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Review

Medicinal uses, phytochemistry and pharmacology of the genus *Uncaria*

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ABSTRACT

Ethnopharmacological relevance: The genus *Uncaria* belongs to the family Rubiaceae, which mainly distributed in tropical regions, such as Southeast Asia, Africa and Southeast America. Their leaves and hooks have long been thought to have healing powers and are already being tested as a treatment for asthma, cancer, cirrhosis, diabetes, hypertension, stroke and rheumatism. The present review aims to provide systematically reorganized information on the ethnopharmacology, phytochemistry and pharmacology of the genus *Uncaria* to support for further therapeutic potential of this genus. To better understanding this genus, information on the stereo-chemistry and structure-activity relationships in indole alkaloids is also represented.

Material and methods: The literature study of this review is based on various databases search (SCIFinder, Science Direct, CNKI, Wiley online library, Spring Link, Web of Science, PubMed, Wanfang Data, Medalink, Google scholar, ACS, Tropicos, Council of Heads of Australasian Herbaria, The New York Botanical Garden, African Plants Database at Genera Botanical Garden, The Plant List and SEINet) and library search for Biological Abstract and some local books on ethnopharmacology.

Results: 19 species of the genus *Uncaria* are found to be important folk medicines in China, Malaysia, Phillippines, Africa and Southeast America, *etc*, and have been served for the treatment of asthma, rheumatism, hyperpyrexia, hypertension and headaches, *etc*. More than 200 compounds have been isolated from *Uncaria*, including indole alkaloids, triterpenes, flavonoids, phenols, phenylpropanoids, *etc*. As characteristic constituents, indole alkaloids have been considered as main efficacy component for hypertension, epilepsy, depressant, Parkinson's disease and Alzheimer's disease. In addition, pharmacokinetic and metabolism investigation reveal that the indole alkaloids are likely to be absorbed, metabolized and excreted at early time points. Moreover, the specific inhibition of CYP isozymes can regulate their hydroxylation metabolites at C-10 and C-11.

Conclusion: Preliminary investigations on pharmacological properties of the *Uncaria* species have enlightened their efficacious remedy for hypertension, asthma, cancer, diabetes, rheumatism and neurodegenerative diseases. To ensure the safety and effectiveness in clinical application, research on bioactive compounds, pharmacological mechanisms and toxicity of the genus *Uncaria* as well as the stereo-chemistry and structure-activity relationships of indole alkaloids seem very important.

Abbreviations: U1, *Uncaria acida* (Hunter) Roxb; *U2*, *Uncaria africana* G. Don; *U3*, *Uncaria attenuate* Korth; *U4*, *Uncaria barbata* Merr; *U5*, *Uncaria bernaysii* F. Muell; *U6*, *Uncaria borneensis* Havil; *U7*, *Uncaria callophylla* Blume ex Korth; *U8*, *Uncaria canescens* Korth; *U9*, *Uncaria cordata* (Lour.) Merr; *U10*, *Uncaria donisii* E. M. A. Petit; *U11*, *Uncaria elliptica* R. Br. ex G. Don; *U12*, *Uncaria florida* Vidal; *U13*, *Uncaria gambier* (Hunt). Roxb; *U14*, *Uncaria glabrata* DC～*Uncaria lanosa* var. *glabrata* (Blume.) Ridsb; *U15*, *Uncaria guianensis* (Aubl.) J. F. Gmel; *U16*, *Uncaria hirsute* Havil; *U17*, *Uncaria homomalla* Miq; *U18*, *Uncaria kunstleri* King; *U19*, *Uncaria laevigata* Wall. ex G. Don; *U20*, *Uncaria lanosa* Wallich var. *appendiculata* Ridsd; *U21*, *Uncaria longiflora* var. *pteropoda*; *U22*, *Uncaria macrophylla* Wall; *U23*, *Uncaria nervosa* Elmer; *U24*, *Uncaria orientalis* Guillaumin; *U25*, *Uncaria perrottetii* (A. Rich.) Merr; *U26*, *Uncaria rhynchophylla* (Miq.) Jacks; *U27*, *Uncaria roxburghiana* Korth; *U28*, *Uncaria scandens* (Smith) Hutch; *U29*, *Uncaria sessilifructus* Roxb; *U30*, *Uncaria sinensis* (Oliv.) Havil; *U31*, *Uncaria sterrophylla* Merr. & L. M. Perry; U32, Uncaria thwaitesii (Hook. f.) Alston; U33, Uncaria tomentosa (Willd. ex Schult.) DC; U34, Uncaria villosa; U35, Uncaria yunnanensis Hsia. C. C.; Aβ, beta-amyloid; ABTS, 2, 2'-azinobis (3-ethyl-benzthiazoline-6-sulfonic acid); AChE, acetylcholinesterase; AD, Alzheimer's disease; APPH, 2, 2-azo-bis (2-amidinopropane) dihydrochloride; AST, aspartate aminotransferase; Cy, cyclophosphamide; DPPH, 1, 1-diphenyl-2-picrylhydrazyl; DXR, doxorubicin; CD, circular dichroism; CE, Cotton effects; ET-1, endothelin-1; ERK, extracellular regulated protein kinases; γ-GABA, γ-aminobutyric acid; GSK-3β, glycogen synthase kinase-3β; HASMC, human aortic smooth muscle cells; 5-HT, 5-hydroxytroptamine; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; KA, kainic acid; LPS, lipopolysaccharide; MAO, monoamine oxidase; MAPKs, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, matrix metalloproteinase; NE, norepinephrine; NF-κB, nuclear factor-κB; NO, nitric oxide; NMR, nuclear magnetic resonance; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PDGF, platelet-derived growth factor; PLCγ1, phospholipase Cγ1; PRTC, peroxyl radical-trapping capacity; RBC, red blood cell; SOD, superoxide scavening activity; TEAC, trolox equivalent antioxidant capacity; TLR, toll-like receptor; TNF-α, tumor necrosisa factor-α; VSMCs, vascular smooth muscle cells

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Contents

1. Introduction

The genus *Uncaria*, belonging to the family Rubiaceae, contains approximately 34 species, which mainly distributed in tropical regions, such as Southeast Asia, Africa and Southeast America (Ridsdale, 1978). It is documented that about 14 species of *Uncaria* occur in Peninsular Malaysia and about 11 species found in China (Burkill, 1935; Ridsdale, 1978; Flora of China, 1999a). Mostly, the hooks of *Uncaria* species are applied to treat wounds and olcers, fever, asthma, rheumatism, hyperpyrexia, hypertension, headaches, gastrointestinal illness, and bacterial/fungal infections, *etc*. (Ahmed et al., 1978; Burkill, 1935; Heitzman et al., 2005; Keplinger et al., 1999; Phillipson et al., 1978; Tanahashi et al., 1997; Xu and Wu, 1981). The hooks of *Uncaria* are often prepared as a decoction and its leaves, roots and bark are also sometimes used (Phillipson et al., 1978; Risdale, 1978; Bridson and Verdcourt, 1988; Laus and Keplinger, 2003). Usually monotherapy treatments are administered but polyherbal treatments have also been described in some traditional herbal prescriptions. It is well known that Chinese traditional medicinal formulation, Diao-teng-san (Cho-Deung-San in Korean and Choto-san in Japanese), which is composed of 11 herbal ingredients, is effective in the treatment of vascular diseases, such as hypertension (Yang et al., 2002; Shimada et al., 2003), stroke (Shimada et al., 2003; Goto et al., 2001; Watanabe et al., 2003), vascular dementia (Itoh et al., 1999; Sanae et al., 2000) and atherosclerosis (Ha et al., 2004). In TCM, *U. rhynchophylla* is major component of Diao-teng-san for these bioactivities. In addtion, yokukansan is one of the traditional Japanese medicines called "kampo" medicines in Japan (Yi-Gan san in Chinese). It is composed of seven kinds of dried medicinal herbs. This medicine has been approved by the Ministry of Health, Labor, and Welfare of Japan as a remedy for neurosis, insomnia, and irritability in children. Recently, yokukansan is reported to improve behavioral and psychological symptoms of dementia such as hallucinations, agitation, and aggressiveness in patients with Alzheimer's disease, dementia with Lewy bodies, and other forms of senile dementia (Iwasaki et al., 2005a,2005b; Mizukami et al., 2009). Among the 7 ingredient herbs of yokukansan, *Uncaria* thorn is found to the highest potency in the treatment of neural degeneration diseases (Kawakami, et al., 2011).

As the medicinal uses of *Uncaria* species, a great deal of studies concerning the phytochemistry and pharmacology of *Uncaria* have been carried out. More than 200 chemical constituents, including indole alkaloids, triterpenes, flavonoids and phenylpropanoids, *etc*, have been isolated from the genus of *Uncaria*. Of these, indole alkaloids are regarded as the main bioactive constituents and are responsible for the broad spectrum of biological properties reported for *Uncaria* species (Heitzman et al., 2005; Zhou and Zhou, 2010). Furthermore, reports indicate that the tetracyclic oxindole alkaloids present in *Uncaria* mainly act on the central nervous system, whereas pentacyclic oxindole alkaloids affect the cellular immune system (Reinhard, 1999). Tetracyclic oxindole alkaloids, likely rhynchophylline **(32)** and isorhynchophylline **(40)** containing chiral carbon at C-7 position, are often characterized by rapid isomerization in aqueous solutions, which is dependent on temperature and pH (Guo and Gu, 1959; Liu et al., 2011a; 2011b; Laus et al., 1996; Sakakibara et al., 1999; Sutter and Wang, 1993). Protonation and decreasing polarity of the solvent have been suggested to slow the process of their isomerization (Keplinger et al., 1999).

Several reviews on the genus *Uncaria* have been reported. Phillipson et al. (1978) describes the collection of botanical, ethnobotanical and alkaloids information from the *Uncaria* species. Laus (2004) and Heitzman et al. (2005) highlight the structures and pharmacological activities of *Uncaria* since the year 1978. Due to the widely investigations on *Uncaria* have been demonstrated in the past ten years, this review, using various databases search and library search to provide constructive information on the ethnopharmacology, phytochemistry and pharmacology of the genus *Uncaria* as well as the stereo-chemistry and structure-activity relationships of the indole alkaloids, aims to

coherently unite these aspects and to encourage further research on *Uncaria*.

2. Medicinal uses

Many general traditional medicinal uses of *Uncaria* include treatments for wounds and ulcers, fevers, headaches, gastrointestinal illnesses, and bacterial/fungal infections (Chang et al., 1989). To provide detail ethnobotanical information of *Uncaria*, this review lists Table 1, which involves the used parts, medicinal uses and distribution. As *Uncaria* species are widely distributed in Southeast Asia, Africa and Southeast America (Ridsdale, 1978), this paper describes the ethnobotany of *Uncaria* in the light of their regions.

In China, *U. homomalla*, *U. lanciflora* and *U. sinensis* serve for the treatment of headaches (Xu and Wu, 1981; Yu et al., 1999; Flora of China, 1999b). *U. macrophylla*, *U. scandens* and *U. sessilifructus* are used to treat arthritis (Xu and Wu, 1981; Yu et al., 1999; Guan et al., 2012). *U. hirsute*, *U. laevigata* and *U. rhynchophylla* are used as remedies for hypertension and epilepsy (Xu and Wu, 1981; Yang et al., 1995). In TCM, *U. rhynchophylla*, as one of resource of "Gouteng", has been recorded in the Chinese medical document "Pu Ji Ben Shi Fang" (普济本事方) since the Song Dynasty. Some prescriptions created by the ancient famous doctors are also adopted its stems and hooks for the treatment of hypertension and epilepsy, such as "Tianma gouteng yin", "Gouteng san", "Gouteng tang" and "Gouteng yin" (Guo and Gu, 1959). Usually the stems and hooks of *U. rhynchophylla* are prepared as a decoction and this plant is added after the addition of other components i.e. other herbs to minimize the conversion of active components (Wu, 1958; Liu et al., 2011a, 2011b). Recently, the aqueous extract of *U. rhynchophylla* have been reported in the treatment of hypertension, cancer and neurological disorders (epilepsy, Alzheimer's disease, *etc*) (Fujiwara et al., 2006; Kim et al., 2008; Lee, 2000; Lee et al., 2003; Suk et al., 2002).

In the Malayan archipelago, *U. gambier* and closely related species provide a polymer tanning mixture, the Gambir catechu, which is extracted from the leaves for the production of the

Table 1
Medicinal plants of the genus *Uncaria*.

Name	Medicinal parts	Medicinal uses	Distribution	Reference
Uncaria africana G. Don	Bark Leaves Root	Relieving pain Treating diarrhoea, dysentery Treating depression	Cameroon, Central African Republic, Ethiopia, Gabon, Guinea-Bissau, Kenya, Madagascar and Tanzania	Walker and Sillans, (1961); Bouquet, (1969); Oliver-Bever, (1968); Bridson and Verdcourt, (1988)
Uncaria cordata (Lour.) Merr	Hook	Treating diabetic, antioxidant,	Gordonvale, Innisfail, Burma, Australia, Thailand, Malaysia	Ford and Hasenpusch (2009); Ghollasimood et al. (2012); Ahamd et al. (2011)
Uncaria elliptica R. Br. ex G. Don	Leaves	Treating inflammation	Sri Lanka, India, Burma, Thailand, Cambodia, Malaysia, Sumatra, Java	Phillipson et al. (1978); Phillipson and Supavita, (1981)
Uncaria gambier (Hunt). Roxb	Leaves and young twings	Treating diarrheal disease, sore throat, spongy gums, dysentery, arteriosclerosis and obesity	Malaysia, Singapore, Borneo Sumatra, Indonesia	Kassim et al. (2011); Ahmed et al. (1978); Das et al. (1967); Phillipson et al. (1978); Yamanobe et al. (2000)
Uncaria guianensis (Aubl.) J. F. Gmel ("garabato", "unganangi")	Inner bark and root bark leaves	Treating inflammation, diabetes, cancer, intestinal affections Treating wounds, abscesses	Central and South America Amazon area, Bangladesh, Upper Burma	Anderson and Taylor, (1994); Sandoval et al. (2002); Piscoya et al. (2001); Vilches,(1997); Laus and Keplinger, 2003 Jones, (1995)
Uncaria hirsute Havil ("Gou-teng")	Stem and hook	Treating hypertension, epilepsy, arthritis	Guangdong, Guangxi, Yunnan, Sichuan, Guizhou, Fujian, Taiwan	Chinese Pharmacopoeia Commission, (2010); Xu and Wu, (1981)
Uncaria homomalla Miq	Stem and hook	Treating migraine, infantile convulsion	Guangxi, Yunnan, India, Bangladesh, Burma, Thailand, Malaysia, Vietnam, Laos, Cambodia, Indonesia	Xu and Wu, (1981); Flora of China, (1999b)
Uncaria laevigata Wall. ex G. Don	Stem and hook	Treating hypertension, lightheadedness, numbness, convulsion	Guangxi, Yunnan, India, Bangladesh, Thailand, Burma, Laos, Indonesia	Xu and Wu, (1981); Yang et al. (1995)
Uncaria lanosa Wallich var. *appendiculata* Ridsd	Stem and hook	Treating hyperpyrexia, analgesia, spasmolysis	Malacca, Philippines,Taiwan	Xu and Wu, (1981); Tanahashi et al. (1997)
Uncaria lanciflora Hutch	Stem and hook	Treating hyperpyrexia, headaches	Yunnan	Xu and Wu, (1981); Xiong, (1995)
Uncaria longiflora var. *pteropoda*	Leave	Treating rheumatism, rhrush, framboesia	Malaysia	Burkill, (1935); Risdale, (1978)
Uncaria macrophylla Wall ("Gou-teng")	Stem and hook	Treating lumbocrural pain, arthritis, osteomyelitis	Guangxi, Yunnan, Guangdong, Hainan, Sichuan, Indo-China, India	Xu and Wu, (1981); Yu et al. 1999
Uncaria perrottetii (A. Rich.) Merr	Hook	Treating hematuria, puerperal fever, puerperal sepsis	Kanawan, Morong, Bataan and Philippines	Duke and Beckstrom-Sternberg, (2002)
Uncaria rhynchophylla (Miq.) Jacks ("Gou-teng")	Stem and hook	Treating hyperpyrexia, epilepsy, preeclampsia, hypertension	Guangdong, Yunnan, Sichuan, Hubei, Hunan, Guizhou, Fujian, Jiangxi, Shanxi, Gansu, Japan	Chinese Pharmacopoeia Commission, (2010); Xu and Wu, (1981)
Uncaria scandens (Smith) Hutch	Stem and hook	Treating arthritis, lumbocrural pain	Guangdong, Guangxi, Yunnan, Hunan, Guizhou, Xizang, Indo-China, India	Xu and Wu, (1981)
Uncaria sessilifructus Roxb ("Gou-teng")	Stem and hook	Treating arthritis, lumbocrural pain, headaches	Guangdong, Guangxi, Yunnan, Indo-China, India	Xu and Wu, (1981); Guan et al. (2012)
Uncaria sinensis (Oliv.) Havil ("Gou-teng")	Stem and hook	Treating arthritis, headaches	Sichuan,Yunnan, Guizhou, Hubei, Hunan, Guangxi Shanxi, Gansu	Xu and Wu, (1981); Yu et al. (1999)
Uncaria tomentosa (Willd. ex Schult.) DC (" Uña de Gato", " cat's claw")	Bark	Treating diabetes, cancer, intestinal affections inflammation	South and Central America liana, Peru	Vilches,(1997); Laus and Keplinger, (2003) Jones, (1995); Reinhard, (1999); De Jong et al. (1999)
Uncaria yunnanensis Hsia. C. C	Stem and hook	Treating lumbocrural pain	Yunnan	Xu and Wu, (1981); Guan et al. (2012)

technically important catechins (Das, 1967; Desmarchelier et al., 1997). In folk medicine, the leaves and young shoots of this plant are adopted for the treatment of diarrheal disease, sore throat, spongy gums, dysentery, athero-sclerosis, obesity and deafness (Burkill, 1966; Ahmed et al., 1978; Das, 1967; Phillipson et al., 1978; Yamanobe et al., 2000; Kassim et al., 2011). Malay also rubbed the leaves of *U. longiflora* var. *pteropoda* on the body to relieve pain from rheumatism and use its juice for thrush and framboesia (Ridsdale, 1978). Regarding the plants used for the therapy in Phillippines, it is concluded that the hooks of *U. lanosa* var. *appendiculata* and *U. perrottetii* are used for the treatment of hyperpyrexia (Xu and Wu, 1981; **T**anahashi et al., 1997; Duke and Beckstrom-Sternberg, 2002). Traditionally, the extract of *U. perrottetii* is used to treat hematuria as well as a remedy to prevent puerperal fever and puerperal sepsis (Duke and Beckstrom-Sternberg, 2002). Recently, studies have demonstrated the antibacterial, antifungal and antiprotozoal effects of this specific plant species (Vital, 2008; Vital and Rivera, 2009). Furthermore, Nudo and Catap (2011) assesses the immunomodulatory potential of *U. perrottetii* that will provide baseline information regarding the potential use of this plant species as an immunonutritional supplement.

