Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Suppl 4, 2011

Research Article

ANTICONVULSANT POTENTIALS OF *SESAMUM INDICUM* AND *ALLIUM SATIVUM* OIL ALONE AND IN COMBINATION IN ANIMAL MODELS

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Received: 5 May 2011, Revised and Accepted: 11 June 2011

ABSTRACT

Sesamum indicum and *Allium sativum* oil which has been used as an antiepileptic remedies in Chhattisgarh region was evaluated for anticonvulsiot activity against experimental seizures in mice. *S. indicum* (10mg/kg), *Allium sativum* oil (10 mg/kg) and combination of (*S. indicum* and *A. sativum*, 1:1, 10ml/kg) were significantly reduced the locomotion and rearing after 60 minutes. *S. indicum* oil and *A. sativum* oil did not produced motor impairment in the wire hanging test and catalepsy test.

S. indicum (10mg/kg), *Allium sativum* oil (10 mg/kg) and combination of (*S. indicum* and *A. sativum*, 1:1, 10ml/kg) was significantly reduced ($p<0.002$) the duration of tonic hind limb extension produced by MES. Only combination of both oil was able to significantly ($p<0.002$) reduced the latency to death induced by the strychnine. *S. indicum* oil was only affective against PTZ induced seizure and both oil separately and in combination were effective against the lithium + pilocarpine induced seizure ($p<0.004$)

It was concluded that combination of *S. indicum* and *A. sativum* oil was affective against experimental induced convulsion.

Keywords: Epilepsy, Sesamum indicum, Allium sativum, Single and Compound formulation

INTRODUCTION

Traditional medicinal practices have remained as a component of health care system of many societies in spite of the availability of well established alternatives. The alternative drug therapy for the management of this disease can be by the use of medicinal plants and their active principles[1]. *Sesamum indicum* Oil is extract from the plant *Sesamum indicum*, family: Pedaliaceae[2]. *Sesamum indicum Oil* offers protection over blood pressure, lipid profiles and lipid peroxidation in hypertensive patients[3]. *Sesamum indicum* Oil attenuates oxidative stress and multiple organ failure triggered by endotoxin lipopolysaccharide in rats[4]. Sesamin and sesaminol are the major phenolic constituents of *Sesamum indicum* Oil which have been reported to possess a broad spectrum of pharmacological effects including antimutagenic[5], antioxidant[6,7,8], antihypertensive[9], anti-inflammatory[8] and antithrombotic[10]. Sesame is a source of edible oil and provides a nutritious food for humans. *Sesamum indicum o*il is especially stable because of the presence of sesamin, sesamolin, sesaminol, sesamel, g-tocopherol[11];

Sesamum indicum Oil, is used to increase resistance to lipid peroxidation and to protect against multiple organ injur[12,13]. *Sesamum indicum* oil consists of various fatty acids and nonfat antioxidants, including 3, 4-methylenedioxyphenol (sesamol). Sesamol decreases lipid peroxidation and protects against organ injury in a septic model[14]. Although sesamol potently reduces oxidative stress and attenuates Fe–NTA-induced hepatocyte damage in vivo[15] and ex vivo[16], its effect on Fe–NTA induced kidney injury is unclear.

Essential oils are an example of natural (biological) compounds which when used in synergy with antimicrobial agents may increase the efficacies of these therapeutic agents[17]. Allicin, one of the volatile sulfur oil compounds from freshly crushed garlic (*Allium sativum*), has a variety of antimicrobial activities[18]. Allicin has been shown to reduce the concentrations of beta lactam antibiotics required for inhibiting the growth of Staphylococcus spp. And Pseudomonas aeruginosa[19] and also has antifungal activity against fungi[20]. Allitridium (diallyl trisulphide) as a popular breakdown product from allicin has been shown to have both in vitro and in vivo antifungal activity[21]. Another allicin derivative with antifungal activity against *Aspergillus Niger* and *Candida albicans* is ajoene[22], Epidemiological studies have associated the consumption of high amounts of garlic with substantial reductions in cancer[23]. *Allium sativum* is one of the world's oldest medicines and has been employed not only for flavouring but also as a medical herb due to its diverse biological activities, including antiatherosclerotic, anticarcinogenic and antioxidant effects[24,25]. Garlic is composed mainly of fructose containing carbohydrates and sulfur compounds.

