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Ethnopharmacology of *Bletilla* orchid species: a comprehensive review on ethnobotany, phytochemistry and pharmacology

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Abstract

Bletilla is an orchid genus with distribution in China, Japan, South Korea, and other Asian countries with many species that are overexploited and vulnerable medicinal plants. Some *Bletilla* have a long history of ethnobotanical application in Asia, especially China, and ethnic groups in Southwest China still use *Bletilla* as medicines to treat cough, dermatitis and pneumonia. About 289 chemical compounds have been isolated from *Bletilla*, mostly phenathrene and phenolic derivatives. These diverse chemical components are responsible for the anti-inflammatory, antineoplastic, antiviral, antioxidant, hemostatic, antibacterial, and other biological activities of *Bletilla*. Various pharmacological activities support the traditional medicinal efficacy of *Bletilla*, implying the medicinal potential of this genus. However, detailed information on the botanical characteristics, ethnobotanical uses, chemical components, pharmacological effects, clinical application, and safety evaluation is limited. To better understand the ethnobotany, phytochemistry, and bioactivity of *Bletilla*, this article assesses recent developments in the field.

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Introduction

Bletilla Rchb. f. is one of the most economically valuable groups of orchids in the world. Due to its ornamental significance, the genus *Bletilla* occupies an important place in the worldwide horticultural market. Furthermore, in China, Japan, South Korea, and other Asian countries, it is highly valued for its medicinal use[1].

There are eight species in the genus *Bletilla*, including *Bletilla chartacea* (King & Pantl.) Tang & F.T. Wang, *Bletilla cotoensis* Schltr., *Bletilla foliosa* (King & Pantl.) Tang & F.T. Wang, *Bletilla formosana* Schltr., *Bletilla guizhouensis* J. Huang & G.Z. Chen, *Bletilla morrisonensis* Schltr., *Bletilla ochracea* Schltr., and *Bletilla striata* Rchb.f.[2,3]. The distribution area spans from northern Myanmar in Asia to Japan *via* China[4]. Five species are native to China, namely, *B. foliosa*, *B. formosana*, *B. guizhouensis*, *B. ochracea*, and *B. striata*. In China, people have assigned various names to *Bletilla* based on its morphology and efficacy, such as *baiji* (白及/白芨), *baigen* (白根), *baige* (白给), *baijier* (白鸡儿), *baijiwa* (白鸡娃), *diluosi* (地螺丝), *gangen* (甘根), *junkouyao* (皲口药), *lianjicao* (连及草), and *yangjiaoqi* (羊角七)[5]. These diverse appellations highlight the importance of this genus in Chinese folk biological culture.

The medicinal material known as '*baiji*' in traditional Chinese medicine (TCM) is usually the dried tuber of *B. striata*, which is also the authentic product included in the Chinese Pharmacopoeia[6]. According to the Chinese Pharmacopoeia (2020), TCM *baiji* is sliced, dried, and crushed into a powder that can be used topically or internally, with a recommended dosage of 3–6 g at a time, offering astringent, hemostatic, detumescence, and myogenic effects. It is often used for conditions such as hemoptysis, hematemesis, traumatic bleeding, sores, and skin chaps[7]. Although only *B. striata* is the authentic product of TCM baiji, the other four *Bletilla* species native to China are also used as substitutes, and this practice is widespread[8].

Modern research indicates that *Bletilla* contains a variety of chemical components, including benzol, dihydrophenanthrene, phenanthrene, and quinone derivatives. These components confer pharmacological effects on *Bletilla*, such as hemostasis, anti-tumor activity, and promotion of cell growth[9]. Due to its outstanding medicinal value, *Bletilla* can be found in nearly every corner of the traditional medicine market (Fig. 1). However, habitat destruction and uncontrolled mining have led to a significant reduction in the native populations of *Bletilla*, making its protection an urgent priority. Therefore, this paper provides a comprehensive review of relevant research up to August 2023, covering botanical characteristics, resource distribution, ethnobotanical uses, chemical components, pharmacological effects, clinical applications, and safety evaluations of *Bletilla*. The aim is to raise awareness and promote the protection and sustainable use of this genus.

Fig. 1 Varieties of *Bletilla* at the traditional March Medicinal Market in Dali, Yunnan, China.

Morphological difference, habitat and distribution

The morphology of different *Bletilla* species is highly similar. The primary taxonomic feature distinguishing each species is the characteristics of the flower, particularly the lip of the flower, including its size, shape, and the number and shape of longitudinal ridges on the lip plate (Table 1, Fig. 2)[10−14].

The flowers of *B. striata* are large and purplish-red or pink, with narrowly oblong sepals and petals measuring 25−30 mm in length and 6−8 mm in width. They have acute apices, nearly as long as the sepals and petals. The lip is obovate or elliptic, predominantly white with purplish-red coloration and purple veins, measuring 23−28 mm in length, slightly shorter than the sepals and petals. The lip disc exhibits five longitudinal folds extending from the base to near the apex of the middle lobe, with waviness occurring only above the middle lobe[11]. In China, *B. striata* is found in regions such as Anhui, Fujian, Guangdong, Guangxi, Gansu, Guizhou, Hubei, Hunan, Jiangsu, Jiangxi, Shaanxi, Sichuan, and Zhejiang. It also occurs in the Korean Peninsula and Japan, thriving in evergreen broad-leaved forests, coniferous forests, roadside grassy areas, or rock crevices, at altitudes ranging from 100−3,200 m[12].

B. ochracea's flowers are medium to large, featuring yellow or yellow-green exteriors on the sepals and petals, while the insides are yellow-white, occasionally nearly white. The sepals and petals are nearly equal in length, oblong, measuring 18−23 mm long and 5−7 mm wide, with obtuse or slightly pointed apices, often adorned with fine purple spots on the reverse side. The lip is elliptic, typically white or light yellow, measuring 15−20 mm in length and 8−12 mm in width, with three lobes above the middle. The lip disc is characterized by five longitudinally ridged pleats, with undulations primarily occurring above the middle lobe[13]. *B. ochracea* is native to southeastern Gansu, southern Shaanxi, Henan, Hubei, Hunan, Guangxi, Guizhou, Sichuan, and Yunnan, thriving in evergreen broad-leaved forests, coniferous forests, or beneath shrubs, in grassy areas or alongside ditches at altitudes ranging from 300−2,350 m[14].

B. formosana's flowers come in shades of lavender or pink, occasionally white, and are relatively small. The sepals and

Table 1. The morphological differences among five species of *Bletilla* plants native to China.

Morphological feature	*Bletilla striata*	*Bletilla formosana*	*Bletilla ochracea*	*Bletilla foliosa*	*Bletilla guizhouensis*
Plant height (cm)	18−60	15−80	25−55	15−20	45−60
Rhizome shape	Compressed	Compressed	Somewhat compressed	Subglobose	Compressed
Rhizome diameter (cm)	1−3	1−2	About 2	1−1.5	3−4
Stem characteristics	Stout	Enclosed by sheaths	Stout	Stout, short	Thin
Leaf shape	Narrowly oblong	Linear-lanceolate	Oblong-lanceolate	Elliptic-lanceolate	Narrowly lanceolate
Leaf size (cm)	8−29 × 1.5−4	6−40 × 0.5−4.5	8−35 × 1.5−2.8	5−12 × 0.8−3	25−45 × 1.2−4.5
Flower color	Purplish red or pink	Pale purple or pink	Yellow	Pale purple	Deep purple
Flower size	Large	Medium	Medium	Small to medium	Large
Inflorescence structure	Branched or simple	Branched or simple	Simple	Simple	Branched
Pedicel and ovary length (mm)	10−24	8−12	About 18	7−9	13−17
Sepal shape	Narrowly oblong	Lanceolate	Lanceolate	Linear-lanceolate	Oblong-elliptic
Petal shape	Slightly larger than sepals	Slightly narrower than sepals	Oblique	Lanceolate	Oblong-elliptic
Lip shape	Obovate-elliptic	Broadly elliptic	Narrowly rhombic-obovate	Narrowly oblong	Narrowly oblong
Lip color	White with purplish veins	Whitish to pale yellow with small dark purple spots	Whitish to pale yellow with small dark purple spots	White with purplish spots and purple edge	White with deep purple edge
Number of lip Lamellae	5 lamellae	5 undulate lamellae	5 longitudinal lamellae	3 fimbriate lamellae	7 longitudinal lamellae
Column characteristics	Subterete, dilated towards apex	Subterete, dilated towards apex	Slender, dilated towards apex	Cylindric, dilated towards apex	Suberect, with narrow wings

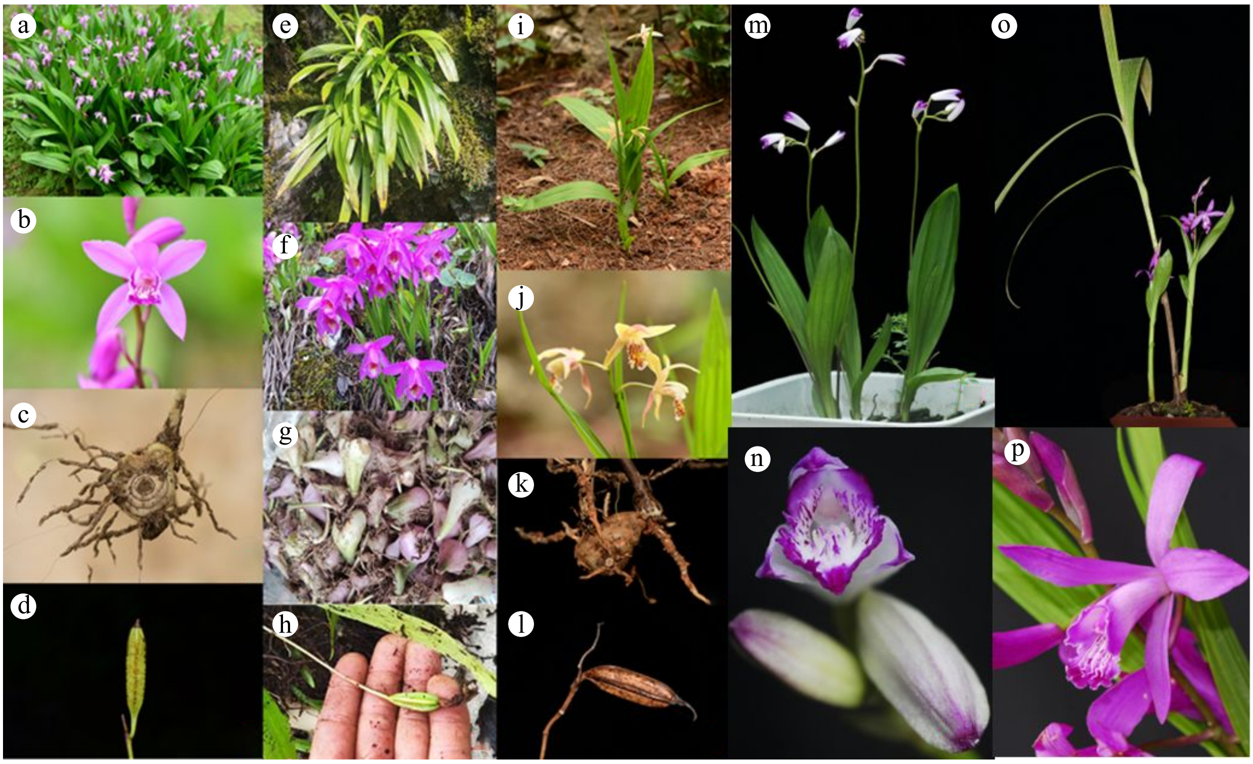

Fig. 2 (a)−(d) *Bletilla striata* (Thunb. ex Murray) Rchb. f. (e)−(h) *Bletilla formosana* (Hayata) Schltr. (i)−(l) *Bletilla ochracea* Schltr. (m), (n) *Bletilla sinensis* (Rolf) Schltr. (o), (p) *Bletilla guizhouensis* Jie Huang & G.Z. Chen (Photographed by Wang Meina, Zhu Xinxin, and He Songhua).

petals are narrowly oblong, measuring 15−21 mm in length and 4–6.5 mm in width, and are nearly equal in size. The sepals have subacute apices, while the petal apices are slightly obtuse. The lip is elliptic, measuring 15−18 mm in length and 8–9 mm in width, with three lobes above the middle. The lip disc exhibits five longitudinal ridge-like pleats, which are wavy from the base to the top of the middle lobe[15]. *B. formosana* is indigenous to southern Shaanxi, southeastern Gansu, Jiangxi, Taiwan, Guangxi, Sichuan, Guizhou, central to northwest Yunnan, southeast Tibet (Chayu), and Japan. It is typically found in evergreen broad-leaved forests, coniferous forests, road verges, valley grasslands, grassy slopes, and rock crevices, at altitudes ranging from 600–3,100 m[16].