In Africa, *U. aficana* is the dominant species, which is widely distributed in Cameroon, Central African Republic, Ethiopia, Gabon, Guinea-Bissau, Kenya, Madagascar, Tanzania, Uganda and Zaire (Bridson and Verdcourt, 1988). The commonly applications of *U. aficana* have been reported as sedatives. Its bark is used to treat naso-pharyngeal affections, pain-killers and venereal diseases. The leaves are used for antidotes (venomous stings, bites, *etc.*), diarrhoea, dysentery, heart, malnutrition and debility. The root is used as emetics and depressants (Prota. http;//www. Prota4u.org/protav8.asp?p=Uncaria+africana)

U. guianensis and *U. tomentosa* are closely related species of the Rubiaceae family, popularly known as Cat's claw (Unha-de-gato or Uña de gato in South America). Both species are large woody vines occurring at the Amazon rain forest and other tropical areas of South and Central America (Anderson and Taylor, 1994) and have been important in traditional healing. Cat's Claw is prepared traditionally as a hot tea to be drunk either hot or cold as a supplement in the treatment of many human disorders including diabetes, cancer, intestinal affections (Jones, 1995; Gupta, 1995; Obregon, 1995; Obregón Vilches,1997; Reinhard, 1999; Vilches,1997; Laus and Keplinger, 2003; De Jong et al., 1999) and inflammatory conditions such as arthritis (Heitzman et al., 2005). Because of its historical medicinal use, Cat's Claw products have been offered commercially in the USA and abroad for hundreds of years in preparations of pulverized plant parts, water and ethanol extractions (Keplinger et al., 1999). During the past twenty years, Cat's Claw (*U. tomentosa*) in different forms has been introduced in Europe to treat patients suffering from cancer and some viral diseases (Sandoval-Chacon et al., 1998). C-Med 100® is a proprietary aqueous extract from Cat's Claw (*U. tomentosa*). This product is derived through water extraction and exclusion of higher molecular weight components (>10 kD) such as tannins (Sheng et al., 2000a), which has been used as an "immune modulator" (Akesson et al., 2003; Sheng et al., 2000b; Lamm et al., 2001).

3. Phytochemistry

The chemical constituents of genus *Uncaira* have been extensively studied since the early 1900s. One of the earliest phytochemical reports on *U. rhynchophylla* published in 1928 reveal the isolation of rhynchophylline **(32)** (Kondo et al., 1928). Up to date, more than 200 compounds have been isolated from *Uncaria*, including alkaloids, triterpenes, flavonoids, phenylpropanoids, *etc*. Tables 2–5 and Fig. 1 show the names, the corresponding plants sources and structures of the isolated compounds. Based on these results, we conclude that indole alkaloids, especially the monoterpene oxindole indole alkaloids, are abundant and bioactive constituents in this genus.

3.1. Alkaloids

Alkaloids are most prominent secondary metabolism in genus *Uncaria*. One hundred and twenty-three **(1–123)** (Table 2) indole alkaloids have been identified, which are classified to be monoterpene indole, monoterpene oxindole and N-oxindole monoterpene indole alkaloids. Of these, oxindole alkaloids are regarded to be major components, especially rhynchophylline **(32)** and isorhynchophylline **(40)** as well as the corresponding unsaturated oxindole alkaloids corynoxeine **(34)** and isocorynoxeine **(78)** (Laus and Teppner, 1996). These kinds of oxindole alkaloids commonly contain chiral carbon atoms, which shows stereochemistry properties at the C-3, C-7, C-15 and C-20 positions. Based on the detailed information on indole alkaloids given by nuclear magnetic resonance (NMR) spectroscopy, we can confirm their stereo-chemistry. For instance, the configuration of H-15 is most likely to be α-orientation (Aimi et al., 1997). On the basis of the correlations of H-15 with H-3 and H-20 in the NOESY spectrum ascertain the configuration of C-3 and C-20. Using the chemical shift of C-3 and C-19 in ^{13}C-NMR spectrum (in $CDCl_3$) further identifies the absolute configuration of C-7 and C-20, respectively. The C-3 chemical shift (δ 74–75) prompts C-*7R* configuration, while δ 70–72 indicates C-*7S* configuration (Wang et al., 2011). The C-19 chemical shift ($\delta\sim24$) is corresponding to C-*20R* configuration and $\delta\sim19$ is attributed to C-*20S* configuration (Sakakibara et al., 1998). Presence of chiral carbon atom at C-7 position further causes the pH-dependent isomer mixtures of oxindole alkaloids in aqueous solutions by a retro-type Mannich reaction (Laus et al., 1994, 1996). According to Laus et al. (1996), these alkaloids could convert to their isomers in acidic decoction. At the condition of pH 4, isorhynchophylline **(40)** and isocorynoxeine **(78)** partially translate to rhynchophylline **(32)** and corynoxeine **(34)** (Sakakibara et al., 1999; Sutter and Wang, 1993). Protonation and decreasing polarity of the solvent have been suggested to slow the process of their isomerization (Keplinger et al., 1999). Moreover, cell pH at transition of heteroyohimbines to oxindoles (Phillipson and Supavita, 1983) is proved to affect the configuration of H-18 of indole alkaloids. Usually the configuration of H-18 in *Uncaria* is α-configuration but in rauniticine-allo-oxindole B **(67)** and rauniticine-allo acid B **(68)** dispaly the β-configuration (Salim et al., 2011).

Besides, alkaloids isolated from the genus *Uncaria* are also divided into tetracyclic and pentacyclic indole alkaloids. The discrimination of tetracyclic and pentacyclic indole alkaloids is described as follows. Firstly, we find that tetracyclic indole alkaloids predominantly contain the β-methoxyacrylic ester, while pentacyclic indole alkaloids has almost no the structural fragment. The presence of β-methoxyacrylic ester can be identified by characteristic nuclear magnetic resonance (NMR) signals, such as the ^{1}H-NMR signals at -CO_2CH_3 ($\delta\sim3.62$, 3H, s), OCH_3 ($\delta\sim3.78$, 3H, s) and H-17 ($\delta\sim8.20$, 1H, s) (Aimi, 1997) and the ^{13}C-NMR signals at C-16 ($\delta\sim111.8$), C-17 ($\delta\sim160.7$), OCH_3 ($\delta\sim61.2$) and $COOCH_3$ ($\delta\sim169.6$ and 51.2 each) (Ernest. et al., 1974). Secondly, the tetracyclic types shows a pseudomolecular ion $[M+H]^+$ at *m/z* 385, while pentacyclic indole alkaloids presents a pseudomolecular ion at *m/z* 369 in electrospray ionization LC-MS/MS method (Montoro et al., 2004). Using these findings, we can quickly identify the structure-skeleton of indole alkaloids.

Table 2
Alkaloids isolated from the genus *Uncaria*.

No.	Compound	Resource	Parts of plant	Reference
1	hirsutine	*U26*	stem	Namera et al. (1996)
		U18;U23;U29	and hook	Phillipson et al. (1978)
		U30	leaves	Laus et al. (1996)
		U33;U3;U15	root	Hemingway and Phillipson (1974);
			leaves	Laus et al. (1997);
				Phillipson and Hemingway, (1975)
2	hirsuteine	*U26*	stem and hook	Namera et al. (1996)
		U23;U33;U3	leaves	Phillipson et al. (1978); Laus et al.(1997); Phillipson and Hemingway, (1975)
		U30	root	Laus et al. (1996)
		U15	leaves	Hemingway and Phillipson (1974)
3	epi-allo-corynantheine	*U3*	leaves	Phillipson and Hemingway, (1975)
		U26	stem and hook	Zhu et al. (1997)
4	corynantheidine	*U22*	the aerial part	Wang et al. (2011)
		U26;U33	leaves	Phillipson et al. (1978); Laus et al.(1997)
5	drocorynantheine	*U22*	the aerial part	Wang et al. (2011)
6	dihydrocorynantheine	*U22*	the aerial part	Wang et al. (2011)
		U33;U2;U26	leaves	Laus et al. (1997); Kam et al. (1992); Ma et al. (2009b)
		U2;U3;U7		
		U9;U11	leaves	Phillipson et al. (1978)
		U23	stem	Goh et al. (1985)
7	gambireine	*U21;U7*	leaves	Kam et al. (1992)
8	gambirine	*U7;U13*	leaves	Kam et al. (1992); Chan (1968)
9	isogambirine	*U7;U13*	leaves	Kam et al. (1992); Chan (1968)
10	villocarines A	*U34*	leaves	Matsuo et al. (2011)
11	geissoschizine methyl ether	*U30*	stem and hook	Sakakibara et al. (1999)
12	vallesiachotamine	*U26*	leaves	Aimi et al. (1982)
13	3-iso-19-epi-ajmalicine	*U11;U3*	leaves	Phillipson and Supavita, (1981)
		U16	stem and hook	Phillipson and Hemingway, (1975)
				Xin et al. (2008a)
14	isorauniticine	*U11*	leaves	Phillipson et al. (1983)
15	14β-hydroxy-3-isoraunitine	*U11*	leaves	Phillipson et al. (1983)
16	akuammigine	*U11;U3*	leaves	Phillipson et al. (1978)
		U26;U29	leaves	Phillipson and Hemingway, (1973b);
		U20;U33;U24		Laus et al. (1997);
				Phillipson and Hemingway, (1975)
17	3-iso-ajmallicine	*U11;U1;U2;*	leaves	Phillipson et al. (1978)
		U3;U16;U17	leaves	Laus et al. (1997);
		U29;U31		Phillipson and Hemingway, (1975)
		U33;U24		
18	tetrahydroalstonine	*U35;U33*	leaves	Tao et al. (2000); Laus et al. (1997)
		U5;U3		Phillison and Hemingway (1973a); Ponglux et al. (1980)
19	ajmallicine	*U35*	leaves	Tao et al. (2000)
		U2	bark	Thushara et al. (1997)
20	19-epi-ajmallicine	*U11;U14*	leaves	Phillipson and Supavita, (1981); Arbain et al. (1993)
		U35	stem and hook	Feng and Fu (1981)
21	rauniticine	*U11;U3;U7*	leaves	Kam et al. (1992); Phillipson and Supavita, (1983); Ponglux et al. (1980),
		U14	the aerial part	Arbain et al. (1998)
22	14α-hydroxyraunitine	*U3*	leaves	Pongluxet al. (1980)
		U14	the aerial part	Arbainet al. (1998)
23	α-yohimbine	*U7;U3*	leaves	Kam et al. (1992); Phillipson and Hemingway, (1975)
24	β-yohimbine	*U7;U3*	leaves	Kam et al. (1992); Phillipson and Hemingway, (1975), Tao et al. (2001)
		U35	root	

Table 2 (*continued*)

No.	Compound	Resource	Parts of plant	Reference
25	alloyohimbine	*U7;U6*	leaves	Kam et al. (1992)
26	yohimbine	*U7;U26*	leaves	Kam et al. (1992)
		U30;U33		
27	pseudoyohimbine	*U7;U6;U34*	leaves	Kam et al. (1992)
28	3-epi-β-yohimbine	*U7;U6*	leaves	Kam et al. (1992)
29	angustine	*U26;U5*	leaves	Phillipson et al. (1978)
		U11;U15	leaves	Tantivatana et al. (1979)
		U17		
30	angustoline	*U26;U15;U17*	leaves	Phillipson et al. (1978)
31	angustidine	*U26;U17*	leaves	Phillipson et al. (1978)
32	rhynchophylline	*U22*	the	Wang et al. (2011)
		U1;U2;U3	aerial part	Phillipson et al. (1978)
		U5;U9;U11	leaves	Wagner et al. (1985); Laus et al. (1996)
		U18;U15;U26U29;	root	
		U31;U21		
		U33;U30		
33	corynoxine B	*U22*	the	Wang et al. (2011)
		U3;U9;U18	aerial part	Phillipson et al. (1978)
		U29;U31	leaves	
34	corynoxeine	*U22*	stem	Zheng and Wang (2009)
		U1;U3;U6	and hook	Phillipson et al. (1978)
		U26	leaves	Laus et al. (1996)
		U30	root	Laus et al. (2003)
		U15	leaves	
35	9-hydroxy corynoxeine	*U26*	leaves	Xie et al. (2013)
36	rhynchohyllic acid	*U30*	stem and hook	Liu and Feng (1993a)
37	18,19-dehydrocorynoxinic acid	*U26*	leaves	Xie et al. (2013)
38	rotundifoline	*U11;U7;U33*	leaves	Phillipson et al. (1978)
		U3	leaves	Laus et al. (1997)
39	villocarines D	*U34*	leaves	Matsuo et al. (2011)
40	isorhynchophylline	*U22*	the	Wang et al. (2011)
		U1;U2;U3;U5U9;U11;	aerial part	Phillipson et al. (1978)
		U18	leaves	Wagner et al. (1985); Laus et al.(1996)
		U15;U26;U29	root	
		U31;U21		
		U33;U30		
41	corynoxine	*U22*	the	Wang et al. (2011)
		U6;U3;U18	aerial part	Phillipson et al. (1978)
		U29;U31	leaves	
42	isocorynoxine	*U22*	stem	Zheng and Wang (2009)
		U3;U6;U26	and hook	Kam et al. (1992); Phillipson and Hemingway, (1975); Yamanaka et al. (1983)
		U15	leaves	Laus et al. (2003)
			leaves and root	
43	9-hydroxy isocorynoxeine	*U26*	stem and hook	Xie et al. (2013)
44	isorhynchophyllic acid	*U30*	stem and hook	Liu et al. (1993a)
45	18,19-dehydrocorynoxinic acid B	*U26*	leaves	Xie et al. (2013)
46	isorotundifoline	*U11;U7*	leaves	Phillipson et al. (1978)
		U33;U3		
47	villocarines B	*U34*	leaves	Matsuo et al. (2011)
48	macrophyllianium	*U22*	the aerial part	Wang et al. (2011)
49	macrophyllines A	*U22*	the aerial part	Wang et al. (2011)
50	macrophyllines B	*U22*	the aerial part	Wang et al. (2011)
51	Us-7	*U3*	stem and hook	Aimi et al. (1997)
52	Us-8	*U3*		Aimi et al. (1997)

Table 2 (*continued*)

No.	Compound	Resource	Parts of plant	Reference
			stem and hook	
53	3-oxo-7-hydroxy-3,7-seco-rhynchohylline	*U3*	leaves	Ponglux et al. (1990)
54	diangoutengjian	*U35*	root	Tao et al. (2001)
55	uncarine D	*U21*	leaves	Yeoh et al. (1966)
		U3;U5;U15	leaves	Phillipson et al. (1978)
		U17;U20;U30	leaves	Thushara et al. (1997)
		U10;U19;U24	leaves	Arbain et al. (1993)
		U27U28;U31		
		U33		
56	uncarine F	*U21*	leaves	Yeoh et al. (1966)
		U5;U17;U20	leaves	Phillipson et al. (1978)
		U29;U3;U10	leaves	Thushara et al. (1997)
		U24;U25;U27		
		U28;U31		
57	uncarine A	*U16*	leaves	Wu and Chan (1994)
		U3;U9;U14	leaves	Phillipson et al. (1978)
		U19;U24;U29		
58	uncarine B	*U16;U3;U32*	leaves	Wu and Chan (1994); Tantivatana et al. (1980); Herath et al. (1978)
		U9;U13	leaves	Phillipson et al. (1978)
		U24;U29		
59	uncarine C	*U30*	stem	Liu et al. (2011a, 2011b)
		U5;U17	and hook	Phillipson et al. (1978)
		U20;U8	leaves	Thushara et al. (1997)
		U10;U25	leaves	Lee et al. (1999)
		U27;U28	bark	Phillipson and Hemingway, (1975); Tanahashi et al. (1997)
		U15	leaves	Wagner et al. (1985)
		U24;U31	root	
		U33		
60	uncarine E	*U5;U17*	leaves	Phillipson et al. (1978)
		U20;U21	leaves	Phillipson and Hemingway, (1975);
		U24;U31	leaves	Tanahashi et al. (1997)
		U10;U19;U25U27;	bark	Thushara et al. (1997)
		U28;U34	root	Lee et al. (1999)
		U15		Wagner et al. (1985)
		U33		
61	pteropodic acid	*U30*	stem	Liu and Feng (1993a)
		U21	and hook	Chan et al. (1966)
			leaves	
62	isopteropodic acid	*U30*	stem	Liu and Feng (1993a)
		U21	and hook	Chan et al. (1966)
			leaves	
63	mitraphylline	*U16;U2;U17*	leaves	Xin et al. (2008b); Phillipson and Hemingway, (1973); Tantivatana et al. (1979)
		U11	bark	Thushara et al. (1997)
		U3;U24	leaves	Phillipson and Hemingway, (1975)
		U33	root	Wagner et al. (1985)
		U15	leaves	Laus et al. (2003)
		U30	and root	Liu and Feng (1993a)
			stem	
			and hook	
64	isomitraphylline	*U16;U17;U24*	leaves	Xin et al. (2008b);
		U11	bark	Tantivatanaet al. (1979);
		U33	root	Phillipson and Hemingway, (1975)
		U15	leaves	Thushara et al. (1997)
			and root	Wagner et al. (1985)
				Laus et al. (2003)
65	mitraphyllic acid	*U30*	leaves	Liu and Feng (1993a)
66	isomitraphyllic acid	*U30*	leaves	Liu and Feng (1993a)
67	rauniticine-allo-oxindole B	*U21*	stem	Salim et al. (2011)
68	rauniticine-allo-acid B	*U21*	stem	Salim et al. (2011)
69	rumberine	*U31*	leaves	Tanahashi et al. (1997)
70	uncaric acid A	*U16*	root	Tao et al. (2001)

