Research papers arising from the present study, presented in various conferences:

Authors	Conference	Title of paper
Iyer M, Belapurkar H, Sherikar O, Kasture S.B	54th IPC, Pune. 2002	Anxiolytic activity of *Trigonella foenum graecum* seeds
Iyer M and Kasture S.B	36th Annual Conference of Indian Pharmacological Society New Delhi, 2003	Acute effect of *Zingiber Officinale* on anxiety in male mice –A study on exploratory behaviour
Mohan.M, Kasture S.B and R.Balaraman	Gujrat Council on Science and Technology – state level paper presentation competition, Anand 2004	Methanolic extract of Fenugreek seeds reverses anxiety and hypertensive responses to *m*-CPP
Mohan.M, Kasture S.B and R.Balaraman	Joint International Conference-2005 Cardiovascular Medicine, Ahmedabad 2005	Antihypertensive effect of Fenugreek seeds- a serotonin mediated effect
Mohan.M, Kasture S.B and R.Balaraman	37th Annual Conference of Indian Pharmacological Society Kolkata, 2005	Behavioral effect of chronic Fenugreek treatment on Elevated T maze model of anxiety **(nominated for GUFIC prize)**
Seema D, Balaraman R, **Mahalaxmi M**	37th Annual Conference of Indian Pharmacological Society Kolkata, 2005	Antihypertensive activity of Fenugreek *(Trigonella Foenum-Graecum)* extract on rat blood pressure
Mohan.M, Kasture S.B and R.Balaraman	38th Annual Conference of Indian Pharmacological Society Chennai, 2005	Anxiolytic effect of chronic ginger treatment on Elevated T maze model in mice **(nominated for GUFIC prize)**

Research papers arising from the present study, published/ selected for publication in various International Journals:

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M.Mohan, S.B Kasture, R.Balaraman. Anxiolytic activity of standardised extract of *ginseng* in elevated T maze in mice. OPEM (2007), 7(1) [In print].

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KHUP

Anxiolytic activity of standardized extract of *Korean ginseng* - a study on exploratory behavior

M Mohan[1,*], SB Kasture[2] and R Balaraman[3]

[1]*Department of Pharmacology, MGV's College of Pharmacy, Panchvati, Nashik, Maharashtra 422 003, India;*
[2]*Department of Pharmacology, NDMVP Samaj's College of Pharmacy, Nashik, Maharashtra 422 002, India;*
[3]*Department of Pharmacy, Faculty of Technology and Engineering, The MS University of Baroda, Kalabhavan, Baroda, Gujrat 390 001, India*

SUMMARY

The roots of the plant *Korean ginseng* have been extensively used in the traditional Chinese herbal medicine. We investigated the standardized extract of *Korean ginseng* on animal models of anxiety based on exploratory behavior. *Korean ginseng* extract (KGE) (3, 10 and 30 mg/kg) was administered intra-peritoneally. The anxiolytic activity was studied using elevated plus maze (EPM) paradigm, light/dark apparatus (LDA), open field apparatus (OFA) and the hole board apparatus (HBA). Diazepam (1mg/kg) was used as a standard anxiolytic drug. In EPM, KGE (10 mg/kg) significantly ($P < 0.05$) increased the time spent in open arms and the number of entries in open arms. In LDA, KGE (10 mg/kg) increased the number of transitions. In OFA, KGE (3 and 10 mg/kg) significantly increased ($P < 0.05$) the number of squares traversed. In HBA the number of head pokes were significantly increased with KGE (3 and 10 mg/kg). KGE at all selected doses did not affect the motor coordination. Thus, the study suggests that saponin containing standardized *Korean ginseng* extract possess anxiolytic activity.

Key words: *Korean ginseng*; Anxiolytic activity

INTRODUCTION

Anxiety is a common emotion in humans and may be understood as a pathological counterpart of normal fear. It has been recognized that anxiety is not a unitary phenomenon. The etiology of most anxiety disorders although not fully understood, it has come into sharper focus into the recent past. Numerous plants have been reported to possess anxiolytic activity. Saponins from *Albizzia lebbeck* (Une *et al.*, 2001), saponins from *Bacopa monniera* (Bhattacharya and Ghosal, 1998), gingerols from *Zingiber officinale* (Vishwakarma *et al.*, 2002), triterpenes from *Sesbania grandiflora* (Kasture *et al.*, 2002) are the active principles mediating anxiolytic effects. *Korean (Panax) ginseng* has a blood pressure lowering effect (Stavro *et al.*, 2004), antistress and anabolic activity (Grandhi *et al.*, 1994) and improves learning and memory (Sung-Ha Jui *et al.*, 1999). It has a true adaptogenic action. It contains triterpene glycosides named ginsenosides which account for the majority of plants medicinal action. At least 13 ginsenosides have been identified falling into 2 groups based upon the aglycone portion: protopanaxodiol (diols) and protopanaxatriol (triols). They are classified according to an alphanumeric system i.e. Ra, Rb, Rb2, Rc, etc. The plant also contains sterols, acetylenic compounds and peptidoglycans named Panaxans.

