene ring of another phenylpropanoid. At present, four neolignans, compounds **303** ~ **306**, were reported from URCU.

4.5. Phytosterols

Phytosterols are steroid derivatives with C-17 side chains of 8–10 carbon atoms, which is a natural active substance widely distributed in plants. Meanwhile, it's one of the components

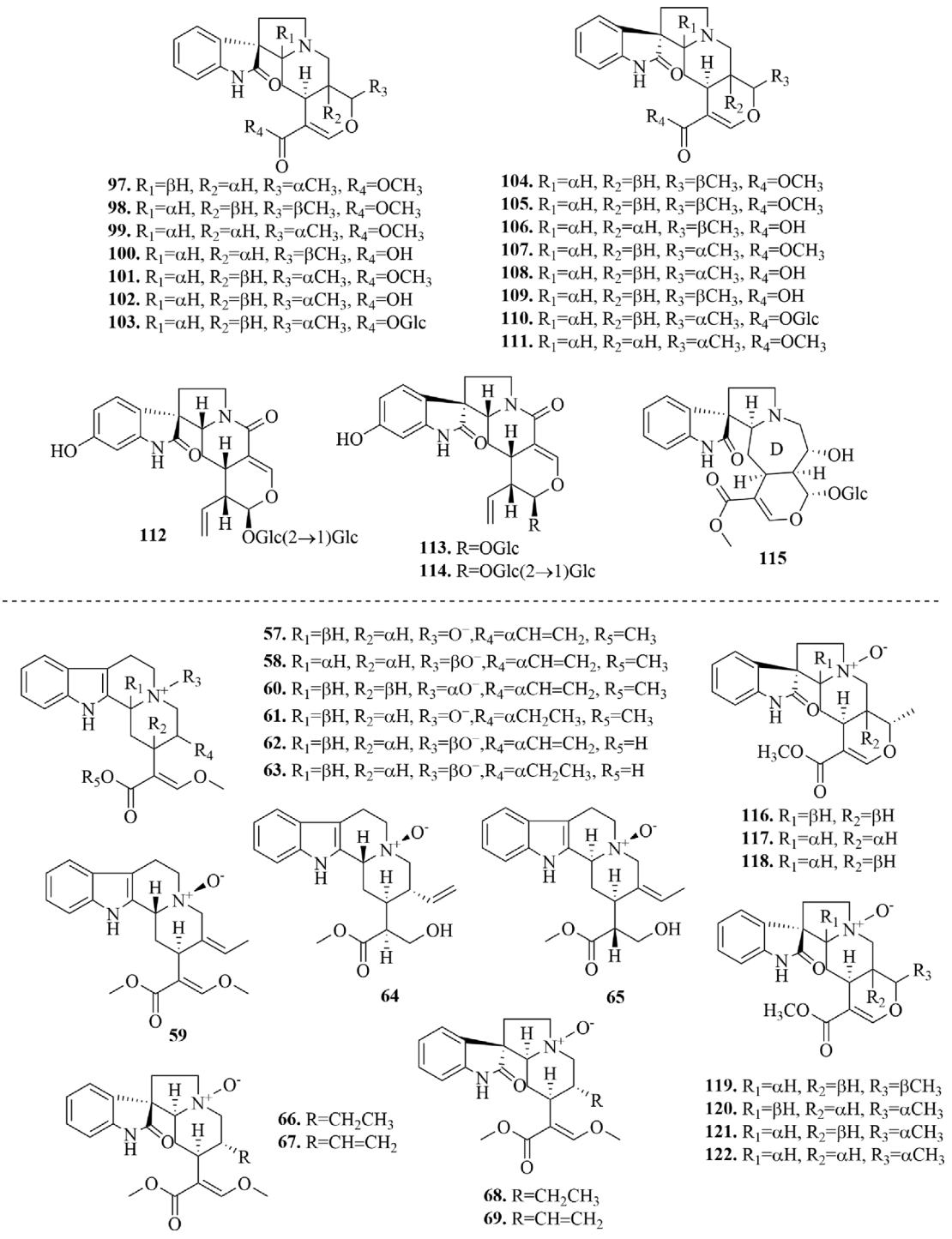


Fig. 6 Structures of pentacyclic monoterpenes oxidize indole alkaloids and *N*-oxide monoterpene indole alkaloids in URCU.

of the cell membrane in plants. Phytosterols in URCU include sitosterols (**307** ∼ **310**), stigmasterols (**311** ∼ **317**) and ergosterols (**318** ∼ **323**) (Fig. 15). Ergosterol is an essential precursor for vitamin D synthesis. It's worth that (22*E*,24*R*)-ergosta-7,22-dien-3*β*,5*α*-diol-6,5-olide (**323**) was a special ergosterol, whose B ring was a 7-membered lactone ring. In addition, most phytosterols existed in a free state, only *β*-daucosterol formed glycoside with glucose at the 3-position hydroxyl.

4.6. Phenolics

Phenolic compounds are important secondary metabolites in plants, which have good antioxidant activity for the existence of phenolic hydroxyl, phenolic compounds. While phenolic acid is a kind of organic acid containing a phenol ring. 12 phenolics (**324** ∼ **335**) and 8 phenolic acids (**336** ∼ **343**) have been isolated from URCU. The specific structures of compounds were shown in Fig. 16.

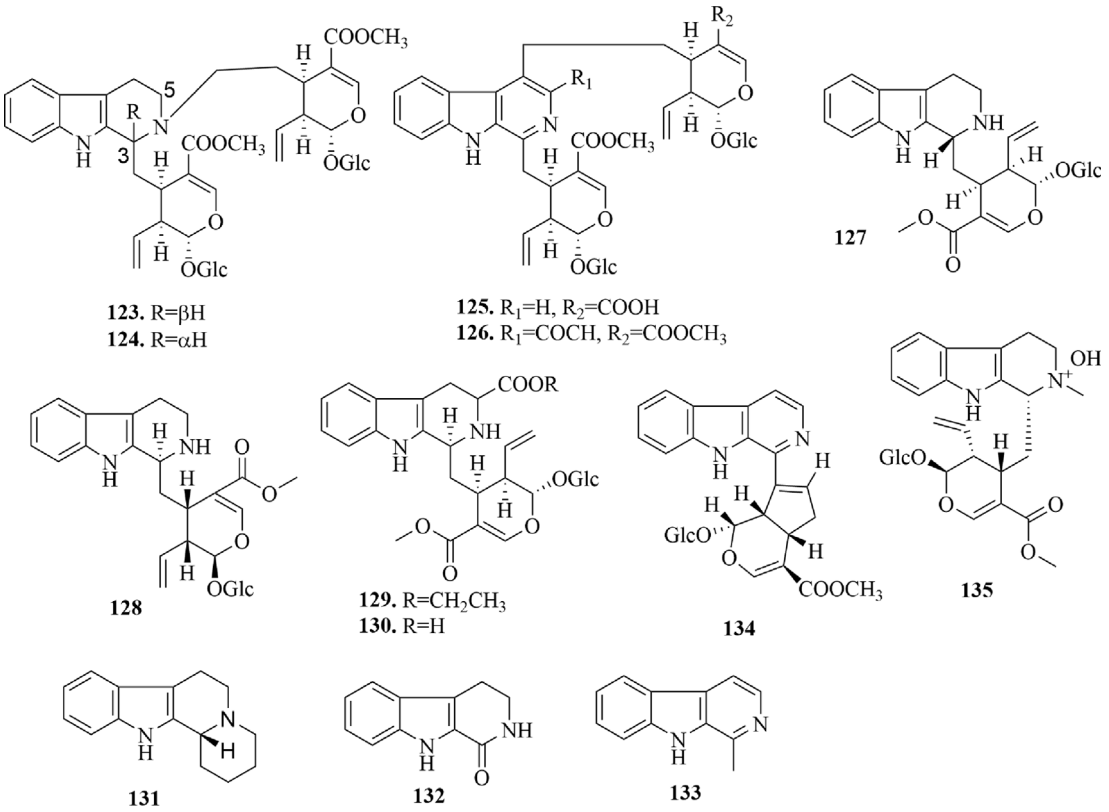


Fig. 7 Structures of *β*-carboline alkaloids in URCU.

4.7. Other compounds

In addition, 28 other compounds (**344** ~ **371**) were isolated from URCU, including saccharides, phthalates, anthraquinones, vitamins, ortho benzoquinones, folate-derived analogues and miscellaneous compounds. The specific structures of other compounds were shown in Fig. 17.

5. Pharmacological activity

5.1. Anti-hypertension

Hypertension is the most common chronic disease and the main risk factor causing cardiovascular and cerebrovascular diseases (Oparil et al., 2018). In vitro, dihydrocorynantheine (**5**) (IC_{50} = 6.73 μg/mL) exhibited a significant vasodilation effect against phenylephrine (Phe)-induced contraction in rat thoracic aorta rings (Wang et al., 2011a). 95 % ethanol extract of *U. rhynchophylla* could exert vasodilatory effects for Phe-induced contraction in SD rat's aortic rings (EC_{50} = 0.028 mg/mL) via activating NO/sGC/cGMP signaling pathways, PGI2, G protein-coupled M_3- and β2 receptors, and all the potassium channels except the Kca channel (Loh et al., 2017). Rhynchophylline (**34**) and isorhynchophylline (**44**) inhibited the contraction of arterial vessels of isolated rats induced by 60 mM KCl (20–30 μM) and induced by Phe and U46619 (100 and 200 μM, respectively) via L-type Ca^{2+} channels and other Ca^{2+} channels (Zhang et al., 2004). Uncarialin A (**14**) exhibited a relaxation effect against Phe-induced contraction (IC_{50} = 0.18 μM) in the manner by significantly inhibiting L-type calcium channel subunit alpha-1C (Cav1.2) via the hydrogen bond interaction with amino acid residue Met1186 (Yun et al., 2020). Likewise, rhynchine A (**151**) and B (**152**) showed strong inhibitory activities against the Cav3.1 calcium channel with IC_{50} values of 6.86 and 10.41 μM (Zhou et al., 2021). Geissoschizine methyl ether (**7**) (EC_{50} = 0.744 μM) was found to alleviate NE (norepinephrine)-induced aorta strip contraction through increasing NO and blocking voltage-dependent Ca^{2+} channels (Yuzurihara et al., 2002). In vivo, isorhynchophylline (**44**) (0.245 mg/kg) exhibited a strong anti-hypertensive role in SHRs by attenuating hypertension-induced the activation of the renin-angiotensin system and sympathetic hyperactivity (Li et al., 2020). The signal pathways related to the anti-hypertensive effect of URCU were shown in Fig. 18. By summarizing, it is found that compounds in URCU mainly dilate blood vessels to reduce blood pressure.

5.2. Anti-inflammation

The development of inflammation is often accompanied by the increase of inflammatory factors such as IL and TNF-α. In vitro, Kim et al. verified that water extract of *U. rhynchophylla* (1 mg/mL) had inhibitory effects on LPS-induced NO and IL-1β production in RAW264.7 Cells through blocking the phosphorylation of Akt and mitogen-activated protein kinase (MAPK) (Kim et al., 2010). In LPS induced N9 microglial cells, rhynchophylline (**34**) and isorhynchophylline (**44**) (0.3–30 μM) dose-dependently abated the production of inflammatory cytokines such as TNF-α, IL-1β and NO by inhibiting

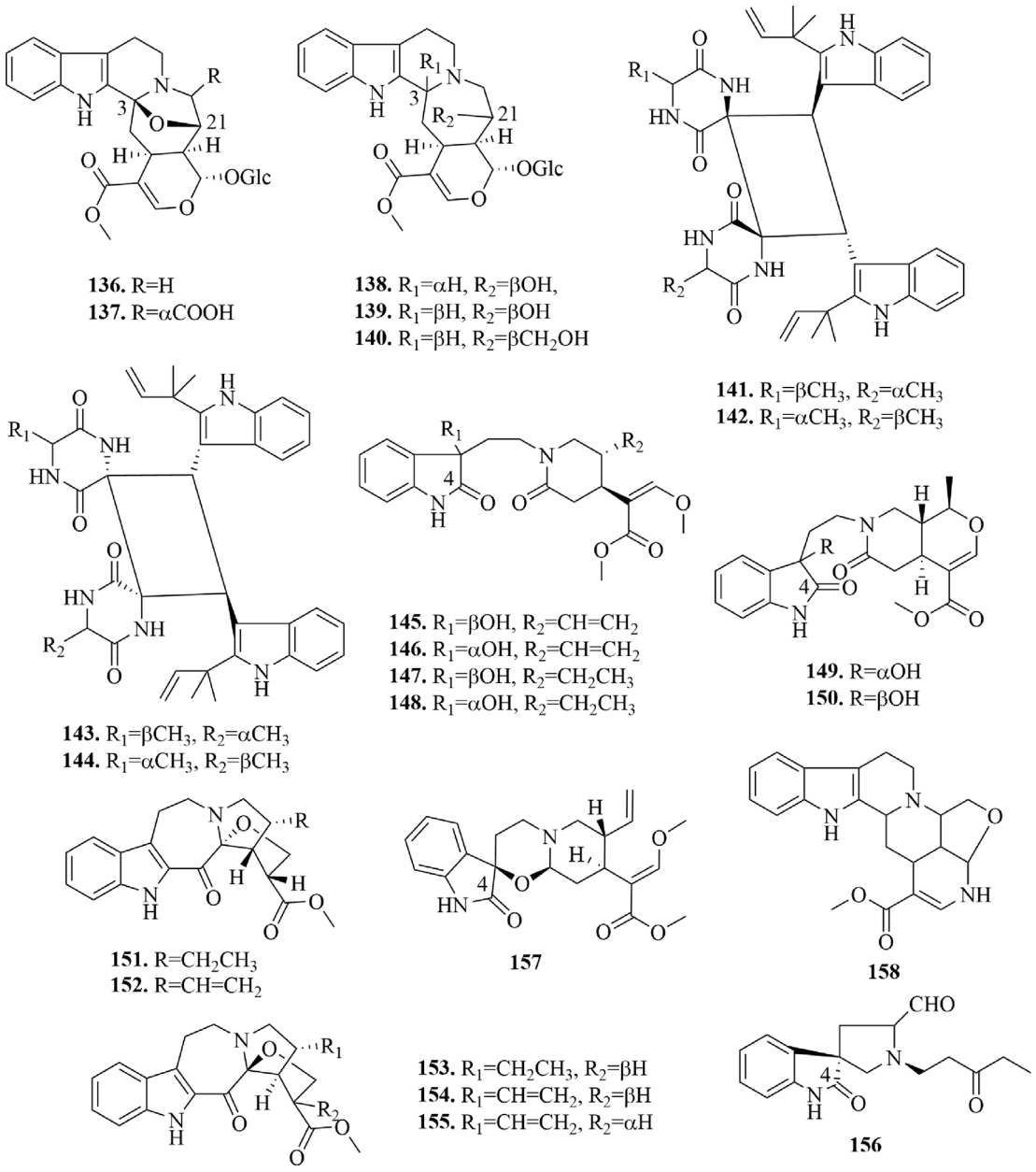


Fig. 8 Structures of cadambine alkaloids, dimeric isoechinulin-type alkaloids and other indole alkaloids in URCU.

iNOS protein expression and blocking the activation of NF-κB and ERK and p38 MAPKs (Yuan et al., 2009). And compound **44** (30 or 40 μM) had a better anti-inflammatory effect in LPS induced murine alveolar macrophages cells by activating the TLR4/NF-κB/nod-like receptor protein 3 (NLRP3) inflammasome pathway (Zhou et al., 2019). In vivo, *U. rhynchophylla* alkaloids extracts (35, 70, and 140 mg/kg) effectively prevented inflammation by inhibiting serum and placental levels of pro-inflammatory cytokines, including IL-6, IL-1β, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) (Wu and Xiao, 2019) in LPS-induced preeclampsia model rats. In summary, URCU can effectively reduce the release of inflammatory factors to achieve anti-inflammatory effects in LPS-induced in vitro and in vivo models.

NO is an important physiological transmitter and intracellular chemical messenger in the body, which plays a complex role in the inflammatory response. In vitro, corynoxeine (**37**), isocorynoxeine (**40**), rhynchophylline (**34**), isorhynchophylline (**44**) and vincoside lactam (**74**) exhibited inhibitory activities on LPS-induced NO release in primary cultured rat cortical microglia with IC_{50} value of 15.7, 13.7, 18.5, 19.0 and 16.4 μM, respectively (Yuan et al., 2008). Strictosidine (**128**) manifested a potent inhibitory activity on LPS-induced NO release in N9 microglia cells with IC_{50} value of 8.3 μM (Ma et al., 2009b). Also, uncarinic acid I (**205**), 3*β*-hydroxy-27-*p*-(E)- coumaroyloxyursan-12-en-28-oic acid (**185**) and 3*β*-hydroxy-27-(*E*)-coumaroyl -oleanen-12-en-28-oic acid (**217**) exhibited inhibitory effects on LPS-induced NO production in RAW264.7 cells with IC_{50} value of 1.48, 7.01, and 1.89 μM, respectively (Zhang et al., 2014). The signal pathways related to the anti-inflammation effect of URCU were shown in Fig. 19.

