Application to Amend the Poisons Standard

Australian Government
Department of Health

ACCESS TO A RESTRICTED CHINESE HERB: APPLICATION FOR RESCHEDULING OF PROCESSED ACONITUM CARMICHAELII DEBX. LATERAL ROOT UNDER THE ACONITUM SPECIES

4 November 2020

Chinese medicine associations: FCMA, AACMA, CMIC and CMASA

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APPLICANT'S DETAILS

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[I] This application has been prepared and is jointly submitted by FCMA, AACMA, CMIC and CMASA. These four associations represent the majority of registered Chinese medicine practitioners in Australia and are dedicated to promoting the safe practice of Chinese medicine and supporting the Chinese medicine profession in Australia.

DECLARATION
I, Sherman Gu on behalf of the applicants (FCMA, AACMA, CMIC and CMASA):

- declare that the information provided in this application is true and current;
- undertake not to publicly disclose the notices of interim decision or final decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) these documents are published pursuant to subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations 1990, respectively.

Name: Sherman Gu, BMed, MAppSc, PhD

Executive Officer, FCMA

Date: 4 November 2020

PART 1 – SUMMARY OF THE APPLICATION

PROPOSED SCHEDULING / RESCHEDULING OR OTHER CHANGE TO THE POISONS STANDARD

1. The Chinese medicine profession in Australia requests a rescheduling of Aconitum spp. as follows:

   Option 1: rescheduling a specific Aconitum substance, processed Aconitum carmichaelii Debx. lateral root, used in Traditional Chinese Medicine from Schedule 2 and Schedule 4 to Schedule 1.
   Note: Schedule 1 is currently blank intentionally in the Poisons Standard.

   Or:

   Option 2: adding an exemption on Aconitum spp. to entries in the current Schedule 2 and Schedule 4.

SUGGESTED SCHEDULING OR OTHER WORDING

Option 1:

Schedule 1, 2 and 4 – Proposed New Entry/Amendment

Schedule 1 – Proposed New Entry

Processed Aconitum carmichaelii Debx. lateral root in preparations or manufactured dosage forms used in Traditional Chinese Medicine for adult use:

a) for oral use in packs each containing 0.6mg or less for single dose or 3.0mg or less for daily dose, of total diester diterpenoid alkaloids, calculated as the total amount of aconitine, hypaconitine and mesaconitine; or
b) for dermal use in packs each containing 0.6mg or less for single dose or 3.0mg or less for daily dose, of total diester diterpenoid alkaloids, calculated as the total amount of aconitine, hypaconitine and mesaconitine.

Schedule 2 – Proposed Amendment

ACONITUM spp. for therapeutic use in adults:

a) **except** when included in Schedule 1; or

b) in preparations for oral use in packs each containing 0.2 mg or less of total alkaloids **except** in packs containing 0.02 mg or less of total alkaloids; or

c) in preparations for dermal use containing 0.02 per cent or less of total alkaloids, in packs each containing 0.2 mg or less of total alkaloids **except** in packs containing 0.02 mg or less of total alkaloids.

Schedule 4 – Proposed Amendment

ACONITUM spp. **except**:

a) when included in Schedule 1 and Schedule 2:

b) in preparations for oral use in packs each containing 0.2 mg or less of total alkaloids **except** in packs containing 0.02 mg or less of total alkaloids; or

c) in preparations for dermal use containing 0.02 per cent or less of total alkaloids, in packs each containing 0.2 mg or less of total alkaloids **except** in packs containing 0.02 mg or less of total alkaloids.

Option 2:

Schedule 2 and 4 – Proposed Amendment

Schedule 2 – Proposed Amendment

ACONITUM spp. for therapeutic use in adults:

a) in preparations for oral use in packs each containing 0.2 mg or less of total alkaloids **except** in packs containing 0.02 mg or less of total alkaloids; or
b) in preparations for dermal use containing 0.02 per cent or less of total alkaloids, in packs each containing 0.2 mg or less of total alkaloids **except** in packs containing 0.02 mg or less of total alkaloids; or
c) **except** processed Aconitum spp. in preparations or manufactured dosage forms used in Traditional Chinese Medicine:
    1) for oral use in packs each containing 0.6mg or less for single dose or 3.0mg or less for daily dose, of total diester diterpenoid alkaloids, calculated as the total amount of aconitine, hypaconitine and mesaconitine; or
    2) for dermal use in packs each containing 0.6mg or less for single dose or 3.0mg or less for daily dose, of total diester diterpenoid alkaloids, calculated as the total amount of aconitine, hypaconitine and mesaconitine.

Schedule 4 – Proposed Amendment

ACONITUM spp. **except**:

a) when included in Schedule 2;
b) in preparations for oral use in adults in packs containing 0.02 mg or less of total alkaloids; or
c) in preparations for dermal use in adults containing 0.02 per cent or less of total alkaloids in packs containing 0.02 mg or less of total alkaloids; or
d) processed Aconitum spp. in preparations or manufactured dosage forms used in Traditional Chinese Medicine:
1) for oral use in packs each containing 0.6mg or less for single dose or 3.0mg or less for daily dose, of total diester diterpenoid alkaloids,

calculated as the total amount of aconitine, hypaconitine and mesaconitine; or

2) for dermal use in packs each containing 0.6mg or less for single dose or 3.0mg or less for daily dose, of total diester diterpenoid alkaloids, calculated as the total amount of aconitine, hypaconitine and mesaconitine.

SUBSTANCE SUMMARY

The substance is a plant material, not a purified chemical compound.

Plant name: Aconitum carmichaelii Debx. (Scientific name),

Plant material: dried lateral root of Aconitum carmichaelii Debx.

Aconiti Radix Lateralis Praeparata (Pharmaceutical name),

Zhi Fu Zi (ZFZ, Chinese pinyin name),

Prepared Common Monkshood Daughter Root (Common English name).

