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 anemofrigid-damp arthralgia, arthralgia, cold hernia and anesthesia analgesia with the effects of expelling wind and removing dampness, warming menstruation and relieving pain. It also is 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).^[1] Some *Aconitum* species have been extensively employed for clinical treatment of pains, rheumatics, 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 (*Acnitum*), which mainly distributes in 2200–3200 m high mountains of southwestern China such as Guizhou, southwestern Sichuan and Yunnan.^[2] It is used as a folk medicine to treat fever, rheumatism, and fracture in Tibet and Lijiang.^[3] 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 stated 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 delavaconine (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), vilmorrianine C (12), 14-acetyltalatisamine (11), 8-deacetylyunaconitine (13) and sczukininc (33), respectively. Four C₁₈ DA, scopaline (6), episcopalisine (7), episcopalisinine (8) and episcopalitine (9), and one C₂₀ DA, episcopalidine (34), were yielded from the plant collected in Heqing^[10] and Yunlong.^[11] Two hetidine-type C₂₀-DAs, deacetylhetophylloidine and hetophylloidine, and one napellines-type C₂₀-DA were obtained from the plant collected in Qiaojia.^[12] The Gong group isolated ten DAs from the plant collected in Lijiang including chasmanine (16), talatizamine, crassicauline A (17), foresaconitine (18), acoforestinine (19), 3-deoxy-8-deacetylyunaconitine (20), yunaconitine (15), leucanthumsine D (27), pengshenine B (28), and macrorrhynine B (29).^[13,14] Four C₁₉ DAs, liaconitine A (24), liaconitine B (25), liaconitine C (26) and secoyunaconitine (30) were obtained.^[15,16] In addition, six C₁₉ DAs, crassicauline A (17), yunaconitine (15), sachaconitine (22), talatisamine (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, episcopalisinine, liaconitine B, episcopalitine, secoyunaconitine, 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, sczukininc, scopaline, episcopalisine, episcopalisine, episcopalitine, episcopalidine
Zhaotong	deacetylheterophyllidine, heterophyllidine, songorine
Lijiang	chasmanine, talatizamine, crassicauline A, foresaconitine, acoforestinine, 3-deoxy-8-deacetyl-yunaconitine, yunaconitine, leucanthumsine D, pengshenine B, macrorrhynine B, liaconitine A, liaconitine B, liaconitine C, secoyunaconitine,
Chuxiong	crassicauline A, yunaconitine, sachaconitine, talatisamine, karacoline, chasmanine
Anhui	anhweiaconitine A, anhweiaconitine B

Table 2 C₁₈-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	scopamine	C ₂₁ H ₃₃ NO ₃
7	episcopalisine	C ₂₉ H ₃₉ NO ₆
8	episcopalisine	C ₂₂ H ₃₅ NO ₅
9	episcopalitine	C ₂₄ H ₃₇ NO ₅

Table 3 C₁₉-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 ₆
12	vilmorrianine C	C ₃₅ H ₄₉ NO ₉
13	8-deacetylyunaconitine	C ₃₃ H ₄₇ NO ₁₀
14	indaconitine	C ₃₄ H ₄₇ NO ₁₀
15	yunaconitine	C ₃₅ H ₄₉ NO ₁₁
16	chasmanine	C ₂₅ H ₄₁ NO ₆
17	crassicauline A	C ₃₅ H ₄₉ NO ₁₀
18	foresaconitine	C ₃₅ H ₄₉ NO ₁₀
19	acoforestinine	C ₂₉ H ₃₉ NO ₆
20	3-deoxy-8-deacetyl-yunaconitine	C ₃₃ H ₄₇ NO ₉
21	crassicauline A	C ₃₅ H ₄₉ NO ₁₀
22	sachaconitine	C ₂₃ H ₃₇ NO ₄
23	karacoline	C ₂₂ H ₃₅ NO ₄
24	liaconitine A	C ₃₅ H ₄₇ NO ₁₀
25	liaconitine B	C ₄₁ H ₅₁ NO ₁₁
26	liaconitine C	C ₃₅ H ₄₉ NO ₉
27	leucanthumsine D	C ₂₃ H ₃₅ NO ₆
28	pengshenine B	C ₂₂ H ₃₃ NO ₅
29	macrorrhynine B	C ₃₃ H ₄₃ NO ₁₀
30	secoyunaconitine	C ₃₃ H ₄₅ NO ₉

Table 4 C₂₀-type diterpenoid alkaloids from *A. episcopale*

No.	Compounds	Molecular formulas
31	deacetylheterophyllidine	C ₂₁ H ₂₇ NO ₃
32	heterophyllidine	C ₂₃ H ₂₉ NO ₄
33	sczukinine	C ₂₃ H ₂₉ NO ₅
34	episcopalidine	C ₃₀ H ₃₃ NO ₆
35	songorine	C ₂₂ H ₃₁ NO ₃

Figure 1 Structures of C₁₈-type diterpenoid alkaloids from *A. episcopale*. Figure 2 Structures of C₁₉-type diterpenoid alkaloids from *A. episcopale*. Figure 3 Structures of C₂₀-type diterpenoid alkaloids from *A. episcopale*. Figure 4 Structures of non-diterpenoid alkaloids from *A. episcopale*.

conitine A and anhwiaconitine B were only reported in *A. episcopale*.

Non-diterpenoid alkaloids

Six non-diterpenoid alkaloids from *A. episcopale* were reported including β -sitosterol (36), stigmasterol (37), paeonol (38) and 4-methoxybenzoic acid (39)^[18] and cholesterol (40) and veratric acid (41)^[19] as shown in Figure 4.

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,^[20] analgesic activity,^[21] anti-arrhythmia,^[22] anti-cancer,^[23] anti-cholinesterase,^[24] immunomodulatory,^[25] anti-diabetics and antihypertensive.^[26] Previous study showed that episcopalidine

(34) from *A. episcopale* had an exclusive anti-arrhythmic effect. Zhang^[27] found that episcopalidine 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 episcopalidine could completely counteract the arrhythmias caused by 20 mg/kg of aconitine. Even the dosage of aconitine increased up to 40 mg/kg and episcopalidine 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. pseudostaphianum* W. T. Wang, *Hemipilia limprichti* Schltr. Ex Limpricht, *Geranium platyrenifolium* Z. M. and *Habenaria finetiana* Schltr, were studied. The results showed that *A. episcopale* had the strongest effect and the value of LD₅₀ was 54.35±0.19 g/kg.^[28] 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*.^[19] Jin et al.^[29] 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 deterrence against the red flour beetle, *Tribolium castaneum*. Four feeding deterrents were identified as chasmanine, talatisamine, karacoline and sachaconitine 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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