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Original Article

STUDY OF CNS ACTIVITIES OF PIPERINE *PERSE* AND ITS BIO-ENHANCING EFFECT ON VARIOUS DRUGS IN EXPERIMENTAL ANIMAL MODELS

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ABSTRACT

Objective: Study of CNS activities of piperine *perse* and its bio-enhancing effect on various drugs in experimental animal models.

Methods: The CNS effects of piperine and its interaction with various drugs were evaluated by maximal electroshock convulsion model, pentobarbitone-induced sleeping time, anxiolytic activity, muscle relaxant activity and antidepressant activity using tail suspension and forced swimming test using standard procedures in experimental animal models. piperine at a dose of 10 and 20 mg/kg orally was used to evaluate CNS activities.

Results: The results revealed that piperine *perse* posses only anticonvulsant activity and other significant CNS effects were not observe. But when it was combined with various drugs piperine increases the effect of the standard drug.

Conclusion: Piperine 10 mg/kg has the potential to be used as a bio-enhancing agent when combined with other drugs. Bio-enhancing effect of piperine will decrease the dose of the standard drug, thereby decreasing the risk of their toxicity.

Keywords: Piperine, Bio-enhancing, MES, Anxiolytic test, Tail suspension test, Forced swimming test, Motor co-ordination, Righting reflex

INTRODUCTION

WHO data suggest that neurological and psychiatric disorders are important and growing cause of morbidity. Around 450 million people currently suffer from mental and behavioral disorders [1]. 70 % of mental health problems have their onset during childhood or adolescence. Young people aged 15 to 24 are more likely to experience mental illness and/or substance use disorders than any other age group [2]. Medicinal plants are one of the oldest healthcare products used widely. The importance of plant products has also increased in developed countries.

Though many allopathic drugs are available to treat mental health but some of these drugs have late onset or associated with various side effects. Plant products have wide therapeutic action along with a better safety profile. Hence, a study was planned to evaluate various CNS activity of Piperine and its interaction with other standard drugs. Piperine is the chief constituent of piper nigrum, which is commonly known as black pepper and is one of the oldest and best-known spices in the world. Belonged to Piperaceae family, which is cultivated in the damp nutrient rich soil of South India, it is also found in Indonesia, Malaysia, and Brazil. In India, it is called "kali mirchi", which is a common household spice.

Its chief constituents are crystalline alkaloid piperine (5-8.25 %), volatile oils (1-2.3 %) and a resin called Chavicin [3]. Black pepper was found to enhance intestinal absorption of methionine and calcium ions [4]. Piperine, the best-known compound of pepper was reported to inhibit fatty acid oxidation in rat liver microsomes [5]. It is also proved that it increases the bioavailability of theophylline, propanolol, and nutrients [6]. In the view of these facts, *perse* activity of piperine and its interaction with other drugs was undertaken.

MATERIALS AND METHODS

Plant material and isolation of piperine [7]

Piperine was obtained from Amsar (P) Ltd, Indore (M. P.), which contained about 95 % of piperine.

The extract was dissolved in 5 ml of Ethyl alcohol and 10 ml of 10 % w/v of alcoholic potassium hydroxide added with constant stirring. It was then filtered and allowed to stand overnight. The yellow needle-shaped crystals of piperine were separated the next day.

The purity of the isolated piperine was verified by checking its melting point (range 128-131 °C), treating it with concentrated Sulphuric acid (blood red color obtained), by Thin Layer Chromatography (single spot obtained) and Ultraviolet Spectrophotometer (absorption maxima at 343 nm for piperine). [8, 9]

Experimental animals

Swiss albino mice and wistar rats of either sex weighing between 25-35 gm and 150-200 gms respectively, were procured from the central animal house, M. G. M Medical College, Indore and acclimatized for a period of 7 d at room temperature (25±2 °C) and 50±15 % relative humidity. They were housed in a standard cage and maintained on standard pellets and water *ab libitum*. The animals described as 'fasted' were deprived of food for 16 h, but had free access to water. The study was carried out in the Department of Pharmacology, M. G. M Medical College, Indore (M. P.), India. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC).