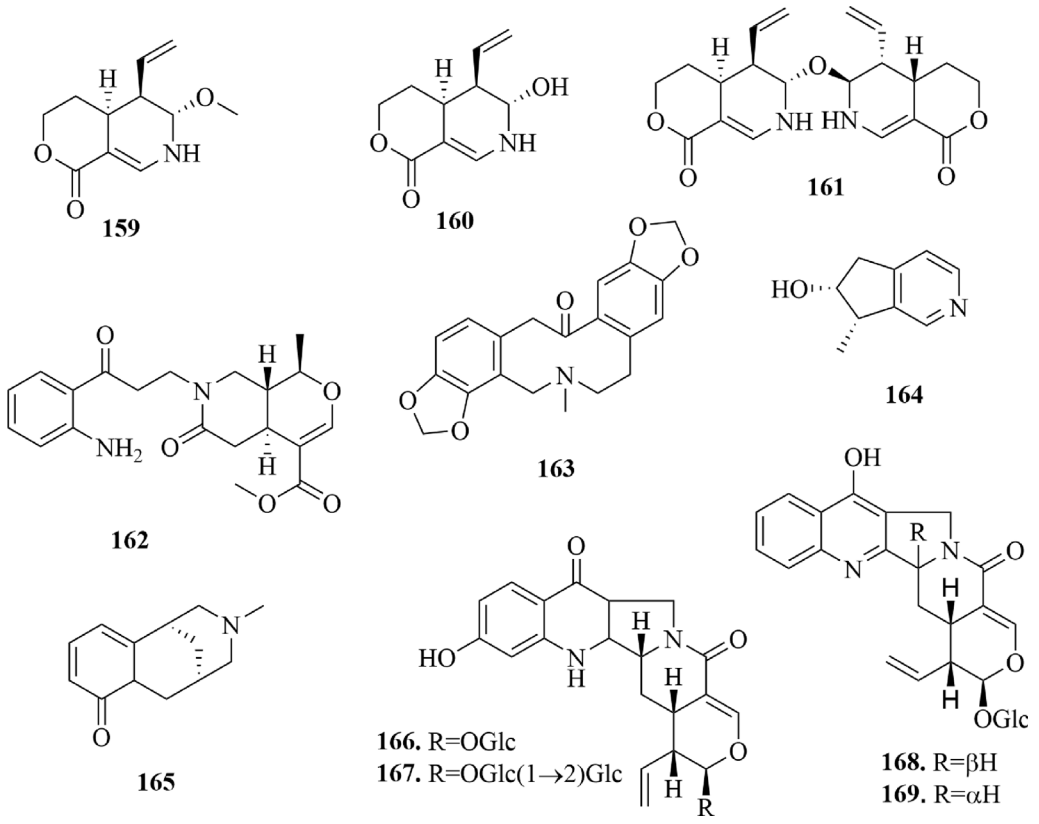


Fig. 9 Structures of other alkaloids in URCU.

5.3. Anticancer

As a global public health problem, cancer seriously endangers human life and health. Studies have found that natural drugs can achieve anti-tumor effects by inhibiting and killing tumor cells, inducing apoptosis, affecting related proteins and enzymes, regulating body immunity, and enhancing antioxidant effects (Liu et al., 2015). Killing tumor cells through the cytotoxic activity of compounds or extracts is a more direct anticancer method. In vitro, Kim et al. found the *n*-BuOH fraction of *U. rhynchophylla* (0.05, 0.1, and 0.2 mg/mL) has strong cytotoxicity towards HepG2 cells via up-regulating expression levels of caspases 7 and 8 and poly ADP ribose polymerase (PARP) (Kim et al., 2014). Rhynchophylline (**34**) (130 μM) was found to induce HepG2 cell apoptosis by eliminating the phosphorylations of p38, ERK, JNK, CREB, Akt and STAT3 signals and strengthening the phosphorylation of p53 signals. Moreover, C-X-C chemokine receptor type 4 (CXCR4), matrix metallopeptidase-9 (MMP-9), and MMP-2 expression were inhibited upon rhynchophylline treatment (Lee et al., 2017). Meanwhile, uncarinic acid E (**216**) (6, 12, 24, 48 μM) also caused apoptosis in HepG2 cells via accumulating p53, altering the Bax/Bcl-2 ratio and activating caspases (Zhao et al., 2006). Ursolic acid (**170**) and rhynchophylline (**34**) (50, 25, 12.5, 6.25 μM) could inhibit the proliferation of HepG2 cells and induce apoptosis. Compound **170** more significantly acted as a disincentive to the growth of HepG2 cells than rhynchophylline (Wu et al., 2017). Sun et al. reported that 3*β*,6*β*,19*α*-trihydroxy-olean-12-en-28-oic acid (**220**) exhibited cytotoxicity in MCF-7 and HepG2 cells with IC_{50} = 78.2 and 73.9 μg/mL, respectively (Sun et al., 2012b).

Suppressing tumor cell proliferation by blocking cell cycle is also an effective way. In vitro, Uncarinic acid A (**214**), uncarinic acid B (**215**), uncarinic acid C (**176**), uncarinic acid D (**177**), uncarinic acid E (**217**), 3*β*-hydroxy-27-(*E*)-coumaroyl-oleanen −12-en-28-oic acid (**210**), 3*β*-hydroxy-27-*p*-(*E*)-coumaroyloxyursan-12-en-28-oic acid (**185**) and 3*β*-hydroxy-27-*p*-(*Z*)-coumaroyloxyursan-12-en-28-oic acid (**184**) restrained the growth of HCT-15, MCF-7, A549, and HT-1197 cells with IC_{50} values of 0.5–6.5 μM (Lee et al., 2000). 3-diethylamino-5-methoxy-1,2-benzoquinone (**368**) and 3-ethylamino-5-methoxy-1,2-benzoquinone (**369**) showed weak antiproliferative activities on A549, HepG2 and A2780 cells (IC_{50} = 50.2–98.8 μM). Isorhynchophyllic acid (**50**) significantly inhibited the proliferation of A549, HepG2 and A2780 cells with IC_{50} value of 5.8, 12.8 and 11.8 μM, respectively (Zhang et al., 2016). In vivo, hirsutine (**1**) (40–80 μM) also limited tumor growth in the A549 xenograft mouse model through GSK-3β dephosphorylation and accelerated apoptosis via ROCK1/phosphatase and tensin homolog (PTEN)/PI3K/Akt signaling (Zhang et al., 2018). In vitro, hirsutine (**1**) (10, 25 and 50 μM) had an inhibitory effect on Jurkat Clone E6-1 cells which could inhibit cell growth in the S and G2/M phases. Meanwhile, it also could promote cell death upon elevating Bax, cleaved-caspase 3/9, Cyto-c protein, caspase-3 and 9, and decreasing Bcl-2 protein (Meng et al., 2021). Corynantheidine (**4**) exhibited moderate cytotoxicity against HL-60 and SW480 cells with IC_{50} values of 13.96 and 23.28 μM, respectively (Wang et al., 2011a). In conclusion, both extracts and compounds from URCU can achieve anti-tumor effects in a variety of ways. Although anticancer is not the traditional use of URCU, the develop-

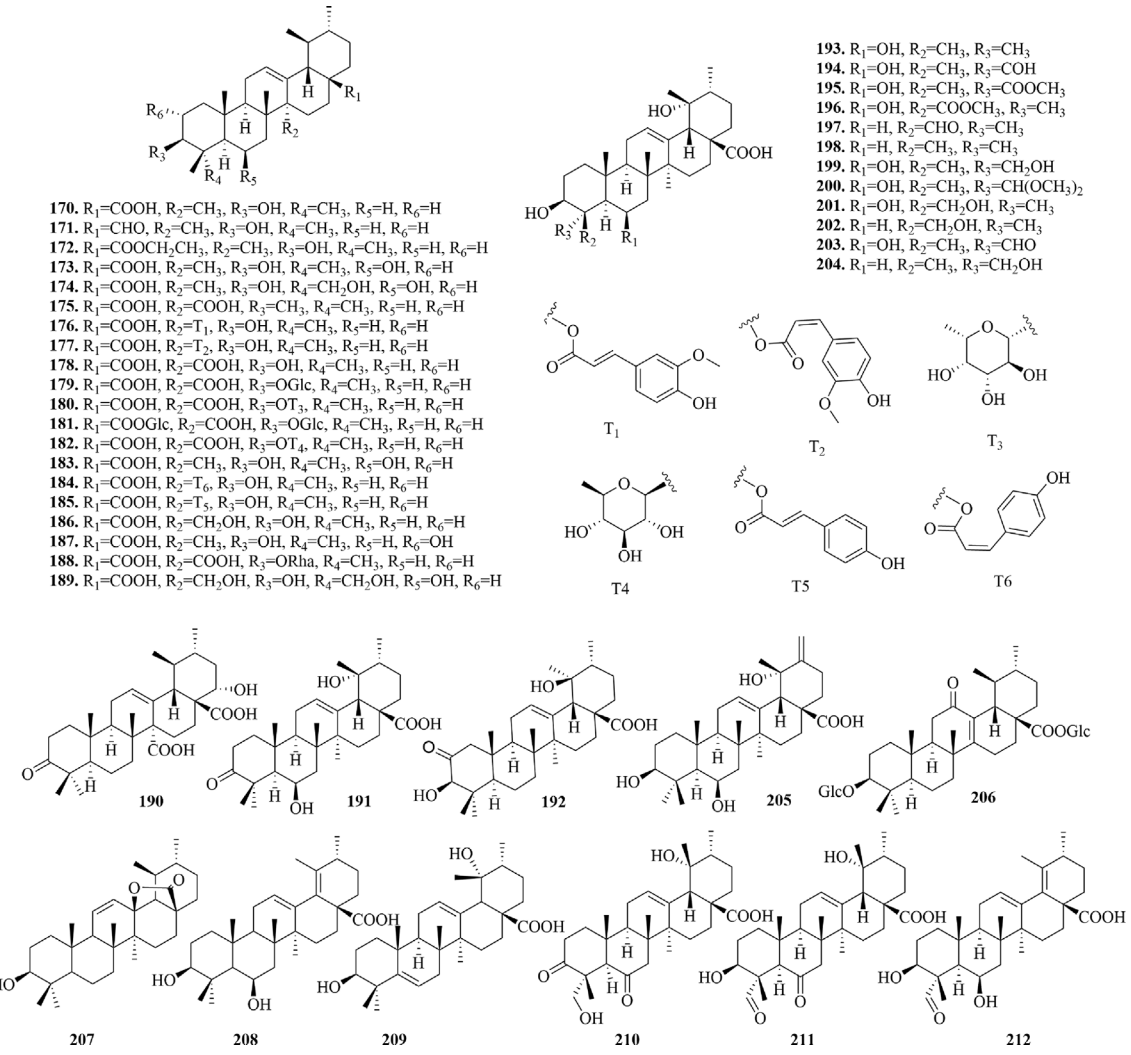


Fig. 10 Structures of ursane type triterpenoids in URCU.

ment of new uses of URCU through modern research is also an effective use of URCU resources.

Breast cancer, the most common cancer in the world, is a major global health challenge, which seriously affects the quality of life of patients. It is worth noting that URCU has a certain therapeutic effect on breast cancer. In vitro, Chen et al. found that treatment of MDA-MB-231 cells with *U. rhynchophylla* proanthocyanidins (UPAs) (5, 10, 20, 30 and 40 μg/mL) increased G2/M cell cycle arrest. Further research showed that UPAs inhibited cell viability and migration ability by increasing cellular ROS production, loss of mitochondrial membrane potential, Bax/Bcl-2 ratio and cleaved caspase 3. Meanwhile, it was interesting that the cytotoxic effects of 5-FU against MDA-MB-231 cells could be enhanced by UPAs (Chen et al., 2017). In addition, hirsutanine D-F (**149**, **150** and **162**) (100 μM) exhibited a slight inhibition effect on the proliferation of the breast cancer cell MDA-MB-23 cells by 18.1 %, 20.5 % and 15.9 %, respectively (Pan et al., 2017). Moreover, hirsutine (**1**) remarkably reduced the viability of human breast cancer MCF-7 and MDA-MB-231 cells with IC_{50} values of 447.79 and 179.06 μM. Compound **1** induced apoptosis of MDA-MB-231 cells by decreasing the Bax/Bcl-2 ratio and activating caspase 9 and 3 (Huang et al., 2018). Furthermore, compound **1** (IC_{50} = 62.82 μM) also showed an inhibition effect for MCF-7 cells via down-regulating HIF-1α, Snail and MMP-9, and up-regulating E-cadherin (Zhai et al., 2017).

Multidrug resistance is one of the main reasons for the failure of tumor treatment, which greatly limits the selection and use of cancer drugs. In vitro, 5 μg/mL total alkaloids of Uncaria reversed multidrug resistance (MDR) for vincristine on KBv200 cell line by 16.8-fold (Zhang et al., 2001). Isorhynchophylline (**44**) (0.5, 1.0 and 1.5 mg/L) reversed the MDR of A549/DDP cells by restraining the efflux of chemotherapeutic drugs and enhancing the induction of apoptosis by chemotherapeutic drugs (Zhou et al., 2009). The signal pathways related to the anti-cancer effect of URCU were shown in Fig. 20.

5.4. Antioxidant

Oxidation inhibitor can effectively inhibit the oxidation reaction of free radicals at low concentrations, which is the main research and development direction of health products and cosmetics enterprises. In vitro, Yin et al. found that different extracts of *U. rhynchophylla* had strong antioxidant capacity,

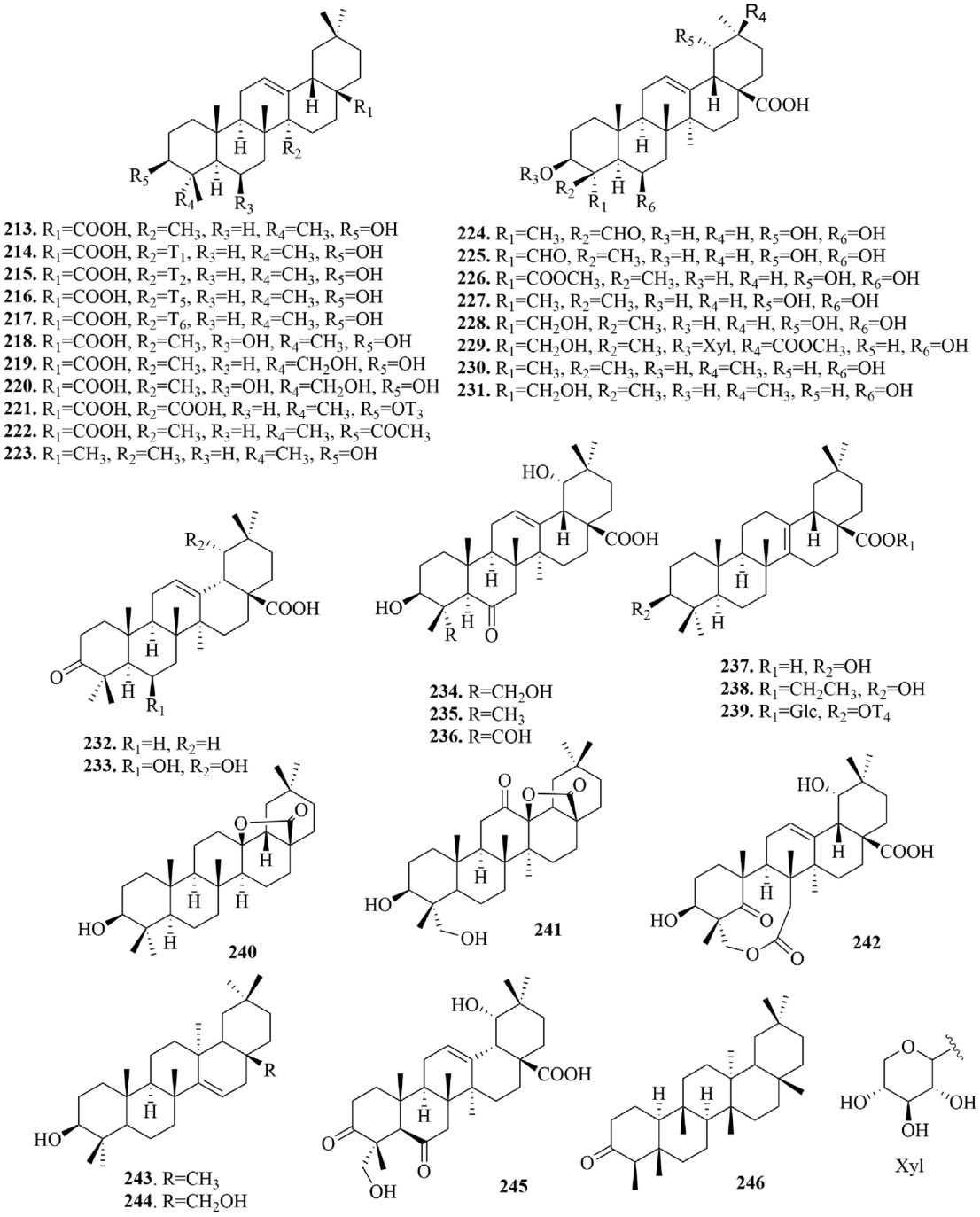


Fig. 11 Structures of oleanane type triterpenoids in URCU.

and the order of antioxidant capacity was ethanol extract > ethyl acetate extract > chloroform extract > petroleum ether extract (IC_{50} = 20.432, 1.547, 0.0283 and 0.00326 g/L) (Yin et al., 2010). Uncariol A (**277**), uncariol B (**278**), (±)-uncarilin A (**141**, **142**), (±)-uncarilin B (**143**, **144**), cinchonain Ia-Id (**279**–**282**), quercetin (**259**), (-)-epicatechin (**276**), methyl caffeate (**336**), quercetin-3-*O*-robinobioside (**265**) and rutin (**264**) showed comparable DPPH radical scavenging potentials with IC_{50} values were 22.26, 16.12, 10.28, 11.32, 12.67, 14.34, 15.72, 8.27, 3.22, 5.84, 7.52, 8.21, 5.35, 8.14, and 2.13 μM, respectively (Li et al., 2017a).

