# Antidepressant Principles of *Valeriana fauriei* Roots

Yoshiteru OSHIMA, Setsu MATSUOKA, and Yasushi OHIZUMI*

*Pharmaceutical Institute, Tohoku University, Aoba, Aoba-yama, Sendai 980–77, Japan.*
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**A methanol extract of the roots of *Valeriana fauriei* (Valerianaceae), exhibited antidepressant activity in mice. The extract was fractionated, monitored by the activity, to afford α-kessyl alcohol as an active principle. The antidepressant activity of some guaiane and valerane types of sesquiterpenoids in the active fraction was also evaluated.**

**Keywords** *Valeriana fauriei* root; antidepressant activity; guaiane; valerane; α-kessyl alcohol

Valerianae Radix, prepared from the rhizomes and roots of *Valeriana* plants (Valerianaceae), is one of the famous crude drugs which have been used for sedative and antispasmodic purposes. Detailed chemical analysis of the essential oil of this group of plants showed that they contain a number of sesquiterpenoids having guaiane and valerane skeletons.[1] Except for the pharmacological report that the guaiane skeletal sesquiterpenoids, kessyl glycol diacetate, kessyl glycol 8-acetate and kessyl glycol 2-acetate, were shown to enhance hexobarbital anesthesia due to their inhibitory effect on the central nervous system,[2] no other works which contribute to clarification of the pharmacological properties of the plants have been carried out.

In continuation of our program to discover new types of antidepressant drugs originating from medicinal plants,[3] we have found that a methanol extract of *Valeriana fauriei* roots exhibited strong antidepressant activity in the forced swimming test using mice. In this paper, we report the isolation of active components of the plant.

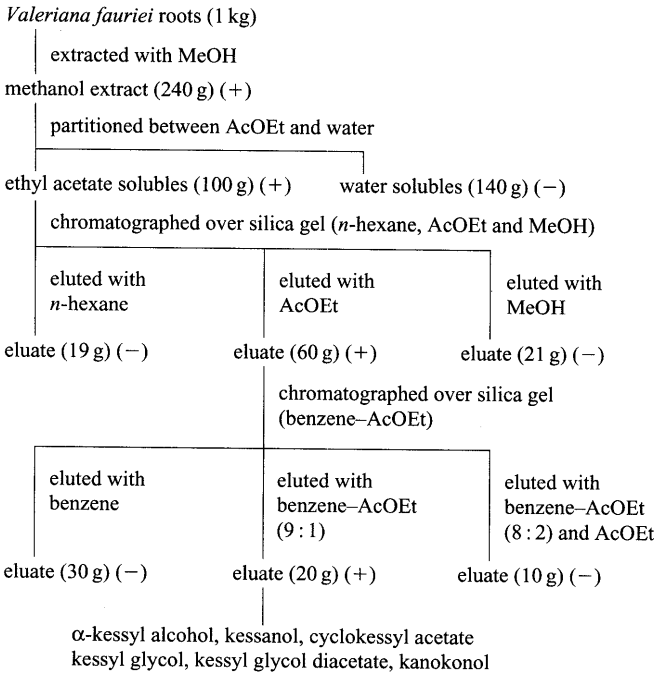


Fig. 1. Fractionation of *Valeriana fauriei* Roots

Scores in parentheses represent the antidepressant activity of the fractions.

The methanol extract of *Valeriana fauriei* roots reduced the duration of immobility of mice in the forced swimming test.[4] Activity-directed fractionation of the methanol extract by solvent partitioning and conventional silica gel column chromatography yielded an active fraction from which α-kessyl alcohol[5] was isolated as an active component (Figs. 1 and 2). α-Kessyl alcohol, at a dose of 30 mg/kg intraperitoneally, caused a decrease in the duration of immobility during the 5 min in the forced swimming test in mice, and this effect of α-kessyl alcohol on the duration of immobility is very close to that of imipramine, which is commonly used as an antidepressant drug in the treatment of depression (Table I). Because the other guaiane and valerane type sesquiterpenoids, in

