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Antidepressant Activity of Karnim in Diabetes Associated Depression in Experimental Animals

[1]Somani Rahul, [1]Khalate Vinay, [1]Jain Dilpesha and [2]Singhai Abhay Kumar
[1]Sinhgad College of Pharmacy, Pune-411 041, India
[2]Department of Pharmaceutical Science, Dr HS Gour University, Sagar-470003, India

Abstract: Background: Diabetic individuals are at greater risk of developing comorbid depression independent of the type of diabetes. Approximately 30% of patients with type 1 or type 2 diabetes are suffering from depression. **Materials and Methods:** In the present study, the antidepressant activity of herbal formulation Karnim (HFK 200 and 400 mg kg^{-1}, p.o.) was evaluated using locomotor activity, forced swim test, monoamine oxidase (MAO) levels and antioxidant enzymes (MDA, NO, SOD, GSH, CAT) in STZ-induced diabetic rats. The diabetic rats exhibited prolong immobility duration, decreased locomotor activity, increased MAO activity and oxidative stress as compared to normal control rats. **Results:** Treatment with HFK significantly reduced the immobility period, decreased MAO levels and reduced oxidative stress. However, HFK could not alter the locomotor activity as compared to diabetic control rats. **Conclusion:** The results of our study indicated that HFK has the potential to be employed as a therapy for depression associated with diabetes.

Key words: Diabetes, depression, karnim, MAO, oxidative stress

INTRODUCTION

Diabetes, an increasingly common metabolic disorder, causes long term metabolic complications which affects the major organs in body such as retina, kidney, muscle, blood vessels and nervous system. Traditionally, it has been considered that diabetic peripheral neuropathy is the only primary nervous system complication associated with diabetes, whereas the Central Nervous System (CNS) was believed to be unaffected by diabetes. But recent studies give evidence of occurrence of primary and secondary CNS complications with functional impairments (Li and Sima, 2004).

Depression is significantly more prevalent in diabetes, affecting approximately 30% of patients with either the insulin-dependent or non-insulin-dependent type (Anderson *et al*., 2001). Various studies have reported the relationship between diabetes and depression (Lustman *et al.,* 1988). There are also indications of increased susceptibility to both psychosocial and cognitive difficulties in some diabetic individuals. Alterations in stress-related hormones, namely, those of hypothalamo-pituitary-adrenal (HPA) and adrenomedullary systems have been reported in diabetic individuals (Shamoon *et al*., 1980; Gustafson and Kalkhoff, 1981; Cameron *et al*., 1984). There are alterations in HPA and adrenomedullary functioning in STZ diabetic rat (De Nicola *et al*., 1977; Berkowitz *et al*., 1980; Yoshida *et al*., 1985). This suggests that there exist a relation between the metabolic changes and behavioral alterations occurring in diabetes. Alterations in central catecholamine activity have also been reported in animal models of diabetes, involving both norepinephrine (Palmer *et al*., 1983; Trulson and Himmel, 1985; Bitar *et al*., 1986) and dopamine (Lozovsky *et al*., 1981; Trulson and Himmel, 1983; Serri *et al*., 1985). It is clear that there are interactions between stress and behavior that affects metabolic stability in the diabetic patients. Thus, stress may have greater impact on diabetes than on other individuals leading to mental depression.

Herbal formulation Karnim (HFK) is composed of medicinal herbs (Table 1) with proven pharmacological actions. The pharmacological actions of individual herbs indicate that the major ingredients of HFK are anti-hyperglycemic in nature and thereby help to reduce elevated blood glucose. *Momordica charantia* has been found effective in lowering the blood glucose (Lotlikar and Rao, 1966). *Azadirachta indica* has been demonstrated to exert hypoglycemic effect in streptozotocin induced diabetes (Bailey *et al*., 1985). Other herbs like *Zingiber officinale* (Kadnur and Goyal, 2005), *Picrorhiza kurroa* (Joy and Kuttan, 1999) also possess anti-hyperglycemic activity. *Ocimum sanctum* enhances uptake of glucose by muscles (Chattopadhyay,

Corresponding Author: Somani Rahul, Sinhgad College of Pharmacy, Pune- 411 041, India
Tel: +91-9423449191 Fax: +91-020-24354720

Table 1: Composition of herbal formulation Karnim

Common name	Botanical name	Part used	Family	Composition (g)
Karela	*Momordica charantia*	Fruit	Cucurbitacae	2.5
Neem	*Azadirachta indica*	Leaves	Meliacae	0.2
Tulsi	*Ocimum sanctum*	Entire plant	Lamiaceae	0.1
Kutki	*Picrorhiza kurroa*	Root	Scrophulariaceae	0.1
Sounth	*Zingiber officinale*	Rhizome	Zingiberaceae	0.1

1999). *O. sanctum* possess the antistress and normalizing effect on brain catecholamines and may play role as possible antidepressant (Ravindran *et al*., 2005).