The flowers of *B. foliosa* are small and lavender, with white sepals and petals featuring purple apices. The sepals are linear-lanceolate, measuring 11−13 mm in length and 3 mm in width, with subacute apices. The petals are lanceolate, also measuring 11−13 mm in length and 3 mm in width, with acute apices. The lip is white, oblong, adorned with fine spots, and features a purple apex. It measures 11−13 mm in length and 5–6 mm in width, tapering near the base and forming a scaphoid shape. The lip is anteriorly attenuated, unlobed, or abruptly narrowing with inconspicuous three lobes and exhibits fringe-like fine serrations along the edge. Three longitudinal ridge-like pleats are present on the upper lip disc[17]. *B. foliosa* typically grows on hillside forests, with its type specimen collected from Mengzi City, Honghe Hani and Yi Autonomous Prefecture, Yunnan Province, China[17].

B. guizhouensis is a recently discovered species in Guizhou, China. In terms of shape, *B. guizhouensis* closely resembles *B. striata*, but it can be distinguished by its ovate-oblong buds, oblong dorsal sepals, obovate lips, and middle lobes of the lips, which are oval in shape. The disc of *B. guizhouensis* features seven distinct longitudinal lamellae, setting it apart from other known *Bletilla* species and establishing it as a distinct species[2]. Presently, *B. guizhouensis* has only been found in Guizhou, China, primarily thriving in evergreen broad-leaved forests at altitudes ranging from 900−1,200 m[3].

Understanding the morphology, habitat, and distribution of *Bletilla* species is crucial for the conservation and propagation of these resources. To effectively implement plant conservation and breeding programs, a comprehensive understanding of the specific morphological characteristics, growth environments, and native habitats of these plants is essential, as without this knowledge, effective results cannot be achieved.

Ethnobotanical uses

The ethnobotanical uses of *Bletilla* worldwide primarily fall into two categories: ornamental and medicinal purposes. *Bletilla* orchids, renowned for their striking and distinct flowers, are commonly cultivated for ornamental purposes across many countries[18]. Valued for their aesthetic appeal, these orchids are frequently grown in gardens and utilized as potted plants. Among the various cultivars, *B. striata* stands out as the most favored choice for ornamental horticulture due to its ease of cultivation and adaptability to diverse climates[19,20].

Contrastingly, in select Asian countries, *Bletilla* assumes a crucial role as a medicinal plant. For instance, influenced by TCM, the tuber of *Bletilla* also serves as a crude drug for hemostatic and anti-swelling purposes in Japan[21]. Likewise, traditional Korean medicine, deeply rooted in TCM principles, extensively documents the versatile use of *Bletilla* in addressing issues such as alimentary canal mucosal damage, ulcers, bleeding, bruises, and burns[22]. In Vietnam, *Bletilla* has been used as a medicinal herb for treating tumors and skin fissures, aligning with practices observed in the ethnic communities of southwest China[23].

In China, *Bletilla* boasts a longstanding medicinal history, with numerous classical ancient Chinese medicine books containing detailed records of its medicinal applications[24−32]. Even in contemporary society, many ethnic groups residing in mountainous areas in China continue to uphold the traditional medical practice of using *Bletilla* medicinally[31].

Ancient medicinal book records

Morphological description

In ancient Chinese medical literature, detailed records of *Bletilla*'s morphology can be traced back to the late Han Dynasty, around 200 AD[24]. The *Mingyi Bielu*, a historical source, documented, '*Bletilla* grows in the valley, with leaves resembling those of *Veratrum nigrum* L., and its root is white and interconnected. The ideal time for harvesting is September'. As awareness of the medicinal significance of *Bletilla* grew, successive dynastic-era Chinese medical texts consistently included descriptions of Bletilla's morphology (Table 2). In the Ming Dynasty, Li Shizhen compiled these earlier accounts of *Bletilla*'s plant characteristics in his work, the *Compendium of Materia Medica*. He even provided an illustrative depiction of this plant genus (Fig. 3)[25].

Generally, ancient Chinese medical texts did not make clear distinctions between different *Bletilla* species. They collectively referred to plants with similar morphological traits as '*baige*', '*baigen*', '*baiji*', '*gangen*', '*lianjicao*', or '*ruolan*'. However, through textual analysis, it has been established that the descriptions of *Bletilla* in ancient texts before the Ming Dynasty largely align with *Bletilla striata* in terms of plant height, pseudo-bulb shape, leaf morphology, flower and fruit colors, and other characteristics. While the *Bletilla* portrayed in attached images may not precisely match *B. striata* in terms of morphology, considering the textual descriptions, it generally corresponds with *B. striata*. In writings from the Ming Dynasty and later periods, more specific descriptions of *Bletilla* emerged, encompassing details about its vascular arrangement, inflorescence, and flower structure, which consistently align with *B. striata*. Consequently, researchers have corroborated that the original plant of *Bletilla* described in ancient texts is *Bletilla striata*[24,33].

Medicinal effect

According to the ancient Chinese medicinal books, *Bletilla* was used to treat a wide variety of conditions, including coughing, bruising, and bleeding, but their most mentioned use in ancient Chinese texts is for skin whitening and freckle removal[25]. Since ancient times, *Bletilla* species have been used consistently for skin care and whitening, and there are many well-known skincare products related to *Bletilla*. These Chinese formulae with *Bletilla* are similar to modern facial masks, face creams, facial cleanser, hand creams and other skin care products[26].

For example, a prescription for 'facial fat (面脂)' in *Medical Secrets from the Royal Library* (752 AD) is made by boiling *Bletilla* with other traditional ingredients, and is applied to the face, resulting in skin whitening, freckle and wrinkle removal[27]. The '*Angelica dahurica* cream (白芷膏)' in the *General Medical*

Table 2. Morphological description of the plants belonging to Bletilla in the ancient Chinese medicinal books.

Dynasty (Year)	Title	Author	Original Chinese	English translation
Late Han (184–220 AD)	Mingyi Bielu	/	白给生山谷, 叶如藜芦, 根白相连, 九月采	*Bletilla* grows in the valley, with leaves like *Veratrum nigrum* L., root is white and connected. September is the time for harvesting.
Wei-Jin period (220–420 AD)	WuPu Bencao	Wu Pu	白根, 茎叶如生姜, 藜芦, 十月花, 直上, 紫赤色, 根白连, 二月, 八月, 九月采	*Bletilla*, stems and leaves like *Zingiber officinale* Roscoe and *V. nigrum*. It blooms in October and is purple and red, the inflorescence is vertical and upward. The roots are white and connected. It can be dug in February, August, and September.
the Northern and Southern (420–589 AD)	Bencao Jizhu	Tao Hongjing	近道处处有之, 叶似杜若, 根形似菱米, 节间有毛	It is everywhere near the road. The leaves are like *Pollia japonica* Thunb. The roots are like the fruit of *Trapa natans* L., and internode are many fibrous roots.
Tang (618–907 AD)	Su Jing, Zhangsun Wuji, etc	Tang materia medica	生山谷, 如藜芦, 根白连, 九月采	Born in the valley, with leaves like *V. nigrum*, root is white and connected. September is the time for harvesting.
Song (960–1279 AD)	Su Song	Commentaries on the Illustrations	白芨, 生石山上。春生苗, 长一尺许, 似栟榈及藜芦, 茎端生一台, 叶两指大, 青色, 夏开花紫, 七月结实, 至熟黄黑色。至冬叶凋。根似菱米, 有三角白色, 角端生芽。二月, 七月采根	*Bletilla* grow on the stone hill. It sprouts in spring and grows about a foot long. The seedlings are like *Trachycarpus fortunei* (Hook.) H. Wendl. and *V. nigrum*. The leaves are two finger-size. In summer, it blooms purple flowers and bears fruit in July. The ripe fruit is yellow-black. The leaves wither in winter. The root is like the fruit of *T. natans*, with three corners, white, and sprouting at the corners. The roots are dug in February and July.
Ming (1368–1644 AD)	Li Shizhen	Compendium of Materia Medica	一棵只抽一茎, 开花长寸许, 红紫色, 中心如舌, 其根如菱米, 有脐, 如凫茈之脐, 又如扁扁螺旋纹, 性难干	Only one stem per herb. The flower is more than one inch long, red and purple, and the center resembles a tongue. Its root is similar to the fruit of *T. natans*, possessing an umbilicus akin to that of *Eleocharis dulcis* (N. L. Burman) Trinius ex Henschel. It has spiral veins and is challenging to dry.

–, Anonymous.

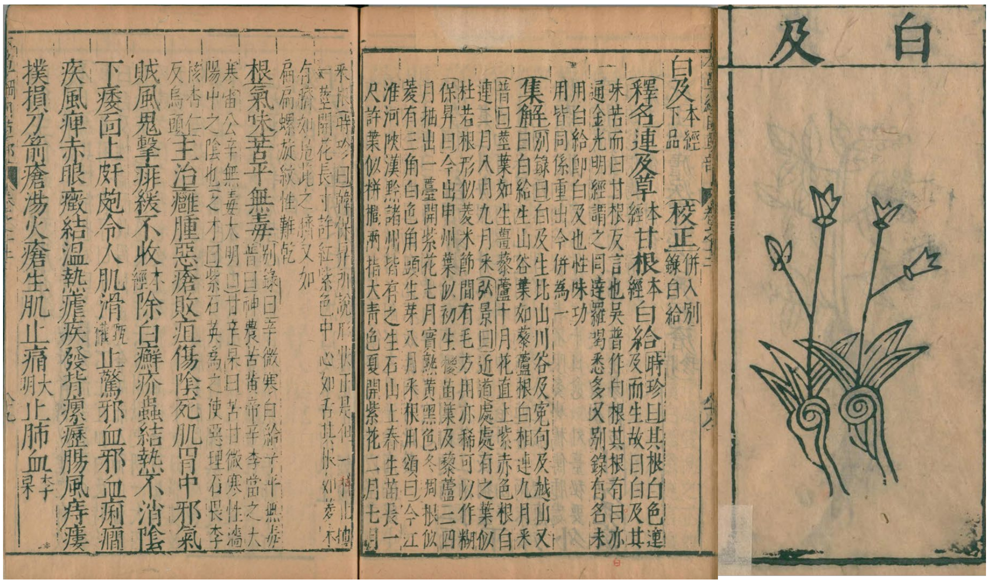

Fig. 3 *Bletilla* in *Compendium of Materia Medica.*

Collection of Royal Benevolence (1111–1125 AD) is reputed to whiten facial skin through a seven-day treatment regiment, and contains *Bletilla* as the main botanical ingredient along with *Angelica dahurica*[28]. *Jingyue Quanshu* (1563-1640 AD) also contains a prescription called 'Yurong powder (玉容散)' for facial skin care. 'Yurong powder' is made of a fine powder of *Bletilla*, *Nardostachys jatamansi* (D. Don) DC., *Anthoxanthum nitens (Weber)* Y. Schouten & Veldkamp and other herbs[29]. Washing the face with Yurong powder in the morning and evening every day is said to make a person's face white without blemishes (Fig. 4)[29].

