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Review

Dihydrophenanthrenes from medicinal plants of Orchidaceae: A review

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A B S T R A C T

The plants of Orchidaceae are widely distributed in the world, 47 species of which have been used as folk medicines with a long history. The tubers and stems of them exhibit diverse efficacy, including clearing heat and resolving toxin, moistening lung and relieving cough and promoting blood circulation. Since dihydrophenanthrenes were responsible for the medical purposes, the characteristic skeletons, pharmacological effects and clinical applications of dihydrophenanthrenes were summarized in this review, so as to provide a theoretical basis for the comprehensive study, development and application of DPs from medicinal plants of Orchidaceae.

Contents

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1. Introduction

Orchidaceae family is the largest group of flowering plants including 24 500 species in 775 genera. Forty-seven species in Orchidaceae family have been used as folk medicines with a long history. For example, the tubers of *Bletilla striata* (Thunb.) Rchb. f. (Baiji) is recorded in the *Chinese Pharmacopoeia* (2020) to relieve swelling and traumatic bleeding. In *Compendium of Materia Medica* (Ben Cao Gang Mu), the tubers of *B. striata* was reported to be used to stop bleeding by grinding the tubers to powder. Some classical folk prescriptions containing *B. striata* are used for epistaxis, lung atrophy, furuncle, coughing and low-grade fever, such as "Baiji San", "Baiji Pipa Wan", "Bai Zi Gao" and "Jin Xian San". At present, the tubers of *B. striata* has been served as the main ingredients of some Chinese patent medicines, and these medicines are recorded in the *Chinese Pharmacopoeia* (2020) and used to treat peptic ulcer, antral gastritis and digestive tracts, such as "Kuai Wei Tablets", "Weikangling Capsules" and "Jianwei Yuyang Granules" (Jiang & Ye, 2013; Pei, 1979). As a traditional Chinese medicine and a Mongolian medicine, pseudobulbs of *Cremastra appendiculata* (D. Don) Makino, one of the botanical origins of Shancigu exhibit the efficacy of clearing heat and resolving toxin, moistening lung and relieving cough. Since the Qing Dynasty, pseudobulbs of *C. appendiculata* have been used to treat breast cancer and gastric cancer. *The New Compendium of Materia Medica* records that pseudobulbs of *C. appendiculata* belongs to "dispelling poison" and can eliminate malignant tumors in human body (Chen, 1996). The pseudobulbs of *C. appendiculata* can not only inhibit the growth and proliferation of cancer cells, induce apoptosis but also interfere with invasion and migration, which has been widely used in clinical practice. Currently, five Chinese patent medicines containing the pseudobulbs of *C. appendiculata* have been developed and marked in China, which are used for the treatment of liver cancer and gastric cancer, such as "Ci Dan Capsules", "Ruanjian Oral Liguid", "Ai Yu Capsules", "Jin Pu Capsules" and "Ru Pi Qing Pills" (Dong, 2014; Yang, 2016). Therefore, their bioactive ingredients and pharmacological effects have attracted much attention of the medicinal chemists.

Phytochemical research showed that medicinal plants of Orchidaceae are rich of dihydrophenanthrenes (DPs), flavonoids, triterpenoids, alkaloids and bibenzyls, in which DPs are the major bioactive ingredients. Modern pharmacological studies showed that DPs in medicinal plants of Orchidaceae possess anti-inflammatory, anti-tumor, anti-oxidation and anti-bacterial activities (Ishiuchi, et al, 2015; Ma, Zhang, Ding, Liu & Ling, 2016). DPs might be used in the quality control of TCMs from Orchidaceae plants, mainly spread in *Pholidota*, *Bletilla*, *Dendrobium* and *Pleione* genus (Fig. 1).

2. DPs isolated from Orchidaceae plants

Up to now, 217 DPs have been isolated from medicinal plants of Orchidaceae. According to the number of DP units, they are usually divided into two major groups: DP monomers and DP polymers (Fig. 2). In addition, the numbers and origins of DPs from medicinal plants of Orchidaceae in each subtype are summarized in Fig. 3.

2.1. DP monomers

Seventy-one percent of the natural DPs from medicinal plants of Orchidaceae are DP monomers (**1**–**155**). According to the feature of substituents in the chemical structures, DP monomers are divided into simple DP monomers, dihydrophenanthrenequinones, dihydrophenanthrofurans and dihydrophenanthropyrans.

2.1.1. Simple DP monomers

More than 80% of simple DP monomers are from *Pholidota*, *Bletilla*, *Dendrobium* and *Spiranthes*. The substituents including hydroxy, methoxy and isoprene groups usually link at C-2, C-6 and C-7. The special type, with a five- or six- membered ring formed at C-4 and C-5, has only been isolated from *Pholidota* genus. The representative structures are afforded in Fig. 4 and the chemical structures, names and origins displayed in Fig. S1 and Table 1.

2.1.2. Dihydrophenanthrenequinones

Several dihydrophenanthrenequinones have been identified with hydroxy, methyl, methoxy and isoprene groups. The representative structures are afforded in Fig. 5 and the chemical structures, names and origins displayed in Fig. S2 and Table 1.

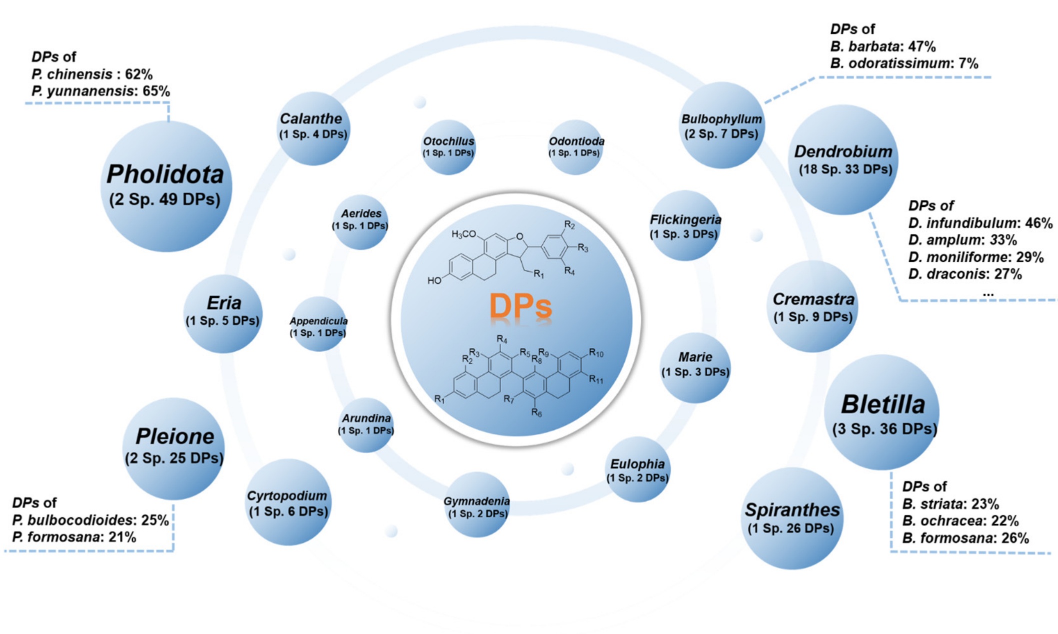

Fig. 1. Distribution of DPs in medicinal plants of Orchidaceae (Sp. = Species).