The present investigation has been undertaken to evaluate antidepressant activity of HFK in various animal models and its effect on monoamine oxidase and oxidative stress in diabetes associated depression in rats.

MATERIALS AND METHODS

Animals: Wistar rats of either sex, weighing 150-250 g were obtained from National Institute of Bioscience, Pune. The animals were maintained under standard laboratory conditions at temperature 23±2°C with relative humidity 55±10% and 12 h light and dark cycle throughout all the experiments. Animals had free access of water and standard laboratory feed (Amrut Feed, Chakan) *ad libitum*. The animals were shifted to the laboratory one hour prior to the experiment. All the experimental procedures and protocols used in this study were reviewed and approved (SCOP/IAEC/Approval/2009-10/07) by the Institutional Animal Ethics Committee (IAEC) of Sinhgad College of Pharmacy, Pune.

Drugs: Metformin was obtained as gift sample (Cipla Pharmaceuticals Ltd., India) and imipramine (Depranil), streptozotocin (Sigma-Aldrich, USA), diagnostic kits (Biolab, India), Karnim (Unijules Lifesciences, India), MDA, SOD, CAT (Sigma-Aldrich, USA), reduced GSH (Loba Chem, India) were purchased.

Experimental design: Streptozotocin (50 mg kg^{-1}) was prepared in cold citrate buffer (pH 4.4, 0.1 M) and administered intraperitoneally in overnight fasted rats. Control rats were injected with cold citrate buffer (pH 4.4, 0.1 M) only. After 48 h, rat with serum glucose levels more than 250 mg dL^{-1} were considered as diabetic and used for the further study. After three weeks of stabilization of diabetes and induction of depression (Gomez and Barros, 2000) (i.e., pre-treatment groups), suspension of HFK (200 and 400 mg kg^{-1}, p.o.) prepared in 2% gum acacia, metformin (200 mg kg^{-1} p.o.) and imipramine (15 mg kg^{-1}, p.o.) were administered for next three weeks (i.e., post-treatment groups) as follows:

- **Group-I (NC):** Normal control rats received vehicle (5 mL/kg/day, p.o.)
- **Group-II (DC):** Diabetic control rats received vehicle (5 mL/kg/day, p.o.)
- **Group-III (DC+HFK -200):** Diabetic rats treated with HFK (200 mg/kg/day, p.o.)
- **Group-IV (DC+HFK-400):** Diabetic rats treated with HFK (400 mg/kg/day, p.o.)
- **Group-V (DC+M-200):** Diabetic rats treated with metformin (200 mg/kg/day, p.o.)
- **Group-VI (DC+I-15):** Diabetic rats treated with imipramine (15 mg/kg/day, p.o.)

Effect on serum glucose level and body weight: Serum glucose level was estimated in pre-treatment and post-treatment groups using GOD/POD method (Trinder, 1969) and body weight was measured gravimetrically using electronic balance.

Locomotor activity: The locomotor activity was measured in post-treatment groups by actophotometer, rat was placed in activity chamber after last dose of drug. Total locomotor activity of each rat was recorded for 5 min (Wang *et al*., 2008).

Forced swim test (FST): The post-treatment groups were forced to swim in a vertical plastic cylinder (diameter 21 cm, height 50 cm) containing water up to 25 cm, maintained at 25±1°C. On the 1st day of experiments, rat was forced to swim for 15 min. After 24 h, rat was re-exposed to forced swim for 5 min and onset of immobility and duration of immobility time was evaluated by two observers who were blind to the kind of treatment each rat. A rat was judged to be immobile whenever it remained floating passively in the water in a slightly hunched but upright position with its head just above the surface. After 5 min rat was removed from the cylinder and returned to its home cage (Porsolt *et al*., 1978).

MAO-A and MAO-B enzyme levels: Rats were sacrificed, brain samples were collected immediately on an ice plate and washed with cold 0.25 M-sucrose 0.1 M Tris-0.02 M EDTA buffer (pH 7.4) and weighed. The collected brain samples were analyzed for MAO-A and MAO-B levels. Rat brain mitochondrial fractions were prepared following the procedure of Schurr and Livne (1976). The MAO-A and MAO-B activity was assessed spectrophotometrically with slight modifications (Charles and McEwen, 1971; Yu *et al*., 2002).

