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Phytochemical and chemotaxonomic study on the Lichen *Lethariella cladonioides*

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ABSTRACT

The comprehensive phytochemical research of *Lethariella cladonioides* (Nyl.) Krog, (Parmeliaceae), a lichen in southwest China, resulted in isolation of eighteen compounds (**1**–**18**), including a new phenolic acid 3,5-dihydroxy-4-methylbenzaldehyde (**1**) and seventeen known compounds, nine phenolic acids (**2**–**10**), one dibenzofuran (**11**), two depsides (**12** and **13**), one alkane (**14**), one glucoside (**15**), two polyols (**16** and **17**), and one fatty acid (**18**). The structures of these compounds were assigned by detailed interpretations of spectroscopic data (1D and 2D NMR, HR-ESI-MS) and comparisons with the published data. Among them, 3,5-dihydroxy-4-methylbenzaldehyde (**1**) is a new one. (−)-hydroxypropan-2′,3′-diol-orsellinate (**10**) have not been reported from any species in the lichens. Compounds **6**, **7**, **9**, **12**, **14**, **16** and **18** were firstly isolated from the genus *Lethariella* (Motyka) Krog. Compounds **2**, **6**, **7**, **9**, **10**, **12**, **14**, **16** and **18** were reported from *L. cladonioides* firstly. The chemotaxonomic significance of these compounds was also discussed.

Authors' contributions

Zhang, Lei Zhang: Writing - Original Draft, data Curation, methodology & Revise. Wei-yun Di: Validation & Revise. Yu Hao: investigation. Li-ning Wang: Conceptualization Ideas, Writing - Review & Editing, Funding acquisition, Supervision. Yan-Ru Deng: Supervision. Jing-Jing Wang: Writing - Review & Editing, Resources.

1. Subject and source

Lethariella cladonioides (Nyl.) Krog, belongs to the family Parmeliaceae, a lichen body which usually grows in high mountains and snow mountains with the altitudes of 3000–5000 m above sea level. *L. cladonioides* exists only in East Asia, mainly in China (Niu et al., 2011). It mainly distributes in Shanxi, Qinghai, Tibet, Yunnan and Sichuan provinces, China. As a traditional Chinese medicine, *L. cladonioides* is used to treat epilepsy, malnutrition, schizophrenia, neurasthenia, headache and dizziness as a sedation, anti-inflammatory and analgesic drug (An Editorial Committee of the Administration Bureau of Traditional Chinese Medicine, 2000). The local people drink it as tea and named it Hong-Xue tea (Niu and Yang, 2012).

In the present study, the whole parts of *L. cladonioides* were purchased in August of 2018 from the medicinal herbs market in city of Dali, Yunnan Province, China. The plant material was authenticated by Prof. Li-Juan Zhang (School of Tianjin University of Traditional Chinese Medicine, China). A voucher specimen (No. LC-2018-C412-1) was deposited at the same institution.

2. Previous work

Up to now, extensive chemical studies on *Lethariella* genus have led to the isolation of a variety of secondary metabolites, including phenolic acids, depsides, steroids, glucosides, fatty acids, dibenzofuran and polyols. All of compounds showed in Table 1. Phenolic acids and depsides are widely distributed in the genus *Lethariella* as characteristic constituents (Huang et al., 2007; Niu, 2008). As can be seen from Table 1, previous phytochemical investigations on *L. cladonioides* revealed the presence of ten depsides, four steroids, thirteen phenolic acids, one dibenzofuran, four polyols, two glucosides, three fatty acids.

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Table 1
Compounds isolated from the genus *Lethariella*.