OVERVIEW

2. Processed Aconitum carmichaelii Debx. lateral root (Aconiti Radix Lateralis Praeparata, 'Zhi Fu Zi' in Chinese pinyin, (hereafter in this application to be referred to as ZFZ to represent the herb) is a Chinese Materia Medica (CMM) used in traditional Chinese medicine (TCM) with a long history of use. It is the processed dried lateral root of Aconitum carmichaelii Debx. In its non-processed state (Aconiti Radix Lateralis, unprocessed Fu Zi, Sheng Fu Zi or Ni Fu Zi in Chinese pinyin name), it contains certain amounts of toxic aconite alkaloids (mainly diester diterpenoid alkaloids (DDAs) including aconitine, hypaconitine and mesaconitine). These DDAs do not contribute to the therapeutic effect of ZFZ. The DDAs can be reduced to levels safe for therapeutic use by proper processing and preparation. Boiling of unprocessed Aconitum carmichaelii Debx. lateral root in water hydrolyses DDAs into much less toxic monoester diterpenoid alkaloids (MDAs) including benzoylaconine, benzoylhyaconine and benzoylmesaconine which provide therapeutic benefits.

Currently, all Aconitum species (spp.) are included in Schedule 2 (S2) and Schedule 4 (S4) in *Poisons Standard June 2020* (*the Poisons Standard*), the Standard for Uniform Scheduling of Medicines and Poisons (SUSMP). ZFZ, as a Chinese herb derived from one of the Aconitum species, is covered by S2 and S4, and therefore Chinese herbal medicine practitioners registered under the National Registration and Accreditation Scheme (NRAS) are unable to use ZFZ.

Chinese medicine is one of the allied health professions regulated by statutory regulation in Australia, with its practitioners registered with the Chinese Medicine Board of Australia (CMBA) under the framework of NRAS. There are three divisions of registration of Chinese medicine: Chinese herbal medicine practitioners, Chinese herbal dispensers and/or acupuncturists. The knowledge skills and attributes of

registered Chinese medicine practitioners are described in the statement of Professional Capabilities issued by the CMBA and practitioners must comply with defined standards, guidelines and its Code of Conduct.

This application proposes to reschedule one of the Aconitum spp. - processed Aconitum carmichaelii Debx. lateral root (ZFZ) from where it is currently scheduled S2 and S4 to a proposed S1 and adopts the international standard for the safe use of oral or dermal Aconitum spp. by setting limits on the total amount of DDAs on Aconitum spp.

Benefits of the proposed rescheduling include but are not limited to:

1) Benefits to the individual patients: better therapeutic outcomes for a wide range of common conditions including digestive disorders, abdominal pain and distension, diarrhoea, palpitations and other Chinese medicine symptomatology related to deficiency of vital energy (Yang Qi in TCM terminology);
2) Research benefits: access to the scheduled herb would enable further research into safety and efficacy of Chinese herbal medicines to improve evidence-based practice of Chinese medicine, including development of clinical management of scheduled herbs;

The safety concerns of the rescheduling include potential adverse reactions related to Aconitum spp. that are most often the result of using the unprocessed herb or improper use. The risk is minimised by using the properly processed herb with a controlled limit of toxic substances (DDAs) for increased protection and safety of patients. In fact, analyses of reported adverse events indicate very few cases related to ZFZ under the recommended dose range and proper use. In addition, ZFZ is now available in commercially prepared forms such as ready-to-use dry herbs (*Yinpian* in Chinese pinyin) or granules and manufactured proprietary CHMs (*Zhong Cheng Yao*, in Chinese pinyin) that contain a limited amount of total DDAs and do not require the need for any preparation of the herb by the patient. A comprehensive review conducted by an independent pharmacological expert provides supporting evidence for the safety usage of ZFZ.

In summary, with proper safeguards in place, the benefits of accessing ZFZ by registered Chinese herbal medicine practitioners are considerable, whilst the risks can be minimised and properly managed.

Based on the current evidence, we propose two options for the Therapeutic Goods Administration (TGA) Scheduling Committee to consider:

Option 1: rescheduling a specific Aconitum substance, processed Aconitum carmichaelii Debx. lateral root used in Traditional Chinese Medicine from Schedule 2 and Schedule 4 to Schedule 1.
Note: Schedule 1 is currently blank intentionally in the Poisons Standard.

Option 2: adding an exemption on Aconitum spp. entries in the current Schedule 2 and Schedule 4.

PART 2 – BODY OF THE APPLICATION

BACKGROUND

3. Under the current SUSMP, registered Chinese herbal medicine practitioners and dispensers are denied access to prescribe and dispense some traditionally used herbs that are therapeutically effective and can be used safely in the hands of a registered practitioner of Chinese herbal medicine following well-established protocols and cautions in relation to processing, administration, dosage, monitoring, and course of treatment. One of these herbs is processed Aconitum carmichaelii Debx. lateral root. (pharmaceutical name: Aconiti Radix Lateralis Praeparata, 'Zhi Fu Zi' [ZFZ] in Chinese pinyin, hereafter in this application to be referred to as ZFZ to represent the herb), a herb commonly used in clinical practice in China and other parts of the world.

The Chinese medicine profession is seeking that registered practitioners of Chinese herbal medicine and registered dispensers of Chinese herbal medicine be permitted to purchase, obtain, prescribe, use, sell, supply and dispense a specific Aconitum species-processed Aconitum carmichaelii Debx.lateral root, (ZFZ in Chinese pinyin).

The current SUSMP includes several Chinese herbs under various schedules which are legally accessible to some health care practitioners including medical practitioners, dentists, veterinary surgeons and pharmacists regardless of whether or not those professionals have proper training in using these herbs and regardless of whether they even have the need to utilise the herbs in their practice. In contrast, access to these herbs is denied to registered Chinese herbal medicine practitioners who have the appropriate training and knowledge of using these herbs safely. ZFZ is one example of such herbs. It is also worth noting that the current SUSMP does not define a limit of toxic diester diterpenoid alkaloids (DAAs) in Aconitum spp. for therapeutic use (which poses a potential risk of using these herbs).