Drugs and chemicals

Gum acacia (Himedia Lab, India), Epsolin injection-PHENYTOIN SODIUM-50 mg/ml-Cadila–H Pharm. Ltd., Tegrital tablet-CARBAMAZEPINE-200 mg-Novartis, Powder PENTOBARBITONE-Rhone Poulenc India Ltd., Midaz injection-MIDAZOLAM-5 mg/ml-Nicholas limited, Calmpose injection-DIAZEPAM-10 mg/2 ml-Ranbaxy limited were purchased from their respective representatives.

Preparation of drugs for animal experiment

Piperine and other drugs were given orally. All Drugs were dissolved in 2 % gum acacia which acted as a vehicle.

Experiment design

(i) Effect of piperine *per se* and its interaction with carbamazepine in "electroshock convulsion in albino mice."

The albino mice were divided into eight groups of 8 each. The eight groups were treated respectively as under Group I received 2 % gum acacia 10 ml/kg, Group II received phenytoin 0.5 mg/kg, Group III received Carbamazepine 15 mg/kg, Group IV received Carbamazepine at a sub-anticonvulsant dose of 7.5 mg/kg [10], Group V received piperine 10 mg/kg, Group VI received piperine 20 mg/kg, Group VII received piperine 40 mg/kg and Group VIII received a combination of carbamazepine and piperine (7.5 mg/kg+10 mg/kg). All drugs were administered orally one hour prior to the application of electroshock. The electroshock was given by electrodes which were applied to pinna of a mouse. 50 mA current was given for 0.2 s. Different stages of MES were noted (an observation on the hind limb extension was mainly focused). Reduction in time or the abolition of tonic extensor phase was noted. A complete abolition of hind limb tonic extension was considered as 100 % protection [11].

(ii) The effect of piperine *per se* and its interaction with "pentobarbitone induced loss of righting reflex in albino rats."

The study was done in 48 male albino rats, divided into six groups of 8 animals each. The six groups were treated respectively as:-Group I received 2 % gum acacia 10 ml/kg, Group II received pentobarbitone 40 mg/kg [12], Group III received piperine 10 mg/kg, Group IV received piperine 20 mg/kg, Group V received piperine 40 mg/kg and Group VI received a combination of pentobarbitone and piperine (40+10 mg/kg).

Time of onset of loss of righting reflex and duration of loss of righting reflex was recorded. The animals were placed in supine with their back on the surface. Time of recovery was noted when animals correct its posture from supine to pronated one (normal). The time of recovery provides us the duration of loss of righting reflex.

(iii) Effect of piperine *per se* and its influence on anxiolytic property of midazolam in albino mice using "elevated plus maze (EPM)" instrument

The elevated plus-maze was introduced by Pellow *et al.* [13] for rats and by Listetil *et al.* [14] for mice. The EPM apparatus consisted of two open arms (30 x 5 cm) and two closed arms (30 x 5 x 20 cm) emanating from a common central platform (5 x 5 cm). The two pairs of identical arms were opposite to each other. The entire apparatus was elevated to a height of 50 cm above the floor level. The albino mice were divided into four groups of 8 each. The four groups were treated respectively as Group I-2 % gum acacia (10 ml/kg), Group II midazolam (0.2 mg/kg), Group III piperine (10 mg/kg) and Group IV midazolam and piperine (0.2 mg/kg+10 mg/kg).

Procedure-The animals received the treatment as per the schedule, 1 hour before the start of the session. At the beginning of the session, a mouse was placed at the center of the maze, its head facing the closed arms and total entries in different arms were recorded. An entry was defined as the presence of all four paws in the arm. The EPM was carefully wiped, with 10 % ethanol after each trial, to eliminate the possible bias due to the odor of the previous animal.

(iv) Effect of piperine *per se* and its influence on skeletal muscle relaxant property of diazepam in albino mice using "Techno ROTA ROD" instrument

The albino mice were divided into four groups of 8 each. The four groups were treated respectively as: Group I-2 % gum acacia (10 ml/kg), Group II diazepam (3 mg/kg) [15], Group III piperine (10 mg/kg) and Group IV diazepam and piperine (3 mg/kg+10 mg/kg).