Antioxidant activity: Blood was withdrawn by puncturing retro-orbital plexus and plasma was separated. The

separated plasma was stored at -70°C until used. The plasma was used for estimation of malonadialdehyde (MDA) (Uchingham and Mishara, 1978), superoxide dismutase (SOD) (Kono, 1978), reduced glutathione (GSH) (Sedlak and Lindsay, 1968), nitric oxide (NO) (Green *et al*., 1982) and catalase (CAT) (Aebi, 1984). The protein concentration was estimated bovine serum albumin as the standard (Lowry *et al*., 1951).

Statistical analysis: Values are expressed as mean±SEM. Statistical analysis was performed using student t test. Whereas $p<0.05$ were considered as statistically significant.

RESULTS

Effect of HFK on serum glucose level and body weight: Injection of STZ (50 mg kg^{-1}, i.p.) significantly ($p<0.001$) increased serum glucose level and decreased body weight as compared to normal control rats. Three weeks repeated dose treatment of HFK (200 and 400 mg kg^{-1}) and metformin in diabetic rats significantly reduced serum glucose level and restored the body weight as compared to diabetic control rats. Whereas, three weeks repeated dose treatment of imipramine could not produce significant effect on blood glucose as well as body weight in diabetic rats (Table 2).

Effect of HFK on locomotor activity: The persistent hyperglycemia (>250 mg dL^{-1}) for three weeks significantly reduced locomotor activity ($p<0.01$) in diabetic rats as compared to normal control rats. Three weeks repeated dose treatment of HFK (200 and 400 mg kg^{-1}) and metformin did not show significant effect on locomotor activity. Whereas, imipramine significantly increased locomotor activity as compared to the diabetic control rats (Fig. 1).

Effect of HFK on onset of immobility and total immobility period in FST: Onset of immobility and total immobility period were significantly changed in diabetic control rats as compared to normal control rats. The treatment of HFK (200 and 400 mg kg^{-1}) and imipramine in diabetic rats significantly increased onset of immobility and decreased total immobility as compared to the diabetic control rats. While metformin could not produce significant effect on onset of immobility as well as total immobility period in diabetic rats (Fig. 2, 3).

Effect of HFK on MAO-A and MAO-B enzyme: Three weeks persistent hyperglycemia (>250 mg dL^{-1}) significantly increased MAO-A and MAO-B enzyme levels in diabetic rats. Treatment of HFK (200 and

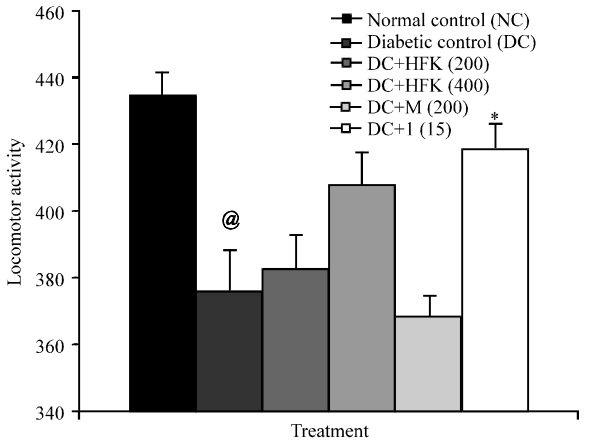

Fig. 1: Effect of three weeks repeated dose treatment of HFK on locomotor activity n = 5, values are Mean±SEM $^{@}p<0.01$ compared to normal control group (Student t-test) $^{*}p<0.05$ compared to diabetic control group (Student t-test)

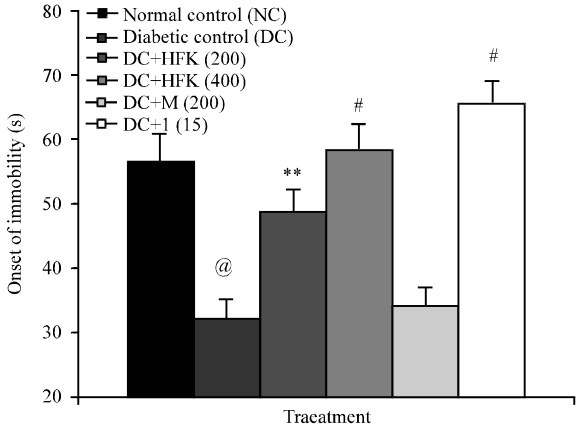

Fig. 2: Effect of three weeks repeated doses treatment of HFK on onset of immobility in FST n = 5, values are mean±SEM $^{@}p<0.001$ compared to normal control group (Student t-test) $^{*}p<0.01$, $^{\#}p<0.001$ compared to diabetic control group (Student t-test)

400 mg kg^{-1}) and imipramine decreased MAO-A and MAO-B levels as compared to diabetic control rats. While metformin could not reduce MAO-A and MAO-B enzyme levels (Fig. 4).

