Anticonvulsant potential of ethanol extracts and their solvent partitioned fractions from *Flemingia strobilifera* root

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**ABSTRACT**

Background: *Flemingia strobilifera* (FS) R.Br. (Fabaceae) is an important medicinal plant. In wealth of India it has been reported that roots of *FS* are used by santals in epilepsy, hysteria, insomnia, and to relieve pain. In Burma also the roots of *F. strobilifera* are used to treat epilepsy. **Objective:** To investigate anticonvulsant potential of 95% ethanol extract and four subsequent fractions (petroleum ether, chloroform, ethyl acetate, and aqueous fractions of the roots of *FS* against pentylentetrazole (PTZ) and maximal electroshock (MES) induced convulsions. **Material and Methods:** All the fractions and crude ethanol extract were administered (i.e., 200, 400, 600 mg/kg, p.o.) for 7 days and at the end of the treatment convulsions were induced experimentally using pentylentetrazole and Maximal electroshock Test. Diazepam and phenytoin (4 mg/kg, i.p. and 20 mg/kg, i.p., respectively) were used as reference anticonvulsant drugs against experimentally induced convulsions. The latency of tonic convulsions and the numbers of animals protected from tonic convulsions were noted. **Results:** High doses (200 and 300 mg/kg, p.o.) of ethyl acetate fraction and 95% ethanol crude extract (400 and 600 mg/kg, p.o.) significantly reduced the duration of seizure induced by maximal electroshock (MES). The same dose also protected from pentylentetrazole-induced tonic seizures and significantly delayed the onset of tonic seizures. However, pet, ether, chloroform, and aqueous fraction at any of the doses used (i.e., 100, 200, 300 mg/kg, p.o.) did not show any significant effect on PTZ and MES induced convulsions. The treatment with crude ethanolic extract and ethyl acetate fraction caused signs of central nervous system depressant action in the locomotor activity test, confirmed by the potentiation of sodium pentobarbital sleeping time. Both did not cause disturbance in motor coordination assessed by rotarod test. **Conclusion:** The data suggest that crude ethanol extract and ethyl acetate fraction of roots of *Flemingia strobilifera* have a central nervous system depressant action and behave as a potential anticonvulsant. It may produce its anticonvulsant effect via non-specific mechanism since it reduced the duration of seizures produced by maximal electroshock as well as delayed the latency of seizures produced by pentylentetrazole.

**Key words:** Antiepileptic, *Flemingia strobilifera*, maximal electroshock, pentylentetrazole, seizures

**INTRODUCTION**

Epilepsy is a condition of spontaneously recurrent seizures. A seizure occurs when there is a sudden imbalance between the excitatory and inhibitory inputs to a network of neurons leading to hyperexcitability. Glutamate and γ-aminobutyric acid (GABA) are quantitatively the most important excitatory and inhibitory neurotransmitters, respectively, in mammalian brain. Thus, receptors for these two neurotransmitters are regarded as important targets for antiepileptic drugs. Despite the state-of-the-art medical treatment, drug resistance remains a major clinical problem for one in three epileptic patients. Approximately 30% of the patients with partial epilepsy and 25% of patients with generalized epilepsy are not well controlled.
on medications. These patients often receive multiple medical treatments to control their seizures. Thus, there is the unmet need for new antiepileptic drugs.[1] Herbal medicine could be a source for new therapeutics. Several plants used for the treatment of epilepsy in different traditional systems of medicine have shown activity when tested in modern bioassays for the detection of anticonvulsant activity and many such plants are yet to be scientifically investigated.[2,3] A convulsion (or seizure or fit) is an abnormal event that results from a sudden change in the electrical function of cells in the brain while epilepsy describes the tendency to have such fits even if there is a long gap between them. Epilepsy occurs when nerve cells in the brain send electrical messages at a rate of up to four times higher than normal which cause a sort of electrical storm in the brain, known as a seizure or convulsion (fit) actually a pattern of repeated seizure is referred to as epilepsy (http://www.patienthealthinternational.com/epilepsy). The most popular and widely used animal seizure models are the traditional MES and PTZ tests. The PTZ test is used because this is one of the first assays developed to conventionally accepted anticonvulsant screening procedure. It is used to identify chemical substances that alter seizure threshold. The MES test is considered to be a predictor of likely therapeutic efficacy against generalized tonic-clonic seizures. By contrast, the PTZ test represents a valid model for human generalized myoclonic and also absence seizures.