Procedure-Motor coordination and balance were tested using accelerating rotarod (Techno Rota Rod System). Mice were placed on a horizontal metal rod (3 cm diameter) rotating at an initial speed of 10 rpm/min. the terminal speed of the rod was 20 rpm in accelerated studies, and rotational velocity of the rod was linearly increased from 10 to 20 rpm within 20 s. The time each animal was able to maintain its balance walking on top of the rod was measured. Before the beginning of all experiments, the riding ability of the animals in the rotarod was checked. Mice were first trained on the rotating rod of the instrument at 25 rounds/minute till mice could balance to keep themselves on rotating rod or till the end of 60 seconds [16]. 3 to 4 trials per day were given for 2 d to all the animals. Those mice that successively completed three trials/day for 2 d were selected. Mice that immediately dropped off (within 30 s) were removed from the experiment [17]. The number of seconds each mouse remained on the rotarod was recorded for 60 seconds on the third day.

(v) Effect of piperine *per se* and its interaction with sertraline HCl in albino mice by using "tail suspension test" (TST)

TST was performed according to Steru *et al.* [18] with slight modifications. In brief, a group of 32 mice were divided at random into four groups (n=8) and treated as follows: Group, I (control) received 2 % gum acacia 10 ml/kg, Group II received sertraline (5 mg/kg), Group III received piperine (10 mg/kg) and Group IV received piperine+sertraline (10+5 mg/kg). All drugs were administered orally 2 hours prior to the TST. Mice were suspended by the tail at the height of 58 cm. above the table top using adhesive tape affixed to the hook. Each mouse was suspended individually. The movements of the mice were measured for 10 min.

(vi) Effect of piperine *per se* and its interaction with sertraline HCl in albino rats by using "forced swimming test" (FST):

This paradigm was performed as described previously by Porsolt *et al.* [19] and Siuciak *et al.* [20] with some modifications [21, 22] and presently considered as the standard method.

Rats were individually forced to swim in an open cylindrical container (diameter 30 cm, height 60 cm); containing water of 45 cm depth at 25±10 ° C. The water level has been increased (45 cm) in order to increase the sensitivity of the test. The rats lack a sense of the water's depth when their tails do not touch the bottom of the cylinder.

Animals were exposed to a pretest session for 15 min, 24 h prior to the 5 min swim test session. Each animal was considered immobile when it ceased to struggle and swim and remained floating in the water, only moving to keep its head above water. The three behaviors scored are defined as follows by Lucki *et al.* [23]; (1) climbing, with the rate making an active attempt to escape from the tank, including visual searching for the escape routes and diving; climbing may be more related to attempts to escape than is swimming; (2) swimming, with the rate staying afloat, pedaling, and making circular movements around the tank; and (3) immobility, with the rat not making any active movements.

Procedure-Briefly, a group of 32 rats, was divided at random into four groups (n=8) and treated as follows: Group, I (control) received 2 % gum acacia 10 ml/kg, Group II received sertraline (5 mg/kg), Group III received piperine (1 0 mg/kg) and Group IV received piperine+sertraline (10+5 mg/kg) all drugs were administered orally. Test solutions were administered once daily between 1—3p. m. over a period of 14 d. Rats were placed in an acrylic cylinder for 15 min (pre-test session) after 14 d treatment.

Twenty-four hours after the pre-test session, the animals were once again exposed to the same conditions for 5 min (test session). Between the pre-test session and main session drug solutions were administered orally three times as follows: just after the pre-test session, 5 h before the main test, and 1 h before the main test. A rat was judged immobile if it remained floating in the water, except for small movements to keep its head above the water. The FST was performed between 1-3 p. m.

Statistical analysis

The results are presented as mean±SEM. The statistical analysis was done using one-way ANOVA followed by multiple Tukey's comparison test. $P<0.05$ was considered statistically significant. All statistical analysis was performed using SPSS 11.5 software.

RESULTS

(i) The effect piperine, phenytoin and carbamazepine on MES in mice and piperine interaction with carbamazepine: Phenytoin abolished the tonic hind limb extension completely and was 100 % protective against convulsions.

While piperine at a dose of 20 and 40 mg/kg decreased the duration of tonic hindlimb extension (6.68 and 6.92 s) and incidence of convulsions was 37.5 %, i.e. out of eight animals, three animals had convulsions and rest five were protected against MES-induced convulsion.

When carbamazepine was administered in sub anticonvulsant dose, it significantly reduced the duration of the tonic hind limb extension (9.99 s) as compared to control group (15.70 s), although all the eight animals in carbamazepine group developed convulsions i.e. 100 % incidence of convulsions was seen.

When carbamazepine was concomitantly administered with piperine, it not only significantly reduced the tonic hindlimb extension (6.32 s) but also 75 % incidence of convulsion was seen i.e. out of eight animals six animals had convulsions while the rest two were protected.

