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Phytochemical and biological research of *Fritillaria* medicinal resources

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[ABSTRACT] The genus *Fritillaria* is a botanical source for various pharmaceutically active components, which have been commonly used in traditional Chinese medicine for thousands of years. Increasing interest in *Fritillaria* medicinal resources has led to additional discoveries of steroidal alkaloids, saponins, terpenoids, glycosides and many other compounds in various *Fritillaria* species, and to investigations on their chemotaxonomy, molecular phylogeny and pharmacology. In continuation of studies on *Fritillaria* pharmacophylogeny, the phytochemistry, chemotaxonomy, molecular biology and phylogeny of *Fritillaria* and their relevance to drug efficacy is reviewed. Literature searching is used to characterize the global scientific effort in the flexible technologies being applied. The interrelationship within Chinese Bei Mu species and between Chinese species, and species distributed outside of China, is clarified by the molecular phylogenetic inferences based on nuclear and chloroplast DNA sequences. The incongruence between chemotaxonomy and molecular phylogeny is revealed and discussed. It is essential to study more species for both the sustainable utilization of *Fritillaria* medicinal resources and for finding novel compounds with potential clinical utility. Systems biology and omics technologies will play an increasingly important role in future pharmaceutical research involving the bioactive compounds of *Fritillaria*.

[KEY WORDS] *Fritillaria*; Chemical components; Chemotaxonomy; Molecular taxonomy; Phylogeny; Medicinal resource

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1 Introduction

Fritillaria is a genus of about 130−165 species [1-2] within the monocot family Liliaceae, and is native to temperate regions of the Northern Hemisphere. *Fritillaria* is a botanical source for various pharmaceutically active components which have been used in traditional Chinese medicine for thousands of years. Many species (such as *F. cirrhosa*, *F. thunbergii* and *F. verticillata*) are used in traditional Chinese cough remedies. In the China Pharmacopoeia (http://www.chp. org.cn/cms/home/) they are listed as Chuan Bei Mu, Zhe Bei Mu, Yi Bei Mu, Hu Bei Bei Mu, and Ping Bei Mu, respectively, and are often found in formulations combined with extracts of Loquat (*Eriobotrya japonica*). *F. verticillata* bulbs are also traded as Bei Mu in Japan. Chuan Bei Mu and Zhe Bei Mu are the most famous Chinese herbal medicines obtained from *Fritillaria* species. The former is from *F. cirrhosa*, *F. unibracteata*, *F. przewalskii*, *F. delavayi*, *F. taipaiensis*, and *F. wabuensis*, while the latter is from *F. thunbergii* and *F. thunbergii* var. *chekiangensis*. According to traditional descriptions, *Fritillaria* is slightly cold, and affects the lungs (to clear heat and moisten dryness, and used for hot-type bronchitis with dry cough) and the heart (to calm heart fire). *Fritillaria* is also used for treating lumps beneath the skin, such as scrofulous swellings and breast lumps. Zhe Bei Mu is often used for the treatment of lumps, and the moistening property attributed to Chuan Bei Mu is not needed. It has been adopted into some Chinese herb formulas for treating cancers. Different *Fritillaria* species possess different chemical profiles, and may have different pharmacological effects. However, it is quite difficult to authenticate *Fritillaria* species only by morphology.

To date, at least 30 *Fritillaria* species have been characterized for their chemical components [3]. Advances in ana-

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lytical chemistry and molecular biology techniques facilitate the in-depth studies of *Fritillaria* pharmaceutical resources. However, it is essential to study more species for both the sustainable utilization of *Fritillaria* medicinal resources and for finding novel compounds with potential clinical utility. In this brief review, we focus on recent progress in the phytochemistry and chemotaxonomy of *Fritillaria*, as well as molecular taxonomy and phylogeny. To date, very few studies have attempted to correlate DNA based phylogeny of medicinal plants with phytochemistry or with medicinal properties [4]. Here the molecular phylogeny of world-wide *Fritillaria* species is reconstructed and the results compared with those of chemotaxonomy. Phylogeny has great explanatory power and offers a unique perspective to complement chemotaxonomy.

2 Chemical Components of the Genus *Fritillaria*

2.1 *Steroidal alkaloids*

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. The steroidal alkaloids from *Fritillaria* can be classified into two groups based on the carbon framework: isosteroidal alkaloids and steroidal alkaloids (Fig. 1). According to the linkage patterns between rings E and F, isosteroidal alkaloids can be divided into cevanine (A), jervine (B) and veratramine (C) types (Figs. 1 and 2). Steroidal alkaloids can be divided into solanidine (D) and secosolanidine (E) types [2], depending on whether the nitrogen atom is incorporated into an indolizidine ring or a piperidine ring (Fig. 1). Steroidal alkaloids found in *Fritillaria* before 2005 have been summarized [3]. Table 1 summarizes the steroidal alkaloids found since 2006.

