Genus *Gentianella* Moench: A Phytochemical and Ethnopharmacological Review

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Abstract: The plants in genus *Gentianella* Moench (Gentianaceae) which comprised approximately 250 species, are mainly distributed in temperate regions of the world. Many *Gentianella* plants are intensely bitter and employed in traditional medicine to stimulate appetite, treat disorders of the gallbladder, and treat fever like the other bitter gentians in various regions of the world. Some species exhibit other remarkable therapeutic effects in the treatments of obesity, diabetes, and heart diseases. Eleven iridoids, twenty-eight xanthones, three *C*-glucoflavonoids, and eight other compounds have been isolated from the genus. Most of these compounds are associated with antimicrobial, anti-inflammatory, anti-oxidant, hypoglycemic, and antitumor activities, which provide an empirical base for the traditional utilization of the plants in genus *Gentinella* Moench.

Key words: ethnopharmacology; *Gentianella* Moench; pharmacology; phytochemistry; traditional medicine
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Introduction

As natural drugs now play an even more important role in medical and healthcare services, the ethnopharmacology of medicinal plants has attracted increasing attention in new drug research and development.

The plants of *Gentianella* Moench (Gentianaceae) mainly distributes in temperate regions of the world. It comprises approximately 250 annual, biennial or perennial species with 4 or 5-merous flowers, obconical or cylindrical corolla which is fimbriate in the throat and with erect or patent lobes, no style, but sessile and stipitate ovary (Von Hagen and Kadereit, 2001). The group is an extremely abundant medicinal plant source. Many species of the genus have traditional remedies for loss of appetite, jaundice, disorders of the gallbladder, fever, etc. In recent years, extracts of some *Gentianella* Moench species have been also patented for improving insulin resistance, liver function, and decreasing blood sugar, uric acid, and obesity in US and Japan (Ogawa *et al*, 2006; Ogawa, 2006; 2007).

Previous phytochemical investigations on the plants of *Gentianella* Moench have resulted in the isolation of xanthones, *C*-glucoflavones, and terpenoids (iridoids, sesterterpenoids, and triterpenes). The occurrence of iridoids, xanthones, and *C*-glucoflavones is typical of genus *Gentianella* Moench (Jensen and Schripsema, 2002; Janković, Krstić, and Ivana, 2005), and the medicinal value of the genus is just due to presence of these compounds. Some plants of *Gentianella* Moench are either very rich in these compounds or have been studied extensively. For example, 14 different compounds have been isolated from *G. nitida* (Grisebach) Fabris (Lacaille-Dubois and Galle, 1996; Kawahara *et al*, 1997; Kawahara, Nozawa, and Kurata, 1999; Kawahara, Nozawa, and Sekita, 2001.).

Recently more and more researchers have increasing interest on the species of *Gentianella* Moench and their biological activities. In this review, the phytochemical and pharmacological research on the species of *Gentianella* Moench together with their traditional uses will be presented

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and critically evaluated.

Traditional medicinal uses

Many plants of *Gentianella* Moench are intensely bitter and employed in traditional medicines to stimulate appetite, treat disorders of the gallbladder and treat fever like the other bitter gentians in various regions of the world, such as *G. florida* (Griseb.) Holub, *G. achalensis* (Gilg.) T. N. Ho et S. W. Liu, *G. austriaca* (A. et J. Kerner) Holub, *G. amarelle* ssp. *acuta* (Michx.) J. M. Gillett, *etc* (Ratera and Ratera, 1980; Nadinic *et al*, 1997; 1999; Vinterhalter *et al*, 2008; Urbain *et al*, 2008). Some species exhibit other remarked therapeutic effects in the treatments of obesity, diabetes, and heart diseases (Ma, 1993; Kawahara *et al*, 1997; Kawahara, Nozawa, and Flores, 2000).

Some representative medicinal species of *Gentianella* Moench are listed:

G. nitida, a biennial medicinal plant growing in the Andes region, is used in traditional Peruvian folk medicine (Commonly known as “Hercampuri” or “Hircampure”) as a cholagogue and for the treatment of hepatitis and obesity (Kawahara *et al*, 1997; Kawahara, Nozawa, and Kurata, 1999; Kawahara, Nozawa, and Sekita, 2000; Kawahara, Nozawa, and Sekita, 2001).

G. achalensis is a small herb distributed in the northwestern and central regions of Argentina. It is locally known as “pasto amargo” (bitter grass). The aerial parts of the plant have been extensively used for digestive and liver problems (Nadinic *et al*, 1999).

G. alborosea (Gilg.) Fabris is a herb which grows in the Peruvian highlands. It has been used since the times of the Incas to relieve stomach pain, regenerate hepatic functions, fight fever produced by malaria, detoxify blood, regulate circulation, and reduce obesity (Kawahara, Nozawa, and Flores, 2000; Acero, Llinares, and Galán, 2006). In addition, the plant is also employed traditionally in acne treatment (Rainer, Bussmann, and Doris, 2008).