F. strobilifera (Linn) R.Br (Fabaceae) an important medicinal plant, is commonly known as Kusrunt and is found in Sind, Rajputana, Bengal, South India, and Andaman.[4,5] Literature reveals that the various parts such as its bracts, leaves, flowers, and roots of the plant Flemingia strobilifera found to be useful in folkloric medicine for its different pharmacological activities such as leaves and flower for tuberculosis, roots for epilepsy, hysteria and swellings, root juices for diarrhea and dysentery.[6] In Burma, the roots of F. strobilifera are used to treat epilepsy. Previous chemical studies showed that flavonoids, flavonoid glycosides, chalcones, epoxychromenes, and pterocarpans were the main constituents found in Flemingia strobilifera.[7,8] However, no scientific data are available to validate the folklore claim. Although few phytochemical and pharmacological studies have been reported on this plant. The aim of the present study was, therefore, to evaluate the anticonvulsant potential of the root extract of F’s in experimental animal models, with a view to providing a pharmacological justification (or otherwise) for the ethno medicinal use of the plant in the management of convulsions and epilepsy in some rural communities of India.

**MATERIALS AND METHODS**

**Plant material**
The roots of Flemingia strobilifera were collected from the Regional Research Institute Tarikhet, Ranikhet in the month of Jan 2008. The plant was identified and authenticated by Dr. G. C. Joshi Research officer there and which was later on confirmed from National Botanical Research Institute (NBRI) Lucknow, India (NBRI/CIF/347). A voucher specimen has been preserved in the Department of Pharmacognosy, School of Pharmaceutical Sciences, IFTM University, Moradabad for further reference.

**Chemicals**
Pentylentetrazole (PTZ, Sigma Aldrich, USA), Diazepam (Cipla, Ahmadabad, India), Phenytoin (Sigma Aldrich, USA)

**Preparation of Plant extracts**
F. strobilifera roots were dried made coarse powder and 100 g of powder were extracted with 95% ethanol for 72 h by refluxing extraction. The extract was then concentrated with a rotary evaporator apparatus at a temperature not exceeding 40°C. The yield of the extract was 10% (w/w). The extract (EE) was stored at 4°C throughout experiments. For solvent fractionation EE (10 g) was suspended in distilled water and extracted successively with equal volumes of petroleum ether (PE), chloroform (CH), and ethyl acetate (EA) leaving a residual aqueous (Aq) fraction. Each fraction was evaporated under reduced pressure to yield the extracts of PE (1.8%), CH (2.5%), EA (21.34%), and Aq fractions (74.36%), respectively. The dried extracts so obtained were placed in a vacuum desiccator and used for further studies.

**Preliminary phytochemical screening**
The freshly prepared extracts of the roots of F. strobilifera were subjected to phytochemical screening tests for the detection of various constituents using standard procedures.[9]

**Experimental animals**
Swiss albino mice of both sexes weighing between 12 and 35 g were used in the present study. Animals were housed in polypropylene cages maintained under standard condition (12 h light/dark cycle; 25±3°C, 45-65% humidity) and had free access to standard rat feed and water ad libitum. All the animals were acclimatized to laboratory conditions for a week before commencement of experiment. Animal care and research protocols were based on the Principles and guidelines adopted by the Guide for the care and use of Laboratory animals (NIH publication no: 85-23, revised in 1985). The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and
Acute oral toxicity study

Acute oral toxicity of the extract was evaluated in Swiss albino mice, weighing about 20-25 g, by modifying the method of Ghosh. The symptoms like tremors, convulsions, tonic extension, muscle spasm, righting reflex, ataxia, lacrimation, diarrhea, salvation, writhing, skin colour etc. and for mortality, if any, at the end of the 24, 48 and 72 h were recorded.[10]

Anticonvulsant activity

Electrically induced seizures

In the electrically induced seizure experiment, the maximal electroshock (MES) method was employed.[11] Seizure was induced in animal by electroconvulsive shock (50 mA for 0.2 s) through corneal electrode by using electroconvulsometer (INCO, Ambala, India). The various phases of convulsion which produced were Flexion, Extension, Clonus, and Stupor. The duration of hind limb tonic extension (HLTE) was compared with control. The animals were divided into 17 groups containing 6 animals each. Group I served as a vehicle control group treated Tween -80 (0.25 ml, p.o.) for 7 days and electric shock was given on 7th day Group II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI served as test group treated with the EE(200, 400, 600 mg/kg, p.o.), PE, CH, EA, and Aq fractions (100, 200, 300 mg/kg, p.o.), respectively, for 7 days and electric shock was given on 7th day. Group XVII as a reference group was treated with phenytoin (20 mg/kg, i.p., 30 min.) once prior to the induction of convulsion. Decrease in duration of hind limb extension was considered as a protective action and was determined for each dose group.