Allium sativum has been found to have a wide range of medicinal properties ranging from antibacterial to anticancer effects[26]. It has hypolipidemic[27], antithrombotic[28] and antiatherosclerotic[29] properties. Therefore, in present investigations attempts were made to evaluated for anticonvulsiot activity against experimental seizures in mice by *Sesamum indicum* and *Allium sativum* alone and in combination to prove ethnomedicinal background as therapeutic potentials.

MATERIAL AND METHODS

Oil of *Sesamum Indicum* and *Allium Sativum* (Fame Drugs Meerut.), obtained from the local market of Bhopal.

Animals for experiment:

Swiss albino mice were obtained from animal house of Pinnacle Biomedical Research Institute. The experiment was conducted as per the permission of Institutional animal ethical committee (IAEC) of PBRI (Reg No. 1283/c/09/CPCSEA).

Toxicity study

The oil of garlic *(GO)* (*Allium Sativum*) and oil of til (SO) (*Sesamum Indicum*) were found to be safe up to the dose of 10 ml/kg. The medial lethal dose of both oil were not carried out because according to USFDA the folklore formulation s are safe and there is no necessity to chek the medial lethal dose.

Locomotion and rearing

The effect of *Sesamum indicum* oil and *allium sativum* oil on locomotion and rearing was studied in an open field as described earlier (Sakina and Dandiya, 1990). The apparatus consisted of a box, made up of plyboard (25×25×12 in.), with 16 squares drawn on the floor. The number of rearings and the number of squares traversed by the animal were recorded for 5 min before and one hour after the administration of the 10ml/kg of *Sesamum indicum* oil and *Allium sativum*. Chlorpromzine (10 mg: kg i.p.) was used as a standard drug for comparison. (Kasture et al 2000)

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minute prior to the experiment.

Group B: Received 10 ml/kg of *Sesamum Indicum* oil 60 minute prior to the experiment.

Group C: Received 10 ml/kg of test *Allium Sativum* 60 minute prior to the experiment.

Group D: Received 1:1, 10 ml/kg of combination of *Sesamum Indicum* oil and *Allium Sativum* oil 60 minut prior to the experiment.

Group E: Received 10 mg/kg of chlorpromazine ip (Standard drug) 30 minut prior to the experiment.

Then mice was allowed to explore in the apparatus, the no. of line crossing and raring done by the animal was noted as locomotor activity in all the groups.

Inverted screen test

The inverted screen test was used to assess the motor toxicity of *Sesamum indicum* oil and *allium sativum* oil. This test was an adaptation by Ginski and Witkin (1994) of that initially described by Coughenour et al. (1977). In this test, compounds with sedative and/or ataxic properties produce a dose dependent increase in screen test failures, whereas other classes of drugs (e.g., psychomotor stimulants) do not (Kasture 2002).

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minut prior to the experiment.

Group B: Received 10 ml/kg of *sesamum indicum* oil 60 minute prior to the experiment.

Group C: Received 10 ml/kg of test *allium sativum* 60 minut prior to the experiment

Group D: Received 1:1, 10 ml/kg of combination of *sesamum indicum* oil and *allium sativum* oil 60 minut prior to the experiment.

Group E: Received 10 mg/kg of diazepam 1 mg/kg ip (Standard drug) 30 minut prior to the experiment.

Then the mice is allowed to explore on the screen after slowly inverting the screen through an angle of 180^0C, the mice were tested during a 2-min trial for their ability to climb to the top, in all the groups.

Wire Hanging Test.