5.5. *Antiviral*

Dengue virus (DENV) is transmitted to humans by Aedes mosquitoes and is a public health issue worldwide. No antiviral drugs specific for treating dengue infection are currently available (Reis et al., 2008). In vitro, mitraphylline (**101**), isomitraphylline (**107**) and uncarine C-F (**99**, **104** and **97**) (1 μg/mL) were found to have significant inhibitory effects by lowering Dengue virus (DENV)-antigen cell rates. Moreover, these compounds exerted strong immunomodulation via declining TNF-α, IFN-α and IL-10 levels (Reis et al.,

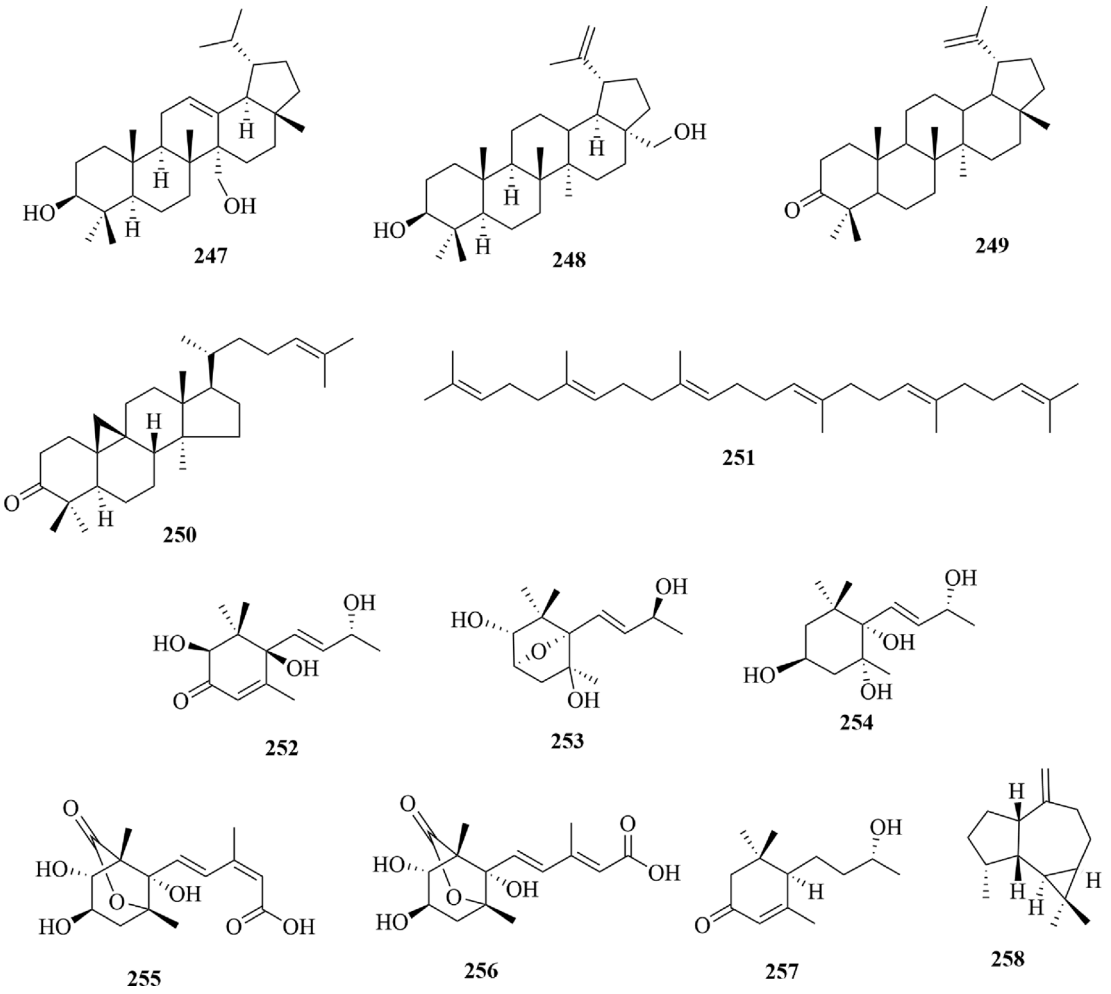


Fig. 12 Structures of other triterpenoids and sesquiterpenes in URCU.

2008). In addition, hirsutine (**1**) (10 μM) showed antiviral activities against all DENV serotypes by inhibiting the viral particle assembly, budding, and release step (Hishiki et al., 2017). Thus, compounds **1**, **97**, **99**, **101**, **104** and **107** may be the potential candidate to treat DENV.

5.6. Antiasthma

Asthma is a chronic inflammatory disease characterized by airway remodeling and inflammation. And proliferation of airway smooth muscle cells (ASMCs) is key to the progression of asthma (Li et al., 2021a). In vitro, rhynchophylline (**34**) (10 μM) inhibited the proliferation of ASMCs by inhibiting TGF-β1-mediated Smad and MAPK signaling pathways (Wang et al., 2019). In addition, it (40 or 80 mg/kg) also suppressed ASMC autophagy by suppressing the JAK2/STAT3 signal to achieve anti-asthma effect (Li et al., 2021a). Zhu reported that isorhynchophylline **(44)** could induce the apoptosis of ASMCs by up-regulating miR-200a and deactivating the FOXC1/NF-kB pathway to achieve anti-asthma effect (Zhu et al., 2020).

5.7. Sedative and hypnotic

Insomnia is a sleep disorder, which seriously affects the quality of human life. Sedation and hypnosis are traditional applications of URCU (Chen et al., 2019). In vivo, Chen et al. found that the stem hook, branch and leaf extracts of *U. rhynchophylla*, *U. macrophylla* and *U. hirsuta* at 15 g/kg could significantly inhibit the number of spontaneous activities in mice and prolong the sleep time of mice induced by pentobarbital (Chen et al., 2019). It was found that corynoxine (**37**) and corynoxine B (**36**) (30 mg/kg), isorhynchophylline (**44**) and geissoschizine methyl ether (**7**) (100 mg/kg) significantly reduced autonomic activity in mice. Meanwhile, compound **36** (30 mg/kg), **44** and **7** (60 mg/kg) also could inhibit the activity of mice (Sakakibara et al., 1999). Notably, rhynchophylline (**34**) (5, 10, 15 mg/kg) can exhibit a sedative effect by raising 5-hydroxyindole acetic acid (5-HIAA) in rat brain striata and hippocampus, and decreasing concentrations of norepinephrine (NE) on hippocampus and frontoparietal lobe of cortex (Lu et al., 2003). Meanwhile, oral administration of compound **37**, **36**, **34** and **44** (100 mg/kg) prolonged the hypno-

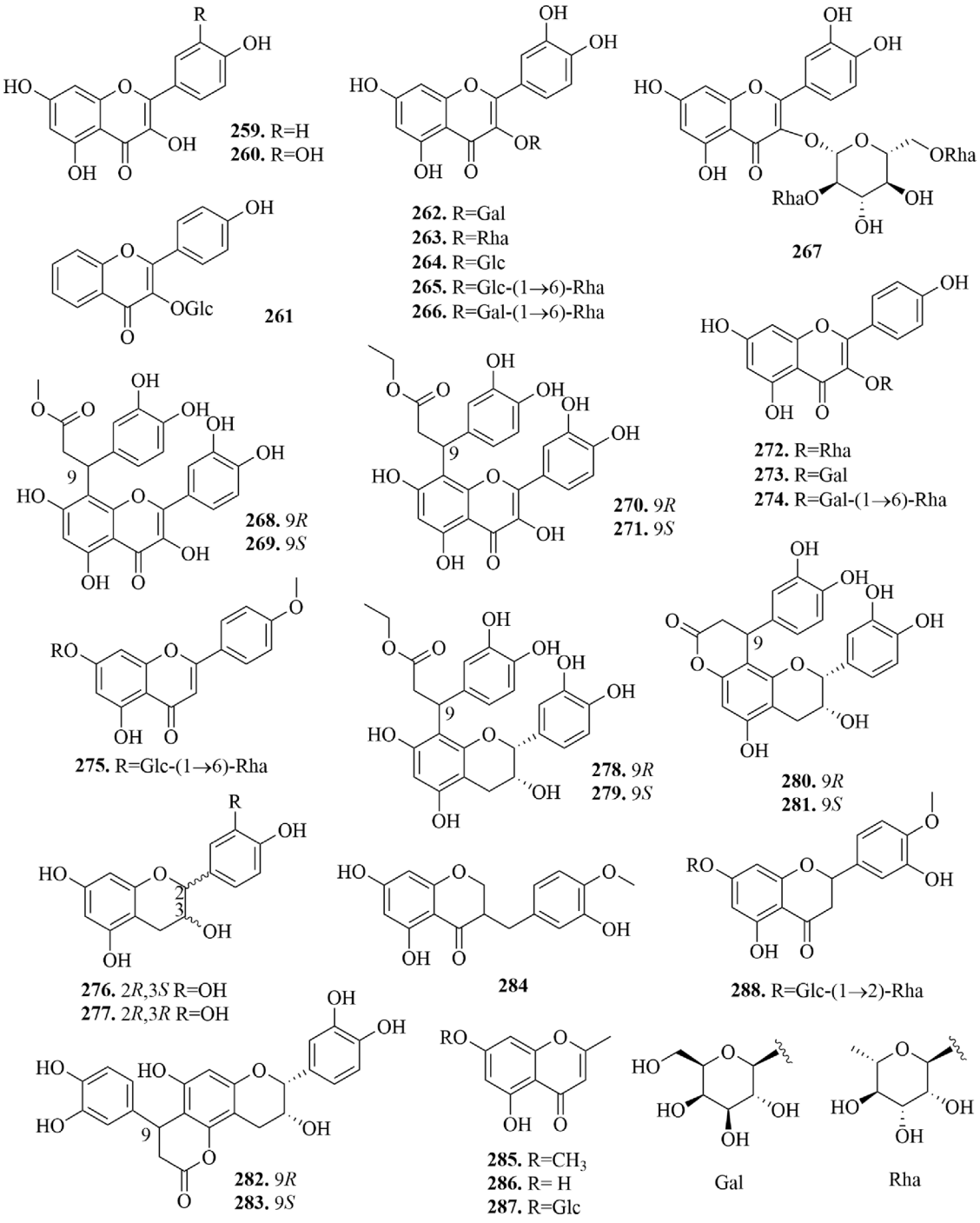


Fig. 13 Structures of flavonoids in URCU.

sis duration induced by thiopental in ICR mice (Sakakibara et al., 1998).

5.8. Anti-epilepsy

Epilepsy is a chronic disease in which sudden abnormal discharges of brain neurons cause transient brain dysfunction (Xu et al., 2001). In vivo, Wang et al. found that rhynchophylline (**34**) (10, 20, 40 mg/kg/d) showed a good antiepilepsy effect by inhibiting the expression of Toll-like receptor 4 and enhancing the activity of SOD (Wang and Cai, 2018). The ethanol extract of *U. rhynchophylla* (1 g/mL) could reduce the peak potential of pyramidal cells in the CA1 region of rat hippocampal slices induced by pilocarpine, which may be related to the inhibitory effect of rhynchophylline (**31**) on calcium influx and glutamate release (Xu et al., 2001). Oral *U. rhynchophylla* extract (1 g/kg, 5d/wk) can inhibit the excessive expression of S100 B protein and receptor of advanced glycation end products (RAGE) through RAGE pathway to reduce epilepsy in kainic acid (KA) induced epileptic SD rats (Tang et al., 2017). Research proved that 70 % alcohol extract of *U. rhynchophylla* (1 g/kg/day) and rhynchophylline (0.25 mg/

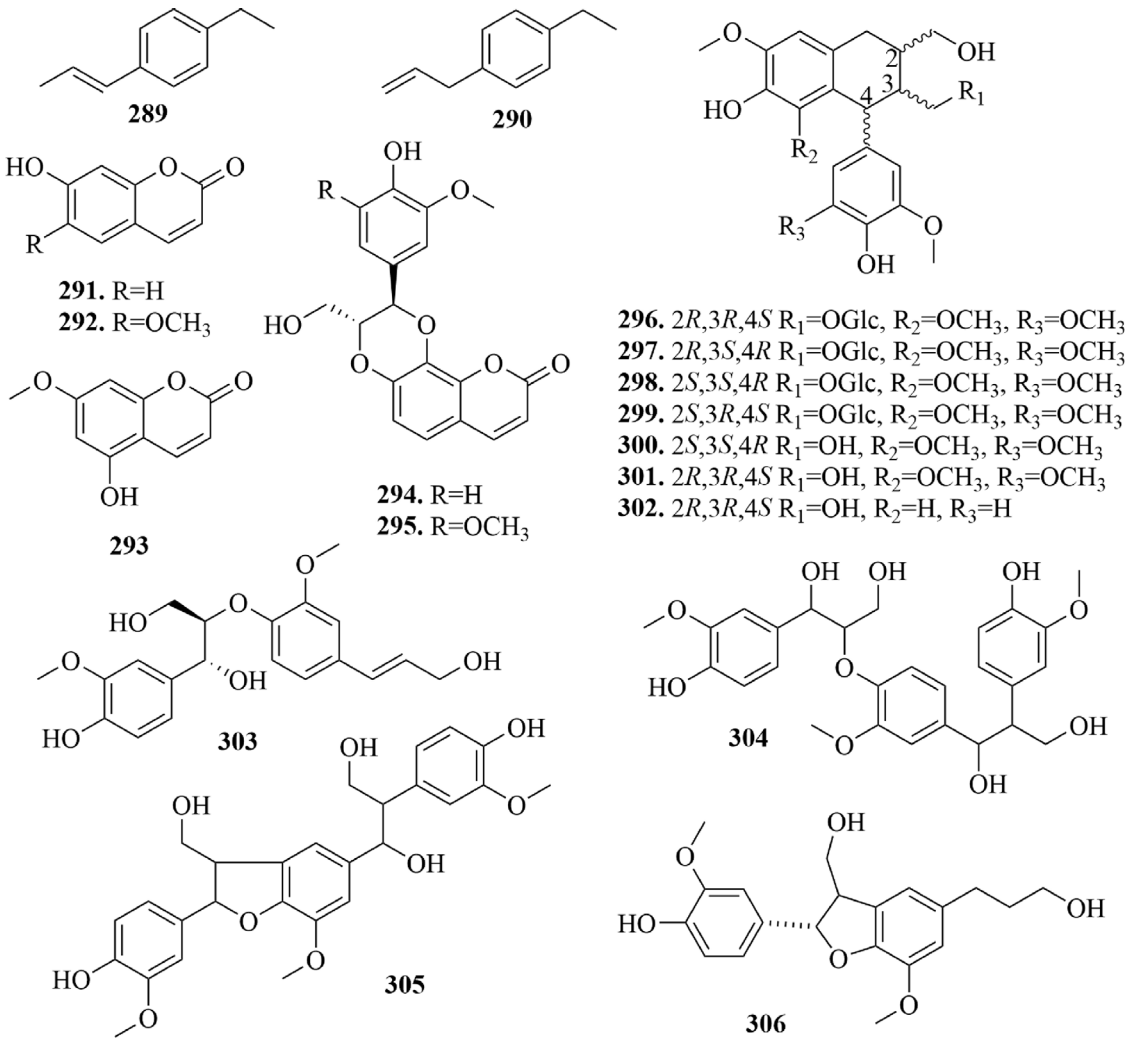


Fig. 14 Structures of phenylpropanoids in URCU.

kg) exhibited anti-convulsive effects in KA-induced rats by inhibiting IL-1β and BDNF gene expressions via suppressing TLR and neurotrophin signaling pathways (Ho et al., 2014). Meanwhile, rhynchophylline (**34**) (100 μM) effectively reduced the severity of seizures and neuronal hyperexcitation by inhibiting the current of persistent sodium (I_{NaP}) and *N*-methyl-D-aspartate receptor (NMDAR) (Shao et al., 2016). Geissoschizine methyl ether (**7**) (1–30 μM) showed antiepileptic activities by inhibiting voltage-gated sodium (Na_v), calcium (Ca_v), and delaying the currents of rectifier potassium (I_K) and the ligand-gated nicotinic acetylcholine (nACh) (IC_{50} = 1.3–13.3 μM). Meanwhile, in the electroshock-induced mouse seizure model, geissoschizine methyl ether (50–100 mg/kg) suppressed generalized tonic-clonic seizures. In the 6-Hz-induced mouse seizure model, oral administration of compound **7** (100 mg/kg) reduced treatment-resistant seizures (Xie et al., 2020). The signal pathways related to the anti-epilepsy effect of URCU were shown in Fig. 21.

