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Review

Ethnobotany, phytochemistry and pharmacology of *Uncaria* (Rubiaceae)

Mary E. Heitzman [a], Catherine C. Neto [a], Elizabeth Winiarz [a], Abraham J. Vaisberg [b], Gerald B. Hammond [c,*]

[a] *Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, MA 02747, USA*
[b] *Facultad de Ciencias y Filosofia, Departamento de Microbiología, Universidad Peruana Cayetano Heredia, Aptdo. 4314, Lima 100, Perú*
[c] *Department of Chemistry, University of Louisville, Louisville, KY 40292, USA*

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Abstract

The *Uncaria* genus is an important source of medicinal natural products, particularly alkaloids and triterpenes. The collected information is an attempt to cover the more recent developments in the ethnobotany, pharmacology and phytochemistry of this genus. During the past 20 years, alkaloids, terpenes, quinovic acid glycosides, flavonoids and coumarins have been isolated from *Uncaria*. Fifty-three novel structures are reported in this review. The species in which the largest number of compounds has been identified is the Peruvian *Uncaria tomentosa* or 'cat's claw.' Pharmacological studies are described according to cytotoxicity, anti-inflammatory, antiviral, immunostimulation, antioxidant, CNS-related response, vascular, hypotensive, mutagenicity and antibacterial properties. The potential for development of leads from *Uncaria* continues to grow, particularly in the area of immunomodulatory, anti-inflammatory and vascular-related conditions. The information summarized here is intended to serve as a reference tool to practitioners in the fields of ethnopharmacology and natural products chemistry.

Keywords: *Uncaria tomentosa*; Cat's claw; Rubiaceae; Uncarines; Quinovic acid; Oxindole alkaloids; Pentacyclic triterpenes; Immunomodulatory; Anti-inflammatory; Vascular

Contents

* Corresponding author. Tel.: +1 502 852 5998.
E-mail address: gb.hammond@louisville.edu (G.B. Hammond).

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1. Introduction

A well known objective for studying medicinal plants is the discovery of new bioactive components, in the search for promising drugs. The *Uncaria* genus has been instrumental in the discovery of medicinal natural products.

A member of the Rubiaceae family, *Uncaria* has been described as a woody climber. It is a vine or shrub with characteristic penduncles that appear as curved hooks on the side shoots. The species are widely distributed in tropical regions, including Southeast Asia, Africa, and South America. Cultivation varies based on the species and region (Risdale, 1978).

The *Uncaria* genus, as restructured by C.E. Risdale in 1978, contains 34 species, some of the more well-known being *U. tomentosa*, *U. rhynchophylla*, and *U. attenuata* (Risdale, 1978). In the same year, J.D. Philipson, Risdale, and S.R. Hemingway reported the collection of botanical, ethnobotanical and alkaloidal information of the *Uncaria* species (Phillipson et al., 1978). To avoid repetition, papers before 1978 do not appear in this review. The table of phytochemical data and the pharmacology review, however, include all compounds known in *Uncaria* species, and is intended as a guide for future research.

Risdale's revisions consisted of a botanical reclassification of *Uncaria* species. For instance, a species once identified as *Uncaria glabrata* is now considered a variety of *Uncaria lanosa*. After Risdale's revision, however, some scientists continued to use the previous categorizing system to identify the plant studied. In this report, all information is organized according to Risdale's revision. Therefore, any information first reported from a previous naming system, such as *U. glabrata* and *U. florida*, was placed into Risdale's categorization of species.

The focus of this review is to provide information on the structures and pharmacological activities of novel compounds isolated and identified from *Uncaria* since 1978. We have also summarized more recent pharmacological studies on *Uncaria* in several areas with particular emphasis on bioactivities related to antiinflammatory properties, stimulation of the immune system, effects on the central nervous system and cardiovascular diseases. Those studies reporting on bioactivities of specific compounds from *Uncaria* feature many of the alkaloids discussed in the 1978 Lloydia review (Phillipson et al., 1978); therefore we discuss new pharmacological findings on these compounds as well.

The depth and breadth of research involving *Uncaria* plants has been organized into easily accessible and comparable information. Using Chemical Abstracts, Napralert, Scifinder Scholar and BIOSIS databases, relevant research papers were selected based on pertinence and specificity to ethnopharmacology and phytochemistry, as well as readability. This collection was then carefully reviewed, and its information extracted and corroborated with data from other sources. This information is presented in three sections: ethnobotany, phytochemistry, and pharmacological activities of *Uncaria* species.

2. Ethnobotanical uses of *Uncaria*

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). The dried hooks of some *Uncaria* species have also been integral components in traditional oriental medicines, and generally have been used as spasmolytics, analgesics, and sedatives for symptoms associated with nervous disorders. One of the primary uses of several *Uncaria* species and the traditional medicines derived from them is the treatment of hypertension; more details are given below.

2.1. Medicinal uses of selected Uncaria species

U. gambier (Hunt). Roxb. – Common in Malaysia and Singapore, and also found in Sumatra, and Borneo. This species has been cultivated for gambir or gambier, a tanning material that is obtained from the aqueous extract of *U. gambier's* leaves and stems (Phillipson et al., 1978; Ahmed et al., 1978).

U. guianensis (Aubl.) Gmel. – This species, also named "garabato" and "unganangi", grows in the Amazon area, as well as Bangladesh, Upper Burma, and many other regions. The Peruvian communities use its aqueous extract to treat cancer, arthritis, diabetes, and inflammation (Yepez et al., 1991; Lee et al., 1999a,b).

U. hirsuta Havil. – This species is distributed in central and northern Taiwan and China, and is identified as one of many *Uncaria* sources of the Chinese folk medicine "Gou-teng" (Wu and Chan, 1994). Reports also indicate this species, when mixed with herbs, is used to treat primary hypertension (Chang et al., 1989).

U. glabrata DC ~ *U. lanosa* var. *U. glabrata* (Bl.) Ridsd. – This species is found on the Malaysian peninsula, Sumatra, Java and Borneo. It is also called "akar kait" in West Sumatra, and used as a remedy for food poisoning (Arbain et al., 1992).

U. machrophylla Wall. – Distributed in the Yunnan province it is identified in the Chinese pharmacopoeia as an original component of the Chinese drug "Gou-teng" (Sakakibara et al., 1998).

U. quadrangularis Geddes – This species grows in southern Thailand. Its leaves are chewed, and are frequently used as a substitute of the leaves of *Mitragyna speciosa*, also known as "kratom" (Tantivatana et al., 1979).

U. rhynchophylla (Miq.) Miq. *ex* Havil. – Distributed in China and Japan, this species has been used as a crude drug in oriental medicines. It is found as one of the "original" ingredients in Chinese "Gou-teng", as well as the Chinese drug "Kampo". Its infusions are also used for therapeutic purposes (Aimi et al., 1982). Other treatments include using the plant's hooks to relieve hypertension, infantile convulsion, and other illnesses (Lee et al., 2000).

U. sinensis (Oliv.) Havil. – This species is distributed in China and Japan. It has been considered the original plant in the Chinese drug "Chotoko" (alternately spelled "Choto-kou") (Aisaka et al., 1985). Within the Chinese medicines, *U. sinensis* has been used against fevers and nervous disorders. One report indicates use of the plant's hooks as spasmolytic, analgesic, and treatment for hypertension (Tanahashi et al., 1997).

U. tomentosa (Willd.) DC. – Found only in Central and South America this species is known as "Uña de gato" or "cat's claw". Reports consider *U. tomentosa* to be one of the most important medicinal plants to the Ashaninka people in the Peruvian rainforest. The significance of Uña de Gato is emphasized by its exclusive use by Ashaninka priests to influence the communication between the physical and spiritual dimensions of human beings (Keplinger et al., 1999). Its many therapeutic uses come from the aqueous extract of the bark or root bark, and include a wide range of treatments. It is reported to be a remedy for abscesses, allergies, arthritis, asthma, cancer, chemotherapy side effects, contraception, disease prevention, fevers, gastric ulcers, hemorrhages, inflammations, menstrual irregularity, recovery from child birth, rheumatism, skin impurities, urinary tract inflammation, viral infections, weakness, wounds, and others (Cerri et al., 1988; Aquino et al., 1991; Rizzi et al., 1993; Wurm et al., 1998; Lemaire et al., 1999).

2.2. Traditional medicines derived primarily from Uncaria

Chotoko – This crude drug is believed to originate from another drug, "Kakoto", which has been recognized as the hooks of *U. sinensis*. Chotoko is also called "Gou-teng" in Chinese, and is reported as a predominant component of another crude drug, "Choto-san" or "Diao-Teng-San" (Sakakibara et al., 1997, 1999a,b).

Gou-teng – Also identified as "Chotoko" in Japanese, Gou-teng is composed of various *Uncaria* species, of which *U. rhynchophylla* is considered the original plant (Zhu et al., 1997). In both China and Japan, this drug is used for its sedative, antispasmodic, analgesic, anticonvulsive, hypotensive, antiepileptic, and antiviral activities (Yano et al., 1991; Lee et al., 1999a,b). More specifically, the crude drug is used to relieve headaches and dizziness caused by hypertension and infantile nervous disorders (Aisaka et al., 1985).

Kampo – This is a term for a traditional Japanese herbal medicine. Therefore, the many preparations vary by plant ingredients as well as use for treatments. One kampo is reported to consist of *U. rhynchophylla* and *U. sinensis*, and is used to relieve hypertension and associated symptoms such as headaches and dizziness (Yano et al., 1991).

3. Phytochemistry

The phytochemistry of the *Uncaria* genus has been extensively studied since the early 1900s. One of the earlier phytochemical reports was published in 1928, and revealed the isolation of rhynchophylline (**1–1**), from *Uncaria rhynchophylla* (Kondo et al., 1928). Today, over 150 compounds have been isolated and identified from the *Uncaria* genus.

3.1. Key classes of compounds prevalent in Uncaria

The compounds most prominent in *Uncaria* are alkaloids. Most of these alkaloids were identified prior to 1978, which demonstrates the intense focus of early research on the *Uncaria* genus. Fig. 1 includes the structures of selected compounds discussed in the pharmacology section of this review that were identified prior to Philipson's 1978 review of *Uncaria* alkaloids in *Lloydia* (Phillipson et al., 1978). Fig. 1 also includes structures of pharmacologically significant compounds found in *Uncaria* that have been previously reported in other plants. The most recognized compound in *Uncaria* is mitraphylline (**1–8**), which has been identified in 20 of the 34 species. Three other alkaloids prevalent within the *Uncaria* genus include rhynchophylline (**1–1**), isomitraphylline (**1–13**), and isorhynchophylline (**1–4**), which have been recognized in 18 species. The uncarines are a group of oxindole alkaloids containing a spirocyclic ring on the indole ring and varying stereochemistry throughout the ring skeleton. Some of them are quite prevalent; uncarine D (speciophylline, **1–11**) for example appears in 16 species while uncarine B (formosanine, **1–14**) only appears in seven.

Variations in the 3-D structure of tetracyclic oxindole alkaloids prevalent in *Uncaria* such as rhynchophylline (**1–1**) and pentacyclic oxindole alkaloids such as mitraphylline (**1–8**) may produce a variety of pharmacological effects. For example, a recent X-ray crystallographic study (Laus and Wurst, 2003) suggests that the ability of tetracyclics to act as antagonists on the immunostimulating effects of pentacyclic alkaloids is due to differences in the position of a side chain relative to the ring core of the molecule. Pharmacological effects of such compounds are discussed in detail in Section 4.

The *Uncaria* genus also contains a variety of interesting pentacyclic triterpenoids, mostly of the ursane-type. This includes a number of cytotoxic phenolic acid esters. The group of uncarinic acids A–E (**2–34** through **2–38**) which includes both ursane and oleanane-type skeletons appear in as many as 16 different species. Various glycosides of another ursane-type pentacyclic triterpene, quinovic acid (**2–39** through **2–51**), have been reported from *U. guianensis*. Many *Uncaria* triterpenoids are highly oxidized. The quinovic acid skeleton is characterized by carboxylation at both C27 and C28. The uncarinic acids are carboxylated at C28 and hydroxylated at C27 with further esterification at this position by ferulic or coumaric acid.

3.2. Novel compounds

During the past 20 years, alkaloids, terpenes, quinovic acid glycosides, flavonoids, and coumarins, have been isolated from *Uncaria*. Since 1978, approximately 53 new compounds have been recognized from *Uncaria* species. The structures of these novel compounds are shown in Fig. 2 and their plant sources are identified in Table 1.