The wire hanging test is a simple approach used to measure neuromuscular ability (muscle tone and grip strength) of a rodent by assessing the animal's ability to hang suspended by its forepaws from a 2mmwire 30 cm above a sawdust covered surface for amaximum time of 1 min (Insel, 2001; Ogura et al., 2001). This method likewise evaluates motor coordination by noting the ability of the animal to recruit its hind limbs and tail in order to grip the wire (Freitag et al., 2003). Latency to fall was measured from the time a mouse was placed hanging by its forepaws on the wire until it fell.The test was performed twice for each mouse with results from each mouse being averaged and data analyzed by one-way ANOVA with a Bonferroni post hoc test. In addition, whether a mouse was able to grip the wire with its hind limbs was also noted with data analyzed by One way ANOVA and multiple comparission with Dunnetts test. (Ezzat Hashemi et al 2007).

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minute prior to the experiment.

Group B: Received 10 ml/kg of *sesamum indicum* oil 60 minute prior to the experiment. **Group C**: Received 10 ml/kg of test *allium sativum* 60 minut prior to the experiment.

Group D: Received 1:1, 10 ml/kg of combination of *sesamum indicum* oil and *allium sativum* oil 60 minut prior to the experiment.

Group E: Received 10 mg/kg of diazepam 1 mg/kg ip (Standard drug) 30 minut prior to the experiment.

Assessing the animal's ability to hang suspended by its forepaws from a 2mm wire 30 cm above a sawdust covered surface for a maximum time of 1 minute in all groups.

Catalepsy test

Catalepsy in laboratory animals is defined as a failure to correct an externally imposed posture. When a normal animal is placed in an unusual posture, it will change its position within seconds. However, a cataleptic animal will maintain this posture for a prolonged period of time. The typical catalepsy test consists of placing an animal into an unusual posture and recording the time taken to correct this posture. The time is regarded as an index of the intensity of the catalepsy (Sanberg et al., 1988).

Group A: Served as a control and received vehicle (distilled water) of dose 10 ml/kg of orally 60 minute prior to the experiment.

Group B: Received 10 ml/kg of *sesamum indicum oil* 60 minute prior to the experiment.

Group C: Received 10 ml/kg of test *allium sativum* 60 minut prior to the experiment.

Group D: Received 1:1, 10 ml/kg of combination of *sesamum indicum* oil and *allium sativum* oil 60 minut prior to the experiment.

Group E: Received 10 mg/kg of chlorpromazine 10 mg/kg ip (Standard drug) 30 minut prior to the experiment.

Then animal's forepaws were gently put on the bar and the time it took the animal to place at least one paw on the floor was measured, in all the groups.

Assessment of Anticonvulsant Activity

Maximum Electric Shock Test

The vehicle,*Sesamum indicum* oil, *allium sativum* oil (10 ml/kg oral), combination of *Sesamum indicum* oil and *allium sativum* (1:1, 10 ml/kg oral) and phenytoin (100 mg/kg ip) was administered in dose to groups of mice, each containing six mice, after one hour, a current stimulus (45 mA for 0.2 s) was delivered using ear pinna electrode to the vehicle, *Sesamum indicum* oil, *allium sativum* oil treated group, and after 30 minute to the phenytoin treated group. The incidence and duration of tonic hindleg extension were noted (Kasture et al 2002). Phenytoin (100 mg/kg ip) was used as a reference standerd.

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minute prior to the experiment.

Group B: Received 10 ml/kg of sesamum indicum oil 60 minute prior to the experiment.

Group C: Received 10 ml/kg of test allium sativum 60 minut prior to the experiment.

Group D: Received 1:1, 10 ml/kg of combination of allium sativum oil and sesamum indicum oil 60 minut prior to the experiment.

Group E: Received 10 mg/kg of chlorpromazine 10 mg/kg ip (Standard drug) 30 minut prior to the experiment.

The incidence and duration of tonic hindleg extension were noted, in all the groups.

