Journal of Applied Pharmaceutical Science Vol. 4 (09), pp. 077-082, September, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.40914
ISSN 2231-3354 

Evaluation of central nervous system activities of *Citrus maxima* leaf extract on rodents

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ARTICLE INFO

Article history:
Received on: 11/06/2014
Revised on: 17/07/2014
Accepted on: 10/08/2014
Available online: 27/09/2014

Key words:
Antidepressant, *Citrus maxima*, Muscle relaxant, Rotarod, Pentylenetetrazole

ABSTRACT

Citrus maxima is a traditional medicine used to treat astringent, constipation, hypnotic, inflammation and antiseptic. Therefore, we aimed to evaluate central nervous system activities of ethanolic extract of *Citrus maxima* (EECM). Oral administration of 200 and 400 mg/kg of EECM was to the depressant, anxiolytic, convulsant, hypnotic and muscle relaxant experimental animals. In the locomotor test, EECM increased the numbers of rearing, central motor and ambulation were reduced. The number of entries and time spent in the open arm was increased, decreased locomotion in elevated-plus-maze and actophotometer test. EECM protected the mice against the pentylenetetrazole and strychnine induced convulsion in a dose dependent manner. Treatment with EECM ($p<0.01$) reduced the duration of the tonic hind limb extension, increased hypnotics time and decreased motor co-ordination of experimental animals. This study concludes *C. maxima* will be an alternative source for psychiatric and neurological disorders.

INTRODUCTION

In the world, each and every day people achieved a lot and lot at the same time stress also increases from young to old age people. Among these, one of the serious mood disorders is depression which ranked as the fourth leading cause of mortality (10-15%), disability, respiratory problems and life threatening diseases (Murray *et al*., 1997). It is characterized by a downcast mood, loss of pleasure, negative thoughts, disturbed sleep or appetite, low energy and suicidal ideations (Belmaker and Galila, 2008). Depression mainly caused by a deficiency in the level of noradrenalin, 5- hydroxytriptamine and dopamine in the central nervous system of the brain.

Many of the currently available antidepressant drugs have proven to be effective, but they caused adverse side effects like tiredness, fatigue and sexual dysfunction (Dhingra and Sharma, 2006). One-eighth of the total populations suffered from the anxiety psychiatric disorders with a lifetime prevalence of 28.8% (Kessler *et al*., 2005). It is characterized by sympathetic hyperactivity, psychomotor tension and vigilance syndromes. Benzodiazepines and Diazepam are commercially available synthetic drugs for treatment of anxiety disorders, while some of them have adverse side effects such as sedation, changes in body weight, physical dependence and so on (Moreno *et al*., 2014). The persistent difficulty in falling or staying asleep is called Insomnia, which inhibits the day time function and caused physiological disorders. The long term use of benzodiazepines by insomnia patients has limited benefits to elevation effects *viz*., impaired cognitive function, memory loss and lack in day time performance. The major neurological disorder is epilepsy, nearly 5% of the world population affected by these disorders. It is associated with high rhythmic high frequency of impulses discharges by a group of neurons in the central nervous system. Chronic toxicity, teratogenic effects and continues seizures are raised while using the antiepileptic drugs (Mattson, 1995). Researchers and pharmacologists focused their interest towards development of lesser side effect drugs using plant system to overcome the above mentioned problems. Commercial antidepressants are cause number of side effects like distorted vision, increases in body weight, feeling sick, dehydration and anxiety. These adversities are not take place in each patient, only patients have less acceptability the drugs. There are four drug discovery strategies for treatment of depression and anxiety such as neurotransmission, neurogenesis, modulation of stress hormone and genetics (Florian *et al*., 2004). In the ancient period of the world

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have documented number of plant drugs supposed to have central nervous system effect. These information has enhance potential bioactive molecules can be used to develop psychiatric drugs. In fact, almost 25% of commercial drugs *viz.*, ephedrine, d-tubocurarine and galanthamine are derived from plants (Carlini, 2003). At present a less number of herbal medicines approved for clinical use because of its complex chemical composition (Vinayak *et al*., 2012). *Citrus maxima* Merr. (Family: Rutaceae) is a tree act as a principal ancestor of the grape fruit. Traditionally it is known as papanasa and the aerial parts of the leaves used to treat cough, fever, purgative, epilepsy, ulcers and gastrointestinal disorders in Southeast Asia and Philippines (Niyomdham, 1991).