5.9. *Anti-depression*

Depression is a mental disease with abnormal low spirit as the main clinical manifestation, which is reflected in the lack of monoamine neurotransmitters in the brain, especially norepinephrine (NE), 5-hydroxytryptamine (HT) and dopamine (DA) (Zhang et al., 2017). In vitro, uncarialin E (**19**), G (**21**), J (**54**) and K (**23**), 3α-dihydrocadambine (**138**), isorhynchophylline (**34**), hirsuteine (**2**), akuammigine (**77**), *Z*-geissoschizine (**13**) and corynoxeine (**37**) displayed significant magonistic effects towards 5-HT_{1A} receptor, whose EC_{50} values were 2.2, 0.1, 7.86, 7.32, 1.6, 2.0, 2.24, 1.18, 1.52, and 3.75 μM, respectively (Liang et al., 2019). In vivo, *U. rhynchophylla* EtOH extract displayed an agonistic effect against the 5-HT_{1A} receptor with an EC_{50} value of 17.42 μg/mL, which could ameliorate CUMS-induced depression-like behaviors in mice (Qiao et al., 2021). In reserpine-induced depression model mouses, isorhynchophylline (**44**) (10, 20 and 40 mg/kg) showed antidepressant activity by significantly up-regulating NE and 5-HT levels and inhibiting MAO-A activity in hippocampus and frontal lobe of mice (Xian et al., 2017). Isorhynchophylline (**44**) (20 or 40 mg/kg/d) reversed CUMS-induced depression via enhancing neurotrophins and up-regulating the phosphatidylinositol 3-kinase/protein kinase B/glycogen synthase kinase-3β (PI3K/ Akt/ GSK-3β) pathway (Xian et al., 2019). And, rhynchophylline (**34**) (25 mg/kg) exhibited rapid antidepressant-like effects by inhibiting EphA4 ephexin1

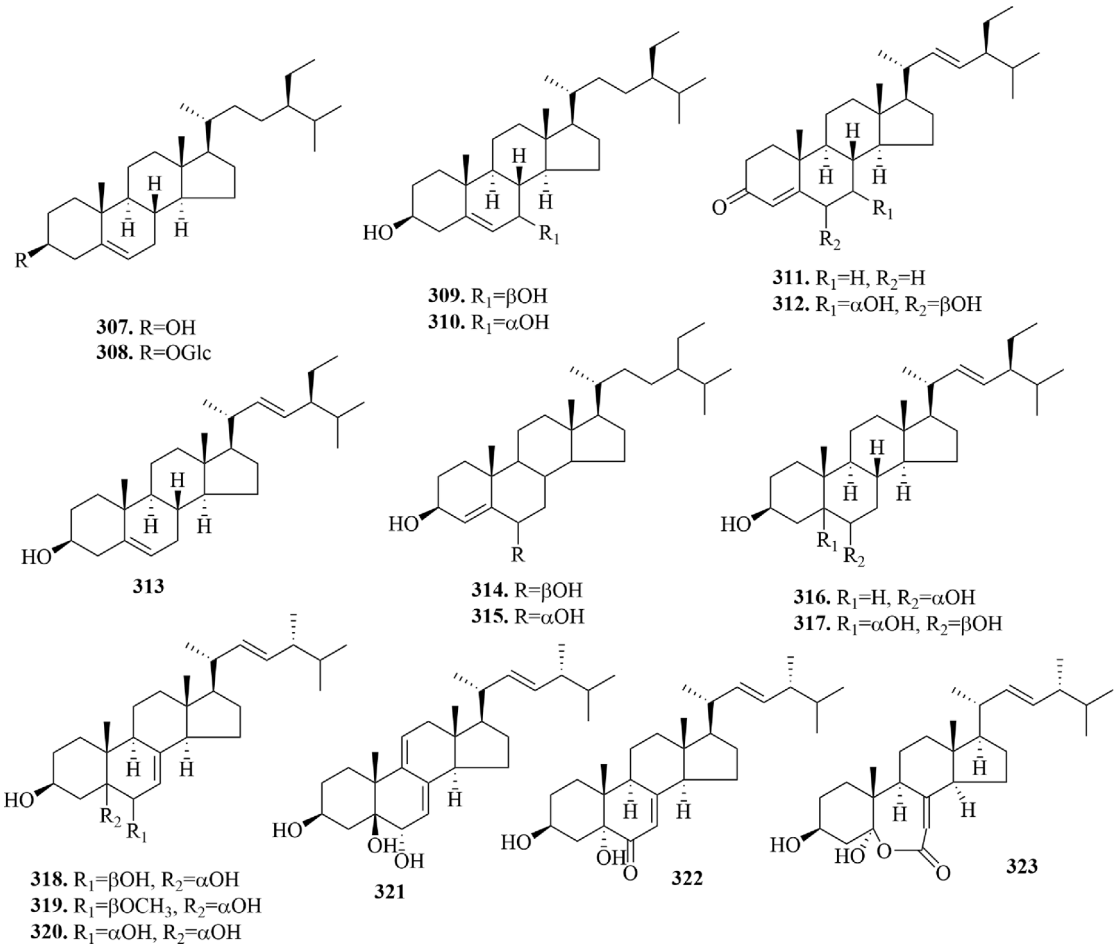


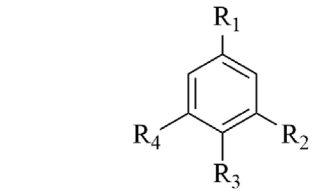
Fig. 15 Structures of phytosterols in URCU.

signaling and activating BDNF-tropomyosin receptor kinase (TrkB) signaling in a mice model of social defeat (Zhang et al., 2017).

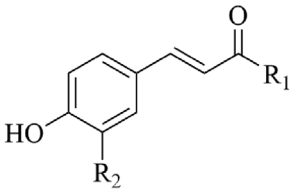
Melatonin (MT), secreted by the pineal gland, can coordinate circadian rhythm and neuroendocrine processes by activating MT1 and MT2 receptors. MT receptors can be used as a target for the treatment of depression, which could treat major depressive disorder by normalizing disturbances of circadian rhythms (Ekmekcioglu, 2006). In vitro, (±)-Uncarilins A and B (**141**–**144**) showed activities on the MT_1 and MT_2 receptors, at the tested concentration of 0.25 mM. And (-)-Uncarilins B (**144**) possessed the most potent activities on MT_1 and MT_2 receptors, with agonistic rates of 11.26 % and 52.44 % (Geng et al., 2017). In addition to alkaloids, catechin (**275**) manifested agonistic effects on melatonin receptors (MT_1 and MT_2), which inhibited MT_1 and MT_2 activities with EC50 values of 25.8 μM and 47.3 μM respectively (Ekmekcioglu, 2006).

5.10. Ischemic brain injury

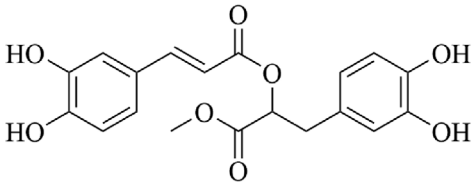
Ischemic brain injury is also known as stroke, which is a group of brain damage caused by sudden rupture of blood vessels in the brain or blood can not flow into the brain due to vascular obstruction (Ramos et al., 2017). In vivo, *U. macrophylla* alkaloids can significantly reduce the volume of cerebral infarction in rat cerebral ischemia model and reduce the damage of neurological function caused by ischemia (Xie, 2009). Methanol extracts of *U. rhynchophylla* (100–1000 mg/kg) were found to significantly protect hippocampal CA1 neurons against transient forebrain ischemia via inhibiting induction of cyclooxygenase-2 (COX-2) expression in hippocampus (Suk et al., 2002). In the permanent middle cerebral artery occlusion model, rhynchophylline (**34**) (30 mg/kg) not only improved neurological deficits and brain edema through activating the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway and inhibiting the TLRs/NF-κB pathway, and reduced infarct volume by increasing claudin-5 and BDNF (Huang et al., 2014). Notably, it (0.02 or 0.2 mg/mL) might protect cerebral ischemia by inhibiting necrosis and apoptosis of primary astrocytes in rats induced by ischemia-repefusion (IR) (Gao et al., 2009). Subsequent studies have shown that rhynchophylline (**34**) (3 μg/mL) protected astrocytes by inducing nuclear factor E2-related factor 2 (Nrf2) nuclear translocation via PI3K signaling pathway to alleviate oxidative damage induced by IR (Ying et al., 2012). In a rat model with MCAO and reperfusion-induced (I/R) injury, isorhynchophylline (**44**) (20 mg/kg) attenuated the infarct volume and improved the neurological function in I/R injury rats through reducing the neuronal death rate, brain water content, and aquaporin-4



324. R_1=$COOCH_2CH_3$, R_2=OH, R_3=OH, R_4=H
325. R_1=COOH, R_2=OCH_3, R_3=OH, R_4=H
326. R_1=COOH, R_2=OCH_3, R_3=H, R_4=OH
327. R_1=OCH_3, R_2=OCH_3, R_3=H, R_4=OCH_3
328. R_1=COOH, R_2=H, R_3=OH, R_4=H
329. R_1=COOH, R_2=OCH_3, R_3=OH, R_4=OCH_3
330. R_1=OH, R_2=H, R_3=OH, R_4=H
331. R_1=COOH, R_2=OH, R_3=OH, R_4=H
332. R_1=OH, R_2=H, R_3=CH_3, R_4=H
333. R_1=CHO, R_2=H, R_3=OCH_3, R_4=H
334. R_1=H, R_2=OH, R_3=OH, R_4=OH
335. R_1=OCH_3, R_2=OCH_3, R_3=OCH_3



336. R_1=OH, R_2=OH
337. R_1=OCH_2CH_3, R_2=OH
338. R_1=OCH_2CH_3, R_2=H
339. R_1=OCH_3, R_2=OH



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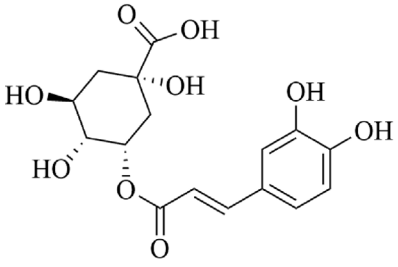

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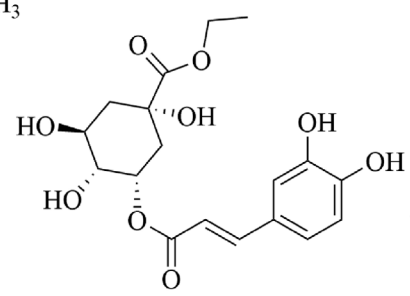

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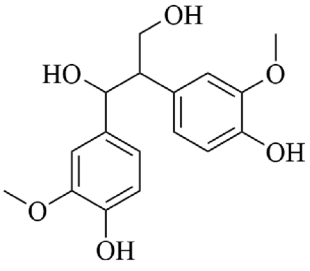

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Fig. 16 Structures of phenolics in URCU.

expression in the ischemic penumbra of I/R injury rats' brains. Besides, it (20 mg/kg) also treated microglial activation and inflammatory response via inhibiting lκB-α degradation, NF-$κB_{p65}$ activation and CX3CR1 expression (Deng et al., 2021).

5.11. Neuroprotection

URCU has the effect of extinguishing wind and settling convulsion. So, it is used to neurological diseases since ancient times (Li et al., 2021d). Modern pharmacological studies have shown that URCU has excellent neuroprotective activity. In vitro, the crude alkaloids of *U. rhynchophylla* (1, 10 and 100 μg/mL) showed a protective effect against NMDA-induced cytotoxicity in the hippocampal slices by suppressing the NMDA-induced expressions of apoptosis-related genes such as c-jun, p53, and Bax (Lee et al., 2003). Rhynchophylline (**34**) (5 or 50 μM) presented a protective effect on DA-induced apoptosis of NT2 cells through suppressing DNA degradation (Shi and Kenneth, 2002). The results showed that isorhynchophylline (**44**) (10 or 50 μM) significantly elevated cell viability, decreased the levels of intracellular ROS and MAD, increased the level of glutathione, and stabilized mitochondrial membrane potential in $Aβ_{25-35}$-treated PC12 cells via significantly suppressing the formation of DNA fragmentation and the activity of caspase-3 and moderating the ratio of Bcl-2/Bax (Xian et al., 2012). Notably, 5*β*-carboxystrictosidine (**130**) and chlorogenic acid (**340**) (12.5, 25, 50 or 100 μM) could protected mouse nerve growth factor (mNGF)-differentiated PC12 cells against toxicity induced by 6-hydroxydopamine (OHDA). They could scavenge ROS with IC_{50} values of 24.5 and 19.7 μM and reduce intracellular calcium levels with respective IC_{50} values of 46.9 and 27 μM, respectively. Meanwhile, they also inhibited caspase 3 and 9 activities with respective IC_{50} values of 25.6 and 24.5 μM for 1 and 19.4 and 16.3 μM for 2 (Lin et al., 2020). Meanwhile, it (10–50 μM) inhibits MPP^+-triggered neurotoxicity of primary cerebellar granule neurons via activating PI3-K/Akt/GSK3β/MEF2D signaling pathway (Hu et al., 2018). Zheng et al. found that rhynchophylline (**34**) exhibited a protective effect against the MPTP-induced decrease in MPP^+-induced neurotoxicity in PC12 cells (20 μM) by activating the PI3K/Akt signaling pathway. In vivo, it also exhibited a protective effect against the MPTP-induced decrease in tyrosine hydroxylase (TH)-positive fibers in C57BL/6 mice (30 mg/kg) by activating the PI3K/Akt signaling pathway (Zheng et al., 2021). The signal pathways related to the neuroprotection effect of URCU were shown in Fig. 22.

5.12. Anti-Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive neuronal loss with

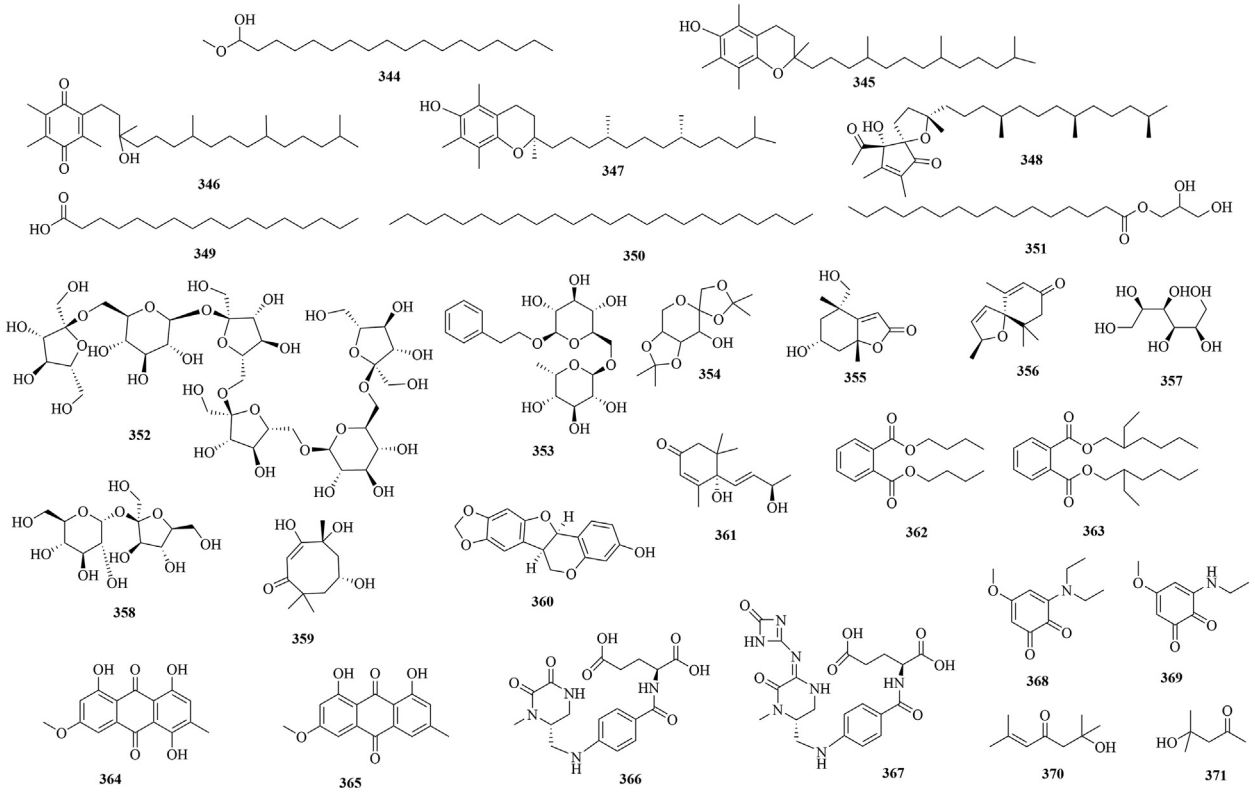

Fig. 17 Structures of other compounds in URCU.

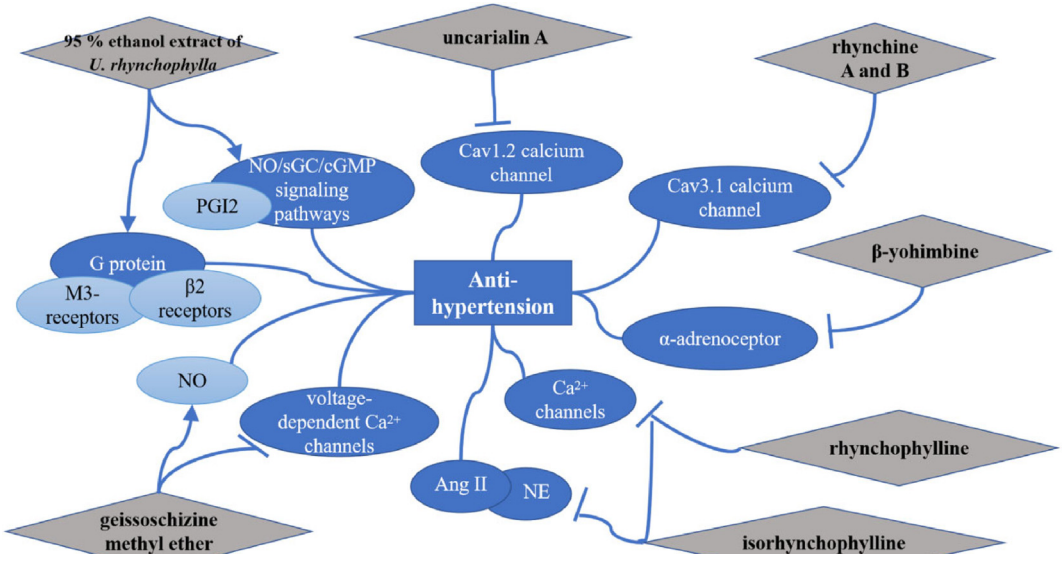

Fig. 18 The signal pathways related to the anti-hypertension effect of URCU.

amyloid β-peptide (Aβ) plaques. In vivo, 70 % ethanol extract of *U. rhynchophylla* (400 mg/kg/d) could attenuate Aβ deposition and Aβ-mediated neuropathology in 5 × FAD mice by alleviating gliosis and neurodegeneration, and impairing adult hippocampal neuron damage (Shin et al., 2018). Rhynchophylline (**34**) (50 mg/kg/d) effectively reduced the EphA4 activity in the hippocampus of amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice by blocking the EphA4- dependent signaling (Fu et al., 2014).