G. acuta (Michx.) Hulten, locally known as *Guixincao*, has been used as herb tea with the health properties of clearing heat and toxic materials, removing pathogenic heat from blood, and increasing secretion of urine in the eastern region of Inner Mongolia (China). In addition, the Owenke (one of 56 ethnic minorities in China) use the aerial parts of *G. acuta* for treating heart diseases (Ma, 1993).

G. nevadensis (Gilg.) Weaver et Rudenberg is known as “dictamo real” in Venezuela. A decoction or an alcoholic beverage of the roots and aerial parts of this plant was employed in folk to relieve pain, regulate the circulation, and promote digestion (Báez, Quintero, and Nieves, 1999).

G. azurea (Bunge) Holub is an annual herb distributed in West China. It is used in Tibetan traditional medicine for clearing heat and drying dampness. The frequently clinical application of the plant has been for the treatment of fever and disorders of the gallbladder (Zhang and Yang, 1994).

In addition, *G. bicolor* (Wedd.) J. S. Pringle, *G. crassicaulis* J. S. Pringle, *G. dianthoides* (Kunth) Fabris ex J. S. Pringle, *G. graminea* (Kunth) Fabris, and *G. thyrsoidea* (Hook.) Fabris are used to treat diabetes and hyperlipoidemia in South America (Tomas, Lock, and Jurupe, 1999; José *et al*, 2005; Rainer and Bussmann, 2006). *G. bruneotricha* (Gilg.) J. S. Pringle, known as “anga macha” in Northern Peru, is employed in folk to treat postnatal infection (Rainer and Bussmann, 2006).

Phytochemistry

Iridoids

Iridoids, a group of monoterpene compounds with a cyclopentanopyram ring structure, are the most common and characteristic compounds in the family Gentianaceae. The majority of iridoids found in nature are in the form of glucosides, and the iridoid glucosides in the plants of *Gentianella* Moench are usually seco-iridoids. The distribution and the structures of iridoids in the plants of *Gentianella* Moench are shown in Table 1 and Fig. 1.

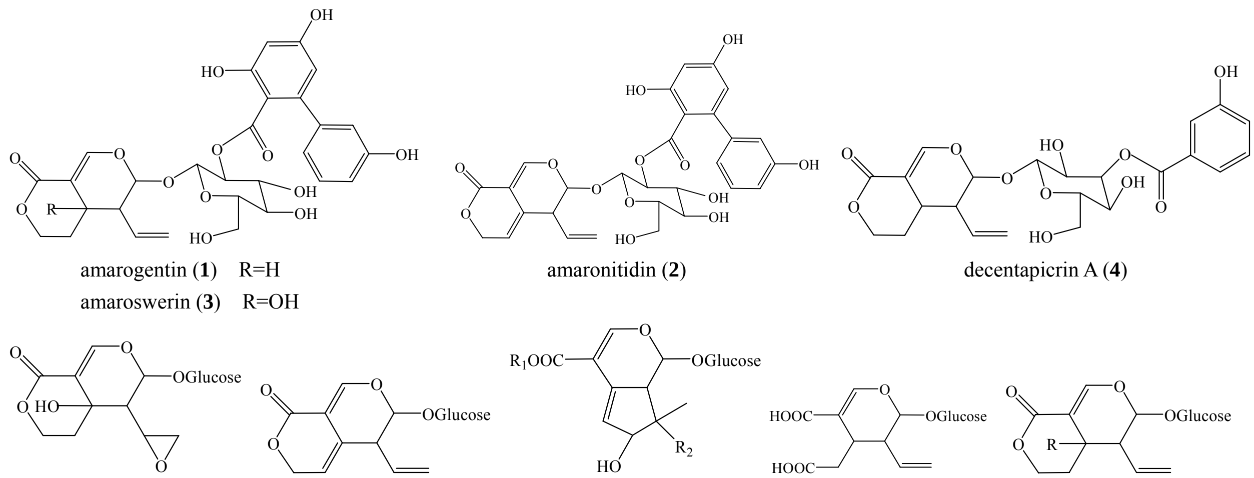
Xanthones

Xanthones are a class of secondary metabolites with a variety of structures in oxidation pattern. Most xanthones are mono- or poly-methyl ethers or are found as glycosides. They have a rather restricted occurrence among higher plants and have been used as chemo-taxonomic markers at infra- and super-genus levels in the family Gentianaceae (Massias, Carbonnier, and Molho, 1982). The known occurrences of xanthones in the plants of *Gentianella* Moench are listed in Table 2. The structures of xanthones in the genus are shown in Fig. 2.

