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Traditional Chinese Medicine — Processed *Aconitum carmichaelii* lateral root

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 249, *Traditional Chinese medicine*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Processed *Aconitum carmichaelii* lateral root (Aconiti Lateralis Radix, Fuzi, 附子) has been used as a herbal medicine in traditional Chinese medicine for a very long time. It remains a highly valued herb today because of its significant effects. *Aconitum carmichaelii* lateral root is one of the most frequently used herbal medicines in traditional Chinese medicine. Of an approximate total of 80 000 traditional Chinese medicine formulas, around 7,04 % of formulations include *Aconitum carmichaelii* lateral root as an ingredient. Among 113 formulas in the *Treatise on Cold Pathogenic Diseases* (伤寒论),^[1] one of four great classics of traditional Chinese medicine, there are 23 formulations with *Aconitum carmichaelii* lateral root (occupying 20,35 %) as an ingredient. Among 202 formulas in the *Synopsis of Golden Chamber* (金匱要略),^[2] another of the four great classics of traditional Chinese medicine, there are 26 prescriptions with *Aconitum carmichaelii* lateral root as an ingredient (12,87 %). Among 148 Kampo medicines for prescription from the Ministry of Health, Labour and Welfare (MHLW) of Japan, there are 10 prescriptions with *Aconitum carmichaelii* lateral root as an ingredient (6,76 %).

Processed *Aconitum carmichaelii* lateral root contains aconitum alkaloids which have anti-inflammatory, analgesic and cardiotoxic activities. These aconitum alkaloids are irreplaceably effective for injuries, arthritis, neuropathic pain, sequelae of apoplexy, stomach pain, stomach crymodynia, menoxenia, abscesses, deep-rooted carbuncles and sores. Aconitum alkaloids are, however, a double-edged sword. At present, international trade in processed *Aconitum carmichaelii* lateral root is restricted in a number of nations due to the high natural toxicity of processed *Aconitum carmichaelii* lateral root. Also, there are sporadic cases of aconitum alkaloid poisoning reported worldwide due to misuse.

Nonetheless, the toxicity of processed *Aconitum carmichaelii* lateral root can be reduced dramatically with proper processing (such as repeated boiling or steaming), prolonged decocting and dose control. However, standards for processed *Aconitum carmichaelii* lateral root are not yet harmonized at an international level and regulatory authorities in many nations do not adequately differentiate highly toxic forms from less-toxic forms (or even non-toxic forms) of *Aconitum carmichaelii* lateral root.

The six aconite alkaloids [Aconitine (AC), mesaconitine (MA), hyaconitine (HA), benzoylaconine (BAC), benzoylmesaconine (BMA) and benzoylhypaconine (BHA)] are commonly used as chemical markers for quality control of processed *Aconitum carmichaelii* lateral root.^[3] AC, MA and HA are toxic diester diterpenoid alkaloids, while BAC, BMA and BHA are active monoester diterpenoid alkaloids. To guarantee safety, efficacy and quality, these six alkaloids are commonly controlled in different pharmacopoeia. Nevertheless, poisoning cases are still occasionally reported. From 1989 to 2010, 140 cases of aconitum poisoning, including one fatal case, were reported in Hong Kong.^[4] Additionally, 17 cases were reported in Taiwan from 1990 to 1999, 2017 cases were reported in China from 1989 to 2008 and 121 cases were reported in Korea from 1995 to 2007.^[5] Multiple reasons for aconitum poisoning exist, include overdoses, inadequate processing, aconitum contamination in other herbs, dispensing and management errors, and hidden risk factors. In the 17 cases reported in Hong Kong, yunaconitine (YAC), crassicauline A (CCA) and 8-deacetyl-yunaconitine (DYA) were detected instead of AC, MA and HA in the urine samples of the aconitum poisoning patients.^[4,6] Because YAC, DYA and CCA were detected in the urine of the aconitum poisoning patients, these alkaloids are considered to be hidden risk factors and should be covered in laboratory screenings for toxic compounds.^[6] Therefore, an International Standard is required for *Aconitum carmichaelii* lateral root for quality control of the herb and its products and to ensure the safe use of these medical materials^[5].

This document provides a systematic and practical International Standard for *Aconitum carmichaelii* lateral root to control and guarantee stable quality, to ensure safe and effective use in clinics, to standardize the global market trade and to reduce cases of aconite poisoning.

As national implementation can differ, national standards bodies are invited to modify the values given in 5.2, 5.3 and 5.5 in their national standards. Examples of national and regional values are given in Annex C.

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Traditional Chinese Medicine — Processed *Aconitum carmichaelii* lateral root

1 Scope

This document specifies minimum requirements and test methods for processed *Aconitum carmichaelii* lateral root (lateral root of *Aconitum carmichaelii* Debx.).