Oligomers of the amyloid-β 42 protein ($A\beta_{42}$) could cause synaptic dysfunction in the pathology of Alzheimer's disease (AD). In vivo, Fujiwara et al. found that three extracts of *U. rhynchophylla* (100 mg/mL) all could inhibit the aggregation of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ (Fujiwara et al., 2006). Whereas rhyn-

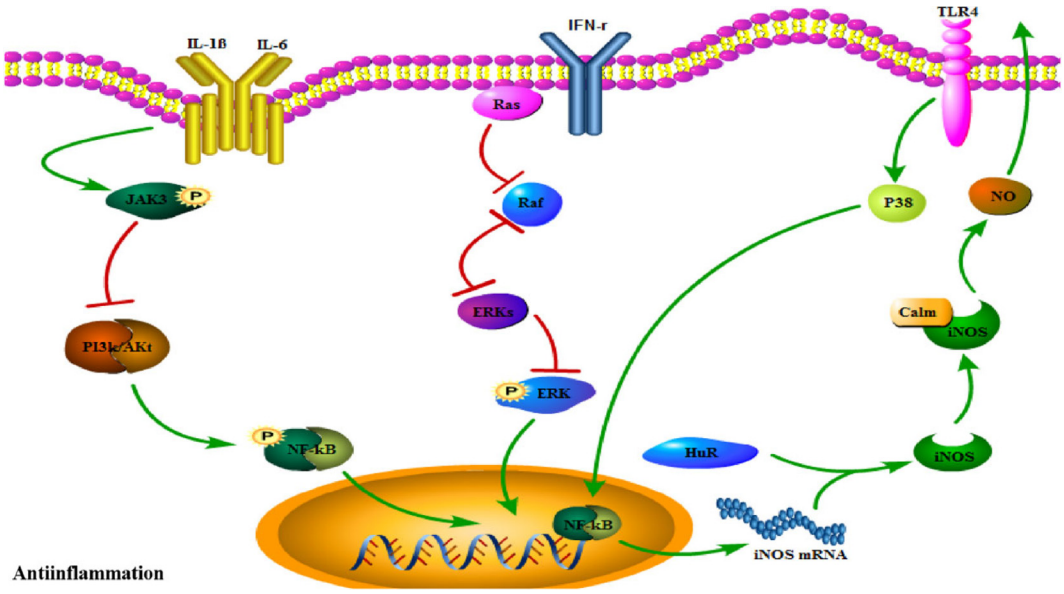

Fig. 19 The signal pathways related to the anti-inflammation effect of URCU.

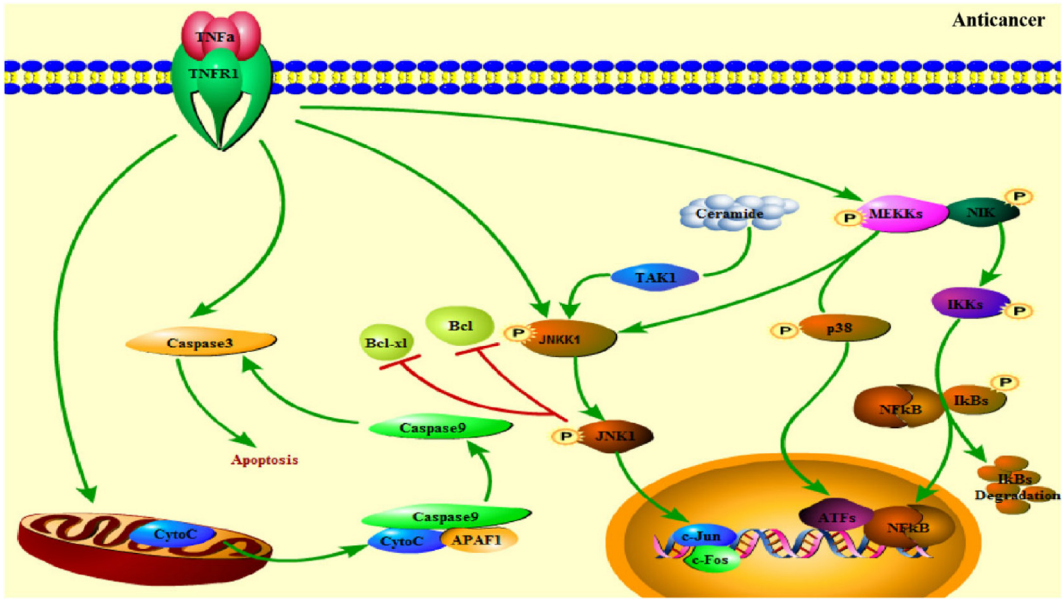

Fig. 20 The signal pathways related to the anti-cancer effect of URCU.

chophylline (**34**) (IC_{50} = 9.0 μM) could remold the spontaneous discharges disturbed by Aβ and counteract the deleterious effect of $A\beta_{1\text{-}42}$ (Shao et al., 2015). In $A\beta_{1\text{-}42}$-induced SD rats, compound **34** (100 μM) efficiently rescued the $A\beta_{1\text{-}42}$-induced spatial learning and memory deficits by reducing extrasynaptic NMDARs-mediated excitatory postsynaptic currents and downregulating GluN2B-NMDAR expression in the DG region (Yang et al., 2018). In vitro, Uncarinic acid C (**176**) (50 μM) was identified as a specific inhibitor of the nucleation phase of $A\beta_{42}$ aggregation. And structure–activity studies suggested that both a C-27 ferulate and a C-28 carboxylic acid group are required for its inhibitory activity (Yoshioka et al., 2016).

During the AD process, abnormally hyperphosphorylated tau protein may impede mitochondrial movement and affect mitochondrial distribution along the axons of cortical neurons, which would induce apoptosis and regional-specific neurodegeneration. Based on the pathological process of AD, corynoxine, isocorynoxeine, dihydrocorynatheine, isorhynchophylline and hirsutine were identified as key alkaloids that regulate tau phosphorylation (Zeng et al., 2021). In vitro, treatment with isorhynchophylline (**44**) (1, 10 or 50 μM) inhibited tau hyperphosphorylation by enhancing the expression of phosphorylated cAMP response element binding protein (p-CREB) through PI3K/Akt/GSK-3β signaling pathway (Xian et al., 2013). In vivo, it (20 or 40 mg/kg) could significantly

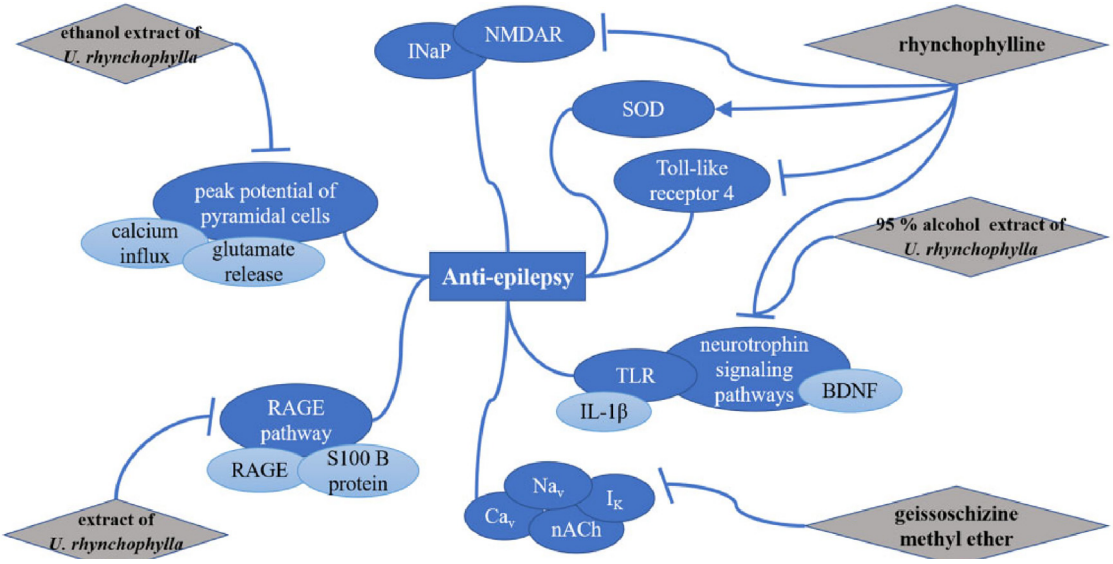

Fig. 21 The signal pathways related to the anti-epilepsy effect of URCU.

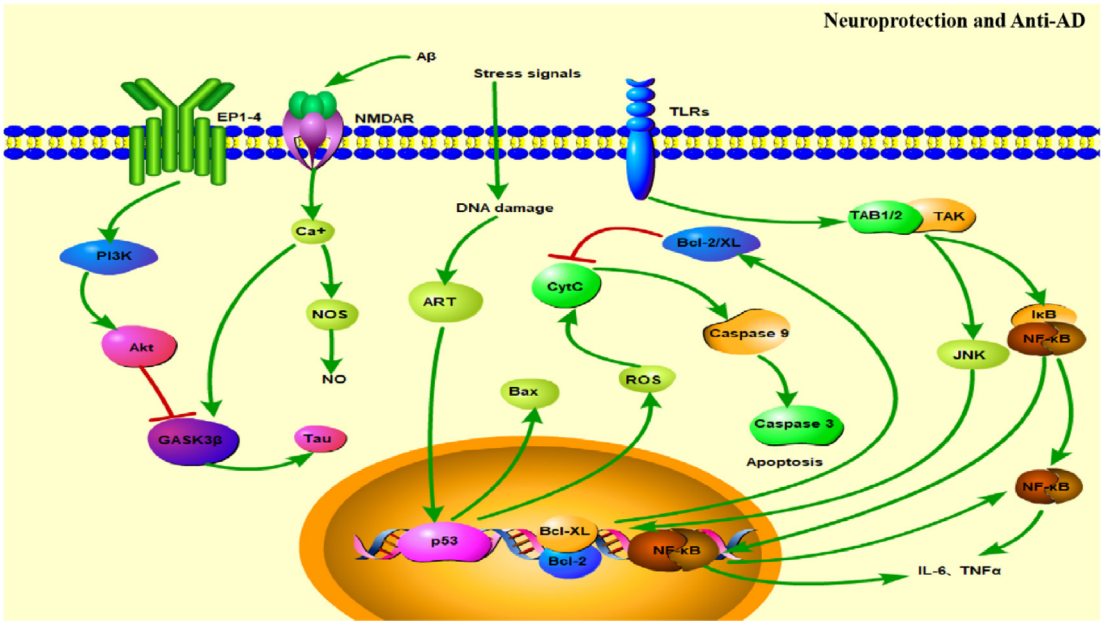

Fig. 22 The signal pathways related to the neuroprotection and anti-AD effect of URCU.

ameliorate the cognitive deficits induced by $A\beta_{25\text{-}35}$ in the rats, which also could attenuate $A\beta_{25\text{-}35}$-induced neuronal apoptosis in the hippocampus by down-regulating the ratio of Bcl-2/Bax, cleaved caspase-3 and caspase-9, as well as suppressing the tau protein hyperphosphorylation. The mechanistic study showed the neuroprotection of IRN is via inhibiting the GSK-3β activity and activating PI3K/Akt signaling pathway. (Xian et al., 2014a).

The massive accumulation of Aβ could directly damage the cell membrane and result in oxidative stress and ROS release. Ultimately it would lead to mitochondrial apoptosis and neuroinflammation. This suggested that we could treat AD by strengthening the anti-oxidation and anti-inflammatory functions of brain tissue. In vivo, Li et al. revealed that isorhynchophylline (**44**) (40 mg/kg) improved cognitive impairment in TgCRND8 transgenic mice. It could reduce Aβ generation and deposition ($A\beta_{40}$, $A\beta_{42}$) through modulating the amyloid precursor protein (APP) processing and phosphorylation. This process mainly including up-regulation of β-site APP cleaving enzyme-1 (BACE-1), phosphorylated APP (Thr668), presenilin-1 (PS-1) and anterior pharynx-defective-1 (APH-1), as well as insulin-degrading enzyme (IDE). Meanwhile, isorhynchophylline (**44**) also could inhabit tau hyperphosphorylation and neuroinflammation (TNF-α, IL-6 and IL-1β) and attenuate the ratios of p-c-Jun/c-Jun and p-JNK/JNK through inhibiting the activation of JNK signaling pathway. Microglia (Iba-1) and astrocytes (GFAP) were suppressed by isorhynchophylline, as well. (Li et al., 2019). Xian et al. demonstrated

that it (20 or 40 mg/kg) was able to ameliorate cognitive deficits induced by D-gal in mice through increasing GSH, SOD, CAT and NF-κB and decreasing MDA, PGE2, NO, COX-2 and iNOS (Xian et al., 2014b).

Based on the cholinergic hypothesis of AD pathogenesis, inhibition of acetylcholinesterase (AChE) activity could significantly increase the content of central acetylcholine, enabling the accumulation of acetylcholine at synapses, thereby improving the cognitive function of patients. In vitro, isorhynchophylline (**44**) (20 or 40 mg/kg) could inhibit AChE activity, and reduce oxidative damage to brain tissue via NF-κB signaling pathway (mainly NF-κB_{p65} and IκBα) to improve $AlCl_3$-induced learning and memory impairment in mice (Li et al., 2018). Notably, geissoschizine methyl ether (**7**), geissoschizine methyl ether *N*-oxide (**58**) and rhynchophylloside J (**93**) exhibited inhibitory activity against AChE with IC_{50} values of 3.7 μg/mL, 23.4 μM, and 10.5 μM, respectively (Yang et al., 2012; Jiang et al., 2015; Guo et al., 2019).

By summarizing the literature on URCU treatment AD, It can be proved that URCU could treat AD by reducing the accumulation of A*β* (especially oligomers of the $Aβ_{42}$), reducing abnormally hyperphosphorylated tau protein and inhibiting AChE. This could provide direction for subsequent research. The signal pathways related to the anti-AD effect of URCU were shown in Fig. 22.

5.13. Anti-Parkinson's disease

Parkinson's disease (PD) is a progressive, age-related, neurodegenerative disorder characterized by tremors, rigidity, and cognitive impairment. In vitro, 95 % EtOH extract of *U. rhynchophylla* (20 μg/mL) inhibited the expression of HSP90, which also could suppress MPP^+-induced SH-SY5Y cell apoptosis and autophagy through increasing the expressions of Bcl-2, Cyclin D1, p-ERK, p-PI3K p85, PI3K p110α, p-AKT, and LC3-I and decreasing cleaved caspase 3, Bax, p-JNK, p-p38, and LC3-II. Meanwhile, it also markedly decreased the apoptotic ratio and elevated mitochondrial transmembrane potential (DΨm) (Lan et al., 2018). In 6-OHDA induced PC12 cells, water extract of *U. rhynchophylla* (0.01–5 μg/mL) significantly reduced cell death and the generation of ROS, increased GSH levels, and inhibited caspase-3 activity. In addition, studies showed that isorhynchophylline (**44**) (0.3–100 μM) significantly reduced MPP^+-induced cell death and oxidative stress in PC12 cells by blocking the generation of ROS in upstream of the apoptosis signal-regulating kinase 1 (ASK1)/JNK pathway and the inositol-requiring enzyme 1 (IRE1)/caspase-12 pathway (Li et al., 2017b). Meanwhile, in vivo, posttreatment with water extract of *U. rhynchophylla* (5 mg/kg/d) significantly reduced dopaminergic neuronal loss in substantia nigra pars compacta in 6-OHDA-lesioned rats (Shim et al., 2009). In conclusion, the chemical constituents or extracts of URCU have been proven to have anti-PD effect in vitro and in vivo.

Accumulation of α-synuclein (α-syn) in the brain is a pathogenic feature and also a causative factor of parkinson's disease. In vitro, corynoxine (**45**) (25 μM) promoted the clearance of wild-type and A53T α-syn uclein, and suppressed p-Akt, p-mTOR, and p-p70 S6 kinase levels via up-regulating the Akt/mTOR pathway (Chen et al., 2014a). Furthermore, corynoxine B (**36**), an enantiomer of corynoxine (**45**), might restore the deficient cytosolic translocation of HMGB1 and autophagy in cells overexpressing SNCA by blocking SNCA-high mobility group box 1 (HMGB1) interaction (Song et al., 2014). Finaly, isorhynchophylline (**44**) (6.25, 12.5, 25 μM) promoted clearance of wild-type, A53T and A30P α-syn monomers, α-syn oligomers and α-syn/synphilin-1 aggresomes in neuronal cells via the autophagy-lysosome pathway. Notably, the autophagy was dependent on the function of Beclin 1 (Lu et al., 2012). Thus, compounds **45**, **36** and **44** may be the potential candidate to treat PD by reducing the accumulation of α-syn in the brain. The signal pathways related to the anti-PD effect of URCU were shown in Fig. 23.

5.14. Bone protection

Regulation of osteoclast differentiation and activity is a major target for preventing and treating pathological bone diseases. In vitro, water extract of the hooks and stems of *U. sinensis* could inhibit RANKL-induced differentiation of murine bone marrow macrophages and RAW264.7 cells into osteoclasts by inhibiting the activation of NF-kB and the expression of nuclear factor of activated *T*-cells, cytoplasmic 1, and suppress RANKL-induced bone loss with a significant amelioration of trabecular bone micro-structures. Furthermore, it also reduced serum TRAP5b activity and C-terminal cross-linked telopeptide of type I collagen levels (Ha et al., 2017). These results suggest that *U. sinensis* could be a promising herbal candidate for preventing and treating bone diseases such as osteoporosis.

All the pharmacological effects of this genus are summarized in Table 3.

