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Anxiolytic effect of Gardeniae Fructus-extract containing active ingredient from Kamishoyosan (KSS), a Japanese traditional Kampo medicine

Kazuo Toriizuka [a,*], Hiroko Kamiki [a], Noriko (Yosikawa) Ohmura [a], Mikio Fujii [a], Yumiko Hori [a], Motonori Fukumura [a], Yasuaki Hirai [b], Susumu Isoda [b], Yukio Nemoto [a], Yositeru Ida [a,b]

[a] *Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan*

[b] *Laboratory of Herbal Garden, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan*

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Abstract

Kamishoyosan (KSS), a Kampo formula used to treat menopausal psychotic syndromes in women, consists of ten crude herbal drugs. The anxiolytic effect of KSS was investigated by the social interaction (SI) test using mice, and whether the effect of KSS was due to the stimulating and/or sedating effects was examined by the open field locomotion test. Furthermore, the present study examined the effect of individual crude drugs in KSS by the SI test to clarify its active components. Oral administration of KSS increased the total SI time in a dose-dependent manner (50–200 mg/kg), but this effect was not observed over a dose of 300 mg/kg. On the other hand, there were no significant changes observed for the open field locomotion test. These results suggest that the appearance of KSS-induced SI behavior is due to an anxiolytic effect. The unaltered results of the open field test indicated that KSS was neither a stimulant nor sedative. To identify the essential herbs in KSS, the effects of "the component herbs in KSS" and "KSS minus one component herb" using the SI test were examined. An increase in the SI time was observed for hot water extracts of Menthae herba and Gardeniae Fructus, the same as for the KSS

* Corresponding author. Tel.: +81 3 3784 8190; fax: +81 3 3784 8191.
E-mail address: k-tori@pharm.showa-u.ac.jp (K. Toriizuka).

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treatment. On the other hand the effect of KSS on the SI time was reduced to the control level for KSS minus Gardeniae Fructus, KSS minus Paeoniae Radix, KSS minus Glycyrrhizae Radix and KSS minus Hoelen. Oral administration of Gardeniae Fructus-extract or its common constituent, geniposide increased the SI time in a dose-dependent manner. These results indicate that Gardeniae Fructus and geniposide play a role in the anxiolytic effect of KSS.

Keywords: Kamishoyosan; Social interaction test; Anxiolytic; Gardenia Fructus; Geniposide; Kampo medicine

Introduction

At the climacteric, various symptoms such as forgetfulness, hot flush, anxiety, insomnia, irritability, depressive neurosis, abnormal sensation, and sleeplessness are often observed. Although the mechanisms underlying menopausal mental disorders are unclear, the decline in ovarian steroids produces functional changes in the central nervous system (Pearlstein et al., 1997). Recently, sex steroid modulation of the central nervous system has been investigated. Progesterone exhibits anxiolytic and hypnotic activities in rodents (Picazo and Fernandez-Guasti, 1995; Celotti et al., 1997). These effects are blocked by the γ-amino-butyric acid $(GABA)_A$ receptor-gated chloride channel antagonist picrotoxin (Reddy and Kulkarni, 1997), indicating the $GABA_A$ receptor-mediated activity of progesterone.

Traditional Chinese herbal medicines are widely used for the treatment of menopausal syndromes in Japan. Kamishoyosan (Jia-wei-xiao-yao-san in Chinese) is one formula used to treat anxiety, irritability and depression in menopausal women (Furuya and Toriizuka, 1996). Previously, the anxiolytic effect of KSS was revealed using a social interaction (SI) test in mice, and it was also reported that the mechanism responsible for these anxiolytic effect was mediated by $GABA_A$/BDZ receptor stimulation involved in the neurosteroids synthesis (Mizowaki et al., 2001). The SI test for this model reflects "neural anxiety", because it does not involve food or water deprivation or electric shock (File, 1980). However, high dose diazepam results in marked sedation and muscle relaxation (Rudolph et al., 1999). Therefore, whether the anxiolytic effect of KSS was due to the stimulating and/or sedating effects of KSS was examined using an open field locomotion test.

KSS consists of 10 kinds of dried medicinal herbs; Bupleuri Radix, Paeoniae Radix, Atractylodis Rhizoma, Angelicae Radix, Hoelen, Gardeniae Fructus, Moutan Cortex, Glycyrrhizae Radix, Zingiberis Rhizoma and Menthae Herba. Ligustilide and butylidenephthalide, the components of Angelicae Radix, reverse the FG7142 (a $GABA_A$/benzodiazepine receptor inverse agonist)-induced decrease in pentobarbital sleep in mice (Matsumoto et al., 1998). These findings show that Angelicae Radix acts on the central nervous system. However, since the effective doses of ligustilide and butylidenephthalide are higher than the actual dose contained in the formula, it is difficult to ascribe the clinical effects of KSS solely to these components.

To determine the anxiolytic effects of KSS, we investigated the effects of KSS using the SI test and open field locomotion test. And the effects of individual herbal drugs in KSS were also investigated using the SI test to evaluate the activity of the combination of herbal drugs and to clarify the active substances in KSS.