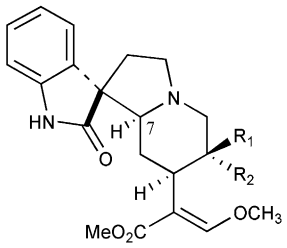
Arbain and co-workers have reported the isolation of glabratine (**2–1**) from *U. glabrata*. This is an unusual indole monoterpenoid glucoalkaloid, characterized by the occurrence of a glucose moiety on its benzenoid ring (Arbain et al., 1992). Aimi and colleagues reported a method of discovering new compounds which demonstrates the usefulness of incorporating known biosynthesis to gain leads of possible novel compounds. In their research, they proposed that corynanthe-type oxindole alkaloids, which are abundant in *Uncaria attenuata*, would undergo an oxidative cleavage to form D-seco alkaloids similar to the newly identified salacin (**2–4**). Two of these expected compounds, US-7 (**2–5**) and US-8 (**2–6**), were identified in *U. attenuata* (Aimi et al., 1997).

Takayama and coworkers reported the stereochemistry of 3-oxo-7-hydroxy-3,7-secorhynchophylline (**2–7**) at the C-7 position. Their research concluded that both the natural and semi-synthetic products contain a diastereomeric mixture of 3-oxo-7-hydroxy-3,7-secorhynchophylline, in which the compounds have C7(*S*) and C7(*R*) configurations (Takayama et al., 1999).

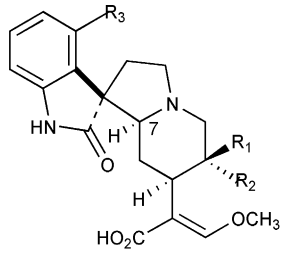
Known pentacyclic oxindole alkaloids (POA) have also been recognized as immunostimulants whereas common isomeric tetracyclic oxindole alkaloids (TOA) do not show this bioactivity (Keplinger et al., 1999). Several novel POA have been identified. These include rauniticine oxindole A (**2–8**), isopteropodic acid (**2–9**), pteropodic acid (**2–10**), mitraphyllic acid (**2–11**), rauniticine pseudoindoxyl (**2–12**), akuammingine pseudoindoxyl (**2–13**), 3-isorauniticine pseudoindoxyl (**2–14**), and 14-β-hydroxy-3-iso-rauniticine (**2–17**) (see table for literature references). Some are closely related to earlier reported alkaloids; the methyl esters of pteropodic and isopteropodic acids are the known pteropodine (uncarine C, **1–9**) and isopteropodine (uncarine E, **1–12**). However, to the authors' knowledge, the immunostimulatory activity of these novel compounds has not yet been reported.

3.3. Occurrence of compounds across Uncaria species

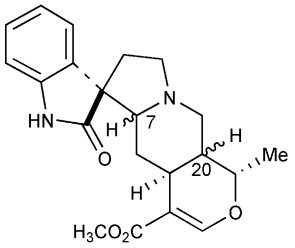
A major consideration of the comparison of identified components in *Uncaria* species is that the chemi-



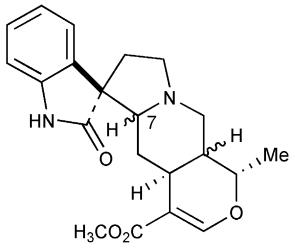
1-1 Rhynchophylline: R_1= H, R_2 = Et
1-2 Corynoxine B: R_1 = Et, R_2 = H
1-3 Corynoxeine: R_1 = H, R_2 = CH=CH_2



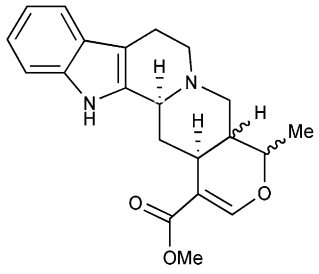
1-4 Isorhynchophylline: R_1 = H, R_2 = Et, R_3 = H
1-5 Corynoxine: R_1 = Et, R_2 = H, R_3 = H
1-6 Isocorynoxeine: R_1 = H, R_2 = CH=CH_2, R_3 = H
1-7 Rotundifoline: R_1 = H, R_2 = Et, R_3 = OH



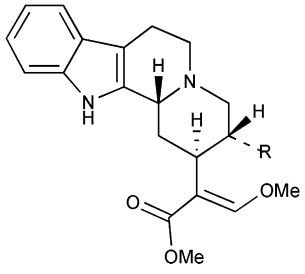
1-8 mitraphylline: H-7 , H-20
1-9 pteropodine: H-7 , H-20
1-10 Uncarine F: H-7 , H-20



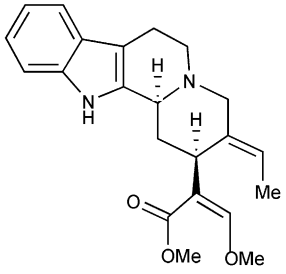
1-11 speciophylline: H-7 H-20 Me-18
1-12 isopteropodine: H-7 H-20 Me-18
1-13 isomitraphylline: H-7 , H-20 Me-18
1-14 formosanine: H-7 , H-20 Me-18



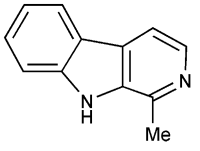
1-15 ajmalicine: Me-20 , H-20
1-16 rauniticine: Me-20 , H-20



1-17 hirsuteine: R = CH=CH_2
1-18 hirsutine: R = Et



1-19 geissoschizine methyl ether



1-20 harmane

Fig. 1. (a) Structures **1–1** through **1–20**, (b) structures **1–21** through **1–30**.

cal composition can vary based on its geographical and seasonal collections. This has specifically been shown with *Uncaria attenuata*, and should not be discounted with other species. Quinovic acid glycosides **2–39** to **2–51**, appear mainly in *U. guaianensis and U. tomentosa*. However, *Uncaria* also contains a large

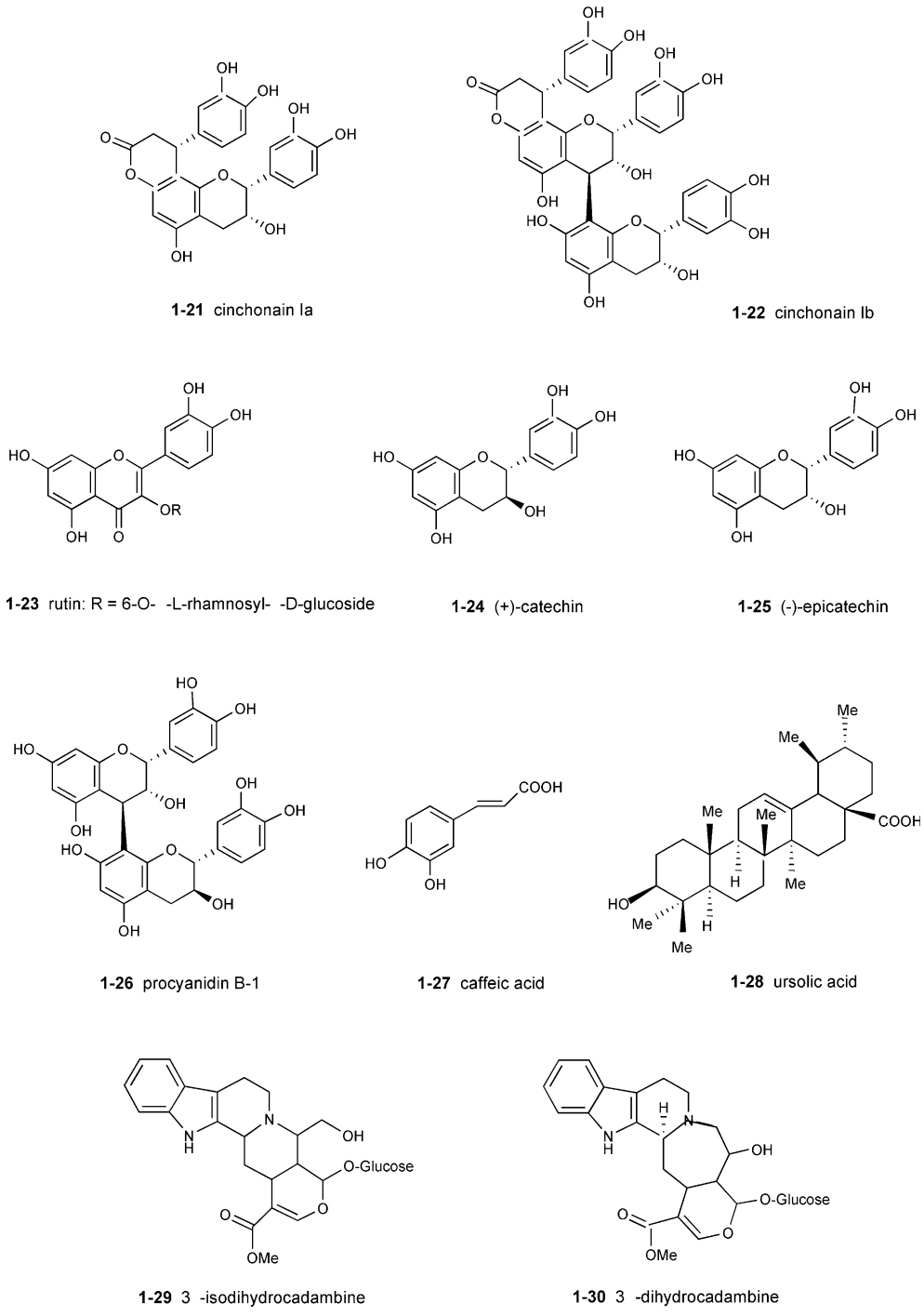


Fig. 1 (*continued*)

population of "common" compounds that occur across a variety of species. It is useful to compare and/or contrast all of these factors when researching past phytochemical analyses of the *Uncaria* genus. Table 1 lists most of the compounds reported in *Uncaria*, including structures discovered before 1978, as well as the species and plant parts from which they have been isolated.

3.4. Structural variation within Uncaria species

The species in which the largest number of compounds has been identified is the Peruvian *U. tomentosa*, or "cat's claw". About 50 different compounds have been isolated from this plant; 35 of which have been identified in only a couple of other species. Interestingly, 15 of these 35 compounds were also reported as novel

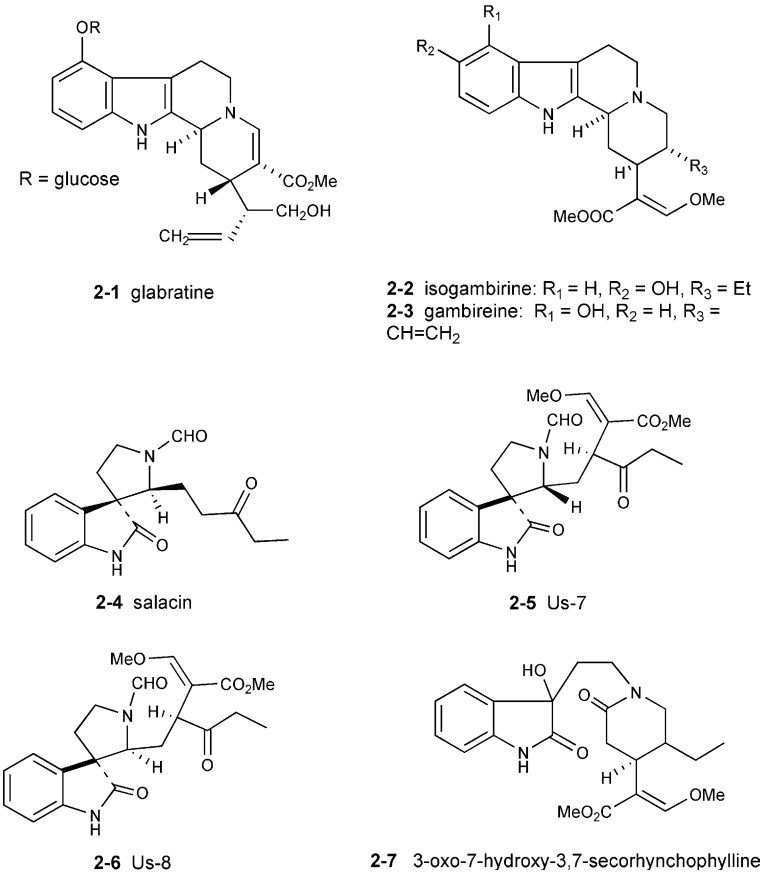


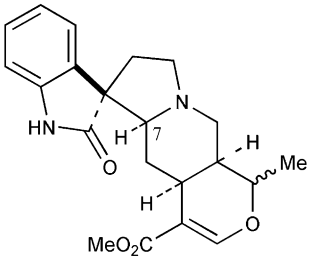
Fig. 2. (a) Novel compounds discovered in Uncaria since 1978. Structures **2–1** through **2–7**, (b) structures **2–8** through **2–18**, (c) structures **2–19** through **2–25**, (d) structures **2–26** through **2–38**, (e) structures **2–39** through **2–51**, (f) structures **2–52** and **2–53**.

constituents. This structurally diverse species includes alkaloids such as rhynchophylline (**1–1**), isorhynchophylline (**1–4**) and their corresponding N-oxides, mitraphylline (**1–8**) and isomitraphylline (**1–13**), the uncarines, and rotundifoline (**1–7**); ursane type pentacyclic triterpenes including a variety of ursolic acid derivatives (**2–26** through **2–33**) and quinovic acid glycosides (**2–39** through **2–51**); and the procyanidins cinchonain Ia and Ib (**1–21** and **1–22**).