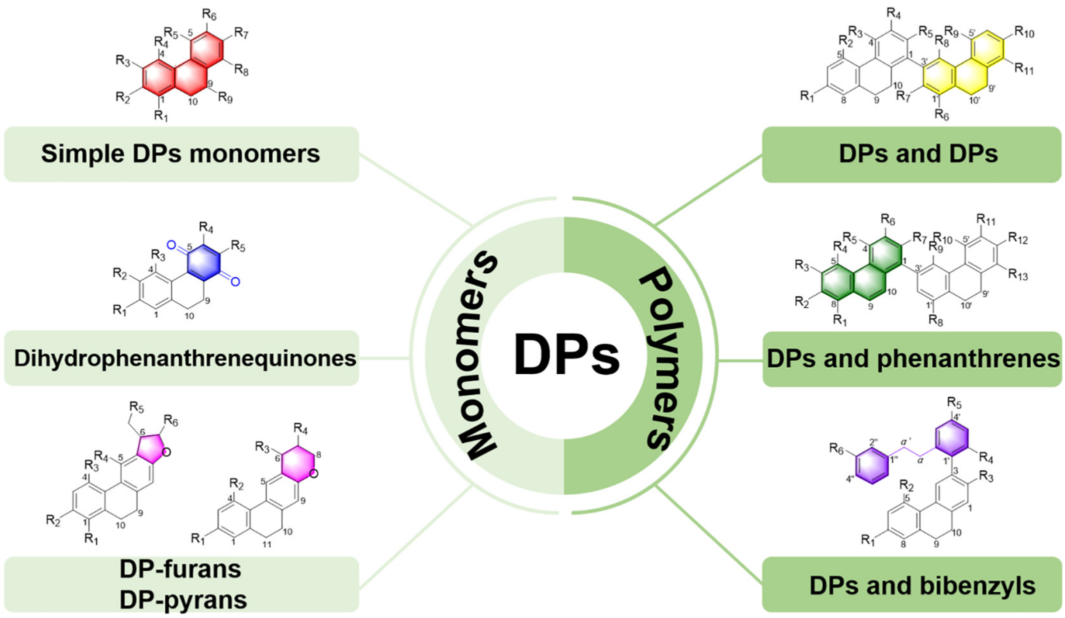

Fig. 2. Chemical structural types of DPs from medicinal plants of Orchidaceae.

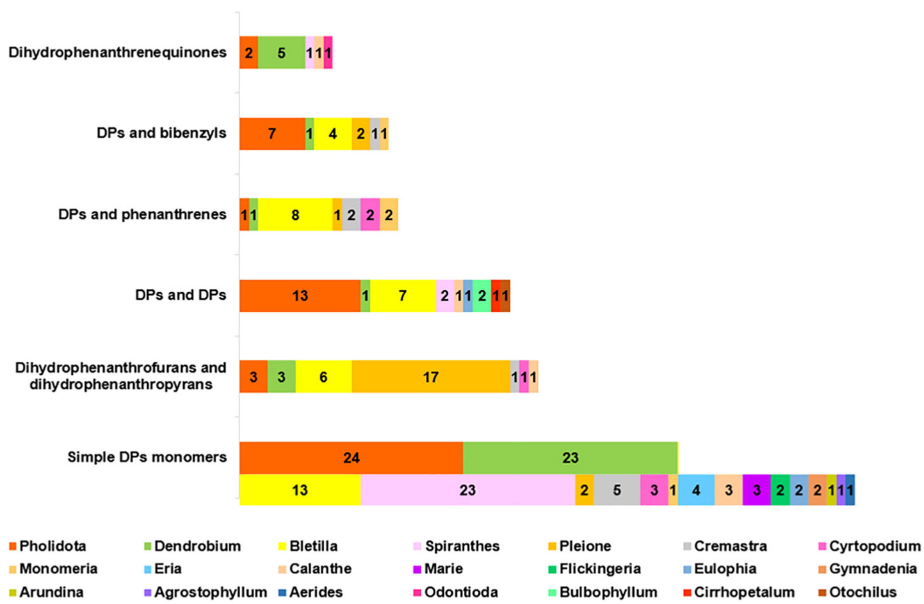

Fig. 3. Numbers of DPs from medicinal plants of Orchidaceae in each subtype.

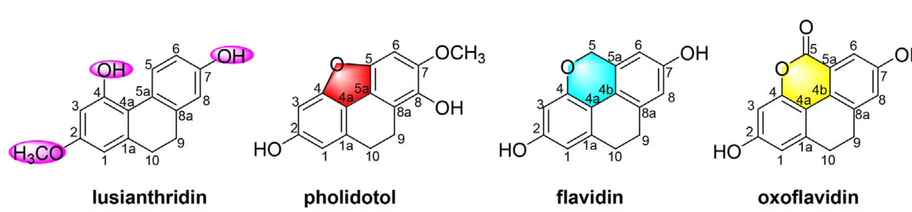

Fig. 4. Representative chemical structures of simple DP monomers.

2.1.3. Dihydrophenanthrofurans and dihydrophenanthropyrans

In dihydrophenanthrofurans and dihydrophenanthropyrans, the rings are mainly attached to the DP core at C-6 and C-7, C-7 and C-8. Moreover, the absolute configuration of most compounds at C-7 was described to be (*R*), C-6 and C-8 were described to be (*S*). The representative structures are afforded in Fig. 6 and the chemical structures, names and origins displayed in Fig. S3 and Table 1.

Table 1
Names, origins of DPs isolated from medicinal plants of Orchidaceae.

No.	Names	Origins	References
1	Lusianthridin	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
2	Cannabidihydrophenanthrene	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
3	4,5-Dihydroxy-2-methoxy-9,10-dihydrophenanthrene	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
4	Eulophiol	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
5	Orchinol	*Pholidota chinensis*	Hu et al. (2018)
6	Coelonin	*Pholidota chinensis*	Rueda, et al. (2014)
7	Hircinol	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
8	2,4,7-Trihydroxy-9,10-dihydrophenanthrene	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
9	7-Methoxy-9,10-dihydrophenanthrene-2,4-diol	*Pholidota chinensis*	Wu, Qu, & Cheng. (2008)
10	Erianthridin	*Pholidota chinensis*	Wang, Wang, & Kitanaka. (2007)
11	7-Hydroxy-2,3,4-trimethoxy-9,10-dihydrophenanthrene	*Pholidota chinensis*	Hu et al. (2018)
12	2,5-Dihydroxy-3,4-dimethoxy-9,10-dihydrophenanthrene	*Pholidota chinensis*	Hu et al. (2018)
13	2,5-Dihydroxyl-3,4,6-trimethoxy-9,10-dihydrophenanthrene	*Pholidota chinensis*	Hu et al. (2018)
14	2,7-Dihydroxy-3,4,6-trimethoxy-9,10-dihydrophenanthrene	*Pholidota chinensis*	Hu et al. (2018)
15	Pholidotol	*Pholidota chinensis*	Hu et al. (2018)
16	Phocantol	*Pholidota chinensis*	Hu et al. (2018)
17	Flavidin	*Pholidota chinensis*	Hu et al. (2018)
18	Flaccidin	*Pholidota chinensis*	Hu et al. (2018)
19	Coelogin	*Pholidota chinensis*	Hu et al. (2018)
20	Imbricatin	*Pholidota chinensis*	Hu et al. (2018)
21	Isoflavidinin	*Pholidota chinensis*	Hu et al. (2018)
22	1-(4′-Hydroxybenzyl)-imbricatin	*Pholidota yunnanensis*	Dong, et al. (2013)
23	*iso*-Oxoflavidinin	*Pholidota chinensis*	Hu et al. (2018)
24	Oxoflavidin	*Pholidota chinensis*	Hu et al. (2018)
25	*O*-methylorchinol	*Bletilla striata*	Bai, Yamaki, Inoue, & Takagi. (1990)
26	2,5,8-Trihydroxy-7-methoxy-9,10-dihydrophenanthrene	*Bletilla striata*	Zhou, et al. (2019)
27	2,7-Dihydroxy-l-(4′-hydroxybenzyl)-9,10-dihydrophenanthrene-4′-*O*-*β*-*D*-glucoside	*Bletilla striata*	Zhou, et al. (2019)
28	Bletillatin C	*Bletilla striata*	Zhou, et al. (2019)
29	2,7-Dihydroxy-1-(p-hydroxybenzyl)-4-methoxyphenanthrene-9,10-dihydrophenanthrene-4′-*O*-*β*-*D*-diglucoside	*Bletilla striata*	Zhou, et al. (2019)
30	1-(*p*-Hydroxybenzyl)-4-methoxy-9,10-dihydrophenanthrene	*Bletilla striata*	Yamaki, Bai, Inoue, & Takagi. (1990)
31	1-(4-Hydroxybenzyl)-4,7-dimethoxy-9,10-dihydrophenanthrene-2,8-diol	*Bletilla striata*	Zhou, et al. (2019)
32	2,7-Dihydroxy-3-(*p*-hydroxybenzyl)-9,10-dihydrophenanthrene-4-*O*-*β*-D-glucoside	*Bletilla striata*	Zhou, et al. (2019)
33	2,7-Dihydroxy-3-(*p*-hydroxybenzyl)-4-methoxy-9,10-dihydrophenanthrene	*Bletilla striata*	Yamaki, Bai, Inoue, & Takagi. (1990)
34	2,7-Dihydroxy-1,6-bis(4-hydroxybenzyl)-4-methoxy-9,10-dihydrophenanthrene	*Bletilla striata*	Yamaki, Bai, Inoue, & Takagi. (1990)
35	2,7-Dihydroxy-1,3-bis(*p*-hydroxybenzyl)-4-methoxy-9,10-dihydrophenanthrene	*Bletilla striata*	Bai, Kato, Inoue, Yamaki, & Takagi. (1991)
36	Bletillatin B	*Bletilla striata*	Zhou, et al. (2019)
37	2,7-bis(Allyloxy)-5-methoxy-3-methyl-9,10-dihydrophenanthrene	*Bletilla ochracea*	Cai, Zhao, & Zhang. (2007)
38	4,7-Dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene	*Dendrobium sinense*	Tan, et al. (2017)
39	4,5-Dihydroxy-2,3-dimethoxy-9,10-dihydrophenanthrene	*Dendrobium sinense*	Cai, et al. (2020)
40	2,5,7-Trihydroxy-4-methoxy-9,10-dihydrophenanthrene	*Dendrobium sinense*	Tan, et al. (2017)
41	Ephemeranthol B	*Dendrobium officinale*	Wang, Ma, Yang, & Pan. (1997)
42	Ephemeranthol A	*Dendrobium officinale*	Cui, Lu, Zhao, Liu, & Zhang. (2019)
43	Cannithrene 2	*Dendrobium nobile*	Li. (2011)