*Correspondence: M Mohan, Department of Pharmacology, MGV's College of Pharmacy, Panchvati, Nashik, Maharashtra 422 003, India.
E-mail: mm_nasik@yahoo.co.in

(Wren, 1988; Mills, 1991). Ginseng administration in animals has shown behavioral changes which seem to be related to the regulation of gamma-amino-butyric acid (GABA) ergic neurotransmission. Ginseng saponin prolonged pentobarbitone sleeping time and delayed the onset of convulsion in high dose (Oh *et al.*, 1969; Jung and Jin, 1996). Ginsenoside Re is a potent inhibitor of neurotransmitter inhibitor, specially, GABA (Tsang *et al.*, 1983). Ginsenosides interact with ligand- bindings of $GABA_A$ and $GABA_B$ receptors (Kimura *et al.*, 1994). Since the anxiolytic study of *K. ginseng* have not been explored much, the current study is aimed at probing the anxiolytic potential of *K. ginseng* using different animal models of anxiety based on exploratory behaviour.

MATERIALS AND METHODS

Extract

The *Korean Ginseng* Extract (KGE) was obtained as a gift sample from Glenmark Pharmaceuticals, Nashik. It was manufactured by Pangin Biotech Co. Ltd, Korea. The standardized and controlled ginseng slender tail roots was extracted 3 times under 70°C for about 8 h in the extraction apparatus with 70% of ethanol. The extract was concentrated in vacuo at a reduced pressure of 500 - 600 mm Hg under 60 - 70°C till the ginseng extract was obtained. It contained 18% w/w of saponins.

Animals

Male albino mice (22 - 25 g) were obtained from Serum Institute Pune. Animals were housed into groups of five at an ambient temp of 25 ± 1°C. Animals had free access to food (Hindustan Lever, India) and water. They were deprived of food but not water 4 h before the experiment. The Institutional Animal Ethical Committee approved the protocol of this study.

Drugs and chemicals

Diazepam (Calmpose, Ranbaxy) was used in the study as a standard anxiolytic drug. Diazepam and KGE were dissolved in the water for injection and administered intraperitoneally.

Behavioral studies

Elevated plus maze (EPM)

The Elevated plus maze (EPM) consisted of two open arms (25 × 5 cm) crossed with two closed arms (25 × 5 × 20 cm). The arms were connected together with a central square of 5 × 5 cm. The apparatus was elevated to a height of 25 cm (Lister, 1987). Mice in groups of 5 were treated with vehicle, diazepam (1 mg/kg) or KGE (3, 10 and 30 mg/kg) 30 min before placing individually in the centre of plus maze. The time spent in open arms, entries in open and closed arms were recorded for a period of 5 min.

Light/dark apparatus test

Two equal sized boxes (20 × 20 × 14, one dark and the other lit) were connected with a tunnel (5 × 7 × 10 cm) (Belzung *et al.*, 1987). Mice in groups of 5 treated with vehicle or Diazepam (1 mg/kg) and KGE (3, 10 and 30 mg/kg) 30 min before were placed individually in the lit area. The number of transitions in the light and dark box and the time spent in the lit box were noted in 5 min.

Open field apparatus test

The apparatus consisted of wooden box (96 × 96 × 5 cm). The floor of the box was divided into 16 (6 × 6cm) squares (Turner, 1972). Mice divided into groups of 5 each received vehicle or diazepam (1 mg/kg) and KGE (3, 10 and 30 mg/kg). After 30 min they were placed individually in one corner of the square. The number of rearing and the number of squares traversed were counted for five min.

Hole board apparatus

The apparatus consisted of wooden box (40 × 40 × 25 cm) with 16 holes (diameter 3 cm) evenly distributed on the floor. The apparatus was elevated to a height of 25 cm (Clark *et al.*, 1971). Mice were treated with vehicle, diazepam (1 mg/kg) or extract 30 min

before placing in the apparatus and the number of head pokes during 5 min were recorded.