Table 2 (*continued*)

No.	Compound	Resource	Parts of plant	Reference
			leaves	Xin et al. (2008c)
71	raunitine pseudoindoxyl	*U11*	leaves	Phillipson and Supavita, (1983)
72	3-isoraunitine pseudoindoxyl	*U11*	leaves	Phillipson and Supavita, (1983)
73	akuammigine pseudoindoxyl	*U11*	leaves	Phillipson and Supavita, (1983)
74	rhynchophylline N-oxide	*U26;U15*	leaves	Ma et al. (2009b); Hemingway and Phillipson (1974)
75	corynoxeine N-oxide	*U26*	leaves	Ma et al. (2009b)
76	villocarines C	*U34*	leaves	Matsuo et al. (2011)
77	isorhynchophylline N-oxide	*U26*	leaves	Ma et al. (2009b)
		U1;U2;U3 U5;U15;U18U21;U22; U33	leaves	Phillipson et al. (1978)
78	isocorynoxeine N-oxide	*U26*	leaves	Ma et al. (2009b)
79	hirsutine N-oxide	*U33*	leaves	Phillipson et al. (1978)
80	hirsuteine N-oxide	*U26*	stem and hook	Jiao et al. (2013)
81	dihydrocorynanthein-N-oxide	*U33*	leaves	Hemingway and Phillipson (1974)
82	uncarine F N-oxide	*U20;U5;U10*	leaves	Phillipson et al. (1978)
		U20;U21 U24;U27 U30;U33;U17	leaves	Tantivatana et al. (1979)
83	uncarine D N-oxide	*U24*	leaves	Phillipson and Hemingway, (1975)
		U5;U10;U17 U21;U27;U28		
		U30;U31	leaves	Phillipson et al. (1978)
84	uncarine C N-oxide	*U24*	leaves	Phillipson and Hemingway, (1975)
		U5;U10;U17 U21;U27		
		U28;U30;U31	leaves	Phillipson et al. (1978)
85	uncarine E N-oxide	*U24*	leaves	Phillipson and Hemingway, (1975)
		U5;U10;U17 U21;U27		
		U28;U30;U31	leaves	Phillipson et al. (1978)
86	mitrahylline N-oxide	*U2;U3;U15*	leaves	Phillipson et al. (1978)
		U16;U17;U19 U20;U21;U24 U25;U28;U29 U33		
87	isomitrahylline N-oxide	*U3;U15;U16 U17;U19;U20 U21;U24;U25*		
		U28;U29	leaves	Phillipson et al. (1978)
88	tetrahydroalstonine N-oxide	*U11*	leaves	Phillipson and Supavita (1981)
89	roxburghine A	*U13*	leaves	Merline et al. (1970)
90	roxburghine B	*U13*	leaves	Merline et al. (1970)
91	roxburghine C	*U13*	leaves	Merline et al. (1970)
92	roxburghine D	*U13*	leaves	Merline et al. (1970)
93	roxburghine E	*U13*	leaves	Merline et al. (1970)
94	roxburghine X	*U11*	woody part	Herath et al. (1979)
95	challophylline	*U7*	leaves	Kam et al. (1991)
96	callophyllines A	*U7*	leaves	Kam et al. (1991)
97	callophyllines B	*U7*	leaves	Kam et al. (1991)
98	glabratine	*U14*	bark	Arbain et al. (1992)
99	deoxycordifoline	*U14*	bark	Arbain et al. (1993)
100	mitraphyllic acid (16→1)-β-D-glucopyranosyl ester	*U30*	leaves	Liu et al. (1993b)
101	isomitraphyllic acid(16→1)-β-D-glucopyranosyl ester	*U30*	leaves	Liu et al. (1993b)
102	cadambine	*U26*	leaves	Ma et al. (2009b)
		U30;U28	stem and hook	Endo et al. (1983); Ma et al. (2008)
103	3α-dihydrocadambine	*U26;U30*	stem and hook	Namera et al. (1996); Endo et al. (1983)
104	3β-isodihydrocadambine	*U30*	stem and hook	Endo et al. (1983)
105	vincoside lactam	*U26*	leaves	Aimi et al. (1982)
		U28	stem and hook	Ma et al. (2008)
106	rhynchophine	*U26*	leaves	Aimi et al. (1982)
107	2′-*O*-β-D-glucopyranosyl-11-hydroxyvincoside lactum	*U26*	leaves	Ma et al. (2009b)

Table 2 (*continued*)

No.	Compound	Resource	Parts of plant	Reference
108	22-*O*-demethyl-22-*O*-β-D-glucopynosylisocorynoxeine	*U26*	leaves	Ma et al. (2009b)
109	strictosidine	*U26*	leaves	Ma et al. (2009b)
110	strictosamide	*U26*	leaves	Ma et al. (2009b)
111	lyaloside	*U33*	leaves and bark	Kitajima et al. (2000b)
112	5(*S*)-5-carboxystrictosidine	*U33*	stem	Kitajima et al. (2000a)
113	3,4-dehydro-5-(*S*)-carboxy-strictosidine	*U33*	stem	Kitajima et al. (2000a)
114	hirsutaside A	*U16*	leaves	Xin et al. (2008c)
115	hirsutaside D	*U16*	leaves	Xin et al. (2011)
116	bahienoside A	*U16*	leaves	Xin et al. (2011)
117	bahienoside B	*U16*	leaves	Xin et al. (2011)
118	neonaucleoside B	*U16*	leaves	Xin et al. (2011)
119	harmane	*U16* *U1;U3;U4* *U6;U7;U8* *U11;U20;U23*	leaves	Xin et al. (2008b)
		U24	leaves	Phillipson et al. (1978)
120	salacin	*U30;U3*	leaves	Liu et al. (1992); Ponglux et al.(1990)
121	hirsutanines A	*U16*	the aerial part	Jia et al. (2014)
122	hirsutanines B	*U16*	the aerial part	Jia et al. (2014)
123	hirsutanines C	*U16*	the aerial part	Jia et al. (2014)

3.2. Triterpenes

Eighty-two triterpenoids **(124–205)** have been isolated from this genus (Table 3). Ursan-type pentacyclic triterpenes constitute the most common triterpenes in *Uncaria*. Among them, quinovic acid are commonly glycosylated at C-3, C-28, C-3,–28 or C-3,–27 positions with various sugar moieties, such as quinovose, rhamnose, glucose, fructose and galactose (Aquino et al., 1988). Characteristic pseudomolecular ion $[M+H]^+$ at *m/z* 469 and $[M+Na]^+$ at *m/z* 655, 817 and 979 in electrospray ionization LC-MS/MS method further indicate the presence of quinovic acid aglycine and mono-, di- and tri- glycosylated quinovic acid glycosides, respectively (Montoro et al., 2004; Pavei et al., 2012). Table 6

3.3. Flavonoids

Forty flavonoids **(206–245)** have been identified from the genus *Uncaria* (Table 4), which are classified to be flavan-3-ols **(208–232)** and flavonols **(233–245)**. Flavan-3-ols and their dimmers as well as flavonols and their 3-glycosides constitute the most common flavonoids in *Uncaria*. The sugar moieties of these flavonoid glycosides are commonly made up of glucose, galactose and rhamnose (Li et al., 2011). It has been reported that the coupling constant of H-2 and H-3 ($J_{2,3}$) in flavan-3-ols reveal the relative configuration of C-2/C-3. The 2,3-*trans* is characteristic by $J_{2,3} > 7.0$ Hz, while the 2,3-*cis* is identified by $J_{2,3} < 7.0$ Hz (Friedrich and Galensa, 2002). The presence of 2,3- *trans* or 2,3-*cis* units is also linked with the chemical shift of C-2. In ^{13}C-NMR spectrum (DMSO-d_6), $\delta_{C\text{-}2}$ 82.5 suggests 2,3-*trans*, while $\delta_{C\text{-}2}$ 78.3 prompts 2,3-*cis* configuration (Taniguchi et al., 2008). As for the absolute configurations of C-2 and C-3 in flavan-3-ols are determined by circular dichroism (CD) Cotton effects (CE), which is attributed to the phenyl chromophores in their structures. In a previous report of similar compounds, the arithmetically CD curves of C-3 shows a strong positive CE at 240 nm for the 3*S* configuration and a negative CE for 3*R* configuration while CD curves of C-2 exhibits positive CE at 280 nm for the 2*S* configuration and a negative CE for 3*R* configuration (Slade et al., 2005). Information above are useful for the determination of flavan-3-ols' configuration at C-2 and C-3 position.

3.4. Others

Other constituents also have been isolated, such as coumarins, lignans, benzene derivatives, steroids and alkanes **(246-263)**. For reasons of simplicity, these compounds are just listed in Table 5.

4. Pharmacological activity

4.1. Antioxidant activities

Aqueous extract of the *U. sinensis* hooks and stems was evaluated for its antioxidative effect *in vitro* against free radical-induced oxidative damage on rat red blood cell (RBC). The extract inhibited the hemolysis of RBC induced by 2,2-zao-bis(2-amidinopropane)dihydrochloride (APPH) in a dose-dependent manner from 50 to 1000 μg/mL(Sekiya et al., 2002). Apea-Bah et al. (2009) have reported that the ethanol extract and ethyl acetate extract of the *U. gambir* dried leaves showed significantly higher ($p < 0.01$) DPPH inhibitory activity than the aqueous soluble. IC_{50} of the organic extracts ranged between 13.8 to 16.2 μg/mL while that of the aqueous extract was 27.4 μg/mL. This suggested that compounds which are responsible for scavenging DPPH free radicals are earlier dissolved in organic solvent, such as quinovic acid and its glycosides, tannins and condensed tannins (Aquino et al., 1991; Wirth and Wagner, 1997). Sandoval et al. (2002) also reported that *U. tomentosa* and *U. guianensis* show DPPH scavenging capacity with IC_{50} values of 12.6 μg/mL and 20.8 μg/mL, respectively. Since the decoction prepared from the bark of *U. tomentosa* have been widely used in traditional Peruvian medicine (Desmarchelier et al., 1997; Sandoval et al., 2000), Gonçalves et al. (2005) evaluated the interactions of the decoction with the superoxide, hydroxyl and peroxyl radicals as well as hydrogen peroxide and hypochlorous acid generated in homogeous model systems to better characteristic its antioxidant potential. The results showed that decoction of *U. tomentosa* has high antioxidant activity. In

Table 3
Terpenoids isolated from the genus *Uncaira*.

No.	Compound	Resource	Parts of plant	Reference
124	ursolic acid	*U22*	stem and hook	Zhang and Guo, (2012)
		U33	leaves	Phillipson et al. (1978)
		U16	stem bark	Wu and Chan (1994)
		U19		Wang et al. (2013)
125	ursolic aldehyde	*U30*	stem and hook	Liu et al. (2011a, 2011b)
126	α-amyrin acetate	*U22*	stem and hook	Wu et al. (2007)
127	6β-hydroxyursolic acid	*U26*	leaves	Ma et al. (2009a)
128	3β,6β,19α-trihydroxyurs-12-en-28-oic acid	*U35*	root	Tao et al. (2001)
		U11	woody part	Diyabalanage et al.(1995)
		U12	leaves	Aimi et al. (1989)
		U19	stem and hook	Wang et al. (2013)
		U22	stem bark	Sun et al. (2012a)
		U26	twing	Deng et al. (2009)
		U33	bark	Aquino et al.(1990)
129	3β,6β,24-trihydroxyurs-12-en-28-oic acid	*U26*	twing	Deng et al. (2009)
130	3β,6β,23-trihydroxyurs-12-en-28-oic acid	*U22*	stem and hook	Wu et al. (2007)
		U26	twing	Denget al. (2009)
131	3β,6β,19α,24-tetrahydroxyurs-12-en-28-oic acid	*U35*	root	Tao et al. (2001)
132	6β,19α-dihydroxy-3-oxo-urs-12-en-28-oic acid	*U26*	twing	Deng et al. (2009)
		U33	leaves	Laus et al. (1997)
133	3β,19α,23-trihydroxy-6-oxo-urs-12-en-28-oic acid	*U33*	leaves and bark	Kitajima et al. (2000a)
134	6β,19α-dihydroxy-3-oxo-24-norurs-12-en-28-oic acid	*U19*	Stem bark	Wang et al. (2013)
135	3β,6β,19α-trihydroxy-23-oxo-urs-12-en-28-oic acid	*U26*	twing	Deng et al. (2009)
		U22	stem bark	Sun et al. (2012b)
		U33	bark	Aquino et al. (1990)
136	3β,6β,19α-trihydroxy-6-oxo-urs-12-en-23-al-28-oic acid	*U33*	leaves and bark	Kitajima et al. (2000a)
137	3β,19α-dihydroxy-6-oxo-urs-12-en-23-al-28-oic acid	*U33*	leaves and bark	Kitajima et al. (2000a)
		U19	stem bark	Wang et al. (2013)
138	3β,19α-dihydroxy-6-oxo-urs-12-en-23-ol-28-oic acid	*U33*	leaves and bark	Kitajima et al. (2000a)
139	19α-hydroxy-3,6-dioxo-urs-12-en-28-oic acid	*U11*	woody part	Diyabalanage et al. (1995)
140	3β,19α-dihydroxy-4,6-dioxo-urs-12-en-28-oic acid	*U33*	leaves and bark	Kitajima et al. (2000b)
141	19α-hydroxy-3,6-diacetoxy-urs-12-en-28-oic acid	*U11*	woody part	Diyabalanage et al. (1995)
142	3β,6β,19α-trihydroxy-urs-12-en-28-oicacid-24-carboxylicacidmethyl ester	*U22*	stem bark	Sun et al. (2012a)
143	3β,6β,19α-trihydroxyurs-12-en-23,28-dimethyloate	*U33*	bark	Aquino et al. (1991)
144	3β,6β,19α-trihydroxyurs-12-en-28-oic acid-23-nor-24-esomethylene	*U35*	root	Tao et al. (2001)
		U12	leaves	Aimi et al. (1989)
145	3β-hydroxy-30-methoxy-6-oxo-urs-12,19(20)-dien- 28-oic-acid	*U19*	stem bark	Wang et al. (2013)
146	2α,19α-dihydroxy-3-oxo-urs-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
147	3β,19α-dihydroxy-6β,7β-epoxyl-urs-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
148	3β,6β-dihydroxy-urs-12,18 (19)-dien-28-oic acid	*U19*	stem bark	Wang et al. (2013)
149	uncaric acid	*U11*	woody part	Herath et al. (1979)
		U12	woody part	Aimi et al. (1989)
		U35	root	Tao et al. (2001)
150	3β-hydroxyurs-12-en-27,28-diolic acid	*U26*	twing	Deng et al. (2009)
151	3β-hydroxy-7-oxo-urs-12-en-27,28-diolic acid	*U33*	bark	Aquino et al. (1997)
152	3β-methoxy-16α-hydroxyurs-12,19(29)-dien- 27,28-diolic acid	*U33*	bark	Aquino et al. (1997)
153	22α-hydroxy-3-oxo-urs-12-en-27,28-diolic acid	*U16*	leaves	Xin et al. (2009)
154	uncarinic acid C	*U26*	hook	Lee et al. (2000)
155	uncarinic acid D	*U26*	hook	Lee et al. (2000)
156	uncarinic acid H	*U26*	stem and hook	Zhang et al. (2014b)
157	uncarinic acid I	*U26*	stem and hook	Zhang et al. (2014b)
158	oleanoic acid	*U22*	stem and hook	Zhang and Guo, (2012)
		U33	bark	Aquino et al. (1991)
		U35	root	Tao et al. (2001)
159	3-oxo-olean-12-en-28-oic acid	*U26*	hook	Shin et al. (2013)
160	3β,6β,19α-trihydroxy-olean-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
161	6β,19α-dihydroxy-3-oxo-olean-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
162	3β,19α-dihydroxy-6-oxo-olean-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
163	19α-hydroxy-3,6-dioxo-olean-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
164	3β,19α,23-trihydroxy-6-oxo-olean-12-en-28-oic acid	*U33*	bark	Montoro et al. (2004)
165	uncarinic acid F	*U26*	stem and hook	Zhang et al. (2014b)
166	uncarinic acid G	*U26*	stem and hook	Zhang et al. (2014b)
167	uncarinic acid J	*U26*	stem and hook	Zhang et al. (2014b)
168	6β,19α-dihydroxy-3-oxo-24-norolean-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
169	19α-hydroxy-3,6-dioxo-24-norolean-12-en-28-oic acid	*U19*	stem bark	Wang et al. (2013)
170	uncarinic acid A	*U26*	hook	Lee et al. (2000)
171	uncarinic acid B	*U26*	hook	Lee et al. (2000)
172	uncarinic acid E	*U26*	hook	Lee et al. (2000)
173	friedelin	*U29*	stem and hook	Zhang et al. (2014a)
174	obtusalin	*U29*	stem and hook	Zhang et al. (2014a)
175	betulin	*U29*	stem and hook	Zhang et al. (2014a)
176	laevigatone A	*U19*	stem bark	Wang et al. (2013)
177	quinovic acid	*U16*	leaves	Xin et al. (2009)
178	quinovic acid-3β-*O*-β-D-quinovopyranoside	*U15*	bark	Yepez et al. (1991)

Table 3 (*continued*)

