· Reviews ·

An Overview on the Progress of Chemical Constituents and Bioactivities of Plants in Urticaceae during 2000－2010

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Abstract: Urticaceae includes about 1300 species in 47 genera which largely spread in wet tropical regions, and 341 species in 25 genera are in China. Some species are used in Chinese folk medicine. So far, studies on chemistry and pharmacology of Urticaceous plants are mainly focused on nettle of *Urtica* L. In this review, the chemical researches on 35 new compounds and related pharmacological effects of the plants in Urticaceae reported during 2000－2010 are described. The 35 new compounds belong to the classes of lignan, secolignan, norlignan, flavonoid, alkaloid, sesquiterpenoid, triterpenoid, sterol, and sphingolipid. The main bioactivities include cytotoxic, antitumor, antimicrobial, antifungal, anti-BPH, anti-HIV, antidiabetic, hypolipidemic, 5α-reductase inhibitory, hair regrowth promotion, and anti-oxidative activities.

Key words: bioactivities; chemical constituents; nettle; *Urtica* L.; Urticaceae

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Introduction

Urticaceous plants are herb, subshrub, or shrub, rarely trees, and very rarely climbing. Stems of Urticaceous plants are often fibrous, sometimes succulent, sometimes armed with stinging hairs. Urticaceae includes about 1300 species in 47 genera, most of which in wet tropical regions extend into temperate regions, and 341 species (163 endemic, one introduced) in 25 genera in China. Boiled young shoots of *Girardinia* Gaudich., *Laportea* Gaudich., and *Urtica* L. are used as vegetables. Some species are used in Chinese folk medicine (Chen *et al*, 2003).

Nettles (*Urtica dioica* L. and *U. urens* L.) belonging to this family have been reported to be effective for the treatment of several human diseases, such as benign prostatic hyperplasia (BPH), rheumatoid arthritis, osteoarthritis, urinary tract infections, *etc* (Chrubasik *et al*, 2007a; 2007b). Other species of *Urtica* L. have also been well studied in chemical constituents besides nettle. However, few studies have been paid towards other genera of this family. In 2007, Chrubasik *et al* reviewed effects and efficacy profiles of nettle (Chrubasik *et al*, 2007a; 2007b). In order to draw the attention of other genera in Urticaceae, we decided to write related review on whole Urticaceae. Previously, we wrote a review on chemical constituents of the plants in Urticaceae according to related literatures (Wang *et al*, 2010). We summarized the research progress on phytochemical and pharmacological effects of the plants in Urticaceae in the past 10 years in this review and hoped that this paper would be valuable for the research and development of the plants in Urticaceae.

Chemical constituents

In the past 10 years, 35 new and some known compounds were isolated from the plants in Urticaceae. The 35 new compounds belong to the classes of lignan,

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secolignan, norlignan, flavonoid, alkaloid, sesquiterpenoid, triterpenoid, sterol, and sphingolipid. The new compounds and the corresponding plant sources are collected in Table 1. Their structures are shown in Fig. 1.

