

EVALUATION OF ANTIDEPRESSANT ACTIVITY OF PICRORRHIZA KURROA USING BACLOFEN INDUCED HYPOTHERMIA IN MICE

Dr. Pragnesh Patani*, Dr. Nishkruti Mehta,

A-One Pharmacy College, Naroda Ahmedabad.

1. INTRODUCTION:

Mental depression is a complex disorder of unknown etiology, which is manifested by low mood, anhedonia, low energy levels, pessimism, guilty feeling and suicidal tendencies. It may range from a very mild condition, bordering on normality, to severe depression—sometimes called “psychotic depression” accompanied by hallucinations and delusions. Patients with major depression have symptoms that reflect changes in brain monoamine neurotransmitters, specifically norepinephrine, serotonin and dopamine. However, most of the marketed anti-depressant drugs exhibit serious side-effects. Therefore, the use of alternative medicines is increasing worldwide. Various herbal drugs (e.g. St. John’s wort) have shown promising results in treating experimental as well as clinical depression and many of these herbal drugs appear to be quite safe.

According to the World Health Organization report, mood disorders are the second leading cause worldwide of disability adjusted life years and the leading cause of years lived with disability in all ages. Each drug used to treat this disorder has a success rate of about 60%. In addition, most therapies require several weeks of treatment before improvement of signs and symptoms is observed and there are numerous side effects caused by antidepressants. Thus, the high prevalence of depression and the fact that a significant proportion of individuals do not respond well to any currently marketed antidepressants or treatments support the need for new therapeutics to treat depression. Numerous antidepressant compounds are now available, presumably acting via different mechanisms including serotonergic, noradrenergic and/or dopaminergic systems. Medical plant therapies may be effective alternatives in the treatment of depression, and has progressed significantly in the past decade (1-7)

Since a long, *Picrorrhiza kurroa* commonly known as kaddu or kutaki has 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 restraint 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) (8-9).

2. MATERIALS & METHODS:

2.1 Procurement of Drug:

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

2.2 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 using soxhlet method.

2.3 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 ($25 \pm 2^\circ\text{C}$) 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.

2.4 Drug administration:

Alcoholic extract of *Picrorrhiza kurroa* (PK) (15, 30 and 60 mg/kg p.o.), Baclofen (40 mg/kg s.c.) and imipramine (10 mg/kg, i.p) were used.

2.5 Baclofen induced hypothermia:[7]

On the day of testing, mice were administered with a dose of 40 mg/kg baclofen s.c. One hour after baclofen administration, the animals were placed in individual cages and treated with vehicle, *Picrorrhizakurroa* extract (15, 30 and 60 mg/kg p.o.) and imipramine (10 mg/kg, i.p.) 60, 60 & 30 min respectively before the test. The rectal temperature was determined using tele-thermometer to constant depth of 2 cms at 0th and

later at 30 min interval for 2 hours. Difference in the rectal temperature was calculated for each time interval with reference to the control.

Table: 1 Baclofen induced hypothermia

| Gr. No. | Group | Treatment and dose | Observation |
|---------|-------------------|---|--|
| 1 | Control (vehicle) | Normal Saline (0.3 ml, p.o.) + Baclofen (40 mg/kg, s.c.) | Rectal temp. after each 30 min up to 2 hrs. |
| 2 | PK-1 | PK (15 mg/kg p.o.) + Baclofen (40 mg/kg, s.c.) | |
| 3 | PK-2 | PK (30 mg/kg, p.o.) + Baclofen (40 mg/kg, s.c.) | |
| 4 | PK-3 | PK (60 mg/kg, p.o.) + Baclofen (40 mg/kg, s.c.) | |
| 5 | Positive control | Imipramine (10 mg/kg, i.p.) + Baclofen (40 mg/kg, s.c.) | |

PK = Alcoholic extract of *Picrorrhizakurroa* (n = 6)