179	quinovic acid-3β-*O*-β-D-fucopyranoside	*U15*	bark	Yepez et al. (1991)
180	quinovic acid-3β-*O*-α-L-rhamnopyranoside	*U33*	bark	Aquino et al. (1997)
181	quinovic acid-(27→1)-β-D-glucopyranosyl ester	*U15*	bark	Yepez et al. (1991)
182	quinovic acid -(28→1)-β-D-glucopyranosyl ester	*U15*	bark	Yepez et al. (1991)
183	quinovic acid-3β-*O*-β-D-quinovopyranosyl-(3→1)-β-D-glucopyranoside	*U33*	bark	Aquino et al. (1997)
184	quinovic acid-3β-*O*-β-D-quinovopyranosyl-(3→1)-β-D-galactopyranoside	*U33*	bark	Aquino et al. (1997)
185	quinovic acid-3β-*O*-α-L-rhamnopyranosyl-(3→1)-β-D-glucopyranoside	*U33*	bark	Aquino et al. (1997)
186	quinovic acid-3β-*O*-α-L-rhamnopyranosyl-(27→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1997)
187	quinovic acid 3β-*O*-β-D-glucopyranoside-(27→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1997)
188	quinovic acid-3β-*O*-β-D-fucopyranoside- (3→1)-β-D-glucopynoside	*U33*	bark	Aquino et al. (1997)
189	quinovic acid-3β-*O*-β-D-fucopyranoside-(27→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1991)
190	quinovic acid-3β-*O*-β-D-quinovopyranoside-(28→1)-β-D-glucopyranosyl ester	*U11*	bark	Diyabalanage et al.(1997)
191	quinovic acid-3β-*O*-β-D-fucopyranoside-(28→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1991)
192	quinovic acid-3β-*O*-β-D-quinovopyranoside-(28→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1991)
193	quinovic acid-3β-*O*-β-D-fucopyranosyl-(3→1)-β-D-glucopyranosyl-(27→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1991)
194	quinovic acid-3β-*O*-α-L-rhamnopyranosyl-(3→1)-β-D-glucopyranosyl-(27→1)-β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1997)
195	quinovic acid-3β-*O*-β-D-fucopyranosyl- (3→1)-β-D- glucopyranosyl-(28→1)- β-D-glucopyranosyl ester	*U33*	bark	Aquino et al. (1991)
196	uncarisaside A	*U16*	leaves	Xin et al. (2009)
197	tomentoside A	*U33*	leaves	Kitajima et al. (2003)
198	tomentoside B	*U33*	leaves	Kitajima et al. (2003)
199	cincholic acid-3β-*O*-β-D-fucopyranosyl- (4→1) -β-D-glucopyranoside	*U33*	leaves	Kitajima et al. (2004)
200	cincholic acid-3β-*O*-β-D-fucopyranoside-28-*O*-β-D-glucopyranosyl ester	*U33*	leaves	Kitajima et al. (2004)
201	cincholic acid-3β-*O*-β-D-fucopyranosyl-(4→1)-β-D-glucopyranosyl -(28→1)-β-D-glucopyranosyl ester	*U33*	leaves	Kitajima et al. (2004)
202	pyrocincholic acid	*U16*	leaves	Xin et al. (2009)
203	pyrocincholic acid ethyl ester	*U16*	leaves	Xin et al. (2009)
204	pyrocincholic acid-3β-*O*-β-D-quinovopynosyl-(28→1)-β-D-glucopyranosyl ester	*U16*	leaves	Xin et al. (2009)
205	3β-hydroxy-27-norolean-13 (28)-lactone	*U16*	leaves	Xin et al. (2009)

additon, the ethanol and hydroethanol extract of *U. tomentosa* also presented antioxidant activity (Amaral et al., 2009; Pilarski et al., 2006; Dreifuss et al., 2010). The studies further indicated that phenoloid and triterpenoid in *U. tomentosa* are predominantly important constituents for its antioxidant activity, especially proanthocyanidins, quercetin **(207)**, ursolic acid **(124)** and oleanoic acid **(158)** (Gonçalves et al., 2005; Falkiewicz and Lukasiak, 2001; Amaral et al., 2009; Bors et al., 1990).

4.2. Antidiabetic activities

Diabetes is a chronic disease caused by metabolic disorders. High blood glucose level of diabetes patients mainly resulted from low production of insulin or low response to insulin. According to the World Health Organization, there are 347 million people with diabetes world wide (World Health Organization, 2013). Inhibitors of carbohydrate-hydrolyzing enzymes were commonly used as therapeutic approaches to retard glucose absorption, such as α-amylase and α-glucosidase (Holman et al., 1999; Satio et al., 1998; Toeller, 1994). Based on these reports, dried leaves of *U. gambier* extracts were investigated to evaluate their potential as an inhibitor of α-glucosidase. The results showed that the ethanol and ethyl acetate extracts as well as the aqueous residue after ethyl acetate extraction and the residue from ethanol extraction all show moderate activity for inhibiting α-glucosidase *in vitro* at IC_{50} rang of 15.2 and 49.5 μg/mL (Apea-Bah et al., 2009). Among eighteen triterpenoid compounds isolated from ethanol extract of *U. laevigata* stem barks, ursolic acid **(124)** and 3β-hydroxy-30-methoxy-6-oxo-urs-12,19(20)-dien-28-oic acid **(1 4 5)** inhibited the activities of α-glucosidase with the IC_{50} value of 16 ± 2.2 and 49 ± 3.7 μM, respectively (Wang et al., 2013). In addition, Domingues et al. (2011) reported that hydroethanol extract of *U. tomentosa* stem bark reduce the glycemic level and delay the diabetes incidence in a dose-dependent manner in immune-mediated diabetes induced by multiple low-doses of streptozotocin (MLDS). The extract at the concentration of 400 mg/kg exhibited high inhibition of diabetes incidence by 15%. The immunological assays further indicated that this protection against immune-mediated diabetes could be determined by a Th2 polarization, an expansion of Foxp3+ regulatory T-cells, or the both. Taken together, *U. gambier*, *U. laevigata* and *U. tomentosa* are worthwhile to be considered in human diabetes treatment and, therefore, should be extensively studied.

4.3. Antimicrobial activities

Micropulverized U. tomentosa was evaluated for its antimicrobial activities in vitro against oral human pathogens, including Streptococcus mutants, Staphylococcus spp, Pseudomonas aeruginosa, Candida albicans and Enterobacteriaceae. Micropulverized U. tomentosa inhibited 8% of Enterobacteriaceae isolates, 52% of Streptococcus mutants and 96% of Staphylococcus spp at the concentration of 30 mg/mL. However, this concentration did not present inhibitory effect on P. aeruginosa and C. albicans (Ccahuana-Vasquez et al., 2007), which differed from that presented by Silva et al. (1998) and Herrera et al. (2010). According to Herrera et al. (2010), the freeze-dried extract of U. tomentosa exhibited inhibition against C. albicans with the zones of inhibition up to 26.5 mm at the concentration of 20 mg/mL. And increasing the concentration to 500 mg/mL, the extract inhibited C. albicans isolates by 66% (Silva et al., 1998). These results revealed that the concentration and type of U. tomentosa employed in the experiments may affect its antibacterial activity and this activity was associated with the oxindole alkaloids, triterpene, vegetal steroids, phenolic compound, glycoside, tannin and flavonoids in U. tomentosa (Aquino et al., 1997; Obregon, 1996; Otake et al., 1991). Besides, pheophoride a ethyl ester, uncarine E **(60)**, rhynchophylline **(32)** and isorhynchophylline **(40)** isolated from Uncaria, also showed antibacterial activity (Prieto Rodríguez et al., 2011; Garcia et al., 2005; Chen et al., 2010).

4.4. Anti-inflammatory

Sandoval et al. (2002) investigated the anti-inflammatory activities of aqueous extract of Cat's claw bark (*U. tomentosa* and *U. guianensis*). *U. guianensis* and *U. tomentosa* showed significantly inhibitory effect on TNF-α productions in LPS-induced RAW 264.7 cells with IC_{50} of 9.5 ng/mL and 14.1 ng/mL, respectively. Aqueous extract of *U. rhynchophylla* stem with hook at the concentration of 2 mg/mL has been reported to decrease the levels of NO, IL-1β to

Table 4
Flavonoids isolated from the genus *Uncaria*.

No.	Compound	Resource	Parts of plant	Reference
206	kaempferol	*U30*	hook	Sun et al. (2012)
207	quercetin	*U30*	hook	Sun et al. (2012)
208	(+)-catechin	*U14*	leaves	Arbian et al. (1998)
		U13	leaves	Hatano et al. (2009)
		U26	hook	Hou et al. (2005)
209	(+)-epicatechin	*U13*	leaves and twing	Taniguchi et al. (2008a)
210	(-)-epicatechin	*U16*	stem and hook	Xin et al. (2008a)
		U30	stem and hook	Sekiya et al. (2002)
		U21	leaves	Salim et al. (2013)
		U26	hook	Hatano et al. (2009)
				Hou et al. (2005)
211	(-)-epiafzelechin	*U21*	leaves	Salim et al. (2013)
212	uncariechin	*U21*	leaves	Salim et al. (2013)
213	procyanidin B_1	*U13*	leaves and twing	Taniguchi et al. (2008a)
214	procyanidin B_3	*U13*	leaves and twing	Taniguchi et al. (2008a)
215	gambiriin A_1	*U13*	leaves and twing	Taniguchi et al. (2008a)
216	gambiriin A_2	*U13*	leaves and twing	Taniguchi et al. (2008a)
217	gambiriin A_3	*U13*	stem and hook	Taniguchi et al. (2008b)
218	gambiriin B_1	*U13*	leaves and twing	Taniguchi et al. (2008a)
219	gambiriin B_2	*U13*	leaves and twing	Taniguchi et al. (2008a)
220	gambiriin C	*U13*	leaves and twing	Taniguchi et al. (2008a)
221	gambiriin D_1	*U13*	leaves and twing	Taniguchi et al. (2008a)
222	gambiriin D_2	*U13*	leaves and twing	Taniguchi et al. (2008a)
223	gambiriin D_3	*U13*	stem and hook	Taniguchi et al. (2008b)
224	gambiriin D_4	*U13*	stem and hook	Taniguchi et al. (2008b)
225	catechin-(4α→8)-ent-epicatechin	*U13*	leaves and twing	Taniguchi et al. (2008a)
226	cinchonain Ia	*U33*	bark	Wirth and Wagner (1997)
227	cinchonain Ib	*U33*	bark	Wirth and Wagner (1997)
228	dehydrodicatechin A	*U13*	leaves	Hatano et al. (2009)
229	catechin- (8→6′)-catechin	*U13*	leaves	Hatano et al. (2009)
230	catechin- (6→6′)-catechin	*U13*	leaves	Hatano et al. (2009)
231	uncariagambirine	*U13*	leaves	Hatano et al. (2009)
232	gambircatechol	*U13*	leaves	Hatano et al. (2009)
233	trifolin	*U26*	leaves	Aimi et al. (1982)
234	buddleoside	*U30*	hook	Sun et al. (2012)
235	afzelin	*U16*	leaves	Xin et al. (2008a)
236	kaemferol-3-O-β-D-galactopyranoside	*U26*	leaves	Ma et al. (2009a)
237	kaemferol-3-O-β-D-galactopyranosyl-(6→1)-α-L-rhamnopyranoside	*U26*	leaves	Ma et al. (2009a)
238	hyperin	*U26*	leaves	Aimi et al. (1982)
239	quercetin-3-O-β-D-galactopyranoside	*U30*	hook	Sun et al. (2012)
240	quercitrin	*U16*	leaves	Xin et al. (2008a)
241	isoquercitrin	*U16*	leaves	Xin et al. (2008a)
242	rutin	*U16*	leaves	Xin et al. (2008a)
		U11	leaves	Phillipson et al. (1978)
		U26	twing	Deng et al. (2009)
243	quercetin-3-O-β-D-galactopyranosyl-(6→1)-α-L-rhamnopyranoside	*U30*	hook	Sun et al. (2012)
		U26	twing	Deng et al. (2009)
244	neohesperidin	*U16*	leaves	Wu and Chan (1994)
245	manghaslin	*U16*	leaves	Xin et al. (2008a)
246	C-(8)-*S*-7-deoxyloganic acid	*U33*	inner bark	Muhammad et al. (2001)
247	umbelliferone	*U16*	leaves	Wu and Chan (1994)
		U29	stem and hook	Zhang et al. (2014a)
248	scopoletin	*U30*	stem and hook	Liu and Feng (1993a)
		U29	stem and hook	Zhang et al. (2014a)
		U21	leaves	Salim et al. (2013)
249	3,4-dihydroxy-7-methoxycoumarin	*U21*	leaves	Salim et al. (2013)
250	cleomiscosin B	*U26*	twing	Deng et al. (2009)
251	cleomiscosin D	*U26*	twing	Deng et al. (2009)
252	(*2 R,3 R,4 S*)-lyoniresinol-3α-O-β-D-glucopyra-noside	*U30*	hook	Sun et al. (2011)
253	(*2 R,3 S,4 R*)-lyoniresinol-3α-O-β-D-glucopyra-noside	*U30*	hook	Sun et al. (2011)
254	(*2 S,3 S,4 R*)-lyoniresinol-3α-O-β-D-glucopyra-noside	*U30*	hook	Sun et al. (2011)
255	(*2 S,3 R,4 S*)-lyoniresinol-3α-O-β-D-glucopyra-noside	*U30*	hook	Sun et al. (2011)

the basal level in LPS-induced RAW 264.7 cells. Its anti-inflammatory effect was associated with blocking NF-κB, Akt, and mitogen-activated protein kinase activation in macrophages (Kim et al., 2010). Alkaloids, quinovic acid glycosides and β-sitosterol **(2 6 0)** interacted synergistically has been though for their anti-inflammatory activities (Yuan et al., 2008; Rojas-Duran et al., 2012; Aquino et al., 1991; Senatore et al., 1989). More details were described as follows: rhynchophylline **(32)**, isorhynchophylline **(40)**, corynoxeine **(34)**, isocorynoxeine **(78)** and vincoside lactam **(105)** inhibited NO release in LPS-activated primary rat cortical microglial cells with IC_{50} ranging from 13.7 to 19.0 μM (Yuan et al., 2008) and mitraphylline **(63)** suppressed the release of IL-1α, IL-1β, IL-4, IL-17 and TNF-α in LPS-induced Balb/c female mice (Rojas-Duran et al., 2012). Montserrat-de la Paz et al. (2015) also found that at the concentration of 25 μM mitraphylline **(63)** reduce the chemotactic capacity of human primary monocytes, promote the polarization of M0 macrophages toward an anti-inflammatory M2 phenotype and reduce the number of classical

Table 5
Other compounds isolated from the genus *Uncaria*.

No.	Compound	Resource	Parts of plant	Reference
256	4-hydroxybenzaldehyde	*U21*	leaves	Salim et al. (2013)
257	methyl-4-hydroxybenzoate	*U21*	leaves	Salim et al. (2013)
258	stigmast-4-en-3-one	*U29*	stem and hook	Zhang et al. (2014a)
259	24-en-cycloartenone	*U29*	stem and hook	Zhang et al. (2014a)
260	*β*-sitosterol	*U29*	stem and hook	Zhang et al. (2014a)
		U33	bark and root	Senatore et al. (1989)
261	*β*-daucosterol	*U29*	stem and hook	Zhang et al. (2014a)
262	squalene	*U29*	stem and hook	Zhang et al. (2014a)
263	1-methoxyoctadecan-1-ol	*U30*	stem and hook	Ahn et al. (2014)

($CD14^{++}CD16^{-}$) and intermediate ($CD14^{++}CD16^{+}$) subsets in LPS-treated cells. The classical and intermediate monocyte subsets have been identified as a pro-inflammatory phenotype that actively produced TNF-α (in response to LPS), IL-1*β*, IL-6, and leaded to the progression of numerous inflammatory disorders such as atherosclerosis (Rogacev et al., 2014). These results represented that oxindole alkoids isolated from *Uncaria* may be dominating components for the anti-inflammatory activity of *Uncaria*'s extracts.

4.5. Immunostimulation

C-Med-100®, a 90-100 °C hot water extract of *U. tomentosa* containing only molecules < 10,000 molecular weight, recovered the white blood cells significantly in leucopenia rats model induced by doxorubicin (DXR). Compared with the positive control (neupogen), the recovery of C-Med-100® treatment was a more natural process, in which all fractions of white blood cells were proportionally increased at doses of 40 and 80 mg/kg (Sheng et al., 2000b). Its mechanism was most likely prolonged lymphocyte survival in peripheral lymphoid organs instead of increasing their proliferation rate (Akesson et al., 2003). Lamm et al. (2001) have characterized C-Med-100® as immune enhancer in human useful in protecting against *Pneumococcal* infections. After oral administration with C-Med-100® at daily dose of 350 mg × 2 for 2 months, the lymphocyte to neutrophil ratios in peripheral blood from volunteers were enhanced without affecting other hematological parameters, which suggested C-Med-100® has selective influence on immune modulating parameter. The esters of quinovic acid and their glycosides containing at least one carboxy ester in their structure (Aquino et al., 1989; Cerri et al., 1988) and condensed tannins (Keplinger et al., 1999; Holderness et al., 2007) have been considered as its active constituents. In addition, induction of dendritic cells was critical for the induction of Ag-specific T lymphocyte responses and essential for the development of human vaccines relying on T cell immunity (Banchereau and Steinman, 1998; Mellman and Steinman, 2001). Uncarinic acid C **(154)** plus IFN-γ-primed dendritic cell have been regarded as potential vaccine for cancer immunotherapy with modulation of dendritic cells favored Th1 cell polarization by activation of IL-12p70 dependent on TLR4 signaling (Bae et al., 2010; Takei, 2010). Besides, the C-2′ configuration have been proved to affect the immune modulatory effect of uncarinic acids C **(154)** and D **(155)**. The *E* configuration in uncarinic acid C **(154)** showed approximately 20 times more potent than that of *Z* configuration in uncarinic acid D **(155)** (Umeyama et al., 2010).

Recently, Nudo and Catap (2011) evaluated the immunomodulating activity of aqueous extract of *U. perrottetii* vinebark *in vitro* and *in vivo* experiments. *In vitro* immune response assays determined the optimum concentration to be 50 μg/mL. At this concentration, *U. perrottetii* extract stimulated peritoneal phagocyte activation, produced a significant increase in the activity of phagocytic cells from the spleen and promoted splenic cellular proliferation with or without LPS when compared with the PBS-treated cells (negative control). *In vivo* experiment further proved that the optimum concentration significantly enhanced respiratory burst and plasma lysozyme activity compared with the cyclophosphamide-injected mice. Based on these results, *U. perrottetii* extract has immunopotentiating activities on the innate immunity of Balb/C mice and the extract could potentially reverse the immunosuppressive effects of cyclophosphamide.