Table 1 New chemical entities (1−35) from plants in Urticaceae during 2000−2010

No.	Compounds	Sources	References
	Lignan		
1	(–)-4-methoxy-8'-acetyl olivil	*U. triangularis*	Yan *et al*, 2008
2	(–)-4-methoxy-8'-acetylolivil-4-*O*-α-arabinopyranosyl-(1→6)-β-glucopyranoside	*U. triangularis*	Yan *et al*, 2008
3	(–)-olivil-9-*O*-β-glucopyranoside	*U. triangularis*	Yan *et al*, 2008
4	cyclo-olivil-9-*O*-β-glucopyranoside	*U. triangularis*	Yan *et al*, 2008
5	pinoresinol 4-*O*-α-*L*-rhamnopyranosyl (1→2)-β-*D*-glucopyranoside	*U. laetevirens*	Zhou *et al*, 2009
6	phenaxolactone 1	*P. angustifolius* *P. rugosus*	Rastrelli *et al*, 2001 Piccinelli *et al*, 2005
7	phenaxolactone 2	*P. angustifolius*	Rastrelli *et al*, 2001
8	phenaxolactone 3	*P. rugosus*	Piccinelli *et al*, 2005
9	phenaxolactone 4	*P. rugosus*	Piccinelli *et al*, 2005
10	phenaxolactone 5	*P. rugosus*	Piccinelli *et al*, 2005
	Secolignan		
11	urticol	*U. mairei*	Wang *et al*, 2008
12	urticene	*U. mairei*	Wang *et al*, 2008
13	{(3*S*,4*S*)-4-[bis (4-hydroxy-3-methoxyphenyl) methyl]-2-oxo-tetrahydrofuran-3-yl} methyl β-*D*-glucopyranoside	*U. fissa*	Ji *et al*, 2009
14	{(3*S*,4*R*)-4-[bis (4-hydroxy-3-methoxyphenyl) methyl]-2-oxo-tetrahydrofuran-3-yl} methyl β-*D*-glucopyranoside	*U. fissa*	Ji *et al*, 2009
15	urticaside A	*U. triangularis*	Feng *et al*, 2010
16	urticaside B	*U. triangularis*	Feng *et al*, 2010
	Norlignan		
17	pouzolignan A	*Pouzolzia occidentalis*	Mohammed *et al*, 2010
18	pouzolignan B	*P. occidentalis*	Mohammed *et al*, 2010
	Flavonoid		
19	5, 2', 4' trihydroxy 7, 8 dimethoxy flavone	*U. dioica*	Chaturvedi, 2001
20	chalcone-6'-hydroxy-2',3,4-trimethoxy-4'-*O*-β-*D*-glucopyranoside	*Boehmeria rugulosa*	Semwal *et al*, 2009
21	isoflavone-3',4',5,6-tetrahydroxy-7-*O*-[β-*D*-glucopyranosyl-(1→3)-α-*L*-rhamnopyranoside]	*B. rugulosa*	Semwal *et al*, 2009
22	isoflavone-3',4',5,6-tetrahydroxy-7-*O*-[β-*D*-glucopyranosyl-(1→6)-β-*D*-glucopyranosyl-(1→6)-β-*D*-glucopyranosyl-(1→3)-α-*L*-rhamnopyranoside]	*B. rugulosa*	Semwal *et al*, 2009
	Alkaloid		
23	3-(4-hydroxyphenyl)-4-(3-methoxy-4-hydroxyphenyl)-3,4-dehydroquinolizidine	*B. siamensis*	Luo, Li, and Zhang, 2001
24	boehmeriasin A	*B. siamensis* *B. rugulosa*	Luo *et al*, 2003 Semwal *et al*, 2009
25	boehmeriasin B	*B. siamensis*	Luo *et al*, 2003
26	(–)-(15*R*)-hydroxycryptopleurine	*B. pannosa*	Cai *et al*, 2006
	Sesquiterpenoid		
27	8-*O*-(*p*-coumaroyl)-5β-hydroperoxy-1(10)*E*,4(15)-humuladien-8α-ol	*Pilea cavaleriei*	Tang *et al*, 2009
28	8-*O*-(3-nitro-*p*-coumaroyl)-1(10)*E*,4(15)-humuladien-5β,8α-diol	*P. cavaleriei*	Tang *et al*, 2009
29	8-*O*-(*p*-coumaroyl)-1(10)*E*,4(5)*E*-humuladien-8-ol	*P. cavaleriei*	Tang *et al*, 2009
30	1-*O*-*p*-coumaroyl-copaborneol	*P. cavaleriei*	Tang *et al*, 2009
	Triterpenoid		
31	3β,19α-dihydroxy-30-norurs-12-ene	*Debregeasia salicifolia*	Akbar, Riaz, and Malik, 2001
32	3β-(*trans*-cinnamoyloxy)-19α-hydroxy-urs-12-ene	*D. salicifolia*	Akbar and Malik, 2002
33	2α,3β,21β,23,28-penta hydroxyl 12-oleanene	*L. crenulata*	Khan *et al*, 2007
	Sterol		
34	niveain A	*B. nivea*	Chen *et al*, 2009
	Sphingolipid		
35	pellioniareside	*Pellionia repens*	Luo *et al*, 2004