3. RESULTS & DISCUSSION:

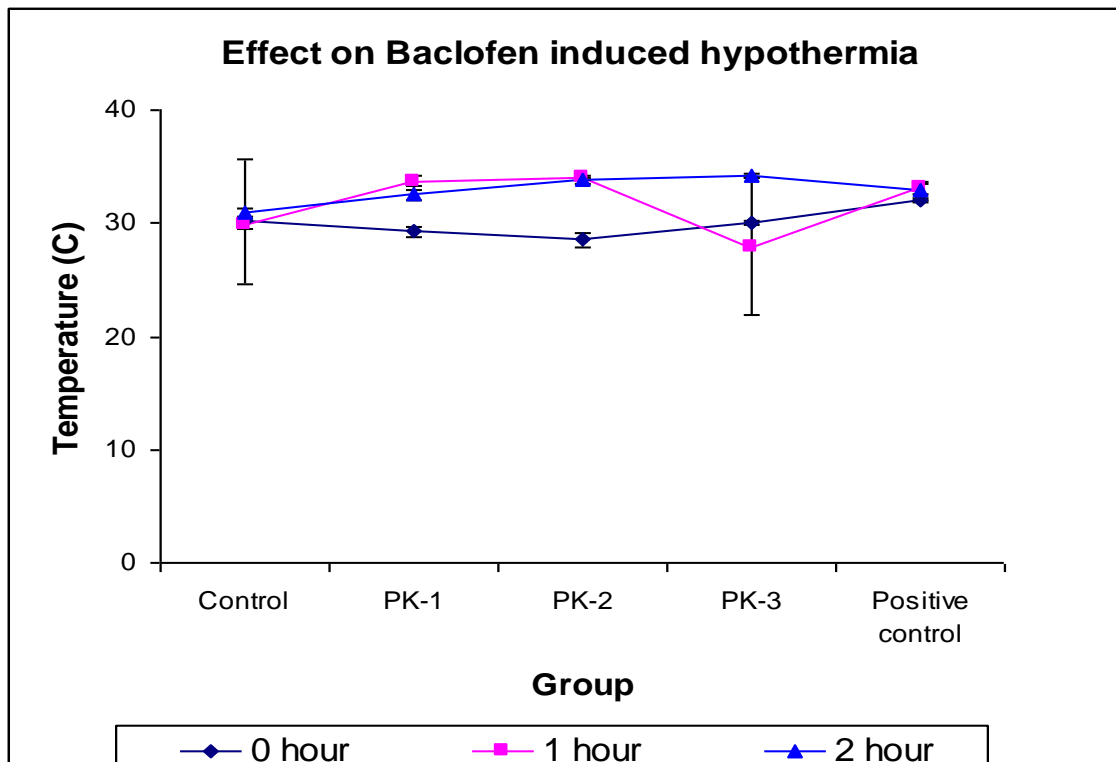
3.1 Effect of *Picrorrhizakurroa* on Baclofen induced hypothermia

Hypothermia produced by Baclofen was not significantly reduced by any dose of *Picrorrhizakurroa* extract or positive control, imipramine (10mg/kg).

Table: 2 Effect of *Picrorrhizakurroa* on Baclofen induced hypothermia (Rectal temperature in °C).

| Sr. No. | Group | Rectal temperature in °C | | |
|---------|------------------|--------------------------|---------|---------|
| | | 0 hour | 1 hour | 2 hour |
| 1 | Control | 26.14 ± | 31.94 ± | 32.92 ± |
| | | 5.59 | 0.39 | 0.37 |
| 2 | PK-1 | 33.30 ± | 33.58± | 32.66 ± |
| | | 0.44 | 0.61 | 0.58 |
| 3 | PK-2 | 33.58 ± | 34.06± | 33.76 ± |
| | | 0.61 | 0.18 | 0.33 |
| 4 | PK-3 | 34.06 ± | 27.96± | 34.18 ± |
| | | 0.18 | 6.04 | 0.13 |
| 5 | Positive control | 33.96 ± | 33.1± | 32.86 ± |
| | | 0.15 | 0.51 | 0.62 |

Values are expressed in Mean ± SEM

Fig: 1 Effect of *Picrorrhizakurroa* on Baclofen 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

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. [10-13]

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. [14]

GABA_B receptor is G-protein coupled receptor, which hyperpolarizes neurons by increasing K⁺ conductance and altering Ca²⁺ flux, which is blocked by baclofen. The primary site of action of baclofen is considered to be in spinal cord where it depresses both polysynaptic and monosynaptic reflexes and produce hypothermia and muscle weakness. Baclofen also induces progressive peripheral depletion of catecholamines and serotonin. It interferes with synthesis of Noradrenaline by blocking the uptake of dopamine into vesicles and releasing stored Noradrenaline, which in turn inhibit conversion of tyrosine to dopa. [15]

The Depletion of biogenic amines (noradrenaline, 5HT, and dopamine) in the brain induces catalepsy, ptosis and hypothermia in rodents. [16-18] Antidepressants and central stimulants antagonize the decrease in body temperature induced by baclofen. Hypothermia induced by baclofen which is GABA receptor agonist, was not reduced as compared to control group at any doses of alcoholic extract of *Picrorrhiza kurroa*. [19-23]

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