Piperine at a dose of 10 mg/kg did not show any anticonvulsant activity.

Table 1: The effect of piperine, phenytoin and carbamazepine on MES in mice and piperine interaction with carbamazepine

Treatment	Dose (mg/kg) orally	Duration of tonic hindlimb extension in seconds	Incidence of convulsion %
Control (2 % gum acacia)	10 ml/kg	15.70±0.48	100
Phenytoin	0.5	-	A
Carbamazepine	15	-	A
Carbamazepine	7.5	9.99±0.38 *	100
Piperine	10	12.33±0.28	100
Piperine	20	6.68±0.30 *	37.5
Piperine	40	6.92±0.43 *	37.5
Carbamazepine +Piperine	7.5+10	6.32±0.29 *,†	75
One Way ANOVA	F	97.63	
	P	<0.05	

One way ANOVA followed by multiple tukey's comparisons test., Values are n= 8 mean±SEM, df= 7, 56, * P<0.05 with respect to control, † P<0.05 with respect to carbamazepine 7.5 mg/kg. A-Absence of convulsion

(ii) Effect of pentobarbitone (40 mg/kg, p. o.) and piperine (10, 20, & 40 mg/kg) and their combination on righting reflex in rats: 2 % gum acacia and piperine at 10, 20 and 40 mg/kg did not showed any loss in righting reflex.

Onset of loss of righting reflex with pentobarbitone reached earlier when it was combined with piperine. The total duration of sleeping was also enhanced when pentobarbitone was combined with piperine (P<0.05).

Table 2: Effect of pentobarbitone, piperine and their combination on righting reflex in rats

Group	Dose (mg/kg) (orally)	Time of onset (min)	Duration (min)
(2 % gum acacia)	10 ml/kg	-	-
Pentobarbitone	40	34.37±1.26 *	71±2.12 *
Piperine	10	-	-
Piperine	20	-	-
Piperine	40	-	-
Pentobarbitone +Piperine	40+10	22.12±1.49 *,†	180.37±5.22 *,†
One way ANOVA	F	303.56	912.60
	P	<0.001	<0.001

One way ANOVA followed by multiple tukey's comparison test., Values are mean±SEM, n=8 in each group, df= 5, 42, * *P*<0.05 as compared to control, † *P*<0.05 as compared to standard (pentobarbitone) group

(iii) Effect of midazolam, piperine and their combination on behavior of mice in elevated plus maze: Midazolam treated mice showed a significant increase in the number of open arm entries, preference for the open arm and the time spent in open arm (3.88, 36.95 & 44.94). They showed a reduction in time spent in the closed arms, when compared to control group.

While the combination of midazolam and piperine showed a greater increased preference for open arm when compared with control group as well as midazolam alone group. Time spent in the closed arm (51.43) was also significantly reduced as compared to midazolam alone group. No significant such activity was seen in piperine group (P>0.05).

(iv) Effect of diazepam, piperine and their combination on behavior of mice in rotarod: Control (2 % gum acacia) and piperine (10 mg/kg) maintained rota rod performance throughout the test period.

While motor coordination in diazepam alone and its combination with *piperine* group was significantly impaired (P<0.05) as compared to control group. Further, in combination group the muscle relaxant activity was more significantly impaired in comparison with the diazepam alone group (P<0.05).

(v) The effect piperine, sertraline and their combination on immobility period in TST: Sertraline at a dose of 5 mg/kg significantly reduces the immobility period (121.44 s) and thereby increased the mobility of animals. This effect was further enhanced to a significant extent when piperine was combined with sertraline (immobility period reduced to 76.53 s).

(vi) The effect piperine, sertraline and their combination on immobility period in FST: Sertraline when co-administered with *piperine*, reduced the immobility period in FST (125.31 s) which was significantly greater than sertraline alone (173.82 s) (P<0.05).