Lithium + pilocarpine induced seizures

The effect of *Sesamum indicum* oil and *allium sativum* oil on the seizures induced by lithium **+** pilocarpine was studied in mice, each group containing six. The severity of convulsions was assessed, till the maximum effect was produced, using the following stages as suggested by Patel et al. (1988). No response, stage 0; fictive scratching, stage 1; tremors, stage 2; head nodding, stage 3; forelimb clonus, stage 4; rearing, falling and clonus, stage 5. (Kasture et al 2000)

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minute prior to the experiment.

Group B: Received 10 ml/kg of sesamum indicum oil 60 minute prior to the experiment.

Group C: Received 10 ml/kg of test allium sativum 60 minut prior to the experiment.

Group D: Received 1:1, 10 ml/kg of combination of allium sativum oil and sesamum indicum oil 60 minut prior to the experiment.

Group E: Received 10 mg/kg of chlorpromazine 10 mg/kg ip (Standard drug) 30 minut prior to the experiment.

The latency of stage 4, raring and falling was noted, in all the groups.

PTZ-induced seizures:

The vehicle, *Sesamum Indicum* oil, *Allium Sativum* oil was administered in dose (10 ml/kg oral) and combination of *Sesamum Indicum* oil, *Allium Sativum* (1:1, 10 ml/kg) to groups of mice, each group containing six, The onset of clonic convulsions and percentage protection in each group were noted. (Kasture et al 2002).

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minute prior to the experiment.
Group B: Received 10 ml/kg of *sesamum indicum* oil 60 minute prior to the experiment.
Group C: Received 10 ml/kg of test *allium sativum* 60 minut prior to the experiment.
Group D: Received 1:1, 10 ml/kg of combination of *sesamum indicum* oil and *allium sativum* oil 60 minut prior to the experiment.
Group E: Received 10 mg/kg of chlorpromazine 10 mg/kg ip (Standard drug) 30 minut prior to the experiment.

The onset of clonic convulsions and percentage protection in each group were noted.

Strychnine induced convulsions

Strychnine induced convulsions (Swinyard et al., 1952). The vehicle sesamum indicum oil, allium sativum oil,in the dose of 10 ml/kg oral, combination of both oil in the dose of 1:1,10 ml/kg oral and diazepam 2 mg/kg ip was administered to groups of mice, each containing six, 60 min before administration of strychnine (1.2 mg/kg sc) and 30 minut befor in case of diazepam. The latency to convulsion, latency to death, and percentage protection were recorded.(Kasture et al 2002)

Group A: Served as a control and received vehicle (normal saline) of dose 10 ml/kg of orally 60 minute prior to the experiment.

Group B: Received 10 ml/kg of sesamum indicum oil 60 minute prior to the experiment.

Group C: Received 10 ml/kg of test allium sativum 60 minut prior to the experiment.

Group D: Received 1:1, 10 ml/kg of combination of allium sativum oil and sesamum indicum oil 60 min. prior to the experiment.

Group E: Received 10 mg/kg of chlorpromazine 10 mg/kg ip (Standard drug) 30 minut prior to the experiment.

The latency to convulsion, latency to death, and percentage protection were recorded.

RESULTS

Locomotion and rearing

The number of ambulations and no of rearing at 0 min and after 60 min, in all the groups are shown in table no.1

Table 1:

Group	No.of ambulation (mean±SEM)		No. of rearing(mean±SEM)	
	0 (min.)	60 (min.)	0 (min.)	60 (min.)
Vehical	246.5±31.62	143.7±58.66	24.5±3.128	26.83±3.4
sesamum indicum	187±18.48	41.86±17.09[b]	22±3.751	15.33±4.006[d]
allium sativum	185.3±16.28	64.57±26.36[b]	26.83±4.556	14.5±2.814[d]
combination	231.3±16.49	51.75±21.13[b]	25±3.022	15.17±2.971[d]
Diazepam	261.2±14.3	10.86±4.432[b]	30.67±1.498	6.667±1.43[d]

[a]*P*<0.044 ambulation before treatment as compare to vehicle
[b]*P*< 0.005 ambulation after treatment as compare to vehicle
[c]*P*< 0.464 raring before treatment as compare to vehicle
[d]*P*< 0.002 raring after treatment as compare to vehicle
(one way ANOVA followed by Dunnetts)

