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Research Paper

CNS ACTIVITY OF ROOTS OF *Andrographis paniculata* IN MICE AND RATS

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Abstract

The aim of the current work was to investigate several neuropharmacological effects of the methanol extract of roots of *Andrographis paniculata* in Wister albino rats and Swiss albino mice. The dried powdered roots were extracted with methanol and the solvent was removed under reduced pressure to obtain a dried extract material. With that extract the general behavior, exploratory behavior, muscle relaxant activity and phenobarbitone sodium-induced sleeping time were studied. The results revealed that the crude extract at 50-150 mg/kg per oral (p.o) caused a significant reduction in spontaneous activity (general behavior profile), and a reduction in muscle relaxant activity (rotarod, 300 inclined screen and traction tests) and also significantly potentiated phenobarbitone sodium-induced sleeping time. Hence it can be concluded that the methanolic extract of the roots of *Andrographis paniculata*(in the doses examined) possess most of the pharmacological characteristics of the psychoactive group of drugs like minor tranquilizers.

Key words: *Andrographys paniculata* roots; Methanol extract; CNS activity; Experimental animals.

INTRODUCTION

Depression is a chronic psychiatric disorder that contributes substantially to mental impairment, physical disability and socioeconomic burden [1]. These disordersare capable of reducing quality of life, productivity, and increase suicidality. World Health Organization predicts, depression will be the second leading cause of disease by 2020 [2,3]. The symptoms of depression such as anhedonia, irritability, difficulties in concentrating and sleep are clear evidences of the complexity of its neurobiology [4].The search for new drugs remains a desirable approach as the current antidepressants including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors are still far from producing optimal effects without side effects. The drugs which act upon the Central Nervous System (CNS) were among the first to bediscovered by primitive human beings and are still the most widely used group ofpharmacological agents. In addition to their use in therapy CNS acting drugs are often usedwithout prescription to increase one's sense of well-

being.Besides the synthetic drugs acting on the CNS, many plant materials so far screened have beenfound to possess immense activity on the CNS. *Andrographis paniculata* belongs to the family ofAcanthaceae. It is also commonly known as "kalmegh,"and a well-known medicinal plant of Ayurveda and has been usedfor centuries in Asian countries. Severalpolyherbal formulationsof this plant are stated in Ayurveda as a popularremedy for the treatment of various disorders. *Andrographispaniculata*is an annual shurb grows abundantly in India andcultivated extensively in China and Thailand. The aerial partsof the plant (leaves and stems) are used to extract the activephytochemicals. The plant extract is known to contain labdane, neoclerodane–type of diterpenoids,sesquiterepenes, flavonoids and stigmasterols[49].Extracts of plants and their major metabolites including labdanediterpenoids, neoclerodanediterpenoids and flavonoids have been reported to exhibit a wide range of biological activities [6-48]of therapeutic importance that include anti-inflammatory, hepatoprotective, antimalarial, antibacterial, antithrombotic, immune stimulant, antidepressive, antiallergic, central nervous system disorders [19, 21, 23, 25, 30-35], anti HIV, and anticancer.
From the literature survey it has been found that the roots of *Andrographis paniculata*have been usedextensively in various mental illnesses in India. To substantiate this claim the present study wasundertaken to evaluate various psychopharmacological effects of methanol extract of roots of *Andrographis paniculata*. The effects of the root extract on general behavioral pattern, potentiationof phenobarbitone sleep, exploratory behavior and muscle relaxant activity were studied ondifferent animal models in rats and mice.

MATERIALS AND METHODS

Plant Material

Fresh roots of *Andrographis paniculata*was collectedfrom Chandigarh, Haryana, India in in October 2014. Botanical identification was done by Prof.Jnanendra Shukla, taxonomist, Ayurvedic medicinal Plants Division, and voucher specimen HR-102/1R was deposited at the herbarium. The roots were collected, dried under shade and pulverized by amechanical grinder. The powder was passed through concerned sieve, and stored in a closed vessel.

Preparation of the extract

Coarsely powdered dried roots (1kg) were successively extracted in cold condition with 95% methanol as solvent for 72 hour at room temperature. The whole extract was collected in a 5liters conical flask, filtered and the solvent was evaporated to dryness under reduced pressure inaEyela Rotary Evaporator (Japan) at 40-45^{o}C. The percentage yield (w/w) of the preparedextract was 12.745% with respect to the dry powder.The preliminary photochemical group test of root extract was done by the standard methods.The photochemical tests of the whole extract were done by qualitative analysis and confirmed bythin layer chromatography (TLC).

