Chemical Constituents and Bioactivities of Aconitum episcopale

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Abstract Aconitum episcopale Levl., known as a characteristic Aconitum specie in China, is a perennial herbaceous plant classified into Aconitum L. (Ranunculaceae), which mainly distributes in northwest Yunnan and southwestern Sichuan. As a commonly traditional Chinese medicine, the root of A. episcopale has been used to treat anemotrigid-damp arthralgia, arthralgia, cold hernia and anesthesia analgesia with the effects of expelling wind and removing damness, warming menstruation and relieving pain. It is also used for solving other Aconitums poisoning in folk. In order to obtain more information for research and development of A. episcopale, the chemical components and pharmacological research on A. episcopale were reviewed. It is beneficial for future research, development and utilization of Aconitum and search for traditional herbal resources.

Keywords Aconitum episcopale Levl., diterpenoid alkaloids, bioactivities

Introduction

Aconitum species, firstly recorded in Shennong Bencao Jing date from 200 B. C. to 200 A. D., is a large genus of Ranunculaceae family comprising approximately 400 species (more than 200 species found in China). Some Aconitum species have been extensively employed for clinical treatment of pains, rheumatic, and neurological disorders in traditional Chinese medicine. Modern medical research shows that Aconitum has anti-inflammatory, analgesic and anti-tumor effects. The famous known chemical constituents are diterpenoid alkaloids that have been reported to exhibit remarkable analgesic, anti-inflammatory, anti-arrhythmia and anti-cancer effects. Aconitum episcopale Levl. belongs to Ranunculaceae (Aconitum), which mainly distributes in 2200—3200 m high mountains of southwestern China such as Guizhou, southwestern Sichuan and Yunnan. It is used as a folk medicine to treat fever, rheumatism, and fracture in Tibet and Lijiang. Based on previous studies, 38 diterpenoid alkaloids and 6 non-diterpenoid alkaloids have been isolated and identified from A. episcopale. Herein, we summarized chemical constituents and bioactivities of A. episcopale in order to provide a reference for better understanding its effective substances.

Chemical Constituents of Aconitum episcopale

The study on chemical constituents of A. episcopale was started from 1950s. There are 38 diterpenoid alkaloids (hereinafter referred to as DAs) and 6 non-diterpenoid alkaloids isolated and determined from A. episcopale.

Diterpenoid alkaloids

DAs are a diverse group of natural products with significant structural complexity and bioactivities, but they have also infamous toxicity. Six Lappaconitine-type C18 DAs, including delavaconitine (1), isoaconitine, delavaconitine C (2), delavaconitine D (3), delavaconitine E (4) and delavacnine (5), and a C19 DAs, yunaconitine (15), were isolated and determined by the Zhu group from A. episcopale collected in Dali.[4-7] They also achieved anhweiaconitine A and anhweiaconitine B from the plant collected in Anhui.[8] In 2020, Shen et al.[9] also isolated five aconitine-type C19 DAs and one hetidine-type C20 DAs from A. episcopale collected in Dali. They were talatisamine (10), indaconitine (14), vilmoriniane C (12), 14-acetyltalatisamine (11), 8-deacetylyunaconitine (13) and szukininic (33), respectively. Four C18 DAs, scopaline (6), episcalpine (7), episcalpine (8) and episcalpine (9), and one C20 DA, episcalpine (34), were yielded from the plant collected in Heqing[10,11] and Yunlong.[12] Two hetidine-type C20 DAs, deacetylheteroxylidobine and heterophysylidobine, and one napelines-type C20 DAs were obtained from the plant collected in Qiaojia.[13,14] The Gong group isolated ten DAs from the plant collected in Lijiang including chasmanine (16), talatizamine, crassicaline A (17), foresacamine (18), acfoestrinine (19), 3-deoxy-8-deacetylyunaconitine (20), yunaconitine (15), leucanthamine D (27), pengshenine B (28), and macrorhynine B (29).[13,14] Four C19 DAs, liaconitine A (24), liaconitine B (25), liaconitine C (26) and secocuconitine (30) were obtained.[15,16] In addition, six C19 DAs, crassicaline A (17), yunaconitine (15), saconitine (22), talatizamine (10), karacoline (23) and chasmanine (16) were obtained from Wuding in Chuxiong.[17] Based on the references, the chemical constituents were obviously different in different regions (Table 1). The structure type of DAs from A. episcopale is multiple. Among the determined 35 DAs, there are 9 C18 DAs that all belong to lappaconitine-type as shown in Table 2 and Figure 1, 21 C19 DAs shown in Table 3 and Figure 2, and 5 C20 DAs shown in Table 4 and Figure 3. Among them, liaconitine A, delavaconitine D, delavaconitine E, episcalpine, liaconitine B, episcalpine, secocuconitine, liaconitine C, anhweia-
Table 1  Diterpenoid alkaloids of A. episcopale from different regions