Wire hanging test

When *sesamum indicum* oil, *allium sativum* oil, and combination of *sesamum indicum* oil, *allium sativum* oil was investigated for its motor coordination activity (table) it was discovered that the *sesamum indicum* oil, *allium sativum* oil, and combination of *sesamum indicum* oil, *allium sativum* oil was having nonsignificant activity at 10 ml/kg dose as compared to vehicle treated group (P<0.011). Significant activity was observed for diazepam only as at 1 mg/kg dose as compared to vehicle treated group (P<0.011) , as shown in TABLE 2.

Maximum Electric Shock Test

The *sesamum indicum* oil, *allium sativum* oil, and combination of *sesamum indicum* oil, *allium sativum* oil was having significant activity (TABLE NO.3) at 10 ml/kg dose as compared to vehicle treated group (P<0.002). Significant activity was also observed for phenytoin as at 100 mg/kg dose as compared to vehicle treated group (P<0.002).

Strychnine induce convulsions in mice:

After receiving strychnine (1.2mg/kg ip) all mice exhibited clonic convulsions. In the vehicle treated group, strychnine induced convulsions were observed after 368.5±12.1 seconds. Both oil (*Sesamum indicum* oil and *Allium Sativum* oil,) separately failed to inhibit strychnine induced seizure and only combination of both oil (*Sesamum indicum* oil and *Allium Sativum* oil, 1:1, 10ml/kg) 520.3±50.38 (**P*<0.002) and diazepam (2mg/kg) inhibited the convulsions induced by strychnine, 337±18.7 (**P*<0.002). The observations are given in TABLE N0.4.

PTZ induced convulsion in mice

Administration of PTZ (80 mg/kg sc) to mice produced clonic convulsions in all animals and the onset of such convulsions in the vehical treated group was 209.3±5.097 s. Prior administration of *Sesamum indicum* oil (10 ml/kg oral) and diazepam (80mg/kg) delayed clonic seizures to 418.5±87.85 and 579.5±81.79 respectively (TABLE 5). Garlic oil and combination of both oil (*Sesamum indicum* oil and *Allium Sativum* oil, 1:1, 10ml/kg) were unable to delay the seizures.

Litium+pilocarpine induced seizure in mice

Administration of pilocarpine (30 mg/kg i.p.). four hour after the injection of lithium sulphate (3 meq/kg i.p.) produced a time-dependent increase in the severity of seizures. *Sesamum indicum* oil (10 ml/kg) 3066±51.63, *Allium Sativum* oil (10 ml/kg) 3074±102.2, combination of both oil (*Sesamum indicum* oil and *Allium Sativum* oil, 1:1, 10ml/kg), 3448±317 and diazepam (0.5mg/kg) 3483±43.65 effectively delayed the onset of seizures and also reduced the severity of seizures as compare to vEhical treated group (Table 6). The Stage 4, i.e., forelimb, clonus was observed only in the vehicle-treated group after 1844±526.8s and not in any group that received the compound. Diazepam (2 mg/kg) inhibited the seizures completely.

B. S. indicum oil and *A. sativum* oil did not produced motor impairment in the wire hanging test and catalepsy test.

Table 2:

Group	Dose	No. of animal	Duration of hung (mean±sem)
Vehicle	10 ml/kg	6	131.8±21.63
Sesamum indicum	10 ml/kg	6	114.7±8.578
Allium sativum	10 ml/kg	6	121.8±27.16
Combination	10 ml/kg	6	143.3±22.68
Diazepam	1 mg/kg	6	43±9.977*

**P*<0.011 as compare to vehicle (one way ANOVA followed by Dunnetts)

Table 3:

Treatment	Dose	Duration of tonic hindleg extension (MEAN±SEM)	Percentage protect
Vehicle	10 ml/kg	12.13±2.183	0
Allium sativum	10 ml/kg	4.988±1.328*	0
Sesamum indicum	10 ml/kg	5.888±1.943*	0
Combination	10 ml/kg	5.257±1.708*	0
Phenytoin	100 mg/kg	1.167±0.5426*	0