In addition, in ancient Chinese medicine texts, *Bletilla* is also a well-known medicine for treating hematemesis, hemoptysis and bruises[23]. According to *Shennong's Classic of Materia Medica* (25–220), grinding the white fungus into fine powder and taking it after mixing with rice soup can be effective for treating lung damage and hematemesis[30]. Among the *Prescriptions for Universal Relief* (1406), 18 traditional Chinese medicines, such as *Bletilla*, are used to make 'snake with raw meat cream', which is said to be useful to treat carbuncles and incised wounds[31]. There is also a record of *Bletilla* powder treating lung heat and hematemesis in the *Collected Statements on the Herbal Foundation* (1624)[32].

In ancient Chinese medicinal texts, most *Bletilla* are said to be useful for lung injury and hemoptysis, epistaxis, metal-inflicted wounds, carbuncles, burns, chapped hands and feet, whitening and especially for skin care. In the ancient medicinal texts, *Bletilla* is used alone or mixed with other traditional Chinese medicines. It is usually used in the form of a powder. The various medicinal effects of *Bletilla* described in these ancient texts suggest the great potential of this genus in clinical application, especially in the market of skin care products and cosmetics.

Traditional folk application

As a skin care herb praised by ancient medical classics, 11 ethnic minorities in China, such as Bai, Dai, De'ang, Jingpo, Lisu, Miao, Mongolian, Mulao, Tu, Wa, and Yi still retain the traditional habit of using *Bletilla* for skin care in their daily life (Table 3). In addition to *B. striata, B. formosana* and *B. ochracea* are also used as substitutes. Although Chinese ethnic groups have

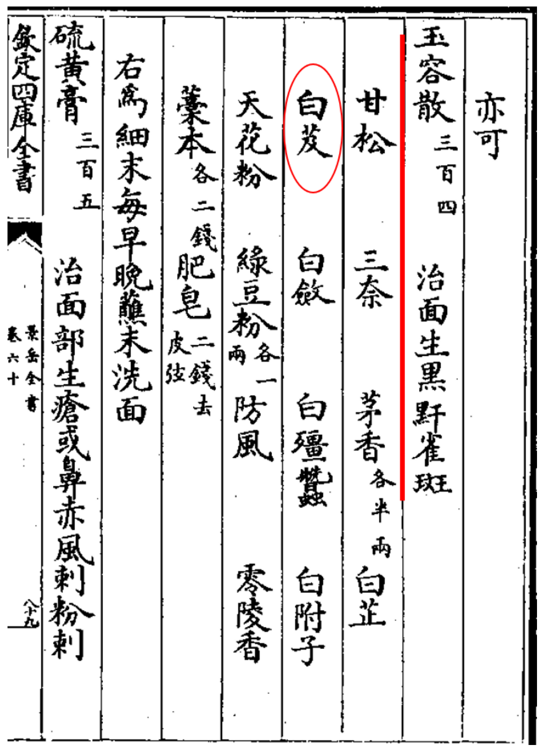
亦可
玉容散 三百四 治面生黑野雀斑
甘松 三柰 茅香各半兩 白芷
白芨 白斂 白殭蠶 白附子
天花粉 綠豆粉各一兩 防風 零陵香
藁本各二錢 肥皂二錢去皮弦
右爲細末每早晚蘸末洗面
硫黃膏 三百五 治面部生瘡或鼻赤風刺粉刺
欽定四庫全書 景岳全書 卷六十

Fig. 4 Yurong powder made of *Bletilla* and other traditional Chinese medicines in *Jingyue Quanshu*.

different names for *Bletilla* spp., the skin care methods are basically the same. Dry *Bletilla* tubers are ground into a powder and applied to the skin[34], and this usage is also confirmed by the records in ancient medical texts[23,24]. The various local names of *Bletilla* by different ethnic groups also indirectly suggests which ethnic groups play an important role in the traditional use. For example, Bai people called *B. striata baijier* (白鸡儿), *goubaiyou* (狗白尤), and *yangjiaoqi* (羊角七) (Table 3).

The formation of traditional medical knowledge among Chinese people is often directly related to the specific living environment and cultural background[34]. For example, the Bai,

Table 3. The traditional medicinal knowledge of *Bletilla* in ethnic communities, China.

Ethnic group	Latin name	Local name	Used part	Use method	Medicinal effect
Achang	*Bletilla striata* (Thunb. ex Murray) Rchb. F.	Baiji	Tuber	After the roots are dried, chew them orally or grind them into powder for external application	Tuberculosis, hemoptysis, bleeding from gastric ulcer, burns and scalds
Bai		Baijier, Goubaiyou, Yangjiaoqi	Tuber		Treatment of tuberculosis hemoptysis, bronchiectasis hemoptysis, gastric ulcer hemoptysis, hematochezia, skin cracking
Dai		Yahejie	Tuber		Used for tuberculosis, tracheitis, traumatic injury, and detumescence
De'ang		Bagerao	Tuber		Tuberculosis, hemoptysis, bleeding from gastric ulcer, burns and scalds
Dong		Shaque, Sanjue	Tuber		Treat hematemesis and hemoptysis
Jingpo		Lahoiban, Pusehzuo	tuber		For tuberculosis, bronchiectasis, hemoptysis, gastric ulcer, hematemesis, hematuria, hematochezia, traumatic bleeding, burns, impotence
Meng		Moheeryichagan, Nixing	Tuber		For tuberculosis hemoptysis, ulcer bleeding, traumatic bleeding, chapped hands, and feet
Miao		Bigou, Wujiu, Sigou	Tuber		Used for hemoptysis of tuberculosis, bleeding of ulcer disease, traumatic bleeding, chapped hands, and feet
Molao		Dajieba	Tuber		Treat internal and external injuries caused by falls
Tibetan		Sanchabaiji	Tuber	Fresh chopped and soaked with honey; Powdered after sun-dried, then taken with honey and water	Mainly used to treat cough, asthma, bronchitis, lung disease and a few gynecological diseases
Tu		Ruokeye	Tuber	After the roots are dried, chew them orally or grind them into powder for external application	Treatment of tuberculosis, hemoptysis, bloody stool, chapped skin
Wa		Baiji	Tuber	After the roots are dried, chew them orally or grind them into powder for external application	For tuberculosis, hemoptysis, gastrointestinal bleeding, scald and burn
Yao		Biegeidai	Tuber		Treat gastric ulcer, pulmonary tuberculosis, cough, hemoptysis, and hematemesis
Yi		Daibaij, Tanimobbaili, Niesunuoqi, Atuluobo	Tuber		Treatment of tuberculosis, hemoptysis, golden wound bleeding, burns, chapped hands and feet
Zhuang		Manggounu	Tuber		Treat stomachache and hemoptysis
Bai	*Bletilla formosana* (Hayata) Schltr.	Baijier, Yangjiaoqi	Tuber	After the roots are dried, chew them orally or grind them into powder for external application	It is used for emesis, hemoptysis due to tuberculosis, and hemoptysis due to gastric ulcer. External application for treatment of incised wound
Miao		Lianwu	Tuber		The effect is the same as that of *B. striata*
Lisu		Haibiqiu	Tuber		It can treat tuberculosis, hemoptysis, epistaxis, golden sore bleeding, carbuncle and swelling poison, scald by soup fire, chapped hands and feet
Yi		Niesunuoqi, Yeruomaoranruo, Atuluobo, Ribumama, Atuxixi, Abaheiji, Binyue, Ziyou	Tuber		It is used for tuberculosis, hemoptysis, traumatic injury, treatment of frostbite, burn, scald, bed-wetting of children and other diseases
Bai	*Bletilla ochracea* Schltr.	Baijier, Yangjiaoqi	Tuber	After the roots are dried, chew them orally or grind them into powder for external application	For hematemesis, epistaxis, hemoptysis due to tuberculosis, hemoptysis due to gastric ulcer; External application of golden sore and carbuncle
Meng		Moheeryichagan, Nixing	tuber		The effect is the same as that of *B. striata*

Dai, De'ang, Jingpo, Lisu Yi, Wa and other ethnic minorities live in mountainous areas. The cold weather in winter and year-round outdoor manual work makes it difficult to maintain their skin[35,36]. In the face of this situation, the ethnic people who are concerned about their physical appearance have long ago chosen local *Bletilla* species for skin care, and have handed down this tradition for many generations[34]. This important traditional skin care tradition is worthy of further in-depth study.

Chemical constituents

The six main classes of *Bletilla* chemical components, phenanthrene derivatives, phenolic acids, bibenzyls, flavonoids, triterpenoids, and steroids, have been described previously. Almost three hundred compounds have been isolated from *Bletilla*, including 116 phenanthrene derivatives, 58 phenolic acids, 70 bibenzyls, 8 flavonoids, 24 triterpenoids and steroid and 13 other compounds (Figs 5–14). Chemical structures of the isolates of *Bletilla* species most are phenanthrene derivatives, which have been demonstrated to possess various pharmacological activities.

Phenanthrene derivatives

The prominent opioids oxycodone, hydrocodone, naloxone, and naltrexone are all phenanthrene derivatives[37]. Currently, phenanthrene derivatives (Fig. 5, **1** to **66**) were isolated from *B. formosana*, *B. ochracea*, and *B. striata*. In 2022, 17 phenanthrene derivatives (**1**–**17**) were isolated from the ethyl acetate (EtOAc) extracts of *B. striata* tubers[38]. Then, other phenanthrene derivatives were isolated from *Bletilla*, such as dihydrophenanthrenes (**18**–**41**), phenanthrenes (**42**–**66**), biphenanthrenes (Fig. 6, **67**–**89**), dihydro/phenanthrenes with uniquestructures (**90**–**112**) and phenanthraquinones (Fig. 7, **113**–**116**). Thus far, this genus has been documented to include these compounds, which have been shown to exhibit pharmacological actions[39–45].

Phenolic acids

Phenolic acids are carboxylic acids created from the skeletons of either benzoic or cinnamic acids[46–48]. Fifty-eight phenolic acids (Figs 8–10, **117** to **174**) were isolated from *B. formosana*, *B. ochracea*, and *B. striata*.

For example, compounds **121**, **126**, **139**, **141**, **148**, **149**, **154**, **155** and **157** were isolated from the rhizomes of *B. formosana*[1,49,50–52]. The structures of these compounds were