There is an evidence that 1,3,5-trihydroxyxanthone (a) and 1,3,7-trihydroxyxanthone (b) represent the primitive

Table 1 Iridoids in plants of *Gentianella* Moench

Compounds	Species	References
amarogentin (**1**)	*G. alborosea*	Singh, 2008
	G. multicaulis (Gillies ex Griseb.) Fabris	Rosella *et al*, 2007
	G. nitida	Lacaille-Dubois and Galle, 1996
amaronitidin (**2**)	*G. nitida*	Kawahara N, Nozawa M, and Sekita, 2001
amaroswerin (**3**)	*G. nitida*	Lacaille-Dubois and Galle, 1996
		Kawahara N, Nozawa M, and Sekita, 2001
decentapicrin A (**4**)	*G. nitida*	Kawahara N, Nozawa M, and Sekita, 2001
eustomoside (**5**)	*G. bulgarica* (Velen.) Holub	Do *et al*, 1987
gentiopicroside (**6**)	*G. acuta*	Lv and Li, 2009
	G. amarelle ssp. *acuta*	Urbain *et al*, 2009
	G. azurea	Zhang and Yang, 1994
	G. bulgarica	Do *et al*, 1987
	G. campestris (L.) Boerner	Urbain *et al*, 2009
	G. multicaulis	Rosella *et al*, 2007
	G. ramosa (Hegetschw.) Holub	Urbain *et al*, 2009
gentioside (**7**)	*G. bulgarica*	Do *et al*, 1987
loganic acid (**8**)	*G. azurea*	Zhang and Yang, 1994
secologanoside (**9**)	*G. nitida*	Lacaille-Dubois and Galle, 1996
sweroside (**10**)	*G. bulgarica*	Do *et al*, 1987
	G. multicaulis	Rosella *et al*, 2007
	G. parviflora (Griseb.) T. N. Ho.	Rosella *et al*, 2007
swertiamarin (**11**)	*G. acuta*	Lv and Li, 2009
	G. azurea	Zhang and Yang,1994
	G. bulgarica	Do *et al*, 1987
	G. parviflora	Rosella *et al*, 2007



amarogentin (**1**) R=H
amaroswerin (**3**) R=OH
amaronitidin (**2**)
decentapicrin A (**4**)
eustomoside (**5**)
gentiopicroside (**6**)
gentioside (**7**) R_1=OCH_3, R_2=OH
loganic acid (**8**) R_1=H, R_2=H
secologanoside (**9**)
sweroside (**10**) R=H
swertiamarin (**11**) R=OH;

Fig. 1 Structures of iridoids in plants of *Gentianella* Moench

state in the two different biosynthetic pathways (Jensen and Schripsema, 2002). The 1,3,5,8- and 1,3,7,8-tetra-substituted xanthones are formed by an oxidation at position 8 of either the basic structures a or b (Jensen and Schripsema, 2002; Lv and Li, 2009). According to the data in the Table 2 and Fig. 2, the predominant oxidation pattern of the xanthones found in the plants of *Gentianella* Moench so far is 1,3,5,8-, and to a lesser extent, 1,3,7,8-substitution.

C-glucoflavonoids

C-glucoflavonoids, in which the sugar is attached to the flavonoid nucleus by a carbon-carbon bond, have limited distribution in the family Gentianaceae in comparison with iridoids and other xanthones (Jensen and Schripsema, 2002; Janković, Krstić, and Ivan, 2005), but are found commonly available in the plants of *Gentianella* Moench (Table 3 and Fig. 3).

Others

About eight other compounds, including two pentacyclic triterpenes (oleanolic acid **43** and ursolic acid **44**) (Zhang and Yang, 1994; Nadinic *et al*, 1997; 1999; Tomas, Lock, and Jurupe, 1999; Lv and Li, 2009), two