Compounds	I		II	III	IV	V	Type	Reference
	Exp.	Ref.	Ref.	Ref.	Ref.	Ref.		
3,5-Dihydroxy-4-methylbenzaldehyde (**1**)	✓						Phenolic acid	Marante et al., 2003 Chang et al., 2013
Ethyl haematommate (**2**)	✓	✓			✓		Phenolic acid	Tuan et al., 2020 Gao and zhang, 2004 Toledo Marante et al., 2003
Methyl-*β*-orcinolcarboxylate (3)	✓	✓	✓		✓		Phenolic acid	Sun et al., 1990 Yuan et al., 2013 Toledo Marante et al., 2003
Ethyl orsellinate (**4**)	✓		✓				Phenolic acid	Tuan et al., 2020 Yuan et al., 2013
Atranol (**5**)	✓	✓			✓		Phenolic acid	Jiang et al., 2001 Toledo Marante et al., 2003
3,5-Dihydroxybenzyl alcohol (**6**)	✓						Phenolic acid	Niu (2008)
5,7-Dihydroxy-1(3H)-isobenzofuranone (**7**)	✓						Phenolic acid	Zheng et al., 2015
Orcinol (**8**)	✓	✓					Phenolic acid	Tuan et al., 2020 Akihiro and Susumu (2005)
Orsellinic acid (**9**)	✓						Phenolic acid	Kumar et al., 2019
(−)-Hydroxypropan-2′,3′-diol-orsellinate (**10**)	✓						Phenolic acid	Talontsi et al., 2012
Haematommie acid		✓			✓		Phenolic acid	Sun et al., 1990 Toledo Marante et al., 2003
Methyl orsellinate		✓	✓				Phenolic acid	Gao and zhang, 2004 Yuan et al., 2013
Salicylic acid		✓					Phenolic acid	Luo and Pei (2005)
Rhizonic acid		✓					Phenolic acid	Luo and Pei (2005)
2-Hydroxy-4-methoxy-3,6-dimethylbenzoic acid		✓					Phenolic acid	Luo and Pei (2005)
Methyl haematommate		✓	✓				Phenolic acid	Li et al., 2017 Yuan et al., 2013
2,4-Dihydroxy-3,6-dimethylbenzoic acid		✓					Phenolic acid	Akihiro and Susumu (2005)
3-Formyl-2,6-dihydroxy-4-methyl-ethyl ester		✓					Phenolic acid	Akihiro and Susumu (2005)
Canarione		✓	✓		✓	✓	Phenolic acid	Niu (2008) Toledo Marante et al., 2003 Takahashi et al., 2011
Sernanderin				✓			Phenolic acid	Kinoshita et al., 2004
Methyl chlorohaematommate					✓		Phenolic acid	Toledo Marante et al., 2003
Ethyl chlorohaematommate					✓		Phenolic acid	Toledo Marante et al., 2003
Chlorohaematommie acid					✓		Phenolic acid	Toledo Marante et al., 2003
Chloroatranol					✓		Phenolic acid	Toledo Marante et al., 2003
7-Chlorocanarione						✓	Phenolic acid	Takahashi et al., 2011
Rubrocashmeriquinone						✓	Phenolic acid	Takahashi et al., 2011
7-Chlororubrocashmeriquinone						✓	Phenolic acid	Takahashi et al., 2011
Rubrosinensiquinones A						✓	Phenolic acid	Takahashi et al., 2011
Rubrosinensiquinones B						✓	Phenolic acid	Takahashi et al., 2011
Rubrosinensiquinones C						✓	Phenolic acid	Takahashi et al., 2011
Usnic acid (**11**)	✓	✓			✓		Dibenzofuran	Nguyen et al., 2020 Jiang et al., 2001 Toledo Marante et al., 2003

(*continued on next page*)

Table 1 (*continued*)