In September 2003, the Expert Committee of Complementary Medicines in the Health System (ECCMHS) lodged a report to the Parliamentary Secretary to the Minister for Health and Aging. The Expert Committee recommended that *"Complementary medicine healthcare practitioners with an appropriate level of training, professional skill and competency should be allowed access to certain more potent complementary medicines that are otherwise restricted under various State and Territory Controlled Substances legislation. An appropriate Schedule in the SUSDP could be used nationally for this purpose."*(See section 2.1.16, pages 20-21, Appendix 1). It should be noted that subsequently Chinese medicine practitioners have been included in the National Registration and Accreditation Scheme (NRAS) since 2012 and registered Chinese medicine practitioners must comply with defined standards, guidelines and a Code of Conduct set by the Chinese Medicine Board of Australia (CMBA) under the framework of the NRAS.

The former Chinese Medicine Registration Board of Victoria (CMBAV) submitted a proposal *"Submission to the Victorian Minister for Health — Scheduling of Chinese Herbs"* to reschedule three Chinese herbs including ZFZ from S2 and S4 to S1 in 2009. (See monograph of Zhi Fu Zi, pages 89-120, Appendix 2) On 4 January 2010 the CMBRV received correspondence advising approval of the then Minister for Health of insertion of an initial list of three herbs into Schedule 1 of the Poisons List in Victoria. A change of government at the 2010 election resulted in a standstill with no final formal approval of the submission.

This application has been prepared and is jointly submitted by Federation of Chinese Medicine & Acupuncture Societies of Australia Ltd (FCMA), The Australian Acupuncture and Chinese Medicine Association Ltd (AACMA), Chinese Medicine Industry Council of Australia Ltd (CMIC) and Chinese Medicine & Acupuncture Society of Australia (CMASA). These four associations represent the majority of registered Chinese medicine practitioners in Australia and are dedicated to promoting the safe practice of Chinese medicine and supporting the Chinese medicine profession in Australia.

Currently, all Aconitum spp. are included in S2 and S4 in the *Poisons Standard*. ZFZ is one of the Aconitum spp. that has been traditionally used for the treatment of various conditions in Chinese medicine for hundreds of years. Following is a précis on the history and use of ZFZ.

The substance is a plant material, not a purified chemical compound.

Plant name: Aconitum carmichaelii Debx. (Scientific name) [1]

Plant material: dried lateral root of Aconitum carmichaelii Debx.

Aconiti Radix Lateralis Praeparata (Pharmaceutical name)

Prepared Common Monkshood Daughter Root (Common English name);

Zhi Fu Zi (Chinese pinyin name, abbreviated as ZFZ).[II]

"Zhi" in Chinese means 'processed'. ZFZ is the processed dry herb. Sheng Fu Zi or Ni Fu Zi is the unprocessed dry herb.

Aconitum carmichaelii Debx. lateral root (processed or unprocessed) has been used in Chinese herbal medicine practice in China and other parts of the world for centuries. It was first recorded as a medicinal herb in the *Shen Nong Ben Cao Jing* (Divine Farmer's Classic of Materia Medica). Written during the Eastern Han Dynasty (25-220 AD), these writings are recognised as the earliest Chinese Pharmacopoeia.[2] Over the last 2,000 years, Chinese doctors have gathered and recorded an immense catalogue of information on herbs, their functions and how to prepare and prescribe them for medicinal use with the five monographs of *Ben Cao* (Materia Medica) in particular recognised as the most influential.[3] The clinical application of Aconitum carmichaelii Debx. lateral root (processed or unprocessed) was explained by Zhang Zhong-Jing (150-219AD) in his classic text the *Shang Han Lun* (known in English as the *Treaties on Cold Damage Diseases*)[4] which is still influential and relevant today. The herb has been included in the editions of modern Chinese Pharmacopeia since 1963.

[II] The CMBA expects registered Chinese herbal practitioners to use pinyin names of the Chinese herbal medicines in clinical practice to avoid any confusion.

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PART 4 OF THE POISONS STANDARD – SCHEDULING OR RESCHEDULING OF SUBSTANCES

(A) RISKS AND BENEFITS ASSOCIATED WITH THE USE OF A SUBSTANCE

4. RISKS

Factors that should be taken into account when considering potential risks of a medicinal substance, set out in the **Scheduling Handbook**[III], include:

a) Toxicity of the substance

b) Purpose of use

c) Potential for abuse and dependence

d) Safety in use, including need for specialist training or personal protective equipment

e) Benefits/needs of access to the substance

These are addressed in the next few pages.

a) Toxicity

The major risk factor of Aconitum spp. is the content of the toxic DDAs including aconitine, hypaconitine and mesaconitine, which are known for neurotoxicity and cardiotoxicity.[5] The unprocessed herb, which is not the focus of this proposal, contains high levels of these toxic alkaloids. Traditional methods and procedures have been used over centuries to process the herb to reduce the DDAs rendering it safe for therapeutic usage. The difference in properties of unprocessed herb and processed herb is basic knowledge for registered Chinese herbal medicine practitioners who are fully aware of the potential toxicities of Aconitum spp. DDAs are not part of the therapeutic use of ZFZ and traditionally the DDAs in unprocessed Aconitum carmichaelii Debx. lateral root have been hydrolysed before use by boiling in water for extended periods, This approach relied on the patient following the correct procedures.[15] However this proposal is for the use of ZFZ in which DDAs have already been hydrolysed.[16]

In addition, in TCM practice, the herb is very rarely used alone but more often in combination with other herbs which can further reduce its toxicity.

b) Purpose of use

[III] https://www.tga.gov.au/sites/default/files/scheduling-handbook-guidance-amending-poisons-standard.pdf [accessed 20 Oct 2019]

