Chapter 3
Achyranthes bidentata Bl. 牛膝
(Niuxi, Twotooth Achyranthes Root)

Minhui Li

3.1 Botanical Identity

Achyranthes bidentata Bl., a perennial herbaceous plant in the family Amaranthaceae, is widely distributed in China. The root of *A. bidentata*, usually called Niuxi or Huainiuxi in Chinese, has become one of the most important Chinese traditional medicinal herbs. It also has been frequently used as a tonic or dietary supplement. Typically, *A. bidentata* is about 70–120 cm tall with green or tinged purple stem and symmetrical branches. Leaves are elliptic or elliptic-lanceolate, rarely oblanceolate, supported by a hairy petiole of 0.5–3 cm long, with a cuneate or broadly cuneate base. The spikes are terminal or axillary, and the flowers are dense, about 5 cm long. Bracts are broadly ovate and reflexed after anthesis, the bracteoles are spiny, 0.25–0.3 cm long [1].

Niuxi grows mainly on the roadsides or hillsides, about 200–1750 m above sea level, and is widely distributed in China except for northeastern provinces, mainly in Henan, Anhui, Fujian, and Hebei provinces, etc. The Huainiuxi originated from Wuzhi, Boai, Qinyang prefectures of Henan province, is one of the famous "Four Huaiqing Chinese Medicines" at home and abroad [1]. The drug is collected in winter when aerial part withered, then removed from rootlet and soil, tied up in a small bundle, sun-dried to be wrinkled externally, cut evenly at the summit and dried thoroughly. There are also other processing methods for some specific medicinal purposes, including alcoholic Niuxi, salt Niuxi and so on [2, 3].

Chuanniuxi, mainly originated in Sichuan province, and Tuniuxi is usually harvested from the wild, has been widely used in traditional Chinese Medicine. Chuanniuxi is the dried root of *Cyathula officinalis* Kuan (Fam. Amaranthaceae), and has been recorded in Chinese Pharmacopoeia Pharmacopoeia. Tuniuxi, the

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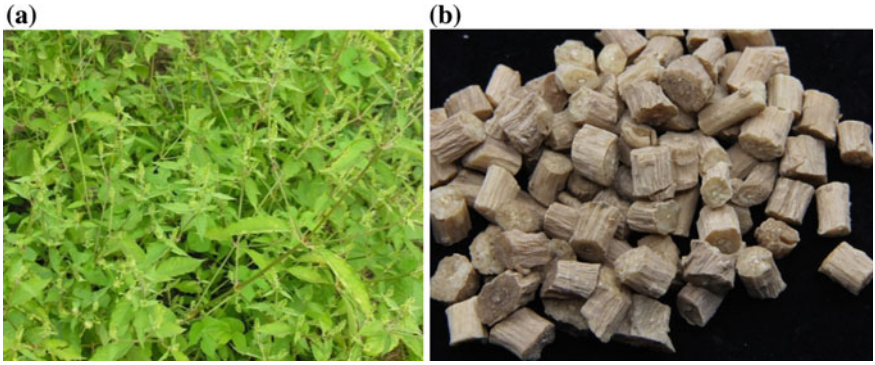


Fig. 3.1 Flowering plant (**a**) and crude drug (**b**) of Niuxi

dried root of *Achyranthes aspera* L., is one of the most important traditional Chinese medicinal materials, and has been frequently used together with other herbs (Fig. 3.1).

3.2 Chemical Constituents

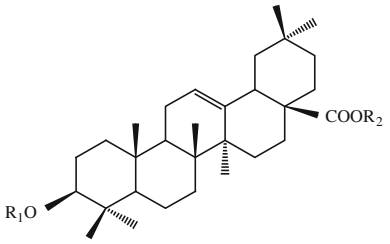
Triterpenoid saponins, polysaccharides and phytoecdysones are three major classes of bioactive compounds found in the root of *A. bidentata*.