Compounds	I		II	III	IV	V	Type	Reference
	Exp.	Ref.	Ref.	Ref.	Ref.	Ref.		
(−) Placodiolic acid			✓				Dibenzofuran	Sun et al., 1990
Methyl 3′-methyllecanorate (**12**)	✓						Depside	Vu et al., 2017
Atranorin (**13**)	✓	✓	✓		✓		Depside	Kumar et al., 2019 Zhang and Hu, 1981 Niu (2008) Toledo Marante et al., 2003
Baeomycesis acid		✓					Depside	Li et al., 2017
Vermicularin		✓	✓				Depside	Luo and Pei (2005) Yuan et al., 2013
Cladonioidesin		✓					Depside	Jiang et al., 2001
Lethaclado acid B		✓					Depside	Huang et al., 2007
Psoromic acid		✓	✓				Depside	Akihiro and Susumu (2005) Niu (2008)
Norstictic acid		✓					Depside	Zhang and Hu, 1981
8′-*O*-Ethylnorstictic acid		✓					Depside	Sun et al., 1990
Virensic acid		✓					Depside	Jiang et al., 2001
Lethaclado acid A		✓					Depside	Huang et al., 2007
Lecanoric acid			✓				Depside	Niu (2008)
Gyrophoric acid			✓				Depside	Niu (2008)
Chloroatranorin					✓		Depside	Toledo Marante et al., 2003
Ergosterol peroxide		✓					Steroid	Jiang et al., 2001
β-Sitosterol		✓					Steroid	Jiang et al., 2001
5,8-Epidioxy-5*α*,8*α*-ergosta-6,22-dien-3*β*-ol		✓					Steroid	Li et al., 2017
4-Sitost-4-en-3-one		✓					Steroid	Li et al., 2017
Stigmasterol			✓				Steroid	Niu (2008)
nonacosane (**14**)	✓						Alkane	Nyemb et al., 2018
Uridine (**15**)	✓	✓					Glucoside	Luo and Pei,2005
Daucosterol		✓					Glucoside	Luo and Pei (2005)
bis(2-hydorxyethyl)ether (**16**)	✓						Polyol	Zheng et al., 2004
Arabitol (**17**)	✓	✓					Polyol	Miyazawa et al., 2012 Luo and Pei (2005)
8*α*,11-Elemodiol		✓					Polyol	Li et al., 2017
Mannitol		✓					Polyol	Luo and Pei (2005)
Glucose		✓					Polyol	Luo and Pei (2005)
9-Octadecenoic acid (**18**)	✓						Fatty acid	Wang (2020)
Succinic acid		✓			An Editorial Committee of the Administration Bureau of Traditional Chinese Medicine, 2000		Fatty acid	Luo and Pei (2005)
Octadecanoic acid		✓					Fatty acid	Jiang et al., 2001
Methyl linolelaidate		✓					Fatty acid	Niu (2008)
8-Hexadecenoic		✓	✓				Fatty acid	Niu (2008)

Note: Exp.: Isolated compounds in our experiment, Ref.: reference compounds,I: *L. cladonioides*, II: Lethariella zahlbruckneri (Dr.) Kro, III: *Lethariella sernanderi* (Mot.) Obermayer, Ⅳ: *Lethariella canariensis* (Ach.) Krog, V: *Lethariella sinensis* Wei and Jiang.

3. Present study

3.1. *Extraction and isolation*

The air-dried whole parts of *L. cladonioides* (5.0 kg) were cut and exhaustively extracted with 95% EtOH (30 L × 3) and then with 75% EtOH (30L × 3) under ultrasonication at room temperature. The concentrated extract (920.0 g) was suspended in H_2O and then partitioned with petroleum ether (PE) and dichloromethane (DCM), respectively.

The PE layer was evaporated under reduced pressure to dryness and the resultant residue (23.6 g) was eluted with a gradient of PE-Ethyl Acetate (EtOAc) (1:100–100:1, v/v) on silica gel column chromatography (CC), twenty-one pooled fractions (Fr. p1-Fr. p21) were obtained according to TLC. Fr. p2 (3.0 g) was subjected to silica gel CC using isocratic solvent system of PE-Acetone (100:1, v/v) to yield compounds **2** (1630.7 mg), **3** (623.0 mg) and **4** (317.2 mg). Fr. p3 (304.3 mg) was subjected to a silica gel CC eluting with PE-DCM at (from 10:1 to 9:1, v/v) to give five pooled fractions (Fr. p31-Fr. p35). Fr. p33 (120.3 mg) was purified on Sephadex LH-20 gel CC by elution with MeOH-DCM (1:1, v/v) to yield compound **18** (11.3 mg). Fr. p9 (369.8 mg) was decolorized on Sephadex LH-20 gel eluted with MeOH-DCM (1:1, v/v), then purified on silica gel CC eluted with PE-EtOAc (10:1, v/v) and Sephadex LH-20 gel eluted with MeOH-DCM (1:1, v/v) to obtain compound **5** (220.3 mg).