Chemically induced seizures

Seizure was induced in animals by administration of PTZ (80 mg/kg) intraperitonially.[11] Jerky movement, convulsant, and percentage protections were recorded. The animals were divided into 17 groups containing 6 animals each and they were treated as described for electrically induced seizure tests. Here Diazepam (4 mg/kg, i.p. 30 min prior to induction) was used as a standard drug.

Test for locomotor activity

The spontaneous locomotor activity of each mouse was recorded individually for 10 min using Actophotometer (INCO, Ambala, India). Three doses of ethanol extract (200, 400, and 600 mg/kg p.o.) and ethyl acetate fraction (100, 200, and 300 mg/kg p.o.) of Flemingia strobilifera drug were administered 60 min before the test and diazepam (4 mg/kg i.p.), used as standard was given 30 min before the test. The control group was treated with 2% w/v Tween 80 orally, 60 min before test.[11]

Potentiation of sodium pentobarbital sleeping time

The vehicle, ethanol extract (200, 400, and 600 mg/kg p.o.), and ethyl acetate fraction (100, 200, and 300 mg/kg p.o.) of Flemingia strobilifera were administered 30 min before i.p. administration of pentobarbital sodium (40 mg/kg). Each animal was placed gently on its back. If the animal remained on its back 30s, loss of the righting reflex was considered to occur. The sleep latency and the sleeping time were recorded. The sleeping time was measured as the interval between the loss and the recovery of the righting reflex.[11]

Motor impairment assessment

The rotarod test was used to determine the effect of the extract on motor coordination. This test is sensitive to damage in the basal ganglia and cerebellum and to drugs that affect motor function. This test is used as a custom built apparatus; which consisted of an elevated rod (diameter of 2.5 cm and height of 25 cm) that rotated at a constant speed (16 rpm). Mice were trained to walk continuously on the rod for a period of 120 s. The animals were then evaluated for motor coordination at 60 min after oral administration of these extracts at doses 200, 400, and 600 mg/kg. The time each animal falls off from the rod was noted. A control group was also used.[11,12]

Statistical analysis

Results were statically analyzed by one way analysis of variance (ANOVA) followed by Dunnet’s test.[13] The results were expressed as mean± standard error mean (SEM). A P-value of <0.05 and <0.01 were considered as significant. All calculations were performed using Graph pad Instant software, version 6.01.

RESULTS

Phytochemical screening

Preliminary phytochemical screening of the ethanol extract revealed the presence of steroids, flavonoids, tannins, and carbohydrates and also reported by Madan et al., 2010[14] while ethyl acetate fraction was found positive for flavonoids and tannins only.

Acute oral toxicity

In acute oral toxicity study extract is devoid of any mortality of animals at dose of 2000 mg/kg in female albino mice by p.o. route and hence >2000 mg/kg was taken as LD₅₀ cut off value and 1/10th of the same i.e., 200 mg/kg was selected for screening dose for further studies.
Anticonvulsant assessment

**Effect of various extracts on maximal electric shock induced convulsions**

MES produced hind limb tonic extension seizures (HLTE) in all the animals used. The vehicle-treated mice showed tonic hind limb extension for the duration of 13.50 ± 0.51 s. EE of *F. strobilifera* at 400 mg/kg and 600 mg/kg protected 80.00 and 100% of animals, respectively. Chloroform fraction (300 mg/kg) protected only 20% of animals and ethyl acetate fraction of *F. strobilifera* at doses 200 and 300 mg/kg, protected 80.00 and 100% of mice, respectively, and significantly reduced the duration of the seizures. The standard antiepileptic drug phenytoin completely inhibited the MES-induced tonic seizures in all the animals used. However, administration of low dose of chloroform fraction (100 and 200 mg/kg p.o.), ethyl acetate fraction (100 mg/kg, p.o.), and all the doses of PE and Aq fraction (100, 200, and 300 mg/kg, p.o.) did not produce any significant effect on HLTE [Table 1].