Effect of HFK on different antioxidant enzymes: In the present study, a significant increase in plasma MDA and NO, whereas decrease in SOD, GSH and CAT were observed in diabetic control as compared to normal control rats. The oral administration of HFK (400 mg kg^{-1}), metformin and imipramine showed significant decrease in

Table 2: Effect of three weeks repeated dose treatment of HFK on serum glucose level and body weight

	Serum glucose level (mg dL^{-1})		Body weight (g)	
Treatment (mg kg^{-1}, p.o.)	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Normal control (NC)	70.0±3.07	72.8±2.90	230.0±3.53	232.0±3.00
Diabetic control (DC)	299.2±9.70	309.8±8.45@	195.0±4.18	192.0±3.74@
DC+HFK (200)	311.0±8.40	180.8± 4.49#	188.0±3.74	201.0±2.91
DC+HFK (400)	297.0±9.13	133.2±4.43#	187.0±3.39	202.0±5.38
DM+M (200)	307.0±7.46	124.4±4.40#	183.0±2.55	211.0±4.30*
DM+I (15)	314.0±9.07	311.0±10.26	184.0±3.67	187.0±2.55

N = 5, values are mean±SEM, @p<0.01 compared to normal control group (Student t-test) *p<0.05, #p<0.001 compared to diabetic control group (Student t-test)

Table 3: Evaluation of antioxidant activity of HFK in plasma

Treatment (mg kg^{-1}, p.o.)	MDA (nmol mg^{-1} of protein)	NO (ng mg^{-1} of protein)	SOD (µg mg^{-1} of protein)	GSH (ng mg^{-1} of protein)	CAT (µg mg^{-1} of protein)
Normal Control (NC)	5.44±0.33	149.80±5.52	74.33±4.17	15.47±1.61	35.99±2.46
Diabetic Control (DC)	10.10±0.95@	241.60±4.20@	41.25±1.44@	7.55±0.31@	25.83±2.16@
DC+HFK (200)	7.52±0.34*	234.50±5.50	45.73± 2.42	11.04±0.89**	31.32±1.56
DC+HFK (400)	7.36±0.64*	161.00±8.00#	65.83±2.62#	15.05±0.99#	33.87±1.65*
DC+M (200)	7.35±0.64*	152.90±3.71#	71.72±3.23#	15.16±1.01#	33.60±3.66*
DC+I (15)	7.17±0.43*	156.00±2.29#	68.24±1.22#	13.48±1.32#	31.26±0.69**

N = 5 in each group, values are mean±SEM, @p<0.001 compared to normal control group (Student t-test) *p<0.05, **p<0.01, #p<0.001 compared to diabetic control group (Student t-test)

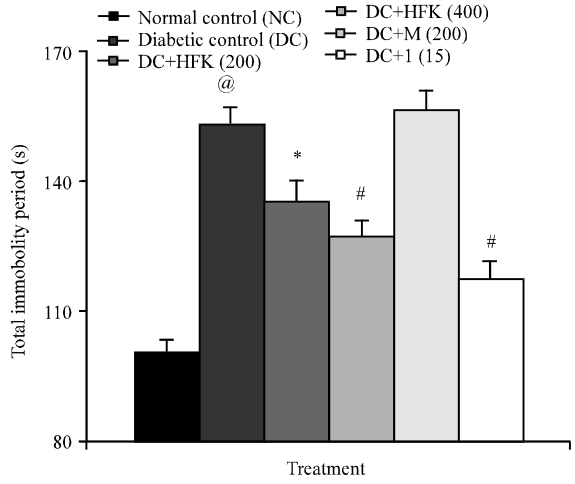

Fig. 3: Effect of three weeks repeated doses treatment of HFK on total immobility period in FST n = 5, values are mean±SEM @p<0.001 compared to normal control group (Student t-test) *p <0.05, #p<0.001 compared to diabetic control group (Student t-test)