This document applies to processed *Aconitum carmichaelii* lateral root that is sold and used as natural medicines in international trade, including Chinese materia medica (whole medicinal materials) and decoction pieces derived from this plant. Processing methods of *Aconitum carmichaelii* lateral root are excluded.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 1575, *Tea — Determination of total ash*

ISO 18664, *Traditional Chinese Medicine — Determination of heavy metals in herbal medicines used in Traditional Chinese Medicine*

ISO 21371, *Traditional Chinese medicine — Labelling requirements of products intended for oral or topical use*

ISO 22217, *Traditional Chinese medicine — Storage requirements for raw materials and decoction pieces*

ISO 22258, *Traditional Chinese medicine — Determination of pesticide residues in natural products by gas chromatography*

ISO 23191, *Traditional Chinese medicine — Determination of selected Aconitum alkaloids by high-performance liquid chromatography (HPLC)*

World Health Organization *Quality control methods for herbal materials*, 2011

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at <https://www.iso.org/obp>

— IEC Electropedia: available at <http://www.electropedia.org/>

3.1

fresh *Aconitum carmichaelii* lateral root

fresh lateral root of *Aconitum carmichaelii* Debx. with the tap root, rootlet and soil removed

3.2

***Aconitum carmichaelii* lateral root**

unprocessed dried lateral root of *Aconitum carmichaelii* Debx.

3.3

processed *Aconitum carmichaelii* lateral root

dried lateral root of *Aconitum carmichaelii* Debx. after processing

Note 1 to entry: This includes commercial varieties such as salted *Aconitum carmichaelii* lateral root, black slice of *Aconitum carmichaelii* lateral root and white slice of *Aconitum carmichaelii* lateral root.

3.4

salted *Aconitum carmichaelii* lateral root

processed *Aconitum carmichaelii* lateral root in bittern

Note 1 to entry: The decoction pieces are processed with the following method: select the large and uniform fresh *Aconitum carmichaelii* lateral root; wash clean and soak overnight in bittern, of which the main ingredient is edible calcium chloride solution; add salt, soak and take out to sun-dry and air-dry every day; gradually prolong the drying time until a lot of salt is crystallized on the surface of the drug and its texture becomes hard.

Note 2 to entry: Bittern is liquid residue of mineral salt, the major constituent being magnesium chloride.

3.5

black slice of *Aconitum carmichaelii* lateral root

processed *Aconitum carmichaelii* lateral root in bittern with dye

Note 1 to entry: The decoction pieces are processed with the following method: select the large and uniform fresh *Aconitum carmichaelii* lateral root; wash clean and soak in bittern for several days; boil in the infusion thoroughly; take out, rinse in water, cut longitudinally into slices about 0,5 cm in thickness; soak and rinse in water once again; stain the slices dark brown (e.g. with black bean decoction, strong tea water) and steam them until they turn oily and lustrous; bake the slices to half-dryness, then sun-dry or bake to complete dryness.

3.6

white slice of *Aconitum carmichaelii* lateral root

processed *Aconitum carmichaelii* lateral root in bittern without bark

Note 1 to entry: The decoction pieces are processed with the following method: select the large and uniform fresh *Aconitum carmichaelii* lateral root; wash clean and soak in bittern for several days; boil in the infusion thoroughly; take out, peel the bark and cut longitudinally into slices about 0,3 cm in thickness; soak and rinse in water, take out, steam thoroughly, sun-dry to dryness.

3.7

boiled slice of *Aconitum carmichaelii* lateral root

processed *Aconitum carmichaelii* lateral root with salt, *Glycyrrhizae* root and black beans

Note 1 to entry: The decoction pieces are processed with the following method: blanch salted *Aconitum carmichaelii* lateral root with water two or three times a day until all the salt is rinsed out; boil together with *Glycyrrhizae* root, black beans and water until the centre of the cut surface is devoid of white core and the cut slice is numb to the tongue; remove *Glycyrrhizae* root and black beans, cut the drug into slices and dry.

