

# Recent progress in Steroidal Alkaloids from *Veratrum*

WEN Wei-feng , ZHAO Wei-jie\* , WANG Shi-sheng

(State key laboratory of Fine Chemical, Dalian university of technology , Dalian 116012, China)

**Abstract :** Steroidal alkaloids are important bioactive constituents from *Veratrum* genus. Lately *Veratrum* alkaloids have been reported to have activities such as hypotensive, antithrombotic and anti-inflammatory etc, which are much concerned. This paper is devoted to a study of the steroidal alkaloids of plants of the genus *Veratrum*. Characteristic spectra and pharmacological activities of the alkaloids subdivided into groups according to structure are discussed.

**Key words:** *Veratrum* ; Steroidal alkaloids ; Characteristic spectra ; Pharmacological activities

## Introduction

The genus *Veratrum* belongs to the family Liliaceae. In the flora of the world, about 40 species of the genus *Veratrum* have been described, which are distributed in Asian, Europe and North American. There are about 20 species of *Veratrum* in China, named *V.patulum*, *V.nigrum* L. var. *ussuriense* Nakai, *V.maackii*, *V.oblongum*, *V.taliense*, *V.stenophyllum*, *V.schindleri* Loes.f., *V.mengtzeanum* Loes.f., *V.dahuricum* etc<sup>[1]</sup>.

*Veratrum* is a well-known medicinal plant widely distributed in northeast region of China. As a source of Chinese crude drug "Lilu", this herbal medicine has been recorded in Chinese medical books and noted for its high toxicity. It has been covered that "Lilu" has exhibited physiological activities as hypotensive, anti-inflammatory, antithrombotic and spasmolytic agents in recent years.

There are alkaloids, flavones, flavonoids, organic acids etc. from the plant of *veratrum*. Among them, steroidal alkaloids are the main active constituents. Lately , as spectral technology (especially 2D-NMR) widely used in the research of chemical structures, the study on structures of alkaloids have become more and more rapid and precise. The constituents of

*Veratrum* plants have been examined extensively and more than one hundred steroidal alkaloids have been isolated so far <sup>[2]</sup>.

## 1. Chemical structure

Steroidal alkaloids in *Veratrum* are divided into two groups in accordance with the structures of the main heterocyclic skeleton: C-nor-D-homo- steroid alkaloids and typical steroidal alkaloids. In C-nor-D-homo-steroid alkaloids, they are divided into the Cevine and Jervine groups. In typical steroidal alkaloids, they are divided into the Veratramine, Solanidine and Verazine groups.

## 2. Spectrum character

### 2.1 UV spectrum

Steroidal alkaloids from *Veratrum* have the following characteristic UV absorption: maxima at 280~300nm (  $\log\epsilon$ 1.70~2.07 ) shows the presence of isolated carbonyl groups. Steroid alkaloids of Cevine and Veratramine groups of maxima at 236~255nm (  $\log\epsilon$ 4.20~4.90 ) and 300~400nm (  $\log\epsilon$ 1.89~2.75 ) show  $\alpha$ ,  $\beta$ -unsaturated ketones. Maxima at 265nm (  $\log\epsilon$ 3.09 ) are characteristic for a substituted benzene ring in steroidal alkaloids of Cevine

group, and a maximum at 238~240nm ( $\log\epsilon 1.83\sim 1.96$ ) shows the presence of a C=N chromophore in the alkaloids of Verazine group. Maxima at 218, 260, 291nm ( $\log\epsilon 4.35, 4.07, 3.75$ ) show the presence of veratric group<sup>[3]</sup>.

## 2.2 IR spectrum

Steroidal alkaloids from *Veratrum* have the following characteristic IR absorption:  $\nu_{\max}$   $\text{cm}^{-1}$  3640~3014, 1080~1020(OH, NH), 1750~1710 (isolated C=O), 1690~1649 and 1625~1602 (conjugated C=O), 1745~1723 and 1270~1230 (ester carbonyl), 3040~3030 and 1679~1660 (HC=C), 3035 and 1050( $^5\text{-}3\beta\text{-OH}$ ), 1600~1500 (benzene ring). In the IR spectra of alkaloids of Cevine group, an absorption band at 2790~2740  $\text{cm}^{-1}$  (Bohlmann bands) shows the presence of trans-quinolizidine, and cis E/F quinolizidine has no Bohlmann bands, which could differentiate the cis or trans E/F. In the IR spectra of alkaloids of Jervine group, characteristic absorption at 927, 984, 1118  $\text{cm}^{-1}$  shows the structure of ether bridge between C<sub>17</sub> and C<sub>23</sub><sup>[3]</sup>.