There are reports indicated the presence of β-sitisterol, acridone, essential oil in *C. maxima*. The aim of this study is to provide scientific evidence of *C. maxima* extracts that have been revealed to have therapeutic effects in animal models of psychiatric and neurological disorders.

MATERIALS AND METHODS

Plant Material

Leaves of *Citrus maxima* were collected from Ooty, Nilgiris district, Tamil Nadu, India during the month of January 2011. The plant was identified and authenticated by Botanical Survey of India, Tamil Nadu Agricultural University Campus, Southern Regional Centre, Coimbatore and (Voucher No.: BSI/SRC/5/23/2012-13/Tech) has been deposited in the herbarium for future references.

Extraction

The leaves were washed with double distilled water, shade dried and powered. 500 g of the powdered material of *C. maxima* was extracted with 80% ethanol for 72h in a cold percolation method. After that the solvent was evaporated under pressure using Rota vapour. Final dark green colour residue was used to further experiment.

Drugs and Chemicals

The experimental drugs Imipramine, Strychnine, Pentalenetetrazole were obtained from Loba Chemie (Mumbai, India), Diazepam (Roche, Mumbai, India) and Pentobarbitone (Rhone-Poulenec, Mumbai, India). All other chemicals used were of analytical grade obtained from (Sigma Aldrich, USA).

Experimental animals

Swiss albino mice (18-22g) and Wistar albino rats (180-220g) were used for this study. The animals were procured from Central Animal House, I.R.T. Perundurai Medical College, Tamil Nadu, India. Animals were maintained at 12h light and dark cycle with relative humidity of 30-70%. All animals were fed with pellet diet (M/s. Hindustan Lever Ltd. India) and water. National Institute of Nutrition protocol for experimental animals was followed and approved by the Institutional Animal Ethics Committee (Reg.No.:688/02/NCP/CPCSEA) of Nandha College of Pharmacy and Research Institute, Tamil Nadu, India.

Acute Toxicity Study

Acute toxicity of ethanolic extract of *C. maxima* (EECM) was evaluated according to the method described by an Organization for Economic Cooperation and Development Guideline (OECD) 423 (Ecobichon, 1997). The animals were kept fasting overnight. Initially 5mg/kg oral administration of EECM to the experimental mice and mortality was observed in 4/6 or 6/6 animals for 3 days. However, if the mortality was found in 1/6, then the dose was increased 50, 300, 500, 1000, and 2000mg/kg b.wt. Control mice were given 10 ml/kg of water. Behavioural changes and mortality of experimental mice were observed for 24 h. After that, continued observations were composed on the 14th day.

Treatment Schedule

24 animals were subdivided into four groups of 6 animals each. Group 1, served as control, treated with 0.5% Carboxy methyl cellulose (CMC) solution (10 ml/kg); Group 2 treated with Diazepam (1 mg/kg); Group 3 and 4 treated with ethanolic extract of *Citrus maxima* (EECM) by doses of 200 and 400 mg/kg respectively. The drugs were administered orally by suspension in 0.5% CMC 30 min before the initiation of the experiment. Forced swim test Imipramine (20 mg/kg) was used as the standard drug.

ANTIDEPRESSANT ACTIVITY

Forced Swim Test

Forced Swim Test is most widely used pharmacological model for assessing antidepressant effect of bioactive substances. The test was carried out with slight modification of Porsolt *et al*. (1977) for rats. The rats were kept in the Plexiglas cylinder (50cm high×20cm wide) for 15 min, 24h prior to the 5 min swim test. EECM (200 and 400 mg/kg), imipramine (20 mg/kg) was administered thrice immediately after 15 min, 6 and 0.5 h prior to the swimming test. During the swimming test climbing, swimming and immobility behavioral responses were recorded. Increases in behavioral responses are considered as an antidepressant effect (Cryan *et al*., 2002).

Tail Suspension Test

In the TST model, the experimental rats administered with 200 and 400mg/kg of EECM were placed on edge of the table and marked a 1cm line on the tail from tip. Any changes in their immobility where notify for 0 to 6 min period. The decreased in their immobility time with respect to vehicle treated group was also calculated (Steru et al., 1985).