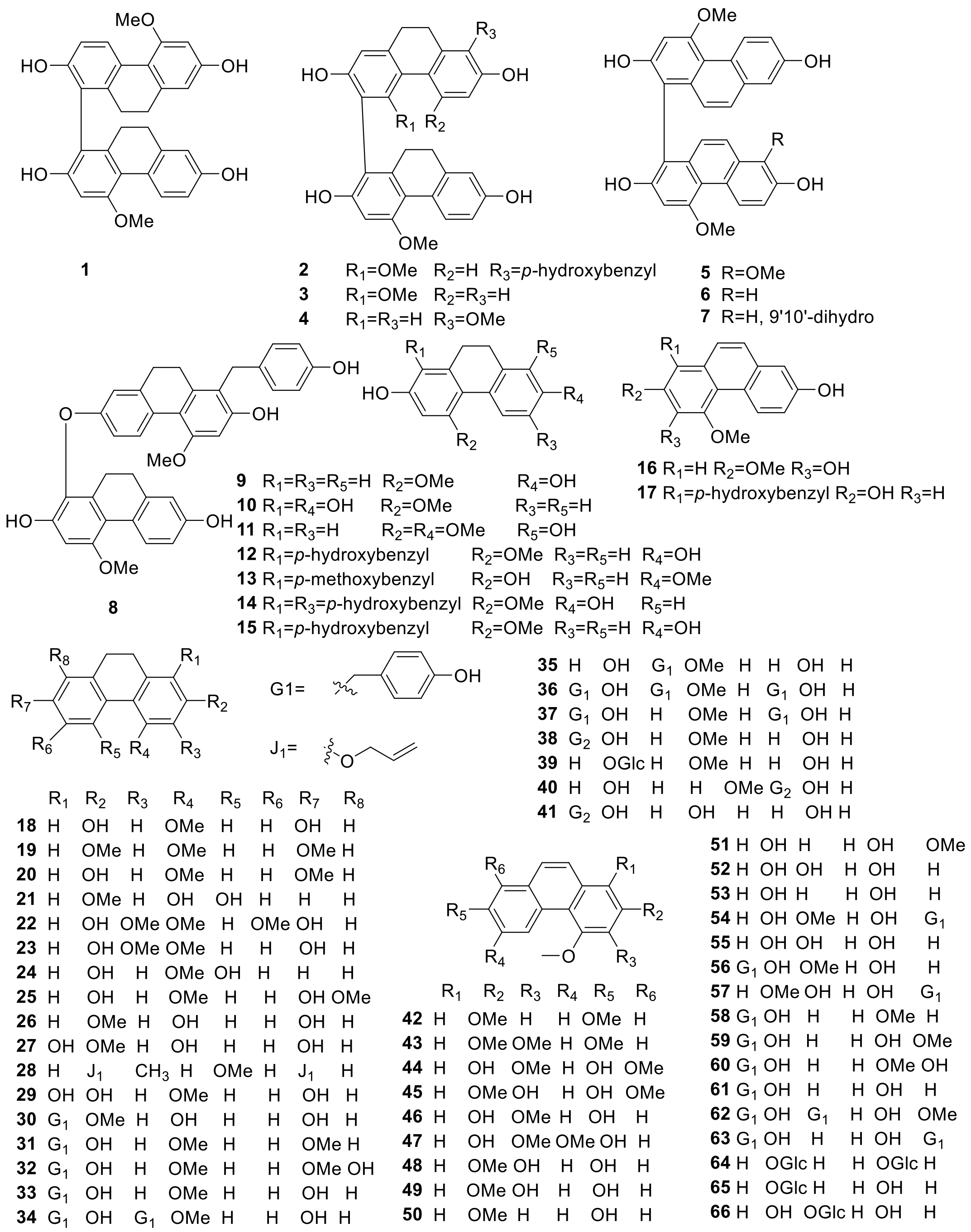

Fig. 5 Phenanthrene derivatives from *Bletilla* species (1–66)[38–41,43–45,47,49,58,70–72,74–79].

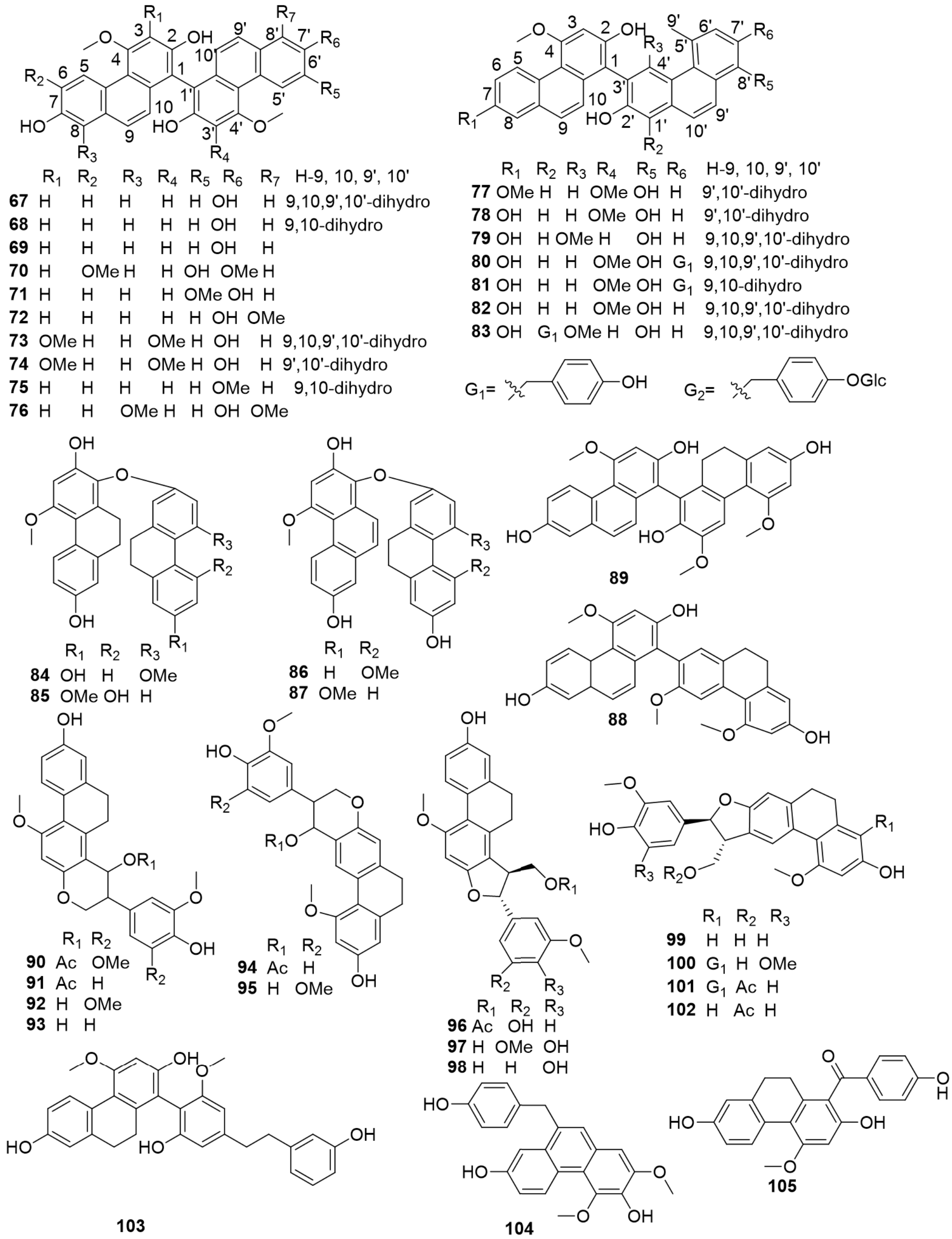

Fig. 6 Phenanthrene derivatives from *Bletilla* species (67−105)[41,43,49,59−61,70,76,79−86].

determined, mostly from their NMR spectroscopy data. Additionally, protocatechuic (**136**) and vanillin (**137**) also have been isolated from *B. striata*[53]. Moreover, some bioactive components such as 2-hydroxysuccinic acid (**164**) and palmitic acid (**165**) have been discovered and identified from *B. striata*[20,54−56].

Bibenzyls

The bibenzyls were small-molecular substances with a wide range of sources, which were steroidal ethane derivatives and resembling the structural moiety of bioactive iso-quinoline alkaloids[57].

For example, depending on their structural characteristics, 70 bibenzyl compounds (Fig. 11, **175** to **244**) can be grouped into three groups, simple bibenzyls (**175**–**186**, **233**–**238**), complex bibenzyls (**189**–**225**) and chiral bibenzyls (**226**-**232**, **239**-**244**)[58−60].

Flavonoids

Flavonoids are among the most common plant pigments. Eight bibenzyls (Fig. 12, **245** to **252**) have been isolated from *B. formosana*, *B. ochracea*, *and B. striata*. Apigenin (**245**) and 8-C-*p*-hydoxybenzylkaempferol (**249)** were isolated from the whole plant of *B. formosana*[45]. Bletillanol A (**250**), bletillanol B (**251**)

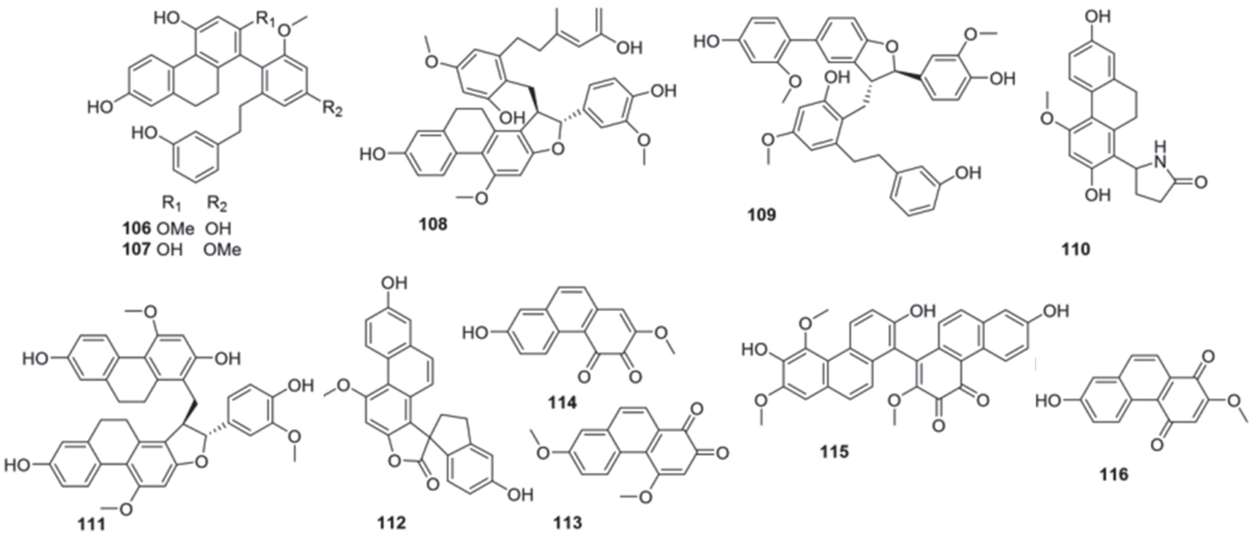

Fig. 7 Phenanthrene derivatives from *Bletilla* species (106−116)[43,49,70,75,84,85,87].

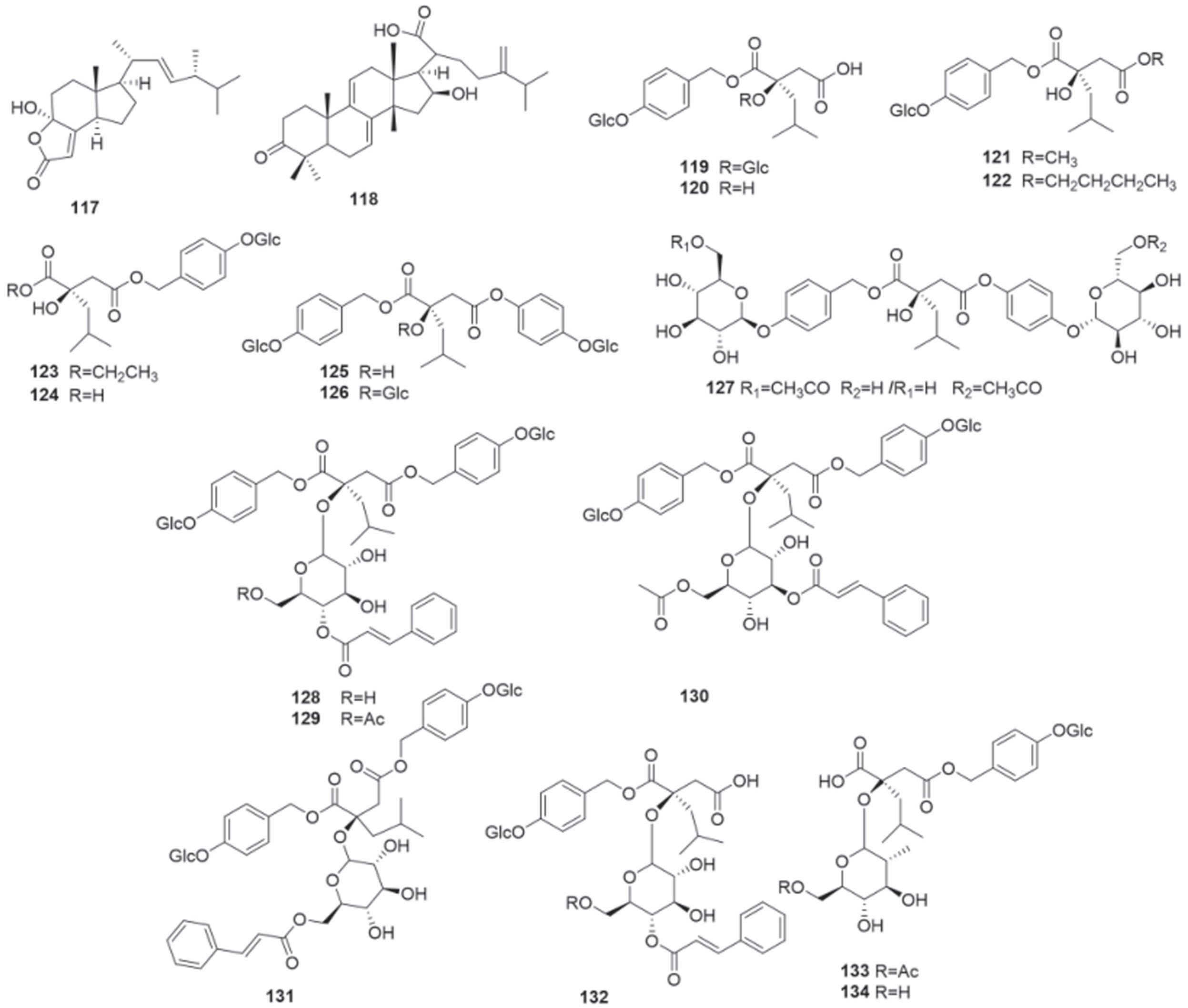

Fig. 8 Phenolic acids from *Bletilla* species (117−134)[1,5,36,47−52,54,67,88,90].