**Effect of various extracts on pentylenetetrazole-induced convulsions**

PTZ produced tonic seizures in all the animals used. Chloroform fraction at dose 300 mg/kg protected 20.00% of animals against seizures and did not affect the onset of seizure to any significant extent. Ethyl acetate fraction of *F. strobilifera* at doses of 200 and 300 mg/kg, respectively, protected 80.00 and 100% of mice against seizures, and significantly delayed the latency of seizures. The standard antiepileptic drug diazepam completely protected the animals from seizures. However, administration of low dose of chloroform extract (100 and 200 mg/kg p.o.), ethyl acetate extract (100 mg/kg, p.o.), and all the doses of PE and Aq fraction (100, 200, and 300 mg/kg, p.o.) did not produce any significant effect on latency of convulsions [Table 2].

**Effect of ethanol extract and ethyl acetate fraction on locomotor activity**

Actophotometer score in 10 min for control was 317.42 ± 7.40 for ethanol extract 234.61 ± 2.65 and for ethyl acetate fraction was 219.55 ± 1.27. These results showed that ethanol extract (600 mg/kg p.o.) and ethyl acetate fraction (300 mg/kg p.o.) decreased the locomotor activity significantly [Table 3].

**Effect of ethanol extract and ethyl acetate fraction in pentobarbital induced sleeping time**

Ethanol extract at 600 mg/kg increased the sleeping time from 128.50 ± 0.17 min. to 203.65 ± 0.61 whereas ethyl acetate fraction at 300 mg/kg to 177.41 ± 0.32 min [Table 4].

### Table 1: Effect of Flemingia strobilifera root extracts on maximal electroshock (MES)-induced Seizures in mice

| Drug/ extract | Dose mg/kg | No. of animals Convulsed/ used | Animals protected % | Duration of HLTE (sec) Mean±SEM |
|---------------|------------|-------------------------------|---------------------|---------------------------------|
| Control       | —          | 10/10                         | 0                   | 13.50±0.53                      |
| Phenyoain     | 20         | 0/10                          | 100                 | 0.00**                          |
| Crude         | 200        | 5/10                          | 50                  | 7.43±0.38                       |
| ethanol       | 400        | 2/10                          | 80.00               | 4.43±0.18*                      |
| extract       | 600        | 0/10                          | 100                 | 1.54±0.19**                     |
| Petroleum      | 100        | 10/10                         | 0                   | 13.52±0.25                      |
| ether          | 200        | 10/10                         | 0                   | 13.45±0.18                      |
| Fraction       | 300        | 9/10                          | 10.00               | 12.38±0.85                      |
| Chloroform     | 100        | 9/10                          | 10.00               | 13.17±0.35                      |
| Fraction       | 200        | 8/10                          | 20.00               | 12.16±0.58                      |
| Fraction       | 300        | 8/10                          | 20.00               | 9.45±0.22                       |
| Ethyl acetate  | 100        | 5/10                          | 50                  | 8.25±1.02                       |
| Fraction       | 200        | 2/10                          | 80.00               | 4.82±0.78*                      |
| Fraction       | 300        | 0/10                          | 100                 | 1.66±0.18                       |
| Aqueous        | 100        | 10/10                         | 0                   | 13.16±2.02                      |
| Fraction       | 200        | 10/10                         | 0                   | 13.42±1.14                      |
| Fraction       | 300        | 10/10                         | 0                   | 12.75±1.91                      |

*P<0.05; **P<0.01 vs. control; Dunnet’s test, HLTE-Hind limb tonic extension seizure