## 2.3 <sup>1</sup>H-NMR

The ring linkages of alkaloids of Cevine group from *Veratrum* are cis A/B, trans B/C, cis C/D, trans D/E, trans E/F. The NMR spectra of the alkaloids of Cevine group contain three signals of three methyl protons: 19 $\beta$ , 21 $\alpha$ , 27 $\beta$ . The signals of 19 $\beta$  methyl protons appear at  $\delta 0.98\sim 1.01$  in the form of a singlet. When a tertiary hydroxyl group is present at C<sub>20</sub>, the chemical shift of the C-21 $\alpha$  methyl group is observed at  $\delta 1.18\sim 1.23$  in the form of a singlet. The signals of 27 $\beta$  methyl protons appear at  $\delta 1.08$  in the form of separate doublets.

## 2.4 <sup>13</sup>C-NMR

There are 27 signals in the skeleton of Cevine alkaloids, and there are three obvious methyl carbon signals C19, C21, C27 at upfield  $\delta 17\sim 21$ . When a carbonyl group is present on the ring, the signals of carbonyl group appear at  $\delta 210\sim 213$ ; When double bonds are present in

rings, the signals of olefinic carbon appear at  $\delta 120\sim 145$ . When a hydroxyl group or ester group are present at C-3, C-7, C-14, C-15, C-16 or C-20, the chemical shifts of them are observed at  $\delta 70\sim 80$ . The chemical shifts of C-22, C-26 and C-18 attached to nitrogen atom appear at downfield, chemical shift of C-22 appears at  $\delta 60\sim 72$ ; chemical shift of C-26 appears at  $\delta 60\sim 64$ ; chemical shift of C-18 appears at  $\delta 58\sim 63$ <sup>[4,5]</sup>

## 2.5 EI-MS

In the mass spectra, strong peaks of ions with  $m/e$  110, 111, 112, 114 and 220 are characteristic for C-nor-D- homosteroid alkaloids, and peaks of ions with  $m/e$  82, 98, 114, 125 and 150 formed by the same scheme are characteristic for the typical steroid alkaloids<sup>[3]</sup>.

In the mass spectra, the base peak of Cevine alkaloids is  $m/e$  112. The formation of peaks of ions with  $m/e$  154, 155, 156 in the mass spectra of the Cevine alkaloids shows the presence of a tertiary hydroxyl group at C<sub>20</sub>. The base peak of Jervine alkaloids is  $m/e$  110, together with other peaks of ions with  $m/e$  97, 117, 124, 125; The base peak of Veratramine alkaloids is  $m/e$  98. The base peak of Solanidine alkaloids is  $m/e$  150. The base peak of Verazine alkaloids is  $m/e$  98, and when they contain  $^{22}\text{(N)}$ , the base peak is  $m/e$  125<sup>[3]</sup>.

## 3. Pharmacological activities

### 3.1 Activities of hypotensive

Li Shuyuan etc<sup>[6]</sup> reported Vera-U iv decreased cardiac contractility, reduced CO, and decreased TPVR. The effects may be partly mechanism of the hypotensive action of Vera-U.

### 3.2 Activities of antithrombotic

Yang Jingxian etc.<sup>[7]</sup> reported Vera-U (20 $\mu\text{g}/\text{kg}$  iv), an alkaloid extracted from *veratrum. Nigrum* var. *ussuriense*, decreased blood viscosity, plasma viscosity and RE in rabbits and high viscosity blooded rats obviously. Vera-U prolonged tail bleeding time in mice significantly.

Han guozhu etc. [8] investigated anti-thrombotic effects of *Veratrum nigrum* L. var *ussuriense* Nakai alkaloids (Vera-U) in rats. Vera-U has powerful inhibitory effects against both arterial and venous thrombosis in rats and acts in a dose- and time- dependant manner. Its effective dose is as low as  $\mu\text{g}$  per kg body weight of rats. The finding of the Vera-U anti-thrombotic effects reveal a bright future of its R & D.

### 3.3 Activities of inhibiting pigmentation

Jin Mu Hyun etc. [8] reported that alkaloids extracted from roots of *V.nigrum* and *V.album* Veratramine, Verazine and epi-Verazine show no side effects on skin and have a superior effect in inhibiting the pigmentation of skin by restraining melanin from being generated.