and tupichinol A (**252)** were isolated from *B. striata*[61]. The names and chemical structures of the flavonoids reported from *Bletilla* are shown below (Fig. 12).

Triterpenoids and steroids

Twenty-four triterpenoids and steroids (Fig. 13, **253** to **276**) have been reported from *Bletilla* (Fig. 13), such as, tetracyclic

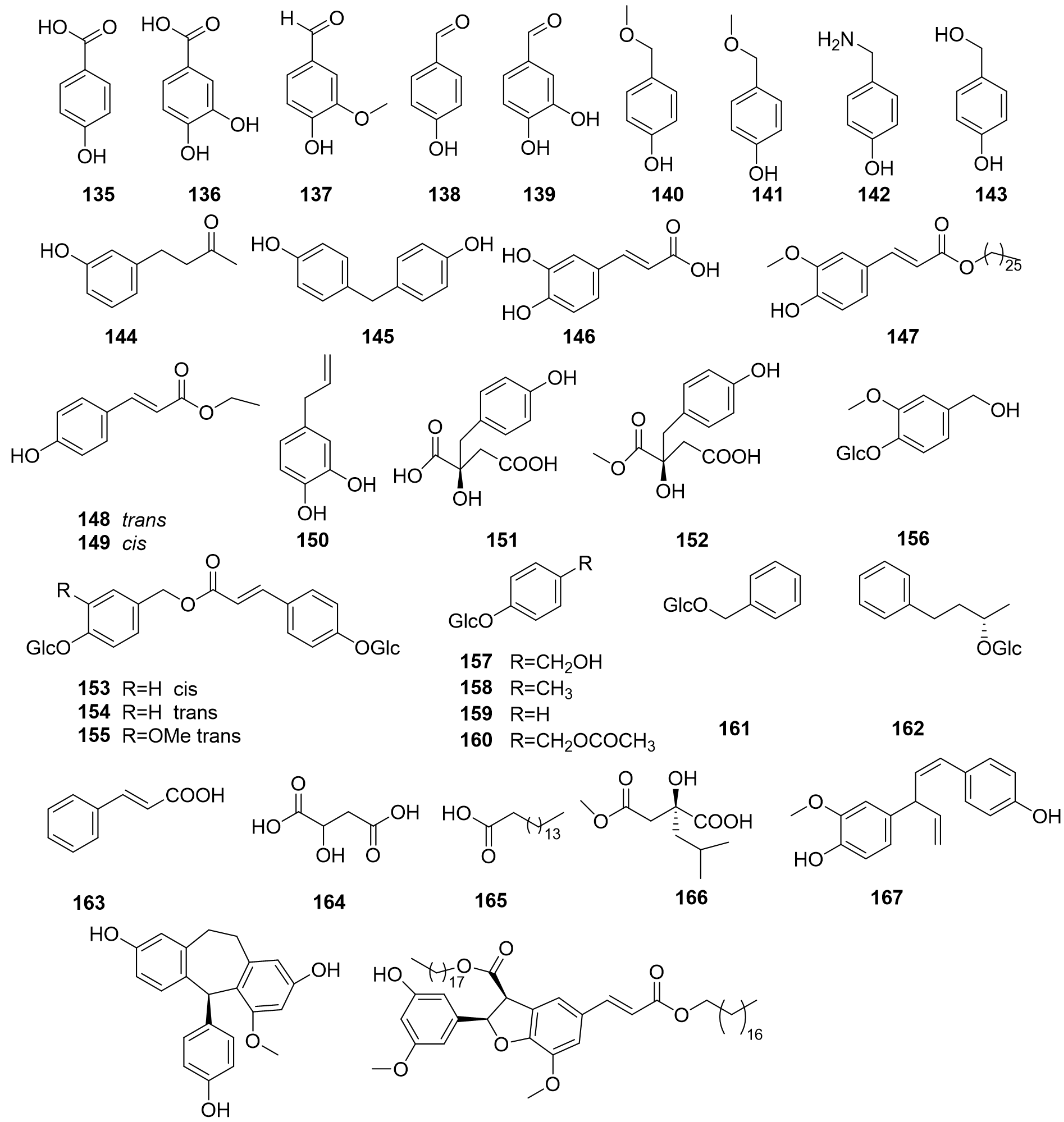

Fig. 9 Phenolic acids from *Bletilla* species (135–169)[39,45,48–54,56,61,68,69,73,76,82,83,89–94].

triterpenes (**253**–**259**) and pentacyclic triterpenes (**189**–**225**) and chiral bibenzyls (**260**)[62–64]. Steroids (**261**–**276**) isolated from the *Bletilla* and have shown some bioactivity. For example, bletilnoside A (**272**) was isolated from *Bletilla* species and displayed anti-tumor activity[65,66].

Other compounds

Thirteen other compounds (Fig. 14, **277** to **289**) were isolated from *B. formosana*, *B. ochracea*, and *B. striata*. These compounds included amino acids, indoles and anthraquinones[67,68]. For example, syringaresinol (**285**) and pinoresinol **(286**) have been described in the methanol extract of the tubers of *B. striata*[61].

Based on the information about the chemical constituents of *Bletilla* species, it appears that there is a substantial body of research on these compounds. However, there are some areas that may warrant further investigation and research. At first, it would be valuable to investigate potential synergistic effects and interactions between the different classes of compounds within *Bletilla* species, as some of the compounds may work together. Besides, it is worth considering the improvement of compound yield. Optimizing extraction methods and finding the most efficient and environmentally friendly techniques are vital for both research purposes and potential commercial applications. It is also important to take into account the variability in chemical composition among different *Bletilla* species and even within the same species from different cultivars.

Pharmacological activities

The rich and varied chemical components make the plants of *Bletilla* have a wide variety of pharmacological activities (Table 4). Many studies have shown that the plants of this genus have anti-inflammatory, antineoplastic, antiviral, antioxidant, hemostatic, antibacterial, and other biological activities, which help to support the traditional medicinal practice of *Bletilla* in folk medicine.

Anti-inflammatory

Many phytochemicals have been well characterized to lessen swelling or inflammation[89]. A series of phenolic acid and

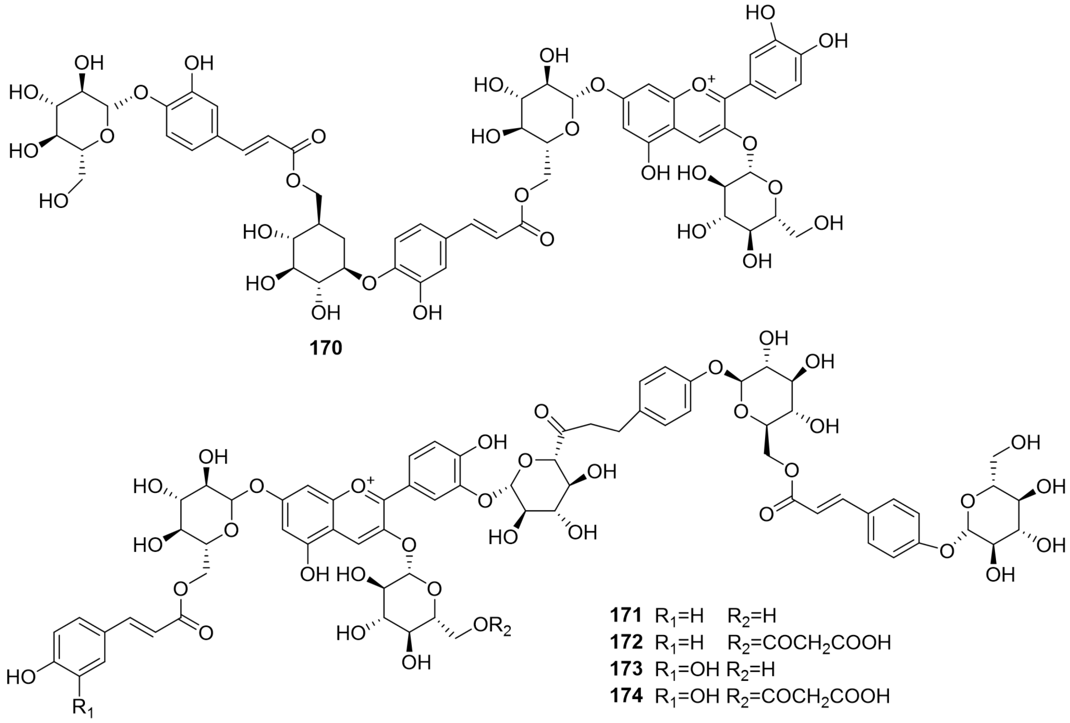

Fig. 10 Phenolic acids from *Bletilla* species (170–174)[20,95].

polysaccharide compounds isolated from *Bletilla* demonstrated anti-inflammatory bioactivity against BV-2 microglial, RAW 264.7, and PC12 cells[96,100−102]. For example, phochinenin K (**106**) exhibited growth inhibitory effects with an IC_{50} of 1.9 μM, and it is a possible candidate for development as neuroinflammation inhibitory agent[43]. Using the H_2O_2-induced PC12 cell injury model, (7*S*)-bletstrin E (**242**), (7*R*)-bletstrin F (**243**) and (7*S*)-bletstrin F (**244**) could clearly protect the cells with the cell viabilities of 57.86% ± 2.08%, 64.82% ± 2.84%, and 64.11% ± 2.52%, respectively[98]. With an IC_{50} of 2.86 ± 0.17 μM, 2,7-dihydroxy-4-methoxyphenanthrene (**53**) showed potential action against NO generation in RAW 264.7 macrophages[54]. The use of *Bletilla* in traditional skin care, it is said to function as an astringent, hemostatic and wound healing[33]. Modern medical pharmacology research has validated that this plant has antibacterial effects, which may may help to explain, in part, its traditional use in skin care[24].

Though it's mentioned that some of these compounds from *Bletilla* have demonstrated anti-inflammatory action, more extensive studies are needed to fully understand their mechanisms of action, potential therapeutic applications, and safety profiles. Conducting *in vivo* studies and clinical trials can provide more concrete evidence of their effectiveness.

