SCREENING OF ANTIDEPRESSANT ACTIVITY OF *PICRORRHIZA KURROA* IN MICE USING CLONIDINE INDUCED HYPOTHERMIA

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1. INTRODUCTION:

Depression is considered as one of the most common psychiatric disorders. By 2020, it is expected to become the second leading cause of disease related disability, following heart disease as per WHO [1].

It has been reported that currently available treatment of depression is often associated with various undesirable side effects. Moreover, it is limitedly effective only in a certain group of the patients [2]. So, a search for novel pharmacotherapy for such psychiatric illnesses like depression from the treasure of medicinal plants has progressed significantly since past decade.

Since a long time, *Picrorrhiza kurroa* commonly known as kaddu or kutakihas been used in indigenous system of medicine. This well-known drug is spoken as Dhanvantarigrasta, the plant eaten by Dhanwantari. According to Charka Samhita, it has been reported that *Picrorrhiza kurroa* possesses antistress properties. It improves stamina and reduces incidence of gastric ulcers produced by restrain and chemical stress, liver damage and mortality induced by Carbon tetrachloride and have a calming effect. Psychosocial stress reduces neurogenesis in rodents, whereas chronic treatment with antidepressants increases neurogenesis and blocks the effects of stress. *Picrorrhiza kurroa* has been shown to potentiate the nerve growth factor (NGF) [3], [4].

2. MATERIALS & METHODS:

Procurement of Drug:

Dried rhizomes of *Picrorrhiza kurroa* (PK) were procured from local ayurvedic market of Pune, Maharashtra.

Authentication and extraction:

Crude drug was authenticated as rhizomes of *Picrorrhiza kurroa* Royle ex Benth, *Scrophulariaceae*at Agharkar Research Institute, Pune (Voucher No. 87437). Rhizomes of *Picrorrhiza kurroa* were powdered and alcoholic extract was prepared by soxhletion method.

Experimental animals:

Albino Swiss mice weighing 22-25 g were obtained from National Institute of Toxicology, Pune. Animals of either sex were housed in groups of five under standard laboratory conditions of temperature (25 ± 2°C) and 12hrs/12hrs-light/dark cycles. They had free access to standard pellet chow and water. Experiments were conducted between 09.00 and 16.00 hrs. Food was withdrawn 6 hrs prior to drug administration till the completion of experiment. The animals were allowed to acclimatize to laboratory conditions for not less than 10 days after their arrival. All the experiments were carried out in accordance with CPCSEA guidelines and approved by AIEC.

Drug administration:

Alcoholic extract of *Picrorrhiza kurroa*(PK) (15, 30 and 60 mg/kg p.o.), Clonidine (0.1mg/kg p.o.) and imipramine (10 mg/kg, i.p) were used.

2.1 Clonidine induced hypothermia:[5],[6]

Mice were administered clonidine (0.1mg/kg p.o.). After clonidine administration the animals were placed in individual cage. 30 min before the clonidine administration, mice were treated with vehicle, *Picrorrhiza kurroa* extract (15, 30 and 60 mg/kg p.o.) or imipramine (10 mg/kg i.p.) and the rectal temperature was measured at 0, 30, 60, 90 and 120 min using tele-thermometer to constant depth of 2 cms. Difference in the rectal temperature was calculated for each time interval with reference to the control.

Table: 1 Clonidine induced hypothermia (n=6)

Gr. No.	Group	Treatment and dose	Observation
1	Control	Normal Saline (0.3 ml, p.o.)+ Clonidine (0.1 mg/kg, s.c.).	Rectal temperature after each 30 min up to 2 hrs.
2	PK-1	PK (15 mg/kg, p.o.) + Clonidine (0.1 mg/kg s.c.).	
3	PK-2	PK (30 mg/kg, p.o.,) + Clonidine (0.1 mg/kg s.c.).	
4	PK-3	PK (60 mg/kg, p.o.) + Clonidine (0.1 mg/kg, s.c.).	
5	Positive control	Imipramine (10 mg/kg i.p.) + Clonidine (0.1 mg/kg, s.c.).	