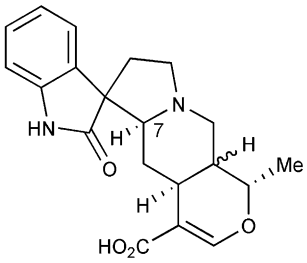
Other species in which numerous compounds have been identified include *Uncaria elliptica* (44 compounds, 10 of which have been reported since 1978), *Uncaria attenuata* (34 compounds, 10 of which are newly reported), and *Uncaria rhynchophylla* (33 compounds, 6 of which are newly reported). *U. attenuata* is nearly as structurally diverse as *U. tomentosa*. In addition to the mitraphyllines, rhynchophyllines, rotundifolines and uncarines, *U. attenuata* includes several ajmalicine (**1–15**) derivatives, corynoxines, rauniticines, and D-seco alkaloids US-7 (**2–5**), US-8 (**2–6**) and salacin (**2–4**). *U. elliptica* includes many of these same alkaloids plus gambirine (**2–3**), isogambirine (**2–2**), harmane (**1–20**), and several roxburghines such as the newly identified Roxburghine X (**2–18**) *U. elliptica* also contains the uncarinic acids (**2–34** through **2–38**) and uncaric acids (**2–22** through **2–24**).

3.5. Recent insights on biosynthesis

A study published in 2002 shed some light on the regulation of biosynthesis of sterols and triterpenes in *U. tomentosa* (Flores-Sanchez et al., 2002). Administration of pectin to *U. tomentosa* cell suspension cultures increased the activity of isopentenyl diphosphate isomerase and squalene synthase, resulting in increased production of ursolic and oleanolic acids but no increase in sterol production or growth. The treated cells also transformed a higher percentage of labeled mevalonic acid precursor into triterpenes and this production was not affected by inhibiting squalene epoxidase. Farnesyl diphosphatase activity was also two times lower than in control cells. These results suggest a biosynthetic flux for sterols and triterpenes controlled by enzymatic complexes involving IPP-isomerase and squalene synthase.



2-8 rauniticine oxindole A
(*allo*, H-3 , H-20 , Me-18 , C-7 A)

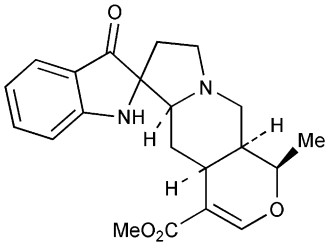


2-9 isopteropodic acid (C7-A, 20- H)

2-10 pteropodic acid (C7-B, C20- H)

2-11 mitraphyllic acid (C7-B, C20- H)

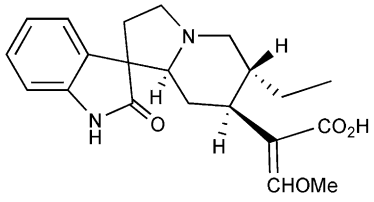
A = oxindole CO below C/D plane
B = above C/D plane



2-12 rauniticine pseudoindoxyl
(H-3 , H-20 , Me-18)

2-13 akuammigine pseudoindoxyl
(*epiallo,* H-3 , H-20 , Me-18)

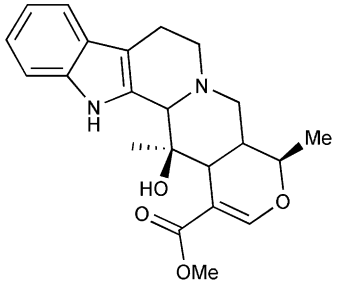
2-14 3-isorauniticine pseudoindoxyl
(*epiallo,* H-3 , H-20 , Me-18)



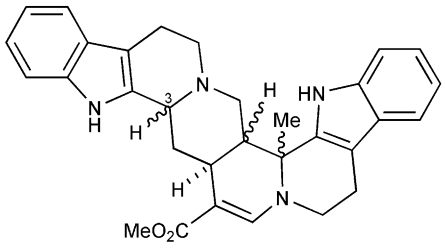
2-15 isorhynchophyllic acid
(C7-A)

2-16 rhynchophyllic acid
(C7-B)

A = oxindole CO below C/D plane
B = above C/D plane



2-17 14- -hydroxy-3-iso-rauniticine

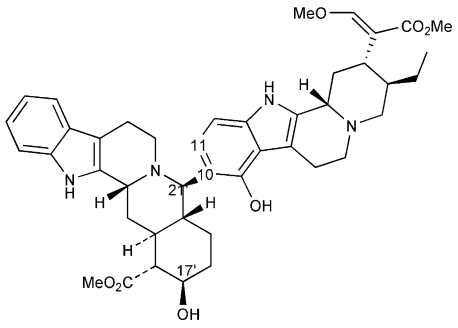


2-18 Roxburghine X

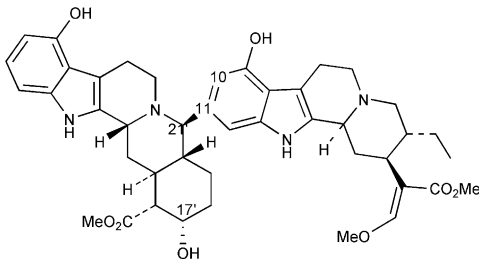
Fig. 2 (*continued*)

4. Pharmacological activity

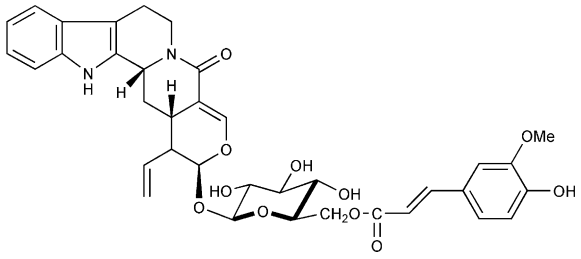
Pharmacological studies have generally focused on the fractions of either a plant species or a "crude drug", considered as a preparation from either a single or a mixture of *Uncaria* plants. A number of studies, however, have focused on the bioactivity of specific isolated compound(s). The information in this section is organized by pharmacological activity, with reference to the crude extract or isolated constituents studied. Of the crude extracts, *U. tomentosa* has been the most widely studied, followed by *U. rhynchophylla*.



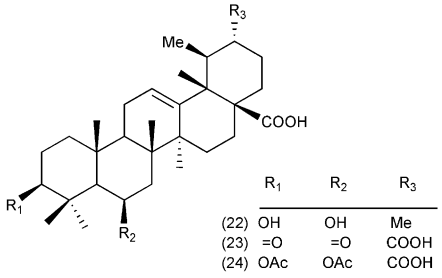
2-19 callophylline A



2-20 callophylline B



2-21 rhynchophine

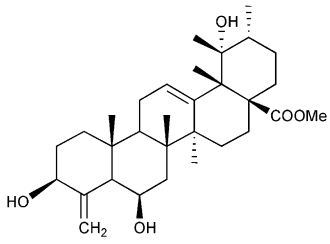


	R_1	R_2	R_3
(22)	OH	OH	Me
(23)	=O	=O	COOH
(24)	OAc	OAc	COOH

2-22 uncaric acid
(3 ,6 ,18 ,-trihydroxyurs-12-en-oic acid)

2-23 diketouncaric acid
(18 -hydroxy-3,6-dioxours-12-en-30-oic acid)

2-24 diacetyluncaric acid
(3 ,6 -diacetoxy-18 -hydroxurs-12-en-30-oic acid)



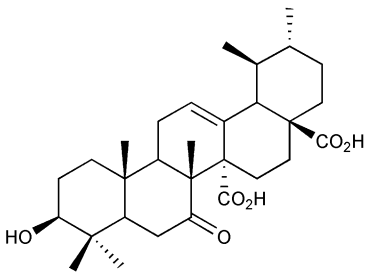
2-25 floridic acid methyl ester

Fig. 2 (*continued*)

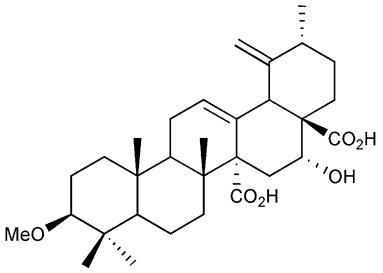
4.1. Cytotoxicity

Cytotoxic activity of *U. rhynchophylla* was determined by bioactivity-guided fractionations, and led to the discovery of two new pentacyclic triterpene esters, uncarinic acids A and B (**2–34** and **2–35**, respectively). These compounds inhibit phospholipase Cγ1 (PLCγ1) (IC_{50} = 35.66, and 44.55 μM, respectively), an enzyme which induces proliferation in human cancer cells (Lee et al., 2000). The compounds also inhibited growth of human cancer cell lines A-549, HCT-15, MCF-7, HT-1197 (Lee et al., 1999a,b). Six other compounds found in *U. rhynchophylla* were reported to also inhibit both PLCγ1 and cancer cell growth (IC_{50} of PLCγ1 = 9.5–4.6 μM, of cancer cells = 0.5–6.5 μg/ml). These compounds included novel uncarinic acids C (**2–37**), D (**2–38**), and E (**2–36**), and three other known pentacyclic triterpene esters (Lee et al., 2000). A cDNA microarray study of *U. rhynchophylla* showed that hyperin isolated from its stem up-regulated 50 genes and down-regulated many others in SNU-668 human gastric cancer cells, many of which are associated with mechanisms of antioxidation (Jeoung et al., 2002).

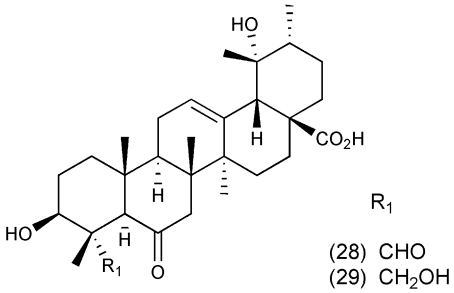
Analysis of *U. tomentosa*'s aqueous extracts included tests of growth inhibitory activity against human leukemia cell lines (K562 and HL60) and a human



2-26 7-oxo-3 -hydroxyurs-12-en-27,28-dioic acid

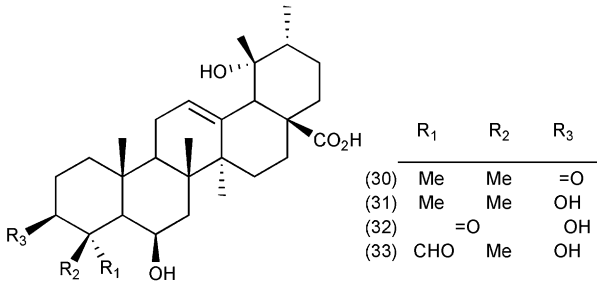


2-27 3 -methoxy-16 -hydroxyursa-12,19(29)-dien-27,28-dioic acid



2-28 3 ,19 -dihydroxy-6-oxo-urs-12-en-23-al-28-oic acid

2-29 3 ,19 -dihydroxy-6-oxo-urs-12-en-23-ol-28-oic acid

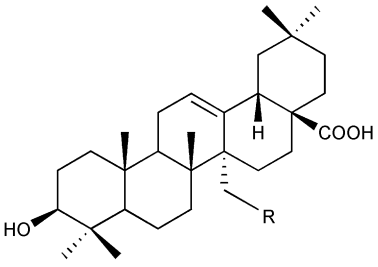


2-30 3-oxo-6 , 19 -dihydroxyurs-12-en-28-oic acid

2-31 3 , 6 ,19 -trihydroxyurs-12-en-28-oic acid

2-32 3 , 6 , 19 -trihydroxy-23-oxo-urs-12-en-28-oic acid

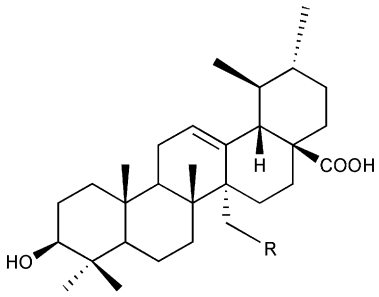
2-33 23-nor-24-esomethylene-3 , 6 , 19 -trihydroxyurs-12-en-28 -oic acid



2-34 uncarinic acid A R = *E*-feruloyl

2-35 uncarinic acid B R = *Z*-feruloyl

2-36 uncarinic acid E R = *E*-coumaroyl



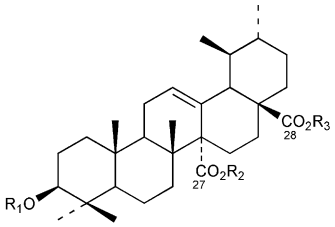
2-37 uncarinic acid C R = *E*-feruloyl

2-38 uncarinic acid D R = *Z*-feruloyl

Fig. 2 (*continued*)

EBV-transformed B lymphoma cell line (Raji). The extracts significantly inhibited proliferation of HL60 and Raji cells, and only moderately affected K562 cells. Observations revealed that the extracts induced apoptosis, in conjunction with DNA fragmentation, providing an explanation for *U. tomentosa*'s anti-tumor activity (Sheng et al., 1998).