Table 3: Effect of midalolam, piperine and their combination on behavior of mice in elevated plus maze paradigm

Treatment	Dose mg/kg orally	Number of entries		% preference to open arm	Time spent (seconds)	
		Open	Total		Open	Closed
(2 % gum acacia)	10 ml/kg	2.13±0.48	5.12±1.26	41.60	16.14±0.68	228.93±7.77
Midazolam	0.2	3.88±0.91	10.50±1.38*	36.95	44.94±1.73*	180.37±3.38*
Piperine	10	2.00±0.38	5.50±1.08	36.36	15.76±1.08	216.65±3.86
Midazolam +Piperine	0.2 +10	7.00±0.46*†	10.25±0.73*†	68.29	114.95±4.61*†	51.43±3.92*†
One-way ANOVA	F	24.43	53.27		336.72	257.40
	P	<0.01	<0.01		<0.01	<0.01

One way ANOVA followed by multiple tukey's comparison test., Values are mean±SEM. df = 3, 28, *P<0.05, compared to control group, †P<0.05, compared to standard (midazolam) group.

Table 4: Effect of diazepam, piperine and their combination on behavior of mice in rotarod paradigm

Treatment	Dose mg/kg orally	Basal reading In seconds	mean time on rotarod after treatment			
			60 min	90 min	120 min	240 min
(2 % gum acacia)	10 ml/kg	60	60	60	60	60
Diazepam	3	60	47.41±1.02*	40.21±0.74*	23.18±1.23*	32.69±1.29*
Piperine	10	60	59.75±0.25	60	60	60
Diazepam +Piperine	3 +10	60	40.78±0.83*†	33.87±2.37*†	16.12±1.36*†	24.74±1.22*†

One way ANOVA followed by multiple tukey's comparison test., Values are mean±SEM. df = 3, 28, *P<0.05, compared to control group, †P<0.05, compared to standard (diazepam) group.

Table 5: The effect of piperine, sertraline and their combination on immobility period in TST

Treatment	Dose (mg/kg) orally	Immobility period (seconds)
Control (2 % gum acacia)	10 ml/kg	191.96±2.45
Sertraline	5	121.44±4.41 *
Piperine	10	187.65±2.31
Sertraline+Piperine	5+10	76.53±2.68 *,†
One Way ANOVA	F	319.18
	P	<0.001

One way ANOVA followed by multiple tukey's comparison test., Values are n= 8 mean±SEM, df= 3, 28, * P<0.05 with respect to control, † P<0.05 with respect to sertraline

Table 6: The effect of piperine, sertraline and their combination on immobility period in FST

Treatment	Dose (mg/kg) orally X 14 d	Immobility period for 5 min (seconds)
Control (2 % gum acacia)	10 ml/kg	244.74±1.96
Sertraline	5	173.82±3.16 *
Piperine	10	259.51±6.83
Sertraline+Piperine	5+10	125.31±3.03 *,†
One Way ANOVA	F	226.70
	P	<0.001

One way ANOVA followed by multiple tukey's comparison test., Values are n= 8 mean±SEM, df= 3, 28, * P<0.05 with respect to control, † P<0.05 with respect to sertraline

DISCUSSION

In the present study piperine isolated from the piper nigrum extract was studied for CNS activity using several animal models such as MES-induced convulsions, loss of righting reflex, anxiolytic activity, muscle relaxant activity and antidepressant activity. The results indicated that piperine at a dose of 20 and 40 mg/kg has anticonvulsant activity. Apart from that piperine *per se* does not have any significant CNS effect.

Black pepper has been used as a traditional anticonvulsant in China. So we too considered observing its anticonvulsant activity on MES-induced convulsions in mice. The study revealed the reduction in the duration of the hind limb extension and a significant protection (62.5 %) against convulsions. Though it was not as protective as phenytoin and carbamazepine in which 100 % protection was observed. It is also being reported by D'Hooge R *et al.*[24] that intraperitoneal injection of piperine in mice inhibits clonic convulsions induced by kainite. Also, they found that seizure activity induced by L-glutamate, N-methyl-D-aspartate or guanidino succinate was not blunted by piperine.

In view of its, reported bioenhancing effect, we considered to observe the response of piperine along with a subtherapeutic dose of carbamazepine. Carbamazepine was selected for the study since it's a drug with low oral bioavailability [25]. Carbamazepine at a dose of 15 mg/kg completely abolished hind limb extension with 100 % protection, while at a dose of 7.5 mg/kg had no protection against convulsions. Hence, the dose of 7.5 mg/kg (subtherapeutic) was selected to study the combined effect of piperine and carbamazepine. The result showed that the duration of hindlimb extension was reduced to 6.32 seconds, but protection against convulsion was seen in only 25 % of animals *i.e.* only two animals out of eight were protected against convulsions while the rest six

had convulsions. It shows that piperine also enhances the bioavailability of carbamazepine. (table no. 1)