ANXIOLYTIC ACTIVITY

Light-Dark Box Test

The light/dark method testing apparatus were used to assess the anxiolytic activity of experimental animals administered with 200 and 400 mg/kg of EECM. When placed in the apparatus, the mice can travel between the compartments and notified how much time spent up to 5min (Zanoli *et al*., 2000).

Elevated Plus Maze

The elevated plus maze test is the most extensively used of all currently accessible animal models of anxiety that depend upon the study of spontaneous behavior. After treatment with EECM (200 and 400 mg/kg), the animals were placed in the centre of the elevated plus maze and noticed the number of open and closed arm entries and time spent on open and closed arm in the mice (Herrera *et al*., 2007).

Loco Motor Activity

After pre treatment with 200 and 400 mg/g of EECM, standard drug the experimental rats were placed in the Actophotometer for 10 min and the number of counts were recorded. Based on the light falling on the photocell, the increase or reduction in the motor activity was determined.

Hole-Board Test

The poking of the nose into a hole is the usual behavior of mice indicating the definite degree of curiosity. The equipment composed of a gray box (50 cm x 50 cm x 50 cm) with four equidistant holes 3 cm in diameter in the floor. After treatment with EECM (200 and 400 mg/kg), each animals were placed in centre of hole-board and watched the number of head dips with in 5 min were analyzed by visual examination (Byung *et al*., 2007).

ANTI CONVULSANT ACTIVITY

Pentylenetetrazole induced Convulsions

Pentylenetetrazole induced seizure brushwood in rodents was considered a model of human absence epilepsy and myoclonic seizure. Pentylenetetrazole (95mg/kg) was administered subcutaneously to induce convulsion. EECM (200 and 400mg/kg) was given orally 30min prior to the administration of Pentylenetetrazole. After treatment, the animals were noticed for duration of convulsion induced by Pentylenetetrazole were recorded (Amabeoke *et al*., 2007).

Strychnine induced Convulsions

The convulsing exploitation of strychnine is due to interferences with post synaptic inhibition mediated by glycine. The extract has quash the action of strychnine and exposed to have anxiolytic property (Vogel *et al*., 2002). Strychnine (2mg/kg) was administered intramuscularly to induce convulsion. EECM (200 and 400 mg/kg) was given orally 30 min prior to the administration of strychnine. After treatment the animals were observed for a period of convulsion induced by strychnine was recorded (Yemitan *et al*., 2005).

Electro-Shock Induced Seizure Model

The electroshock attempt in mice is primarily used as a sign for extracts in grand mall epilepsy. EECM (200 and 400 mg/kg) was administered orally to the animal 60min prior to the electro shock. The electro shock induced in animals through passing a current of 45 mA for 0.2 sec duration through electro convulsio meter (Techno, India) using corneal electrodes. Followed by the treatment animals were noticed for the incidence and duration of extensor tonus was noted (Achliya *et al*., 2005).

HYPNOTIC ACTIVITY

Pentobarbitone induced Sleeping Time

In the present study, single dose of pentobarbitone was used for the induction of sleeping in experimental animals. After treatment, the effects of EECM (200 and 400mg/kg) was recorded as follows: time beyond among the administration of pentobarbitone until loss righting reflex the sedative action was recorded as the time from the lose to its revival was measured as the duration of sleep (Herrera *et al*., 2007).

MUSCLE RELAXANT ACTIVITY

Rotarod Method

Rotarod test is used to evaluate the activity of EECM (200 and 400mg/kg) interferes with motor coordination. The equipment consists of a horizontal metal rod covered with rubber to 3cm diameter attached to a motor with speed accustomed to 2rotations/min.

The 75cm rod is partitioned with 6 sections using plastic discs, it facilitate the concurrent testing of six animals. Cages were provided below the sections for prevent the movement of experimental animals. The number of animals falling from the roller during this time was counted (Achliya *et al*., 2005).

Climbing Test

The mice were formed to climb a chain of (6cm long) floating from a clamp of a retort stand (100cm above ground). Only those mice that climb the chain within 10sec were selected for the test. After treatment with EECM (200 and 400mg/kg), experimentation took place for 10min, the climbing capability was observed (Salahdeen *et al*., 2006).