Anti-tumor

There are important antineoplastic agents that have originated from plant natural products[103]. In recent years, several bibenzyl and flavonoid compounds have been discovered from *Bletilla* that have antineoplastic activity against A549 cells and other cells. For example, 7-hydroxy-2-methoxy-phenanthrene-3,4-dione (**160**) and 3′,7′,7-trihydroxy-2,2′,4′-trimethoxy-[1,8′-biphenanthrene]-3,4-dione (**163**) have shown strong antiproliferative effects and induced ROS production after 24 h in A549 cells[87]. The doxorubicin (Dox)/FA (folate)-BSP-SA (stearic acid) modified *Bletilla striata* polysaccharide micelles boosted the drug enrichment in tumors and improved the *in vivo* anticancer effects[104,105]. Micelles, nanoparticles, microspheres, and microneedles are examples of *B. striata* polysaccharide-based drug delivery systems that exhibit both drug delivery and anti-cancer functionality. These experiments confirmed that some of the compounds isolated from the *Bletilla* have potential activity for the treatment of cancer.

However, most of the evidence presented in the previous studies is based on *in vitro* experiments or cell culture studies. It is highly necessary to use animal models to study the *in vivo* anti-tumor effects of *Bletilla* extracts or compounds. These studies can help evaluate the safety and effectiveness of treatments based on *Bletilla*. Additionally, through such methods, researchers can further investigate the mechanisms of *Bletilla's* anti-tumor activities, exploring how *Bletilla* compounds interact with cancer cells, immune responses, and signaling pathways involved in tumor growth and metastasis.

Antiviral

Antiviral medications are essential for preventing the spread of illness, and are especially important nowadays with pandemics and drug-resistant viral strains[5,6]. Therefore, it is vitally necessary to find novel, safe, and effective antiviral medications to treat or prevent viral infections[106]. *B. striata* plant contains compounds that have been recorded in ancient texts to cure cough, pneumonia, and skin rashes, and these may be related to potential antiviral constituents[23]. Some constituents of *B. striata* have antiviral activity, for example, phenanthrenes and diphenanthrenes from *B. striata* displayed potent anti-influenza viral in a Madin-Darby canine kidney model and embryonated eggs model, diphenanthrenes with parentally higher inhibitory activity than monophenanthrenes[107]. But more research is needed to further determine the antiviral activity of *Bletilla*, understand how *Bletilla* compounds interact with viral proteins or the host immune response, and conduct

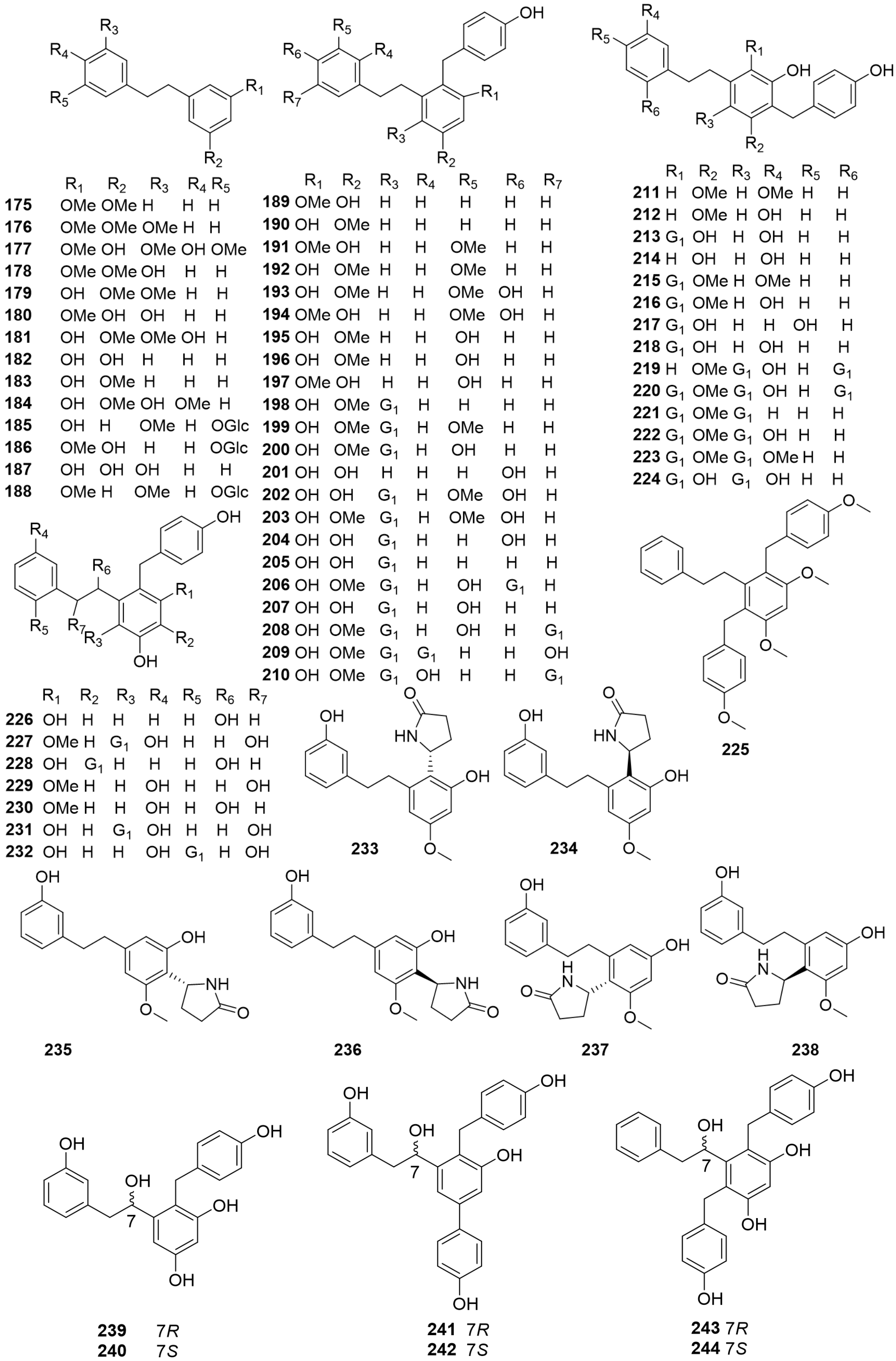

Fig. 11 Bibenzyls from *Bletilla* species (175-244)[1,40−42,47,49,50,58−60,70,73,76,96−99].

safety and toxicity studies, which are crucial for the development of related materials.

Antioxidant

Free radicals have the potential to exacerbate lipid peroxidation and harm cell membranes, which can lead to several prevalent human diseases, including cancer, cataracts, and coronary heart disease[108]. Research has shown that extracts from *Bletilla* possess strong antioxidant activity. However, this

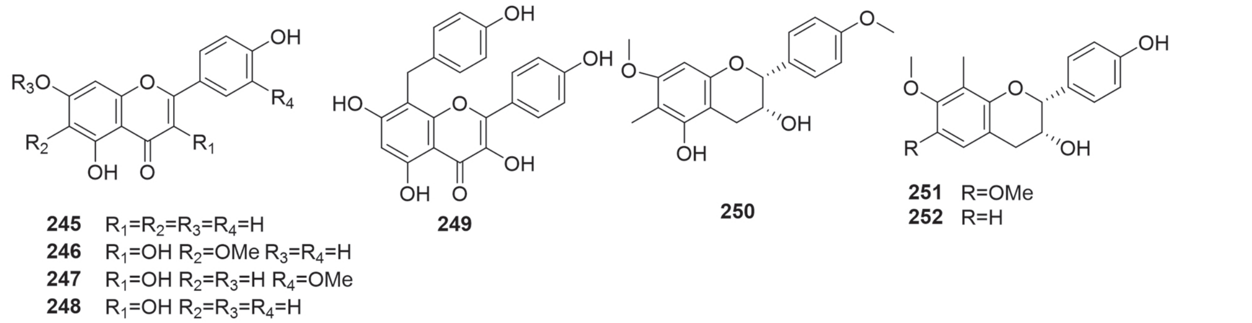

Fig. 12 Flavonoids from *Bletilla* species (245–252)[45,61].

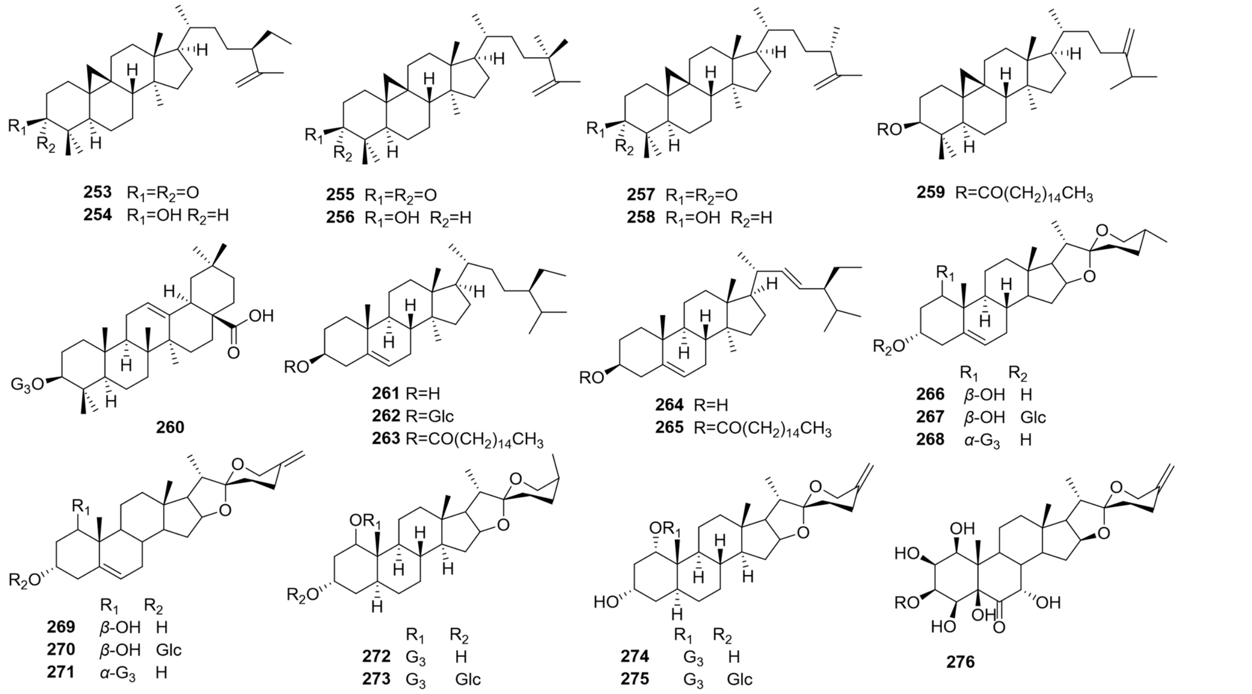

Fig. 13 Triterpenoids and steroid compounds from *Bletilla* species (253-276)[56,62–65].