Table 2 Xanthones in plants of *Gentianella* Moench

Compounds	Species	References
1-hydroxy-3,5,8-trimethoxyxanthone (**12**)	*G. thyrsoidea*	Tomas, Lock, and Jurupe, 1999
1-hydroxy-3,6,7,8-tetramethoxy-xanthone (**13**)	*G. thyrsoidea*	Tomas, Lock, and Jurupe, 1999
1,5,8-trihydroxy-3,4-dimethoxy-xanthone (**14**)	*G. parviflora*	Rosella *et al*, 2007
1,7,8-trihydroxy-3,4-dimethoxy-xanthone (**15**)	*G. parviflora*	Rosella *et al*, 2007
3-methylcorymbiferin (**16**)	*G. antarctica* (Kirk) T.N.Ho et S.W.Liu	Benn *et al*, 2009
	G. cerina (Hook.f.) T.N.Ho et S.W.Liu	Benn *et al*, 2009
	G. corymbifera (Kirk) Holub	Benn *et al*, 2009
	G. patula (Kirk) Holub	Benn *et al*, 2009
bellidifolin (**17**)	*G. achalensis*	Nadinic, Penna, and Saavedra, 2002
	G. acuta	Lv and Li, 2009
	G. albanica (Javorka) Holub	Janković, Krstić, and Ivana, 2005
	G. amarelle ssp. *acuta*	Urbain *et al*, 2009
	G. antarctica	Benn *et al*, 2009
	G. azurea	Zhang and Yang, 1994
	G. bellidifolia (Hook.f.) Holub	Benn *et al*, 2009
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Urbain *et al*, 2009
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. florida	Nadinic *et al*,1997
	G. multicaulis	Rosella *et al*, 2007
	G. nevadensis	Báez, Quintero, and Nieves, 1999
	G. patula	Benn *et al*, 2009
	G. parviflora	María *et al*, 2007
	G. ramosa	Urbain *et al*, 2009
	G. serotina (Cockayne) T.N.Ho et S. W. Liu	Massias, Carbonnier, and Molho, 1982
	G. thyrsoidea	Tomas, Lock, and Jurupe, 1999
corymbiferin (**18**)	*G. antarctica*	Benn *et al*, 2009
	G. albanica	Janković, Krstić, and Ivana, 2005
	G. bellidifolia	Benn *et al*, 2009
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. patula	Benn *et al*, 2009
corymbiferin-1-*O*-glucoside (**19**)	*G. albanica*	Janković, Krstić, and Ivana, 2005
	G. amarelle ssp. *acuta*	Urbain *et al*, 2009
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Urbain *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. ramosa	Urbain *et al*, 2009
corymbiferin-3-*O*-glucoside (**20**)	*G. amarelle* ssp. *acuta*	Urbain *et al*, 2009
	G. campestris	Urbain *et al*, 2009
	G. ramosa	Urbain *et al*, 2009
demethylbellidifolin (**21**)	*G. acuta*	Lv and Li, 2009
	G. albanica	Janković, Krstić, and Ivana, 2005
	G. amarelle ssp. *acuta*	Urbain *et al*, 2009
	G. antarctica	Benn *et al*, 2009
	G. azurea	Zhang and Yang, 1994
	G. bellidifolia	Carbonnier *et al*, 1977; Benn *et al*, 2009
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Carbonnier, Massias, and Molho, 1977; Urbain *et al*, 2009
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. florida	Nadinic *et al*, 1997
	G. germanica (Willd.) Börner	Carbonnier, Massias, and Molho, 1977
	G. multicaulis	Hostettmann and Jacot, 1978
	G. nitida	Rosella *et al*, 2007
	G. nevadensis	Lacaille-Dubois and Galle, 1996
	G. ramosa	Báez, Quintero, and Nieves, 1999
	G. tenella (Rottb.) Börner	Carbonnier, Massias, and Molho, 1977; Urbain *et al*, 2009
	G. parviflora	Carbonnier, Massias, and Molho, 1977
	G. patula	Rosella *et al*, 2007
		Benn *et al*, 2009

To be continued

Continued Table 1

Compounds	Species	References
demethylswertipunicoside (**22**)	*G. antarctica*	Benn *et al*, 2009
	G. bellidifolia	Benn *et al*, 2009
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. patula	Benn *et al*, 2009
gentisein (**23**)	*G. stenocalyx* Harry Sm.	Massias, Carbonnier, and Molho, 1982
isobellidifolin (**24**)	*G. achalensis*	Nadinic, Penna, and Saavedra, 2002
	G. antarctica	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. bellidifolia	Benn *et al*, 2009
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. florida	Nadinic *et al*, 1997
	G. multicaulis	Rosella *et al*, 2007
	G. patula	Benn *et al*, 2009
	G. parviflora	Rosella *et al*, 2007
	G. serotina	Massias, Carbonnier, and Molho, 1982
lanceoside (**25**)	*G. albanica*	Janković, Krstić, and Ivana, 2005
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. crispata	Janković, Krstić, and Ivana, 2005
mangiferin (**26**)	*G. acuta*	Lv and Li, 2009
	G. antarctica	Benn *et al*, 2009
	G. bellidifolia	Benn *et al*, 2009
	G. campestris	Massias, Carbonnier, and Molho, 1982
	G. caucasica	Jensen and Schripsema, 2002
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. germanica	Hostettmann-Kalda and Jacot, 1978
	G. multicaulis	Rosella *et al*, 2007
	G. nitida	Lacaille-Dubois and Galle,1996
	G. patula	Benn *et al*, 2009
	G. parviflora	Rosella *et al*, 2007
	G. ramosa	Hostettmann-Kalda and Jacot, 1978
	G. serotina	Massias, Carbonnier, and Molho, 1982
	G. stenocalyx	Massias, Carbonnier, and Molho, 1982
	G. thyrsoidea	Tomas, Lock, and Jurupe, 1999
norswertianine (**27**)	*G. nitida*	Lacaille-Dubois and Galle, 1996
norswertianine 1-*O*-glucoside (**28**)	*G. nitida*	Lacaille-Dubois and Galle, 1996
norswertianolin (**29**)	*G. albanica*	Janković, Krstić, and Ivana, 2005
	G. amarelle ssp. *acuta*	Urbain *et al*,2009
	G. austriaca	Janković, Krstić, and Ivana, 2005
	G. bellidifolia	Benn *et al*, 2009
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Benn *et al*, 2009
	G. campestris	Urbain *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. germanica	Benn *et al*, 2009
	G. multicaulis	Rosella *et al*, 2007
	G. nitida	Lacaille-Dubois and Galle, 1996
	G. parviflora	Rosella *et al*, 2007
	G. ramosa	Urbain *et al*, 2009
	G. thyrsoidea	Tomas, Lock, and Jurupe, 1999
swerchirin (**30**)	*G. antarctica*	Benn *et al*, 2009
	G. azurea	Zhang and Yang, 1994
	G. bellidifolia	Benn *et al*, 2009
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. florida	Nadinic *et al*, 1997
	G. multicaulis	Rosella *et al*, 2007
	G. patula	Benn *et al*, 2009
	G. parviflora	Rosella *et al*, 2007
	G. thyrsoidea	Tomas, Lock, and Jurupe, 1999
swertiabisxanthone-I (**31**)	*G. amarelle* ssp. *acuta*	Urbain *et al*, 2009
	G. campestris	Urbain *et al*, 2009
	G. ramosa	Urbain *et al*, 2009
swertiabisxanthone-I 8'-*O*-glucoside (**32**)	*G. amarelle* ssp. *acuta*	Urbain *et al*, 2009
	G. campestris	Urbain *et al*, 2009
	G. ramosa	Urbain *et al*, 2009
swertianine (**33**)	*G. nitida*	Lacaille-Dubois and Galle, 1996
swertianine 1-*O*-primeveroside (**34**)	*G. nitida*	Lacaille-Dubois and Galle, 1996