**P*<0.002 as cmpare wiyh vehicle treated group (one way ANOVA followed by Dunnetts)

Table 4:

Treatment	Dose	Latency to death	Percentage protect
Vehicle	10 ml/kg	368.8±7.683	0
Allium sativum	10 ml/kg	493±43.13	0
Sesamum indicum	10 ml/kg	484.2±33.62	0
Combination	10 ml/kg	520.3±50.38*	0
Diazepam	2 mg/kg	337±18.7*	0

**P*<0.002 as compare to vehicle (one way ANOVA followed by Dunnetts test)

Table 5:

Treatment	Dose	Onset of convulsion	Percentage protect
Vehicle	10 ml/kg	290.3±5.097	0
Allium sativum	10 ml/kg	368.8±24.81	0
Sesamum indicum	10 ml/kg	418.5±87.85*	0
Combination	10 ml/kg	353.2±23.51	0
Diazepam	2 mg/kg	579.5±81.79*	0

Table 6:

Treatment	Dose	Onset of forlimb clonus in seconds [mean±S.E.M.]	Percentage protection
Vehicle	10ml/kg	2110±28.12	0
Allium sativum oil(GO)	10ml/kg	3066±51.63*	0
Sesamum indicum oil (SO)	10ml/kg	3074±102.2*	0
Combination	10ml/kg	3448±317*	0
Diazepam	0.5mg/kg	3483±436.5*	0

**P*<0.004 as compare to vehicle. (One wqy ANOVA followed by Dunnetts test)

DISCUSSION AND CONCLUSION

The result of acute toxicity study indicated that the fractions have a broad margin of safety in mice. In lower doses, all the fractions used in this study, produced signs of depression such as reduced locomotion and rearing, passivity, prostration, decreased muscle strength. There is evidence that both stimulatory and depressant effects can be induced simultaneously (Nutt and Glue, 1991; Leewanich et al., 1996). Rearing activity in rodents is described as a complex pattern of stereotyped behaviour (Dandiya et al., 1969), whereas decrease in rearing as well as locomotion is suggestive of depression (Pal and Dandiya, 1993).

Sesamum indicum oil was affective against PTZ-induced convulsions but GO and combination of both oil failed to protect PTZ-induced convulsions. This suggests that the anticonvulsant action of the *Sesamum indicum* oil is mediated by the chloride channel of GABA: benzodiazepine receptor complex and not by the chloride channel of glycine receptors. Since PTZ is a GABA A receptor antagonist, the SO may be acting by increasing GABA concentration in the brain.

The oil also reduced the severity of status epilepticus induced by lithium ┼pilocarpine. Lithium alone does not have proconvulant effect in rats (Clifford et al., 1985; Ormandy et al., 1991; Kofman et al., 1991, 1992). However, rats pretreated with lithium have limbic seizures, following subconvulsant doses of pilocarpine. The combined treatment with lithium–pilocarpine results in an accumulation of inositol monophosphate and reduction in cortical inositol that are about ten times greater than the effects obtained

with either drugs alone (Sherman et al., 1985). There is a massive increase in the concentration of acetylcholine and choline in cerebral cortex and hippocampus, which may play a role in seizure maintenance and lethality associated with status epilepticus (Jope and Gu, 1991). SO,GO, combination of both oil and diazepam prevented the occurrence of lithium┼ pilocarpine induced seizures (Sherman, 1991). Since status epilepticus appears to be linked to low GABA levels in brain, we therefore investigated the effect of the oils on the brain contents of GABA. The fractions increased GABA contents of the brain and this could be the mechanism of anticonvulsant action of the oils used in this study.

SO and GO seperatedly was ineffective against seizures induced by the glycine receptor antagonist strychnine. But both oil in yhe combination affective against the strychnine induced seizure in mice. As in combination both oil may be act as agonist of glycine recepter

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