To further explore the mechanism of action of the anticonvulsant effect of piperine, whether there is some role of GABA, the effect of piperine was observed on the righting reflex in rats which was not abolished with the increasing graded dose. Thus, it rules out the role of GABA in the mechanism of anticonvulsant action of piperine. Also in view of enhancing effect the same experiment was repeated in combination with pentobarbitone orally. The pentobarbitone sleeping time was earlier in onset and enhanced in duration (table no. 2). Since piperine is not having any inhibiting effect on GABA, hence the enhanced activity of pentobarbitone could be concluded as bioenhancing effect.

This study is also supported by other experiments where the activity of midazolam (an antianxiety drug) was assessed in the presence of piperine. Elevated plus maze method was used to evaluate the activity of midazolam. The number of entries in open arms, increase preference towards the open arm and time spent in open arm were the criteria for the antianxiety effect. Piperine alone did not produce any change in these parameters. However, piperine significantly enhanced the effect of midazolam. The antianxiety effect of midazolam in the dose of 0.4 mg/kg converted to the sedative effect (the animals became drowsy with the loss of their normal exploratory nature. They remain immobile at the site where they were left). So we reduced the dose of midazolam to 0.2 mg/kg and the same study was repeated in presence and absence of piperine. Midazolam was little less effective in this reduced dose (table no. 3). However, when combined with piperine the effect was nearly equal to 0.4 mg/kg of midazolam. It clearly reflects that there is some bioenhancing effect on midazolam too.

The constant observation of an increase in the effect of various drugs forced us to think over the bioenhancer effect of piperine. This enhancement may be either due to increase in absorption or reduction in metabolism of the drug. Our next experiment gave us an interesting result that the muscle relaxant effect of diazepam, as observed by rotarod method was increased, as suggested by a reduction in maintenance time on rotarod though the total duration of activity was not increased. It reflects that piperine perhaps increases the absorption of diazepam (table no. 4).

In order to take the advantage of bioenhancer effect in reduction of required doses of few more experiments were planned. The antidepressant drug sertraline HCl which is having about 60 % oral bioavailability as compared to fluoxetine that has about 99 % oral bioavailability was taken for the study.

The study was planned on both acute and chronic depressant models in albino mice and rats (tail suspension test and forced swim test respectively table no. 5 & 6). Piperine did not show any individual effect, but when combined with sertraline a significant increase in the immobility period was observed in comparison to sertraline alone. It further reflects that there is some increase in the bioavailability of sertraline.

All the experiments suggested that piperine has bio-enhancing property. There are various studies which suggest that piperine increases the bioavailability of the drugs. The probable mechanisms are, by promoting rapid absorption and by increasing the solubility of the drugs [26]. It enhances the gastrointestinal blood flow as shown by a study done by Annamalai AR *et al.* [27] and stimulates Gamma–glutamyl transpeptidase activity, thereby increasing the uptake of drugs by gastrointestinal epithelium [28].

Another very important mechanism of action of bio-enhancement is by inhibition of drug metabolism by piperine. Piperine has been shown to inhibit different cytochrome P450 isoforms as well as UDP–glucuronyl transferase and other phase II reactions, thus decreasing the metabolism of other drugs [29, 30].

CONCLUSION

Piperine has the potential to be used as a bioenhancer when combined with various drugs where it would reduce the dose of the standard drug and thereby possibly reduce their adverse effects. Piperine also has the potential to provide additional benefits in anticonvulsant therapy, which will immensely be helpful in reducing the adverse effect related to conventional antiepileptic drugs.