To be continued

Continued Table 1

compounds	Species	References
swertianine 8-*O*-glucoside (**35**)	*G. nitida*	Lacaille-Dubois and Galle, 1996
swertianolin (**36**)	*G. acuta*	Lv and Li, 2009
	G. albanica	Janković, Krstić, and Ivana, 2005
	G. amarelle ssp. *acuta*	Urbain *et al*, 2009
	G. azurea	Zhang and Yang, 1994
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Urbain *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. multicaulis	Rosella *et al*, 2007
	G. parviflora	Rosella *et al*, 2007
	G. ramosa	Urbain *et al*, 2009
swertipunicoside (**37**)	*G. antarctica*	Benn *et al*, 2009
	G. bellidifolia	Benn *et al*, 2009
	G. cerina	Benn *et al*, 2009
	G. corymbifera	Benn *et al*, 2009
	G. patula	Benn *et al*, 2009
triptexanthoside C (**38**)	*G. amarelle* ssp. *acuta*	Urbain *et al*, 2009
	G. campestris	Urbain *et al*, 2009
	G. ramosa	Urbain *et al*, 2009
veratriloside (**39**)	*G. albanica*	Janković, Krstić, and Ivana, 2005
	G. amarelle ssp. *acuta*	Urbain *et al*, 2009
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Urbain *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. ramosa	Urbain *et al*, 2009

sesterterpenoids (nitidasin **45** and alborosin **46**) (Kawahara *et al*, 1997; Kawahara, Nozawa, and Flores, 2000), a flavonoid (luteolin **47**) (Lv and Li, 2009), a lignan glycoside (oivil 4'-*O*-glucose **48**), a sterol (daucosterol **49**), and a fatty alcohol (1-triacontanol **50**) (Zhang and Yang, 1994) were also isolated from the genus (Fig. 3).

Biological activities

Anti-oxidative and radioprotective properties

Some species of *Gentianella* Moench were reported to possess strong anti-oxidant properties, for example, *G. alborosea* and *G. nitida* extracts showed a noticeable radical scavenging activity by using DPPH assay (Rosario *et al*, 2004; Acero Llinares, and Galán, 2006). *G. austriaca* can significantly reduce lipid peroxidation (Leskovac *et al*, 2004), and the xanthones and flavone *C*-glucosides existed in *G. austriaca* may contribute to the anti-oxidative properties of the plant (Janković, Savikin, and Menkovic, 2008).

The species of *Gentianella* Moench also possessed radio- protective properties (Leskovac *et al*, 2004). In a recent study, the radioprotective effects of the different fractions of *G. austriaca* as well as the pure isolated compounds (demethylbellidifolin, demethylbellidifolin 8-*O*-glucoside, bellidifolin 8-*O*-glucoside, and swertisin) were investigated in irradiated human lymphocytes *in vitro*. The results suggested that the ethyl ether and methanol fractions of *G. austriaca* showed significant protection in treatment of human lymphocytes after gamma-irradiation than the isolated compounds (Janković, Savikin, and Menkovic, 2008).