(*continued on next page*)

Table 1 (*continued*)

No.	Names	Origins	References
44	1,5-Dihydroxy-3,4,7-trimethoxy-9,10-dihydrophenanthrene	*Dendrobium moniliforme*	Zhao, Yang, Zhang, Chen, & Chen. (2016)
45	4,6-Dimethoxy-9,10-dihydrophenanthrene-2,3,7-triol	*Dendrobium amplum*	Majumder, Rahaman, Roychowdhury, & Dhara. (2008)
46	2,4,5-Trihydroxy-9,10-dihydrophenanthrene	*Dendrobium fimbriatum*	Xu, Xu, & Hou. (2014)
47	Emphernathol A	*Dendrobium plicatile*	Chen, et al. (2020)
48	2,4,7-Trimethoxy-9,10-dihydrophenanthrene-3-ol	*Dendrobium hainanense*	Zhang, et al. (2015)
49	3,4,7-Trimethoxy-9,10-dihydrophenanthrene-2,8-diol	*Dendrobium nobile*	Yang, Sung, & Kim. (2007)
50	4,7-Dimethoxy-9,10-dihydrophenanthrene-2-ol	*Dendrobium nobile*	Yang, Sung, & Kim. (2007)
51	3,4-Dimethoxy-1-(methoxymethyl)-9,10-dihydrophenanthrene-2,7-diol	*Dendrobium hainanense*	Zhang, et al. (2019)
52	Dendroinfundin A	*Dendrobium infundibulum*	Na Ranong, Likhitwitayawuid, Mekboonsonglarp & Sritularak. (2019)
53	Dendroinfundin B	*Dendrobium infundibulum*	Na Ranong, Likhitwitayawuid, Mekboonsonglarp & Sritularak. (2019)
54	Rotundatin	*Dendrobium loddigesii*	Majumder, Banerjee, Lahiri, Mukhoti, & Sen. (1998)
55	(9*S*)-9,10-dihydro-5-methoxy-4,7,9-phenanthrenetriol	*Dendrobium denneanum*	Lin, Wang, & Yang. (2013)
56	(9*S*)-9,10-dihydro-4-methoxy-2,5,7,9-phenanthrenetetrol	*Dendrobium nobile*	Ladan & Ali. (2017)
57	(9*S*)-9,10-dihydro-5-methoxy-2,4,7,9-phenanthrenetetrol	*Dendrobium denneanum*	Lin, Wang, & Yang. (2013)
58	(9*R*)-5,9-dihydroxy-4-methoxy-9,10-dihydrophenanthrene-2-yl-2-hydroxyacetate	*Dendrobium nobile*	Zhou, Zheng, Wu, Chen, & Zhang (2017)
59	2,5,9-Trihydroxy-9,10-dihydrophenanthrene-4-yl-2-hydroxyacetate	*Dendrobium primulinum*	Ye, Mei, Yang, Cheng, & Kong. (2016)
60	1,2,4,9*R*-tetrahydroxy-9,10-dihydrophenanthrene-5-*O*-β-D-glucopyranoside	*Dendrobium denneanum*	Lin, Wang, & Yang. (2013)
61	Spiranthesphenanthrene D	*Spiranthes sinensis*	Liu, et al. (2019a)
62	2,4-Dihydroxy-5-methoxy-9,10-dihydrophenanthrene	*Spiranthes sinensis*	Liu, et al. (2019a)
63	Sinensol A	*Spiranthes sinensis*	Liu, Li, Zhong, Yang, & Li, 2013
64	Sinensol H	*Spiranthes sinensis*	Lin, Wang, Kuo, & Liu, 2001
65	Spiranthon A	*Spiranthes sinensis*	Liu, Li, Zhong, Yang, & Li, 2013
66	Spiranthesol B	*Spiranthes sinensis*	Lin, Huang, Don, & Kuo, 2000
67	Sinensol C	*Spiranthes sinensis*	Liu, Li, Zhong, Yang, & Li, 2013
68	Sinensol G	*Spiranthes sinensis*	Lin, Wang, Kuo, & Liu, 2001
69	Spiranthol B	*Spiranthes sinensis*	Liu, et al. (2019a)
70	Spirasineol A	*Spiranthes sinensis*	Lin, Huang, Don, & Kuo, 2000
71	Sinensol B	*Spiranthes sinensis*	Lin, Huang, Don, & Kuo, 2000
72	Sinensol F	*Spiranthes sinensis*	Lin, Huang, Don, & Kuo, 2000
73	Shancidin	*Pleione bulbocodioides*	Zhu (2014)
74	Pleioanthrenin	*Pleione formosana*	Zhu (2014)
75	7-Hydroxy-4-methoxy-9,10-dihydrophenanthrene-2-*O*-β-D-glucopyranoside	*Cremastra appendiculata*	Sun et al. (2018)
76	7-Hydroxy-5-methoxy-9,10-dihydrophenanthrene-2-*O*-β-D-glucopyranoside	*Cremastra appendiculata*	Sun et al. (2018)
77	4-Methoxy-9,10-dihydrophenanthrene-2,7-diyl-*O*-β-D-glucopyranoside	*Cremastra appendiculata*	Wang, Guan, & Meng. (2013)
78	2,7-Dihydroxy-1-(4-hydroxybenzyl)-4-methoxy-9,10-dihydrophenanthrene	*Cremastra appendiculata*	Liu, et al. (2015)
79	1-(3′-Methoxy-4′-hydroxybenzyl)-7-methoxy-9,10-dihydrophenanthrene-2,4-diol	*Cremastra appendiculata*	Zhu (2014)
80	Cephathrene A	*Cyrtopodium paniculatum*	Auberon, et al. (2016)
81	Cephathrene B	*Cyrtopodium*	Auberon, et al. (2016)