3.2.1 Saponins

About 38 saponins have been isolated from *A. bidentata*, among which triterpenoid saponins is an important medicinal ingredient, especially the oleanane-type triterpenoid saponins. There are at least 15 oleanane-type triterpenoid saponins isolated from *A. bidentata*. 1–4 molecules of glucose, glucuronic acid or rhamnose occupy C-3 or C-28 of oleanolic acid, which composes the oleanane-type monodesmoside and bisdesmosides (shown in Fig. 3.2) [4].

3.2.2 Phytoecdysones

Phytoecdysones are the main effective components in *A. bidentata*. According to the Chinese Pharmacopoeia, β-ecdysone is the representative component used as the standard compound for evaluation of the quality of crude medicinal Niuxi [3]. A large number of phytoecdysones have been isolated from *A. bidentata*, among



Saponins	R_1	R_2
Achhybidensaponins I	Rha-(1→3)-GluA	Glc
Achhybidensaponins II	GlcA	Glc
Bidentatoside I	3′-glycolyl-2,3-dioxopropionyl-GlcA	Glc
Bidentatoside II	2′- (2"-O-glycolyl)-glyoxylyl	Glc
Chikusetsusaponin V methyl ester	Glc-(1→2)-6-Me-GluA	Glc
Ginsenoside Ro	Glc-(1→2)-GluA	Glc
PJS-1	H	Glc
Aachyranthoside I	2′-O-Glc-3′-O-(2"-OH-1"- carboxyethoxycarboxypropyl)]-GlcA	Glc
Aachyranthoside II	Glc-3′-O-(2"-OH-1"-carboxyethoxycarboxypropyl)]-GlcA	Glc
Aachyranthoside C	3-[2-Carboxy-1-(carboxymethoxy)-2-hydroxyethyl]-Glc	Glc
Aachyranthoside C dimethyl ester		
Aachyranthoside C butyl dimethyl		
Aachyranthoside E	3-[1-Carboxy-1-(carboxymethoxy)methyl]-Glc	Glc
Aachyranthoside E dimethyl ester		
Aachyranthoside Ebutyl dimethyl		

Fig. 3.2 Representative oleanane-type saponins isolated from Niuxi. *Glc* β-D-glucopyranosyl; *GluA* β-D-glucironopyranosyl; *Rha* α-L-rhamnopyranosyl; *Me* methyl

them, ecdysterone (**1**), inokosterone (**2**) and rubrosterone (**3**) being the primary ones. Recent research has found that there are other phytoecdysones in *A. bidentata*, such as serfurosterone A, achyranthesterone A, rhapontisterone B and stachysterone D (shown in Fig. 3.3) [5, 6].

3.2.3 Polysaccharides

Polysaccharide (ABP) is a purified polysaccharide isolated from *A. bidentata*. Polysaccharide sulfate (ABPS) of *A. bidentata* was a sulfated derivate from ABP, which was isolated and identified from *A. bidentata* [7, 8]. Recent studies indicate that ABP exerts a wide spectrum of immunomodulatory effects on the cells of

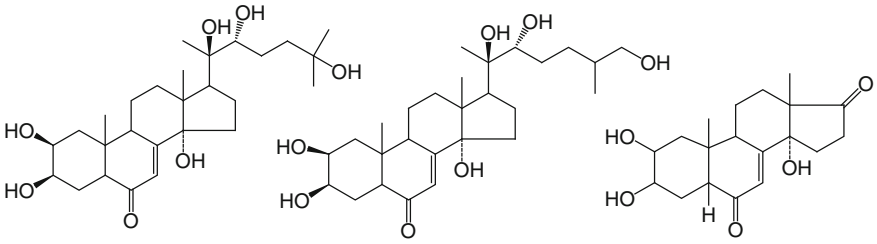


Fig. 3.3 Representative phytoecdysones isolated from Niuxi

immune system [8]. ABAB, a peptide polysaccharide, which has an immunological effect, is also isolated from *A. bidentata*. It is composed of D-glucuronic acid, D-galactose, D-galacturonic, L-arabinose and L-rhamnose. In addition, some researchers have found a water soluble polysaccharide called AbS that is composed of six glucose residues and three mannose residues [2].