ZFZ is a common ingredient in many medicinal formulae used in Chinese medicine to treat a wide variety of conditions or imbalances in the body. In the Chinese Materia Medica (CMM), ZFZ is an herb in the category of *Herbs that Warm the Interior and Expel Cold*. Its properties, according to Chinese medicine theory, are to strongly revive deficient Yang (qi), warm the internal fire and assists yang and disperse cold, warm the channels/meridians and alleviate pain.[6] Thus, it is used commonly in Chinese medicinal formulae (which are typically combinations of herbs) where a Chinese medicine syndrome diagnosis of yang qi deficiency and internal cold is found. In Chinese medicine, diseases are subcategorised according to typically 4-6 different Chinese medicine syndromes or patterns of disharmony (each of which is characterised by different signs/symptoms and is reflective of the underlying aetiology and pathogenesis, as understood according to Chinese medicine theory). Each Chinese medicine syndrome is treated with quite different combinations of herbs (formulae).

c) Potential for abuse and dependence

Neither ZFZ alone nor when used in a formula has been reported in the literature to be associated with abuse or dependence. The constituents of ZFZ do not exhibit narcotic and psychotropic properties.

d) Safety in use

Chinese medicine practitioners registered in the Division of Chinese Herbal Medicine are all trained in the correct and safe use of ZFZ. Thus, access to ZFZ should be confined (outside of those already with access) to registered Chinese medicine practitioners in the Division of Chinese Herbal Medicine. This could be achieved through the appropriate naming of Schedule 1.

The potential risk of Aconitum spp. to patients can be minimised by:

1) only using the processed herb (ZFZ) in which the total amount of DDAs has been reduced to levels safe for therapeutic use through processing;
2) using the dose range of 3-15 grams of ZFZ per day recommended by the Chinese Pharmacopoeia 2015;[16]
3) using the herb in the form of commercial ready-to-use dry herbs of ZFZ (Y*inpian* in Chinese pinyin) defined by the Chinese Pharmacopoeia 2015: *Heishunpian* or *Baifupian.*[16]
4) using the herb in the form of commercial granules which are prepared with the same traditional methods for the processing of the herb. It usually involves a decoction process that produces a liquid concentrate which is then combined with excipients to stabilise the preparation and transform the liquid decoction into dry granules.[7, 8] Granule herbal extracts can provide further insurance of a consistent product if standardised and that will also enable greater control on dosage.[9] Appendix 4 provides a sample of a quality control report of ZFZ granules and DDAs were not detected.

e) The benefits/needs of access to the substance

As discussed previously in section b) Purpose of use, ZFZ is commonly used in medicinal formulae where a Chinese medicine syndrome diagnosis of Yang qi

deficiency and internal cold is found. It is one of the key herbs in the CMM for strengthening deficient yang when associated with internal cold and ZFZ for this reason is included in key medicinal formula with centuries of use. There is a wide range of medical conditions for which medicinal formulae which include ZFZ are indicated. Because of its beneficial effects in strengthening deficiency yang qi, particularly when the deficiency is quite severe, there is no equivalent herb that can be substituted for this herb. This herb is commonly used in China and other parts of the world by qualified Chinese herbal medicine practitioners. By allowing access to appropriately qualified registered Chinese herbal medicine practitioners in Australia, it would allow them access to an accepted and extremely beneficial herb.

Benefits of the proposed rescheduling include but are not limited to the following:

1) Benefits to individual patients: better therapeutic outcomes for a wide range of common conditions including digestive disorders, abdominal pain and distension, diarrhoea, and other Chinese medicine symptomatology related to deficiency of vital energy (Yang qi in TCM terms).
2) Research benefits: access to the scheduled herb would enable further research into safety and efficacy of Chinese herbal medicines to improve evidence-based practice of Chinese medicine, including development of clinical management of scheduled herbs.

(B) THE PURPOSES FOR WHICH A SUBSTANCE IS TO BE USED AND THE EXTENT OF USE OF THAT SUBSTANCE

5. The substance (ZFZ) will be used in TCM practice in preparations of decoction, granules extracts or manufactured proprietary CHMs (Zhong Cheng Yao in Chinese pinyin) as a single herb or as an ingredient of a complex herbal formulation which contains multiple herbs. The formula may be used internally or externally.

As an "indispensable botanical substance" (See Appendix 5) there is no herb or combination of herbs that can be adequately substituted for ZFZ.

In traditional terms, the actions of ZFZ and its indications for use in Chinese medicine practice include: restoring devastated Yang and rescuing patient from collapse, warming up the body and dispersing cold, warming the channels and alleviating pain. [6] Symptoms that could indicate the need for ZFZ in a combination herbal formula include diarrhoea with undigested food, deep chills, cold or deep aching and heaviness of the extremities, joint and low back pain with weakness, pallor, profuse sweating, impotence and difficult urination or frequency.[6] This covers a number of conditions or disorders in the cardiovascular, gastrointestinal, respiratory and skeletal muscle systems. Studies of ZFZ have shown a variety of therapeutic effects and beneficial impacts on those systems as well as its antimicrobial, anti-inflammatory and anti-epileptiform effects.[10, 11]

The holistic nature and individualised treatment delivered in Chinese medicine practice as well as the knowledge and skill of the trained and registered Chinese herbal medicine practitioners in establishing a diagnosis and treatment principle would be the defining factors in prescribing the use of ZFZ as part of an herbal formula. (See Appendix 6)

(C) TOXICITY AND SAFETY OF THE SUBSTANCE

6. See (A) 4 and the followings.
7. See Part 3 – "Supporting Data".

Aconitum carmichaelii Debx. lateral root in its unprocessed form has long been recognised as a toxic material. The level of its toxic ingredients depends on the source and preparation of the herb.[6, 8]

The principal toxins of all Aconitum spp. including unprocessed Aconitum carmichaelii Debx. lateral root are DDAs with aconitine, hypaconitine and mesaconitine being the main three.[11, 12]

The symptoms of aconite poisoning can present neurologically, cardio-vascularly and gastro-intestinally, including numbness of face and mouth and weakness and numbness of the limbs, low blood pressure, palpitations, chest pain and heart arrhythmias, nausea, vomiting, diarrhoea and abdominal pain.[13]

Poor processing of the herb and/or high dosage are risk factors for adverse effects or aconite poisoning.