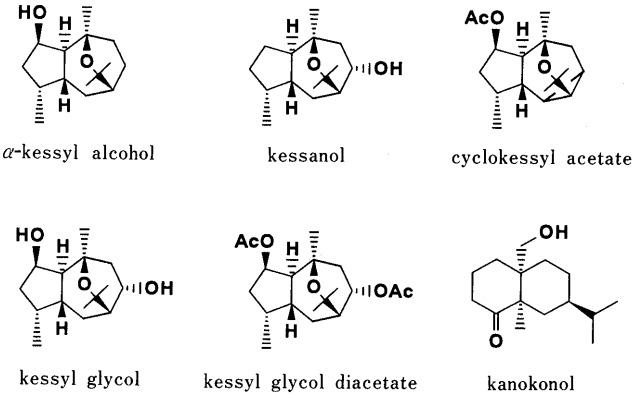


Fig. 2. Structure of *Valeriana fauriei* Root Constituents

TABLE I. Effects of α-Kessyl Alcohol and Other Constituents of *Valeriana fauriei* Roots on the Duration of Immobility in Mice during a 5 min Test

| Drug | Dose (mg/kg, i.p.)[a] | Relative duration of immobility[b] |
|---|---|---|
| Control (Tween 80) | — | 100[c] |
| α-Kessyl alcohol | 30 | 53.9± 3.9[d] |
| Kessanol | 30 | 60.6± 5.1[d] |
| Cyclokessyl acetate | 30 | 66.1± 4.5[d] |
| Kessyl glycol | 30 | 98.7± 8.7 |
| Kessyl glycol diacetate | 30 | 101.5±10.9 |
| Kanokonol | 30 | 92.6±10.3 |
| Imipramine | 15 | 58.8± 4.2[d] |

*a*) 7 mice/sample. *b*) Expressed as the mean percent of the control ±standard error. *c*) Duration of immobility: 104.9±7.1 s. *d*) Significantly different from the control, $p<0.05$.

addition to α-kessyl alcohol, were found to be contained in the pharmacologically active fraction, their antidepressant activity was also evaluated (Fig. 2 and Table I). As a result, two guaiane type sesquiterpenoids, kessanol[6] and cyclokessyl acetate,[7] also exhibited remarkable antidepressant activity, while the valerane type sesquiterpenoid, kanokonol,[8] as well as kessyl glycol[5] and kessyl glycol diacetate[5] bearing hydroxyl or ester groups at both the 2 and 8-positions of the guaiane skeleton were not active. In view of the fact that some of the α-kessyl alcohol derivatives elicited antidepressant activity, it may be concluded that the overall effect of the plant is mediated by all these principles, although the structure–activity relationship of the sesquiterpenoids still remains to be solved.

The forced swimming test using mice or rats is selectively sensitive to clinically effective antidepressant drugs and non-pharmacological antidepressant treatments such as electroconvulsive shock and rapid eye movement (REM) sleep deprivation,[9-11] and it is generally known that the efficacy of clinically effective antidepressant drugs such as imipramine and mianserine in the test is closely related to the clinical data.[12] These facts, therefore, suggest that the kind of sesquiterpenoids we are examining might be potential antidepressant drugs which are expected to be clinically beneficial. Detailed studies on the structure–activity relationship and the pharmacological properties of the sesquiterpenoids is of great value for the development of a new type of antidepressant drug.

## Experimental

**Isolation of Sesquiterpenoids** Dried roots of *Valeriana fauriei* BRIQUET (1 kg) (collected in Hokkaido in 1991) were extracted with methanol (201 × 3) at room temperature. The solvent was removed from the combined extracts under reduced pressure to afford an extract (240 g), which was partitioned between ethyl acetate and water. The ethyl acetate soluble (100 g) was chromatographed over silica gel (1 kg) and the column was eluted with *n*-hexane, ethyl acetate and methanol. The ethyl acetate-eluting fractions were repeatedly chromatographed over silica gel to give kessanol (14 mg), kanokonol (30 mg), cyclokessyl acetate (15 mg), α-kessyl alcohol (28 mg), kessyl glycol diacetate (3.5 g) and kessyl glycol (18 mg), which were identified by direct comparison of $[\alpha]_D$, and MS, IR and $^1$H-NMR spectral data with those of the authentic samples.

**Pharmacological Test** Male ddY strain mice weighing 24—27 g were used. They were housed under standard laboratory conditions (room temperature, 23 ± 1 °C; constant humidity) for at least 4 d before the experiment. The samples were either dissolved in saline solution or dispersed in a suspension of Tween 80 (0.5% w/v, 0.9% NaCl). The duration of immobility in mice was carried out using the modified method of Porsolt *et al.*[4] Mice were individually placed for 5 min in vertical glass cylinders (height, 20 cm; diameter, 10 cm) containing water (25—26 °C) at a height of 8 cm. They were removed and allowed to dry in a drying room. On the next day, 1 h after intraperitoneal injection of the samples, they were again put into the glass cylinders and the total duration of immobility was measured during a 5 min period. The mice were judged to be immobile whenever they remained floating passively in the water in a slightly hunched but upright position with their head above the surface.

**Statistical Analysis** Data of the swimming tests were analyzed with one-way analysis of variance (ANOVA), and the statistical significance of the results was calculated according to Dunnette's tests.

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