The aqueous extract of *U. tomentosa* had also been tested for toxicity against Chinese hamster ovary cells. Tests performed by three methods, the Neutral red assay, total protein content, and tetrazolium assay, led to the conclusion that *U. tomentosa* is not toxic in vitro at the specified concentrations (Santa Maria et al., 1997).



	R_1	R_2	R_3
2-39	3 -O- -D-quinovopyranosyl	H	H
2-40	3 -O- -D-fucopyranosyl	-D-glucopyranosyl	H
2-41	3 -O-[-D-glucopyranosyl-(1 3)- -D-fucopyranosyl]	-D-glucopyranosyl	H
2-42	3 -O-[-D-glucopyranosyl-(1 3)- -D-fucopyranosyl]	H	-D-glucopyranosyl
2-43	3 -O-[-D-glucopyranosyl-(1 3)- -D-fucopyranosyl]	H	H
2-44	3 -L-rhamnopyranosyl	H	H
2-45	3 -L-rhamnopyranosyl-(3 1)- -D-glucopyranosyl	H	H
2-46	3 -D-quinovopyranosyl-(3 1)- -D-glucopyranosyl	H	H
2-47	3 -D-quinovopyranosyl-(3 1)- -D-galactopyranosyl	H	H
2-48	3 -L-rhamnopyranosyl-(3 1)- -D-glucopyranosyl	-D-glucopyranosyl	H
2-49	H	-D-glucopyranosyl	H
2-50	3 -O-(-D-quinovopyranosyl)	-D-glucopyranosyl	H
2-51	3 -O-(-D-quinovopyranosyl)	H	-D-glucopyranosyl

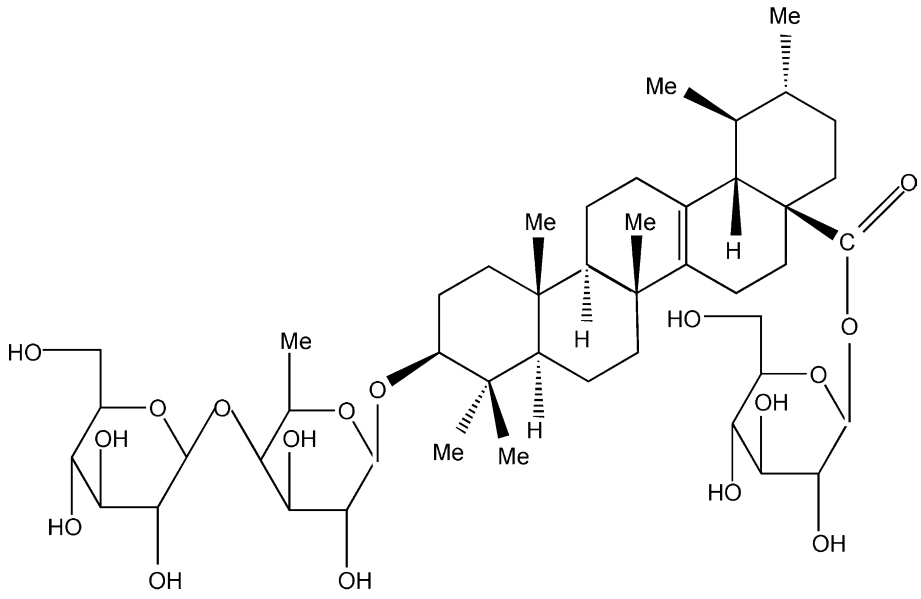
Fig. 2 (*continued*)

The cytotoxicity of several uncarines: uncarine C (also called isospeciophylline or pteropodine), (**1–9**) uncarine D (speciophylline) (**1–11**) and uncarine E (isopteropodine) (**1–12**) has been studied. Uncarines C and E were isolated from the bark of *U. guianensis* by a bioactivity-guided fractionation. Both compounds were reported to exhibit cytotoxicity and DNA damaging activity by RS321 and RS322 yeast assays. Weak but selective activity (IC_{12} = 140 μg/ml for RS321 and 120 μg/ml for RS322) was observed, as well as moderate cytotoxic activity to mammalian cell lines (IC_{50} values were between 17 and 51 μg/ml) (Lee et al., 1999a,b). Uncarines C, D and E isolated from the inner bark of *U. tomentosa* were assayed for cytotoxicity against SK-MEL, KB, BT-549, SK-OV-3 and VERO cell lines. Uncarine D (**1–11**) was the most cytotoxic, with IC_{50} ranging from 30 to 40 μg/ml in all cell lines (Muhammad et al., 2001).

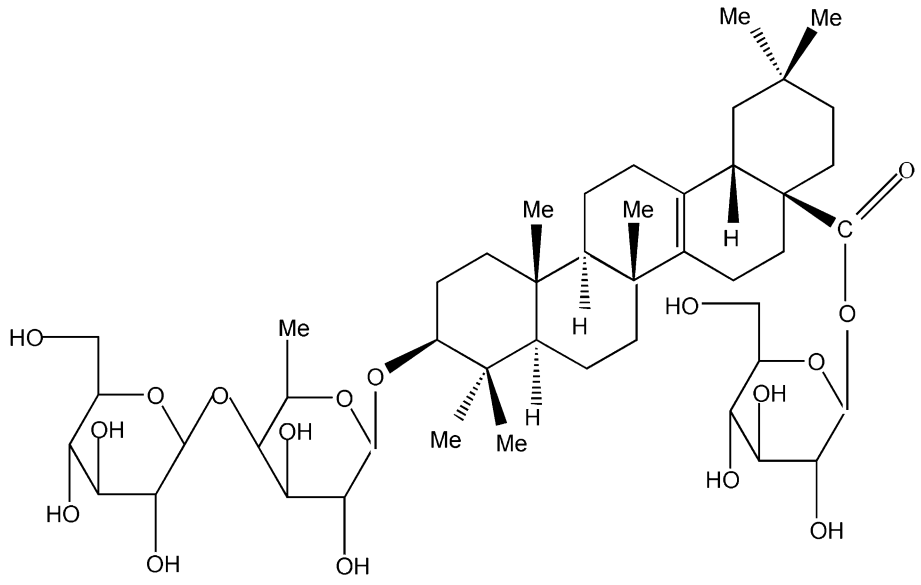
Ursolic acid (**1–28**) was isolated from *U. hirsuta* via bioassay-guided fractionation targeting cytotoxicity. Many studies have reported the bioactivity of ursolic acid, including its anti-inflammatory, anti-arthritic, anti-diabetic, antiulcer, hypolipidemic, anti-atherosclerotic, anti-HIV and cytotoxic activities (Safayhi and Sailer, 1997). A number of substituted ursolic acid derivatives have been reported since 1978 (**2–26** through **2–33**), however only one report deals with their bioactivity (Lee et al., 2000).

4.2. Anti-inflammatory activity

"Cat's claw", used to treat numerous inflammatory disorders, is usually prepared from bark and root of either *U. tomentosa* or *U. guianensis* (Sandoval et al., 2002). Anti-inflammatory activity of both species was compared in vitro by inhibition of TNFα and nitrite production from RAW 264.7 cells. Despite a much higher total oxindole and pentacyclic alkaloid content, *U. tomentosa* was significantly less potent as an antiinflammatory agent than *U. guainensis*, suggesting that antiinflammatory activity is independent of the alkaloid content (Sandoval et al., 2002). The authors also observed the same trend for radical-scavenging activity. Another study compared the anti-inflammatory properties of two extracts prepared from *U. tomentosa* bark; a hydroalcoholic extract prepared in EtOH–H_2O (4:1) and an aqueous extract. The hydroalcoholic extract had much higher activity in a mouse paw edema model and suppressed NF-κB to a much greater extent than the aqueous extract (Aguilar et al., 2002). While it was noted that the total oxindole alkaloid content of the hydroalcoholic extract was much higher than the



2-52 Tomentoside A



2-53 Tomentoside B

Fig. 2 (*continued*)

aqueous, the oxindole alkaloids were not tested separately. It is believed that the strong anti-inflammatory activity of *U. tomentosa* is likely to result from a combination of compounds that work synergistically to enhance the anti-inflammatory activity (Rizzi et al., 1993).

A quinovic acid glycoside (q.a. 3 β-*O*-(β-D-quinovopyranosyl)-(27-1)-β-D-glucopyranosyl ester (**2–50**)), was reported as an anti-inflammatory agent. By an hourly analysis of the organism's inflammatory response, the observed compound was shown to cause 33% inhibition of inflammation at a dose of 20 mg/kg (Aquino et al., 1991).

Given the diversity of constituents in *U. tomentosa*, several antiinflammatory pathways are possible. However, a screening of 68 plant extracts for inhibitory effects on phospholipase A_2 (PLA_2), an enzyme which stimulates the cyclooxygenase and 5-lipoxygenase inflammatory pathways, found that *U. tomentosa* extracts actually increased PLA_2 activity (Bernard et al., 2001). These findings suggest that PLA_2 inhibition is not a mechanism for antiinflammation in cat's claw.

A clinical trial was conducted to evaluate the efficacy of *U. tomentosa* for the treatment of rheumatoid arthritis (Mur et al., 2002). The extract chosen was of a chem-