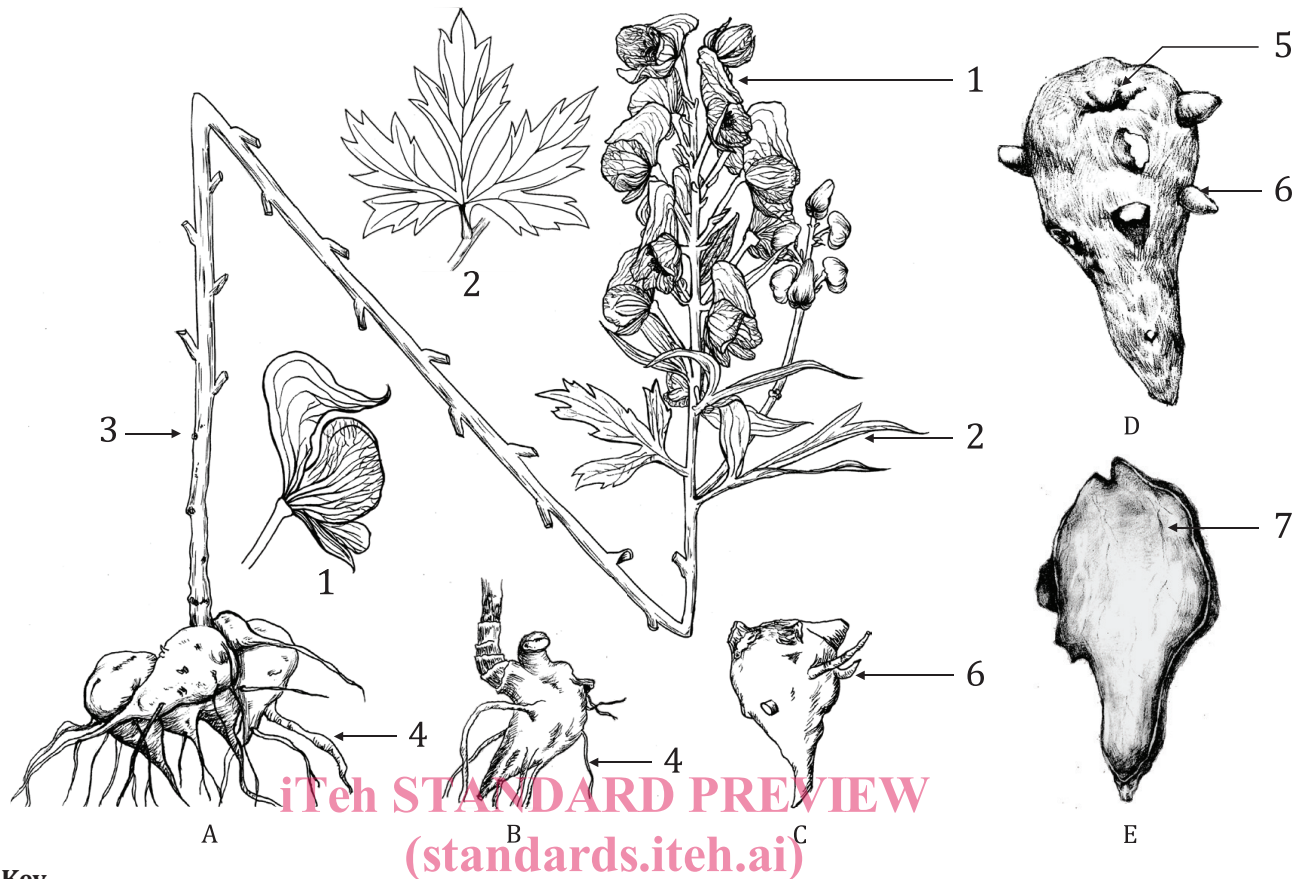
3.8

batch

samples collected from the same particular place at the same time, of no more than 5 000 kg

4 Descriptions

Processed *Aconitum carmichaelii* lateral root is derived from the dried lateral root of *Aconitum carmichaelii* Debx. (Family Ranunculaceae) after processing (Figure 1).



Key

A	plant of <i>Aconitum carmichaelii</i> Debx.	1	flower
B	main root of <i>Aconitum carmichaelii</i> Debx.	2	leaf
C	lateral root of <i>Aconitum carmichaelii</i> Debx.	3	stem
D	unprocessed <i>Aconitum carmichaelii</i> lateral root	4	rootlet
E	black slice of <i>Aconitum carmichaelii</i> lateral root	5	depressed bud scar
		6	tuberclad short rootlet
		7	longitudinal vascular bundles

Figure 1 — Structure of *Aconitum carmichaelii* lateral root

5 Requirements

5.1 Morphological features of root

5.1.1 Salted *Aconitum carmichaelii* lateral root

Lateral root is conical, 4 cm to 7 cm long, 3 cm to 5 cm in diameter. The colour is externally greyish-black, covered with fine powder of salt, topped with depressed bud scars and encircled with tuberclad short rootlets or rootlet scars. The texture is heavy. The transversely cut surface is greyish brown, showing small clefts filled with fine powder of salt and a polyangular cambium ring, and vascular bundles arranged irregularly inside the ring. The odour is slight.

5.1.2 Black slice of *Aconitum carmichaelii* lateral root

Longitudinal slices, the upper portion wide and the lower portion narrow, 1,7 cm to 5 cm long, 0,9 cm to 3 cm wide, 0,2 cm to 0,5 cm thick. The outer bark is blackish brown; the cut surface is dark yellow, oily

and lustrous, translucent and showing longitudinal vascular bundles. The texture is hard and fragile. The fracture is horny. The odour is slight.