Table 1 (*continued*)

No.	Names	Origins	References
		paniculatum	
82	(9*S*)-3,4-dimethoxy-9,10-dihydrophenanthrene-2,7,9-triol	*Cyrtopodium paniculatum*	Auberon, et al. (2016)
83	1-(*p*-Hydroxybenzoyl)-2-methoxy-4,7-dihydroxy-9,10-dihydrophenanthrene	*Monomeria barbata*	Yang et al. (2010a)
84	5,7-Dimethoxy-9,10-dihydrophenanthrene-2,6-diyl diacetate	*Eria flava*	Majumder, Pal, & Joardar. (1990)
85	Flavanthrinin diacetate	*Eria flava*	Majumder, Pal, & Joardar. (1990)
86	Nudol diacetate	*Eria flava*	Majumder, Pal, & Joardar. (1990)
87	Lusianthrin diacetate	*Eria flava*	Majumder, Pal, & Joardar. (1990)
88	9,10-Dihydro-2,5-dimethoxy-4,6-phenanthrenediol	*Calanthe arisanensis*	Lee, et al. (2009)
89	5,7-Dimethoxy-9,10-dihydrophenanthrene-1,4,6-triol	*Calanthe arisanensis*	Lee, et al. (2009)
90	9,10-Dihydro-5,6-dimethoxy-1,4,7-phenanthrenetriol	*Calanthe arisanensis*	Lee, et al. (2009)
91	Marylaurencinol A	*Marie laurencin*	Yoshikawa et al. (2012)
92	Marylaurencinol B	*Marie laurencin*	Yoshikawa et al. (2012)
93	Marylaurencinoside A	*Marie laurencin*	Yoshikawa et al. (2012)
94	2,3,4,7,8-Pentamethoxy-9,10-dihydrophenanthrene	*Flickingeria fimbriata*	Wu et al. (2017)
95	5-Methoxy-9,10-dihydrophenanthrene-2,7,8-triol	*Flickingeria fimbriata*	Wu et al. (2017)
96	Septeophiol diacetate	*Eulophia graminea*	Bhandari & Kapadi. (1983)
97	9,10-Dihydro-2,5-dimethoxy-1,7-phenanthrenediol	*Eulophia macrobulbon*	Temkitthawon, Changwichit, Khorana, Viyoch, Suwanborirux, & Ingkaninan. (2017)
98	Gymconopin A	*Gymnadenia conopsea*	Wang, Wang, Zhai, Liao, Zhang, & Huang. (2012)
99	Gymconopin B	*Gymnadenia conopsea*	Matsuda, Morikawa, Xie, & Yoshikawa (2004)
100	Arundigramin	*Arundina graminifolia*	Auberon, et al. (2016)
101	Callosin	*Agrostophyllum callosum*	Majumder, Banerjee, Lahiri, Mukhoti, & Sen. (1998)
102	Aerosin	*Aerides rosea*	Cakova, et al. (2015)
103	Ochrone A	*Pholidota chinensis*	Hu et al. (2018)
104	Phocantone	*Pholidota chinensis*	Hu et al. (2018)
105	Denbinobin B	*Dendrobium sinense*	Chen, et al. (2013b)
106	Dendronone	*Dendrobium cariniferum*	Chen. (2013a)
107	Ephenmeranthoquinone	*Dendrobium densiflorum*	Chen. (2013a)
108	2-Hydroxy-4-methoxy-9,10-dihydrophenanthrene-1,4-dione	*Dendrobium draconis*	Sritularak, Anuwat, & Likhitwitayawuid. (2011)
109	Ephenmeranthoquinone B	*Odontioda Marie Noel*	Masuda, Suzuki, & Sakagami. (2012)
110	3-Hydroxy-2,4-dimethoxy-9,10-dihydrophenanthrene-1,4-dione	*Calanthe arisanensis*	Lee, Yen, Chang, Wud, & Wu. (2014)
111	Dendrodevonin B	*Dendrobium devonianum*	Wu, Lu, Ding, Zhao, Xu, & Chou. (2019)
112	Spiranthoquinone	*Spiranthes sinensis*	Tezuka, Ji, Hirano, Ueda, Nagashima, & Kikuchi. (2010)
113	Bleochranol C	*Bletilla ochracea*	Li, et al. (2018)
114	Bleochranol D	*Bletilla ochracea*	Li, et al. (2018)
115	{(9*S*,10*R*)-3-hydroxy-9-(4-hydroxy-3-methoxyphenyl)-1-methoxy-6,8,9,10-tetrahydro-5*H*-cyclopenta[*b*]phenanthren-10-yl}methyl acetate	*Bletilla striata*	Zhou, et al. (2019)
116	2-(4-Hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3,9,10-tetrahydrophenanthro[2,3-*b*]furan-5-ol	*Pholidota chinensis*	Hu et al. (2018)
117	2-(4-Hydroxy-3,5-dimethoxyphenyl)-3-hydroxymethyl-8-methoxy-2,3,10,11-tetrahydrophenanthro[1,2-*b*]furan-5,6-diol	*Pholidota chinensis*	Hu et al. (2018)
118	(7′*S*,8′*R*-*trans*)-7-hydroxy-7′-(4′-hydroxy-3′,5′-dimethoxyphenyl)-8′-hydroxymethyl-5-methoxy-9,10,7′,8′-tetrahydrophenanthro [2,3-*b*]furan	*Pleione bulbocodioides*	Li. (2016)
119	Bletillatin A	*Bletilla striata*	Zhou, et al. (2019)
120	Shanciol H	*Pleione bulbocodioides*	Liu, et al. (2019b)
121	Shanciol B	*Pleione bulbocodioides*	Liu, et al. (2019b)
122	{3-Hydroxy-9-(4′-hydroxy-3′-methoxyphenyl)-11-methoxy-5,6,9,10-tetrahydrophenanthro [2,3,-*b*]furan-10-yl}methyl acetate	*Pleione bulbocodioides*	Zhu (2014)
123	9-(4′-Hydroxy-3′-methoxyphenyl)-10-(hydroxymethyl)-11-methoxy-5,6,9,10-tetrahydrophenanthro[2,3,-*b*]furan-3-ol	*Pleione bulbocodioides*	Liu, et al. (2019b)
124	4,5-Epoxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-3-hydroxymethyl-1-methoxy-2,3,9,10-	*Pholidota*	Hu et al. (2018)

(*continued on next page*)

Table 1 (*continued*)