Table 1
Compounds found in *Uncaria* species

Compound	Species and plant part from which compound was isolated	References
7α-acetoxydihydronomilin	*U. tomentosa (B)*	(Ahmed et al., 1978)
afzelin	*U. hirsute (L)*	(Wu and Chan, 1994)
ajmalicine (**1–15**)	*U. africana (L)*, *U. elliptica (B, L)*, *U. orientalis (L)*	(Phillipson and Supavita, 1981, 1983)
19-epi-ajmalicine	*U. africana (L)*, *U. elliptica (X, L)*	(Phillipson and Supavita, 1981; Tantivatana et al., 1980)
19-epi-3-iso-ajmalicine	*U. attenuata (L)*, *U. elliptica (X, L)*,	(Phillipson and Supavita, 1981; Tantivatana et al., 1980; Kam et al., 1992)
3-iso-ajmalicine	*U. acida (L)*, *U. africana (L)*, *U. attenuata (L)*, *U. elliptica (L)*, *U. hirsuta (F)*, *U. homomalla (L)*, *U. orientalis (L)*, *U. sessilifructus (L)*, *U. sterrophylla (L)*	(Phillipson et al., 1978; Wurm et al., 1998)
3-iso-19-ajmalicine	*U. africana (L)*, *U. attenuata (L)*, *U. orientalis (L)*, *U. sessilifructus (L)*	(Phillipson et al., 1978)
akuammigine	*U. attenuata (L)*, *U. bernaysii (L, S, F)*, *U. elliptica (L)*, *U. lanosa (L)*, *U. orientalis (L)*, *U. rhynchophylla (R, X)*, *U. sessilifructus (L)*	(Phillipson et al., 1978)
akuammigine pseudoindoxyl (**2–13**)	*U. elliptica (L)*	(Phillipson and Supavita, 1981)
angustine	*U. bernaysii (F)*, *U. elliptica (B)*, *U. guiainensis (L, S, F)*, *U. homomalla (L, S)*, *U. rhynchophylla (L)*	(Phillipson et al., 1978)
angustidine	*U. homomalla (L, S)*, *U. rhynchophylla (L)*	(Phillipson et al., 1978)
angustoline	*U. guianensis (L, S, F)*, *U. homomalla (L, S)*, *U. rhynchophylla (L)*	(Phillipson et al., 1978)
3α-dihydrocadambine (**1–30**)	*U. sinensis (H)*	(Aisaka et al., 1985; Shimada et al., 1999)
3β-isodihydrocadambine (**1–29**)	*U. sinensis (H)*	(Aisaka et al., 1985; Shimada et al., 1999)
callophylline A (**2–19**)	*U. callophylla (L)*	(Goh and Junan, 1985)
callophylline B (**2–20**)	*U. callophylla (L)*	(Goh and Junan, 1985)
(+)-catechin (**1–24**)	*U. lanosa (X)*	(Arbain et al., 1998)
caffeic acid (**1–27**)	*U. sinensis (H)*	(Sekiya et al., 2002)
chlorogenic acid	*U. hirsuta (L)*	(Wu and Chan, 1994)
cinchonain Ia (**1–21**)	*U. rhynchophylla (X)*, *U. tomentosa (X)*	(Wirth and Wagner, 1997)
cinchonain Ib (**1–22**)	*U. rhynchophylla (X)*, *U. tomentosa (X)*	(Wirth and Wagner, 1997)
corynantheine	*U. rhynchophylla (R, S)*	(Phillipson et al., 1978; Laus and Teppner, 1996)
epi-allo-corynantheine	*U. attenuata (L)*	(Phillipson et al., 1978)
dihydrocorynantheine pseudoindoxyl	*U. africana (L)*, *U. attenuata (L)*	(Phillipson et al., 1978)
corynoxeine (**1–3**)	*U. acida (L)*, *U. attenuata (L, S, B)*, *L. borneensis (L)*, *U. longiflora (L, X)*, *U. rhynchophylla (L, S, H, R, C)*, *U. sinensis (H)*	(Kam et al., 1992; Laus and Teppner, 1996)
corynoxine (**1–5**)	*U. attenuata* (*S*, *H*), *U. cordata (L)*, *U. kunstleri (L)*, *U. macrophylla (L)*, *U. sessilifructus (L)*, *U. sterrophylla (L)*	(Phillipson et al., 1978; Lee et al., 2000)
corynoxine B (**1–2**)	*U. attenuata (L)*, *U. cordata (L)*, *U. kunstleri (L)*, *U. macrophylla (L)*, *U. sessilifructus (L)*, *U. sterrophylla (L)*	(Phillipson et al., 1978; Lee et al., 2000)
isocorynoxeine (**1–6**)	*U. attenuata (L, S, B)*, *U. borneensis (L)*, *U. lanosa (L)*, *U. longiflora (L, X)*, *U. rhynchophylla (L, S, H, R, C)*, *U. sinensis (H)*	(Phillipson et al., 1978; Laus and Teppner, 1996)
dihydrocorynantheine	*U. africana (L)*, *U. attenuata (L, S)*, *U. callophylla (L, H, S)*, *U. cordata (L, S, X, F)*, *U. elliptica (L, S)*, *U. guianensis (L, S, X, F)*, *U. longiflora (L)*, *U. nervosa (L)*, *U. rhynchophylla (R, S)*	(Phillipson et al., 1978; Kam et al., 1992; Goh and Junan, 1985)
C-8-(*S*)-7-deoxyloganic acid	*U. tomentosa (B)*	(Muhammad et al., 2001)
(−)-epicatechin (**1–25**)	*U. elliptica (L, S)*, *U. rhynchophylla (X)*, *U. tomentosa (X, L)*	(Wirth and Wagner, 1997)
floridic acid methyl ester (**2–25**)	*U. lanosa (X)*	(Kitajima et al., 2003)

(*continued on next page*)

Table 1 (*continued*)

Compound	Species and plant part from which compound was isolated	References
formosanine (Uncarine B, **1–14**)	*U. attenuata (L)*, *U. elliptica (B)*, *U. gambir (L)*, *U. hirsuta (L, X, B, F)*, *U. laevigata (L)*, *U. orientalis (L)*, *U. sessilifructus (L)*,	(Phillipson et al., 1978; Wu and Chan, 1994; Tantivatana et al., 1980; Herath et al., 1978)
gambireine (**2–3**)	*U. callophylla (L)*, *U. longiflora (L)*	(Kam et al., 1992, 1991)
gambirine (9-hydroxydihydrocorynantheine)	*U. callophylla (L, S)*, *U. elliptica (L)*, *U. longiflora (L)*	(Phillipson et al., 1978; Kam et al., 1991, 1992; Goh and Junan, 1985)
gambirdine	*U. gambir (S)*	(Phillipson et al., 1978)
isogambirdine	*U. gambir (S)*	(Phillipson et al., 1978)
isogambirine (**2–2**)	*U. callophylla (L)*	(Kam et al., 1992)
glabratine (**2–1**)	*U. lanosa (L, B)*, *U. longiflora (L)*	(Arbain et al., 1992, 1993)
geissoschizine methyl ester	*U. sinensis (H)*	(Phillipson et al., 1978)
geissoschizine methyl ether (**1–19**)	*U. rhynchophylla (X)*	(Phillipson et al., 1978)
neohesperidin	*U. hirsuta (L)*	(Wu and Chan, 1994)
harmane (**1–20**)	*U. acida (L)*, *U. attenuata (L)*, *U. barbata (L, F)*, *U. borneensis (L)*, *U. callophylla (L)*, *U. canescens (L)*, *U. elliptica (L)*, *U. lanosa (L)*, *U. nervosa (L)*, *U. orientalis (L, S)*	(Phillipson et al., 1978)
hirsuteine (**1–17**)	*U. attenuata (L, S)*, *U. guianensis (L, S, X, F)*, *U. nervosa (L)*, *U. rhynchophylla (L, R, S)*, *U. sinensis (H)*, *U. tomentosa (F)*	(Phillipson et al., 1978; Laus and Teppner, 1996)
hirsutine N-oxide	*U. tomentosa (L, S)*	(Phillipson et al., 1978)
hirsutine (**1–18**)	*U. attenuata (L, S)*, *U. guianensis (L, S, X, F)*, *U. kunstleri (L)*, *U. nervosa (L)*, *U. rhynchophylla (L, R, S)*, *U. sessilifructus (L)*, *U. sinensis (H)*, *U. tomentosa (L, F)*	(Phillipson et al., 1978; Laus and Teppner, 1996)
hyperin	*U. hirsuta (L)*	(Wu and Chan, 1994)
mitraphyllic acid (**2–11**)	*U. sinensis (H)*	(Liu et al., 1992)
mitraphylline (**1–8**)	*U. africana (L)*, *U. attenuata (L)*, *U. bernaysii (F)*, *U. callophylla (L)*, *U. elliptica (B)*, *U. gambir (L, S)*, *U. guianensis (L, S, R, X, F)*, *U. hirsuta (L, F)*, *U. homomalla (L)*, *U. laevigata (L)*, *U. lancifolia (L)*, *U. lanosa (L, S, F)*, *U. longiflora (L)*, *U. orientalis (L)*, *U. perrottetii (L)*, *U. scandens (L)*, *U. sessilifructus (L)*, *U. sterrophylla (L)*, *U. tomentosa (L, R, F)*, *U. veluntina (L)*	(Phillipson et al., 1978; Tantivatana et al., 1979, 1980; Wagner et al., 1985; Herath et al., 1978)
mitraphylline N-oxide	*U. africana (L)*, *U. attenuata (L)*, *U. guianensis (L)*, *U. hirsuta (L)*, *U. homomalla (L)*, *U. laevigata (L)*, *U. lancifolia (L)*, *U. lanosa (L)*, *U. longiflora (L)*, *U. orientalis (L)*, *U. perrottetii (L)*, *U. scandens (L)*, *U. sessilifructus (L)*	(Phillipson et al., 1978)
isomitraphylline (**1–13**)	*U. africana (L)*, *U. bernaysii (F)*, *U. callophylla (L)*, *U. elliptica (B)*, *U. guianensis (L)*, *U. hirsuta (L, F)*, *U. homomalla (L, S)*, *U. laevigata (L)*, *U. lancifolia (L)*, *U. lanosa (L, S, F)*, *U. longiflora (L)*, *U. orientalis (L)*, *U. perrottetii (L)*, *U. scandens (L)*, *U. sessilifructus (L)*, *U. sterrophylla (L)*, *U. tomentosa (L, R, F)*, *U. veluntina (L)*	(Phillipson et al., 1978; Tantivatana et al., 1979; Wagner et al., 1985; Diyabalanage et al., 1997a,b)
isomitraphylline N-oxide	*U. attenuata (L)*, *U. guianensis (L)*, *U. hirsuta (L)*, *U. homomalla (L)*, *U. laevigata (L)*, *U. lanosa (L)*, *U. longiflora (L)*, *U. orientalis (L)*, *U. perrottetii (L)*, *U. scandens (L)*, *U. sessilifructus (L)*	(Phillipson et al., 1978)
neohesperidin	*U. hirsuta*	(Wu and Chan, 1994)
3β-hydroxy-27-p-(Z)-coumaroyloxyolean-en-28-oic acid	*U. rhynchophylla (H, X)*	(Lee et al., 2000)
oleanolic acid	*U. tomentosa (R)*	(Aquino et al., 1991)
procyanidin B-1 (**1–26**)	*U. sinensis (H)*	(Sekiya et al., 2002)
pteropodic acid (**2–10**)	*U. sinensis (H)*	(Liu and Feng, 1993)