4.6. Antihypertension

According to Chinese pharmacopoeia, the traditional Chinese medicine-"Gou-teng" was mainly used to treat cardiovascular ailments, especially for hypertension (Chinese Pharmacopoeia Commission, 2010; Ndagijimana et al., 2013). Several studies have demonstrated the relationships between indole alkaloids and antihypertensive activity of "Gou-teng". These results suggested that rhynchophylline **(32)** and isorhynchophylline **(40)** exert antihypertensive activities by inhibiting of the vasomotor center, sympathetic nerves and ganglia and blocking of L-type decrease of calcium (Ca^{2+}) channels (Song et al., 2000; Shi et al., 1989; Wang and Li, 1998; Zhang et al., 2004; Li et al., 2013); Villocarine A **(10)** and geissoschizine methyl ether **(11)** acted on rat aortic ring to show vasorelaxation activities. The underlying mechanisms of villocarine A **(10)** mainly described as follows: (i) inhibited calcium influx from extracellular space through voltage-dependent calcium channels and/or receptor-operated Ca^{2+}-channels; (ii) promoted the release of NO from endothelial cells; (iii) stimulated the opening of voltage-gated K^{+}-channels (Matsuo et al., 2011). Different from villocarine A **(10)**, geissoschizine methyl ether **(11)** affected aortic ring through endothelial dependency with nitric oxide at low concentrations of 0.1-3 μM and endothelial independency with Ca^{2+} channel blockade at higher concentrations of 10-100 μM (Yuzurihara et al., 2002). The abnormal proliferation of vascular smooth muscle cells (VSMCs) has been regarded as an inductor of hypertension (Victor et al., 2002). Recently, corynoxeine **(34)** and isorhynchophylline **(40)** showed inhibitory of VSMCs proliferation. The blockage of extracellular signal regulated kinase 1/2 phosphorylation or regulation of G_0/G_1 phase cell cycle may be their potential mechanisms (Kim et al., 2008; Guo et al., 2014).

4.7. Anticancer activities

Among *Uncaria* species, *U. tomentosa* was considered as effective antitumor candidate to inhibit cancer cells growth, such as HL-60 (leukemia) (Cheng et al., 2007; Bacher et al., 2006), MCF7 and MT-3 (breast) (Riva et al., 2001; Sun et al., 2012a; Pilarski et al., 2010; García Giménez et al., 2010), Walker-256 (liver) (Dreifuss et al., 2013), T24 and RT4 (bladder) (Kaiser et al., 2013; Dietrich et al., 2014), MHH-ES-1 (sarcoma) (García Giménez et al., 2010), as well as SKN-BE (neuroblastoma) and GAMG (glioma). *etc.* (Garcia Prado

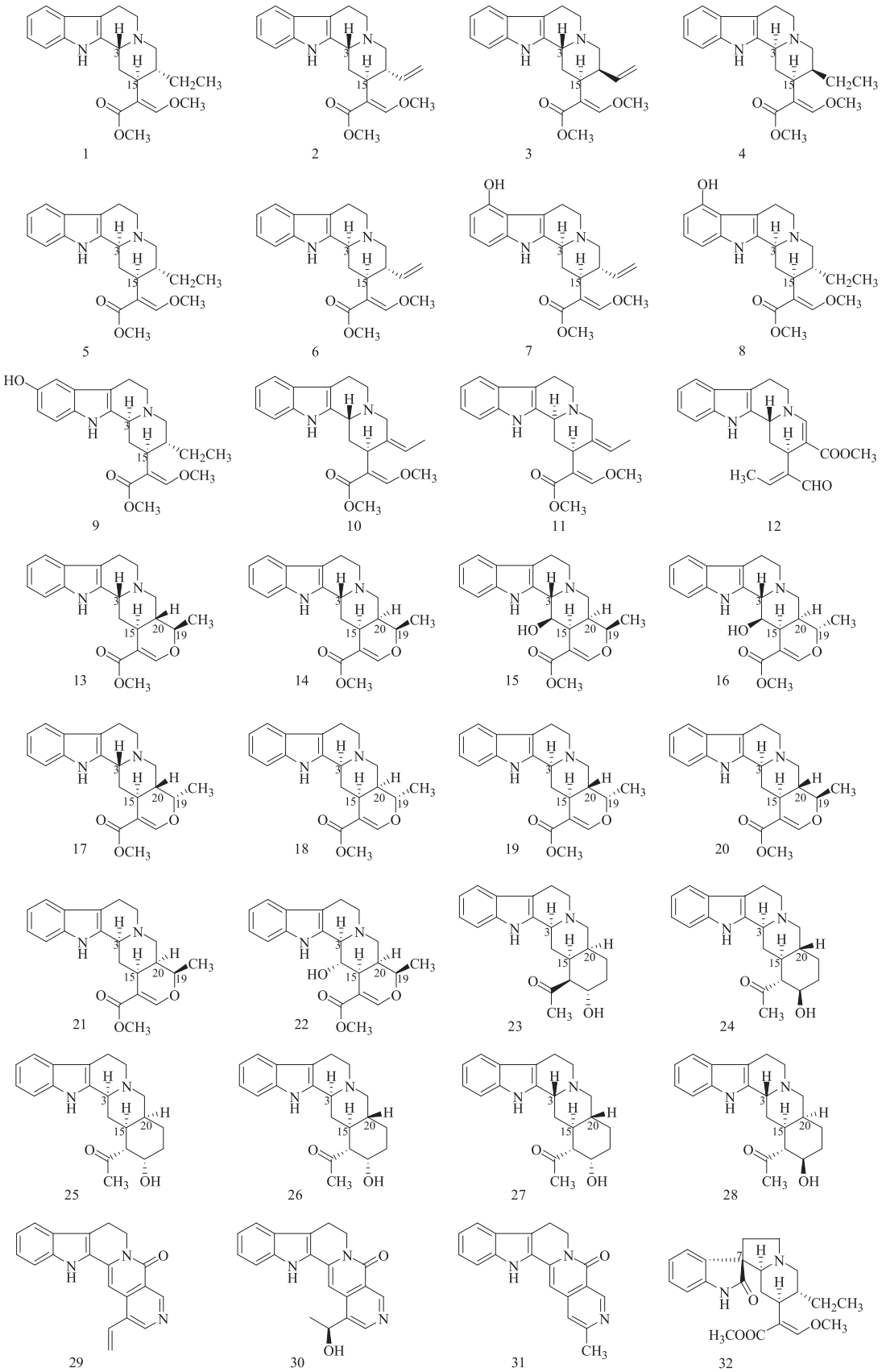


Fig. 1. Chemical structure from the genus *Uncaria*.

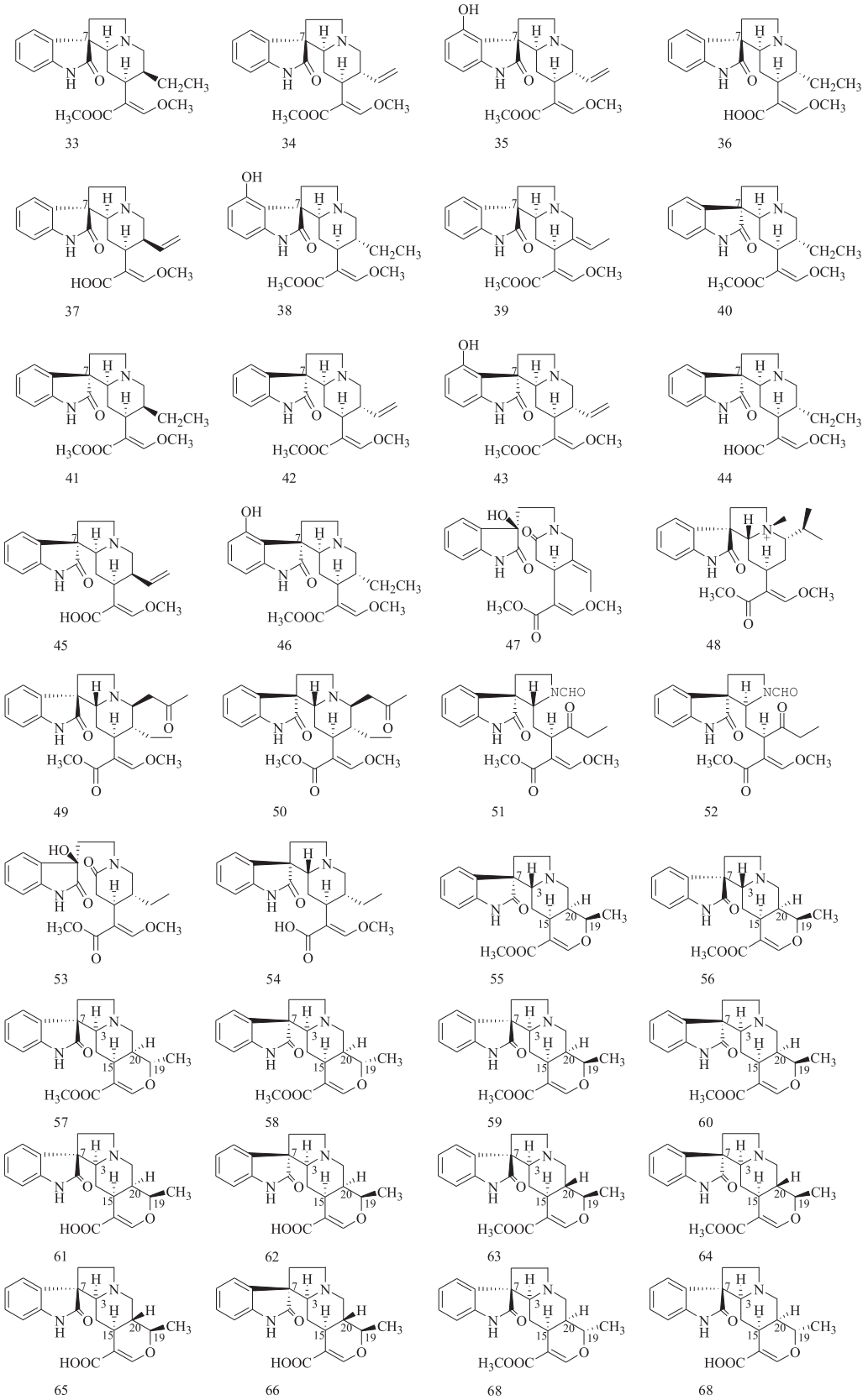
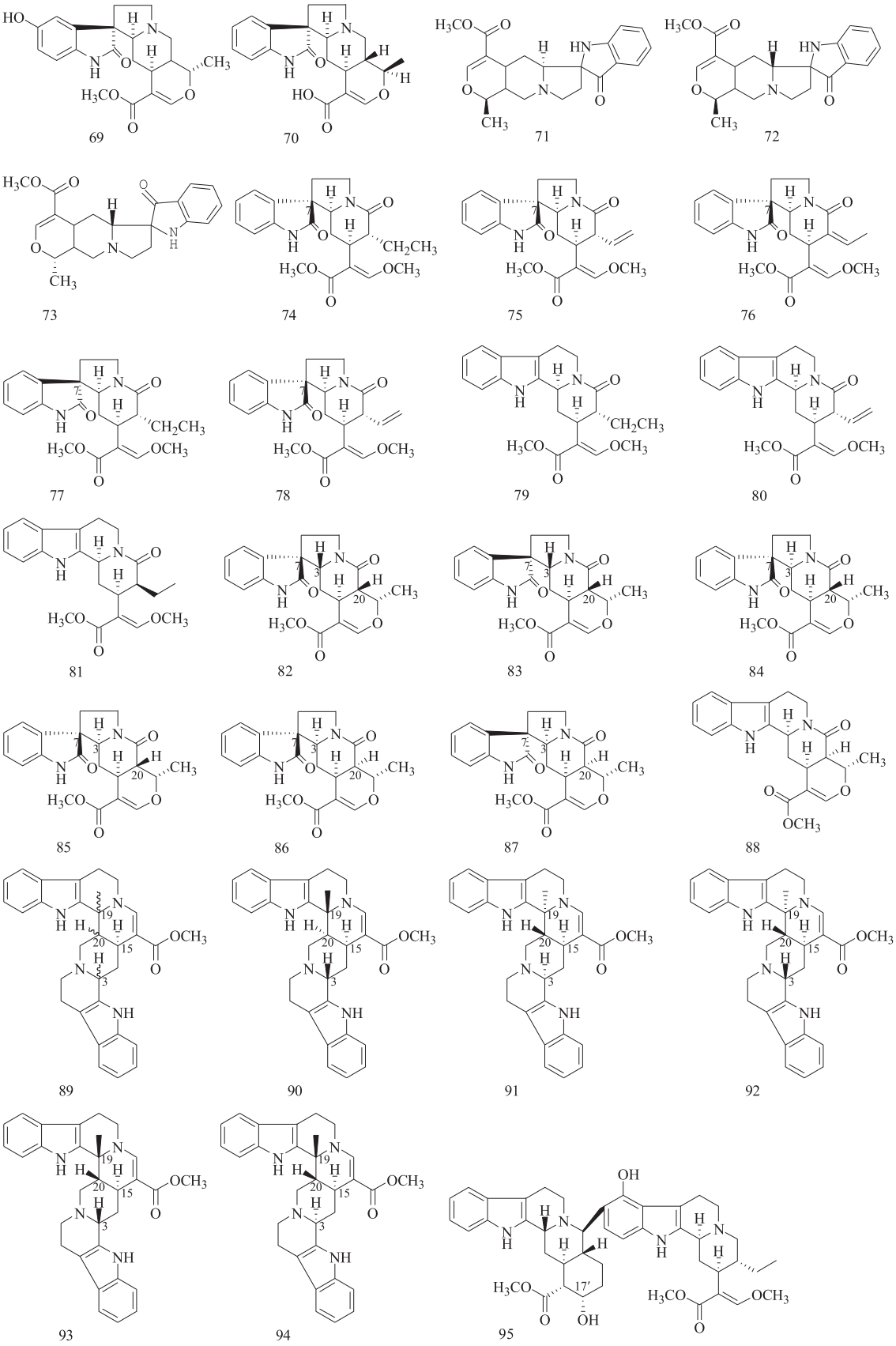


Fig. 1. (*continued*)



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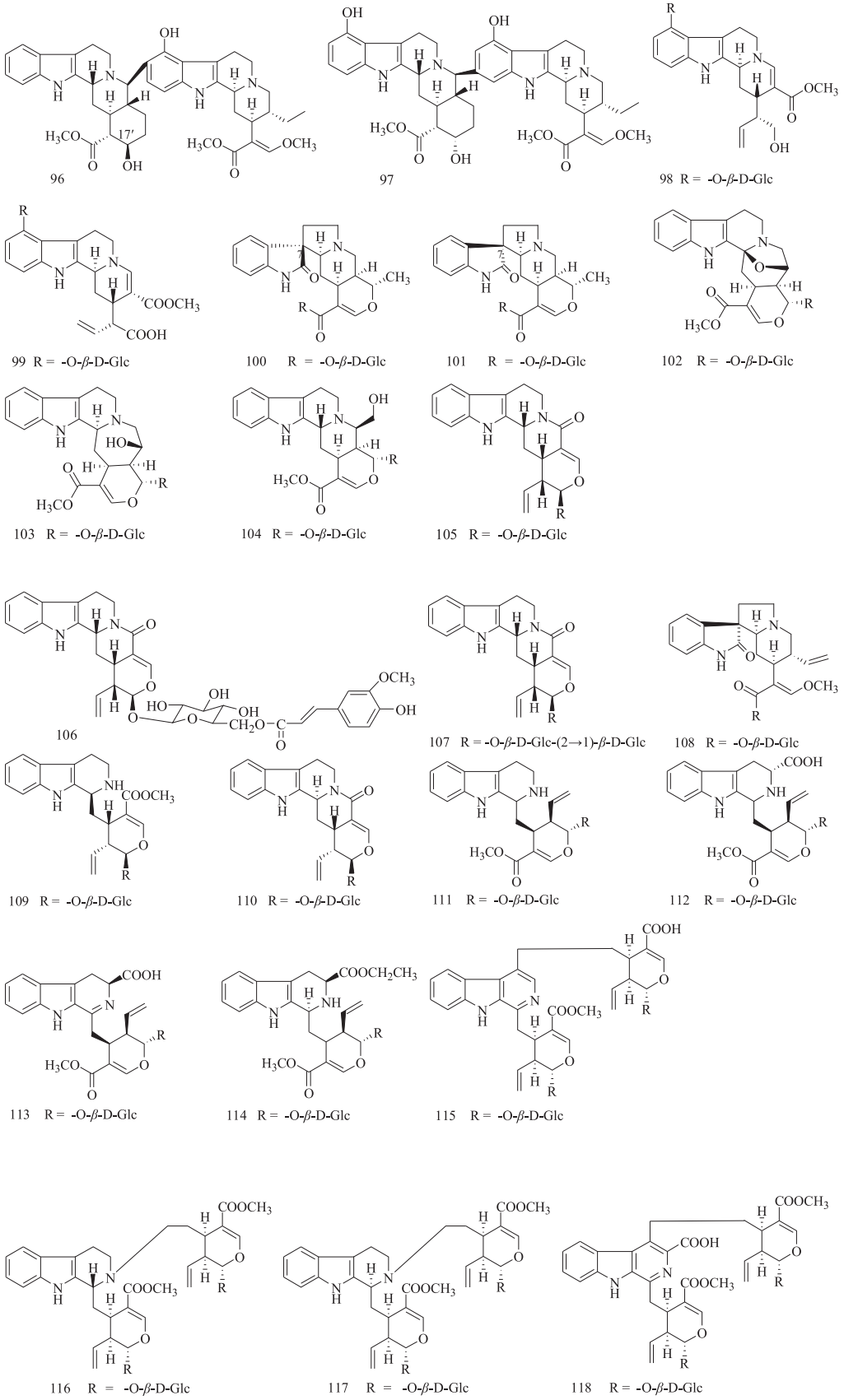


Fig. 1. (*continued*)