No.	Names	Origins	References
	tetrahydrophenanthro[2,3-*b*]furan-7-ol	*chinensis*	
125	{(2*R*,3*S*)-7-hydroxy-2-(3-hydroxy-5-methoxyphenyl)-10-methoxy-2,3,4,5-tetrahydrophenanthro[2,1-*b*]furan-3-yl}methyl acetate	*Bletilla striata*	Zhou, et al. (2019)
126	(2,3-*trans*)-2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-10-methoxy-2,3,4,5-tetrahydrophenanthro[2,1-*b*]furan-7-ol	*Cremastra appendiculata*	Sun et al. (2018)
127	Cyrtonesin B	*Bletilla striata*	Zhou, et al. (2019)
128	Pleionesin D	*Pleione bulbocodioides*	Liu, et al. (2019b)
129	Pleionesin B	*Pleione yunnanensis*	Liu, et al. (2019b)
130	Pleionesin C	*Pleione bulbocodioides*	Liu, et al. (2019b)
131	Shanciol G	*Pleione bulbocodioides*	Liu, et al. (2019b)
132	(2*R*,3*R*)-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-*N*-(4-hydroxyphenethyl)-10-methoxy-2,3,4,5-tetrahydrophenanthro[2,1-*b*]furan-3-carboxamide	*Cyrtopodium paniculatum*	Auberon, et al. (2016)
133	4-Hydroxy-2-methoxy-8-furano[4′,5′,7,8]-9,10-dihydrophenanthrene	*Spiranthes sinensis*	Liu, Su, Li, Wen, & Li. (2012)
134	Spiranthesphenanthrene C	*Spiranthes sinensis*	Liu, et al. (2019a)
135	Spiranthesphenanthrene F	*Spiranthes sinensis*	Liu, et al. (2019a)
136	Spirantol C	*Spiranthes sinensis*	Tezuka, Ji, Hirano, Ueda, Nagashima, & Kikuchi. (2010)
137	Sinensol E	*Spiranthes sinensis*	Lin, Huang, Don, & Kuo, 2000
138	Shanciol D	*Pleione bulbocodioides*	Liu, et al. (2019b)
139	Bletilol C	*Pleione bulbocodioides*	Zhu (2014)
140	Chrysotoxol A	*Dendrobium chrysotoxum*	Hu, Fan, Dong, Miao, & Zhou. (2012)
141	Chrysotoxol B	*Dendrobium chrysotoxum*	Hu, Fan, Dong, Miao, & Zhou. (2012)
142	Shanciol E	*Pleione bulbocodioides*	Li. (2016)
143	Shancil	*Pleione bulbocodioides*	Li, Chen, & Xin. (2014)
144	Shanciol F	*Pleione bulbocodioides*	Liu, et al. (2019b)
145	Shanciol C	*Pleione bulbocodioides*	Liu, et al. (2019b)
146	Bletilol A	*Pleione bulbocodioides*	Zhu (2014)
147	Bletilol B	*Pleione bulbocodioides*	Zhu (2014)
148	Dendrocandin P2	*Dendrobium. officinale*	Zhao, Deng, & Zhang (2018)
149	Erathrins A	*Eria bambusifolia*	Zhan, Wang, Yin, Liu, & Chen, 2016
150	Spiranthesphenanthrene A	*Spiranthes sinensis*	Liu, et al. (2019a)
151	Spirasineol B	*Spiranthes sinensis*	Tezuka, Ji, Hirano, Ueda, Nagashima, & Kikuchi. (2010)
152	4-Hydroxy-2-methoxy-8-{2′,2′-dimethylpyrano[5′,6′,7,8]}-9,10-dihydrophenanthrene	*Spiranthes sinensis*	Liu, Su, Li, Wen, & Li. (2012)
153	Spiranthesphenanthrene B	*Spiranthes sinensis*	Liu, et al. (2019a)
154	Spiranthesphenanthrene E	*Spiranthes sinensis*	Liu, et al. (2019a)
155	Sinensol D	*Spiranthes sinensis*	Lin, Huang, Don, & Kuo, 2000
156	Phochinenin A	*Pholidota chinensis*	Yao, Tang, Li, & Ye. (2009)
157	Phochinenin G	*Pholidota chinensis*	Hu et al. (2018)
158	Phochinenin H	*Pholidota chinensis*	Hu et al. (2018)
159	Gymconopin C	*Pholidota chinensis*	Hu et al. (2018)
160	2,2′-Dihydroxy-5,5′,7,7′-tetramethoxy-9,9′,10,10′-tetrahydro-3,3′-biphenanthrene	*Spiranthes sinensis*	Li et al. (2013)
161	Phoyunnanin C	*Pholidota chinensis*	Hu et al. (2018)
162	Blestrianol A	*Bletilla striata*	Bai, Kato, Inoue, Yamaki, & Takagi. (1991)

Table 1 (*continued*)

No.	Names	Origins	References
163	Blestrianol B	*Bletilla striata*	Bai, Kato, Inoue, Yamaki, & Takagi. (1991)
164	Bleformin D	*Bletilla formosana*	Lin, et al. (2016)
165	Bleformin H	*Bletilla formosana*	Lin, et al. (2016)
166	Amplumthrin	*Dendrobium. amplum*	Majumder, Rahaman, Roychowdhury, & Dhara. (2008)
167	Flavanthrin tetraacetate	*Cirrhopetalum maculosum*	Majumder, Pal, & Joardar (1990)
168	Flavanthrin	*Pholidota chinensis*	Hu et al. (2018)
169	9,9′,10,10′-Tetrahydro-2,2′-dimethoxy-(1,1′-biphenanthrene)-4,4′,7,7′-tetrol	*Pholidota chinensis*	Hu et al. (2018)
170	9,9′,10,10′-Tetrahydro-2,2′-dimethoxy-(1,1′-biphenanthrene)-4,4′,7-triol	*Pholidota chinensis*	Hu et al. (2018)
171	2,2′-Dimethoxy-4,4′,7,7′-tetrahydroxy-9,9′,10,10′-tetrahydro-1,1′-biphenanthrene	*Flickingeria fimbriata*	Chen (2013a)
172	4,7,4′-Trimethoxy-9′,10′-dihydro(1,1′-biphenanthrene)-2,2′,7′-triol	*Bletilla striata*	Lin, Huang, Don, & Kuo, 2000
173	2,2′,4,4′,7,7′-Hexamethoxy-9,9′,10,10′-tetrahydro-1,1′-biphenanthrene	*Bletilla yunnanensis*	Yang (2016)
174	Phochinenin C	*Pholidota chinensis*	Yao, Tang, Li, & Ye. (2009)
175	Phochinenin D	*Pholidota chinensis*	Yao, Tang, Li, & Ye. (2009)
176	Phochinenin E	*Pholidota chinensis*	Yao, Tang, Li, & Ye. (2009)
177	Phoyunnanin E	*Pholidota chinensis*	Hu et al. (2018)
178	Blestrin A	*Pholidota chinensis*	Hu et al. (2018)
179	Bulbophythrin B	*Bulbophyllum odoratissimum*	Xu, Yu, Qing, Zhang, Liu, & Chen. (2009)
180	Spiranthesol	*Spiranthes sinensis*	Liu, Li, Zhong, Yang, & Li, 2013
181	Bulbophythrin A	*Bulbophyllum odoratissimum*	Xu, Yu, Qing, Zhang, Liu, & Chen. (2009)
182	8,8′-Biflavidin	*Otochilus porrectus*	Shi, et al. (2010)
183	Blestrin B	*Bletilla striata*	Yamaki, et al. (1992)
184	Monbarbatain D	*Monomeria barbata*	Yang et al. (2010a)
185	4,4′-Dimethoxy-9,10-dyhydro(6,1′-biphenanthrene)-2,2′,7,7′-tetraol	*Cremastra appendiculata*	Sun et al. (2018)
186	4,7,7′-Trimethoxy-9′,10′-dihydro(1,3′-biphenanthrene)-2,2′,5′-triol	*Bletilla striata*	Lin, Huang, Don, & Kuo, 2000
187	4,4′,7-Trimethoxy-9′,10′-dihydro(1,3′-biphenanthrene)-2,2′,7′-triol	*Cremastra appendiculata*	Liu, Li, Zeng, Jiang, & Tu. (2016)
188	5,6,7′-Trimethoxy-9′,10′-dihydro(1,3′-biphenanthrene)-2,2′,5′,7-tetraol	*Cyrtopodium paniculatum*	Auberon, et al. (2016)
189	3,4,7′-Trimethoxy-9′,10′-dihydro(1,3′-biphenanthrene)-2,2′,5′,7-tetraol	*Cyrtopodium paniculatum*	Auberon, et al. (2016)
190	Monbarbatain B	*Monomeria barbata*	Yang, Cai, & Tai. (2010b)
191	Blestrianol C	*Bletilla striata*	Bai, Kato, Inoue, Yamaki, & Takagi. (1991)
192	Bleformin I	*Bletilla formosana*	Lin, et al. (2016)
193	Bulbocodioidin G	*Pleione bulbocodioides*	Wang, Shao, Han, & Li. (2019)
194	Phochinenin B	*Pholidota chinensis*	Yao, Tang, Li, & Ye. (2009)
195	Blestriarene B	*Bletilla striata*	Yang, Tang, Zhao, Shu, & Mei. (2012)
196	4,7,3′,5′-Tetramethoxy-9′,10′-dihydro(1,1′-biphenanthrene)-2,2′,7′-triol	*Bletilla striata*	Lin, Huang, Don, & Kuo, 2000
197	Monbarbatain A	*Monomeria barbata*	Yang, Cai, & Tai. (2010b)
198	4,7,3′,5′-Tetramethoxy-9′,10′-dihydro(1,2′-biphenanthrene)-2,7′-diol	*Bletilla striata*	Zhou et al. (2019)
199	Blestrin E	*Appendicula reflexa*	Apel, Dumontet, Lozach, Meijer, Guéritte & Litaudon. (2012)
200	Blestrin C	*Bletilla striata*	Yamaki, et al. (1992)
201	(2,3-*trans*)-3-[(2,7-Dihydroxy-4-methoxy-phenanthren-1-yl)methyl]-2-(4-hydroxy-3-methoxyphenyl)-10-methoxy-2,3,4,5-tetrahydro-phenanthro[2,1-*b*]furan-7-ol	*Dendrobium amplum*	Majumder, Rahaman, Roychowdhury, & Dhara. (2008)
202	Phoyunnanin A	*Pholidota yunnanensis*	Hu et al. (2018)
203	Phochinenin I	*Pholidota chinensis*	Hu et al. (2018)
204	Phochinenin J	*Pholidota chinensis*	Hu et al. (2018)