Inclined Screen Test

The inclined plane test is to determine the skeletal muscle relaxant activity (Vogel *et al*., 2002). The Plane consists of transparent glass were left on an inclined at 30 ºC. The mice, try to move out of the plane glass without sliding off, were used for the test. The investigation was made at 15-30 min intervals, subsequent to the oral administration of EECM (200 and 400 mg/kg). The mice were kept in the superior part of the inclined plane and are given 30sec to hang on or to fall off (Salahdeen *et al*., 2006).

RESULT

Acute Toxicity Studies

EECM did not produce any mortality orally up to 2000mg/kg was observed for 5h after administration. There were not any visible signs of delayed toxicity and mortality observed for 14 days.

Table 1: Antidepressant activity of EECM using Forced Swim Test and Tail Suspension Test.

Group	Forced Swim Test			Tail suspension test
	Immobilization time (sec)	Swimming time (sec)	Climbing counts (numbers)	Immobility time (seconds)
Control (0.5% CMC)	240.57±1.46	129.96±0.89	8.25±0.06	171.87±1.68
Imipramine (1mg/kg)	178.93±1.63*	219.61±1.79*	4.11±0.05*	106.12±0.23*
EECM (200mg/kg)	212.46±3.18**	187.09±1.19**	6.19±0.05**	144.14±0.36**
EECM (400mg/kg)	196.81±0.98**	204.08±1.26**	5.22±0.20**	141.79±0.57**

The data represent the mean±SD (n = 6). $*P$ <0.05, $**P$<0.01 significantly different compared to normal control

Table 2: Anxiolytic activity of EECM (a) Light-Dark Box Test and Elevated Plus Maze.

Group	Light-Dark Box Test		Elevated Plus Maze			
	Time spent in light (sec)	Time spent in dark (sec)	Entries in open arm (sec)	Time spent in open arm (sec)	Entries in closed arm (sec)	Time spent in closed arm (sec)
Control (0.5% CMC)	110.33±1.37	189.67±1.37	3.07±0.03	71.07±0.70	11.38±0.29	219.73±9085
Diazepam(1mg/kg)	180.33±1.63*	119.67±1.63*	12.09±0.08*	272.62±4.212*	2.11±0.05*	50.12±0.22*
EECM (200mg/kg)	166.17±3.45**	133.83±3.48**	9.73±0.13**	230.15±1.36**	4.57±0.16**	122.29±2.97**
EECM (400mg/kg)	174.67±2.66**	125.33±2.66**	11.25±0.27**	242.42±0.84**	4.08±0.03**	60.44±0.51**

The data represent the mean±SD (n = 6). $*P$ <0.05, $**P$<0.01 significantly different compared to normal control

Antidepressant Studies

In the case of group 2, Imipramine (1mg/kg) serotonin re-uptake inhibitor markedly decreased the immobility time. The reduced immobility time and increased climbing behavior were observed significantly (p<0.01) in EECM treated rats. In the TST model, duration of immobility was decreased in (106.12±0.23) group 2 and (141.79±0.57) group 3 rats Compared to the control (Table 1). The 400 mg/kg of EECM showed potential antidepressant activity.

Anxiolytic Studies

Light - dark test measures was summarized in Table 2. Diazepam (1mg/kg) and EECM (200 and 400mg/kg) significantly increased time spent in light arena 166.17±3.45 and 174.67±2.66, in dark 133.83±3.48 and 125.33±2.66. The number of crossings was considerably increased in Diazepam (1 mg/kg), EECM (400 mg/kg) compared to control group (p<0.01). Treatment with EECM (200 and 400 mg/kg) to the rats causes the significant (P<0.01) increases in the frequency of the open arm entries (Table 3). Significant and dose dependent increase in the duration of time spent in the open arm were observed in EECM (200 and 400 mg/kg) treated rats. Extract at doses of 200 and 400 mg/kg produce a low number of entries in the closed arm, while control (10 ml/kg) had the highest closed arm entry value of 11.38±0.29. The effects of EECM (200 and 400 mg/kg) and diazepam resulted in significant increases in the total number of entries into the two arms. In the hole board test, there was a significant decrease in the number of head dips 13.12±0.04 of Diazepam (1 mg/kg), EECM (400 mg/kg) compared to control 2.07±0.03 to 6.25±0.07 (Table 3).