3.3 Pharmacological Studies

A. bidentata is a commonly prescribed Chinese medicinal herb with the property of strengthening bones and muscles and ensuring proper downward flow of blood in terms of the therapeutic theory of traditional Chinese medicine. Modern pharmacological studies indicate that *A. bidentata* is an immunostimulant with anti-tumor, anti-fertility, analgesic, anti-bacteria, cognition-enhancing, anti-inflammation, anti-senile and anti-osteoporosis properties [2, 9]. *A. bidentata* also has a significant effect on uterine smooth muscle based on the species of animals or on whether they pregnant. The liquid extract and decoction of Niuxi have contractile effect on the isolated uterus of rabbits whether they pregnant or not. For pregnant cats, Niuxi appears to produce shrinkage effect on the uterus; however cats that are not pregnant show a flaccid [10, 11]. It has been reported that ecdysterone and inokosterone are the main components for anti-diabetic activity with low toxicity and side effects. In addition, ecdysterone and inokosterone promote protein assimilation and the synthesis of protein. RNA of cell nucleus and cytoplasm in liver are also increased observably [12]. The phytoecdysones show protective activities of heart and cerebral vessels system, respiratory system and endothelial cells [13]. ABP, as a major polysaccharide, has significant bioactivities in the aspects of immune adjustment, anti-coagulation, anti-tumor and anti-inflammatory [14]. Saponins from *A. bidentata* have been proven to possess various bioactivities such as anti-fertility, anti-tumor, analgesic and anti-inflammatory. It has also been proven to improve circulation [15].

3.4 Applications and Dietary Usage

3.4.1 Applications

Niuxi is one of the most popular herbs used in TCM. *A. bidentata* is bitter and sour in flavor, mild in nature and contributive to the liver and kidney meridians. As described previously, Niuxi is used as a tonic, emmenagogue, antiarthritic, diuretic, and antifertility agent to nourish the liver and kidneys, strengthen bones and muscles, and invigorate circulation [6]. In Chinese Pharmacopoeia 2010, Niuxi has been recorded to promote blood circulation, remove blood stasis, nourish the liver and kidney, strengthen bones and muscles, induce diuresis to treat stranguria and ensure proper downward flow of blood [3]. There are many practical formulations used historically, including Niuxi decoction, Niuxi powder, Niuxi wine, Sanmiaowan and so forth.

3.4.2 Dietary Usages

Niuxi is not only a nontoxic plant often used as a prescription ingredient, but also a valuable dietary plant, which has been included in the list of Chinese herbal medicines that can be used in health foods. Niuxi combined with other herbs can be used to prepare Niuxi wine, Niuxi paste and so on.

3.4.2.1 Niuxi Wine

Niuxi can be available to make herbal wines for hemiplegia and rheumatoid arthritis. One method for this is to soak Niuxi (roots of *A. bidentata*, 15 g), Chuanwu (parent root tubers of *Aconitum carmichaelii*, 15 g), Caowu (root tubers of *Aconitum kusnezoffii*, 15 g), Wumei (fruits of *Prunus mume*, 15 g), Daqingye (leaves of *Isatis indigotica*, 15 g) and Jinyinhua (flower buds or opening flowers of *Lonicera japonica*, 10 g) in 500 ml of Chinese spirit for ten days or more. The procedure is to drink 5–10 ml every morning and evening [16]. The other method is to boil Niuxi (roots of *A. bidentata*, 500 g) and soak sticky rice (1000 g) in the resulting juice of Niuxi. This concoction is then fermented in a warm place. Taking a daily dose of this boiled Niuxi wine orally is beneficial as a liver and kidney tonic, and invigorating the circulation [17]. In addition, Niuxi can also be used to make herbal wines in combination with many other herbs and the dose depends on the desired effect.