Traditionally, hydrolysing ZFZ through water decoction has been employed to decrease its toxicity for therapeutic use.[8, 13] Boiling of Aconitum carmichaelii Debx. lateral root in water hydrolyses DDAs into much less toxic monoester diterpenoid alkaloids (MDAs) including benzoylaconine, benzoylhyaconine and benzoylmesaconine.[14] In 2018, Sun et al studied the toxicity of detoxified Aconitum carmichaelii Debx. lateral root using High Performance Liquid Chromatography (HPLC). They state: "*These aconitines were undetected by HPLC in Fuzi after 2 h-decoction (FZ-120), indicating seemingly non-toxicity of FZ-120. Unlike the non-decocted Fuzi (FZ-0) and 60 min-decocted Fuzi (FZ-60) with lethal toxicity, FZ-120 at 130 g/kg did not cause any deaths or side effects in mice regarding body weight and biochemical parameters.*" [15]

Currently, the amounts of total DDAs and MDAs have been used as markers for quality assurance and control of ZFZ as set by the Chinese Pharmacopoeia 2015. [14, 16] For DDAs: "*It (ZFZ) contains not more than 0.020 per cent of the total amount of mesaconitine ($C_{33}H_{45}NO_{11}$), hyaconitine ($C_{33}H_{45}NO_{10}$) and aconitine ($C_{34}H_{47}NO_{11}$) following the methods for the crude drug".* For MDAs: "*It contains not less than 0.010 per cent of the total amount of benzoylmesaconine ($C_{31}H_{43}NO_{10}$), benzoylaconine ($C_{32}H_{45}NO_{10}$) and benzoylhyaconine ($C_{31}H_{43}NO_9$), calculated with reference to the dried drug.*" [16]

There are two ready-to-use dry herbs of ZFZ (*Yinpian* in Chinese pinyin) defined by the Chinese Pharmacopoeia 2015: [16] Heishunpian (Figure 1) and Baifupian. (Figure 2)

Figure 1: ZFZ (product name: Heishunpian)

Figure 2: ZFZ (product name: Baifupian)

(Photos were downloaded from internet)

Briefly, unprocessed Aconitum carmichaelii Debx. lateral root (Sheng Fu Zi or Ni Fu Zi) is processed with a mother liquid of minimal salt (brine), boiling and drying. The final ready-to-use products are Heishunpian or Baifupian. Heishunpian is further processed with brown sugar and vegetable oil according to the Chinese Pharmacopoeia 2015.[16] Heishunpian or Baifupian contain less than 0.020% (weight/weight, w/w) of total DDAs calculated as total amount of aconitine, mesaconitine and hyaconitine and not less than (NLT) 0.010% of total MDAs calculated as total amount of benzoylaconine, benzoylmesaconine and benzoylhyaconine.[16] These forms of ZFZ are ready for decoction (the decoction here is not necessary to further detoxify the DDAs but in order to extract the therapeutic benefits of ZFZ) or further extracted for granules or used as an ingredient in manufactured pr herbs.

While the aconite alkaloids (MDAs derived from DDAs via processing) are responsible for both the therapeutic effect and toxicity, and therefore safety of use is paramount. Standardising the processing of the herb through boiling plus the concurrent use with other herbs provides a reduction of risk.[13, 15] Regulators in some countries have set maximum limits on the total amounts of DDAs. Both Canada and China have set a 0.020% w/w limit on DDAs in ZFZ.[16] (See Appendix 8). Aconitum carmichaelii Debx. as a dry processed herb is currently listed under the *Natural and Non-Prescription Health Products Directorate (NNHPD)* and regulated under *Schedule 1, Natural Health Products Regulations (NHPR)* in Canada.[17] Canadian

consumers are able to buy and use any products listed on *NNHPD* from a licensed supplier. (See Appendixes 7 to 10)

This proposal aims to reschedule a substance, processed Aconitum carmichaelii Debx. lateral root, derived from one of the Aconitum spp., from current S2 and S4 to a proposed S1 (or alternatively, include an exception in the current S2 and S4) to allow the registered Chinese herbal medicine practitioners to access the herb for therapeutic use in their TCM practice. It is also recommended that the TGA Scheduling Committee consider adopting the approaches of the Canadian *NNHPD* and the Chinese Pharmacopoeia 2015 by setting limits on the total amount of DDAs for the safe oral or dermal use of Aconitum spp.

A comprehensive review including toxicity of the DDAs and MDAs conducted by an independent pharmacological expert provides more information regarding the toxicity and safety of ZFZ (see Appendix 13).

(D) DOSAGE, FORMULATION, LABELLING, PACKAGING AND PRESENTATION OF A SUBSTANCE

8. Dosage:
   In clinical practice, ZFZ can be prescribed in the forms of decoction pieces (*Yinpian*, or dried herbs), granules and pills. The daily dose for the decoction pieces is 3.0 - 15g as recommended by the Chinese Pharmacopoeia 2015.[16]
   The doses for commercial granules and pills are equivalent to those of decoction pieces (3.0 -15g). The level of DDAs in the substance will be tested and certified by the authorised agents before they are supplied to Chinese herbal medicine practitioners. (See Appendix 4)

Formulation:

In clinical practice, ZFZ is generally used in a formula together with other herbal ingredients and seldom used as a single herb. The *Shang Han Lun* (*Treaties on Cold Damage Diseases*) is the classical text that describes the use of ZFZ, dating back more than 1,800 years.[4] (See Appendix 6). This classical text describes 23 formulas that include ZFZ for treating a variety of different health conditions. Many of these formulas are still used in treatments today in countries around the world.[4, 6]

Proposed guidelines for prescribing ZFZ as an ingredient in a formula should include the following:

- Must use a product processed and/or manufactured by a licensed Good Manufacturing Practice (GMP) manufacturer;
- Each batch of the product must have a Certificate of Analysis (COA) as evidence of compliance with quality standards (including but not limited to the actual level of DDAs assayed);
- Registered Chinese herbal medicine practitioners will be expected to purchase ZFZ and its contained products from importer/suppliers who are signatories to a wholesaler's Code of Practice for herbal materials which is currently being implemented;
- Patients must be warned not to consume alcohol when taking ZFZ;
- Practitioners are required to follow the guidelines set by the CMBA for safe of Chinese herbal medicine practice (see Appendix 11) , and are recommended to

start at a low dose and gradually increase the dosage up to the limit set by the Chinese Pharmacopoeia 2015. [16]

Labelling, Packaging and Presentation.