Anticonvulsant Studies

Pentylenetetrazole produced tonic seizures animals treated with EECM the dose of 200 and 400mg/kg protected 22.84 0.41 and 20.30 ±0.17 of the mice against seizures and significantly (P<0.01) increased the latency of the seizures. Strychnine elicited convulsions rats treated with 200 and 400mg/kg of EECM seizures from 50.75±0.25 in control to 22.55 ±0.32 and 20.23 ±0.10s, respectively and showed dose dependent increase in the anticonvulsant activity. Similarly, Diazepam 5 mg/kg pre treatment significantly (P < 0.05) increased the latency of strychnine induced seizures from 55.25±0.50 s to 14.28 ±0.20 with 100% protection. In the Maximal electroshock model, administration of EECM (200-400 mg/kg) showed a dose dependent increase in the delay of the onset time of seizures induced by maximal electroshock induced convulsion and also decreased duration of tonic hind limb extension (Figure 1).

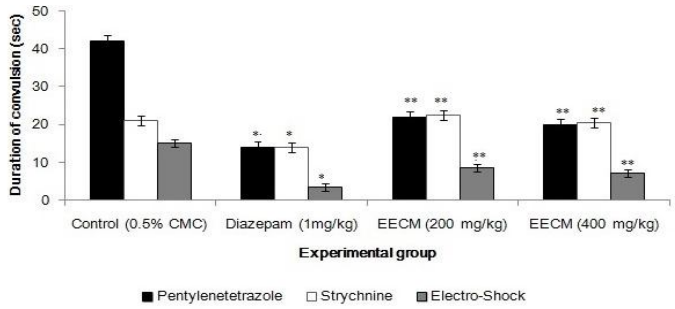

Fig. 1: Effect of oral administration of EECM on convulsion time in experimental animals. $*P$< 0.05 and $**P$ < 0.01 indicate significant difference from control.

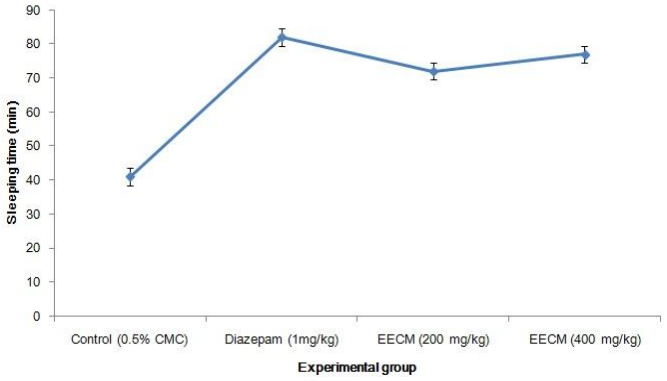

Fig. 2: Effect of oral administration of EECM on sleeping time in experimental animals.

Table 3: Anxiolytic activity of EECM using locomotor and Hole Board test.

Group	Locomotor		Hole Board	
	Rearing (numbers)	Crossing (numbers)	Head dips (numbers)	
			(30 min)	(60 min)
Control (0.5% CMC)	19.57±0.07	47.24±0.42	3.11±0.03	2.07±0.03
Diazepam(1mg/kg)	26.30±0.42*	59.04±0.31*	11.10±0.04*	13.12±0.04*
EECM (200mg/kg)	20.76±0.06**	49.59±0.29**	4.84±0.07**	5.35±0.05**
EECM (400mg/kg)	21.35±0.17**	51.24±0.11**	5.12±0.05**	6.25±0.07**

The data represent the mean±SD (n = 6). $*P$ <0.05, $**P$<0.01 significantly different compared to normal control

Table 4: Muscle Relaxant activity of EECM by Rotarod Method

Group	Time Taken To Fall (Min)				
	0 min	30 min	60 min	90 min	120 min
Control (0.5% CMC)	178.16±0.19	178.15±0.29	177.65±0.42	177.47±0.09	175.41±0.11
Diazepam(1mg/kg)	177.30±0.28*	35.16±1.26*	50.34±0.05*	92.34±0.22*	98.58±0.34*
EECM (200mg/kg)	175.30±0.20**	136.99±0.33**	150.57±0.37**	115.56±0.42**	131.03±0.16**
EECM (400mg/kg)	175.52±0.08**	130.41±0.38**	124.95±0.62**	99.05±0.14**	101.90±0.18**