| Regions | DAs |
|---------|-----|
| Dali    | delavaconitine, isoaconitine, delavaconitine C, delavaconitine D, delavaconitine E, delavaconine, yunaconitine, talatisamine, indaconitine, vilmorrianine C, 8-deacetylyunaconitine, 14-acetyltalatisamine, sczukinine, scopolaline, episcopalisine, episcopalisinine, episcopaliline, episcopalidine |
| Zhaotong| deacetylheterophyllidine, heterophyllidine, songorine |
| Lijiang | chasmanine, talatizamine, crassicauline A, foresaconitine, acoforestinine, 3-deoxy-8-deacetyl-yunaconetin, |
| Chuxiong| yunaconitine, leucanthumssine D, pengshenine B, macrorhynine B, liaconitine A, liaconitine B, liaconitine C, secoyunaconitine, |
| Anhui   | episcopalisine A, episcopalisine B |

Table 2  C$_{18}$-type diterpenoid alkaloids from A. episcopale

| No. | Compounds         | Molecular formulas |
|-----|-------------------|--------------------|
| 1   | delavaconitine    | C$_{29}$H$_{39}$NO$_6$ |
| 2   | delavaconitine C  | C$_{29}$H$_{39}$NO$_5$ |
| 3   | delavaconitine D  | C$_{31}$H$_{41}$NO$_6$ |
| 4   | delavaconitine E  | C$_{31}$H$_{41}$NO$_7$ |
| 5   | delavaconine      | C$_{22}$H$_{35}$NO$_5$ |
| 6   | scopolaline       | C$_{21}$H$_{33}$NO$_3$ |
| 7   | episcopalisine    | C$_{22}$H$_{35}$NO$_5$ |
| 8   | episcopalisinine  | C$_{22}$H$_{35}$NO$_5$ |
| 9   | episcopiline      | C$_{24}$H$_{37}$NO$_5$ |

Table 3  C$_{19}$-type diterpenoid alkaloids from A. episcopale

| No. | Compounds         | Molecular formulas |
|-----|-------------------|--------------------|
| 10  | talatisamine      | C$_{24}$H$_{39}$NO$_5$ |
| 11  | 14-acetyltalatisamine | C$_{26}$H$_{41}$NO$_5$ |
| 12  | vilmorrianine C   | C$_{28}$H$_{43}$NO$_5$ |
| 13  | 8-deacetylyunaconitine | C$_{30}$H$_{41}$NO$_{10}$ |
| 14  | indaconitine      | C$_{28}$H$_{41}$NO$_{10}$ |
| 15  | yunaconitine      | C$_{28}$H$_{41}$NO$_{11}$ |
| 16  | chasmanine        | C$_{28}$H$_{41}$NO$_6$ |
| 17  | crassicauline A   | C$_{28}$H$_{41}$NO$_{10}$ |
| 18  | foresaconitine    | C$_{28}$H$_{41}$NO$_{10}$ |
| 19  | acoforestinine    | C$_{28}$H$_{41}$NO$_{10}$ |
| 20  | 3-deoxy-8-deacetyl-yunaconetin | C$_{30}$H$_{41}$NO$_{10}$ |
| 21  | crassicauline A   | C$_{28}$H$_{41}$NO$_{10}$ |
| 22  | sachaconitine     | C$_{28}$H$_{41}$NO$_{10}$ |
| 23  | karacoline        | C$_{28}$H$_{41}$NO$_{10}$ |
| 24  | liaconitine A     | C$_{28}$H$_{41}$NO$_{10}$ |
| 25  | liaconitine B     | C$_{28}$H$_{41}$NO$_{11}$ |
| 26  | liaconitine C     | C$_{28}$H$_{41}$NO$_{9}$ |
| 27  | leucanthumssine D | C$_{28}$H$_{41}$NO$_{9}$ |
| 28  | pengshenine B     | C$_{28}$H$_{41}$NO$_{9}$ |
| 29  | macrorhynine B    | C$_{28}$H$_{41}$NO$_{9}$ |
| 30  | secoyunaconitine  | C$_{28}$H$_{41}$NO$_{9}$ |