Antimicrobial activity

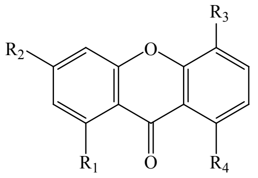
The crude ethanolic extract of *G. nitida* possessed mainly antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes* and *Microsporum gypseum* (Rosario *et al*, 2004). Some studies reported that *G. achalensis* and *G. nevadensis* showed anti-bacterial activity against *Bacillus subtilis* (Báez, Quintero, and Nieves, 1999; Nadinic, Penna, and Saavedra, 2002). In addition, *G. alborosea* was reported to show strong inhibition of *Staphylococcus aureus* which might explain their efficacy in traditional acne treatment (Rainer, Bussmann, and Doris, 2008).

Anti-inflammatory activity

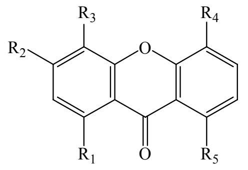
The dichloromethane extracts of *G. achalensis* showed marked anti-inflammatory activity in TPA-induced ear edema test (Nadinic *et al*, 1999).

Hypoglycemic activity

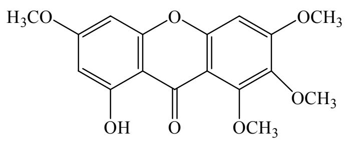
The crude extracts of *G. nitida* and *G. tristicha* (Gilg) Fabris ex T. N. Ho & S. W. Liu were reported to significantly lower the loaded glucose level in normal as well as alloxan-induced diabetic rats (Ninosca *et al*, 2001). The dichloromethane, methanol, and aqueous extracts of *G. thyrsoidea* also showed hypoglycemic and



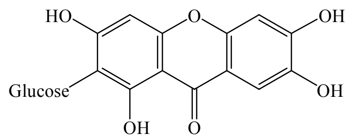
1-hydroxy-3,5,8-trimethoxyxanthone (**12**) R_1=OH, R_2, R_3, R_4=OCH_3
bellidifolin (**17**) R_1, R_3, R_4=OH, R_2=OCH_3
demethylbellidifolin (**21**) R_1, R_2, R_3, R_4=OH
isobellidifolin (**24**) R_1, R_2, R_4=OH, R_3=OCH_3
norswertianolin (**29**) R_1, R_2, R_3=OH, R_4=*O*-glucose
swerchirin (**30**) R_1, R_4=OH, R_2, R_3=OCH_3
swertianolin (**36**) R_1, R_3=OH, R_2=OCH_3, R_4=*O*-glucose



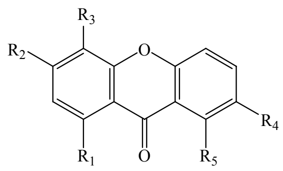
1,5,8-trihydroxy-3,4-dimethoxy-xanthone (**14**) R_1, R_4, R_5=OH, R_2, R_3 =OCH_3
3-methylcorymbiferin (**16**) R_1, R_5=OH, R_2, R_3, R_4=OCH_3
corymbiferin (**18**) R_1, R_2, R_5=OH, R_3, R_4 =OCH_3
corymbiferin-1-*O*-glucoside (**19**) R_1=O-Glucose, R_2, R_5=OH, R_3, R_4 =OCH_3
corymbiferin-3-*O*-glucoside (**20**) R_1, R_5=OH, R_2=O-Glucose, R_3, R_4 =OCH_3



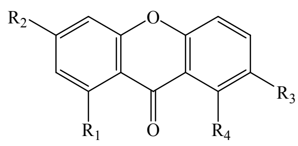
1-hydroxy-3,6,7,8-tetramethoxy-xanthone (**13**)



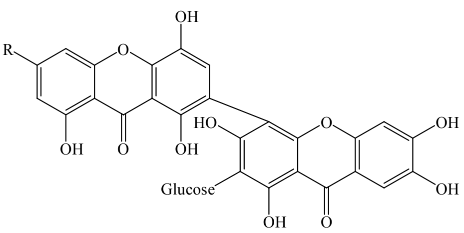
mangiferin (**26**)



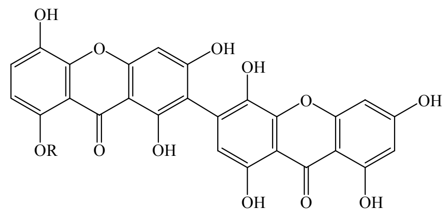
1,7,8-trihydroxy-3,4-dimethoxy-xanthone (**14**)
R_2, R_3=OCH_3, R_1, R_4, R_5=OH
lanceoside (**25**) R_1, R_5=OH, R_2, R_4=OCH_3 R_3=*O*-glucose
triptexanthoside C (**38**) R_1, R_5=OH, R_2, R_3=OCH_3, R_4=*O*-glucose
veratriloside (**39**) R_1=OH, R_2, R_3=OCH_3, R_4=*O*-glucose, R_5=H