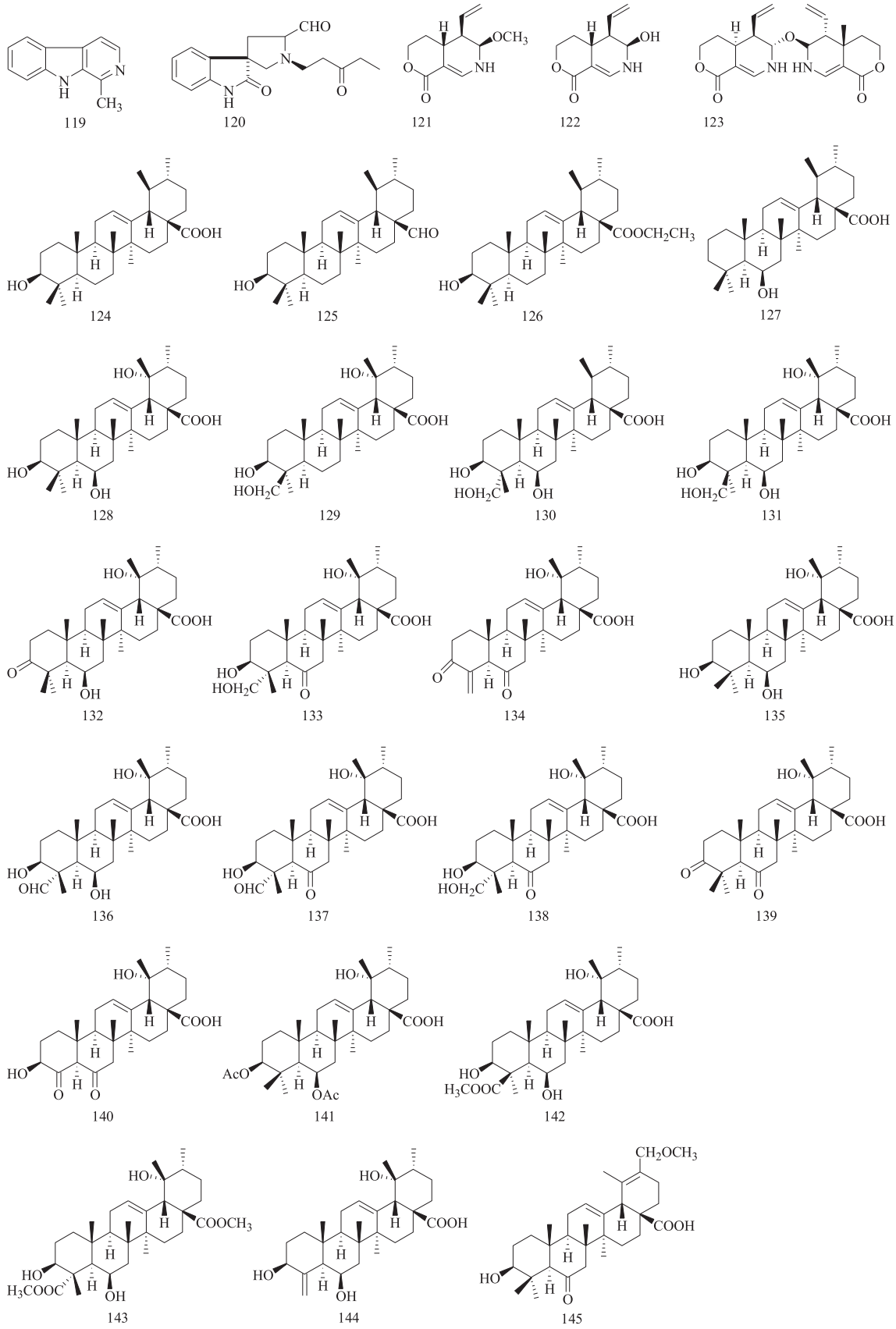
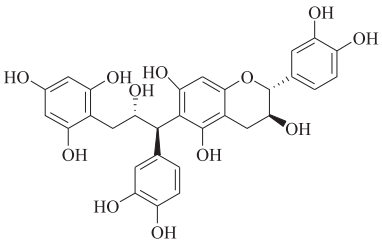


Fig. 1. (*continued*)



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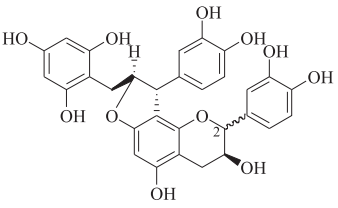
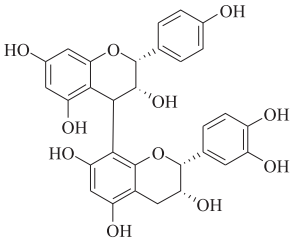


No. 2
218 *R*
219 *S*



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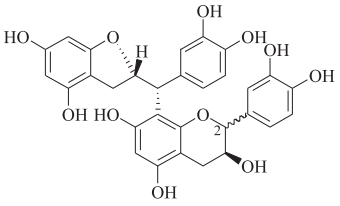
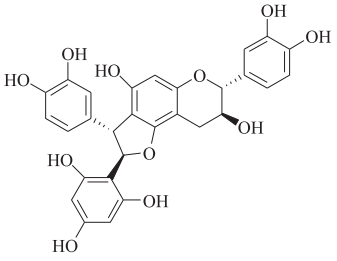


No. 2
221 *R*
222 *S*



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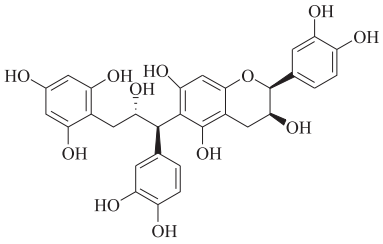

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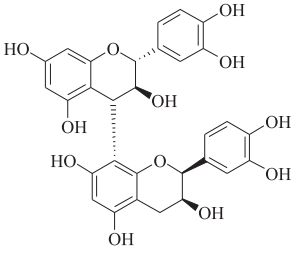

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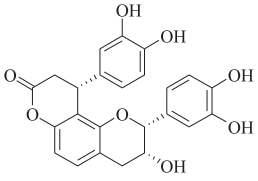

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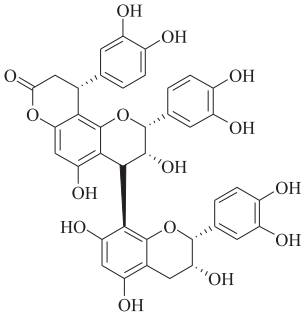

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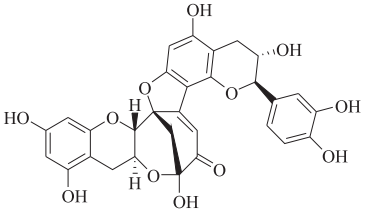

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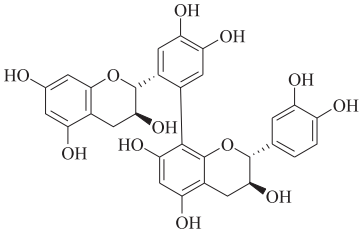

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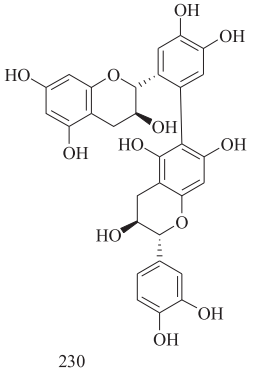

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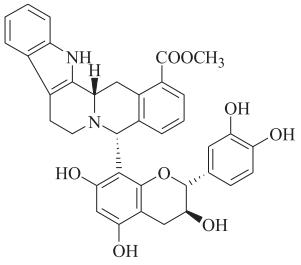

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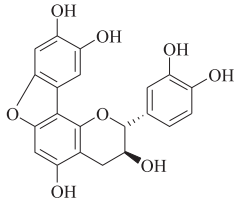

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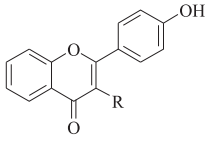
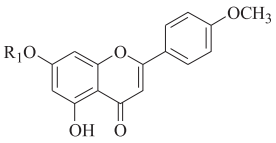
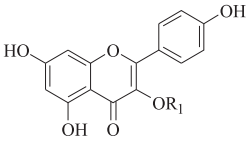


233 R = -*O*-*β*-D-Glc

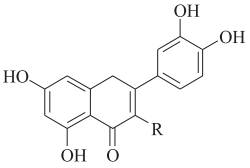
Fig. 1. (*continued*)



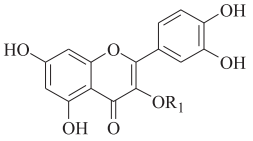
234 R_1= Rha-(1→6)-Glc



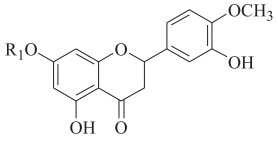
No.	R_1
235	Rha
236	Gal
237	Gal-(6→1)-Rha



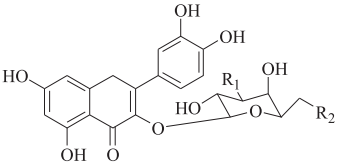
238 R = -*O*-*β*-D-Glc



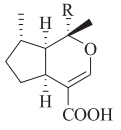
No.	R_1
239	Gal
240	Rha
241	Glc
242	Rha-(6→1)-Glc
243	Gal -(6→1)-Rha



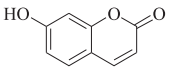
244 R_1= Glc-(2→1)-Rha



245 R_1=R_2= Rha



246 R = -O-*β*-D-Glc



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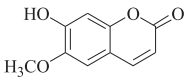

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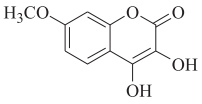

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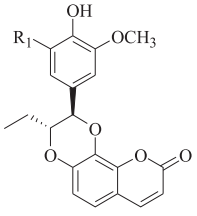
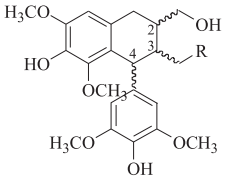
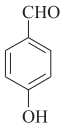


No.	R_1
250	H
251	OCH_3



No.	2	3	4	R
252	*R*	*R*	*S*	-O-*β*-D-Glc
253	*R*	*S*	*R*	-O-*β*-D-Glc
254	*S*	*S*	*R*	-O-*β*-D-Glc
255	*S*	*R*	*S*	-O-*β*-D-Glc



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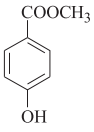

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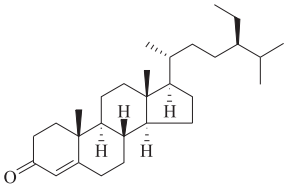

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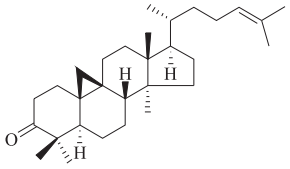

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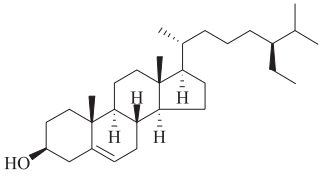

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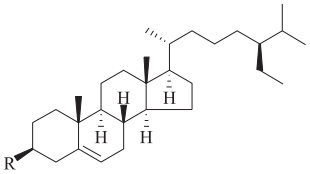
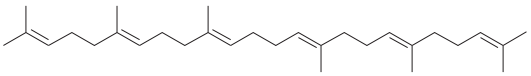


261 R = -O-*β*-D-Glc



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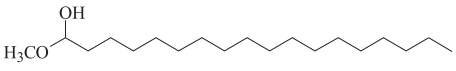
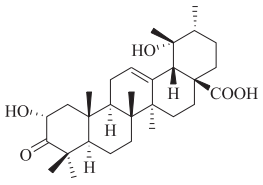


263

Fig. 1. (*continued*)



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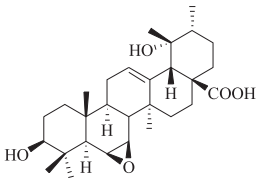

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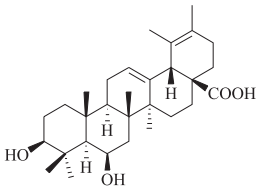

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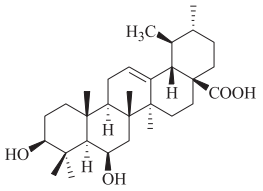
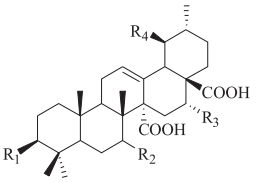
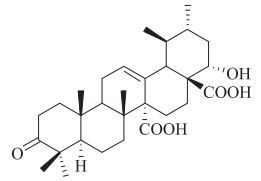


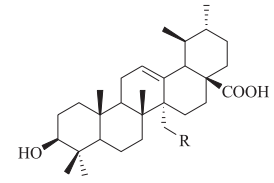
149



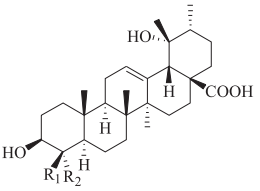
No.	R_1	R_2	R_3	R4
150	OH	H	H	CH_3
151	OH	=O	H	CH_3
152	OCH_3	H	OH	$=CH_2$



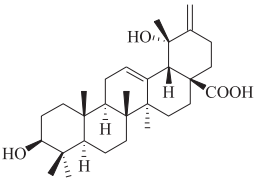
153



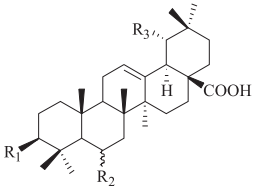
No.	R
154	*E*-feruloyl
155	*Z*-feruloyl



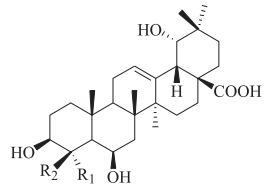
No.	R_1	R_2
156	CHO	CH3



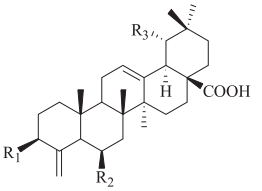
157



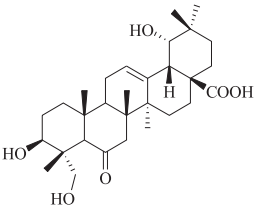
No.	R_1	R_2	R_3
158	OH	H	H
159	=O	H	H
160	OH	*β*-OH	OH
161	=O	*α*-OH	OH
162	OH	=O	OH
163	=O	=O	OH



No.	R_1	R_2
165	CH_3	CHO
166	CHO	CH_3
177	$COOCH_3$	*CH*$_3$



No.	R_1	R_2	R_3
168	=O	OH	OH
169	=O	OH	=O



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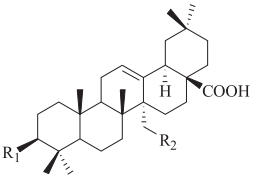
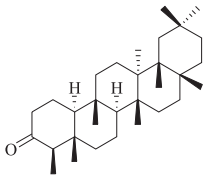


No.	R_1	R_2
170	OH	*E*-feruloyl
171	OH	*Z*-feruloyl
172	OH	*E*-coumaroyl



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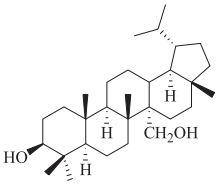

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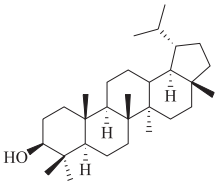

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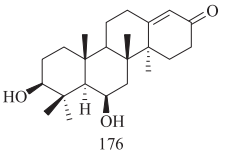
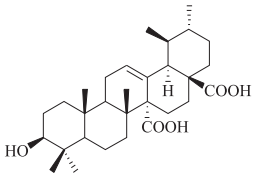
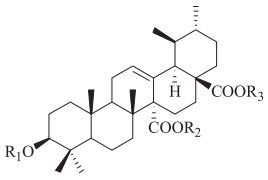


176

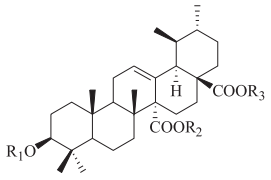
Fig. 1. (*continued*)



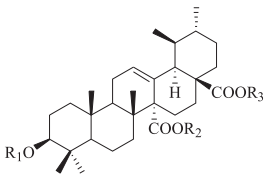
177



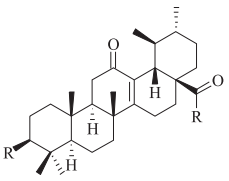
No.	R_1	R_2	R_3
178	Qui	H	H
179	Fuc	H	H
180	Rha	H	H
181	H	Glc	H
182	H	H	Glc



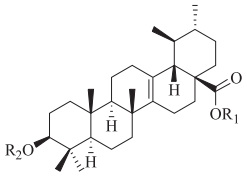
No.	R_1	R_2	R_3
183	Qui-(3→1)-Glc	H	H
184	Qui-(3→1)-Gal	H	H
185	Rha-(3→1)-Glc	H	H
186	Qui	Glc	H
187	Glc	Glc	H
188	Glc-(3→1)-Fuc	H	H
189	Fuc	Glc	H
190	Qui	H	Glc
191	Fuc	H	Glc
192	Qui	H	Glc



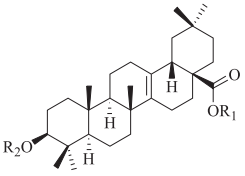
No.	R_1	R_2	R_3
193	Glc-(3→1)-Fuc	Glc	H
194	Rha-(3→1)-Glc	Glc	H
195	Fuc-(3→1)-Glc	H	Glc



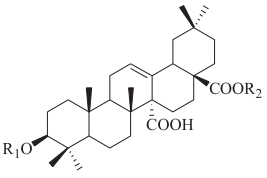
196 R = -O-β-D-Glc



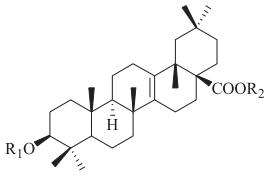
197 R_1 = Glc R_2 = Rha-(4→1)-Glc



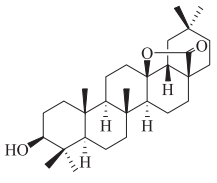
198 R_1 = Glc R_2 = Rha-(4→1)-Glc



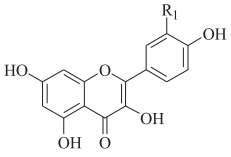
No.	R_1	R_2
199	Fuc-(4→1)-Glc	H
200	Fuc	Glc
201	Fuc-(4→1)-Glc	Glc



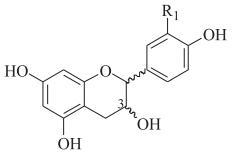
No.	R_1	R_2
202	OH	H
203	OH	Et
204	Qui	Glc



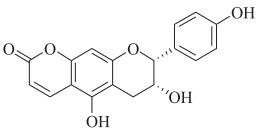
205



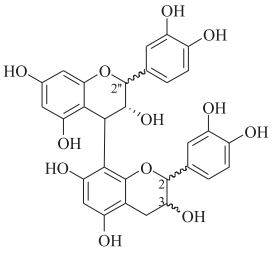
No.	R_1
206	H
207	OH



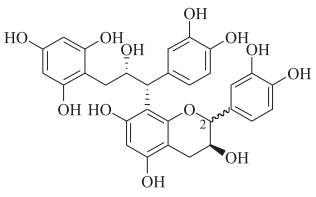
No.	2	3	R_1
208	*R*	*S*	OH
209	S	S	OH
210	*R*	*R*	OH
211	*R*	*R*	H



212



No.	2	3	2"
213	*R*	*S*	*R*
214	*S*	*R*	*S*



No.	2
215	*R*
216	*S*

Fig. 1. (*continued*)

Table 6
The bioactivities of extracts and compounds from the genus *Uncaria*.