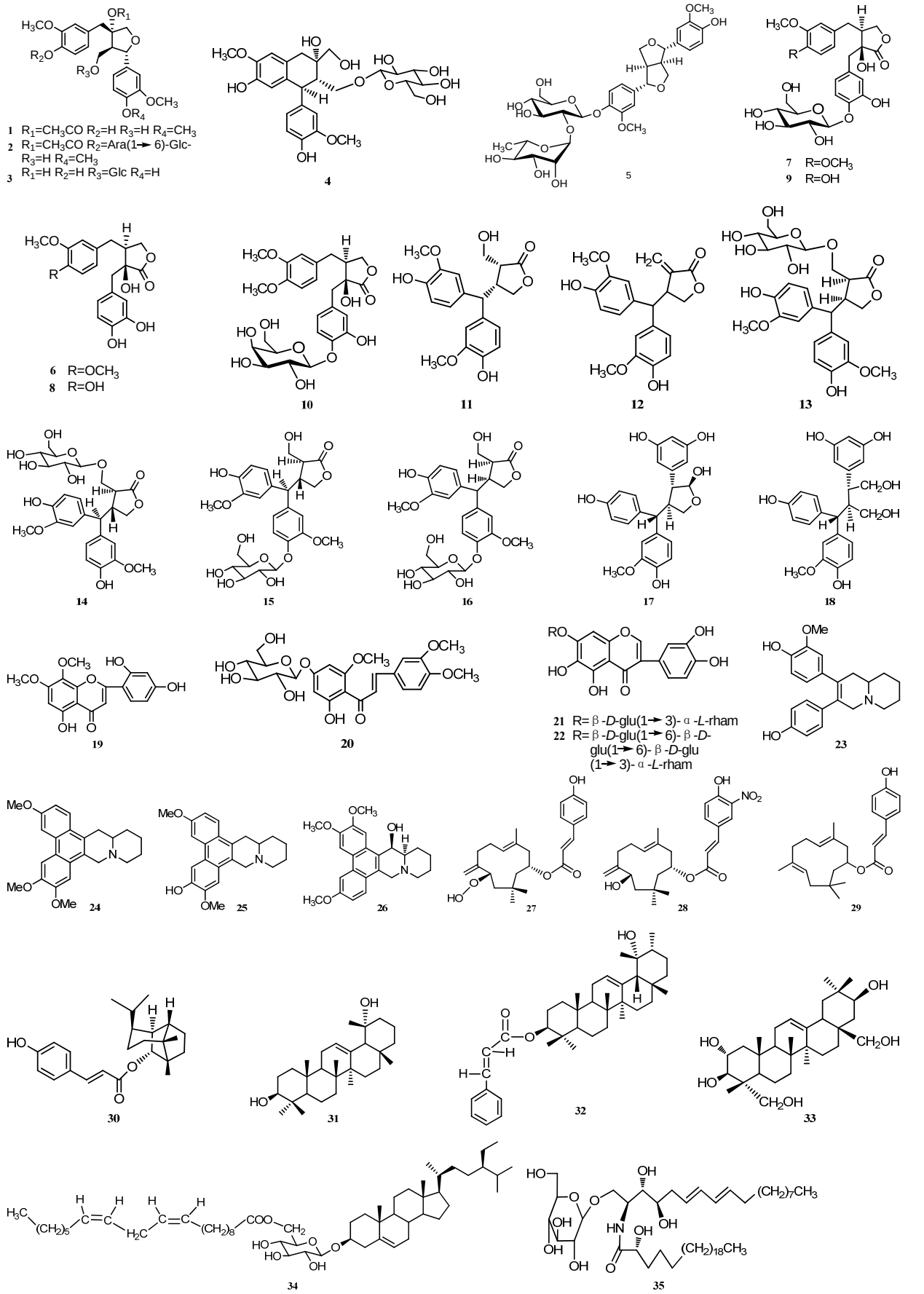

Fig. 1 Chemical structures of compounds 1—35 isolated from plants in Urticaceae

Lignan

Ten new lignans (**1**－**10**) were isolated from *U. triangularis* Hand.-Mazz. (Yan *et al*, 2008), *U. laetevirens* Maxim. (Zhou *et al*, 2009), *Phenax angustifolius* Wedd. (Rastrelli *et al*, 2001), and *P. rugosus* Wedd. (Piccinelli *et al*, 2005).