6. Clinical application

As a traditional Chinese medicine, URCU had the effect of clearing heat and calming the liver, extinguishing wind and settling convulsion. So, URCU preparations are more widely used to treat hypertension and neurological diseases. This article collected Chinese patent medicines or preparations, which contained URCU, such as empirical prescriptions used in folklore, in-hospital preparations, and marketed drugs in Table 4.

6.1. Applications in the treatment of hypertension

Hypertension is a clinical syndrome characterized by increased systemic arterial blood pressure, which can be divided into primary hypertension and secondary hypertension (Oparil et al., 2018). For the treatment of hypertension, TCM has the advantages of fewer side effects, flexible dialectical treatment and remarkable curative effect.

Total of 42 cases of hypertension were treated with Gastrodia and Uncaria Decoction. The Blood pressure and incidence of adverse reactions was significantly shortened and the effective rates were 95.24 % (Zhao, 2021). In addition, 53 cases of senile hypertension complicated with depression were treated with Gouteng Jiangya Decoction combined with paroxetine and captopril. The effective rate of the treatment group was 96.23 % (Ye et al., 2019). Liu et al. found that Gastrodia and Uncaria Decoction combined with labetalol and magnesium sulfate injection was beneficial to control blood pressure level and significantly reduce adverse reactions (Liu et al., 2020). Xu et al. used Tianteng Jiangya Decoction combined

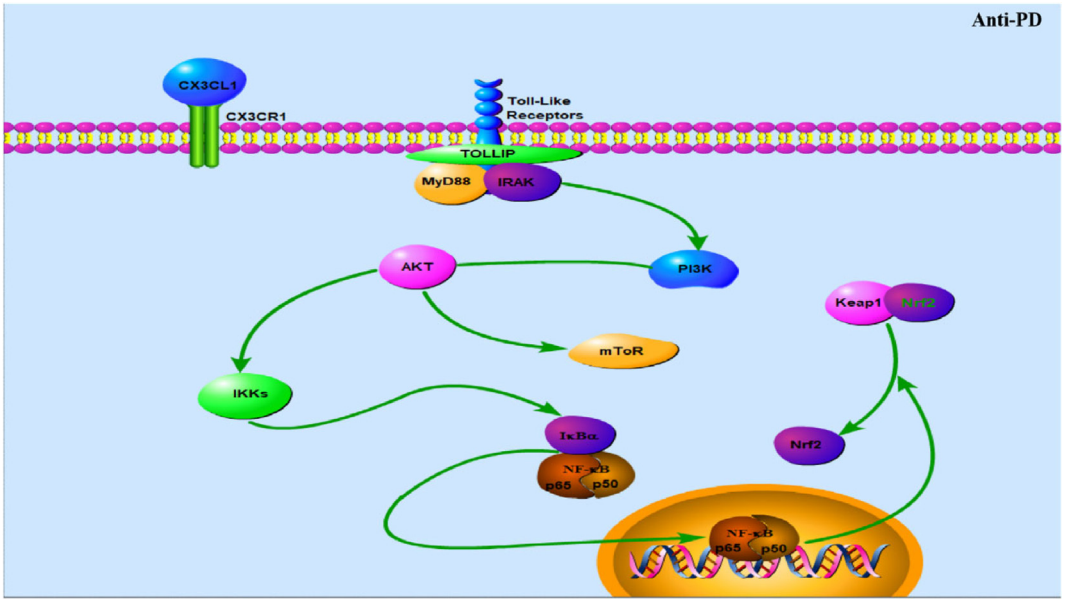

Fig. 23 The signal pathways related to the anti-PD effect of URCU.

with enalapril in the treatment of essential hypertension, the effective rate was 93.75 %. Meanwhile, headache and palpitation symptoms were significantly reduced (Xu and Zou, 2017). Dai used ionic antagonist and Lingjiao Gouteng Decoction to treat 45 elderly hypertensive patients. After 3 months of treatment, the effective rate was 93.3 % (Dai, 2017). Tianma Jiangya Granule and amlodipine were used to treat 30 patients with hypertension. After treatment, the blood pressure of patients was well controlled (Gao and Ding, 2017). Chen used Qinggan Antihypertension Granule in the treatment of 30 patients with hypertension, the effective rate was as high as 96.6 % (Chen, 2005). Li used Tengfu Jiangya Tablets to treat 30 patients with hypertension, and the effective rate was 93 % (Li, 2016).

6.2. Applications in the treatment of neurological diseases

6.2.1. Treatment of dementia

Dementia is a progressive disorder of intelligence, including Alzheimer's disease and vascular dementia. Li et al. used Tianma Gouteng Yin combined with nimodipine to treat 50 patients with vascular dementia and found that it could effectively improve the cognitive function, daily living ability and dementia degree of patients (Li et al., 2021d). Xu et al. used Gouteng powder in the treatment of 35 cases of alzheimer's disease patients and found that the treatment of AD is reliable, can improve the treatment efficiency and improve the cognitive function of patients (Xu et al., 2016). Chen et al. used Tianma Gouteng Granule to treat 40 patients with alzheimer's disease and found that it could significantly improve the cognitive function and self-living ability of patients (Chen and Guan, 2018).

6.2.2. Treatment of epilepsy

Epilepsy is a chronic disease of sudden abnormal discharge of brain neurons, resulting in transient brain dysfunction. Liu reported 40 cases of drug-resistant epilepsy treated with Chaibei Zhixian Decoction combined with carbamazepine. Three months later, the attack frequency and attack degree of patients were reduced. At the same time, the patient's energy and attention are improved (Liu, 2020).

6.2.3. Treatment of Parkinson's disease

Parkinson's disease, also known as tremor paralysis, is characterized by tremor, rigidity and pseudofacial appearance. Hu et al. used Jiawei Tianma Gouteng Yin combined with madopar and senfuluo to treat 20 patients with early Parkinson's disease. After 1 month, the patient's condition was improved. After discontinuing the use of Jiawei Tianma Gouteng Yin to continue to use madopar and senfuluo for one month, the therapeutic effect decreased (Hu et al., 2017). Yang et al. used Tianma Gouteng decoction combined with madopar tablets in the treatment of 48 patients with parkinson's disease had a good curative effect, which could improve the patient's tremor, insomnia and other main symptoms (Yang et al., 2017). Gu reported that the effective rate of Zhichan particles combined with Madopar in the treatment of 38 patients with Parkinson's disease was 97.30 % (Gu, 2019). Lin reported that Pinggan Maitong Tablets combined with dobutazide tablets in the treatment of parkinson's 29 cases, the patient's movement disorders were reduced (Lin, 2019).

6.2.4. Treatment of headache

Wang et al. used Pinggan Huayu Decoction to treat 38 cases of headache and found that the headache of patients was effectively improved. And the curative effect is better than flunarizine hydrochloride capsules group (Wang, 2012). Wu et al reported that Tianma Gouteng Yin was superior to flunarizine capsules in treating headache (Wu and Chen, 2020).

6.2.5. Treatment of insomnia

Insomnia usually refers to sleep difficulty or difficulty in maintaining sleep, which is a common set of sleep disorders. Cai et al found that Gouteng Powder was effective in treating insomnia. Patients with parkinson's disease often have sleep disorders (Cai and Wang, 2020). Wang et al. used Tiangouteng

Table 3 Pharmacological Activities of URCU.

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
Anti-hypertension	isorhynchophylline	In vivo	SHRs	0.245 mg/kg	renin-angiotensin and sympathetic system↓ (Ang II, NE↓)	(Li et al., 2020)
	dihydrocorynantheine	In vitro	Phe-induced contraction in rat thoracic aorta rings	IC_{50} = 6.73 μg/mL	–	(Wang et al.,2011a)
	95 % ethanol extract of *U. rhynchophylla*	In vitro	Phe-induced contraction in SD rats aortic rings	EC_{50} = 0.028 mg/mL	NO/sGC/cGMP signaling pathways, PGI2, G protein-coupled M3- and β2 receptors, and all the potassium channels except the Kca channel ↑	(Loh et al., 2017)
	rhynchophylline and isorhynchophylline	In vitro	contraction of arterial vessels of isolated rats induced by 60 mM KCl (by 1 μM Phe) (by 10 nM U46619)	IC_{50} = 20–30 μM IC_{50} = 100 μM IC_{50} =200 μM	L-type Ca2 + channels and a variety of other Ca2 + channels↓	(Zhang et al., 2004)
	uncarialin A	In vitro	Phe-induced contraction of rat mesenteric arteries	IC_{50} = 0.18 μM	L-type calcium channel subunit alpha-1C (Cav1.2)↓	(Yun et al., 2020)
	rhynchine A and B	In vitro	HEK293T cells and molecular docking	IC_{50} = 6.86 and 10.41 μM	Cav3.1 calcium channel ↓	(Zhou et al., 2021)
	geissoschizine methyl ether	In vitro	NE- rats aorta strip induced contraction	EC_{50} = 0.744 μM	NO↑, voltage-dependent Ca2 + channels↓	(Yuzurihara et al., 2002)
Antiinflammation	water extract of *U. rhynchophylla*	In vitro	RAW 264.7 cells	1 mg/mL	Akt and MAPK ↓ (NO and IL-1β↓)	(Kim et al., 2010)
	U. rhynchophylla alkaloids extracts	In vivo	LPS-induced preeclampsia rat model	35, 70, and 140 mg/kg (gavage)	IL-6, IL-1β, TNF-α, and IFN-γ ↓	(Wu and Xiao, 2019)
	rhynchophylline and isorhynchophylline	In vitro	LPS-induced N9 microglial cells	0.3–30 μM	NF-κB and ERK and p38 MAPKs ↓ iNOS protein ↓ (TNF-α, IL-1β and NO↓)	(Yuan et al., 2009)
	isorhynchophylline	In vitro	LPS-stimulated murine alveolar macrophages	(30 or 40 μM)	TLR4/NF-κB/ NLRP3pathway↑ (TNF-α, IL-1β, IL-6, and PAI-1↓)	(Zhou et al., 2019)
	corynoxeine, isocorynoxeine, rhynchophylline, isorhynchophylline and vincoside lactam	In vitro	LPS-induced primary cultured rat cortical microglia	IC_{50} = 15.7, 13.7, 18.5, 19.0 and 16.4 μM	–	(Yuan et al., 2008)
	strictosidine	In vitro	LPS-induced N9 microglia cells	IC_{50} = 8.3 μM	–	(Ma et al., 2009b)
	uncarinic acid I, 3β-hydroxy-27-p-(E)-coumaroyloxyursan-12-en-28-oic acid and 3β-hydroxy-27-(E) - coumaroyl-oleanen-12-en- 28-oic acid	In vitro	LPS-induced RAW264.7 cells	IC_{50} = 1.48, 7.01, and 1.89 μM	–	(Zhang et al., 2014)

Table 3 (*continued*)

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
Anticancer	*n*-BuOH fraction of *U. rhynchophylla*	In vitro	HepG2 cells	0.05, 0.1, and 0.2 mg/mL	caspases 7, 8 and PARP↑	(Kim et al., 2014)
	rhynchophylline	In vitro	HepG2 cells	130 μM	p38, ERK, JNK, CREB, Akt and STAT3 signals↓ and p53 signals↑ CXCR4, MMP-9, and MMP-2↓	(Lee et al., 2017)
	uncarinic acid E	In vitro	HepG2 cells	6, 12, 24, 48 μM	p53↑, Bax/Bcl-2 ↓ and caspases↑	(Zhao et al., 2006)
	ursolic acid and rhynchophylline	In vitro	HepG2 cells	50, 25, 12.5 and 6.25 μM	–	(Wu et al., 2017)
	3*β*,6*β*,19α-trihydroxy-olean-12-en-28-oic acid	In vitro	MCF-7 and HepG2 cells	IC_{50} = 78.2 and 73.9 μg/mL	–	(Sun et al., 2012b)
	U. rhynchophylla proanthocyanidins	In vitro	MDA-MB-231 cells	IC_{50} = 5, 10, 20, 30 and 40 μg/mL	G2/M cell cycle arrest (ROS, Bax/Bcl-2 and cleaved caspase 3 ↑ , mitochondrial membrane potential ↓)	(Chen et al., 2017)
	hirsutanine D-F	In vitro	MDA-MB-231 cells	100 μM	–	(Pan et al., 2017)
	hirsutine	In vitro	MCF-7 and MDA-MB-231 cells	IC_{50} = 447.79 and 179.06 μM	Bax/Bcl-2 ↓ caspase 9 and 3 ↑	(Huang et al., 2018)
	hirsutine	In vitro	MCF-7 cells	IC_{50} = 62.82 μM	HIF-1α, Snail and MMP-9 ↓ E-cadherin↑	(Zhai et al., 2017)
	hirsutine	In vivo	A549 xenograft mouse model	40–80 μM	ROCK1/PTEN/PI3K/ Akt signaling ↑	(Zhang et al., 2018)
	uncarinic acid A, uncarinic acid B, uncarinic acid C, uncarinic acid D, uncarinic acid E,3β-hydroxy-27-(E) -coumaroyl-oleanen-12-en-28 -oic acid, 3β-hydroxy-27-p-(E) -coumaroyloxyursan-12-en-28-oic acid and 3β-hydroxy-27-p-(Z) - coumaroyloxyursan-12-en-28-oic acid	In vitro	HCT-15, MCF-7, A549, and HT-1197 cells	IC_{50} = 0.5–6.5 μM	–	(Lee et al., 2000)
	3-diethylamino-5-methoxy-1,2-benzoquinone and 3-ethylamino-5-methoxy-1, 2-benzoquinone	In vitro	A549, HepG2 and A2780 cells	IC_{50} = 50.2–98.8 μM	–	(Zhang et al., 2016)
	isorhynchophyllic acid			IC_{50} = 5.8, 12.8 and 11.8 μM		
	hirsutine	In vitro	Jurkat Clone E6-1 cells	10, 25 and 50 μM	Bax, cleaved-caspase 3/ 9, Cyto-c protein, caspase-3 and 9 ↑ Bcl-2 protein ↓	(Meng et al., 2021)
	corynantheidine	In vitro	HL-60 and SW480 cells	IC_{50} = 13.96, 23.28 μM	–	(Wang et al., 2011a)
	total alkaloids of Uncaria	In vitro	MDR for vincristine on KBv200 cell line	5 μg/mL	–	(Zhang et al., 2001)

(*continued on next page*)

Table 3 (*continued*)

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
	isorhynchophylline	In vitro	MDR of A549/ DDP cells	0.5, 1.0 and 1.5 mg/L	efflux of chemotherapeutic drugs ↓	(Zhou et al., 2009)
Antioxidant	petroleum ether extract, chloroform extract, ethyl acetate extract, and ethanol extract of *U. rhynchophylla*	In vitro	OH radical scavenging assay	20.432, 1.547, 0.0283 and 0.00326 g/L	–	(Yin et al., 2010)
	Uncariol A, uncariolB, (±)-uncarilin A, (±)-uncarilin B,cinchonain Ia-Id, quercetin, (-) -epicatechin, methyl caffeate, quercetin-3-O-robinobioside and rutin	In vitro	DPPH radical scavenging assay	IC_{50} = 22.26, 16.12, 10.28, 11.32, 12.67, 14.34, 15.72, 8.27, 3.22, 5.84, 7.52, 8.21, 5.35, 8.14, and 2.13 μM, respectively	–	(Li et al., 2017a)
Antiviral	including mitraphylline, isomitraphylline and uncarine C-F	In vitro	Dengue Virus	1 μg /mL	DENV-antigen ↓ TNF-α, IFN-α and IL-10 ↓	(Reis et al., 2008)
	hirsutine	In vitro	A549 cells infected with DENV-1	10 μM	viral particle assembly, budding, and release step ↓	(Hishiki et al., 2017)
Antiasthma	rhynchophylline	In vitro	TGF-β1 induced hyperplasia of ASMCs	10 μM	TGF β1 induced Smad and MAPK signaling pathways ↓ (Smad4 and phosphorylation of Smad2 and Smad3 ↑, p-ERK1/2 and p-p38 ↑, Smad7↓)	(Wang et al., 2019)
	rhynchophylline	In vivo	OVA induced BALB/c mice asthma	40 or 80 mg/kg (gavage)	JAK2/STAT3 signaling pathway↓ (IL-6 ↓, SOD, CAT ↑)	(Li et al., 2021a)
			ASMCs isolated from BALB/c mice	10 μM or 20 μM	LC3 II, beclin-1, and ATG5 ↑, *P*62 ↓	
	isorhynchophylline	In vivo	OVA induced BALB/c mice asthma	40 mg/kg (gavage)	FOXC1/NF-kB pathway↓ miR-200a↑	(Zhu et al., 2020).
		In vitro	ASMCs isolated from BALB/c mice	10 μM	(IL-E, IL-13, IL-4, and IL-5↓)	
Sedative and hypnotic	ethanol extracts of *U. rhynchophylla, U. macrophylla* and *U. hirsute*	In vivo	Spontaneous activity test in Kunming mice pentobarbital sodium induced Kunming mice sleep time test	15 g/kg (gavage)	–	(Chen et al., 2019)
	corynoxine and corynoxine B isorhynchophylline and geissoschizine methyl ether	In vivo	ICR mice	30 mg/kg (gavage) 100 mg/kg (gavage)	mediating of the central dopaminergic system	(Sakakibara et al., 1999)
	rhynchophylline	In vivo	Wistar rats	5, 10, 15 mg/kg (intravenous injection)	5-HIAA↑, NE↓	(Lu et al., 2003)
	corynoxine, corynoxine B, rhynchophelline, and isorhynchophelline	In vivo	ICR mice	100 mg/kg (gavage)		(Sakakibara et al., 1998)

Table 3 (*continued*)