The DCM fraction (66.8 g) was loaded into silica gel CC eluting with DCM-EtOAc (from 100:1 to 10:1, v/v) to obtain nine fractions (Fr. d1-Fr. d9). Fr. d3 (120.3 mg) was purified by recrystallization with DCM-EtOAc (5:1, v/v) to yield compound **13** (43.1 mg). Fr. d9 (731.5 mg) was isolated to silica gel CC eluting with MeOH-DCM (from 100:0 to 0:100, v/v) and purified by Sephadex LH-20, ODS CC and semi-preparative HPLC to afford three compounds, including **1** (11.2 mg), **11** (5.1 mg) and **12** (7.1 mg).

The water fraction (213.0 g) was eluted with AB-8 macroporous resin CC with gradient H_2O/EtOH (from 100:0 to 0:100, v/v) to get four fractions (Fr. w1-w4). Fr. w2 (56.6 g) was isolated to silica gel CC eluting with MeOH-DCM (from 100:0 to 0:100, v/v) and purified by Sephadex LH-20, ODS CC and semipreparative HPLC to afford compounds **6** (5.7 mg), **7** (11.3 mg), **8** (3709.2 mg), **9** (1.6 mg), **10** (2.1 mg), **14** (1.2 mg), **15** (8.3 mg), **16** (68.2 mg) and **17** (2207.5 mg).

Compound **1**: Colourless needle crystals. HR-ESI-MS (positive) *m/z*

Fig. 1. The structure of compound **1**.

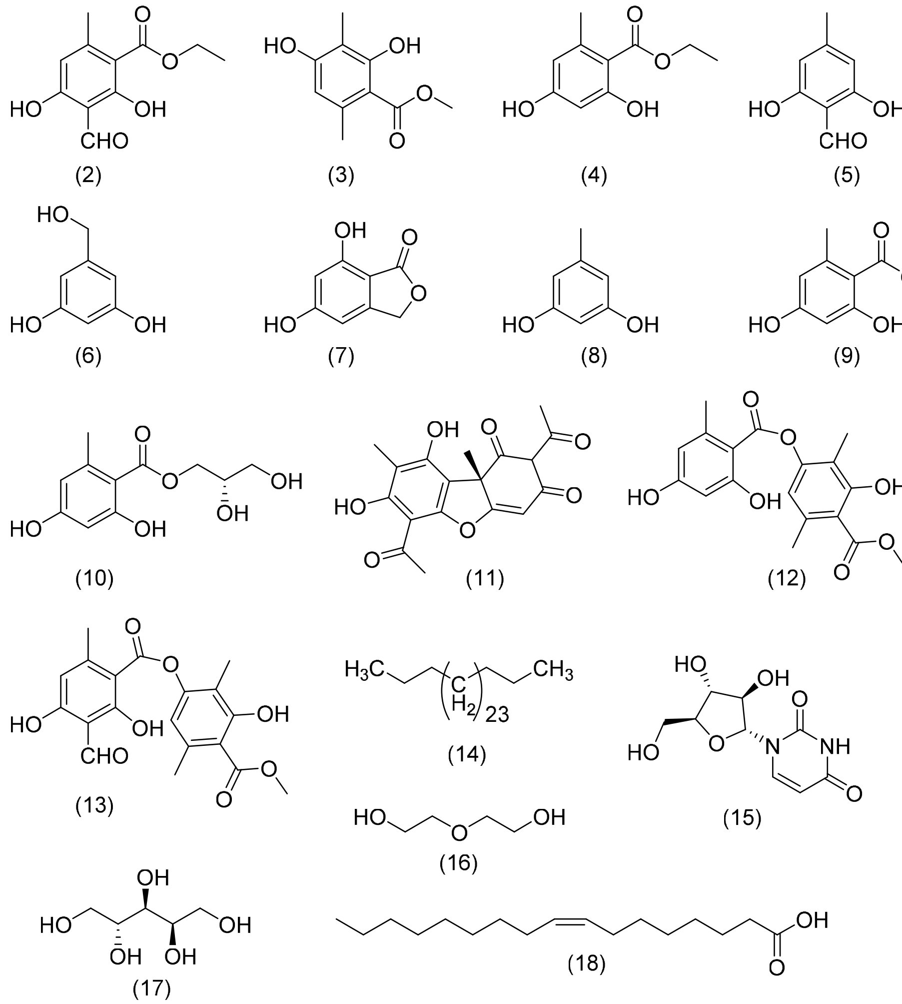

Fig. 2. Structures of compounds **2**–**18**.