(*continued on next page*)

Table 1 (*continued*)

No.	Names	Origins	References
205	Phoyunnanin B	*Pholidota yunnanensis*	Hu et al. (2018)
206	Phochinenin M	*Bletilla striata*	Zhou et al. (2019)
207	Phochinenin K	*Bletilla striata*	Zhou et al. (2019)
208	Bulbocodioidin H	*Pleione bulbocodioides*	Wang, Shao, Han, & Li. (2019)
209	Bleformin C	*Bletilla formosana*	Lin, et al. (2016)
210	Phochinenin L	*Pholidota chinensis*	Yao, et al. (2008)
211	Phoyunnanin D	*Pholidota yunnanensis*	Hu, et al. (2018)
212	Shancilin	*Pleione bulbocodioides*	Liu et al. (2019b)
213	Monbarbatain E	*Monomeria barbata*	Yang, Cai, Fang, Yang, Fang, & Ding. (2014)
214	Bleochranol A	*Bletilla ochracea*	Li, et al. (2018)
215	(2,3-*trans*)-3-[2-Dihydroxy-6-(3-hydroxyphenyl)-4-methoxyphenyl]-2-(4-hydroxy-3-methoxyphenyl)-10-methoxy-2,3,4,5-tetrahydrophenanthro[2,1-*b*]furan-7-ol	*Cremastra appendiculata*	Wang, Guan, & Meng. (2013)
216	Phochinenin F	*Pholidota chinensis*	Yao, Tang, Li, & Ye. (2009)
217	Dendrosignatol	*Dendrobium signatum*	Mittraphab, Muangnoi, Likhitwitayawuid, Rojsitthisak, & Sritularak. (2016)

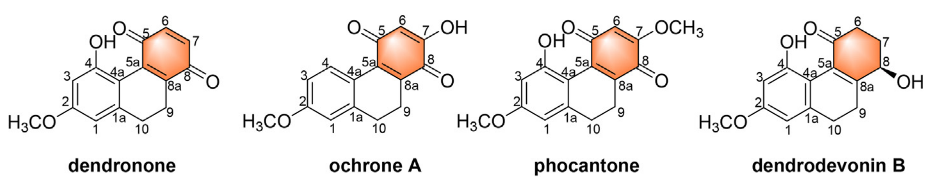

Fig. 5. Representative chemical structures of dihydrophenanthrenequinones.

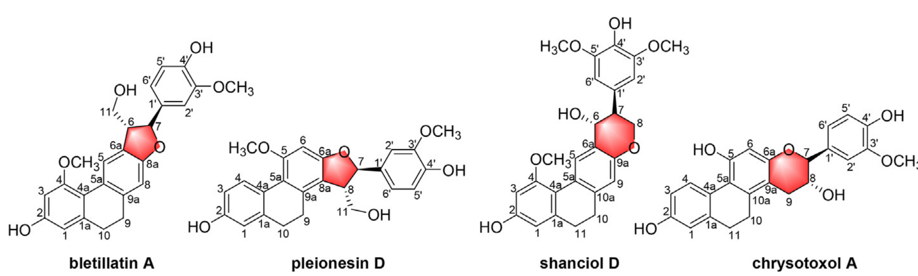

Fig. 6. Representative chemical structures of dihydrophenanthrofurans and dihydrophenanthropyrans.

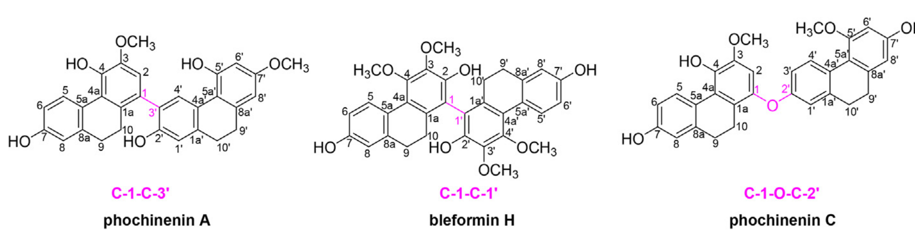

Fig. 7. Representative chemical structures of DPs and DPs.

2.2. DP polymers

Until now, 61 dimers and a trimer have been reported from medicnal plants of Orchidaceae. DP monomers can connect by their substituents or a single C–C', CH_2, CH_2-CH_2 or C-*O*-C' coupling. According to the different polymeric fragments, DP polymers could be classified into DPs and DPs, DPs and phenanthrenes, DPs and bibenzyls.

2.2.1. DPs and DPs

Twenty-nine constituents belong to this type and connect at different positions, such as C-1,3′ (**156**–**160**, **169**–**171**, **175**, **177**), C-1,1′ (**161**–**163**, **172**–**174**, **176**, **181**–**183**), C-2,2′ (**179**), C-3,1′ (**178**, **184**) and C-1,2′ (**164**–**168**, **180**). The representative structures are afforded in Fig. 7 and the chemical structures, names and origins displayed in Fig. S4 and Table 1.

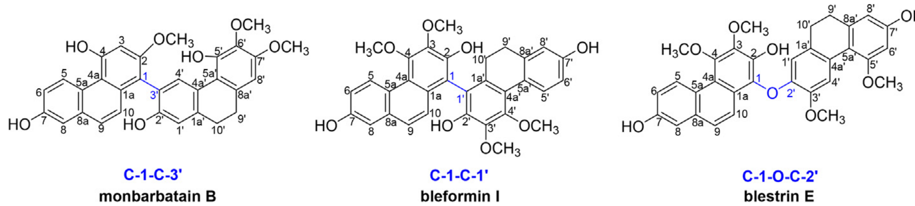

Fig. 8. Representative chemical structures of DPs and phenanthrenes.