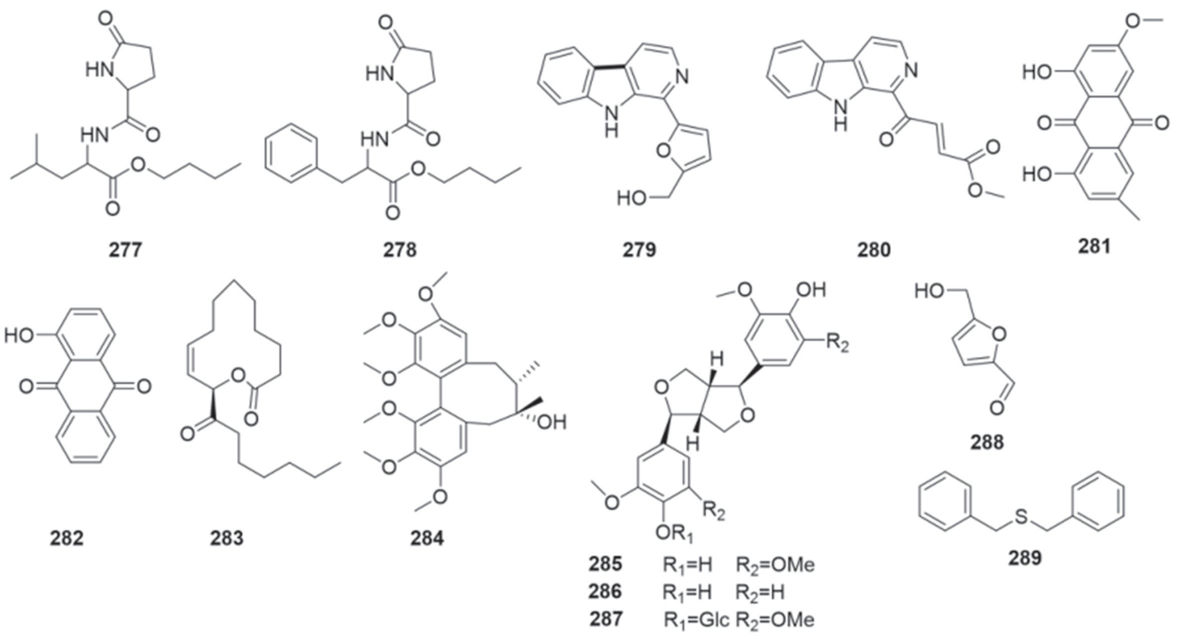

Fig. 14 Others compounds from *Bletilla* species (277–289)[50,54,61,62,67,68,94,97].

Table 4. Summary of the pharmacological activities of *Bletilla* species.

Pharmacological activity	Tested substance/part	Tested system/organ/cell	Tested dose/dosing method	Results	Refs.
Anti-inflammatory	Ethanol extract of *Bletilla striata*	RAW264.7 cells	RAW264.7 cells were pre-treated with ethanol extract of *B. striata* for 1 h and then stimulated with LPS (200 ng/mL) for 12 h, 0.05% DMSO was applied as the parallel solvent control. The culture supernatant was collected for IL-6 and TNF-α detection.	Ethanol extract of *B striata* significantly inhibited LPS-induced interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) expression at 2.5 µg/mL.	[41]
	The ethyl acetate-soluble (EtOAc) extract of tubers of *B. striata*	H_2O_2-induced PC12 cell injury model	PC12 cells were seeded in 96-well multiplates at a density of 1.5×10^5 cells/mL. After overnight incubation at 37 °C with 5% CO_2, 10 µM test samples and H_2O_2 (final concentration of 450 µM) were added into the wells and incubated for another 12 h.	It protected the cells with the cell viabilities of 57.86 ± 2.08%, 64.82 ± 2.84%, and 64.11 ± 2.52%.	[98]
	Ethanol extract of tubers of *B. striata*	RAW264.7 cells	Cells were treated with ethanol extracts (25 µM) dissolved in DMSO, in the presence of 1 µg/mL lipopolysacchride (LPS) for 18 h	The anti-inflammatory activity with IC_{50} of 2.86 ± 0.17 µM.	[54]
	PE extract of the tubers of *B. striata*	LPS-stimulated BV2 cells	Cells treated with extract (0, 1, 10, 30, 100 µg/mL) and dihydropinosylvi (0, 1, 10, 30, 100 µM) in presence of LPS (1 µg/mL)	The anti-inflammatory activity with IC_{50} values of 96.0 µM.	[96]
	Ethanol extract of the roots of *B. striata*	Cox-1 and Cox-2	Treated with the ethanol extracts at various concentrations (0, 1, 10, 100 µM)	The compounds with sugar moieties displayed selective inhibition of Cox-2 (N90%).	[38]
	B. striata polysaccharide (BSPb)	Human mesangial cells (HMCs)	HMCs were pre-treated with BSPb (5, 10, 20 µg/mL)	BSPb efficiently mediated expression of NOX4 and TLR2, to attenuate generation of ROS and inflammatory cytokines.	[12]
	Compounds extracted from the rhizomes of *Bletilla ochracea*	RAW264.7 cells	After 24 h preincubation, cells were treated with serial dilutions in the presence of 1 µg/mL LPS for 18 h. Each compound was dissolved in DMSO and further diluted in medium to produce different concentrations. NO production in the supernatant was assessed by adding 100 µL of Griess regents.	It showed the inhibitory effects with IC_{50} values in the range of 15.29–24.02 µM.	[76]
	Compounds extracted from the rhizomes of *B. ochracea*	Murine monocytic RAW264.7 cells	After 24 h preinubation, RAW 264.7 cells were treated with compounds (25 µM) dissolved in DMSO, in the prenence of 1 µg/mL LPS for 18 h. NO production in each well was assessed by adding 100 µL of Giress regent	It showed the inhibitory effects with IC_{50} 2.86 ± 0.17 µM.	[86]
	Compounds extracted from the rhizomes of *Bletilla formosana*	Elastase Release Assays	Neutrophils (6×10^5 cells/mL) were equilibrated in MeO-Suc-Ala-Ala-Pro-Val-p-nitroanilide (100 µM) at 37 °C for 2 min and then incubated with a test compound or an equal volume of vehicle (0.1% DMSO, negative control) for 5 min.	Most of the isolated compounds were evaluated for their anti-inflammatory activities. The results showed that IC_{50} values for the inhibition of superoxide anion generation and elastase release ranged from 0.2 to 6.5 µM and 0.3 to 5.7 µM, respectively.	[49]
Anti-tumor	Two compounds from *Bletilla striata*	A549 cells	Compounds were tested for their ability to induce ROS generation in A549 cells at concentrations of 20 two compounds for 24 h, the cells were harvested to evaluate the ROS production.	The two compounds exhibited antiproliferative effects using the MTT test; these effects may be due to cell cycle arrest and inducing ROS generation.	[87]
	Stilbenoids from *B. striata*	BCRP-transduced K562 (K562/BCRP) cells	—	It showed antimitotic activity and inhibited the polymerization of tubulin at IC_{50} 10 µM.	[78]

(to be continued)

Table 4. (continued)

Pharmacological activity	Tested substance/part	Tested system/organ/cell	Tested dose/dosing method	Results	Refs.
	Compounds extracted from the rhizomes of *B. ochracea*	The human tumor cell lines HL-60 (acute leukemia), SMMC-7721 (hepatic cancer), A-549 (lung cancer), MCF-7 (breast cancer), and SW480 (colon cancer)	100 μL of adherent cells were seeded into each well of 96-well cell culture plates. After 12 h of incubation at 37 °C, the test compound was added. After incubated for 48 h, cells were subjected to the MTS assay.	All isolated metabolites except 7 were evaluated for cytotoxic activity against five human cancer cell lines (HL-60, SMMC7721, A-549, MCF-7 and SW480).	[76]
Antiviral	The tuber of *B. striata*	Madin-Darby canine kidney model and embryonated eggs model	As simultaneous treatment with 50% inhibition concentration (IC_{50}) ranging from 14.6 ± 2.4 to 43.3 ± 5.3 μM.	Phenanthrenes from *B. striata* had strong anti-influenza viral activity in both embryonated eggs and MDCK models.	[107]
	The 95% ethanol Extract of *B. striata*	BALB/C mice	—	It has significant anti-influenza virus effect in mice, which may be related to the increase of IL-2, INFα, INF-β and thus enhance the immune function of mice.	[12]
Antioxidant	Compounds extracted from the rhizomes of B. formosana	DPPH radical-scavenging assay	Solutions containing 160 μL of various concentrations of sample extract, 160 μL of various concentrations of BHA, 160 μL of various concentrations of ascorbic acid, and the control (160 μL of 75% methanol) were mixed separately with 40 μL of 0.8 mM DPPH dissolved in 75% methanol. Each mixture was shaken vigorously and left to stand for 30 min at room temperature in the dark.	Tthe seedlings grown by tissue culture of *B. formosan* collected in Yilan County had the best antioxidant capacity. In addition, *B. formosana* collected in Taitung County had the best scavenging capacity in the tubers, leaves and roots.	[93]
	Fibrous roots of *B. striata*	DPPH model and superoxide anion system	The $ABTS^+$ solution was prepared by reacting 7 Mm ABTS with 2.45 mM potassium persulfate (final concentrations both dissolved in phosphate buffer, 0.2 M, pH 7.4) at room temperature for 12–16 h in the dark.	It removed free radicals and inhibit tyrosinase activity.	[33]
	B. striata extracts (BM60)	The murine macrophage cells NR8383, male SD mice (180~200 g)	NR8383 were pretreated with extracts (1, 10 and 100 g/mL) for 4 h and then 65 stimulated with 1 g/mL of LPS for 24 h. Acute lung injury was induced in mice by nonhexposure intratracheal instillation of LPS (3.0 mg/kg). Administration of the BM60 extract of 35, 70, and 140 mg/kg (L, M, H) was performed by oral gavages.	The BM60 treatment reduced the production of NO in NR8383 macrophages. Treatments with BM60 at the doses of 35, 70, 140 mg/kg significantly reduced macrophages and neutrophils in the bronchoalveolar lavage fluid (BALF).	[12]
	The crude polysaccharides obtained from *B. striata*	DPPH free radical scavenging activity	Concentration range of 2.5–5.0 mg/mL	The IC_{50} of BSPs-H was 6.532 mg/mL.	[35]
Hemostasis	B. striata polysaccharide (BSP)	Diabetes mellitus (DM) mouse models were induced by high fat-diet feeding combined with low-dose streptozocin injection	DM mouse models were induced by high fat-diet feeding combined with low-dose streptozocin injection. The BSP solutions were applied on the surface of each wound at a volume of 50 μl. RD mice were assigned as normal controls and received saline treatment (n = 6). All mice were treated with vehicle or BSP once daily from the day of wounding (d0) until 12 days later (d12).	BSP administration accelerated diabetic wound healing, suppressed macrophage infiltration, promoted angiogenesis, suppressed NLRP3 inflammasome activation, decreased IL-1β secretion, and improved insulin sensitivity in wound tissues in DM mice.	[112]
	B. striata Micron Particles (BSMPs)	Tail amputation model and healthy male Sprague-Dawley (SD) rats (250 ± 20 g, 7 weeks of age)	Rats were divided into six groups of five treated with cotton gauze and BSMPs (350–250, 250–180, 180–125, 125–75, and < 75 μm), respectively.	Compared to other BSMPs of different size ranges, BSMPs of 350–250 μm are most efficient in hemostasis. As powder sizes decrease, the degree of aggregation between particles and hemostatic BSMP effects declines.	[109]

(to be continued)

Table 4. (continued)