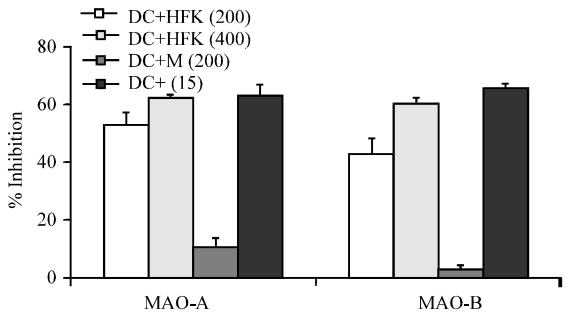

Fig. 4: Effect of three weeks repeated dose treatment of HFK on MAO-A and MAO-B enzyme levels

plasma MDA and NO levels whereas increase in SOD, GSH and CAT levels. However HFK (200 mg kg^{-1}) could significantly increase plasma GSH level only (Table 3).

DISCUSSION

It has been recognized that patients with either type 1 or type 2 diabetes are at higher prevalence of developing major depression and depressive symptoms than the general population (Anderson *et al*., 2001). Psychological troubles, including depression, are likely to adversely affect glycemic control, and may be regarded as risk factors for the development of diabetes related complications. The pathophysiology of diabetic depression is complex and associated with many neurochemical and neurovascular factors. These include reduced brain monoamines level, neuronal loss, increased MAO activity, altered neuronal synaptic plasticity, abnormal functioning of HPA axis and increased oxidative stress (Li and Sima, 2004).

In the present study, STZ-induced diabetic rats showed the depressive behavior in various tests of depression after three weeks of persistent hyperglycemia. These behavioral and biochemical changes are similar to previous reports (Belush and Rowland, 1989). Treatment with HFK showed antidepressant effect as well as decreased blood glucose and restore body weight in diabetic animals. The antidiabetic effect of HFK might be attributed to either increase in insulin secretion, inhibition

of the intestinal absorption of glucose and increase in glucose metabolism due to combination of various medicinal plants each having different mechanisms of action for antidiabetic activity.

The forced swim test has been validated as a suitable tool to evaluate drugs with putative antidepressant effects. In this assay, rats were forced to swim in a restricted space from which there is no escape, and they develop a state of despair characterized by a lowered motivation for escaping, as evidenced by increased period of immobility. It is well known that clinically effective antidepressants (such as imipramine) typically increase the swimming efforts of the animal seeking a solution to the problem and, therefore, they decrease the duration of immobility in the forced swimming test (Porsolt *et al*., 1978). It was observed in the present study that diabetic rats show decreased onset of immobility and prolonged total immobility period as compared to normal control rats, indicating significant depression. HFK treatment dose dependantly increased onset of immobility and decreased total immobility period as compared to diabetic control rats. Whereas HFK could not produce significant effect on locomotor activity of diabetic animals.

Monoamine oxidase (MAO) plays an important role in the pathogenesis of psychiatric disorders, including clinical depression and anxiety. In the present study, HFK significantly reduced the rat whole brain MAO-A and MAO-B enzyme levels as compared to diabetic control group, hence exerted antidepressant action by inhibiting the metabolism of monoamines. MAO regulates the metabolic degradation of catecholamines, serotonin and other endogenous amines in central nervous system. Inhibition of this enzyme causes a reduction in metabolism and subsequent increase in concentration of biogenic amines (Krishanan, 1998).

It has been reported that diabetes increases oxidative stress (Rahimi *et al*., 2005). While some studies have also shown that Reactive Oxygen Species (ROS) play a role in the pathogenesis of neuropsychiatric disorders (Bilici *et al*., 2001; Khanzode *et al*., 2003). It is well known that oxidation of monoamines and catecholamines can lead to ROS production in brain tissue (Fridovich, 1983). Excessive ROS production can cause oxidative damage to macromolecules including lipids, proteins, and DNA (Niebroj-Dobosz *et al*., 2004; Zhao *et al*., 2008), culminating in neuronal dysfunction and depression (Manji and Duman, 2001; Fuchs *et al*., 2004). Diabetes was found to impair the antioxidant status of plasma, presumably through production of excessive ROS. In the present study a significant increase in MDA and NO was found in plasma while the SOD, GSH and catalase were decreased in diabetic rats. The administration of HFK significantly decreased MDA and NO levels whereas SOD, GSH and catalase levels were significantly increased in plasma of rats as compared diabetic control rats.

In conclusion, our current preclinical study showed that herbal formulation Karnim is effective in diabetes associated depression. It may be foreseen that more knowledge on biogenic amines should be explored so that HFK can be used as an interesting source of new therapeutic approaches in this chronic disease.

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