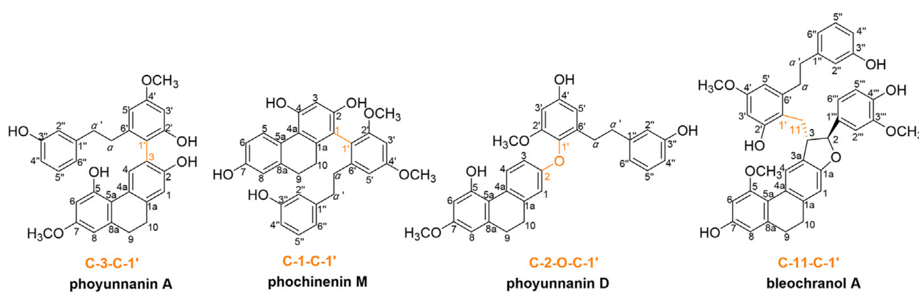

Fig. 9. Representative chemical structures of DPs and bibenzyls.

2.2.2. DPs and phenanthrenes

The second type is characterized between DPs and phenanthrenes monomers and the connection position at C-1,1′ (**185**, **188**–**190**, **199**–**200**), C-1,3′ (**186**–**187**, **194**–**198**, C-1,2′ (**191**–**193**) and C-2,9′ (**201**). The representative structures are afforded in Fig. 8 and the chemical structures, names and origins displayed in Fig. S5 and Table 1.

2.2.3. DPs and bibenzyls

All DPs are of bibenzyl origin, and a number of DPs and bibenzyls polymers are formed through C-3,1′ (**202**–**204**, **206**), C-1,1′ (**207**, **209**–**211**, **213**), C-2,1′ (**205**, **214**), C-4,1′ (**215**), C-11,1′ (**212**), C-12,1′ (**217**) linkages between two monomers. The representative compositions are afforded in Fig. 9 and the chemical structures, names and origins displayed in Fig. S6 and Table 1.

3. Pharmacology

The applications of medicinal plants of Orchidaceae have a long history. The tubers of *B. striata*, stems of *Dendrobium nobile* Lindl., whole herbs of *Pholidota chinensis* Lindl. and roots of *Spiranthes sinensis* (Pers.) Ames have been used as traditional Chinese medicines with the efficacy of clearing heat and resolving toxin, moistening lung and relieving cough, promoting blood circulation. However, very few studies have elaborated the relationship between traditional efficacy and modern pharmacology of DPs in medicinal plants of Orchidaceae. At present, some researches have demonstrated that DPs of medicinal plants of Orchidaceae have a wide range of biological activities such as cytotoxic, anti-oxidant, anti-inflammatory activities.

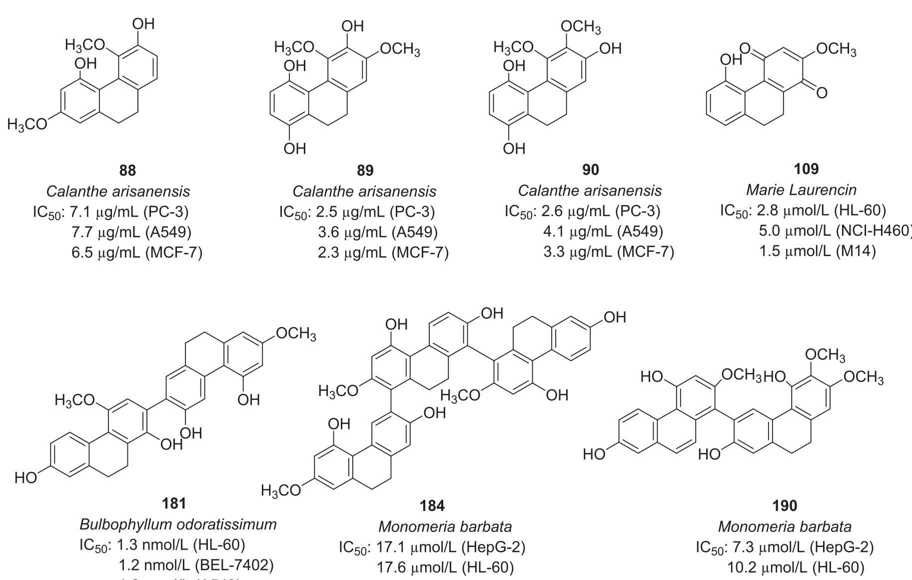

Fig. 10. DPs from medicnal plants of Orchidaceae with significant cytotoxic activities.

3.1. Cytotoxic activity

A large number of natural DPs have been proved to exhibit cytotoxic effects. Xu et al. noticed that the whole herbs of *Bulbophyllum odoratissimum* (Sm.) Lindl. showed strong cytotoxic activities in human leukemia cell lines K562 and HL-60, human lung adenocarcinoma A549, human hepatoma BEL-7402 and human stomach cancer SGC-7901. Bulbophythrin A (**181**), reported as a new dimeric DP, could inhibit the growth of HL-60, BEL-7402 and A549 with IC_{50} values of 1.3, 1.2 and 1.2 nmol/L (Xu, Yu, Qing, Zhang, Liu, & Chen, 2009).

Compounds **88**–**90**, isolated from the roots of *Calanthe arisanensis* Hayata, exhibited strong cytotoxic activities against A549, MCF-7 and PC-3 cancer cell lines with IC_{50} values ranged from 2.3 to 7.7 μg/mL by sulforhodamine B assays (Lee, et al., 2009).

Using water-soluble tetrazolium-8 and lactatedehydrogenase assays, ephenmeranthoquinone B (**109**), being present with high concentration in the roots of *Marie laurencin*, could inhibit the growth of HL-60, NCI-H460 and M14 cell lines with IC_{50} values of 2.8, 5.0 and 1.5 μmol/L (Williams et al., 2012).

Monbarbatains B and D (**190**, **184)** from the stems of *Monomeria barbata* and showed cytotoxic activities against HepG-2 (IC_{50}: 17.1 μmol/L; IC_{50}: 17.6 μmol/L) and HL60 (IC_{50}: 7.3 μmol/L; IC_{50}: 10.2 μmol/L) cell lines by MTT assays (Yang, Tang, Zhao, Shu, & Mei, 2010).

DP monomers have stronger cytotoxic activity compared to polymers. Furthermore, compared with **89** and **90**, it appears that the 6-OH and 7-OCH_3 groups might increase the cytotoxic activity. The structures and IC_{50} values of DPs from medicinal plants of Orchidaceae with significant cytotoxic activities displayed in Fig. 10.

3.2. Anti-inflammatory activity

Inflammation is the defense response of the living tissues to the simulations of injury factors, which plays an important role in the occurrence and development of many diseases (Hou, Sun, Gao & Xiao, 2015).

Lin et al. (2013) reported that compounds **3**, **55**, **58** and **60** from the ethanol extract of the stems of *Dendrobium denneanum* Lindl.

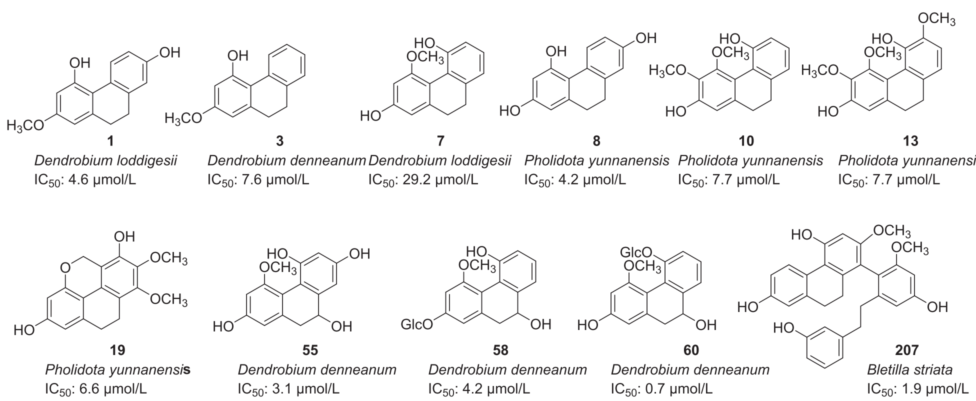

Fig. 11. DPs from medicinal plants of Orchidaceae with significant anti-inflammatory activities.