Pharmacological activity	Tested substance/part	Tested system/organ/cell	Tested dose/dosing method	Results	Refs.
	Rhizoma Bletillae polysaccharide (RBp)	Adult male SD rats weighing 220 ± 20 g	After incubation for 1 min at 37 °C, 300 μL of PRP was dealt with different concentrations of RBp (50, 100, 150, and 200 mg/L) under continuous stirring, and the vehicle was used as the blank control.	RBp significantly enhanced the platelet aggregations at concentrations of 50−200 mg/L in a concentration-dependent manner.	[113]
Antibacterial	Bibenzyl derivatives from the tubers of *Bletilla striata*	*S. aureus* ATCC 43300, *Bacillus subtilis* ATCC 6051, *S. aureus* ATCC 6538 and *Escherichia coli* ATCC 11775	Using a microbroth dilution method, bacteria were seeded at 1×10^6 cells per well (200 μL) in a 96-well plate containing Mueller-Hinton broth with different concentrations (from 1 to 420 μg/mL, 300 μg/mL and so on; 2-fold increments) of each test compound.	It showed inhibitory activities with MIC of (3−28 μg/mL) against *S. aureus* ATCC6538	[116]
	The crude extract of *B. striata*	*S. album*, *A. capillaris*, *C. cassia*	They were seeded at 1×10^6 cells per well (200 μL) in a 96-well plate containing Mueller−Hinton broth (meat extracts 0.2%, acid digest of casein 1.75%, starch 0.15%) with different concentrations (from 1 to 128 μg/ml; 2-fold increments) of each test compound.	It showed *S. album* (0.10%), *A. capillaris* (0.10%), and *C. cassia* (0.10%) to have the strongest antibacterial properties.	[118]
	The ethyl acetate-soluble (EtOAc) extract of tubers of *B. striata*	*S. aureus* ATCC 43300, *S. aureus* ATCC 6538, and *Bacillus subtilis* ATCC 6051) and *Escherichia coli* ATCC 11775)	Bacteria were seeded at 1×10^6 cells per well (200 μL) in a 96-well plate containing Mueller Hinton broth with different concentrations (from 1 to 420 μg/ml; 2-fold increments) of each test compound.	The extract was effective against three Gram-positive bacteria with minimum inhibitory concentrations (MICs) of 52−105 μg/ml.	[98]
	The phenanthrene fraction (EF60) from the ethanol extract of fibrous roots of *Bletilla striata* pseudobulbs	*S. aureus* ATCC 25923, *S. aureus* ATCC 29213, *S. aureus* ATCC 43300, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 27853, *Bacillus subtilis* 168	EF60 was active against all tested strains of Staphylococcus aureus, including clinical isolates and methicillin-resistant S. aureus (MRSA). The minimum inhibitory concentration (MIC) values of EF60 against these pathogens ranged from 8 to 64 μg/mL.	EF60 could completely kill *S. aureus* ATCC 29213 at 2× the MIC within 3 h but could kill less than two logarithmic units of ATCC 43300, even at 4× the MIC within 24 h. The postantibiotic effects (PAE) of EF60 (4× MIC) against strains 29213 and 43300 were 2.0 and 0.38 h, respectively.	[117]
Anti-adhesive	*Bletilla striata* extraction solution	PPA was induced by cecal wall abrasion, and *Bletilla striata* was injected to observe its efect on adhesion in rats	The rats in the sham operation group was not treated; the other rats of the three experimental groups were intraperitoneally injected with 8 ml of phosphate-buffered saline (Control group), 15% Bletilla striata extraction solution (BS group), and 0.2% hyaluronic acid solution (HA group), respectively.	*Bletilla striata* decreased the development of abdominal adhesion in abrasion-induced model of rats and reduced the expression of the important substance which increased in PPAs.	[120]
Immunomodulatory	*B. striata* polysaccharide (BSPF2)	Mouse spleen cells	To observe the immune activity of BSPF2, mouse spleen cells were stimulated with BSPF2 at 10−100 g/mL for 72 h.	Immunological assay results demonstrated that BSPF2 significantly induced the spleen cell proliferation in a dose-dependent manner.	[121]
Anti-pulmonary fibrosis	*B. striata* polysaccharide	Clean grade male SD rats	SD rats were randomly divided into 5 groups, sham operation group (equal volume of normal saline), model group (equal volume of normal saline), tetrandrine positive control (24 mg/kg) group and white and Polysaccharide low (100 mg/kg) and high (400 mg/kg) dose groups.	The *Bletilla striata* polysaccharide has remarkable regulation effect on anti-oxidation system and immune system, but cannot effectively prevent lung fibrosis.	[127]
	Small molecule components of *Bletilla striata*	Clean grade male SD rats	SD rats were randomly divided into 5 groups, sham operation group (0.5 mL normal saline), model group (0.5 mL normal saline), and positive control group (tetrandrine 24 mg/kg) and low (20 mg/kg) and high (40 mg/kg) dosage groups of the small molecule pharmacological components of Bletilla, which were administered by gavage once a day for 2 consecutive months.	The small molecule components of *Bletilla striata* can effectively prevent lung fibrosis though regulating the anti-oxidation system, immune system and cytokine level; SMCBS is one of the active components of Bletilla striata on silicosis therapy	[124]

—, not given.

antioxidant activity can vary depending on the different growing environments of the plant. Additionally, the antioxidant capabilities of extracts from different parts of the *Bletilla* plant also vary[93]. Clinical studies have shown that traditional Chinese medicine formulas containing *Bletilla* can inhibit tyrosinase activity and possess antioxidant properties, thus resulting in skin-whitening effects[108]. Furthermore, some research reveals that the polysaccharides in the plant exhibit significant antioxidant activity, effectively scavenging free radicals and inhibiting tyrosinase activity[33]. This highlights the skin-whitening potential of the fibrous root of *Bletilla striata*, indicating promising prospects for the comprehensive utilization of the *B. striata* plant[33]. However, most studies on the pharmacological activities of *Bletilla* have focused solely on *B. striata*, neglecting other species within the genus. Different species may possess varying phytochemical compositions and antioxidant properties, which can lead to an incomplete understanding of the genus as a whole.

Hemostasis

Available hemostatic agents are expensive or raise safety concerns, and *B. striata* may serve as an inexpensive, natural, and promising alternative[109]. Polysaccharides of *B. striata* displayed hemostatic activity through inhibition of the NLRP3 inflammasome[110−112]. The ADP receptor signaling pathways of P2Y1, P2Y12, and PKC receptors may be activated as part of the hemostasis[113]. Alkaloids from *Bletilla* have hemostatic activities through platelet deformation, aggregation, and secretion. In addition, polysaccharides of *Bletilla striata* have potential wound-healing medicinal value[110]. Currently, *Bletilla* plants have been used in various traditional systems, such as traditional Chinese medicine and Ayurveda, to control bleeding.

Antibacterial

Previous studies revealed that *Bletilla* displayed antibacterial effects[114]. For example, bletistrin F, showed inhibitory activities with MIC of (3–28 μg/mL) against *S. aureus* ATCC 6538[115,116]. Antimicrobial screening of *Bletilla* showed *S. album* (0.10%), *A. capillaris* (0.10%), and *C. cassia* (0.10%) to have the strongest antibacterial properties[117,118]. In addition, phenanthrenes are worthy of further investigation as a potential phytotherapeutic agent for treating infections caused by *S. aureus* and MRSA[119]. However, further *in vivo* studies on the antibacterial activity of *Bletilla* are lacking, which is needed for clinical application. For example, the specific mechanism of antibacterial activity of *Bletilla* still needs to be elucidated. While research on the antibacterial activity of *Bletilla* plants is promising, it faces several shortcomings and challenges that need to be addressed for a more comprehensive understanding of their potential therapeutic applications. Further studies with standardized methodologies, mechanistic insights, clinical trials, and consideration of ecological and safety concerns are essential to advance this field.

Other

There are other pharmacological activities of *Bletilla*, like antifibrosis activity, anti-adhesive activity, and immunomodulatory activity. For example, *B. striata* has been studied as a new and cheaper antiadhesive substance which decreased the development of abdominal adhesion abrasion-induced model in rats[120]. However, the natural resources of *Bletilla* are also getting scarcer. To preserve the sustainable development of *Bletilla* species, proper farming practices are required, along with the protection and economical use of these resources. The immunomodulatory activity of the *Bletilla* species was assessed using the ^{3}H-thymidine incorporation method test, and BSP-2 increased the pinocytic capacity and NO generation, which improved the immunomodulatory function[121,122].

B. striata extract was shown to have anti-pulmonary fibrosis effect[123]. *B. striata* polysaccharide can successfully prevent lung fibrosis through established by invasive intratracheal instillation method and evaluated by lung indexes[123,124]. Moreover, *Bletilla* species need further investigations to evaluate their long-term *in vivo* and *in vitro* activity before proceeding to the development of pharmaceutical formulation.

While there is currently a deep understanding of the pharmacological activity of plants in the *Bletilla* genus, there are still many gaps that need to be addressed. To overcome these shortcomings, future research on the pharmacological activity of *Bletilla* species should emphasize comprehensive, well-designed studies with a focus on species-specific effects, mechanistic insights, and rigorous clinical trials. Additionally, collaboration among researchers, standardization of methods, and transparent reporting of results can help advance our understanding of the therapeutic potential of *Bletilla* plants. Researchers should also consider safety aspects and explore potential herb-drug interactions to ensure the responsible use of Bletilla-based therapies.

Application status and safety evaluation

There are several common clinical applications of *Bletilla striata* in TCM. The gum of *B. striata* has unique viscosity characteristics and can be used as thickener, lubricant, emulsifier and moisturizer in the petroleum, food, medicine, and cosmetics industries[125−130]. *B. striata* is used as a coupling agent, plasma substitute, preparation adjuvant, food preservative and daily chemical raw material[131−133]. In clinical practice, *B. striata* glue has also been proven to control the infections and is beneficial to the healing of burns and wounds[133−135].

In ethnic communities in Southwest China, the locals chew fresh *Bletilla* tubers directly or take them orally after soaking in honey to treat cough, pneumonia and other diseases[33,34]. This traditional use is common in local communities in Southwest China, and suggests at the safety of *Bletilla*. However, current research shows it is still necessary to control the dosage when using *Bletilla*[136].

Zebrafish embryos and larvae respond to most drugs in a manner similar to humans[137]. Militarine, the main active ingredient of *Bletilla*, was tested in a zebrafish embryo development assay at concentrations of 0.025 g/L and 0.05 g/L, and with the increased concentration, the heart rate of zebrafish embryos is slowed. Mortality and malformation rates of zebrafish embryos gradually increased with time and militarine concentration[138]. Although *Bletilla* species are safe at therapeutic dose ranges, further research on their safety is required[136]. More in-depth studies should be carried out on *Bletilla* to extract effective ingredients and make better preparations for clinical use[139].

Conclusions and prospects

According to the traditional medicinal knowledge in ancient Chinese texts, *Bletilla* has been an important ingredient for skin care since ancient times. Many ethnic minority groups in China still retain the practice of using *Bletilla* for skin care, and the plant parts and preparation methods of use are consistent with the records in ancient texts. Almost 300 phytochemicals have been identified from *Bletilla*, and some of them possess important pharmacological activities, which support its traditional uses and suggest the important medicinal development potential of this genus. This review has demonstrated that *Bletilla*, as an important medicinal plant of Orchidaceae, still requires further research to fathom its medicinal potential.

For instance, it is necessary to enhance the quality control procedures based on the chemical components and pharmacological activity of *Bletilla*. The chemical composition and pharmacological properties of *Bletilla* are critical areas of current research. According to previous studies, the main bioactive components of *Bletilla* can vary greatly according to its origin, harvest time, distribution, storage, and adulteration. However, variation in bioactivities caused by the differences in *Bletilla* constituentshave not been explored extensively yet. To develop clinical applications of *Bletilla*, it is crucial to further explore the mechanism of action between its chemical composition variation and its pharmacological actions.

In addition, although the tuber has historically been the main medicinal part of *Bletilla*, research has shown that the chemical composition in other parts of *Bletilla*, such as stems, leaves, and flowers, also give these parts a variety of pharmacological activities. Further in-depth analysis of the chemical components and pharmacological activities of different parts of this genus is worthwhile, to explore the specific chemical basis of its pharmacological activities, develop related drugs, and promote clinical applications. For example, *Bletilla* polysaccharide has good hemostasis and astringent wound effects[110], so it may have the potential to be developed into a drug or related medical materials to stop bleeding and heal wounds.

Finally, as a cautionary note, many unrestrained collections and the destruction of habitats have made the resources of wild *Bletilla* rarer. In addition to protecting the wild populations of *Bletilla*, appropriate breeding techniques should be adopted to meet the commercial needs of this economically important genus, thereby allowing its sustainable use in commerce.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design, funding acquirement: Long C; data analysis, draft manuscript preparation, literature review: Fan Y, Zhao J; manuscript revise and language editing: Wang M, Kennelly EJ, Long C. All authors reviewed the results and approved the final version of the manuscript.

Data availability

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation, to any qualified researcher. Requests to access these datasets should be directed to Yanxiao Fan (fanyanxiao0510@163.com).

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Conflict of interest

The authors declare that they have no conflict of interest.

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