Isolariciresinol 9-*O*-β-*D*-glucopyranoside was first isolated from *U. laetevirens* (Zhou *et al*, 2009).

Secolignan

Secolignans had only been found in Piperaceae before they were isolated from *Urtica* L. Six new secolignans (**11**－**16**) were isolated from *U. mairei* Levl. (Wang *et al*, 2008), *U. fissa* E. Pritz (Ji *et al*, 2009), and *U. triangularis* (Feng *et al*, 2010).

Norlignan

Two new norlignans (**17**－**18**) were isolated from *Pouzolzia occidentalis* (syn. *P. palmieri*) Wedd. The 2-methyl ether of compound **17**, like an artifact, was also isolated (Mohammed *et al*, 2010).

Flavonoid

Four novel flavonoids (**19**－**22**) were isolated from *U. dioica* (Chaturvedi, 2001) and *Boehmeria rugulosa* Wedd. (Semwal *et al*, 2009).

Ten flavonoid glycosides including apigenin 6,8-di-*C*-β-*D*-glucopyranoside, luteolin 7-*O*-neohe- speridoside, luteolin 7-*O*-β-*D*-glucopyranoside, 5-methoxy-luteolin 7-*O*-β-*D*-glucopyranoside, rutin, isovitexin, isoquercitrin, astragalin, afzelin, and quercitrin were first isolated from *U. laetevirens* (Zhou *et al*, 2009) and *U. cannabina* Linn. (Aishan *et al*, 2010).

Three flavonoids, such as vitexin, isovitexin, and quercetin 3-*O*-α-*L*-rhamnopyranoside were isolated from *P. angustifolius* (Rastrelli *et al*, 2001) and *P. rugosus* (Piccinelli *et al*, 2005). Quercetin and quercetin-7-*O*-β-*D*-glucopyranoside were isolated from *B. rugulosa* (Semwal *et al*, 2009).

A prenylated isoflavone, 5-methoxy-4'-hydroxy-2",2"-dimethylpyrano (3",3",7,8) isoflavone, was isolated from *P. indica* (L.) Gaudich. (Sayeed *et al*, 2003).

Alkaloid

Four new alkaloids (**23**－**26**) were isolated from *B. siamensis* Craib (Luo, Li, and Zhang, 2001; Luo *et al*, 2003), *B. rugulosa* (Semwal *et al*, 2009), and *B. pannosa* Nakai & Satake (Cai *et al*, 2006).

(–)-Cryptopleurine was isolated from *B. pannosa* (Cai *et al*, 2006). 3,4-Dimethoxy-ω-(2'-piperidyl)-acetophenone was isolated from *B. rugulosa* (Semwal *et al*, 2009).

Sesquiterpenoid

Three new humulane-type sesquiterpenes (**27**－**29**) and a new copaborneol derivative (**30**) were isolated from *Pilea cavaleriei* Lévl. subsp. *crenata* C. J. Chen (Tang *et al*, 2009).

Triterpenoid

Three new triterpenoids (**31**－**33**) were isolated from *Debregeasia salicifolia* D. Don (Akbar, Riaz, and Malik, 2001; Akbar and Malik, 2002) and *Laportea crenulata* Gaud. (Khan *et al*, 2007).

Eight triterpenoids including lupeol, oleanolic acid, uvaol, 3β,19α-dihydroxy-urs-12-ene, ursolic acid, pomolic acid, pomolic acid methyl ester, and tormentic acid were reported for the first time from *D. salicifolia* (Akbar, Riaz, and Malik, 2001; Akbar and Malik, 2002). Lupeol was also isolated from *Pellionia repens* (Lour.) Merr. (Luo *et al*, 2004).

Three triterpenoids including betulinic acid, oleanolic acid, and 19α-hydroxyursolic acid were isolated from *B. nivea* (L.) Gaudich. (Chen *et al*, 2009).

Sterol

A new daucosterol (**34**) was isolated from *B. nivea* (Chen *et al*, 2009).

(22*E*,20*S*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3-β-ol was isolated from *P. repens* (Luo *et al*, 2004).