Behavioral assessment

To investigate the central actions of the KGE (50 mg/kg), the method described by Irwin *et al.* (1968) was employed. The procedure involved an initial phase of undisturbed observations and later a manipulative phase during which the animals were subjected to the least provoking stimuli. During the initial phase the animals were observed for body position, locomotion, rearing, respiration, tremors, gait, and in the later phase the effect on grip strength, passivity, pain response, righting reflex and lacrimation was observed. The animals were observed for 2 h after the treatment.

Neurotoxicity test

In this test a knurled rod (2.5 cm in diameter) was rotated at a speed of 10 rpm. All animals were trained to remain on the rotating rod for 5 min. A normal mouse could maintain its equilibrium for long periods. In a drug treated mouse the neurological deficit was indicated by the inability of the mouse to maintain equilibrium for 3 min in each of the 3 trials as described earlier (Dunham and Miya, 1957). KGE was administered at doses of 10, 30 and 50 mg/kg, and the animals were tested for neurological deficit 30 min after the drug treatment. The control group received diazepam at a dose of 1 mg/kg.

Statistics

All data are shown as mean ± SEM. Statistical Analysis was performed with one way ANOVA followed by Dunett's test. Differences of $P < 0.05$ was considered statistically significant.

RESULTS

Elevated plus maze

The vehicle treated mice spent 22.8 ± 6.44 seconds in the open arm, whereas animals treated with KGE (10 mg/kg) spent significantly more time in the open arm and also increased the entries in both the open arms significantly. The observations are given in Table 1.

Light/dark test

The vehicle treated group spent 81 ± 11.48 sec in the lit box and showed 7.22 ± 0.74 as number of transitions, whereas animals treated with KGE (10 mg/kg) showed a significant increase in the number of transitions. The observations are given in Table 2.

Open field test

The vehicle treated mice traversed 102.6 ± 5.48 squares during the observation interval of 5 min. KGE (3 and 10 mg/kg) significantly increased the number of squares traversed while, KGE (10 mg/kg) significantly ($P < 0.05$) increased the rearings. The observations are given in Table 3.

Table 1. Effect of KGE on time spent in open arms and entries in open and closed arms in mice

Sr.No	Treatment (mg/kg)	Elevated Plus Maze		
		Time spent in O.A (sec)	Entries in O.A	Entries in C.A
1	Vehicle	22.8 ± 6.44	2.8 ± 0.86	6.2 ± 0.58
2	Diazepam (1)	78 ± 7.90*	8.33 ± 0.76*	8.16 ± 0.60
3	KGE (3)	38.4 ± 9.76	4.4 ± 1.53	9.6 ± 1.86
4	KGE (10)	87 ± 15.91*	6.6 ± 1.07*	9.6 ± 1.20
5	KGE (30)	34 ± 5.35	2.8 ± 0.2	6.6 ± 0.65
	F (4, 20)	8.48	6.11	2.15

n = 5 The observations are mean ± SEM. *$P < 0.05$, as compared to vehicle (ANOVA followed by Dunnett's test). O.A = Open arms, C.A = Closed arms

Table 2 Effect of KGE on time spent in lit zone and number of transitions in light/dark apparatus

Sr. No.	Treatment (mg/kg)	Time spent in lit zone. (sec)	Number of transitions
1	Vehicle	81 ± 11.48	7.22 ± 0.74
2	Diazepam(1)	121.7 ± 7.95*	14.2 ± 1.39*
3	KGE (3)	60 ± 16.07	12.8 ± 3.07
4	KGE (10)	94.2 ± 7.27	17.6 ± 2.35*
5	KGE (30)	75.6 ± 12.48	12.2 ± 1.02
	F (4, 20)	4.06	3.82

n = 5. The observations are mean ± SEM. *$P < 0.05$, as compared to vehicle (ANOVA followed by Dunnett's test).

Table 3 Effect of KGE on rearing and locomotion in open field test in mice

Sr. No.	Treatment (mg/kg)	No. of squares traversed	Rearings
1	Vehicle	102.6 ± 5.48	19.2 ± 2.67
2	Diazepam (1)	173.6 ± 18.73*	23.6 ± 4.94
3	KGE (3)	180 ± 20.25*	26.8 ± 3.83
4	KGE (10)	186.4 ± 13.38*	40.6 ± 3.65*
5	KGE (30)	135.6 ± 11.79	28.6 ± 1.8
	F (4, 20)	5.72	5.12

n = 5. The observations are mean ± SEM. *$P < 0.05$, as compared to vehicle (ANOVA followed by Dunnett's test).

Hole board apparatus

The vehicle treated mice showed 24.2 ± 4.69 head dips. KGE (3 and 10 mg/kg) significantly increased the number of head dips (Table 4).