Animals used

Swiss albino mice (20-25 g) and Wister albino rats (150-180 g) of either sex were used. Theanimals were housed in groups of 10 per cage (standard metal cages) prior to pharmacologicalstudies with free access to standard diet and water ad libitum for at least 2 weeks on a 12/12 hour
light/dark cycle (from 08:00 to 20:00 hour). All animals were fasted overnight before conducting
the experiment. The ambient temperature was 22 ± 10^{o}C, except phenobarbitone sodium induced
sleeping time experiments, which were carried out at 30 ± 10^{o}C. Plant extracts and standard drugswere suspended in propylene glycol immediately prior to use and given orally 1 hour before theexperiments in a dose of 5 ml/kg body weight in mice (0.1 ml/20 g) and rats (0.75 ml/150 g).Control animals received the same dose of vehicle under the same conditions. Behavioralobservations took place between 08:00 and 15:00 hour and each animal was used only once.Injections were normally made intraperitoneally unless otherwise mentioned.

Drugs

The drugs used for this experiment were chlorpromazine hydrochloride (Indus Pharmaceuticals Limited, India), diazepam (Lupin Laboratories Ltd., India), phenobarbitone sodium (Rhone-Poulenc India Ltd., India), pethidine (Ranbaxy Laboratories Ltd., India) and propylene glycol (SRL Laboratories, India).

LD_{50} in mice

An acute toxicity study was done by determining LD50 calculated from the lethal dose within 3days after p.o. administration, of different doses of the crude extract of roots of *Andrographis paniculata*byLitchfield and Wilcoxon method.

RESULTS

General behavioral profiles

Evaluation of general behavioral profile was performed by the literature method. Fifty adult albino male mice were divided into 5 groups (n=10). The first three groups wereinjected with methanolic extract of roots of *Andrographis paniculata* at doses of 50, 100 and 150mg/kg intraperitoneally.

Touch response

The touch response was recorded by touching the mice with a pencil or forceps at various parts of the body (i.e. on the side of the neck, abdomen and groin).

Pain response

The pain response was graded when a small artery clamp was attached to the base of the tail, andresponse was noted.

Sound response

Albino mice normally utter no sound, so that vocalization may indicate a noxious stimulus.

Analgesic activity

Analgesic activity was studied by (i) tail immersion and (ii) tail flick tests.

Tail immersion test

Swiss albino mice of either sex were divided into 5 groups of 10 animals each. Propylene glycol (5 ml/kg), MEOS at the doses of 50, 100 and 150 mg/Kg and pethidine (5 mg/kg) wereadministered intraperitonialy. The tail (up to 5 cm) was then dipped into a pot of water maintained at 55 ± 0.5^0C. The time in seconds to withdraw the tail out of water was taken as the reaction time. The reading was taken after 30 min of administration of the test drugs.

Tail flick test

Wister strain of albino rats of either sex weighing between 150 and 180 g were selected anddivided into 5 groups of 10 animals each. The tail of the rat was placed on the nichrome wire of ananalgesiometer (Techno, Lucknow, India) and the time taken by the animal to withdraw(flick) its tail from the hot wire was taken as the reaction time. The methanol extract of roots of *Andrographis paniculata* in doses of 50, 100and 150 mg/kg and pethidine (5 mg/kg) were injected intraperitonialy. Propylene glycol at **(**5ml/kg) was served as control. Analgesic activity was measured after 30 min of administration of test and standard drugs.

Table. 1. Analgesic effect of methanol extract on tail flick and tail immersion tests in mice and rats

Treatment	Dose	Tail flick test (reaction time in sec)	Tail immersion test (reaction time in sec)
Propylene glycol	5 mL/Kg	2.15 ± 0.14	2.30 ± 0.16
Pethidine	5 mL/Kg	4.25 ± 0.18	4.45 ± 0.12
Methanol extract	50mL/Kg	2.50 ± 0.16	2.40 ± 0.02
Methanol extract	100mL/Kg	3.02 ± 0.07	3.05 ± 0.02
Methanol extract	150mL/Kg	3.85 ± 0.21	3.83 ± 0.15

Values are mean ± S.E., n =10. All the data are significant at P<0.001 *vs*. control, Student's t-test.

Effect of sodium phenobarbitone-induced sleeping time

Mice were divided into 4 groups of 10 each. Animals received 40 mg/kg (i.p.) phenobarbitonesodium 30 minutes after injection of MEOS at dose of 50, 100 and 150 mg/Kg and controlvehicle propylene glycol (5 ml/kg). The sleeping time was recorded, and measured as the time
interval between the loss and regaining of the righting reflex [11,12].