β-Sitosterol was first isolated from *D. salicifolia* (Akbar, Riaz, and Malik, 2001) and *L. crenulata* (Khan *et al*, 2007), and it also reported from *B. nivea* (Chen *et al*, 2009) and *B. rugulosa* (Semwal *et al*, 2009). β-Sitosterol 3-β-*D*-glucopyranoside was first isolated from *L. crenulata* (Khan *et al*, 2007).

Stigmasterol was isolated from *D. salicifolia* firstly (Akbar, Riaz, and Malik, 2001). Daucosterol was isolated from *P. repens* (Luo *et al*, 2004) and *B. nivea* (Chen *et al*, 2009).

Sphingolipid

A new glucoceramide (**35**) was isolated from *P. repens* (Luo *et al*, 2004).

Megastigmane

Two megastigmanes (Fig. 2), (+)-blumenol A and (+)-dehydrovomifoliol, were isolated from *U. cannabina*. This is the first report of megastigmanes in

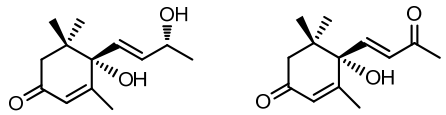

Fig. 2 Chemical structures of megastigmanes isolated from *U. cannabina*

the plants of Urticaceae (Aishan *et al*, 2010).

Fatty acid and related derivative

Six active fatty acids including α-linolenic, linoleic, palmitic, elaidic, oleic, and stearic acids were isolated from *B. nipononivea* Kodiz. (Shimizu *et al*, 2000).

Olein was isolated from *B. nivea* and it was first reported from this genus (Chen *et al*, 2009).

Phenolic acid

Three phenolic acids, (+)-catechin, chlorogenic acid, and rutin were identified in *Pipturus albidus* (Hook. & Arn.) A. Gray (Mamaki) (Kartika *et al*, 2007).

Others

Uracil was isolated from *P. repens* (Luo *et al*, 2004).

The components of essential oil from *Elatostema laetevirens* Maxim. and *E. umbellatum* Blume var. *majus* Maxim. were investigated. As a result, 79 compounds from *E. laetevirens* and 80 compounds from *E. umbellatum* were identified, respectively. The major components of essential oil from *E. laetevirens* are phytol, neophytadiene, and γ-himachalene. The essential oil from *E. umbellatum* contains phytol, linoleic acid, and palmitic acid as the major components. (2*E*)-Hexenal and (2*E*, 4*E*)-nonadienal are the most aroma compounds of *E. laetevirens* oil. It seemed that these components made the green-floral odor. On the other hand, it seemed that (2*E*)-hexenal, (3*Z*)-hexenol, and 1-octen-3-ol made the green-oily odor of *E. umbellatum* oil (Miyazawa, Utsumi and Kawata, 2009).

Three polysaccharides were isolated from *U. fissa*, and they are mainly composed of *D*-arabinofuranosyl, *D*-galactopyranosyl, and *D*-glucopyranosyl residues with different structural characteristics (Li *et al*, 2009).

Polyphenol oxidase (PPO) of *U. dioica* was extracted and purified. In addition, one isoenzyme of PPO was detected (Gulcin, Kufrevioglu, and Oktay, 2005).

Bioactivities

Cytotoxic and antitumor effects

Boehmeriasin A (**24**) isolated from *B. siamensis* exhibited cytotoxic activity against 12 cell lines from six panels of cancer including lung cancer, colon cancer, breast cancer, prostate cancer, kidney cancer, and leukemia with GI_{50} between 0.2 and 100 ng/mL (Luo, Li, and Zhang, 2001). Bioactivity assay *in vitro* demonstrated that compound **24** had wide-range and strong antitumor activity. It potently inhibited the proliferation of breast cancer cell MDA-MB-231 via the G1 phase cell cycle arrest and differentiation induction (Yan *et al*, 2006)

The cytotoxic activities of crude extracts and 2α,3β,21β,23,28-penta hydroxyl 12-oleanene (**33**) from the roots of *L. crenulata* were observed by brine shrimp bioassay and LC_{50} of compound **33** was found to be 27.54 μg/mL (Rahman *et al*, 2008).