Behavioral assessment

The animals did not exhibit any abnormal signs. In the initial phase, body position, locomotion, rearing, respiration were normal. There were no tremors and gait was normal. The grip strength, pain response and righting reflex were not affected by KGE (50 mg/kg).

Table 4 Effect of KGE on number of head poking in hole board apparatus in mice

Sr. No.	Treatment (mg/kg)	No. of head poking
1	Vehicle	24.2 ± 4.69
2	Diazepam (1)	42.8 ± 2.08*
3	KGE(3)	47.6 ± 5.24*
4	KGE(10)	52 ± 6.18*
5	KGE(30)	31.4 ± 6.90
	F(4, 20)	4.77

n = 5. The observations are mean ± SEM. *$P < 0.05$, as compared to vehicle (ANOVA followed by Dunnett's test).

Neurotoxicity test

Mice treated with KGE (10, 30 and 50 mg/kg) were able to maintain equilibrium on the rotating rod for more than 5 min, whereas the animals treated with diazepam exhibited motor in-coordination and the fall off time was significantly ($P < 0.05$) reduced to 56 ± 2.81 sec.

DISCUSSION

The present study indicates that saponin containing *Korean ginseng* extract possess anxiolytic activity. In the EPM test, decreased occupancy in the open arm and/or reduction in the open arm entries in relation to the open arm entries, provides a measure of fear-induced inhibition of exploratory activity which is attenuated by anxiolytics and increased by anxiogenic agents. (Pellow and File, 1986; Pellow *et al.*, 1987). Imaizumi *et al.* (1994) have shown that diazepam (4 and 8 mg/kg) increased

the open arm entries and time spent in open arm without changes in total arm entries. Researchers have reported different effects of buspirone on EPM *i.e* anxiolytic (Dunn *et al.*, 1989; Soderpalm *et al.*, 1989; Kshama *et al.*, 1990; Luscombe *et al.*, 1992; Lee *et al.* 1997) non-effective (Moulton *et al.*, 1990; Wada *et al.*, 1991) anxiogenic (Pellow *et al.*, 1987; Moser, 1989; Redfern and Williams, 1989; Kostowski *et al.*, 1990; Klint, 1991; Critchley *et al.*, 1992). A drug may have both anxiolytic and anxiogenic activities and either of the activities may be dependent on experimental conditions (Handley and McBlane, 1993). Drugs must be carefully assessed on elevated plus maze test and therefore in the present study EPM is supported by other tests. In our study we observed that KGE (10 mg/kg) significantly ($P < 0.05$) increased the time spent in open arms and number of entries in open arms. An inverse U dose - response was obtained which is the characteristic of anxiolytic agents (Pal *et al.*, 1995; Hasenohrl *et al.*, 1998; Une, 2001).

The Light/Dark test is based on the natural preference of mice for a dark place rather than a brightly lit area. It is interesting that many studies in the Light/Dark test have been conducted using mice rather than rats. Crawley reported that rats were not respondent to treatment with diazepam in this paradigm (Crawley, 1985) and that their exploratory tendencies appeared considerably lower than in mice, suggesting that rats were not useful in this test. Anxiolytic benzodiazepines, chlordiazepoxide and clonazepam, increased light-to-dark transitions and total locomotion in mice at non-sedative doses but did not change the time spent. (Crawley and Goodwin, 1980; Crawley, 1981). In our study KGE (10 mg/kg) increased the number of transitions.

The triols and diols have opposing action, generally stimulating and sedating respectively. It appears that in times of stress or fatigue the stimulating properties predominate. In these situations *Korean ginseng* will increase locomotor activity and the ability to respond to external stimuli (Bensky and Gamble, 1986; D'Angelo *et al.*, 1986; Hsou-Mou and Pui-Hay, 1986; Weiss, 1988; Wren, 1988; Mills, 1991; Teeguarded, 1994). This is in accordance with our observation. In open field test, KGE (10 mg/kg) showed a significant increase in squares traversed and increase in the tendency to reach to the walls and rear rather than rearing without support. Decrease in locomotion is indicative of diminished dopaminergic transmission, which may be secondary to the rise in 5-HT level caused by anxiogenic agents (Kahn *et al.*, 1988; Jones *et al.*, 1992).

File and Wardil (1975) have assessed the anxiogenic and anxiolytic activity of some agents using the hole board test. We observed a significant ($P < 0.05$) increase in head poking with KGE (3 and 10 mg/kg). In light of the above discussion, our findings suggest that saponin containing *Korean ginseng* possess anxiolytic activity.

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