Puqiedine **1** and 3*α*-puqiedin-7-ol **2** were isolated from *F. puqiensis*, their structures being determined on the basis of NMR spectroscopy and MS [5]. The new cevanine-type alkaloids, (3*β*, 5*α*)-20-hydroxy-6-oxocevan-3-yl acetate **7** and (3*β*, 5*α*, 6*α*)-6, 20-dihydroxycevan-3-yl acetate **8**, were isolated from bulbs of *F. hupehensis* and characterized by spectral analysis [6]. Bulbs of *F. unibracteata* in Sichuan, China, contained the new glycoalkaloid puqiedinone-3-*O*-*β*-D-glucopyranoside **11**, whose structure was elucidated by spectroscopic and chemical methods [7]. Phytochemical investigation of the bulbs of *F. lichuanensis* yielded a new isosteroidal alkaloid hupehenizioside **13** [8]. A further investigation of bulbs of *F. lichuanensis* resulted in the isolation of two unique cevanine-type alkaloids, lichuanine ((20*S*, 25*R*)-5*α*, 14*α*-cevanine-3*β*, 6*β*-diol) **14** and lichuanisinine ((20*S*, 25*S*)-5*α*, 14*α*-cevanine-3*β*, 6*β*-diol-*N*-oxide) **15** [9]. Extraction of the bulbs of *F. puqiensis* yielded three new veratramine-type alkaloids, namely puqienine C **3**, puqienine D **4** and puqienine E **5** [5]. Alkaloids **9** and **10** were obtained from *F. hupehensis*. Their structures were deduced to be (3*β*, 5*α*, 13*α*, 23*β*)-7, 8, 12, 14-tetradehydro-5, 6, 12, 13-tetrahydro-3, 23-dihydroxyveratraman-6-one and (3*β*, 5*α,* 13*α*, 23*β*)-7, 8, 12, 14-tetradehydro-5, 6, 12, 13-tetrahydro-3, 13, 23- trihydroxy-veratraman-6-one, respectively, on the basis of chemical shift comparisons and ^{1}H, ^{1}H-COSY, HMBC correlations [6]. Bulbs of *F. ussuriensis* have yielded a new alkaloid pingbeimunone A **16** with an aromatized D-ring, whose structure was elucidated on the basis of spectral analysis. Chemical investigation of the bulbs of *F. puqiensis* afforded puqienine F **17**. This novel veratramine alkaloid possessed a 12, 16-epoxy ring [10]. Peimisine-3-*O*-*β*-D-glucopyranoside **12**, possessing the furan ring E fused onto a piperidine ring system forming an ether bridge between carbon atoms C17 and C23, was isolated from *F. unibracteata*, which might be identical

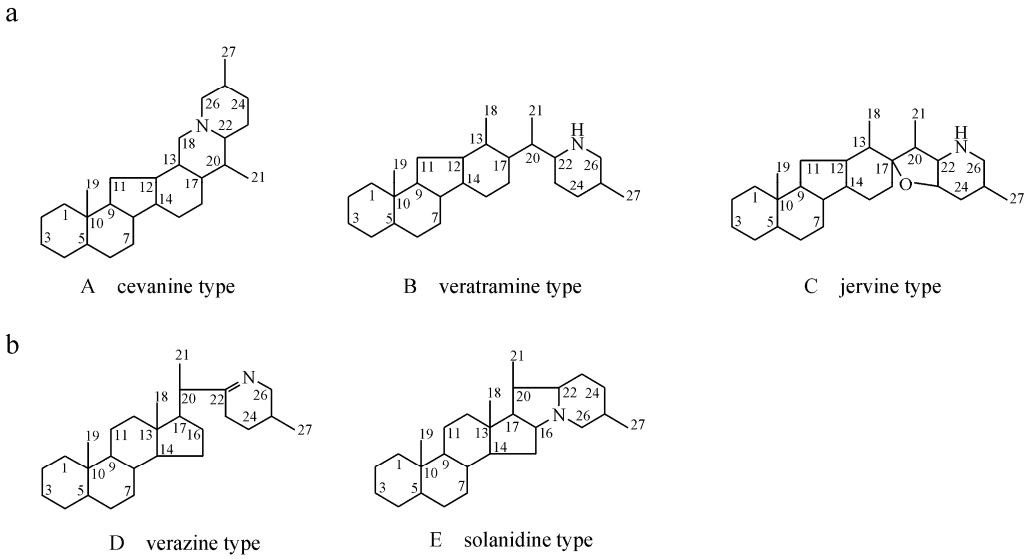

Fig. 1 Types of steroidal alkaloids in *Fritillaria*. a, isosteroidal alkaloids; b, steroidal alkaloids. Refer to Table 1 for more details