8-*O*-(*p*-coumaroyl)-1(10)*E*,4(5)*E*-humuladien-8-ol (**29**) isolated from *P. cavaleriei* exhibited weak cytotoxic activities against three human tumor cell lines K562 (IC_{50} = 12.01 μg/mL), AGZY (IC_{50} = 27.82 μg/mL), and A549 (IC_{50} = 25.60 μg/mL) (Tang *et al*, 2009).

A methanol extract in the roots of *B. pannosa* potently inhibited hypoxia-inducible factor-1 (HIF-1), which could be an important target of cancer chemotherapy, and the activation was induced by hypoxia (80% inhibition at 0.8 μg/mL) in an HIF-1-mediated reporter gene assay. (−)-Cryptopleurine and (−)-(15*R*)-hydroxy-cryptopleurine (**26**) from the roots of *B. pannosa* potently inhibited the hypoxia-induced expression of a reporter gene under the control of a hypoxia response element (HRE) with IC_{50} values of 8.7 and 48.1 nmol/L, respectively. Furthermore, the two compounds suppressed the accumulation of HIF-1α protein in a dose-dependent manner, but not the HIF-1β protein, and inhibited the expression of vascular endothelial growth factor (VEGF) by hypoxia (Cai *et al*, 2006).

Antimicrobial and antifungal effects

5-Methoxy-4'-hydroxy-2",2"-dimethylpyrano(3",3", 7,8) isoflavone isolated from *P. indica* exhibited potent antimicrobial and antifungal activities. The minimum inhibitory concentration and cytotoxic activity (LC_{50}) of the compound were found to be 32 μg/mL against *Escherichia coli* and 24.92 μg/mL against brine shrimp nauplii, respectively (Sayeed *et al*, 2003).

3β-(*Trans*-cinnamoyloxy)-19α-hydroxy-urs-12-ene

(**32**), 3β,19α-dihydroxy-urs-12-ene, and pomolic acid methyl ester from *D. salicifolia* showed significant antimicrobial activity (Akbar and Malik, 2002). The antifungal activity of 2α,3β,21β,24β,28-pentahydroxy-olean-12-ene (**33**) obtained from the roots of *L. crenulata* was studied against *Aspergillus flavus* Link, *A. niger* Tiegh., *Candida albicans*, and *Rhizopus aurizae*, and compared with the activity of nystatin (30 μg/disc). This compound showed moderate activity against tested fungi (Khan *et al*, 2007). Crude extract and compound **33** obtained from the root of *L. crenulata* exhibited remarkable antibacterial activities against both Gram-positive and Gram-nagative bacteria (Rahman *et al*, 2008).

The ethanolic extract of *B. rugulosa* as well as the isolated compounds, chalcone-6'-hydroxy-2',3,4-trimethoxy-4'-*O*-β-*D*-glucopyranoside (**20**), isoflavone-3',4',5,6-tetrahydroxy-7-*O*-[β-*D*-glucopyranosyl-(1→3)-α-*L*-rhamnopyranoside] (**21**), and isoflavone-3',4',5,6-tetrahydroxy-7-*O*-[β-*D*-glucopyranosyl-(1→6)-β-*D*-glucopyranosyl-(1→6)-β-*D*-glucopyranosyl-(1→3)-α-*L*-rhamnopyranoside] (**22**) (25 mg/mL) showed potent antimicrobial activity against two bacterial species (*Staphylococcus aureus* and *Streptococcus mutans*) and three fungus pathogens (*Microsporum gypseum*, *M. canis*, and *Trichophyton rubrum*). The activities of the isolated compounds **20**－**22** had been compared with positive controls, novobiocin, and erythromycin (15 mg/mL) (Semwal *et al*, 2009).

Anti-BPH effects

The crude polysaccharide from the roots and stems of *U. fissa* (UFP) significantly inhibited prostatic hyperplasia in animal models at doses of 62.5, 125, and 250 mg/kg (administered orally). Histopathological examination showed that proliferation of prostatic epithelial cells and fibrotic tissues were significantly inhibited (Zhang *et al*, 2008).

The BPH rats induced by testosterone propionate were taken as the animal model to screen the 20% EtOH extracts of the *Urtica* plants. *U. fissa* was found to lower the prostatic weight of the model animals, decrease the density of lecithin corpuscle, and increase the acid phosphatase level (Ji *et al*, 2009).