153.0580 $[M+H]^+$ (calcd. for $C_8H_8O_4$, 153.0552). UV (CH_3OH) λ_{max} (log ε) 205 (4.02), 226 (3.82), 281 (3.88) nm; IR ν_{max} (film) 3393, 3259, 3014, 2926, 2658, 2360, 2116, 1648, 1436, 1353, 1287, 1205, 1142, 1080, 1017, 951, 809, 765, 706 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δH : 2.27 (3H, s, H-7) , 6.22 (2H, s, H-2, H-6) , 10.28 (1H, s, –CHO)。13C-NMR (CD3OD, 125 MHz) δC : 23.5 (C-7) , 108.3 (C-2, C-6) , 150.8 (C-3, C-5) , 193.3 (-CHO)。

3.2. Structure elucidation of compounds

The molecular formula of the new compound **1** was determined to be $C_8H_8O_4$ with 5 degrees of unsaturation based on HR-ESI-MS (positive) *m/z* 153.0580 $[M+H]^+$ (calcd. for $C_8H_8O_4$, 153.0552) and NMR data (See above). The ^{1}H-NMR spectrum also showed corresponding proton signals including a methyl hydrogen signal at δ_H 2.27 (3H, s, H-7), an aromatic hydrogen signal at δ_H 6.22 (2H, s, H-2, H-6) suggests the presence of a symmetrical benzene ring, and an active hydrogen signal at δ_H 10.28 (1H, s, H-8), which empirically suggests the presence of an aldehyde hydrogen in the structure. The ^{13}C-NMR spectra displayed 4 carbon signals including a methyl carbon signal at δ_C 22.5 (C-7), two aromatic carbon signals at δ_C 108.3 (C-2, C-6) and δ_C 150.8 (C-3, C-5), and a carbonyl carbon signal at δ_C 193.3 (C-8). Comparison of the HR-

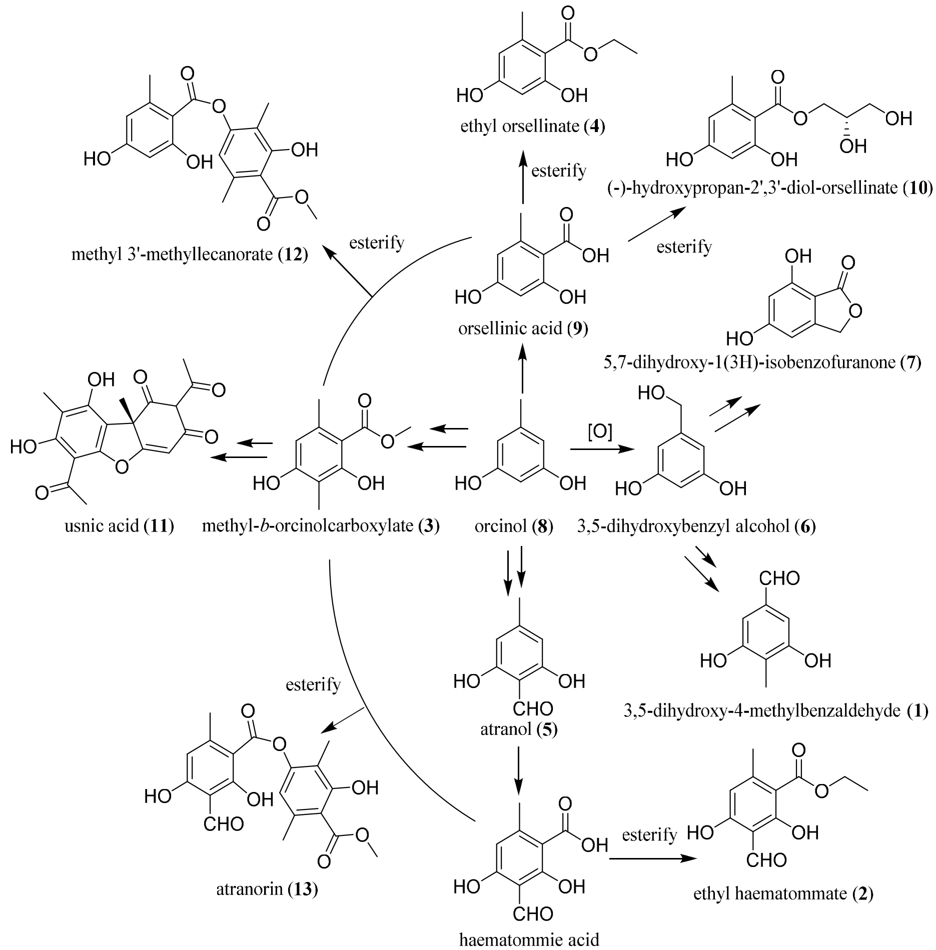

Fig. 3. Plausible biosynthetic pathways for compounds **1**–**13**.