gentisein (**23**) R_1, R_2, R_3=OH, R_4=H
norswertianine (**27**) R_1, R_2, R_3, R_4=OH
norswertianine 1-*O*-glucoside (**28**) R_1=*O*-Glucose, R_2, R_3, R_4=OH
swerchirin (**30**) R_1, R_3, R_4=OH, R_2 =OCH_3
swertianine 1-*O*-primeveroside (**34**) R_1=*O*-primeverose, R_2=OCH_3, R_3, R_4=OH
swertianine 8-*O*-glucoside (**35**) R_1, R_3=OH, R_2 =OCH_3, R_4=*O*-glucose



demethylswertipunicoside (**22**) R=OH
swertipunicoside (**37**) R=H



swertiabisxanthone-I (**31**) R=H
swertiabisxanthone-I 8'-*O*-glucoside (**32**) R=glucose

Fig. 2 Structures of xanthones in plants of *Gentianella* Moench

and hypocholesterolemic activities in rats (Tomas, Lock, and Jurupe, 1999). Bellidifolin, a common xanthone in plants of *Gentianella* Moench, was reported to be a potent hypoglycemic agent in STZ-induced diabetic rats by both oral and ip administration. This compound also lowered blood triglyceride levels significantly. It stimulated glucose uptake activity in Rat 1 fibroblasts expressing human insulin receptors (José *et al*, 1995). In Japan the extract of *G. alborosea* has been patented in the treatment of diabeties, obesity, and liver disorder, and as health food for improving insulin resistance and decreasing blood sugar (Ogawa, 2006; 2007).

Anticholinergic activity

Swertiamarin and mangiferin, widely distributed in plants of *Gentianella* Moench, have shown anticholinergic properties (Bhattacharya *et al*, 1976; Yamahara *et al*, 1991). In a recent study, triptexanthoside C, isolated from *G. amarella* ssp. *acuta* also showed active against acetylcholinesterase, with an IC_{50} of (13.8 ± 1.6) μmol/L (Urbain *et al*, 2008).

Table 3 *C*-glucoflavonoids in plants of *Gentianella* Moench

Compounds	Species	References
isoorientin (**40**)	*G. acuta*	Lv and Li, 2009
	G. albanica	Janković, Krstić, and Ivana, 2005
	G. azurea	Zhang and Yang, 1994
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. campestris	Janković, Krstić, and Ivana, 2005
	G.corymbifera	Benn *et al*, 2009
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. germanica	Janković, Krstić, and Ivana, 2005
	G.. multicaulis	Rosella *et al*, 2007
	G. nitida	Lacaille-Dubois and Galle,1996
	G.. parviflora	Rosella *et al*, 2007
	G. ramosa	Janković, Krstić, and Ivana, 2005
	G. serotina	Massias, Carbonnier, and Molho, 1982
isovitexin (**41**)	*G.corymbifera*	Benn *et al*, 2009
	G.. multicaulis	Rosella *et al*, 2007
	G.. parviflora	Rosella *et al*, 2007
	G. stenocalyx	Massias, Carbonnier, and Molho, 1982
swertisin (**42**)	*G. albanica*	Janković, Krstić, and Ivana, 2005
	G. austriaca	Janković, Krstić, and Ivana, 2005
	G. bulgarica	Janković, Krstić, and Ivana, 2005
	G. crispata	Janković, Krstić, and Ivana, 2005
	G. campestris	Massias, Carbonnier, and Molho, 1982
	G.corymbifera	Benn *et al*, 2009
	G. germanica	Hostettmann and Jacot, 1978
	G.. multicaulis	Hostettmann and Jacot, 1978
	G. ramosa	Rosella *et al*, 2007
	G. serotina	Massias, Carbonnier, and Molho, 1982
	G. stenocalyx	Massias, Carbonnier, and Molho, 1982
	G. parviflora	Rosella *et al*, 2007

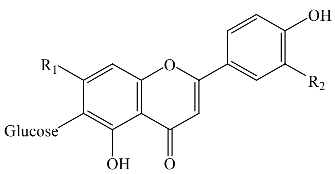
Hepatoprotective activity

Gentiopicroside, which is ubiquitous secoiridoid constituents in plants of *Gentianella* Moench, has shown hepatoprotective activities on the two hepatic injury models (carbon tetrachloride-induced and lipopoly-ccharide-nduced hepatitides) (Kondo *et al*, 1994), and is being used as an antihepatitis drug. Mangiferin and sweroside, two common constituents in plants of *Gentianella* Moench plants, were reported to show hepato-protective activities (Zhou, 1991; Dar *et al*, 2005).