Pharmacological activities	Extract/Compound	Types	Testing subjects	Dose	Effects	Reference
Antioxidant activities	*aqueous extract* of *U. sinensis*	*in vitro*	red blood cells from Wistar rats	50 to 1000 μg/mL	inhibited AAPH-induced hemolysis	Sekiya et al., 2002
	aqueous extract of *U. tomentosa*	*in vitro*	DPPH- radicals ABTS- radicals	1 to 100 μg/mL	inhibited DPPH, ABTS- radicals	Sandoval et al., 2002
	aqueous extract of *U. guianensis*	*in vitro*	DPPH- radicals ABTS- radicals	1 to 100 μg/mL	inhibited DPPH, ABTS- radicals	Sandoval et al., 2002
	U. tomentosa bark extracts: aqueous extract and 50% ethanol extract	*in vitro*	TEAC, PRTC, SOD	1 mg/mL	TEAC,PRTC and SOD of ethanol extract were 57 mol/g, 52 mmol/g and 0.39 U/mg, respectively. TEAC, PRTC and SOD of aqueous extract were 34 mol/g, 19 mmol/g and 0.10 U/mg, respectively.	Pilarski et al., 2006
	hydroethanol extract of *U. tomentosa*	*in vitro*	hypochlorous acid	1 to 100 μM	inhibited the hypochlorous acid-mediated thionitrobenzoic acid oxidation	Amaral et al., 2009
	aqueous extract of *U. gambir* ethanol extract of *U. gambir*	*in vitro*	DPPH radicals	10 to 200 μg/mL	inhibited 92% DPPH at 30 g/mL	Apea-Bah et al., 2009
	hydroethanol extract of *U. tomentosa*	*in vivo*	male Wistar rats-inoculated with W-256 cells	10 to 100 μg/mL	normalized the activities of catalase, glutathione-*S*-transferase and superoxide diamutase	Dreifuss et al., 2010
Antidiabetic activities	aqueous extract of *U. gambir* ethanol extract of *U. gambir*	*in vitro*	α-glucosidase	10 to 200 μg/mL	inhibit α-glucosidase	Apea-Bah et al., 2009
	hydroethanol extract of *U. tomentosa*	*in vivo*	C57BL/6 male mice-treated with MLDS (40 mg/kg)	oral 50 to 400 mg/kg for 21 days	reduced the glycemic levels and diabetes incidence; higher doses presented $CD4^+$ and $CD8^+$ T-cell values	Domingues et al., 2011
	ursolic acid	*in vivo*	α-glucosidase	10 μL	inhibited α-glucosidase	Wang et al., 2013
	3*β*-hydroxy-30-methoxy-6-oxo-urs-12, 19 (20)-dien-28-oic acid	*in vivo*	α-glucosidase	10 μL	inhibited α-glucosidase	Wang et al., 2013
Antimicrobial activities	micropulverized *U. tomentosa*	*in vitro*	*Streptococcus mutans*, *Staphylococcus spp*, *Candida albicans*, *Pseudomonas aeruginosa*strains	2.5 to 50 mg/mL	inhibited 8% of Enterobacteriaceae isolates, 52% of *S. mutans* and 96% of *Staphylococcus* spp growth at 30 mg/mL without affecting *P. aeruginosa* and *C. albicans*.	Ccahuana-Vasquez et al., 2007
	U. tomentosa gel	*in vitro*	*Staphylococcus spp*, *Candida albicans*, *Enterococcus faecalis*	20 mg/mL	inhibited *E.faecalis* and *C. albicans* growth	Herrera et al., 2010
	pheophoride a ethyl ester	*in vitro*	*Staphylococcus aureus* 6538, *Enterococcus faecalis* 29212, *Escherichia coli* 25922, *Salmonella typhimurium* 14028, *Salmonella yphimurium* Ms 7953	2 μg/μL	showed significant activities against *S. aureus* 6538, *E. faecalis* 29212, *E. coli* 25922, *S. yphimurium* Ms 7953	Prieto Rodríguez et al., 2011
	rhynchophylline isorhynchophylline	*in vitro*	rat intestinal microvascular endothelial cells- treated with *Listerionlysin O*	10 μg/mL	prevented the morphological changes; decreased cell death; prevented disordered NO and ET-1 production in rat intestinal microvascular endothelial cells induced by *Listerionlysin O*	Chen et al., 2010
Anti-inflammatoy	aqueous extract of *U. tomentosa*	*in vitro*	RAW 264.7 cells-treated with LPS	0.1 to 100 μg/mL	inhibited TNF-α production	Sandoval et al., 2002
	aqueous extract of *U. guianensis*	*in vitro*	RAW 264.7 cells-treated with LPS	0.1 to 100 μg/mL	inhibited TNF-α production	Sandoval et al., 2002
	ethanol extract of *U. tomentosa*	*in vitro*	THP-1 cells-treated with LPS	1 μL, 10 μL	inhibited LPS-dependent expression of IL-1 and TNF-α; blocked ERK1/2 and MEK1/2 phosphorylation	Allen-Hall et al., 2007
	aqueous extract of *U. rhynchophylla*	*in vitro*	RAW 264.7 cells-treated with LPS	0.5 to 2 mg/mL	inhibited LPS-induced NO and IL-1*β* secretion as well as iNOS expression; suppressed LPS-induced NF-κB activation, phosphorylation, and degradation of IκB-*α*, phosphorylation of Akt, ERK1/2, p38 and JNK kinase	Kim et al., 2010
	rhynchophylline isorhynchophylline corynoxeine isocorynoxeine vincoside lactam	*in vitro*	microglia cells-treated with LPS	3 to 15 μg/mL	inhibited NO release in LPS-activated primary rat cortical microglial cells	Yuan et al., 2008
	aqueous extract of *U. tomentosa*	*in vivo*	male SD rats-treated with indomethacin	oral 5 mg/mL for 3 days	elicited a protective effect and attenuated the degree of gastric mucosal injury	Sandoval et al., 2002
	mitraphylline	*in vivo*	macrophages-treated with LPS	25 μM	reduced the chemotactic capacity of human primary monocytes; promoted the polarization of M0 macrophages toward an anti-inflammatory M2 phenotype; reduced	Montserrat-de la Paz et al. (2015)

Table 6 (*continued*)

Pharmacological activities	Extract/Compound	Types	Testing subjects	Dose	Effects	Reference
					the number of classical (CD14 $^{++}$ CD16^{-}) and intermediate (CD14 $^{++}$ CD16^{+}) subsets in LPS-treated cells.	
	mitraphylline	*in vivo*	Balb/c female mice-treated with LPS	oral 30 mg/kg/day for 3 days	inhibited the release of IL-1α, IL-1β, IL-4, IL-17 and TNF-α	Rojas-Duran et al., 2012
Immunostimulation	C-Med-100® (aqueous extract of *U. tomentosa*)	*in vitro*	spleen cell	oral 125 to 500 mg/kg	increased number of lymphocytes	Akesson et al., 2003
	uncarinic acid C	*in vitro*	human dendritic cell	0.1 μM	enhanced the T cell stimulatory capacity; promoted the production of IL-12p70 and Th1 polarization	Kim et al. 2011
	aqueous extract of *U. tomentosa*	*in vitro*	human γδT cells	44.0 μg/mL	induced IL-2Rα expression on γδT cells and some cell division	Holderness et al., 2007
	aqueous extract of *U. perrottetii*	*in vitro*	Balb/C mice	10 to 100 μg/mL	stimulated peritoneal phagocyte activation; produced a significant increase in the activity of phagocytic cells from the spleen; promoted splenic cellular proliferation	Nudo et al. 2011
	C-Med-100®	*in vivo*	W/Fu rats-treated with doxorubicin	oral 40 and 80 mg/kg 16 days	promoted the white blood cell recovery induced doxorubicin	Sheng et al., 2000b
	C-Med-100®	*in vivo*	human	oral 350 mg × 2 daily dose for two months	increased the lymphocyte/neutrophil ratios of peripheral blood; reduced decay in the 12 serotype antibody titer responses to pneumococcal vaccination at 5 months	Lamm et al., 2001
	aqueous extract of *U. perrottetii*	*in vivo*	Balb/C mice-treated with cyclophosphamide	50 μg/mL	significantly enhanced respiratory burst and plasma lysozyme activity compared with the cyclophosphamide-injected mice	Nudo et al. 2011
Anti-hypertension	rhynchophylline	*in vitro*	thoracic aorta from male SD rats	3 to 300 μM	mediated L-type Ca^{2+} channels	Zhang et al., 2004
	isorhynchophylline	*in vitro*	thoracic aorta from male SD rats	3 to 300 μM	mediated L-type Ca^{2+} channels	Zhang et al., 2004
	villocarine A	*in vitro*	thoracic aortic rings	30 μM	inhibitied calcium influx from extracellular space through voltage-dependent calcium channels and/or receptor-operated Ca^{2+}-channels; mediated the increased release of NO from endothelial cells and opening of voltage-gated K^{+}-channels	Matsuo et al., 2011
	corynoxeine	*in vitro*	PASMCs-treated with PDGF-BB	5 to 50 μM	inhibited the PDGF-BB-induced DNA synthesis of VSMCs; inhibited PDGF-BB-induced ERK1/2 activation	Kim et al., 2008
	isorhynchophylline	*in vitro*	PASMCs-treated with PDGF-BB	10 mg/mL	inhibited PDGF-BB-induced proliferation of PASMCs; caused G_0/G_1 phase cell cycle arrest; downregulated of Cyclin D1 and CDK6; increased p27Kip1 level	Guo et al., 2014
	rhynchophylline	*in vitro*	human mesenteric artery	20 to 100 μM	blocked L-type calcium channels	Li et al., 2013
	isorhynchophylline	*in vivo*	pulmonary arterial hypertension in rats induced by monocrotaline (MCT)	10 mg/mL	alleviated the MCT-induced increase of RV hypertrophy and fibrosis as well as pulmonary vascular remodeling and PASMCs proliferation	Guo et al., 2014
Anticancer activities	aqueous extract of *U. tomentosa*	*in vitro*	HL-60 cells	100 μg/mL	inhibited the growth of HL-60 cells	Cheng et al., 2007
	aqueous extract of *U. tomentosa* alkaloid-enriched extract of *U. tomentosa*	*in vitro*	HeLa cells HCT116 cells SW480 cells	10-200 μg/mL	reduced expression of the Wnt-target gene: c-Myc	Gurrola-Díaz et al. 2011
	quinovic acid glycosides purified fraction of *U. tomentosa*	*in vitro*	T24 cells RT4 cells	5 to 150 μg/mL	decreased the cell growth and viability of T24 and RT4 cells	Dietrich et al., 2014
	mitraphylline	*in vitro*	GAMG cells SKN-BE cells	5 to 40 μM	inhibited the growth of GAMG and SKN-BE cells	Garcia Prado et al., 2007
	mitraphylline	*in vitro*	MHH-ES-1 cells MT-3 cells	5 to 40 μM	inhibited the growth of MHH-ES-1 and MT-3 cells	García Giménez et al., 2010
	3β,6β,19α-trihydroxy-12-oleanen-28-oic acid	*in vitro*	MCF-7 cells HepG2 cells	0.625 to 10 μg/mL	inhibited the growth of MCF-7 and HepG2 cells	Sun et al., 2012
	hydroethanol extracts of *U. tomentosa*	*in vivo*	Walker-256 cancer model.	50 mg/ mL for 14 days	reduced tumour weight and volume; modulated anti-oxidant systems; increased	Dreifuss et al., 2013

Table 6 (*continued*)

Pharmacological activities	Extract/Compound	Types	Testing subjects	Dose	Effects	Reference
	n-butanol extracts of *U. tomentosa*				the survival time of the tumour-bearing animals	
	hydroethanol extract of *U. tomentosa*	*in vivo*	Walker-256 cancer model.	10 to 100 μM for 14 days	reduced the tumor growth; showed no effect on the increase of LDH and GGT plasma levels	Dreifuss et al., 2010
Anti-amnesic	70% methanol extract of *U. hook*	*in vivo*	male ICR mice-treated with ethanol	250 mg/kg	impaired memory acquisition and dopamine in the hippocampus and changed 5-hydroxytryptamine and glutamic acid neuronal activities in ethanol-treated mice	Lee et al., 2004
Anti-depressant	ethanol extract of *U. lanosa*	*in vivo*	male ICR albino mice	0.125 to 0.5 g/kg for two for 14 days	decreased the immobility time in forced swimming test and tail suspension test; increased in monoamines levels in the hippocampus, cortex, striatum, and hypothalamus of mice	Hsu et al., 2012
	rhynchophylline isorhynchophylline	*in vitro*	hippocampal slices from male Wistar rats	10 to 100 μM	inhibited NMDA and 5-HY2 receptor-mediated neurotoxicity during ischemia	Kang et al., 2004
	rhynchophylline	*in vivo*	Wistar rats	5 to 15 mg/kg	increased the levels of 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenylacetic acid and homovanillic acid and decreased norepinephrine level in striatum and hippocampus of cerebral ischemic rats.	Lu et al., 2004
	geissoschizine methyl ether	*in vivo*	male ddY mice	5 to 30 mg/kg for 30 min	reduced 5-hydroxy-L-tryptophan plus clorgyline-induced head twitch response; decreased the rectal temperature of mice	Pengsuparp et al., 2001
	geissoschizine methyl ether	*in vitro*	Chinese hamster ovary cell membranes	0.01 to 100 μM	strongly inhibited the binding of 8-hydroxy-2-(di-n-propylamino) tetralin to 5-HT_{1A} receptors	Nishi et al., 2012
	geissoschizine methyl ether	*in vitro*	human embryonic kidney 293 cells	50 μM	strongly inhibited the binding of to 5-HT_7 receptors	Ueki et al., 2013
Anti-convulsion	ethanol extract of *U. rhynchophylla*	*in vivo*	male SD rats-treated with kainic acid (KA)	1 g/kg/day	improved KA-induced epileptic seizures; downregulated the KA-induced IL-1 and BDNF gene expressions	Ho et al., 2014
	rhynchophylline	*in vivo*	male SD rats-treated with kainic acid (KA)	0.25 mg/kg/day	improved KA-induced epileptic seizures; downregulated the KA-induced IL-1 and BDNF gene expressions	Ho et al., 2014
Anti-Parkinson's disease	methanol extract of *U. rhynchophylla*	*in vitro*	monoamine oxidase B (MAO-B)	100 μg/mL	inhibited of MAO-B activity	Hou et al., 2005
	aqueous extract of *U. rhynchophylla*	*in vitro*	PC12 cells-treated with 6-OHDA	0.1 to 1 μg/mL	reduced cell death and the generation of ROS; increased GSH levels; inhibited caspase-3 activity	Shim et al., 2009
	aqueous extract of *U. tomentosa*	*in vitro*	SH-SY5Y cells-treated with 6-OHDA	50 to 200 mg/L	had scavenging ability to free radicals; attenuated 6-OHDA-induced cell death; inhibited the activation of iNOS and NF-κβ	Shi et al. (2010)
	aqueous extract of *U. tomentosa*	*in vitro*	transgenic *Caenorhabditis elegans* model NL5901	10 μg/ml	reduced the aggregation of a-synuclein by 40% in NL5901 *C. elegans*	Shi et al., 2013
	aqueous extract of *U. rhynchophylla*	*in vivo*	male SD rats-treated with 6-OHDA	5 mg/kg/day for 14 days	reduced apomorphine-induced rotation; dopaminergic neuronal loss in substantia nigra pars compacta	Shim et al., 2009
Anti-Alzheimer's disease	isorhynchophylline	*in vitro*	PC12 cells-treated with Aβ_{25-35}	1 to 50 μM	reduced the levels of intracellular reactive oxygen species and malondialdehyde; increased the level of glutathione; stabilized mitochondrial membrane; suppressed the formation of DNA fragmentation and the activity of caspase-3 and moderated the ratio of Bcl-2/Bax.	Xian et al., 2012b
	rhynchophylline	*in vitro*	PC12 cells-treated with Aβ_{25-35}	100 μM	decreased Aβ-induced cell death, intracellular calcium overloading, and tau protein hyperphosphorylation	Xian et al., 2012a
	isorhynchophylline	*in vitro*	PC12 cells-treated with Aβ_{25-35}	100 μM	decreased Aβ-induced cell death, intracellular calcium overloading, and tau protein hyperphosphorylation	Xian et al., 2012a
	hydroethanol extract of *U. rhynchophylla*	*in vivo*	male ICR mice-treated with D-galactose (D-gal)	200 or 400 mg/kg	increased the levels of acetylcholine and glutathione; decreased the activity of acetylcholinesterase and the level of malondialdehyde in the brains of D-gal-treated mice.	Xian et al., 2013
	isorhynchophylline	*in vivo*	male SD rats-treated with Aβ_{25-35}	20 or 40 mg/kg for 21 days	ameliorated the cognitive deficits; attenuated neuronal apoptosis in hippocampus by down-regulating the protein and mRNA levels of the ratio of Bcl-2/Bax, cleaved caspase-3 and caspase-9, as well as suppressing the tau protein hyperphosphorylation at the Ser396, Ser404, and Thr205 sites.	Xian et al., 2014

et al., 2007). The correlations between pharmacological properties of *U. tomentosa* and active compounds revealed that oxindole alkaloids and triterpenes are major bioactive constituents. For instance, oxindole alkaloids and quinovic acid glycosides from *U. tomentosa* effectively induced apoptosis in T24 and RT4 cells via modulation of NF-κB (Kaiser et al., 2013; Dietrich et al., 2014). Mitraphylline **(63)** inhibited the growth of MT-3, SKN-BE and GAMA cells with IC_{50} value of 11.80 μM, 12.3 μM and 20 μM, respectively (García Giménez et al., 2010; Garcia Prado et al., 2007). Uncarines F, C, E **(56**, **59** and **60**, resp.**)** and isomitraphylline **(64)** showed antiproliferative effect on human lymphoblastic leukaemia T cells. Uncarines F and C **(56** and **59)** further inducted apoptosis in both proliferating and G_0/G_1 arrested stage (Bacher et al., 2006). Ursolic acid **(124)** and 3*β*,6*β*,19*α*-trihydroxy-olean-12-en-28-oic acid **(160)** induced apoptosis in A549, SK-OV-3, HCT-15 and MCF-7 cells (Kim et al., 1998; Sun et al., 2012a).