isopteropodic acid (**2–9**)	*U. sinensis (H)*	(Liu and Feng, 1993)
pteropodine (uncarine C, **1–9**) 3B-hydroxy-27-(*E*)-feruloyloxyurs-12-en-28-oic acid	*U. bernaysii (L, F)*, *U. donisii (L)*, *U. guianensis (R, B)*, *U. homomalla (L, S, B)*, *U. lanosa (all parts)*, *U. longiflora (L, S, B, R)*, *U. orientalis (L, S, F)*, *U. perrottetii (L)*, *U. roxburghiana (L)*, *U. scandens (L)*, *U. sinensis (L, F, D)*, *U. sterrophylla (L, S, B)*, *U. tomentosa (R)*, *U. veluntina (L)*	(Phillipson et al., 1978; Lee et al., 1999a,b; Tantivatana et al., 1979; Tanahashi et al., 1997; Wagner et al., 1985; Arbain et al., 1993; Kam et al., 1991; Aquino et al., 1997)
pteropodine N-oxide	*U. bernaysii (L, S, F)*, *U. donisii (L)*, *U. homomalla (L, S)*, *U. lanosa (L, S, F, D)*, *U. longiflora (L)*, *U. orientalis (L, S)*, *U. roxburghiana (L, S)*, *U. scandens (L)*, *U. sinensis (L, F, D)*, *U. veluntina (L)*	(Phillipson et al., 1978)
isopteropodine (Uncarine E, **1–12**) 3B-hydroxy-27-p-(*E*)-coumaroyloxy-olean-12-en-28-oic acid	*U. bernaysii (L, F)*, *U. donisii (L)*, *U. guianensis (B)*, *U. homomalla (L, S, B)*, *U. laevigata (L)*, *U. lanosa (all parts)*, *U. longiflora (L, S, R, B)*, *U. orientalis (L, S, F)*, *U. roxburghiana (L, S)*, *U. scandens (L)*, *U. sinensis (L, F, D)*, *U. sterrophylla (L, S, B)*, *U. tomentosa (R)*, *U. veluntina (L)*	(Phillipson et al., 1978; Lee et al., 1999a,b; Tantivatana et al., 1979; Tanahashi et al., 1997; Wagner et al., 1985; Arbain et al., 1993; Kam et al., 1991; Aquino et al., 1997)
isopteropodine N-oxide	*U. bernaysii (L, S, F)*, *U. donisii (L)*, *U. homomalla (L, S)*, *U. lanosa (L, S)*, *U. longiflora (L)*, *U. orientalis (L, S)*, *U. roxburghiana (L)*, *U. scandens (L)*, *U. sinensis (L, F, D)*, *U. veluntina (L)*	(Phillipson et al., 1978)
quercitrin	*U. hirsuta*	(Wu and Chan, 1994)
rauniticine (**1–16**)	*U. lanosa (X)*, *U. attenuata (L)*, *U. elliptica (X, L)*	(Phillipson and Supavita, 1983, 1981; Arbain et al., 1998; Ponglux and Supavita, 1980)
rauniticine oxindole A (**2–8**)	*U. elliptica (L)*	(Phillipson and Supavita, 1983)
rauniticine pseudoindoxyl (**2–12**)	*U. elliptica (L)*	(Phillipson and Supavita, 1983)
hydroxy-3-isorauniticine	*U. elliptica (L)*	(Phillipson and Supavita, 1983)
14-α-hydroxyrauniticine	*U. attenuata (L, S, H)*, *U. lanosa (X)*	(Herath et al., 1979; Ponglux et al., 1990; Ponglux and Supavita, 1980)
14-β-hydroxy-3-isorauniticine (**2–17**)	*U. elliptica (L)*	(Phillipson and Supavita, 1983)
Isorauniticine	*U. elliptica (X, L)*	(Phillipson and Supavita, 1983, 1981; Tantivatana et al., 1980)
3-isorauniticine pseudoindoxyl (**2–14**)	*U. elliptica (L)*	(Phillipson and Supavita, 1983)
rhynchophyllic acid (**2–16**)	*U. sinensis (H)*	(Liu et al., 1992)
isorhynchophyllic acid (**2–15**)	*U. sinensis (H)*	(Liu et al., 1992)
rhynchophylline (**1–1**)	*U. acida (L, S)*, *U. africana (L)*, *U. attenuata (L, S, H, B)*, *U. bernaysii (L)*, *U. borneensis (L)*, *U. callophylla (L)*, *U. cordata (L, S, F)*, *U. elliptica (L)*, *U. guianensis (L, S, X, F)*, *U. kunstleri (L)*, *U. longiflora (X, S, L)*, *U. macrophylla (L, S)*, *U. rhynchophylla (L,S, H,R, C)*, *U. sessilifructus (L)*, *U. sinensis (H)*, *U. sterrophylla (L)*, *U. talbotii (L)*, *U. tomentosa (L, S, R, F)*	(Phillipson et al., 1978; Sakakibara et al., 1998; Wagner et al., 1985; Kam et al., 1991; Laus and Teppner, 1996; Ponglux et al., 1990)
rhynchophylline N-oxide	*U. acida (L)*, *U. africana (L)*, *U. attenuata (L)*, *U. bernaysii (L)*, *U. guianensis (L, S, X, F)*, *U. kunstleri (L)*, *U. longiflora (L, S)*, *U. macrophylla (L, S)*, *U. rhynchophylla (L)*, *U. tomentosa (L, F)*	(Phillipson et al., 1978)
isorhynchophylline (**1–4**)	*U. acida (L, S)*, *U. africana (L)*, *U. attenuata (L, S, H, B)*, *U. bernaysii (L)*, *U. borneensis (L)*, *U. callophylla (L)*, *U. cordata (L, S, F)*, *U. elliptica (L)*, *U. guianensis (L, S, X, F)*, *U. kunstleri (L)*, *U. longiflora (X, S, L)*, *U. macrophylla (L, S)*, *U. rhynchophylla (L, S, H, R, C)*, *U. sessilifructus (L)*, *U. sinensis (H)*, *U. sterrophylla (L)*, *U. talbotii (L)*, *U. tomentosa (L, S, R, F)*	(Phillipson et al., 1978; Sakakibara et al., 1998; Wagner et al., 1985; Kam et al., 1991; Laus and Teppner, 1996; Ponglux et al., 1990)
isorhynchophylline N-oxide	*U. acida (L)*, *U. africana (L)*, *U. attenuata (L)*, *U. bernaysii (L)*, *U. guianensis (L, S)*, *U. kunstleri (L)*, *U. longiflora (L, S)*, *U. macrophylla (L, S)*, *U. rhynchophylla (L)*, *U. tomentosa (L, F)*	(Phillipson et al., 1978)

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Table 1 (*continued*)

Compound	Species and plant part from which compound was isolated	References
3-oxo-7-hydroxy-3,7-secorhynchophylline (**2–7**)	*U. attenuata (S, H)*	(Ponglux et al., 1990)
rhynchophine (**2–21**)	*U. rhynchophylla (L)*, *U. tomentosa (L)*	(Aimi et al., 1982)
rotundifoline (**1–7**)	*U. attenuata (L)*, *U. callophylla (L)*, *U. elliptica (L)*, *U. tomentosa (L, S, F)*	(Phillipson et al., 1978; Kam et al., 1992)
isorotundifoline	*U. attenuata (L)*, *U. callophylla (L)*, *U. elliptica (L)*, *U. tomentosa (L, S, F)*	(Phillipson et al., 1978)
roxburghine C, D, E and X (**2–18**)	*U. elliptica (B, L)*	(Herath et al., 1979)
rumberine	*U. lanosa (H, L, S)*	(Tanahashi et al., 1997)
rutin (**1–23**)	*U. elliptica (L, S)*, *U. hirsuta (L)*	(Wu and Chan, 1994)
salacin (**2–4**)	*U. attenuata (S, H)*	(Liu et al., 1992; Ponglux et al., 1990)
scopoletin	*U. sinensis (H)*	(Liu et al., 1992)
β-sitosteryl glucoside	*U. hirsuta (L)*	(Wu and Chan, 1994)
speciophylline (uncarine D, **1–11**) 3B-hydroxy-27-(Z)-feruloyloxyurs-12-en-28-oic acid	*U. attenuata (L)*, *U. bernaysii (L, F)*, *U. donisii (L)*, *U. guianensis (R)*, *U. homomalla (L, S)*, *U. laevigata (L)*, *U. lanosa (all parts except R)*, *U. longiflora (L)*, *U. orientalis (L, S, F)*, *U. perottetii (L)*, *U. roxburghiana (L, S)*, *U. scandens (L)*, *U. sinensis (L, F, D)*, *U. sterrophylla (L, S, B)*, *U. tomentosa (R)*, *U. veluntina (L)*	(Phillipson et al., 1978; Tanahashi et al., 1997; Arbain et al., 1993)
speciophylline N-oxide	*U. bernaysii (L, S)*, *U. donisii (L)*, *U. homomalla (L, S)*, *U. lanosa (L, S, F, D)*, *U. longiflora (L)*, *U. orientalis (L, S)*, *U. roxburghiana (L, S)*, *U. scandens (L)*, *U. sinensis (L, F, D)*, *U. sterrophylla (L)*, *U. veluntina (L)*	(Phillipson et al., 1978)
strictosamide	*U. rhynchophylla (L)*, *U. tomentosa (L)*	(Aimi et al., 1982)
5α-carboxystrictosidine	*U. tomentosa (R)*	(Aquino et al., 1991)
3,4-dehydro-5(*S*)-5-carboxystrictosidine	*U. tomentosa (S, B)*	(Kitajima et al., 2000, 2002)
tetrahydroalstonine	*U. africana (L)*, *U. attenuata (L)*, *U. bernaysii (L, S, F)*, *U. elliptica (L)*	(Phillipson et al., 1978; Phillipson and Supavita, 1981; Ponglux and Supavita, 1980)
tetrahydroalstonine-N-oxide	*U. elliptica (L)*	(Phillipson and Supavita, 1981)
trifolin	*U. rhynchophylla (L)*, *U. tomentosa (L)*	(Aimi et al., 1982)
uncarine A	*U. attenuata (L)*, *U. cordata (B)*, *U. gambir (L)*, *U. hirsuta (L, F)*, *U. laevigata (L)*, *U. orientalis (L)*, *U. sessilifructus (L)*,	(Phillipson et al., 1978; Wu and Chan, 1994)
uncarine F (**1–10**)	*U. bernaysii (L, F)*, *U. donisii (L)*, *U. homomalla (L, S)*, *U. lanosa (L, S, H, F, T, D, W)*, *U. longiflora (L)*, *U. orientalis (L, S)*, *U. perrottetii (L)*, *U. roxburghiana (L, S)*, *U. scandens (L)*, *U. sessilifructus (L)*, *U. sinensis (L, F, D)*, *U. sterrophylla (L, B)*, *U. veluntina (L)*	(Phillipson et al., 1978; Tanahashi et al., 1997)
uncarine F N-oxide	*U. bernaysii (L, S)*, *U. donisii (L)*, *U. homomalla (L, S)*, *U. lanosa (L, S)*, *U. longiflora (L)*, *U. orientalis (L, S)*, *U. roxburghiana (L)*, *U. sinensis (L, F, D)*, *U. tomentosa (R)*, *U. veluntina (L)*	(Phillipson et al., 1978; Tanahashi et al., 1997)
uncaric acid (**2–22**)	*U. thwaitesii (B)*, *U. elliptica*	(Herath et al., 1978)
uncaric acid D	*U. cordata (R)*	(Phillipson and Supavita, 1983)
diacetyluncaric acid (**2–24**)	*U. elliptica (B)*, *U. thwaitesii (B)*	(Herath et al., 1978)
diketouncaric acid (**2–23**)	*U. elliptica (B)*, *U. longiflora (L)*, *U. thwaitesii (B)*	(Herath et al., 1978)

uncarinic acids A (**2–34**), B (**2–35**), C (**2–36**), D (**2–37**) and E (**2–38**)	*U. rhynchophylla (H)*	(Lee et al., 2000, 1999a,b)
umbelliferone	*U. hirsuta (L)*	(Wu and Chan, 1994)
ursolic acid (**1–28**)	*U. tomentosa (R)*	(Wu and Chan, 1994; Aquino et al., 1991)
3β-hydroxy-27-*p*-coumaroyloxyurs-12-en-28-oic acid, *E* and *Z* isomers	*U. rhynchophylla (H, X)*	(Lee et al., 2000)
3β,19α-dihydroxy-6-oxo-urs-12-en-23-al-28-oic acid (**2–28**)	*U. tomentosa (X)*	(Kitajima et al., 2000)
3β,19α-dihydroxy-6-oxo-urs-12-en-23-ol-28-oic acid (**2–29**)	*U. tomentosa (X)*	(Kitajima et al., 2000)
3,6-dioxo-19α-hydroxyurs-12-ene-28-oic acid	*U. elliptica (X)*	(Diyabalanage et al., 1995)
3β,6β-diacetoxy-19-hydroxyurs-12-ene-28-oic acid	*U. elliptica (X)*	(Diyabalanage et al., 1995)
3β,6β,19α-trihydroxy-23-oxo-urs-12-en-28-oic acid (**2–32**)	*U. tomentosa (B, R)*	(Aquino et al., 1990; Aimi et al., 1989)
3β,6β,19α-trihydroxyurs-12-en-28-oic acid (**2–31**)	*U. lanosa (X)*, *U. tomentosa (B, R)*, *U. elliptica (X)*	(Aquino et al., 1991; Aimi et al., 1989; Diyabalanage et al., 1995)
3β,6β,19α-trihydroxyurs-12-en-23-al-28-oic acid	*U. tomentosa (X)*	(Kitajima et al., 2000)
3β,6β,19α-trihydroxyurs-12-en-23,28-dimethyloate	*U. tomentosa (R)*	(Aquino et al., 1991)
3β,6β,19α,23-tetrahydroxyurs-12-en-28-oic acid	*U.tomentosa (R)*	(Aquino et al., 1997; Kitajima et al., 2000)
3β-methoxy-16α-hydroxyursa-12,19 (29)-dien-27,28-dioic acid (**2–27**)	*U. tomentosa (R)*	(Aquino et al., 1997)
3-oxo-6β,19α-dihydroxyurs-12-en-28-oic acid (**2–30**)	*U. tomentosa (R)*	(Aquino et al., 1997)
7-oxo-3β-hydroxyurs-12-en-27,28-dioic acid (**2–26**)	*U. tomentosa (R)*	(Aquino et al., 1997)
23-nor-24-esomethylene-3β,6β,19α-trihydroxyurs-12-en-28-oic acid (**2–33**)	*U. tomentosa (B, R)*	(Kitajima et al., 2003)
quinovic acid 3β-*O*-β-D-quinovopyranosyl-(28-1)-β-D-glucopyranosyl ester	*U. elliptica (B)*, *U. tomentosa (B, X)*	(Diyabalanage et al., 1997a,b)
quinovic acid (28-1)-β-D-glucopyranosyl ester	*U. tomentosa (B)*	(Yepez et al., 1991)
quinovic acid 3β-*O*-β-D-fucopyranosyl-(28-1)-β-D-glucopyranosyl ester	*U. tomentosa (B)*	(Yepez et al., 1991)
quinovic acid 3β-*O*-β-D-quinovopyranosyl-(28-1)-β-D-glucopyranosyl ester	*U. tomentosa (B)*	(Yepez et al., 1991)
quinovic acid 3β-*O*-β-D-quinovopyranoside (**2–39**)	*U. guiainensis (B)*	(Yepez et al., 1991)