3. RESULTS & DISCUSSION:

3.1 Effect of *Picrorrhiza kurroa* on Clonidne induced hypothermia:

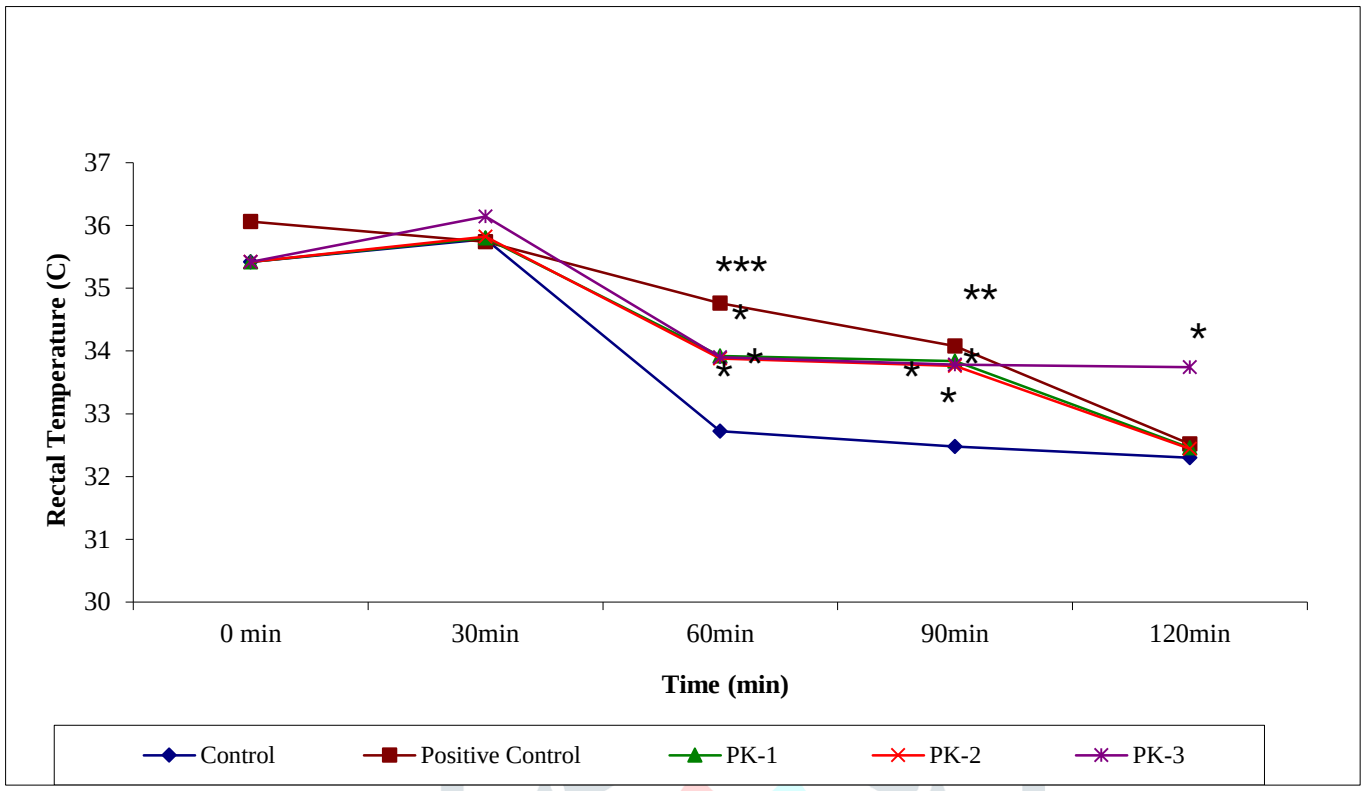
The hypothermia caused by Clonidine was reversed significantly by PK-1 at 60 & 90 min ($p<0.001$ & $p<0.01$ respectively), by PK-2 & PK-3 at 60 & 90 min ($p<0.05$) and by Imipramine at 60, 90 and 120 min ($p<0.05$).

Table: 3 Effect of *Picrorrhiza kurroa* on clonidine induced hypothermia (Rectal temperature in ºC).

Sr. No.	Group	Rectal temperature in ºC				
		0 min	30 min	60 min	90 min	120 min
1	Control	35.42 ± 0.34	35.78 ± 0.59	32.72 ± 0.20	32.48 ± 0.33	32.30 ± 0.24
2	PK-1	35.42 ± 0.34	35.80 ± 0.28	33.92 ± 0.25*	33.84 ± 0.29*	32.46 ± 0.36
3	PK-2	35.42 ± 0.34	35.82 ± 0.20	33.88 ± 0.32*	33.76 ± 0.26*	32.44 ± 0.34
4	PK-3	35.42 ± 0.34	36.14 ± 0.25	33.90 ± 0.27*	33.78 ± 0.28*	33.74 ± 0.25*
5	Positive Control	36.06 ± 0.27	35.74 ± 0.22	34.76 ± 0.23***	34.08 ± 0.26**	32.52 ± 0.28

Values are expressed in Mean ± SEM

Fig: 1 Effect of *Picrorrhiza kurroa* on clonidine induced hypothermia



*** = p < 0.001, ** = p < 0.01, * = p < 0.05

Data analysed using ANOVA followed by Tukey's Multiple Comparison Test

PK-1 = 15 mg/kg dose of *Picrorrhiza kurroa* extract

PK-2 = 30 mg/kg dose of *Picrorrhiza kurroa* extract

PK-3 = 60 mg/kg dose of *Picrorrhiza kurroa* extract

In the model of clonidine induced hypothermia, the PK extract was reported to inhibit the hypothermia. Clonidine mediates these activities by agonistic effect on α_{2A}, α_{2B}& α_{2C}. These receptors activates $G_{i/o}$, decreases cAMP, and inhibits voltage-gated Ca^{2+} channels and activates Ca^{2+} dependent K^{+} channels. Clonidine activates α adrenoreceptors, which exists in vasomotor center and hypothalamus. Clonidine is α_2 adrenoceptor agonist, which decreases noradrenaline release and produces fall in the body temperature. Antidepressant drugs like imipramine antagonize its action and delay the development of clonidine-induced hypothermia. Psychiatric morbidity associated with depression can often be accompanied or even precipitated by stress. There is close clinical and biochemical resemblance between depressive symptoms and the response to stressful experiences, which led to the hypothesis that depression represents activation of the primary mediators of the stress response. As a result, dysregulation of the HPA axis has been implicated in depression and its treatment. Clinical data indicates that *a* subset of patients with depression exhibit hyperactivity of the HPA axis, which is normalized after successful antidepressant therapy. [8-12]

Novel approaches to enhanced central adrenergic function include the use of α_2 adrenergic receptor antagonists. This is one of the several activities of the complex atypical antidepressants mianserin and mirtazapine**. [13]**

The Depletion of biogenic amines (noradrenaline, 5HT, and dopamine) in the brain induces catalepsy, ptosis and hypothermia in rodents. [14-22]

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