Regarding the underlying mechanisms of *Uncaria* plants for the therapy of cancers, it was concluded that the inhibition of phospholipase Cγ1 (PLCγ1) (Lee et al., 2000), induction of apoptosis in cancer cells (Cheng et al., 2007; Pilarski et al., 2010), regulation of Wnt-signaling pathway (Gurrola-Díaz et al., 2011) and scavenging of free radicals (Dreifuss et al., 2010) are contribute to the treatment of cancers. More details are given below.

Firstly, PLCγ1 was reported to play a key role in proliferation and progression of human cancer (Arteage et al., 1991; Noh et al., 1994; Hill et al., 1994). In the course of screening medicinal plants, the $CHCl_3$ extract of *U. rhynchophylla* hooks exhibited inhibition of PLCγ1 to 35.4% at the concentration of 250 μg/mL. By bioactivity-guided isolation, six triterpene esters were identified as PLCγ1 inhibitors with the IC_{50} of 9.5-44.6 μM. The structure-activity relationships in these compounds revealed that ursan moiety, *trans* configuration and *p*-coumaroyloxy group of these triterpene esters are potent functional groups for inhibiting PLCγ1 activity (Lee et al., 2000).

Secondly, Cheng et al. (2007) evaluated antiproliferative activities of various extracts of *U. tomentosa* bark on human promyelocytic leukemia HL-60 cell lines. The ethyl acetate extract induced apoptosis in HL-60 cells in a dose-dependent and time-dependent manner with IC_{50} of 18.0 μg/mL. Its mechanisms were related with mitochondrial pathway and receptor-mediated pathway, in which phosphatidylserine and cytochrome *c* were increased and Fas, Bid cleavage and caspase-8 were activated. 96% ethanol extract of *U. tomentosa* bark was further reported to decrease the G_2/M phase in MCF7 cells at a daily-dose of 0.5 mg and its water extract proved to demonstrate G_1/ G_0 cell cycle arrest at a daily-dose of 0.05 mg (Pilarski et al., 2010).

Thirdly, alterations on Wnt-signaling pathway, a central regulator, played a crucial role on cancer pathophysiology (Logan and Nusse, 2004; Nusse, 2005). Aqueous extract of *U. tomentosa* decreased Wnt-signaling activities in a dose-dependent manner in HeLa, HCT116 and SW480 cancer cells with IC_{50} of 278 μg/mL, 150 μg/mL and 190 μg/mL, respectively. Its signaling inhibitory effect was operated by downstream of beta-Catenin, thereby reducing the expression of Wnt target genes (Gurrola-Diaz et al., 2011).

Last but not least, Dreifuss et al. (2010) have revealed that antitumoral properties of hydroethanol extract of *U. tomentosa* bark in Walker-256 cells is closely related to its antioxidant activities via ROS-regulating mechanisms and metabolism homeostasis. The sole substances responsible for its anti-neoplastic effect was a synergic combination of substances based on antioxidant activity rather than just oxindole alkaloids (Coussens and Werb, 2002; Mantovani et al., 2008; Dreifuss et al., 2013).

In brief, these findings displayed potential mechanisms of *U. tomentosa* as anticancer remedy.

4.8. Effects on the central nervous system

Therapeutic effects of *Uncaria* plants on central nervous system diseases have been widely studied *in vitro* and *in vivo* methods. *In vitro* investigations have shown that *Uncaria* plants ameliorate amyloid-*β*-induced neuronal death, methamphetamine-induced rat cortical neurons death, glutamate-induced PC12 cell death and LPS-induced hippocampal cell death, *etc* (Jung et al., 2013; Kawakami et al., 2011; Mo et al., 2006; Xian et al., 2012b). *In vivo* experiments have revealed that *Uncaria* plants improve learning and memory impairments and dementia-like behaviors in various animal models (Fujiwara et al., 2011; Xian et al., 2011; Xian et al., 2014a). To better understand pharmacological properties of the genus *Uncaria* on central nervous system, the content in this review was arranged as follows: anti-amnesic, anti-depressant, anti-convulsion, anti-Parkinson′s disease and anti-Alzheimer's disease.

4.8.1. Anti-amnesic

Repeated orally administration of methanol extract of *Uncaria hooks* at dose of 250 mg/kg reduced the latency in rats induced by ethanol. Neurotransmitter analysis showed that the extract significantly suppressed the activities of dopamine, 5-HT and glutamic acid without affecting *γ*-GABA and cholinergic neuronal activities (Lee et al., 2004).

4.8.2. Anti-depressant

Depression, a widespread incapacitating psychiatric ailment, was characterized by a disturbance of mood associated with alteration in behavior, energy and appetite (Neal, 2009; Nemeroff, 2007). Ethanol extract of *U. lanosa* stem and hook was shown to decrease the immobility time in forced swimming test and tail suspension test. And the antidepressant-like mechanism of the extract may be related with the increase in monoamines levels in the hippocampus, cortex, striatum, and hypothalamus of mice (Hsu et al., 2012). Several studies have reported that rhynchophylline **(32)**, isorhynchophylline **(40)** and geissoschizine methyl ether **(11)** have agonistic activities on the 5-HT receptors (Kang et al., 2004; Pengsuparp et al., 2001; Nishi et al., 2012; Ueki et al., 2013). Moreover, rhynchophylline **(32)** affected the levels of serotonin in cortex, striatum, hippocampus and hypothalamus (Lu et al., 2004; Shi et al., 1993).

4.8.3. Anti-convulsion

Hydroethanol extract of *U. rhynchophylla* and rhynchophylline **(32)** have been proved to have neuroprotective and anti-convulsive activities (Kang et al., 2004; Lin and Hsieh, 2011). Pretreatment of *U. rhynchophylla* (1 g/kg) and rhynchophylline **(32)** (0.25 mg/kg) significantly reduced paw tremors and facial myoclonia in kainic acid (KA)-induced rats. Their potential mechanisms might be associated with (i): inhibition of c-Jun N-terminal kinase phosphorylation and NF-κB activation; (ii): regulation of Toll-like receptor (TLR) and neurotrophin signaling pathways; (iii): downregulation of IL-1*β* and BDNF gene expressions (Hsieh et al., 2009; Ho et al., 2014).

4.8.4. Anti-Parkinson's disease

Parkinson′s disease (PD) was nervous system degenerative disease with characteristic of decrease level of dopamine and occurrence of pathological changes in substantia nigra and striatum pathway (Schapira et al., 1998). Previous study have proved that oxidative stress is an intermediary risk factors which can initiate and promote degeneration of dopamingic neurons (Beal, 1995). To better understand the neuroprotection of aqueous extract of *U. tomentosa* bark on dopamingic neurons, Shi et al. (2010) used the 6-OHDA-induced SH-SY5Y cells model. The results

showed that the extract has scavenging ability to free radicals, attenuate 6-OHDA-induced cell death and inhibit the activation of iNOS and NF-κβ, which suggested that *U. tomentosa* is a potential neuroprotective antioxidant for the precaution candidate of Parkinson′s disease. Shi et al. (2013) continued to work on the neuroprotective properties of a standardized aqueous extract of *U. tomentosa* and found that 10 μg/mL of the extract could reduce the aggregation of *a*-synuclein by 40% in transgenic *Caenorhabditis elegans* model NL5901.

In addition, aqueous extract of *U. rhynchophylla* hook also showed neuroprotective activity *in vitro* and *in vivo* models of PD. In PC12 cells, the extract (0.01-1.0 μg/mL) significantly reduced cells death and generation of ROS, increased glutathione levels and inhibited caspase-3 activity induced by 6-OHDA. At the concentration of 5 mg/kg/day for 14 days, the extract showed behavioral recovery and protection of dopaminergic neurons in the 6-OHDA animal model. All these results proposed that the neuroprotective effect of *rhynchophylla* was related to its antioxidative and anti-apoptotic activities (Shim et al., 2009). In addition, inhibition of monoamine oxidase B (MAO-B) activity provided protection against oxidative neurodegeneration and was used as part of the treatment of Parkinson′s disease (Nagatsu, 2004). Hou et al. (2005) reported that methanol extract of *U. rhynchophylla* hook inhibit MAO-B activity by 85.2% at the concentration of 100 μg/mL. Bioactive compounds, (+)-catechin **(208)** and (-)-epicatechin **(210)**, suppressed activities of MAO-B with IC_{50} of 88.6 μM and 58.9 μM, respectively (Hou et al., 2005). Besides, *U. rhynchophylla* showed inhibitory effect on activation of microglial, which suppressed the progression of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (Sugama et al., 2009; Tang et al., 2010; Stoll and Jander, 2008; Kaul et al., 2001). The structure-activity in bioactive compounds, corynoxeine **(34)**, isocorynoxeine **(78)**, rhynchophylline **(32)**, isorhynchophylline **(40)** and vincoside lactam **(105)**, indicated that the C-7 configuration seems not to affect their microglial activation activity, although it has been reported that the antagonistic activity of these compounds on 5-HT_{2A} receptors in the brain is closely related to the 7 *S* configuration of the oxindole moiety (Matsumoto et al., 2005).

4.8.5. Anti-Alzheimer's disease

Alzheimer's disease (AD) was a multifaceted neurodegenerative disorder characterized by deterioration of cognitive, learning and memory and might be delayed by acetylcholinesterase (AChE) inhibitors (Houghton et al., 2006). Xian et al. (2011) reported that 70% hydroethnaol extract of *U. rhynchophylla* hook-bearing stem and branch (200 or 400 mg/kg) significantly increased exploratory behavior and improved spatial learning and memory function in D-galactose-induced rat cognitive deficits model. This function on increasing acetylcholine and glutathione levels and decreasing acetylcholinesterase activity and malonodialdehyde level in the rat brains might be related to the inhibition of acetylcholinesterase activity and enhancement of antioxidant statue in brain tissues. The latter researchers found that isorhynchophylline **(40)** can ameliorate memory deficits through enhancing the antioxidant statues and anti-inflammatory effect of brain tissues in D-galactose-induced mouse (Xian et al., 2014b).

Another critical cause in the pathogenesis of Alzheimer's disease (AD) was considered as beta-amyloid peptide (Aβ) (Hardy, 1997; Selkoe, 2000). Modulation of Aβ-induced neurotoxicity has emerged as a possible therapeutic approach to ameliorate the onset and progression of AD. Rhynchophylline **(32)** and isorhynchophylline **(40)** have a protective activity against beta-amyloid-(Aβ)-induced neuronal toxicity, resulting from the inhibiting intracellular calcium overloading and tau protein phosphorylation (Xian et al., 2012a). Furthermore, the remarkable effect was observed for isorhynchophylline **(40)** in combination with inhibition of oxidative stress and mitochondrial pathway of cellular apoptosis, downregulation of GSK-3β activity and suppression of PI3K/Akt signaling pathway activation (Xian et al., 2012b; 2014a).

5. Pharmacokinetic and metabolism

Metabolites of bioactive indole alkaloids of *Uncaria* species have been investigated over the past decade. It was thought that these alkaloids can metabolize to their 10- and 11- hydroxyl metabolites, such as rhynchophylline **(32)**, isorhynchophylline **(40)**, corynoxeine **(34)** and isocorynoxeine **(78)** (Wang et al., 2010a; 2010b; 2014; Qi et al., 2015). The specific inhibition of CYP isozymes can regulate their hydroxylation metabolites at C-10 and C-11 (Wang et al., 2010a, 2010b). Different from above compounds, hirsutine **(1)** and hirsuteine **(2)** only produced their 11-hydroxy metabolites in rats (Nakazawa et al., 2006). Recently, Chen et al. 2014 and Qi et al., 2015 reported that the possible oxidation and hydroxylation metabolites of isorhynchophylline **(40)** and isocorynoxeine **(78)**, which was important to further understand their metabolites (Chen et al., 2014; Qi et al., 2015).

Kushida et al. (2013) further investigated the pharmacokinetics of *Uncaria* hook alkaloids after oral administration of Yokukansan (0.25, 1 and 4 g/kg). The results showed that rhynchophylline **(32)**, hirsutine **(1)**, hirsuteine **(2)** and geissoschizine methyl ether **(11)** exist in rat plasma. The data of rhynchophylline **(32)** (t_{max}=0.42-1.0 h; $t_{1/2}$=1.4 h), hirsutine **(1)** (t_{max}=0.50-0.83 h; $t_{1/2}$=3.4 h), hirsuteine **(2)** (t_{max}=0.50 to 2.0 h; $t_{1/2}$=1.9 to 3.6 h) and geissoschizine methyl ether **(11)** (t_{max}=0.42 to 0.67 h; $t_{1/2}$=1.5 to 2.0 h) indicated that these alkaloids were likely to be absorbed, metabolized and excreted at early time points after administration. The fact that rhynchophylline **(32)** and geissoschizine methyl ether **(11)** are detected in rat brain further suggested that the two compounds can cross blood-brain barrier to produce a directly pharmacological effect in the central nervous system (Wang and Ma, 2010a; Imamura et al., 2011; Kushida et al., 2013; Lee et al.; 2014).

6. Toxicity

The aqueous extracts of *U. tomentosa* barks have been evaluated for their potential toxic effects using mammalian and bacterial cells by different research groups. Santa Maria et al., (1997) reported that the aqueous extracts of *U. tomentosa* barks do not show cytotoxicity at the concentrations tested (10-100 mg/ml) by Neutral red assay, total protein content and tetrazolium assay. Sheng et al. (2000a) continued to work on the toxic effects of aqueous extract of *U. tomentosa* bark in female W/Fu rats and found that this extract represent no acute or chronic toxicity signs with LD_{50} > 8 g/kg and MTD > 8 g/kg after oral administration of the extract at the doses of 10-80 mg/kg/day for 8 week or 160 mg/kg/day for 4 weeks. And no body weight, food consumption, organ weight and kidney, liver, spleen, and heart pathological changes were found to be associated with the aqueous extract treatment in human clinical study (Lamm et al., 2001; Sheng et al., 2001). In addition, the aqueous extract of *U. tomentosa* bark showed a non-toxic effect in *Hyphessobrycon eque* (LD_{50}=1.816 mg/mL) (Yunis et al., 2014), *Photobaterium phosphoteum* (Santa Maria et al., 1997) and *Salmonella typhimurium* (Rizzi et al., 1993) as well as non-genotoxicity in *Drosophila melanogaster* (Romero-Jimenez et al., 2005).

Despite the lack of establishment of the effective oral dosage for medical application of *U. tomentosa* extracts, Falkiewicz and Luckasiak, (2001) provided information on its appropriate choice. As general immunostimulat, daily doses ranging from 0.5 g to 1 g of the extract were recommended in from of tablets or capsules. Standardized extracts from *U. tomentosa* root, in form of a powder,

was used 2-3 times a day at doses from 20 to 60 mg/kg in western Europe. Since the toxicity of *Uncaria* plants were limited according the reported data, comprehensive toxicological investigations of *Uncaria* plants should be carried out in the future.

7. Conclusions

Uncaria species are endemic to many parts of Southeast Asia, Africa and Southeast America and are widely used in traditional medicine for various applications. *Uncaria*, on its own or as part of a polyherbal preparation is a valuable remedy for vascular and neurosis diseases. The phytochemical results have indicated a significantly variety of structural types of chemical constituents. Pharmacological studies indicated that these plants and ingredients possessed various biological activities, especially in the areas of antioxidant, anti-inflammatory, immunostimulation, anti-hypertension, anticancer, anti-convulsive, anti-Parkinson's and anti-Alzheimer's disease, *etc*. To a certain extent, pharmacological results provided that (i) traditional uses of gastroenteritis and bacterial/fungal infections, diarrhea and thrush were related to antimicrobial activities; (ii) wounds and ulcers, fevers, arthritis and rheumatism illnesses were associated with anti-inflammatory activities; (iii) vascular dementia, epilepsy and cerebral ischemia were affected by regulation of central nervous system; (iv) diabetes and hypertension diseases have been investigated by *in vitro* and *in vivo* experiments. Regarding the constituents contributed to therapeutic values, the findings indicated that indole alkaloids are major components for the treatment of hypertension, epilepsy, depressant, Parkinson's disease and Alzheimer's disease. These kinds of oxindole alkaloids, likely rhynchophylline **(32)** and isorhynchophylline **(40)**, usually contain chiral carbon atoms. It is imperative to discuss the stereo-chemistry and structure-activity relationships of oxindole alkaloids for evaluating pharmacological activities of *Uncaria* species. Although great progresses on the phytochemistry and pharmacolofy of the genus *Uncaria* have been made, there still need more conclusive studies on the safety, efficacy and in *vivo* toxicity of extracts and pure compounds to gain a better understanding of this genus.

Collectively, this present review provides systematically information on the ethnopharmacology, phytochemistry and pharmacology of the genus *Uncaria*, which supports the further clinical use of *Uncaria* species in modern medicine.

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