Table 4  C$_{20}$-type diterpenoid alkaloids from A. episcopale

| No. | Compounds         | Molecular formulas |
|-----|-------------------|--------------------|
| 31  | deacetylheterophyllidine | C$_{21}$H$_{35}$NO$_5$ |
| 32  | heterophyllidine   | C$_{23}$H$_{35}$NO$_5$ |
| 33  | sczukinine        | C$_{23}$H$_{35}$NO$_5$ |
| 34  | episcopalidine    | C$_{23}$H$_{35}$NO$_5$ |
| 35  | songorine         | C$_{23}$H$_{35}$NO$_5$ |
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**Bioactivities of Aconitum episcopale**

There are about 200 species of the *Aconitum* genus in China and DAs are the main characteristic active compounds. They exhibited diverse bioactivities such as anti-inflammatory, analgesic activity, anti-arrhythmia, anti-cancer, anti-cholinesterase, immunomodulatory, anti-diabetics and antihypertensive. Previous study showed that episcopalidine...
A. episcopale had an exclusive anti-arrhythmic effect. Zhang[10] found that epicapalidine could have a protective effect against arrhythmia induced by aconitine only and showed a significant dose-effect relationship within a certain dose range. However, it had not an obvious effect on arrhythmia caused by BaCl2 and chloroform. 5 mg/kg of epicapalidine could completely counteract the arrhythmias caused by 20 mg/kg of aconitine. Even the dosage of aconitine increased up to 40 mg/kg and epicapalidine was 10 mg/kg, arrhythmia was still not affected. The anti-arrhythmic effects, induced by aconitine of five original plants used as “DuLa” in Yi nationality of China including A. episcopale, A. pseudostapffianum W. T. Wang, Hemipila limprichti Schtr. Ex Limpchrt, Geranium platyrenifolium Z. M. and Habenaria finetiana Schtrl, were studied. The results showed that A. episcopale had the strongest effect and the value of LD50 was 54.35±0.19 g/kg.[10]

In addition, the total base and 95% ethanol extract were the active section, which had a great practical significance for the studies on the anti-arrhythmic effect of A. episcopale.[10] Jin et al.[20] confirmed that alkaloids from the root tuber A. episcopale had a good local anesthetic effect. The effect of 1% of the alkaloid solution was about twice of cocaine and the effect lasts for a long time even. The ethanol extract of A. episcopale roots possessed significant feeding deterrent against the red flour beetle, Tribolium castaneum. Four feeding deterrents were identified as chasmanine, talatisamine, karacoline and sachaonitine with EC50 values of 297.0, 342.8, 395.3 and 427.8 ppm, respectively. However, Yunaconitine and crassicauline A possessed feeding deterrent activity against T. castaneum adults with EC50 values of 653.4 and 1134.5 ppm, respectively.[17]

Conclusion and Perspective

In summary, A. episcopale as a folk medicine and special Aconitum specie in China is mainly distributed in southwestern China. Although deep studies on A. episcopale are limited according to current references, the structure types of DAs from A. episcopale are diverse causing a wide range of pharmacological activities. It should be pointed out that future studies on A. episcopale not only focus on finding compounds, but also conducting in-depth research on bioactivities and mechanisms. For more rationally and effectively to develop resources in A. episcopale, researchers should perform further research on its chemical constituents, bioactivities and the mechanism of action in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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