3.4.2.2 Niuxi Used in Medicated Foods

In some documentary records, Niuxi can be used for breast enhancement. One of the formulas is Longxiong Shiliao soup, which is composed of mutton (1000 g), pure honey (200 g), Dihuang (root tubers of *Rehmannia glutinosa*, 200 g), Danggui (roots of *Angelica sinensis*, 200 g), Xuduan (roots of *Dipsacus asper*, 200 g), Niuxi (roots of *A. bidentata*, 100 g) and Huangqi (roots of *Astragalus membranaceus*, 50 g) [17]. Niuxi (roots of *A. bidentata*, 50 g) can also be combined with Roucongrong (fleshy stems with scales of *Cistanche deserticola*, *Cistanche tubulosa*, 500 g), Danggui (roots of *Angelica sinensis*, 50 g) and double honey to make Niuxi Danggui Honey paste, which is good for preventing constipation [18].

3.5 Clinical Evidences

As a therapeutic medicine, Niuxi is widely used in clinics. It can be used alone, or in combination with other herbs.

Uncombined, Niuxi can be used to induce abortion and arthrophlogosis. In addition, the Niuxijing capsule made of Niuxi polysaccharide has a preventive effect on leukopenia caused by chemotherapy.

In clinical practice, it is used for blood stasis syndrome with irregular menstruation, dysmenorrhea, amenorrhea, postpartum abdominal pain and trauma with pain. For irregular menstruation, dysmenorrhea, amenorrhea and postpartum abdominal pain, it is usually combined with Honghua (flowers of *Carthamus tinctorius*), Taoren (seeds of *Prunus persica*, *Prunus davidiana*), Danggui (roots of *Angelica sinensis*), Ruxiang (resin of *Boswellia carterii*, *Boswellia bhaw-dajiana*), Moyao (resin of *Commiphora myrrha*, *Commiphora molmol*) and Xuduan (roots of *D. asper*), etc. In combination with Danggui (roots of *Angelica sinensis*), Mutong (lianoid steams of *Akebia quinata*, *Akebia trifoliata*, *Akebia trifoliata* (Thunb.), Koidz. var. *australis*), and Huashi (Talcum), it is used to treat hematuria, dysuria and urethralgia. Huoxue Qianjiang decoction, a classical Chinese prescription composed of Niuxi (roots of *A. bidentata*), Gouteng (hook-bearing branchs of *Uncaria rhynchophylla*, *Uncaria macrophylla*, *Uncaria hirsuta*, *Uncaria sinensis*,) and Danshen (roots and rhizomes of *Salvia miltiorrhiz*) has a significant effect on anti-hypertension. Simiao Wan, which composed of Niuxi (roots of *A. bidentata*), Cangzhu (rhizomas of *Atractylodes lancea*, *Atractylodes chinensis*), Huangbai (barks of *Phellodendron chinensis*) and Yiyiren (kernels of *Coix lacryma-jobi*), is used to relieve pain in the loins and knees as well as weakness of lower limbs due to downward flow of damp-heat [19].

3.6 Safety Evaluation and Toxicity Data

As described previously, Niuxi is one of the most popular herbs used in TCM, but it has few clinical reports on toxicity or side effects. It was reported that the HepG2 cells were selected to evaluate cytotoxicity of Niuxi, and the results indicated that this medicinal herb had no toxicity in vitro to the HepG2 cells within the dose range of 0.25–4.0 μg/ml, and that its desired biological activity could be elicited without inducing in vivo toxicity [9]. According to animal experiments on mice, the LD_{50} of ecdysterone is 6.4 g/kg, and inokosterone is 7.8 g/kg. The LD_{50} of Niuxi decoctum is 146.49 g/kg. The Niuxi decoctum of 75 g/kg was administrated to the mice intragastrically. After 3 days, there was no toxic reaction or abnormal action. In a sub-acute toxicity test, 60 g/(kg days) Niuxi decoctum was given to mice for 7 days continuously or 48 g/(kg days) for 30 days continuously, and there was no toxic reaction, abnormal blood parameters, liver-kidney function or body weight changes observed. In addition, there was no toxic reaction or side effect on the mice filled with 0.2–2 g/(kg days) of ecdysterone and inokosterone mixture for 35 days [2]. In conclusion, the toxicity of Niuxi is low.

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