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
Anti-epilepsy	rhynchophylline	In vivo	lithium chloride-pilocarpine induced model of SD rats after status convulsion	10、20、40 mg/kg/d (intraperitoneal injection)	Toll-like receptor 4↓, SOD↑	(Wang et al., 2018)
	ethanol extract of *U. rhynchophylla*	In vitro	SD rat hippocampal slices induced by pilocarpine	1 g/mL	peak potential of pyramidal cells in CA1 region of rat hippocampal slices ↓ (calcium influx and glutamate release ↓)	(Xu et al., 2001)
	U. rhynchophylla extract	In vivo	KA induced epileptic SD rats	1 g/kg, 5 d/wk (gavage)	RAGE pathway ↓ (S100 B protein and RAGE ↓)	(Tang et al., 2017)
	rhynchophylline	In vivo	KA induced epileptic SD rats	0.25 mg/kg	TLR and neurotrophin signaling pathways↓ (IL-1β and BDNF ↓)	(Ho et al., 2014)
	70 % alcoholextract of *U. rhynchophylla*			1 g/kg/d		
	rhynchophylline	In vivo	pilocarpine induced SD rats	100 μM	INaP and NMDAR ↓	(Shao et al., 2016).
	geissoschizine methyl ether		SD rats (IC_{50} = 1.3–13.3 μM)	1–30 μM (gavage)	Na_v, Ca_v, I_K and nACh ↓	(Xie et al., 2020)
		In vivo	maximal electroshock - induced mouse	50–100 mg/kg (gavage)		
		In vivo	6-Hz-induced mouse seizure model	100 mg/kg (gavage)		
Anti-depression	*U. rhynchophylla* EtOH extract	In vivo	CUMS-induced depression-like behaviours in mice	EC_{50} = 17.42 μg/mL	5-HT_{1A}↑ CREB, BDNF and PKA↑	(Qiao et al., 2021)
	isorhynchophylline	In vivo	reserpine-induced BALB/c mouse depression model	10, 20 and 40 mg/kg (gavage)	NE, 5-HT ↑ MAO-A ↓	(Xian et al., 2017)
	uncarialin E, G, J and K, 3α-dihydrocadambine, isorhynchophylline, hirsuteine, akuammigine, Z-geissoschizine and corynoxeine	In vitro	Chinese hamster ovary CHO-K1 cell line	EC_{50} = 2.2, 0.1, 7.86, 7.32, 1.6, 2.0, 2.24, 1.18, 1.52, and 3.75 μM	5-HT_{1A} receptor ↓	(Liang et al., 2019)
	(±)-uncarilins A and B	In vitro	HEK293 cells	0.25 mM	MT_1 and MT_2 receptors↑	(Geng et al., 2017)
	catechin	In vitro	HEK293 cells	EC50 = 25.8 μM and 47.3 μM	MT_1 and MT_2 receptors↑	(Ekmekcioglu, 2006)
	isorhynchophylline	In vivo	CUMS-induced depression-like behaviors	20 or 40 mg/kg/d (gavage)	neurotrophins and PI3K/ Akt/ GSK-3β pathway ↑	(Xian et al., 2019)
	rhynchophylline	In vivo	Social defeat C57BL/6 mice	25 mg/kg (intraperitoneal injection)	EphA4 ephexin1 signaling ↓ and BDNF-TrkB signaling ↑	(Zhang et al., 2017)
Ischemic brain injury	*U. macrophylla* alkaloids	In vivo	Focal ischemic model SD rats	–	–	(Xie et al., 2009)
	methanol extracts of *U. rhynchophylla*	In vivo	transient global ischemia using 4-vessel occlusion model in Wistar rats	100–1000 mg/kg (intraperitoneal injection)	COX-2 ↓	(Suk et al., 2002)

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Table 3 (*continued*)

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
	rhynchophylline	In vivo	pMCAO model SD rats	30 mg/kg (intraperitoneal injection)	PI3K/Akt/mTOR signaling pathway↑ and TLRs/NF-κB pathway↓ (claudin-5 and BDNF↑)	(Huang et al., 2014)
	rhynchophylline	In vitro	primary astrocytes in rats induced by ischemia-repeffusion	0.02 or 0.2 mg/m	necrosis and apoptosis of astrocytes↓	(Gao et al., 2009)
	rhynchophylline	In vitro	astrocytes induced by ischemia reperfusion	3 μg/mL	PI3K signaling pathway↓ (Nrf2 nuclear translocation↑)	(Yin et al., 2012)
	isorhynchophylline	In vivo	a rat model with MCAO and I/R injury (microglial)	20 mg/kg (gavage)	aquaporin-4 expression ↓, lκB-α ↑ NF-κBp65, CX3CR1 expression↓	(Deng et al., 2021)
Neuroprotection	crude alkaloids of *U. rhynchophylla*	In vitro	NMDA-induced cytotoxicity in the hippocampal slices	1, 10, 100 μg/mL	c-jun, p53, and bax↓	(Lee et al., 2003).
	rhynchophylline	In vitro	DA-induced apoptosis of NT2 cells	5 or 50 μM	DNA degradation↓	(Shi and Kenneth, 2002)
	isorhynchophylline	In vitro	$A\beta_{25\text{-}35}$-treated PC12 cells	10 or 50 μM	ROS and MAD↓, glutathione↑ DNA fragmentation ↓ caspase-3 ↓ and Bcl-2/ Bax ↑	(Xian et al., 2012).
	5*β*-carboxystrictosidine and chlorogenic acid	In vitro	6-OHDA induced mNGF -differentiated PC12 cells	12.5, 25, 50 or 100 μM	ROS↓ (IC_{50} = 24.5 and 19.7 μM) intracellular calcium levels↓ (IC_{50} = 46.9 and 27 μM)caspase 3↓ (IC_{50} = 25.6 and 19.4 μM)caspase 9 ↓ (IC_{50} = 24.5 and 16.3 μM)	(Lin et al., 2020).
	rhynchophylline	In vivo	MPTP-induced neurotoxicity in C57BL/6 mice	30 mg/kg (intraperitoneal injection)	PI3K/Akt signaling pathway↑ (LDH and ROS↓)	(Zheng et al., 2021)
		In vitro	MPP + -induced neurotoxicity in PC12 cells	20 μM	PI3K/Akt signaling pathway↑ (Bax and caspase-3↓, Bcl-2 ↑)	
	rhynchophylline	In vitro	MPP + -triggered neurotoxicity of primary cerebellar granule neurons	10–50 μM	PI3-K/Akt/GSK3β/ MEF2D signaling pathway ↑	(Hu et al., 2018)
Anti-Alzheimer's disease	70 % ethanol extract of *U. rhynchophylla*	In vivo	Aβ-mediated neuropathology in 5 × FAD mice	400 mg/kg/d (gavage)	gliosis, neurodegeneration and hippocampal neuron damage ↓	(Shin et al., 2018)
	rhynchophylline	In vivo	APP/PS1 transgenic mice	50 mg/kg/d (gavage)	EphA4-dependent signaling ↓ (EphA4 ↓)	(Fu et al., 2014)

Table 3 (*continued*)

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
	water, methanol and ethanol extracts of U. rhynchophylla	In vitro	$A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$	100 mg/mL	–	(Fujiwara et al., 2006)
	rhynchophylline	In vivo	$A\beta_{1\text{-}42}$-induced spontaneous discharges in the hippocampal CA1 region of SD rats	IC_{50} = 9.0 μM (intrahippocampal injection)	spontaneous discharges ↓	(Shao et al., 2015)
	rhynchophylline	In vivo	$A\beta_{1\text{-}42}$-induced spatial cognition function impairment of SD rats	100 μM (intrahippocampal injection)	extrasynaptic NMDARs-mediated excitatory postsynaptic currents↓ (GluN2B-NMDAR expression ↓)	(Yang et al., 2018)
	uncarinic acid C	In vitro	$A\beta_{42}$	50 μM	–	(Yoshioka et al., 2016)
	isorhynchophylline	In vitro	-induced neurotoxicity in rat PC12 cells	1, 10 or 50 μM	PI3K/Akt/GSK-3β signaling pathway (tau protein↓ and p-CREB↑)	(Xian et al., 2013)
	isorhynchophylline	In vivo	$A\beta_{25\text{-}35}$-induced neuronal apoptosis in hippocampus	20 or 40 mg/kg (gavage)	GSK-3β↓ and PI3K/Akt signaling pathway↑ (Bcl-2/Bax, cleaved caspase-3,9 and tau protein hyperphosphorylation ↓)	(Xian et al., 2014a)
	isorhynchophylline	In vivo	TgCRND8 transgenic mice	40 mg/kg (gavage)	Aβ40, Aβ42↓ and APP processing and phosphorylation↓ (BACE-1, Thr668, PS-1, APH-1 and IDE↑) TNF-α, IL-6 and IL-1β↓ tau hyperphosphorylation↓ JNK signaling pathway ↑ (p-c-Jun/c-Jun and p-JNK/JNK↓)	(Li et al., 2019)
	isorhynchophylline	In vivo	D-gal induced cognitive deficits of mice	20 or 40 mg/kg (gavage)	GSH, SOD, CAT and NF-κB ↑ MDA, PGE2, NO, COX-2 and iNOS ↓	(Xian et al., 2014b)
	isorhynchophylline	In vivo	$AlCl_3$-induced learning and memory impairment in mice	20 or 40 mg/kg	NF-κB signaling pathway↓ ($NF\text{-}\kappa B_{p65}$ and IκBα↓) AChE ↓	(Li et al., 2018)
	geissoschizine methyl ether	In vitro	AChE	IC_{50} = 3.7 μg/mL	–	(Yang et al., 2012)
	geissoschizine methyl ether *N*-oxide	In vitro	AChE	IC_{50} = 23.4 μM	–	(Jiang et al., 2015)
	rhynchophylloside J	In vitro	AChE	IC_{50} = 10.5 μM	–	(Guo et al., 2019)

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Table 3 (*continued*)

Pharmacological effects	Effective fraction/ Compounds	Vitro or vivo	Models	Dosage	Pathway or possible target site	Ref.
Anti-Parkinson's disease	95 % EtOH extract of *U. rhynchophylla*	In vitro	MPP + -induced SH-SY5Y cells	20 μg/mL	Bcl-2, Cyclin D1, p-ERK, p-PI3K$_{p85}$, PI3K$_{p110\alpha}$, p-AKT, and LC3-I ↑ cleaved caspase 3, Bax, p-JNK, p-p38, and LC3-II.↓, DΨm↓	(Lan et al., 2018)
	water extract of *U. rhynchophylla*	In vitro	6-OHDA induced PC12 cells	0.01–5 μg/mL	ROS↓, GSH↑ and caspase-3↓	(Shim et al., 2009)
		In vivo	6-OHDA-lesioned rats	5 mg/kg/d (gavage)	dopaminergic neuronal loss ↓	
	isorhynchophylline	In vitro	MPP + -induced PC12 cells	0.3–100 μM	ASK1/JNK pathway and IRE1/caspase-12 pathway↓ (ROS↓)	(Li et al., 2017b)
	corynoxine	In vitro	PC12 cells	25 μM	wild-type and A53T α-syn uclein↓ Akt/mTOR pathway ↑ (p-Akt, p-mTOR, and p-p70 S6↓)	(Chen et al., 2014a)
	corynoxine B	In vitro	PC12 cells	–	SNCA-HMGB1 interaction↓	(Song et al., 2014)
	isorhynchophylline	In vitro	neuronal cells	6.25, 12.5, 25 μM	wild-type, A53T and A30P α-syn monomers↓, α-syn oligomers and α-syn/ synphilin-1 aggresomes ↓	(Lu et al., 2012)
Bone protection	water extract of the hooks and stems of *U. sinensis*	In vitro	RANKL-induced murine bone marrow macrophages and RAW264.7 cells	10–80 μg/mL	NF-kB and *T*-cells, cytoplasmic 1↓, serum TRAP5b and C-terminal cross-linked telopeptide of type I collagen↓	(Ha et al., 2017)

"–" means no reports were found.

decoction combined with Madopar to treat 38 patients with parkinson's insomnia. After treatment, the total sleep time was prolonged and the number of awakenings was reduced (Wang et al., 2013). Wang et al found that after taking Xinlekang tablets, the total sleep time of 43 patients with insomnia was prolonged, the sleep latency and wake time after sleep were shortened, and the sleep efficiency was improved (Wang et al., 2011b). Kong used Tianma Jiangya Granule combined with amlodipine to treat 30 patients with essential hypertension complicated with sleep disorders, and the effective rate was 74.6 % (Kong, 2020). Li used Zhenan decoction combined with zopiclone tablets in the treatment of 32 elderly patients with insomnia. The sleep quality, sleep latency and sleep persistence of the patients were better than those of the control group (Li, 2019).

6.2.6. Treatment of cerebral stroke

On the basis of conventional treatment, zhao et al. used Tian Ma Gou Teng Yin to treat 17 cases of lacunar cerebral infarction, 15 cases were cured, 2 cases were improved, and the effective rate was 100 % (Zhao and Zhang, 2014). Wu used Huatan Tongluo Decoction to treat 30 patients with transient cerebral ischemia. The neurological deficits of patients were restored and daily living abilities were improved (Wu, 2016). Likewise, Xu et al. used Sanchong Banxia Baizhu Tianma Decoction to treat 45 patients, of which 36 cases were significantly improved, accounting for 80 %; 5 cases were improved, accounting for 11.11 % (Xu, 2019).

6.2.7. Treatment of migraine

Cai used Tiangong Xiaoyao decoction combined with flunarizine hydrochloride capsules to treat migraine. The clinical effective rate of 42 patients was 92.86 % (Cai, 2021). Wang reported that headache granules reduced the number and duration of migraine attacks in 35 patients (Wang, 2021). Tang used Yangxue Qingnao Granule to treat 45 patients with migraine, found that it could effectively improve the symptoms of migraine patients and reduce the possibility

Table 4 Chinese patent medicines or preparations containing URCU.

Prescription Name	Prescription composition	Functions and Treatments
Gastrodia and Uncaria Decoction (Tian Ma Gou Teng Yin)	Shi jue ming, Tian ma, Yi mu cao、Du zhong、Gou teng, Huang qin, Niu xi, Sang ji sheng, Shou wu teng, Zhi zi	Primary hypertension Pregnancy hypertension Vascular dementia Parkinson 's disease Insomnia Cerebral stroke
Gouteng Jiangya Decoction	San qi, Bai shao, Tian ma, Zhi zi, Sang ji sheng, Du zhong, Mu li, Di long, Gou teng, Luo bu ma, Suan zao ren, Gan cao, Xiang fu, Dan shen	Senile hypertension complicated with depression
Tianteng Jiangya Decoction	Tian ma, Ju hua, Gou qi zi, Sheng di huang, Niu xi, Bai shao yao, Jue ming zi, Gou teng, Ge teng, Du zhong	Primary hypertension
Lingjiao Gouteng Decoction	Sheng di, Gou teng, Ju hua, Fu shen, Bai shao, Zhu ru, Sang ye, Chuan bei, Gan cao, Ling yang jiao	Senile hypertension Acute cerebral hemorrhage
Tianma Jiangya Granules	Tian ma, Gou teng, Shi jue ming, Zhi zi, Niu xi, Yi mu cao, Suan zao ren	Hypertension Insomnia
Qinggan Antihypertension Granule	Huang lian, Gou teng, Ze xie, Xuan shen	Primary hypertension
Tengfu Jiangya Tablets	Gou teng, Lai fu zi	Hypertension
Gouteng powder	Gou teng, Chen pi, Bna xia, Mai dong, Fu lin, Fu shen, Ren shen, Ju hua, Fang feng, Gan cao, Shi gao	Alzheimer's disease Insomnia
Tianma Gouteng Granules	Shi jue ming, Tian ma, Yi mu cao、Du zhong、Gou teng, Huang qin, Niu xi, Sang ji sheng, Shou wu teng, Zhi zi	Alzheimer's disease
Chaibei Zhixian Decoction	Chai hu, Tian ma, Zhe bei mu, Di long, Ban xia, Shi chang pu, Mu li	Epilepsy
Jiawei Tianma Gouteng Yin	Shi jue ming, Tian ma, Yi mu cao、Du zhong、Gou teng, Huang qin, Niu xi, Sang ji sheng, Shou wu teng, Zhi zi, Hong jing tian, Jiang huang	Parkinson 's disease
Zhichan particles	Huang qi, Dan shen, Gou teng, Zhi mu, Bai shao, Da hunag, Sheng ma	Parkinson 's disease
Pinggan Maitong Tablets	Tian ma, Gou teng, Shi jue ming, Tian ma, Dan nan xing, Tian zhu huang, Bei mu, Zhi zi, Shui zhi, Di long	Parkinson 's disease
Pinggan Huayu Decoction	Tian ma, Gou teng, Chuan qiong, Bai shao, Dang gui, Sheng di, Huang qin, Dan pi,Dan shen, Di long, Wu gong, Gan cao	Headache
Xinlekang tablets	Gou teng, Suan zao ren, Luo fu mu	Insomnia
Zhenan decoction Decoction	Di huang, Dang gui, Bai shao, Tian ma, Gou teng, Suan zao ren, Ye jiao teng, Xia ku cao, Huang qin, Da zao	Insomnia
Huatan Tongluo Decoction	Ban xia, Ju hong, Zhi qiao, Chan xiong, Hong hua, Yuan zhi, Shi chang pu, Fu lin, Dang shen, Dan shen, Tian ma, Gou teng, Xiang fu, San qi, Dang gui, Chi shao, Ge gen, Gan cao	Cerebral stroke
Sanchong Banxia Baizhu Tian ma Decoction	Quan xie, Wu gong, Jiang can, Gou teng, Tian ma, Fu lin, Pu huang, Ban xia, Bai zhu, Bai shao, Chuan xiong, Gan cao	Cerebral stroke
Tianwu Xiaoyao Decoction	Tian ma, Gou teng, Chai hu, Shi jue ming, Bai shao, Dang gui, Ge gen, Chuan niu xi, Wu gong, Quan xie, Chuan xiong, Yan hu suo, Bai zhi, Fu lin, Gan cao	Migraine
Touteng Granules	Tian ma, Gou teng, Chai hu, Huang qin, Chuan lian zi, Chuan xiong, Bai shao, Dang gui, Yan hu suo, Zhi zi, Yu jin, Jiang huang, Jiang can, Chan tui, Gan cao	Migraine
Yangxue Qingnao Granules	Dang gui, Chuan xiong, Zhen zhu mu, Bai shao, Xia ku cao, Jue ming zi, Yan hu suo, Xi xin, Di huang, Ji xue teng, Gou teng	Migraine
Gouju Qingxiang Decoction	Gou teng, Ju hua, Xia ku cao, Zhi zi, Qing xiang zi, Mu li, Dan shen, Gan cao	Migraine
Shentian Zhidong Decoction	Tai zi shen, Tian ma, Bai zhu, Fu lin, Shi chang pu, Yu jin, Gou teng, Zhen zhu mu, Yi zhi ren, Bai shao	Ticdisorder
Qingre Pinggan Granules	Xia ku cao, Tian ma, Gou teng, Ju hua, Chan tui, Man jin zi, Ji li, Shi hu, Bai shao, Long gu, Mu li, Dang shen, Chen pi, Gan cao	Ticdisorder
Qinggan Dingjing Decoction	Shi chang pu, Yu jin, Gou teng, Tian ma, Shi jue ming, Quan xie, Jiang can, Chuan xiong, Ju hua, Gan cao	Ticdisorder
Gouteng Yinzi	Quan xie, Chan tui, Fang feng, Jin yin hua, Chuan xiong, Lian qiao, Jiang can, Jie geng, Niu bang zi, Dan dou chi, Gou teng, Dang shen, Tian ma, Gan cao	Ticdisorder
Sangye Gouteng Decoction	Sang ye, Gou teng, Ju hua, Chan tui, Jiang can, Can sha, Hu lu cha, Lian qiao, Huang qin, Gan cao, Pu gong ying, Chai hu, Chen pi	Ticdisorder
Gouteng Dingfeng Decoction	Gou teng, Chuan lian zi, Shi jue ming, Gou qi, Bai ji li, Quan xie, Chan tui, Di long, Sheng di, Shu di, Gan cao	Ticdisorder