The general guidelines for the safe prescribing and dispensing of CHMs have already been established in *Guidelines for Safe Chinese Herbal Medicine Practice* issued by the CMBA in 2017 (See Appendix 11) and *Competencies Required to Prescribe Medicines* in 2012. (See Appendix 12) Relevant sections of the *Poisons Standard* will apply to ZFZ if is listed at S1 (or alternatively if an exception is added to the current entries in S2 and S4). In addition, special requirements for the dispensing and manufacturer's labelling and packaging of ZFZ are recommended as follows:

1) Strong and prominent labelling of inclusion of ZFZ in relevant prescriptions / preparations / medications , and a statement that the ZFZ-containing medication must only be prescribed by a registered Chinese herbal medicine practitioner;
2) Strong warning on the label: "*If you experience any following symptoms contact your practitioner and/or seek medical help urgently: tingling and numbing sensation of the lips, tongue, mouth, throat, salivation, nausea, vomiting, dizziness, diarrhoea, visual blurring or yellow-green colour vision distortion, weakness, delirium and paraesthesia over the entire body, breathing or speech difficulty*."
3) Patient-centred labels approach and compliance with CMBA guidelines as follows:
   Information to include:
   - Patient's name
   - Dosage and quantity supplied
   - Date of dispensing or supply
   - Initials of the dispenser (and if different, the initials of the dispenser checking and issuing the medicine)
   - Name, address and telephone number of the dispensing clinic
   - Storage directions and expiry date of the medicine
   - Inclusion of the warning "Keep out of reach of children"
   - General formatting suggestions:
     - use larger font sizes (e.g. 12 point and above)
     - present complex information in lists rather than paragraphs when possible
     - use numbers rather than words to convey numeric information, for example 'take 2 grams...' rather than 'take TWO grams...'
     - provide explicit dosing instructions, for example 'take 2 grams in the morning, and take 2 grams in the evening' rather than 'take TWO grams TWICE a day'
     - use standard dosing times for medicine administration, for example 'morning, noon, evening, night rather than 'TWICE daily', 'FOUR times daily' or 'every SIX hours'
     - include the indication for the medicine when possible.

4) Prescription medicine label of TGO 91 Protocol (Therapeutic Goods Order No. 91) as required for all manufactured proprietary CHMs (Zhong Cheng Yao in Chinese pinyin) containing ZFZ;
5) Therapeutic Goods Order No. 95 – Child resistant packaging requirements for medicines 2017 (TGO 95) as required for all manufactured proprietary CHMs (Zhong Cheng Yao in Chinese pinyin) containing ZFZ.

(E) POTENTIAL FOR MISUSE/ABUSE OF THE SUBSTANCE

9. There is a public misconception that herbal products are safe because they are of natural origin. Toxicity of herbal medicines may arise from various reasons, including inherent toxic ingredients in the herbs or interactions with conventional drugs, misidentification, adulteration, misuse, abuse, or overdose. Regulatory authorities are undertaking to provide a reasonable assurance of safety, quality and efficacy of herbal products through scheduling and monitoring programs of herbs that are known to be toxic.

Most aconite poisoning cases reported in mainland China were from the use of the main root of Aconitum carmichaelii Debx. (known as Chuan Wu in Chinese pinyin) or Aconitum kusnezoffii Reichb. (known as Cao Wu in Chinese pinyin). They were not prescribed therapeutically but consumed as vegetables or made into a soup with other cooking ingredients with amounts of 50-500g, which greatly exceeded the recommended dosage of 1.5-3g per day indicated by the Chinese Pharmacopoeia 2015.[16] Causes of aconite poisoning in mainland China included misadministration of the herb (inadequate boiling time or misuse of the fresh herb when it is mistaken for wild celery); use of unprocessed Aconitum spp.; drinking of homemade herbal liquors containing with Aconitum spp.; overdose or self administration of the herb.[20]

In North America, accidental aconite poisoning is extremely rare. There was one confirmed case of accidental aconite poisoning.[21] The case involved a 25-year-old man who died suddenly following a recreational outing with friends where he consumed a number of wild berries and plants including one that was later identified as Monkshood (Aconitum napellus). The concentrations in the blood and urine were similar to that reported in other aconite-related deaths. This case illustrates the dangers of consuming unidentified plants, and documents concentrations of aconitine in blood and urine in a fatal case of Aconitum napellus-related poisoning.

There were two aconite poisoning cases, one of them fatal, occurred in Perth in August 1989.[22] The two independent patients in Perth were given and brewed Chinese herbs by a Chinese herbalist for their neck pain. Soon after ingestion of the herbal decoction, the patients felt unwell and were hospitalised immediately. One of them died from cardiac arrest. Evidence of usage of Aconitum kusnezoffii Reichb (Cao Wu in Chinese pinyin) was found in the fatal case. The report did not state what Chinese herbs were given to the mild case. Another aconite poisoning case in Melbourne was reported in 2014.[23] The patient was prescribed Chinese herbs for her chronic low back pain. The formula contained Aconitum carmichaelii Debx. lateral root (it is unclear whether the herb was processed or not) and other Aconitum species (Chuan Wu and Cao Wu). The patient made a full recovery after receiving proper medical care.