The data represent the mean±SD (n = 6). $*P$ <0.05, $**P$<0.01 significantly different compared to normal control

Table 5: Muscle Relaxant Activity of EECM by Climbing and Inclined screen test

Group	**Time taken for climbing (Sec)**		
	Climbing test		**Inclined screen test**
	30min	**60min**	
Control (0.5% CMC)	8.09±0.02	33.02±0.24	8.22±0.02
Diazepam(1mg/kg)	18.19±0.12*	20.17±0.08*	21.20±0.44*
EECM (200mg/kg)	12.84±0.06**	28.38±0.29**	20.62±0.32**
EECM (400mg/kg)	14.71±0.05**	25.36±0.17**	14.81±0.06**

The data represent the mean±SD (n = 6). $*P$ <0.05, $**P$<0.01 significantly different compared to normal control.

Hypnotic Studies

The oral treatment of mice with EECM (200-400mg/kg) significantly increased duration of the hypnosis was showed in figure 2.

Muscle relaxant Studies

The standard drug Diazepam (p<0.05) and 400 mg/kg of EECM (p<0.01) treated animals reduced their time spent in the rota rod model. The results of climbing test indicated the time taken to climb the chain was also found to be delayed in the EECM treated groups than the control (Table 4). Treatment with EECM at a dose of 200 and 400 mg/kg and Diazepam decreased sliding time of experimental animals compared with the control group (Table 5). The 400 mg/kg of EECM showed potential muscle relaxant activity than compared to 200 mg/kg.

DISCUSSION

Number of ayurvedic medications pointed out the use of plant origin drug formulations played a vital role in the treatment of psychiatric disorders (Sembulingam *et al*., 1997). In the present study, the ethno medicinally valuable plant species *C. maxima* has been evaluated for its latent pharmacological effect on psychiatric and neurological disorders. The experimental rats administrate with EECM developed immobility while they suspended their tail during TST and placed in an inescapable cylinder of water using FST model, it reflects the termination of their escape behavior and showed as potential antidepressant agents. In the case of *in vivo* pharmacological studies, the experimental animals whenever subjected to mysterious environment exhibits a rigorous form of behavioural inhibition, termed as anxiety. The use of plant extracts for psychiatric and neurological disorders which might be directly or indirectly regulate the central nervous system and neuro-transmitter activity was reported (Dhawan *et al*., 2003; Magaji *et al*., 2014).

In this concern, oral administration of EECM had shown a significant increase in open arm entry and time spent in the open arm in a dose dependent manner using the elevated plus maze apparatus. Selective competitive antagonist strychnine, it blocks the inhibitory effect of glycine amino acids at all receptors (Ishola *et al*., 2013). The EECM treated experimental animals increased the seizures onset significantly in a dose dependent manner which reflects its anticonvulsant activity. Similarly, ethanolic extracts were reported to reduce the hind limb extension and duration of convulsion than compared to standard drug phenytoin and diazepam (Shivakumar *et al*., 2009). EECM nearer to the action of Diazepam which belongs to benzodiazepine group, it has a binding site on the GABA receptor type ionophore complex and decreases the activity (Huang *et al*., 2007). At a dose of 400 mg/kg of EECM showed highly significant skeletal muscle relaxant activity at 60min of duration by climbing test. It might be explained by the action of alkaloids, beta sterols and essential oils. The ethanolic extract of *C. maxima* had vital central nervous system activity than compared to the aqueous extract (Potdar and Kibile, 2011). Earlier reports pointed out the necessity of *In silico* docking of plants ligands against target molecules, will reduce the use of animals and economic expenses (Manigandan and Ramanathan, 2014).

CONCLUSION

We conclude the potentiality of *C. maxima* will be an alternative source for psychiatric and neurological disorders.

Further studies will determine bioactive compound responsible for the mechanism of action of *C. maxima* using *in silico* and clinical models.

ACKNOWLEDGEMENTS

The authors thank to the Principal, Nandha College of Pharmacy and Research Institute and BioMed Research Management Services, Tamil Nadu, India for providing the necessary support.

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How to cite this article:

Haja Sherief Sheik, Niraimathi Vedhaiyan, Sengottuvelu Singaravel. Evaluation of Central Nervous System Activities of *Citrus maxima* Leaf Extract on Rodents. J App Pharm Sci, 2014; 4 (09): 077-082.