ESI-MS (positive) results with the ^{13}C-NMR spectrum indicates the presence of carbon signals not detected in compound **1**. The inferences were also confirmed by 2D NMR data (Fig. 1). Compound **1** was confirmed by the correlations of HMBC from H-7 to C-2, 6 and C-3, 5, the correlations from H-2, 6 to C-7 and C-2, 6, and the correlations from H-8 to C-2, 6. Based on the above presumed structural information and the literature (Marante et al., 2003; Chang et al., 2013), the structure is presumed to be 3,5-dihydroxy-4-methylbenzaldehyde. It is worth mentioning that the structure of compound **1** was a phenolic acid and closely similar to the structure of compound **4**, but compound **1** is much less polar than compound **4**.

In addition, the seventeen known compounds can be identified as ethyl haematommate (**2**) (Tuan et al., 2020), methyl--β-orcinolcarboxylate (**3**) (Toledo Marante et al., 2003), ethyl orsellinate (**4**) (Tuan et al., 2020), atranol (**5**) (Toledo Marante et al., 2003), 3, 5-dihydroxybenzyl alcohol (**6**) (Niu, 2008), 5,7-dihydroxy-1(3H)-isobenzofuranone (**7**) (Zheng et al., 2015), orcinol (**8**) (Tuan et al., 2020), orsellinic acid (**9**) (Kumar et al., 2019), (−)-hydroxypropan-2′, 3′-diol-orsellinate (**10**) (Talontsi et al., 2012), usnic acid (**11**) (Nguyen et al., 2020), methyl 3′-methyllecanorate (**12**) (Vu et al., 2017), atranorin (**13**) (Kumar et al., 2019), nonacosane (**14**) (Nyemb et al., 2018), uridine (**15**) (Li et al., 2019), bis(2-hydorxyethyl)ether (**16**) (Zheng et al., 2004), arabinitol (**17**) (Miyazawa et al., 2012) and 9-octadecenoic acid (**18**) (Wang, 2020) (Fig. 2).

4. Chemotaxonomic significance

In this investigation, eighteen compounds have been isolated from the air-dried plant *L. cladonioides*, including ten phenolic acids (**1**–**10**), one dibenzofuran (**11**), two depsides (**12**–**13**), one alkane (**14**), one glucoside (**15**), two polyos (**16**–**17**) and one fatty acid (**18**). Notably, compound **1** is new and compound **10** were first reported from lichens. Compounds **6**–**7**, **9**, **12**, **14**, **16** and **18** were first reported from the genus *Lethariella*, and nine compounds (**4**, **6**, **7**, **9**, **10**, **12**, **14**, **16** and **18**) were first reported from *L. cladonioides*.

Phenolic acids and depsides appear to be typical secondary metabolites of the genus *Lethariella*. Previously chemical investigation on the genus *Lethariella* led to the isolation of plenty of phenolic acids and depsides (see Table 1). In present study, **10** was first isolated from lichens, of which **10** was only isolated from an endophytic fungus *Cryptosporiopsis* sp. of Zanthoxylum leprieurii (Guill. et Perr.) Engl (Talontsi et al., 2012). The isolation of compound **10** provided the new chemical information for the lichen chemotaxonomic classification.