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Table 4 (*continued*)

Prescription Name	Prescription composition	Functions and Treatments
Tianteng Zhichou Granules	Tian ma, Gou teng, Long gu, Mu li, Jiang can, Chen pi, Bai zhu, Gan cao	Ticdisorder
Wenshen Gouteng Decoction	Dang shen, Gou teng, Lian zi xin, He huan pi, Fu shen, Fu xiao mai, Huai shan yao, Bu gu zhi	Menopausal syndromes
Juhua Gouteng Decoction	Ju hua, Gpu teng, Bai Shao, Fu lin, Ji li, Niu xi, Di huang, Dan pi, Long gu, Mu li	Menopausal syndromes
Tiangou Erxian Decoction	Tian ma, Gou teng, Shi ju ming, Huai niu xi, Ye jiao teng, Sang ji sheng, Du zhong, Huang qin, Zhi zi, Chuan xiong, Dang gui, Yi mu cao, Xian mao, Xian ling pi, Ba ji tian, Huang bai	Menopausal syndromes
Qingxin Zishen Fang	Lian zi xin, Huang lian, Gou teng, Chao zao ren, Di huang, Shan zhu yu, Dan shen, Fu xiao mai	Menopausal syndromes
Gouqin Disui Decoction	Gou teng, Huang qin, Bai shao, Dang gui, Chuan xiong, Mu gua, Ren dong teng, Gan cao	Hemifacial spasm
Shaoyao Gouteng Muer Tang	Bai shao, Gou teng, Gan cao, Yu li ren, Quan xie, Tian ma, Jiang can, Bai ju zi, Hei mu er	Postherpetic neuralgia

of recurrence (Tang, 2020). Li ussed Gouju Qingxiang decoction combined with sibelium to treat 31 migraine patients, the symptoms of patients were significantly improved (Li, 2020).

6.2.8. Treatment of ticdisorders

Ticdisorder is a complex and chronic neuropsychiatric disorder characterized by rapid, involuntary, sudden, repetitive, single or multiple muscle movements and vocal tic. Su used Shentian Zhidong decoction in the treatment of tic disorder, the frequency, complexity and tic frequency of 30 patients were reduced (Su, 2017). Fan used Qingre Pinggan granules to treat 30 patients, including 1 case of clinical control, 11 cases markedly effective and 16 cases effective, the total effective rate was 93.30 %, which could effectively reduce the frequency, intensity and complexity of motor and vocal tic (Fan, 2020). Xu used Gouteng Yinzi to treat 30 cases of tic disorder, the effective rate was 93.33 %, and the therapeutic effect was remarkable. Sangye Gouteng Decoction can significantly improve the motor tic and tic symptoms of children in the middle and late stages of tic disorder treatment (Xu, 2020). Gouteng Dingfeng Decoction in the treatment of 31 patients with ticdisorder, 8 cases were cured, 14 cases markedly effective, 6 cases effective, 3 cases ineffective, the total effective rate was 90.3 % (Zhang, 2019). In addition, the effect of Tianteng Zhichou Granules had the same effect as sulpiride hydrochloride in improving motor tic, and the effect is better than sulpiride hydrochloride in improving the type and complexity of vocal tic (Mou, 2020).

6.3. Applications in the treatment of menopausal syndrome

The menopausal syndrome refers to a series of physical and mental symptoms caused by the fluctuation or reduction of sexual hormones in women before and after menopause. Zong et al. used Wenshen Gouteng Decoction combined with tamoxifen in the treatment of 30 patients with perimenopausal syndrome after breast cancer surgery. It was found that it could not only alleviate the symptoms of patients with the menopausal syndrome but also improve the endocrine level of patients (Zong et al., 2021). Lin reported that Juhua Gouteng Decoction combined with nilestriol promoted the rapid disappearance of symptoms in 88 patients, improved the secretion of sex hormones, increased bone mineral density, reduced endometrial thickness (Lin, 2022). Likewise, Tiangou Erxian Decoction in the treatment of 60 patients with menopausal syndromes had a good curative effect, which can improve symptoms (Zhou et al., 2017). Moreover, Yao used Qingxinzishen Decoction to treat 30 patients with menopausal syndrome, and the total clinical effective rate was 86.67 %. It could effectively alleviate the clinical symptoms of patients and improve the level of sex hormone indicators (Yao, 2021).

6.4. Applications in other diseases

Jiang reported that the therapeutic effect of Gouqin Disui Decoction in the treatment of 30 HFS patients was remarkable. The total effective rate of the experimental group was 83.33 % (Jiang, 2018). Deng et al reported that Shaoyao Gouteng Muer Decoction had good clinical efficacy in the treatment of postherpetic neuralgia, and the effective rate of 28 patients was 92.86 % (Deng et al., 2016). Li et al. used Lingjiao Gouteng Decoction combined with glycerol fructose to treat acute cerebral hemorrhage with remarkable clinical effect, which could effectively promote the reduction of cerebral hematoma and peripheral edema, improve cerebral blood flow, alleviate local inflammatory response, protect cerebral nerve cells (Li et al., 2021e).

7. Discussion

This review summarized current research development regarding botany, phytochemistry, pharmacology and clinical application of URCU. More than 371 compounds have been isolated and identified from this genus. Meanwhile, modern pharmacological research revealed that URCU had significant pharmacological properties including anti-hypertension, anti-inflammation, anticancer, antioxidant, antiviral, anti-epilepsy, anti-depressant, ischemic brain injury, neuroprotection, anti-Alzheimer's disease, anti-Parkinson's disease and antiasthma. Regardless, there are still several aspects that need to be concerned in the further development of URCU.

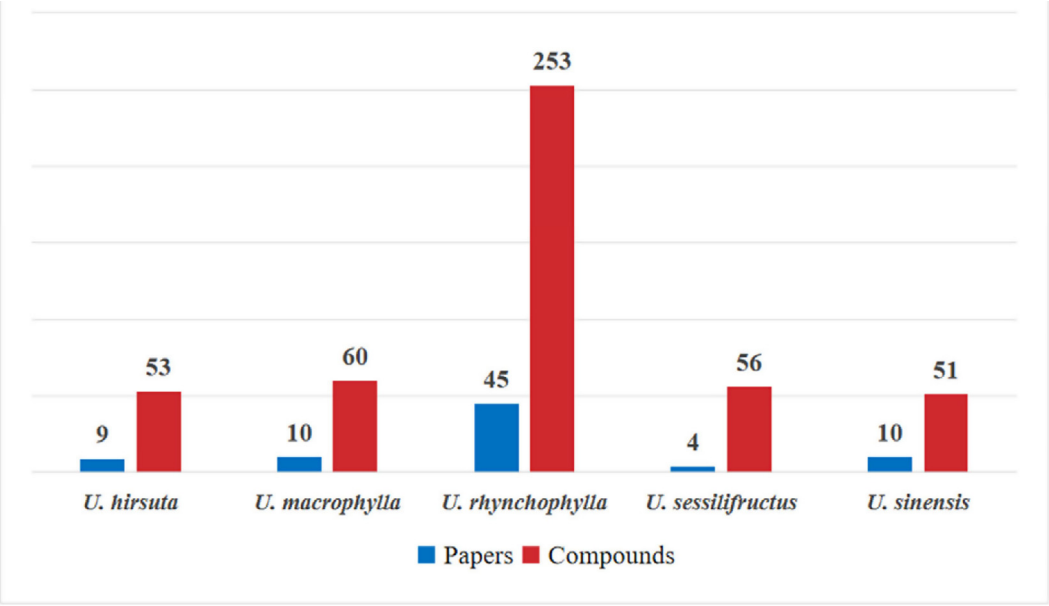

Fig. 24 The amount of all published chemical reports and secondary metabolites regarding URCU.

Firstly, we collected 75 papers about the chemical constituents of URCU, including 45 papers about *U. rhynchophylla*, 9 papers about *U. hirsuta*, 10 papers about *U. macrophylla*, 7 papers about *U. sinensis* and 4 papers about *U. sessilifructus*. In addition, 371 compounds have been reported from URCU, including 53 from *U. hirsuta*, 60 from *U. macrophylla*, 253 from *U. rhynchophylla*, 56 from *sessilifructus* and 51 from *U. sinensis* (Fig. 24). Based on these statistics, we knew that the current phytochemical studies on URCU mainly focused on *U. rhynchophylla* and other URCU had not yet been comprehensively investigated.

Secondly, 169 alkaloids have been reported from URCU, including 122 monoterpene indole alkaloids, 13 *β*-carboline alkaloids, 5 cadambine alkaloids, 4 dimeric isoechinulin-type alkaloids, 14 other indole alkaloids and 11 other alkaloids (Figs. 25-26). Meanwhile, monoterpene indole alkaloids are the main alkaloids. It is worth noting that the chemical structure of monoterpene indole alkaloids is often unstable due to the existence of multiple chiral centers. The structure is easily affected by many factors such as temperature, PH and solvent polarity, which also leads to the difficulty in the separation of alkaloids from URCU. How to solve this problem is the breakthrough and key to finding more novel alkaloids.

Thirdly, monoterpene indole alkaloids are the main active compounds, which have a variety of pharmacology activities. Rhynchophylline (**34**) and isorhynchophylline (**44**) showed excellent activity in anti-Alzheimer's disease (Yang et al., 2018; Xian et al., 2014a), antiinflammation (Yuan et al., 2009) and anti-hypertension (Zhang et al., 2004). Hirsutine (**1**) has significant anticancer (Huang et al., 2018) and antiviral (Moradi et al., 2018) effects. But more monoterpene indole alkaloids with various activities also need to be found in this genus. Of course, it can not be ignored that monomeric compounds with outstanding pharmacological activities can be

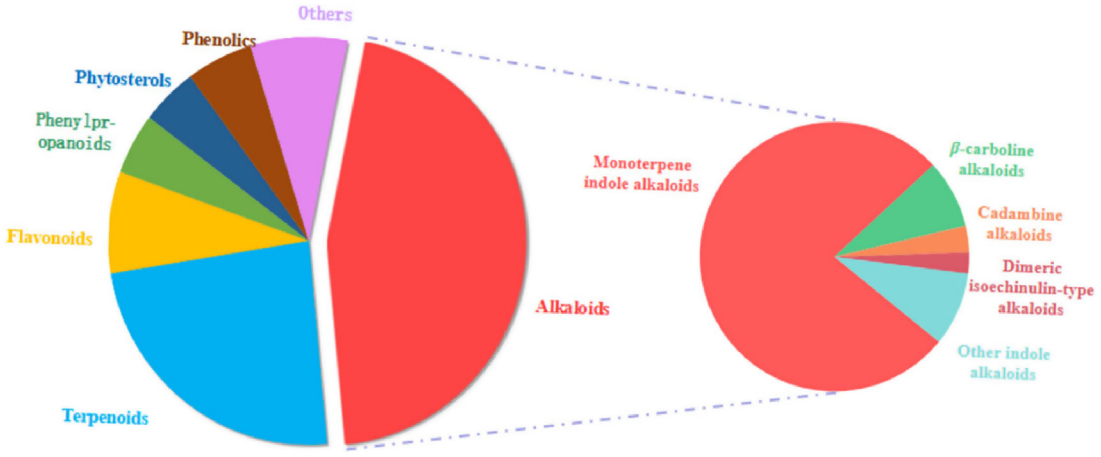

Fig. 25 Distribution of the secondary metabolites among URCU.

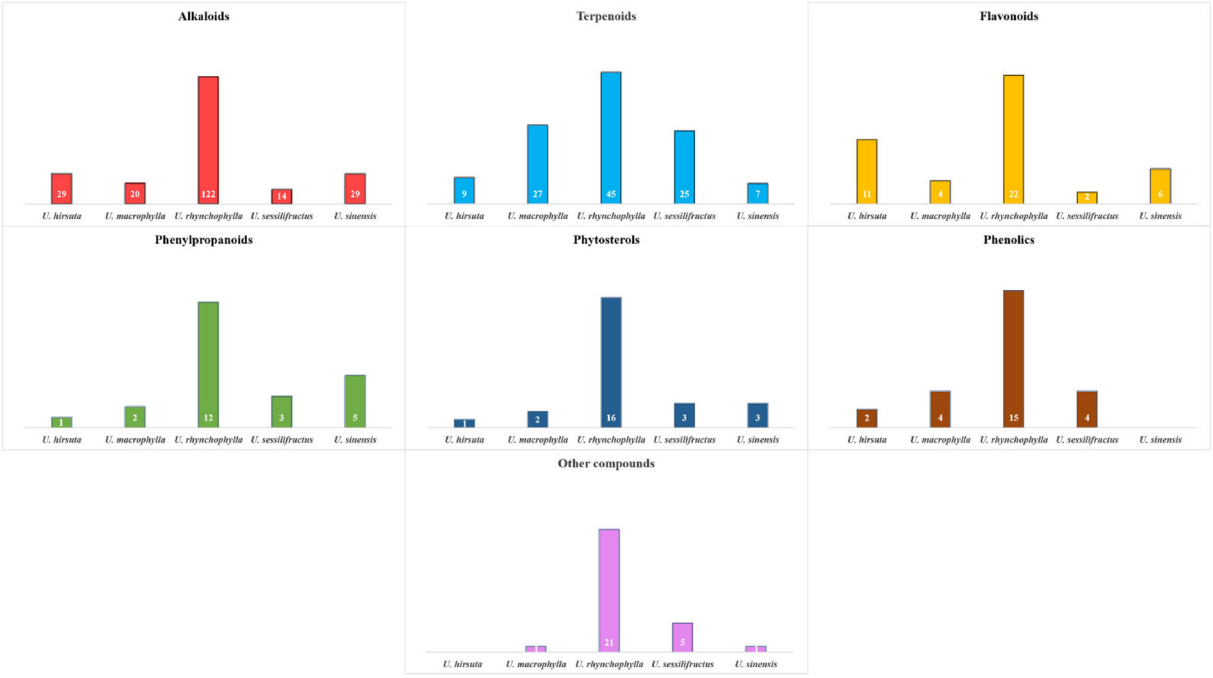

Fig. 26 The amount of each chemical classes among URCU.

considered the source of new drugs with excellent therapeutic effects.

Fourth, the traditional medicinal part of URCU is the stems with hooks. Leaves, stems without hooks and other parts are not effectively utilized. After reviewing the chemical constituents of URCU, we found that there were also a large number of active components in leaves and stems. Therefore, attention should also be paid to the development of the non-medical parts of URCU, to realize the effective utilization of URCU resources.

Finally, URCU are valuable plant resources that deserve further research and development. This review could be a useful tool in assisting researchers in the selection of interesting species or isolated compounds for further studies, as well as expand the research of URCU.

8. Conclusion

URCU (Uncariae Ramulus Cum Uncis) is a common TCM used to extinguish wind and settle convulsion, which has been used in Traditional Chinese medicines or folk medicines to treat various diseases. This review summarized all the compounds of URCU, including alkaloids, terpenoids, flavonoids, phenylpropanoids, phytosterols and phenolics. Alkaloids were generally considered major bioactive ingredients in URCU, exhibiting various important qualities. In addition, pharmacological studies showed that compounds and extracts isolated from URCU possessed a wide range of pharmacological activities, such as anti-hypertension, antiinflammation, anticancer, antioxidant, antiviral, anti-epilepsy, anti-depressant, ischemic brain injury, neuroprotection, anti-alzheimer's disease, anti-parkinson's disease and antiasthma. In short, as a source of traditional folk medicine, the URCU has been widely used in medicine. Therefore, we believe it's necessary to review it, which will help to gain a greater understanding and appreciation of URCU.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Funding

We thank the foundations of the National Natural Science Foundation of China (82104368) and Shaanxi Provincial Science and Technology Department Project (2021JQ-744) for financial support of this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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