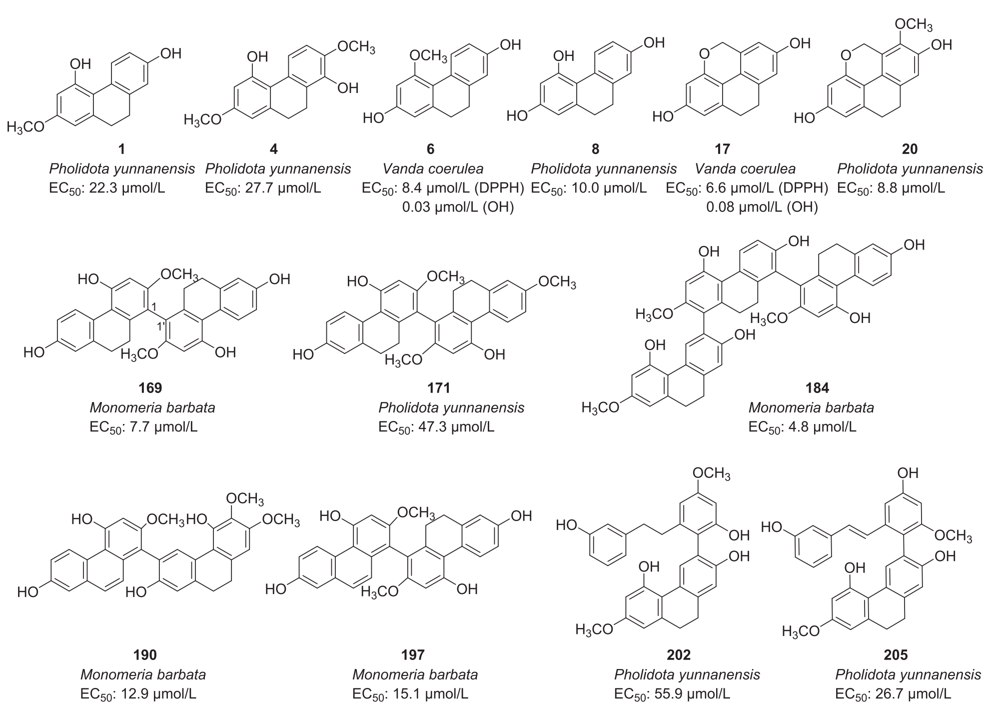

Fig. 12. DPs from medicinal plants of Orchidaceae with significant anti-oxidant activities.

showed inhibitory effects on NO production in lipopolysaccharide (lipopolysaccharide (LPS)-activated mouse macrophage RAW 264.7 cells) (IC_{50}: 7.6 μmol/L; IC_{50}: 3.1 μmol/L; IC_{50}: 4.2 μmol/L; IC_{50}: 0.7 μmol/L).

Lusianthridin (**1**) and hircinol (**7**) isolated from 80% ethanol extract of the stems of *Dendrobium loddigesii* Lindl., exerted inhibitory activities on LPS-induced NO production in a murine macrophage-like cell line RAW 264.7 with IC_{50} values of 4.6 and 29.2 μmol/L. Lusianthridin (**1**) was more active than that of the positive control aminoguanidine (IC_{50}: 17.5 μmol/L) (Ito et al., 2010).

Phochinenin K (**207**) was isolated from the dried tubers of *B. striata* and evaluated by LPS-stimulated BV-2 cells with IC_{50} value of 1.9 μmol/L (Zhou, et al., 2019). Compounds **1**, **8**, **13**, **19** and **22**, isolated from *Pholidota yunnanensis* were evaluated for their anti-inflammatory activities on LPS-induced NO production in RAW 264.7 cells and showed growth inhibitory effects in the concentration range of 4.2–7.7 μmol/L with MG-132 used as the positive control (IC_{50}: 17.5 μmol/L) (Dong, et al., 2013).

Coelonin (**6**), an active component isolated from the ethanol extract of the tubers of *B. striata*. It significantly inhibited LPS-induced IL-1β, IL-6 and TNF-α expression at 2.5 μg/mL by using the LPS-induced macrophage inflammation model and phosphoantibody arrays (Jiang, et al., 2019).

Based on the molecular structures and bioassay activities, we found that most active ingredients were monomers. In addition, we found that 2, 5-OGlc group might play a role in enhancing anti-inflammatory activity. The structures and IC values of DPs from medicinal plants of Orchidaceae with significant anti-inflammatory activities displayed in Fig. 11.

3.3. Anti-oxidant activity

The excessive free radicals can lead to aging, cancer and other diseases, and antioxidants can overcome the damage caused by excess free radicals (Meng et al., 2018). Compounds **1**, **4**, **8**, **20**, **171**, **202** and **205** were isolated from the whole herbs of *Pholidota yunnanensis*, and proved to be as active (EC_{50}: 22.3 μmol/L; EC_{50}: 27.7 μmol/L; EC_{50}: 10.0 μmol/L; EC_{50}: 8.8 μmol/L; EC_{50}: 47.3 μmol/L; EC_{50}: 55.9 μmol/L; EC_{50}: 26.7 μmol/L) as the positive control resveratrol (EC_{50}: 21.2 μmol/L) using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assays (Chen et al., 2013b).

Among the isolated compounds of the whole herbs of *Monomeria barbata* Lindl, compounds **169**, **184**, **190** and **197** showed antioxidant activity when using the DPPH radical scavenging assays (Yang et al. 2010; Yang et al. 2014). The antioxidant capacities of coelonin (**6**), flavidin (**17**) and imbricatin (**20**) were measured by DPPH radical-scavenging assays and •OH assays (IC_{50} values: 8.4, 6.6, and 8.5 μmol/L, DPPH assay; IC_{50} values: 0.03, 0.08, and 0.08 μmol/L, •OH assay) (Simmler, Antheaume & Lobstein, 2010).

In the above-mentioned compounds, it can be revealed that DPs with 2, 6-OCH_3, 5, 7-OH groups show higher antioxidant activity. The structures and IC values of DPs from medicinal plants of Orchidaceae with significant anti-oxidant activities displayed in Fig. 12.

4. Clinical applications

Over the years, medicinal plants of Orchidaceae showed a wide range of efficacy including clearing heat and resolving toxin, moistening lung and relieving cough and promoting blood circulation. DPs are the major bioactive ingredients of medicinal plants of Orchidaceae, which can prevent and treat diseases in clinic.

Silicosis is a chronic lung disease caused by long-term exposure to silica dust, characterized by progressive pulmonary fibrosis and lung inflammation (Guo, Zhang, & Shao, 2018). The innate immune response mediated by alveolar macrophage plays a key role in silicosis. Coelonin (**6**), a classical DP monomer was isolated from the tubers of *B. striata* can remarkably elevate the serum SOD level and lower the malondialdehyde, NO level; and it dose dependently decrease all the inflammatory cytokines, and lower hydroxyproline content. Therefore, coelonin (**6**) can effectively prevent lung fibrosis and through regulating the anti-oxidation system, immune system and cytokine level (Deng et al., 2016).

5. Summary

DPs from medicinal plants of Orchidaceae are responsible for the medicinal usage and attract more and more attention. DP structures, especially DP polymers have a lot of chiral centers and are the sources of diverse activities and stereoselectivities. In recent years, most studies on DPs are only focused on simple drug efficacy, more comprehensive pharmacological effects and mechanisms of action have not been fully elucidated. The further studies on the representative components of DPs are helpful to clarify the common material basis of medicinal plants of Orchidaceae and provide scientific basis for new drug development. As a kind of skeleton of active lead compounds, DPs can expand the structural diversity and provide a reference for the development of small molecule drugs by structural modifications, synthesis and other methods.

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.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2021.10.004.

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