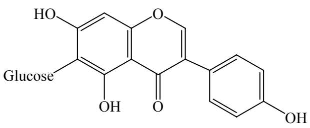
Other activities

Some studies reported bellidifolin and demethyl-bellidifolin isolated from species of *Gentianella* Moench were selective inhibitors of monoamine oxidases A enzymes (Báez, Quintero, and Nieves, 1999; Tovilović *et al*, 2005; Urbain *et al*, 2008), while swertianolin, the 8-*O*-lucopyranoside form of bellidifolin, gave 93.6% inhibition of MAO B activity at 10^{-5} mol/L (Urbain *et al*, 2008).

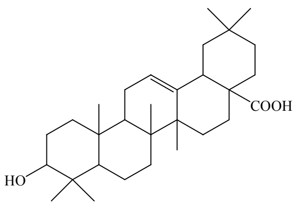
The extract of *G. alborosea* was reported to induce apoptosis on HeLa cells (ATCC and CCL-2), and the effects were dose-dependent (higher tested concen-trations have the higher percentage of apoptotic nuclei) (Acero *et al*, 2006).



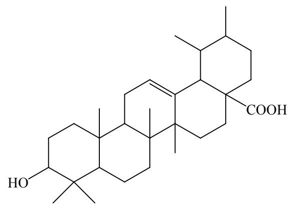
isoorientin (**40**) R_1, R_2=OH
swertisin (**42**) R_1=OCH_3, R_2 =H



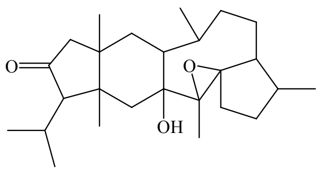
isovitexin (**41**)



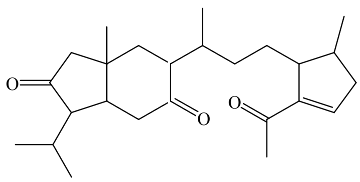
oleanolic acid (**43**)



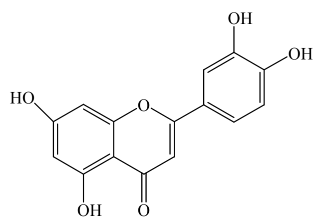
ursolic acid (**44**)



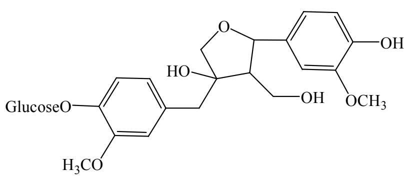
nitidasin (**45**)



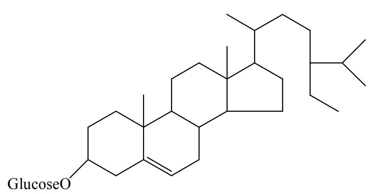
alborosin (**46**)



luteolin (**47**)



oivil 4'-*O*-glucose (**48**)



daucosterol (**49**)

CH_3-$(CH_2)_{28}$-CH_2OH

1-triacontanol (**50**)

Fig. 3 Structures of *C*-glucoflavonoids and other compounds in plants of *Gentianella* Moench

In addition, nitiol, a sesterterpenoid isolated from *G. nitida*, possessed enhancement activity of IL-2 gene expression in Jurkat cells (a human T cell line) (Kawahara *et al*, 1999).

Toxicity

The toxicity of fractions obtained from extracts of *G. nevadensis* was tested using the brine shrimp (*Artemia salina*) assay. For ethyl acetate extract, the lowest values of median lethal concentrations were found in the fractions 4, 5, and 6 (72.97, 216.33, and 746.79 ppm, respectively), while for dichloromethane extract, fractions 2 and 3 showed higher toxicity against *A. salina* (LC_{50} 31.11 and 232.63 ppm, respectively) (Báez, Quintero, and Nieves, 1999).

It was reported that overdosing of *G. dianthoides* could cause miscarriage in pregnant women, and exceeding dosage of *G. graminea* can lead to blindness (Rainer and Bussmann, 2006).

Conclusion

In literature, only a few species among the 250 known from the plants of *Gentianella* Moench have been reported in their chemical investigations and pharmalogical activities. But clearly, members of the plants of *Gentianella* Moench possess significant potentials for their pharmacological activities in the context of ethnomedicinal knowledge, especially in the treatments of heart diseases, diabetes, and hyper-poidemia. Eleven iridoids, 28 xanthones, three *C*-glucoflavonoids, and eight other compounds were isolated from the genus. Most of these compounds are associated with anti- crobial, anti-inflammatory, anti-oxidant, hypoglycemic, and antitumor activities, which provide an empirical base for the traditional utilization in the plants of *Gentinella* Moench. The extracts from many species are also added to many health-related products including diet pills, hair-loss products, homeopathic medicines, body cleansing products, and others. The species of *Gentianella* Moench described in this review do not appear to have sustainable supply issue and might serve as an important source of medicine in the world.

It is important to note that the species of *Gentianella* Moench species have not been fully explored concerning either safety or toxicity aspects. Only a little published data concerned the overdosing and toxicity of some species. Therefore the toxicities of the traditional remedies and isolated chemical compounds should be further assessed.

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