5.1.3 White slice of *Aconitum carmichaelii* lateral root

White slice of *Aconitum carmichaelii* lateral root is yellowish-white, translucent, about 3 mm thick, without outer bark.

5.1.4 Boiled slice of *Aconitum carmichaelii* lateral root

In longitudinal cut slices, the upper end wider than the lower end, 1,7 cm to 5 cm long, 0,9 cm to 3 cm wide, 0,2 cm to 0,5 cm thick. Externally brown. Cut surface brown, translucent and showing longitudinal vascular bundles. Texture hard, fracture horny. Odour slight.

5.2 Moisture

The moisture content in percentage mass should not be more than 15,0 %.

5.3 Total ash

The total ash content in percentage mass should not be more than 19,0 %.

5.4 Thin-layer chromatogram (TLC) identification

The identification of extracts of *Aconitum carmichaelii* lateral root with thin-layer chromatogram (TLC) shall present the spots or bands with the same colour and position corresponding to those of reference solutions.

5.5 Marker compounds

The content of marker compounds in percentage mass shall be determined. The total content of aconitine, mesaconitine and hypaconitine in percentage mass should not be more than 0,02 %. The total content of benzoyleaconine, benzoylmesaconine and benzoylhypaconine in percentage mass should not be less than 0,01 %. The content of yunaconitine, 8-deacetyl-yunaconitine and crassicauline A, respectively, should not be detected. Relevant structural formulae of the marker compounds are given in [Table 1](#).

Table 1 — Structural formulae of the marker compound(s)

Name	Abbreviation	Molecular formula	CAS ^a No.	Molar mass g/mol
Aconitine	AC	C ₃₄ H ₄₇ NO ₁₁	302-27-2	645,74
Mesaconitine	MA	C ₃₃ H ₄₅ NO ₁₁	2 752-64-9	631,71
Hypaconitine	HA	C ₃₃ H ₄₅ NO ₁₀	6 900-87-4	615,71
Benzoyleaconine	BAC	C ₃₂ H ₄₅ NO ₁₀	466-24-0	603,78
Benzoylmesaconine	BMA	C ₃₁ H ₄₃ NO ₁₀	63 238-67-5	589,68
Benzoylhypaconine	BHA	C ₃₁ H ₄₃ NO ₉	63 238-66-4	573,67
Yunaconitine	YAC	C ₃₅ H ₄₉ NO ₁₁	70 578-24-4	659,76
8-deacetyl-yunaconitine	DYA	C ₃₃ H ₄₇ NO ₁₀	93 460-55-0	617,72
Crassicauline A	CCA	C ₃₅ H ₄₉ NO ₁₀	79 592-91-9	643,76

5.6 Heavy metals

The contents of heavy metals such as arsenic, mercury, lead and cadmium should be determined.

5.7 Pesticide residues

The contents of pesticide residues should be determined.

6 Sampling

Sampling shall be carried out in accordance with the method described in the World Health Organization's *Quality control methods for herbal materials*, 'General advice on sampling'. Sampling of *Aconitum carmichaelii* lateral root shall be conducted according to the following steps:

- a) From a batch of five containers or packaging units, take a sample from each.
- b) From a batch of between six and 50 units, take a sample from five.
- c) From a batch of over 50 units, sample 10 %, rounding up the number of units to the nearest multiple of 10. For example, a batch of 51 units would be sampled as for 60, i.e. take samples from six packages.
- d) From each container or package selected, take three original samples from the top, middle and bottom of the container or package.
- e) Combine the three original samples into a pooled sample and mix carefully.
- f) Obtain the average sample by quartering:
 - take the pooled sample, adequately mixed into an even and square-shaped heap;
 - divide it diagonally into four equal parts;
 - take two diagonally opposite parts and mix carefully;
 - repeat the process as necessary until the required quantity, to within ± 10 %, is obtained.
- g) Using the same quartering procedure, divide the average sample into four final samples, taking care that each portion is representative of the bulk material.
- h) Test the final samples for the measure and analyses specified in [Table 2](#).

Table 2 — Maximum mass of batch and minimum mass of final sample

Maximum mass per batch kg	Minimum mass of final sample g		
	For measure of root mass and root length	For analysis of marker compound(s)	For other analyses
5 000	500	250	250

NOTE 1 The establishment of the requirement is based on processed *Aconitum carmichaelii* lateral root collected from different producing areas.

NOTE 2 Other analyses include macroscopic identification, the determinations of moisture, total ash, water-soluble extractives, polysaccharides, heavy metals, pesticide residues and TLC identification.

7 Test methods

7.1 Macroscopic identification

Take samples of not less than 500 g from each batch randomly. These samples are examined by observation in sunlight and by smell.