In relation to potential for abuse, there are no reports of abuse in association with ZFZ. The established therapeutic use of ZFZ is primarily in combination with other herbal ingredients in Chinese medicine practice. Neither ZFZ alone nor when used in a formula has reported to be associated with abuse or illicit use. The constituents of ZFZ do not exhibit narcotic and psychotropic properties.

The potential for the conversion of ZFZ into a Schedule 8 item is unlikely. The constituents of ZFZ do not exhibit narcotic and psychotropic properties. The metabolites of the key constituents of ZFZ do not exhibit narcotic or psychotropic

properties. For instance, the aconite alkaloids are primarily metabolised by cytochrome P450 enzymes, carboxylesterases and intestinal bacteria. MDAs and nontoxic alcohol amines in ZFZ are the primary DDAs metabolites detected in the blood. (See Appendix 13)

(F) ANY OTHER MATTER THAT MAY BE RELEVANT TO THE SCHEDULING OF A SUBSTANCE

10. Proposed herbal substances for therapeutic use in S1 must be:

1) accurately identified and labelled;
2) have appropriate quality control that standardises and limits the content of toxic ingredients in these substances.

Risk management in the use of ZFZ may include:

1) Adequate training (including knowledge of antidotes and other emergency procedures) of registered Chinese herbal medicine practitioners. The knowledge skills and attributes of registered Chinese medicine practitioners are described in the statement of Professional Capabilities issued by the CMBA (Appendix 14) and practitioners must comply with defined standards, guidelines and a Code of Conduct;
2) Dosage and administration protocols;
3) Quality assurance – quality control standard and authorised testing of DDAs content of ZFZ-containing products, including decoction pieces, granules, tinctures or manufactured forms; (See Appendix 4)
4) Guidelines for adverse event monitoring and reporting.

Recommendations

1) It is recommended that the total amount of DDAs are controlled, including aconitine, hypaconitine and mesaconitine, in Aconitum spp. in the current S2 and S4, as these three DDAs are the main toxic constituents in the Aconitum spp. providing a better marker for safety control. It is also consistent with international standards in other countries such as Canada and China;
2) The recommended clinical dose for dry herb of processed Aconitum carmichaelii Debx. lateral root (ZFZ) ranges from 3.0g to 15g per day set by the Chinese Pharmacopoeia 2015;[16]
3) Acceptable limit of total DDAs calculated as the total amount of aconitine, hypaconitine and mesaconitine for ZFZ must be NMT 0.020% w/w as set by the Health Canada Guidelines (Appendix 8) and the Chinese Pharmacopoeia 2015;[16]
4) Currently the International Organisation for Standardisation (ISO) is developing an international standard ZFZ for TCM, with various control parameters including morphological features, identification, marker

compounds, heavy metals, pesticide residues, packaging, storage, transportation, and labelling, as well as sampling and test methods. It is recommended to adopt this ISO standard once published and if this proposal is approved; (See Appendix 13)

5) As there is no international quality standard currently available for the herbal granules, it is recommended to adopt the same DDAs limit for granules and other manufactured dosage forms. For this reason, a mandatory requirement of COA from a TGA accredited laboratory is recommended for every batch of ZFZ or ZFZ-containing products, with the contents of total alkaloids calculated as total DDAs of NMT 0.020% w/w;
6) To achieve the bioequivalence of ZFZ, the amount of total DDAs contained in single dose of the herb is calculated as: 3.0g (the minimum single dosage of the dry herb recommended by the Chinese Pharmacopoeia 2015) x 1000mg x 0.020% = 0.6mg. The amount of total DDAs contained a daily dose of the herb is calculated as: 15g (the maximum daily dosage of the dry herb) x 1000mg x 0.020% = 3.0mg; Thus, a limit of NMT 0.6mg of total DDA's for a single dose and NMT 3.0mg of total DDAs for a daily dose is recommended for both oral or dermal use of ZFZ. Safety of the limited DDAs ingestion has been confirmed; (See Appendix 13)
7) Table 1 outlines the criteria for Aconitum spp. listed on proposed S1 and the current S2 and S4 of *the Poisons Standard*.

Table 1 Criteria for ACONITUM spp. listed on Proposed S1 and current S2 and S4 of *the Poisons Standard*

Criteria	Proposed S1	Current S2	Current S4
Scheduled substance	Processed Aconitum carmichaelii Debx. lateral root in preparations or manufactured dosage forms used in TCM	All Aconitum spp.	All Aconitum spp.
Limit of daily oral intake or dermal use of dry herbs	3.0g to 15.0g	No limit	No limit
Limit of aconite alkaloids	Calculated as total DDAs and ≤ 0.020% w/w	Oral use in packs each containing 0.2 mg or less of total alkaloids. Dermal use containing 0.02% or less of total alkaloids	Oral use in packs each containing 0.2 mg or less of total alkaloids. Dermal use containing 0.02% or less of total alkaloids

Total aconite alkaloids calculation	Total amount of DDAs calculated as total amount of aconitine, hypaconitine and mesaconitine	Not set	Not set
Limit of single dose oral intake or dermal use of total amount of DDAs calculated as aconitine, hypaconitine and mesaconitine	≤ 0.6mg	Not set	Not set
Limit of daily oral intake or dermal use of total amount of DDAs calculated as aconitine, hypaconitine and mesaconitine	≤ 3.0mg	Not set	Not set

Note: DDAs: Diester diterpenoid alkaloids; S1: Schedule 1; S2: Schedule 2; S4: Schedule 4; spp.: species; TCM: Traditional Chinese Medicine

PART 2.2 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PARTS 1-3 OR PART 5 OF THE POISONS STANDARD

11. Not applicable.

CONCLUSION

12. The benefits of providing access to ZFZ to appropriately qualified, registered Chinese herbal medicine practitioners includes the potentially greater efficacy of treatment of a wide range of conditions with Chinese herbal medicine. This herb has a long history of use in China and other parts of Asia. The potential benefits far outweigh the potential risks which are mitigated through limits on concentration of potentially toxic components, appropriate labelling and limiting the entry in S1 to ZFZ.