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CONFLICTS OF INTERESTS

All authors have none to declare

REFERENCES

1. WHO health report. Mental disorders affect one in four people. Available from: http://www.who.int/whr/2001/media_centre/press_release/en/. [Last accessed on 08 Dec 2015].
2. Centre for Addiction and Mental Health. Mental Illness and Addictions: Facts and Statistics. Available from http://www.camh.ca/en/hospital/about_camh/newsroom/for_reporters/Pages/addictionmentalhealthstatistics.aspx. [Last accessed on 08 Dec 2015].
3. Johri RK, Zutshi U. An Ayurvedic formulation 'Trikatu and its constituents. J Ethnopharmacol 1992;37:85-91.
4. Chun H, Shin DH, Hong BS, Cho WD, Cho HY, Yang HC. Biochemical properties of polysaccharides from black pepper. Biol Pharm Bull 2002;25:1203-8.
5. Dhuley JN, Raman PH, Mujumdar AM, Naik SR. Inhibition of lipid peroxidation by piperine during experimental inflammation in rats. Indian J Exp Biol 1993;31:443-5.
6. Bano G, Raina RK, Zutshi U. Effect of piperine on bioavailability and pharmacokinetics of propanolol and theophylline in healthy volunteers. Eur J Clin Pharmacol 1991;4:615-7.
7. Kokate CK. Textbook of practical pharmacognosy. 4th ed. Vallabh Prakashan, New Delhi; 2003. p. 143.
8. Harry Lawless. Oral chemical irritation: psychophysical properties. Chem Senses 1984;9:143-55.
9. The Merck Index. 12th ed. Merck and Co., Inc., Whitehouse Station, NJ, USA; 1996. p. 1286.
10. Luszczki JJ, Antkiewicz-Michaluk L, Czuczwar SJ. 1-Methyl-1,2,3,4-tetrahydroisoquinoline enhances the anticonvulsant action of carbamazepine and valproate in the mouse maximal electroshock seizure model. Neuropharmacology 2006; 50:133-42.
11. Macdonald RL, Kelly KM. Antiepileptic drug mechanisms of action. Epilepsia 1995;36 Suppl 2:2-12.
12. Dandiya PC, Cullumbine H. Studies on *acorus calamus* (iv): investigations on the mechanism of action in mice. J Pharmacol Exp Ther 1959;126:334.
13. Pellow S, Chopin P, File SE, Briley M. Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 1985;14:149-67.
14. Lister RG. The use of a plus-maze to measure anxiety in the mouse. Psychopharmacology 1987;92:180-5.
15. Löw. Molecular and neuronal substrate for the selective attenuation of anxiety. Science 2000;131:290.
16. McIlwain KL, Merriweather MY, Yuva-Paylor LA, Paylor R. The use of behavioral test batteries: effects of training history. Physiol Behav 2001;73:705–17.
17. Vogel HG, Vogel WH. Drug discovery and evaluation, pharmacological assay. Springer, Berlin; 1997. p. 260-1.
18. Kamei J, Miyata S, Morita K, Saitoh A, Takeda H. Effects of selective serotonin reuptake inhibitors on the immobility time in tail suspension test in streptozotocin-induced diabetic mice. Pharmacol Biochem Behav 2003;75:247-54.
19. Porsolt R, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature 1977;266:730-2.
20. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay R. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 1997;56:131-7.

21. Butterweck V, Nishibe S, Sasaki T, Uchida M. Antidepressant effects of apocynum venetum leaves in a forced swimming test. Biol Pharm Bull 2001;24:848-51.
22. Detke MJ, Lucki l. Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: the effect of water depth. Behav Brain Res 1996;73:43-6.
23. Lucki I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav Pharmacol 1997;8:523-32.
24. D'Hooge R. Anticonvulsant activity of piperine on seizures induced by excitatory amino acid receptor agonists. Arzneim Forsch 1996;46:557-60.
25. Goodman, Gillman. The pharmacological basis of therapeutics. McGraw Hill. 11th edition; 2005. p. 1805.
26. KW Lee, H Everts, AC Beynen. Essential oils in broiler nutrition. Int J Poult Sci 2004;3:738-52.
27. Annamalai AR, Madhavan R. Effects of trikatu and its individual components and piperine on the gastrointestinal tract. Trikatu: a bioavailability enhancer. Indian Drugs 1989;27:595-604.
28. Johri RK, Thusu N, Khajuria A, Zutshi U. Piperine-mediated changes in the permeability of intestinal epithelial cells. Biochemical Pharmacol 1992;43:1401-7.
29. Singh J. Piperine-mediated inhibition of glucuronidation activity in isolated epithelial cells of the guinea-pig small intestine: evidence that piperine lowers the endogenous UDP-glucuronic acid content. J Pharmacol Exp Ther 1986; 236:488-93.
30. Reen RK. Piperine impairs cytochrome P4501A1 activity by direct interaction with the enzyme and not by down-regulation of CYP1A1 gene expression in the rat hepatoma 5L cell line. Biochem Biophys Res Commun 1996;218:562-9.