As one of the main compounds, **4** was first isolated from *L. cladonioides* and previously from *L. zahlbruckneri* (Yuan et al., 2013). Compound **6** was first isolated from the genus *Lethariella* and previously from the Lichen *Lobaria kurokawae* Yoshim. (Niu, 2008). Compound **7** was previously present in higher plants, such as *Lasiosphaera fenzlii* Reich. (Gao et al., 2010), *Polygonum cuspidatum* (Hu Zhang and Mexican Bamboo) (Shen et al., 2013), *Gnaphalium adnatum* (Wall. ex DC.) Kitam (Zheng et al., 2014). and *Reynoutria japonica* Houtt. (Khalil et al., 2019). However, in 2021 it was isolated from lichen *Parmotrema cristiferum*

(Tayl.) Hale (Pham et al., 2021). Within the *Lathariella*, the phenolic acid 8, has only been reported as a main compound in *L. cladonioides* to date (Laxinamu et al., 2013; Akihiro and Susumu, 2005). Compound 8 might be a useful chemotaxonomic marker for L. *cladonioides*. Compound 9 was also first isolated from the genus *Lethariella*, while its methyl ester and ethyl esters were isolated from other species of *Lethariella* (Yuan et al., 2013). Phenolic acids **4**, **6** and **9** could confirm the chemotaxonomic relationship between *L. cladonioides* and other *Lethariella* species. In addition, phenolic acids **2**–**3** and **5** were three other high-abundance compounds in *L. cladonioides*. Phenolic acid **2** was previously isolated from the *L. canariensis* (Toledo Marante et al., 2003), **3** from *L. zahlbruckneri* (Yuan et al., 2013) and *L. canariensis* (Toledo Marante et al., 2003) and **5** from the lichens *Parmotrema tinctorum* (Nyl.) Hale (Tuan et al., 2020), *L. canariensis* (Toledo Marante et al., 2003) and *Stereocaulon evolutum* Graewe (Vu et al., 2015, 2017).

Depsides are the other characteristic secondary metabolites within the genus *Lethariella*. In this paper, two depsides **12** and **13** have been isolated. This is the first report of **12** from the genus *Lethariella*, it could serve as another chemical marker to differentiate *L. cladonioides* from other species of *Lethariella*. It was previously reported from the lichens *Stereocaulon evolutum* (Vu et al., 2015, 2017) and *Evernia Prunastri* (L.) ACH. (Nicollier et al., 1979). Depside **13** has been previously reported from various lichens, such as *Sulcaria virens* (Tayl.) Bystr (Zhou et al., 2007); *Stereocaulon montagneanum* Lamb. (Ismed et al., 2017); *L. zahlbruckneri* (Niu, 2008) and *L. canariensis* (Toledo Marante et al., 2003). In the genus *Lethariella*, depside **13** distributed mainly in the cortex (Niu, 2008). And it was also obtained as a high content compound in *L. cladonioides*.

Usnic acid **11** has a unique dibenzofuran scaffold and has been reported from many species of lichens, was especially abundant in *Alectoria asiatica* DR. (Sun et al., 1986), *Cladonia stellaris* (Opiz.) (Wang and Yang, 2004), *Usnea longissima* Ach. (Feng et al., 2009), *Ramalina conduplicans* Vain (Tang et al., 2015). and *Parmelia nimandairana* A.Z. (Zhang et al., 2013). In species of *Lethariella*, a small amount of usnic acid **11** had been previously isolated from *L. cladonioides* and *L. canariensis* (Toledo Marante et al., 2003).

Further, compounds **14**–**18** occur as minor chemical constituents of the genus *Lethariella*. This is the first report of **14**, **16** and **18** from *L. cladonioides*.

To summarize, compounds **1**, **4**, **6**, **7**, **9**, **10**, **12**, **14**, **16** and **18** were broadened the phytochemical diversity of *L. cladonioides.* Compounds **3**, **13** can be used as characteristic components of this genus. Compounds **2**, **3**, **5**, **11** and **13** were present as major products in *L. cladonioides* and *L. canariensis*. So, these findings confirm the close chemotaxonomic relationships between *L. cladonioides* and *L. canariensis.* Up to now, **6**–**8**, **10** and **12** have not been found in other species of genus *Lethariella*, which may be used as the basis for the distinction between *Lethariella cladonioides* and other species. The results of this study have important implications for future phytochemical and chemotaxonomic studies in *L. cladonioides*.

A plausible biosynthetic process for compounds **1**–**13** is shown in Fig. 3. In this proposal, phenolic acid **8** is considered as the key precursor compound. Compounds **1**–**13** were isolated in this study.

Declaration of competing interest

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

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