### 3.4 Insecticidal activity

*Veratrum* alkaloids and related derivatives have insecticidal activities determined by topical application to adult houseflies and milkweed bugs. The activities are attributable to their modification of the properties of the  $\text{Na}^+$  channel [10].

### 3.5 Other activities

*Veratrum* alkaloids are  $\text{Na}^+$  activators(as local anesthetic), spasmolytic agents, cardiaes etc.

## 4. Conclusions

The plant of *Veratrum* is widely distributed in China with rich resources, and widely different with chemical constituents in different species. Scholars all over the world have studied several species of *veratrum* to obtain more than one hundred new bioactive constituents, such as steroidal alkaloids, indolal alkaloids, peptides, stilbenoids etc. Many constituents with small quantity have not been identified effectively, which need to be studied further.

So far, most of the studies are related to the hypogeeal parts (roots and rhizoma) of *Veratrum* plants, and there are few to investigate the epigeal parts of *Veratrum* plants. Studying the epigeal parts of the plant further, elucidating constituents

of all parts of the plant and obtaining more bioactive constituents will do great to find more officinal values.

## Reference

- [1] Chiang Su New Medical College. **Dictionary of Chinese Crude Drugs** [M] Shanghai: Shanghai Scientific Technologic Publisher , 1977 .
- [2] ATTA-UR-RAHMAN, Choudhary, M. Diterpenoid and steroidal alkaloids[J]. **Nat.Prod.Rep**, 1997 , **14**: 191-203 .
- [3] R. SHAKIROV, S. YU. YUNUSOV. Alkaloids of *Veratrum* , *Petilium* and *Korolkowia* [J] .**Khim. Pri. Soedin**, 1980, **1**: 3-22 .
- [4] WEIJIE ZHAO, YASUHIRO TEZUKA, TOHRU KIKUCHHI *et al* . Studies on the constituents of *Veratrum* Plants, .Constituents of *Veratrum nigrum* L. Var. *ussuriense*(1). Structure and  $^1\text{H}$ - and  $^{13}\text{C}$ -Nuclear Magnetic Resonance Spectra of a New Alkaloid, Verussurinine, and Related Alkaloids [J]. **Chem. Pharm. Bull**, 1991, **39(3)**: 549-554 .
- [5] WEIJIE ZHAO, YASUHIRO TEZUKA, TOHRU KIKUCHI *et al*. Studies on the Constituents of *Veratrum* Plants . Constituents of *Veratrum maackii* REG; Isolation and structure Determination of a New Alkaloid, Maackinine[J] .**Chem. Pharm. Bull**, 1989, **37(11)**: 2920-2928 .
- [6] LI SHUYUAN , ZHAO WEIJIE , GUO YONGTIAN *et al* . Effect of Vera-U on hemodynamics in anesthetized dogs [J] . **Chinese Pharmaceutical Journal**, 1997, **32(7)**: 407-409 .
- [7] YANG JINGXIAN , HAN GUOZHU , ZHAO WEIJIE *et al* . Effects of Vera-U on hemorrhology in rabbits and rats and bleeding time in mice [J]. **Pharmacol Clin Chin Mater Med**, 1998, **14(6)**: 22-24 .
- [8] HAN GUOZHU, LI XINYAN , ZHAO WEIJIE, *et al* . Antithrombotic effects of *Veratrum nigrum* var. *ussuriense* alkaloids [J]. **Chinese Traditional and Herbal Drugs**, 2003, **34(12)**: 1107-1110 .
- [9] JIN MUHYUN, KIM HOJEONG, KANG SANGJIN *et al*. Three melanogenesis inhibitors from the roots of *Veratrum nigrum* [J] . **Saengyak**

**Hakhoechi**, 2002, **33(4)**: 399-403.

[10] ISTVAN UJVARY, BRYAN K.EYA, RICHARD L.GRENDELL *et al.* Insecticidal Activity of Various 3-Acyl and Other Derivatives of Veracevine Relative to the Veratrum Alkaloids Veratridine and Cevdine [J]. **J. Agric. Food. Chem.**, 1991, **39**: 1875-1881.

[11] YASUHIRO TEZUKA, WEIJIE ZHAO, EIJI

ISHII *et al.* Anti-Helicobacter pylori Activity of steroidal alkaloids obtained from three *Veratrum* plants [J]. **Journal of Traditional Medicines**, 1999, **16**: 196-200.

[12] WANG SHISHENG, ZHAO WEIJIE, LIU ZHIGUANG. Bioactive of natural polyhydroxystilbenoids [J]. **World Pharmacy**, 2001, **16(1)**: 9-11.