Analyses of aconite poisoning cases reported indicate that most are not related to ZFZ. With few reported adverse events having been reported in relation to the therapeutic use of ZFZ over a long period of time; the herb is considered safe when used appropriately.

Two options have been proposed in this application, set out below. Option 1 would be the preferred option, however if S1 is to remain blank, Option 2 would be an acceptable alternative.

Option 1: rescheduling a specific Aconitum substance, processed Aconitum carmichaelii Debx. lateral root used in Traditional Chinese Medicine from Schedule 2 and Schedule 4 to Schedule 1.
Note: Schedule 1 is currently blank intentionally in the Poisons Standard.

Option 2: adding an exemption on Aconitum spp. entries in the current Schedule 2 and Schedule 4.

PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

13. Table 2: List of Appendixes and Addendums

Items	Titles	Resources
Appendix 1	Complementary Medicines in the Australian Health System	Expert Committee on Complementary Medicines in the Health System. Report to the Parliamentary Secretary to the Minister for Health and Ageing September 2003
Appendix 2	Submission to the Victorian Minister for Health — Scheduling of Chinese Herbs	A submission to the Victorian Minister for Health recommending herbs to be inserted in Schedule 1 of the Victorian Poisons List in the *Drugs, Poisons and Controlled Substances Act 1981*, for prescribing and dispensing by suitably trained and endorsed Chinese herbal medicine practitioners and Chinese herbal dispensers. September 2009
Appendix 3	CMRBV Newsletter March 2010	CMRBV March 2010
Appendix 4	Report of Quality Evaluation of a Granular Chinese Herbal Medicine Zhi Fu Zi	Jiang Yin Tian Jiang Pharmaceutical Co Ltd, China April 2019
Appendix 5	Supporting letter from Dr Arnaud Versluys 9 June 2020	Arnaud Versluys, PhD, MD, LAc Director, Institute of Classics in East Asian Medicine, USA June 2020
Appendix 6	Supporting letter from Professor Huang Huang 8 June 2020	Prof Huang Huang, International Jing Fang Institute, Nanjing University of Traditional Chinese Medicine, China June 2020
Appendix 7	Supporting letter from	Dr Eric Brand

	Dr Eric Brand 11 June 2020	Chair of the USA delegation for ISO/TC249 from 2014–2017 June 2020
Appendix 8	Drugs and Health Products Organism - Aconitum carmichaelii	Health Canada http://webprod.hc-sc.gc.ca/nhpid-bdipsn/ingredReq.do?id=5842&lang=eng accessed on 28 October 2020
Appendix 9	Supporting letter from Mr Mark Gearing 10 June 2020	Mark Gearing PhD Candidate June 2020
Appendix 10	Support letter from Mr Kevin V. Ergil 11 June 2020	Kevin V. Ergil, MA, MS, DACM, L.Ac, Diplomate in Oriental Medicine (NCCAOM) Director of Health Sciences, Wells College, Aurora NY. USA June 2020
Appendix 11	Guidelines for Safe Chinese Herbal Medicine Practice	Issued by the Chinese Medicine Board of Australia November 2017
Appendix 12	Competencies Required to Prescribe Medicines	Prescribing Competencies Framework 2012
Appendix 13	Summary of research on processed Aconitum carmichaelii lateral root Zhi Fu Zi-an expert report	Professor Chun Guang Li October 2020
Appendix 14	Professional capabilities for Chinese medicine practitioners	Issued by the Chinese Medicine Board of Australia February 2020
Addendum 1	Declaration of the expert	Professor Chun Guang Li October 2020
Addendum 2	Bio of the expert	Professor Chun Guang Li October 2020

SUPPORTING DATA DETAILS

14. See Table 1: List of Appendixes and Addendums.

15. See Addendums 1 and 2.

COPIES OF PAPERS REFERENCED

16. An USB with references, supporting letters and expert’s report will be sent via registered mail.

17. Not applicable.

PART 4 – BIBLIOGRAPHY

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ACRONYMS AND ABBREVIATIONS

AACMA:	Australian Acupuncture and Chinese Medicine Association Ltd
CHMs:	Chinese herbal medicines
COA:	Certification of Analysis
CMASA:	Chinese Medicine & Acupuncture Society of Australia
CMBA:	Chinese Medicine Board of Australia

CMIC:	Chinese Medicine Industry Council of Australia Ltd
CMM	Chinese Materia Medica
CMRBV:	Chinese Medicine Registration Board of Victoria
DDAs:	Diester diterpenoid alkaloids
ECCMHS:	Expert Committee of Complementary Medicines in the Health System
FCMA:	Federation of Chinese Medicine & Acupuncture Societies of Australia Ltd
GMP:	Good Manufacturing Practice
HPLC:	High Performance Liquid Chromatography
ISO:	International Organisation for Standardisation
MDAs:	Monoester diterpenoid alkaloids
NHPR:	Natural Health Products Regulations
NLT:	Not less than
NMT:	Not more than
NNHPD:	Natural and Non-prescription Health Products Directorate
NRAS:	National Registration and Accreditation Scheme
spp.	Species
SUSMP	Uniform Scheduling of Medicines and Poisons
TGA:	Therapeutic Goods Administration
w/w:	Weight-Weight
ZFZ:	Zhi Fu Zi (processed Aconitum carmichaelii Debx. lateral root)

PART 5 – SUBMITTING THIS APPLICATION

19. All applications to amend the Poisons Standard for medicine-related substances should be emailed to the *Medicines Scheduling Secretariat*:

    Medicines.Scheduling@tga.gov.au.

    Sent on 4 November 2020

20. All applications to amend the Poisons Standard for chemical-related substances (non-medicines) should be emailed to the *Chemicals Scheduling Secretariat*:

    Chemicals.Scheduling@health.gov.au.

Not applicable.