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Table 1 (*continued*)

Compound	Species and plant part from which compound was isolated	References
quinovic acid 3β-*O*-β-D-fucopyranosyl-(27-1)-β-D-glucopyranosyl ester (**2–40**), quinovic acid 3β-*O*-β-D-glucopyranosyl-(1-3)-β-D-fucopyranosyl-(27-1)-β-D-glucopyranosyl ester (**2–41**)	*U. guiainensis (B)*, *U. tomentosa (R)*	(Cerri et al., 1988; Aquino et al., 1991)
quinovic acid 3β-*O*-β-D-glucopyranosyl-(1-3)-β-D-fucopyranosyl-(28-1)-β-D-glucopyranosyl ester (**2–42**), quinovic acid3β-*O*-β-D-glucopyranosyl-(1-3)-β-D-fucopyranoside (**2–43**)	*U. tomentosa (B)*	(Cerri et al., 1988)
quinovic acid 3β-*O*-α-L-rhamnopyranoside (**2–44**), quinovic acid 3β-*O*-α-L-rhamnopyranosyl-(3-1)-β-D-glucopyranoside (**2–45**), quinovic acid 3β-*O*-β-D-quinovopyranosyl-(3-1)-β-D-glucopyranoside (**2–46**), quinovic acid 3β-*O*-β-D-quinovopyranosyl-(3-1)-β-D-galactopyranoside (**2–47**), quinovic acid 3β-*O*-α-L-rhamnopyranosyl-(3-1)-β-D-glucopyranosyl-(27-1)-β-D-glucopyranosyl ester (**2–48**), quinovic acid (27-1)-β-D-glucopyranosyl ester (**2–49**)	*U. tomentosa (R)*	(Aquino et al., 1997)
quinovic acid 3β-*O*-β-D-quinovopyranosyl-(27-1)-β-D-glucopyranosyl ester (**2–50**)	*U. tomentosa (R)*	(Aquino et al., 1991)
quinovic acid 3β-*O*-β-D-quinovopyranosyl-(28-1)-β-D-glucopyranosyl ester (**2–51**)	*U. elliptica (B)*	(Diyabalanage et al., 1997a,b)
US-7 (**2–5**) and US-8 (**2–6**)	*U. attenuata (X)*	(Aimi et al., 1997)
tomentosides A (**2–52**) & B (**2–53**): pyroquinovic acid & pyrocincholic acid, 3β-*O*-β-D-glucopyranosyl-(1-4)-β-D-fucopyranosyl-28-*O*-β-D-glycopyranosyl esters	*U. tomentosa (S, B)*	(Kitajima et al., 2003)
α-yohimbine and β-yohimbine	*U. callophylla (L)*	(Kam et al., 1992)
alloyohimbine	*U. borneensis (L)*	(Kam et al., 1991)
3-epi-β-yohimbine	*U. borneenis (L)*, *U. cordata (L)*	(Kam et al., 1991)
pseudoyohimbine	*U. bernaysii (L)*, *U. borneensis (L, H, S)*	(Kam et al., 1992; Goh and Junan, 1985)
vallesiachotamine	*U. rhynchophylla (L)*, *U. tomentosa (L)*	(Aimi et al., 1982)
vincoside lactam	*U. rhynchophylla (L)*, *U. tomentosa (L)*	(Aimi et al., 1982)

Key to plant parts: B: bark, F: flower, H: hooks/stems, L: leaf, R: roots, S: shoots, W: whole plant, X: plant part not known.

otype rich in immune-modulating pentacyclic oxindole alkaloids but free of tetracyclic oxindole alkaloids which often inhibit this immune stimulation. After 24 weeks of treatment, the occurrence of painful joints was reduced by 53.2% in the treated group vs. 24.1% in the control group. The authors did not quantify potentially antiinflammatory non-alkaloid agents in the extract.

4.3. Antiviral activity

A quinovic acid glycoside [(28)-β-D-glucopyranosyl β-D-glucopyranosyl ester] from *U. tomentosa* was reported to exhibit activity against rhinovirus type 1B infection in HeLa cells (Aquino et al., 1989). The procyanidins cinchonain Ia (**1–21**) and cinchonain Ib (**1–22**), and (−)-epicatechin (**1–25**), isolated from the bark of *U. tomentosa*, are considered responsible for both antiinflammatory and antiviral activity (Aquino et al., 1989). These studies support the suggestion that both forms of bioactivity in *U. tomentosa* (anti-inflammatory and antiviral) are due to a combination of active compounds.

4.4. Immunostimulation

Immunostimulant activity of pentacyclic oxindole alkaloids (POA) from *U. tomentosa* may occur by increasing phagocytosis of human granulocytes and macrophages and blocking the proliferation of myeloid cell lines (Keplinger et al., 1999). POA known to be in *U. tomentosa* were synthesized and tested for their effects on B and T lymphoblasts. Based on the results, the POA stimulate human endothelial cells (EA.hy926) to release a factor which increases the production of normal human resting B and T lymphocytes. In the regulation of lymphocyte proliferation by alkaloid-stimulated endothelial cells it was shown that the pentacyclic isomers do not affect directly the proliferation but rather induce endothelial cells to release a yet to be identified factor which influences the proliferation of lymphocytes. The secretion of the factor was affected by the pentacyclic alkaloids but not by the tetracyclic alkaloids. Rather, it was shown that the tetracyclic alkaloids act antagonistically on the release of the factor (Keplinger et al., 1999). This factor also inhibits the production of lymphoblasts and lymphoblastoid cell lines, which suggests that POA behave as regulators to immune-responses (Lemaire et al., 1999). The studied POA included speciophylline (**1–11**), uncarine F (**1–10**), mitraphylline (**1–8**), isomitraphylline (**1–13**), pteropodine (**1–9**) and isopteropodine (**1–12**), isomeric alkaloids common in *Uncaria*. This study also reported that the common isomeric tetracyclic oxindole alkaloids (TOA) rhynchophylline (**1–1**) and isorhynchophylline (**1–4**), were not active.

U. tomentosa has also demonstrated strong immunostimulant activity through in vitro and in vivo phagocytosis tests. Of six compounds isolated from the roots of *U. tomentosa*-isopteropodine (uncarine E, **1–12**), pteropodine (uncarine C, **1–9**), isomitraphylline (**1–13**), isorhynchophylline (**1–4**), rhynchophylline (**1–1**), and mitraphylline (**1–8**) – all but the two latter compounds caused a prominent enhancement on phagocytosis (Wagner et al., 1985).

Another study reported similar effects of extracts of *U. tomentosa* toward the production of macrophages interleukin-1 (IL-1) and interleukin-6 (IL-6). Results indicated a dose-dependent stimulation of IL production by macrophages, as well as enhancement of the IL in lipopolysaccharide-stimulated macrophages (Lemaire et al., 1999).

Immunomodulatory activity of *U. tomentosa* is also thought to be related to its ability to suppress TNFα synthesis (Sandoval et al., 2002); activity that also may lead to its antiinflammatory activity as previously discussed. A mouse feeding study was used to explore the effect of aqueous extracts of *U. tomentosa* on the immune system in vivo. Mice were fed drinking water containing commercial extract C-Med 100, an extract of *U. tomentosa* which does not contain the higher molecular weight components such as tannins. Immune cells including B, T and NK cells, granulocytes and memory lymphocytes were observed to increase in number; it was concluded that this was the result of prolonged cell survival rather than increased rate of proliferation. The authors suggested that prolonged survival may result from *U. tomentosa's* ability to protect cells against oxidative stress and NF-κB activation, counteract apoptosis and increase DNA repair. They also stressed that the identification of the active components would be helpful in elucidating the mechanisms underlying its immunoprotective effects (Akesson et al., 2003).

4.5. Antioxidant properties

Recent studies have revealed that certain *Uncaria* species contain tannins and condensed tannins with antioxidant properties which are likely to be responsible for some of Uncaria's pharmacological effects (Desmarchelier et al., 1997; Wirth and Wagner, 1997). These compounds have been previously identified in other plants and their structures are shown in Fig. 1(**1–21** through **1–27**).

The bark and root extracts of *U. tomentosa* have been tested in vitro for antioxidant activity. Analysis included three methods: a *tert*-butyl-hydroperoxide-initiated chemiluminescence assay, which determines the free radical scavenging activity, showed that both methanol extracts (the bark and roots) quenched free radicals. This is not surprising since the bark reportedly contains cinchonains (**1–21, 1–22**) which are members of a class of known antioxidants, the proanthocyanidins (Wirth and Wagner, 1997). This assay also showed that the

aqueous bark and decoction extracts were only active at higher concentrations. Substances from the bark and root methanol extracts that were shown to possess antioxidant activity by reaction with thiobarbituric acid were also observed to moderately inhibit free radical-mediated DNA-sugar damage. The methanol extracts also inhibited oxidative DNA sugar damage induced from iron (II) salts, which indicates hydroxyl radical scavenging activity (Desmarchelier et al., 1997).

A comparison study of aqueous extracts of bark from *U. tomentosa* and *U. guianensis* (Sandoval et al., 2002) found that the free-radical scavenging activity of both were in the μg/ml range, with *U. guianensis* having greater activity than *U. tomentosa* despite the higher concentration of flavanols in *U. tomentosa*. No other phenolics were quantified in the study, but the authors concluded that alkaloid content had no effect on antioxidant activity.

A screening of 28 plants for their ability to scavenge peroxynitrite radical, a cytotoxic reactive species which can contribute to DNA strand breakage and apoptosis, found that a methanolic extract of *U. tomentosa* scavenged 76% of peroxynitrite radical at 5 μg/ml. The active principles were not identified, but the authors suggested that this activity may be useful toward the prevention and treatment of diseases such as Alzheimer's and rheumatoid arthritis which may involve damage by these radicals (Choi et al., 2002).

Choto-san, made primarily from *U. sinensis*, is used in treatment of vascular diseases and is thought to have protective effects on blood cell membranes, stemming from its antioxidative properties. A study of rat red blood cell lysis induced by a free-radical initiator showed that ingestion of an aqueous infusion of *U. sinensis* caused a dose-dependent decrease in susceptibility of RBC to lysis (Sekiya et al., 2002). The phenolic extracts used in the study included procyanidin B-1 (**1–26**), catechin (**1–24**), epicatechin (**1–25**) and caffeic acid (**1–27**). Caffeic acid was detected in rat plasma and was observed to also protect against RBC lysis on its own. The contributions of the other antioxidants in Choto-san were not evaluated.

4.6. CNS-related activity and effects on locomotion response

Reports of *Uncaria* interaction with CNS receptors include agonistic activity of geissoschizine methyl ether (**1–19**) from *U. sinensis* against the central serotonergic receptor (Kanatani et al., 1985) and binding of an aqueous extract of *U. rhynchophylla* to the α-adrenoceptor, 5HT, dopamine and GABA receptors (Zhu et al., 1996). Further exploration of the CNS activity of *Uncaria* was undertaken in a study of indole alkaloid effects on locomotion (Sakakibara et al., 1999a,b). Aqueous extracts of the species *U. rhynchophylla*, *U. sinensis*, and *U. macrophylla*, were analyzed for locomotive activity by force-feeding the extracts to mice. Based on results from this test, the order of depressed locomotive activity was reported as: *U. macrophylla* > *U. sinensis* > *U. rhynchophylla.* To further understand the relative locomotive activities of these extracts, nine isolated components were tested under conditions which either enhanced dopamine release or dopamine uptake. The compounds rhynchophylline (**1–1**), isorhynchophylline (**1–4**), corynoxeine (**1–3**), isocorynoxeine (**1–6**), corynoxine B (**1–2**), corynoxine (**1–5**), geissochizine methyl ether (**1–19**), hirsuteine (**1–17**), and hirsutine (**1–18**) were tested for ability to depress locomotion response. Studies revealed that corynoxine, corynoxine B, and isorhynchophylline significantly depressed locomotive activity while geissochizine methyl ether's depressive effects were not as significant. Discussion of their modes of action suggested that corynoxine B, geissoschizine methyl ether, and isorhynchophylline may be central dopaminergic receptor antagonists and corynoxine may be an inhibitor of central dopamine release (Sakakibara et al., 1999a,b). Geissoschizine methyl ether was selected for further pharmacological study in mice central serotonin neurons which indicated that the compound may have very specific activity, acting as an agonist for 5-HT_{1A} receptors while blocking 5-HT_{2A} receptors (Pengsuparp et al., 2001). It is structurally similar to other 5-HT receptor agonists such as rauwolscine.