Table. 2. Effect of MEOS on phenobarbitone sodium induced sleeping time

Experiment	Dose	Sleeping time in mins.
control	0.1 saline/10 g	45±1.62
Methanol extract	50 mg/kg	53.4±1.49*
Methanol extract	100 mg/kg	64.5±1.14
Methanol extract	150 mg/kg	84.6±2.08*

methanol extract of roots of *Andrographis paniculata*. Values are (mean ±S.E.; n=10)
*P<0.001 compared with control.

Muscle relaxant activity

The effect of extract on muscle relaxant activity was studied by the (i) Traction test and (ii)Rotarod test (iii) 30^0 inclined screen test.

Traction test

The screening of animals was done by placing the forepaws of the male mice in a small twistedwire rigidly supported above a bench top. Normally the mice grasp the wire with forepaws, andplace at least one hind foot on the wire within 5 sec when allowed to hang free. The test wasconducted in five groups of animals (n=10) which were previously screened, 30 min after theinjection of either methanol extract of roots of *Andrographis paniculata* (50,100 and 150 mg/kg), diazepam (10 mg/Kg) or propylene glycol**(**5ml/kg) as vehicle control. Inability to put up at least one hind foot considered failure in thetraction test.

Rotarod Test

Fresh mice were placed on a horizontal wooden rod (32 mm. diameter) rotating at a speed of 5rpm. The mice capable of remaining on the rod for 3 minutes or more, in three successive trialswere selected for the study. The selected animals were divided into 5 groups (n=10). Groups 1, 2and 3 were injected intraperitoneally with methanol extract of roots of *Andrographis paniculata*(50, 100, 150 mg/kg). Groups 4 and 5 werereceived either propylene glycol (5 ml/kg) or diazepam (10 mg/kg). Each group of the animalswas then placed on the rod at an interval of 30, 60, 90,120 and 150 minutes. The animals failedmore than once to remain on the rotating rod for 3 minutes were considered as positive result.

30^oInclined screen test

In this test the groups of 10 male mice, in 5 groups, were injected intraperitoneally with eitherpropylene glycol **(**5 ml/kg) or methanol extract of roots of *Andrographis paniculata* (50, 100, 150 mg/Kg) or diazepam (10 mg/kg)respectively. The animals were left on a 300 inclined screen at least for 4 hours to observe aparalysant effect sufficient to cause the mouse slide off the screen.

Table. 3. Percentage effect of methanol extract of roots of *Andrographis paniculata* on Muscle relaxant activity in mice

Treatment & dose	% of animals showing negative test		
	Traction Test	30^oInclined Test	Rotarod Test
Propylene glycol	0	0	0
Diazapem (10 mg/kg)	100	100	100
Methanolextract(50mg/kg)	68.5[a]	50[a]	70[a]
Methanolextract (100mg/kg)	80[a]	68[a]	70[a]
Methanolextract(150mg/kg)	90[a]	80[a]	79[a]

methanol extract of roots of *Andrographis paniculata*. Values are the percentage of animals showing a negative result; n=10. a= p< 0.5 compared with control Chi-square test

Statistical analysis

The data were expressed as the mean ± S.E. Significance was evaluated by the Student's t- test inall the experiments, and Chi-square tests for muscle relaxant activity. A value less than 0.05were considered significant.

Toxic study

The root extract was found to be non-toxic up to doses of 3.0 g/kg and did not cause any death ofthe animals tested.

DISCUSSION

The results indicated that the methanol extract of roots of *Andrographis paniculata* influences general behavioral profiles, as evidenced in the spontaneous activity, sound, touch and pain responses. The methanol extract of roots of *Andrographis paniculata* possesses significantanalgesic activity compared with the standard drug pethidine in a dose-dependent manner. Thisactivity may be due to its action on central nervous system like pethidine.The extractsignificantly potentiated the phenobarbitone sleeping time, possibly through a CNS depressantaction or a tranquilizing action. The possible CNS activity of the methanol extract wasfurther investigated by other common psychopharmacological tests like the rotarod test, 30^{o}inclined screen test, and traction test. The reduction in exploratory behavior in animals treatedwith the methanol extract of the roots of *Andrographis paniculata*is similar with the action of otherCNS depressant agents. A significant lack in motor coordination and muscle relaxant activitywas also noted in animals treated with the crude extract.

The present investigation for the first time, confirms that there is a moderate to strong degree ofantipsychotic activity in the methanol extract of roots of *Andrographis paniculata*. In conclusion, the vernacular medicinal use of roots of*Andrographis paniculata*for mental tension and disturbance as well as to induce sleep is validated by ourfindings.

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