Anti-HIV effect

Phenaxolactones 1－5 (**6**－**10**), flavones vitexin, and isovitexin isolated from *P. angustifolius* and *P. rugosus* were evaluated for their inhibitory activity against HIV-1_{MN} in infected C8 166 cells. The most promising compound was phenaxolactones 1 (**6**) with an EC_{50} of 3.0 μmol/L, and no cytotoxicity was observed at 112 μmol/L and a therapeutic index value of 37.3 (Piccinelli *et al*, 2005).

Antidiabetic and hypolipidemic effects

The methanol/methylene chloride extract in the aerial parts of *Laportea ovalifolia* (Schum.) Chew appeared to possess antidiabetic and hypolipidemic properties at least in rats with alloxan-induced diabetes (Momo *et al*, 2006).

The ethanolic extract in the leaves of *B. rugulosa* showed significant hypoglycemic activity on alloxan-induced diabetic mice (Semwal *et al*, 2009).

5α-Reductase inhibitory and hair regrowth promotion effects

The acetone extract of *B. nipononivea* showed both potent 5α-reductase inhibitory activity and hair regrowth promotion effects on mice. The extract of *B. nipononivea*, and α-linolenic, elaidic, and stearic acids exhibited a hair regrowth effect (Shimizu *et al*, 2000).

Anti-oxidative effects

PPO of *U. dioica* was identified as an anti-oxidative principle (Gullcin, Kufrevioglu, and Oktay, 2005).

The total anti-oxidant activity (TAA) in Mamaki (*P. albidus*) leaves was quantified, which was expressed in equivalents to ascorbic acid (AA). Mamaki teas contained relatively low amounts of TAA compared to green teas and lipton teas (Kartika *et al*, 2007).

Conclusion

Chemical constituents and their bioactivities of nettle had been investigated before the year of 2000, so there was only one new flavone isolated from stinging nettle (*U. dioica*) in the past 10 years. But the researches promoted the studies on other species of *Urtica* L., and five new lignans, six new secolignans were isolated from other species of *Urtica* L. in this decade. A new quinolizidine and three new phenanthroquinolizidine alkaloids from *Boehmeria* Jacq. were reported, while alkaloid hasn't been found in the plants of *Urtica* L. and other genera up to now. Phenanthroquinolizidine alkaloids are a small group

of alkaloids and display interesting biological properties including cytotoxic activity and inhibitory activity to enzymes involved in the synthesis of protein. In future, such compounds may be adopted as possible candidates for cancer chemotherapeutic agents or cancer chemopreventive agents (Luo *et al*, 2003). Significant attention has been paid to the simple sphingolipids, particularly ceramide, and glucosylceramide, each of them appears to be involved in the regulation of specific aspects of neuronal proliferation, differentiation, survival, and apoptosis. Pellioniareside (**35**), a new sphingolipid, may be the active component of *P. repens* to treat icterus, acute and chronic hepatitis, and allergic dermatitis (Luo *et al*, 2004).

Although many researchers have done systematic and deep researches on stinging nettle, only a few active components have been identified and the mechanism of action is still unclear (Chrubasik *et al*, 2007b). We hope the researches on the plants of *Urtica* L. will promote all the researches on the plants in Urticaceae. We also should spend more time on researches of chemical constituents and bioactivities of the plants in Urticaceae so as to make better use of them.

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The 3rd International Conference and Exposition on the Modernization of Traditional Chinese Medicine

The 3rd International Conference and Exposition on the Modernization of Traditional Chinese Medicine was held during Nov. 25－26, 2010 in Chengdu (Sichuan, China), editorial director CHEN Chang-qing associated with other members of *Chinese Herbal Medicines* (CHM) editorial office attended this meeting.

An encouraging and inspiring report named “The first journal in English on Chinese materia medica greatly moving forward” was given by editorial director CHEN Chang-qing. The report mainly covered the foundation process, foundation purpose, and results that have been achieved since the initial issue was distributed.

CHM has been included in Ulrich's Periodicals Directory, Index of Copernicus (IC) in Poland, and Chemical Abstracts Service (CAS) in USA since 2009. All the figures in each database revealed that articles published in CHM were frequently cited and downloaded. The results achieved in the past demonstrate that the internationalization of CHM is greatly moving forward!

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