Another study involving rat 5-HT2 receptors showed that oxindole alkaloids pteropodine (**1–9**) and isopteropodine (**1–12**) positively modulate both 5-HT2 receptors and muscarinic M1 receptors (Kang et al., 2002). These activities are thought to affect cognitive processes by interaction with central cholinergic systems. Other studies had shown that these compounds and mitraphylline (**1–8**) ameliorated memory disruption brought about by anticholinergic agents (Abdel-Fattah et al., 2000). However, the receptor study showed that unlike the other two compounds, mitraphylline did not exhibit modulatory effects. This is postulated to be related to the difference in configuration at the D/E rings of the three compounds; pteropodine and isopteropodine are *cis* whereas mitraphylline is *trans* (Kang et al., 2002).

4.7. Effects on vascular diseases

The cardiovascular effects of dihydrocorynantheine, isolated from the dried leaves and stems of *U. callophylla*, was tested in both conscious and anaesthetized normotensive rats to follow up on earlier observations that leaf and stem extract lowered blood pressure of normotensive rats. The results of this test revealed that the arterial pressure in both types of rats fell substantially, while the heart rate of only the anaesthetized rats also decreased (Chang et al., 1989).

Another compound active toward cardiovascular systems is rutin (**1–23**). It was one of several flavonoids isolated from the leaves of *U. hirsuta* and found abundantly in various parts of *U. elliptica.* (Balz and Das, 1979) Rutin (**1–23**) and its hydroxyethyl derivatives are currently used as drugs named ''Venoruton'' and ''Paroven'' to treat blood capillary ailments (Law and Das, 1990).

4.8. Hypotensive effects

One of the most common uses of *Uncaria* species and the traditional medicines derived from them is the treatment of hypertension. This activity has been linked to the presence of certain alkaloids. Gou-teng is a Chinese folk medicine used for various purposes including hypertension and its associated effects (Zhu et al., 1997). Corynoxeine (**1–3**), isocorynoxeine (**1–6**), rhynchophylline (**1–1**), and isorhynchophylline (**1–4**) have been isolated from Gou-teng prepared from the hooks of *U. rhynchophylla.* Studies found that only isorhynchophylline exhibited hypotensive activity in spontaneous hypertensive rats (Zhu et al., 1997). These studies also showed that the composition of aqueous extract of these hooks changed from isorhynchophylline and isocorynoxeine to rhynchophylline and corynoxeine within 15 min. This conversion is important because the hypotensive activity of extracts can concomitantly change. The study concluded that conversion was based on the acidic conditions of the water extract, and their results showed that this conversion can be slowed by a buffering action of Shi-gao (Zhu et al., 1997).

Two other known compounds, 3α-dihydrocadambine (**1–30**) and 3β-isodihydrocadambine (**1–29**), were isolated from Chotokou in efforts to find the origin of this crude drug's hypotensive activity. Studies on urethane-anesthetised rats have demonstrated very strong and lasting hypotensive activity, in comparison to rhynchophylline and its analogues (Shimada et al., 1999). 3α-dihydrocadambine and rhynchophylline were isolated from *U. sinensis*, and a more in-depth analysis was conducted to identify the hypotensive – responsible component. The research included observed changes in blood pressure, heart rate, electrocardiogram, and respiratory rate in both anesthetized and conscious spontaneously hypertensive rats (Shimada et al., 1999). Other studies involved hemodynamic effects in unanesthetized and immobilized dogs, and blood flow effects in anesthetized dogs. Results of these studies showed that 3α-dihydrocadambine exhibits significant hypotensive and antihypertensive activities in vitro, as well as other related effects (Aisaka et al., 1985). A separate study showed that the indole alkaloid geissoschizine methyl ether (**1–19**) extracted from *U. ramulus* (et Uncus) acted as a vasorelaxant on isolated rat aorta (Yuzurihara et al., 2002). The authors postulate that this activity occurs by mechanisms associated with both endothelial dependency with nitric oxide and endothelial independency with voltage-dependent calcium channel blocking.

4.9. Effects on vascular dementia and ischemia

Choto-san prepared primarily from the hooks of *Uncaria sinensis* is prescribed in China and Japan for the treatment of psychiatric symptoms associated with dementia, particularly sleep disturbance. Corynoxine (**1–5**), corynoxine B (**1–2**), rhynchophylline (**1–1**), and isorhynchophylline were isolated from *Uncaria macrophylla* and evaluated for their ability to prolong a state of hypnosis in mice (Sakakibara et al., 1998). The study concluded that 100 mg/kg of each compound, orally administered to mice resulted in prolongation of thiopental-induced hypnosis. Isorhynchophylline, corynoxine (**1–5**), and corynoxine B (**1–2**) significantly prolonged sleeping times compared to controls.

Reactive oxygen species may damage membranes during ischemia, inflammation and aging processes; thus antioxidants may play a protective role in related conditions including vascular dementia. *U. sinensis* extracts rich in phenolic antioxidants, including procyanidin B-1 (**1–26**), catechin (**1–24**), epicatechin (**1–25**) and caffeic acid (**1–27**), were evaluated for their ability to inhibit free-radical induced lysis of rat red blood cells and were found to exhibit a strong and dose-dependent protection of the cell membrane (Sekiya et al., 2002).

In a study that has implications for brain cell survival under conditions of stroke, a methanol extract of *U. rhynchophylla* was investigated for its neuroprotective effects in rats upon transient global ischemia (Suk et al., 2002). It was observed that the extract significantly reduced death of CA1 hippocampal neurons, by 72% at a dose of 100 mg/kg body weight. The authors also found that ischemic induction of COX-2 expression was inhibited by administration of the extract and postulated that this inhibition is a key factor in protection of neurons. A separate study of several traditional Chinese stroke medicines screened extracts including Gou-teng (*U. rhynchophylla*) for their ability to act as *N*-methyl-D-aspartate (NMDA) receptor antagonists. NMDA receptors are believed to mediate calcium-dependent neurotoxicity associated with ischemia and hypoxia (Meldrum et al., 1987). Among the medicines tested, an aqueous extract of Gou-teng was one of the most effective blockers of NMDA-induced neuron death (Sun et al., 2003). Both studies suggested that further research is needed to further characterize the active compounds in *U. rhynchophylla*, which may supply leads for the development of safe drugs for stroke therapy.

4.10. Mutagenicity

U. tomentosa's bark extracts and fractions were tested for both in vitro and in vivo anti-mutagenic activities. The

Salmonella/mammalian microsome test was employed with various strains of *S. typhimurium*, with and without metabolic activation. Results showed slightly toxic activity, and a protective effect against photomutagenesis. Analysis revealed anti-mutagenic activity in vitro, and a significant decrease of mutagenic potential by the end of in vivo treatments. The authors suggested that the plant's anti-mutagenic activity in vitro is linked to its antioxidant activity (Wurm et al., 1998).

4.11. Antibacterial properties

Although the *Uncaria* genus is not used extensively to treat infections in traditional medicine, some reports evaluating antibacterial activity have appeared as early as 1965. An extract of *U. glabrata* was observed to inhibit the growth of *Streptococcus aureus* and *Escherichia coli* as evaluated by the disk diffusion method (Arret et al., 1971). One use of *U. glabrata* in traditional medicine which may be related to its antibacterial activity is in the treatment of food poisoning.

As part of an antimutagenicity study of *U. tomentosa*, toxicity against *Salmonella typhimurium* TA 98 and TA100 strains was evaluated. Results indicated toxicity only at the highest concentrations (1000 μg/plate) (Wurm et al., 1998). Toxicity of *U. tomentosa* towards *Photobacterium phosphoreum* was evaluated using a Microtox assay which showed no toxicity of aqueous extracts at concentrations up to 100 μg/ml (Sandoval et al., 2002).

5. Conclusions

Uncaria has proven to be a very valuable genus to the discovery and utilization of medicinal natural products, particularly alkaloids and pentacyclic triterpenes. The collected information provides a means to understand the latest developments in the pharmacology and phytochemistry of the genus. The potential for development of leads from *Uncaria* continues to grow, particularly in the area of immunomodulatory, inflammatory and vascular-related conditions. The information summarized here is intended to serve as a reference tool to people in all fields of ethnopharmacology and natural products chemistry.

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Mary E. Heitzman received her B.Sc. degree in Chemistry (major) with a minor in Earth & Environmental Studies from Lehigh University (1999). She then joined the Patrick Center for Environmental Research at the Academy of Natural Sciences in Philadelphia, Pennsylvania where she investigated pesticide levels extracted from river sediments. In 2000 she enrolled at the University of Massachusetts Dartmouth and obtained her M.Sc. in Chemistry in 2002 for her research work on Peruvian antimicrobial plants. Mary is currently a doctoral candidate in science education at the University of Michigan (Ann Arbor).

Catherine C. Neto is Assistant Professor of Organic Chemistry at the University of Massachusetts-Dartmouth. She received her Ph.D. in chemistry from Brown University in 1988. Following a postdoctoral fellowship in biochemical pharmacology at Brown, Dr. Neto joined the chemistry faculty at the University of Massachusetts Dartmouth, where her research interests turned towards the study of biologically active plant natural products. She has collaborated with Dr. Hammond in research on Peruvian medicinal plants with anticancer and antibacterial properties since 1997. Dr. Neto's current research interests include the structure and anticancer mechanisms of plant triterpenoids and the chemistry, pharmacology and health benefits of flavonoids and other polyphenolics from *Vaccinium* fruit. Dr. Neto's multidisciplinary research includes collaborations with chemists and biologists from Canada, the United States and Peru. She is a member of the American Chemical Society and the American Society of Pharmacognosy.

Elizabeth Winiarz is science librarian at the University of Massachusetts Dartmouth. She has a B.Sc. in Biology and M.L.S. in Library Science from McGill University in Montreal, Canada. She has worked in the Patent and Legal Library at DuPont Canada, Inc., as biology librarian at Concordia University in Montreal, as an online information specialist at the Massachusetts Institute of Technology, and as a reference assistant at Tufts University Medical School library. Her interest in plants began when she worked as a summer naturalist at the Gault Estate of McGill University. Historical and medicinal uses of local plants were a highlight of the nature walks she led. Elizabeth collaborates in research efforts and literature searching with science faculty at the University of Massachusetts Dartmouth.

Dr. Abraham J. Vaisberg is Professor of Microbiology and Dean of the Faculty of Sciences and Philosophy of the Universidad Peruana Cayetano Heredia (UPCH) in Lima, Perú. He obtained his B.Sc. degree from UPCH in 1970 and received his Ph.D. in Biology from Brandeis University in 1975. At Brandeis University, he was awarded a Wien International Scholarship and a Kessner Predoctoral fellowship. Following graduation, Dr. Vaisberg returned to UPCH as assistant professor of Microbiology. He was one of the founders of the Laboratorios de Investigación y Desarrollo de Ciencia y Tecnología (LIDCT) at UPCH, and is currently its director. His research focuses in the areas of medical virology, mainly immunomodulation in measles disease and response of children to measles vaccination; and natural products research, with emphasis on wound healing, antitumor and antimicrobial activity of Peruvian plants.

Gerald B. 'GB' Hammond is Professor of Organic Chemistry and University Scholar at the University of Louisville. He received his B.Sc. from the Pontificia Universidad Católica del Perú in 1975, his M.Sc. from the University of British Columbia, Canada, in 1979, and his Ph.D. from the University of Birmingham, England in 1985. After a postdoctoral fellowship and visiting professorship at the University of Iowa, Dr. Hammond joined the University of Massachusetts Dartmouth in 1990, where he was promoted to professor in 1999. In 2004, he joined the University of Louisville in Kentucky. Dr. Hammond's awards include the Henry Dreyfus Teacher-Scholar Award (1996), UMass Dartmouth Scholar of the Year Award (1998), and Camille and Henry Dreyfus Scholar-Fellow (2001). In 2002 he was awarded a Fulbright Scholarship at UNAM in Mexico working with Mexican purgative plants. His research interests focus on the development of fluorinated molecular building blocks, the systematic study of bioactive plants from Peru, and the synthesis of small libraries of organic compounds for chemical genetics studies involving intracellular trafficking.