### Table 2: Effect of Flemingia strobilifera root extracts on pentylenetetrazole (PTZ)-induced Seizures in mice

| Drug/ extract | Dose mg/kg | No. of animals Convulsed/ used | Animals protected % | Latency of tonic Mean±SEM |
|---------------|------------|-------------------------------|---------------------|---------------------------|
| Control       | —          | 10/10                         | 0                   | 44.65±0.23                |
| Diazepam      | 4          | 0/10                          | 100                 | 282.13±0.54               |
| Crude         | 200        | 7/10                          | 30.00               | 152.40±0.56*              |
| ethanol       | 400        | 5/10                          | 50                  | 187.53±0.32*              |
| Extract       | 600        | 2/10                          | 80.00               | 224.43±0.51**             |
| Pet. Ether    | 100        | 10/10                         | 0                   | 66.45±1.78                |
| Fraction      | 200        | 10/10                         | 0                   | 83.06±2.41                |
| Fraction      | 300        | 9/10                          | 10.00               | 91.54±1.73                |
| Chloroform    | 100        | 10/10                         | 0                   | 112.42±0.52               |
| Fraction      | 200        | 8/10                          | 20.00               | 137.54±1.32               |
| Fraction      | 300        | 8/10                          | 20.00               | 145.48±0.75               |
| Ethyl acetate | 100        | 5/10                          | 50                  | 173.91±0.42*              |
| acetate       | 200        | 2/10                          | 80.00               | 197.04±0.37*              |
| Fraction      | 300        | 0/10                          | 100                 | 236.45±0.11**             |
| Aqueous       | 100        | 10/10                         | 0                   | 63.70±1.64                |
| Fraction      | 200        | 10/10                         | 0                   | 76.52±1.73                |
| Fraction      | 300        | 10/10                         | 0                   | 80.25±2.11                |

*P<0.05; **P<0.01 vs. control; Dunnet’s test

### Table 3: Effect of ethanol extract and ethyl acetate fraction in rotarod test

Time spent on revolving road for control was 327.08 ± 14.82 s for ethanol extract 299.15 ± 4.85 s and for ethyl acetate fraction it was 301.44 ± 6.31 s. Thus, there is no disturbance of motor coordination [Table 5].

### Table 4: Effect of ethanol extract and ethyl acetate fraction in pentobarbital induced sleeping time

Ethanol extract at 600 mg/kg increased the sleeping time from 128.50 ± 0.17 min. to 203.65 ± 0.61 whereas ethyl acetate fraction at 300 mg/kg to 177.41 ± 0.32 min [Table 4].
anticonvulsant potential of *F. strobilifera* was examined following daily administration for 7 days.

PTZ- and MES-induced seizure models are the most commonly used preliminary screening tests for finding the anticonvulsant potential of drugs. MES model is a characteristic model for the assessment of generalized tonic clonic seizures, whereas PTZ model is considered to be a predictor of generalized absence seizure. The results of the present study indicate that ethyl acetate fractions of the roots of *F. strobilifera* possess anticonvulsant activity in mice. Sedation and anxiety are primarily mediated in the CNS by the GABA-A receptor complex, which is also involved in other physiological and neurological disorders, such as epilepsy, depression, Parkinson syndrome, and Alzheimer disease. GABA is the major inhibitory neurotransmitter in the brain while glutamic acid is an excitatory neurotransmitter in the brain. It plays a key role in the overall balance between neuronal excitation and inhibition, regulating convulsions, anxiety, and sleep. The inhibition of GABA neurotransmitter and the enhancement of the action of glutamic acid have been shown to be the underlying factors in epilepsy. Our study shows that the ethyl acetate fraction of *F. strobilifera* protected some of the animals against seizures induced by MES and PTZ.

In the present study, MES produced seizures in all the animals used. Antiepileptic drugs that block MES-induced tonic extension are known to act by blocking seizure spread. Moreover, drugs that inhibit voltage dependant Na+ channels such as phentoin can prevent MES-induced tonic extension. PTZ may elicit seizures by inhibiting gabaaergic mechanisms. Standard antiepileptic drugs, diazepam and phenobarbitone, are believed to produce their effect by enhancing GABA mediated inhibition in the brain. It is therefore possible that the anticonvulsant effects shown in this study by the drugs against seizures produced by PTZ might be due to the activation of GABA neurotransmission. Since the extract similarly antagonized seizures elicited by PTZ in mice, it is probable, therefore, that it may also be exerting its anticonvulsant effects by affecting gabaergic mechanisms. Most of the flavanoids interact with GABA receptors in brain and modulate its function and were found to be ligands for the GABA-A receptors in the CNS, which led to the hypothesis that they act as benzodiazepine like molecules whereas isoflavonoids have protective effect against PTZ induced seizure. Various chemical constituents of plant origin, such as terpenoids, particularly triterpenoids and flavonoids, are reported to have anticonvulsant property in various animal models of epilepsy like PTZ, MES, electrical kindling etc.

**DISCUSSION**

The data obtained in this study for the first time demonstrated that Crude ethanol extract and ethyl acetate fractions of *F. strobilifera* had significantly inhibited the MES-induced generalized tonic clonic convulsions and PTZ-induced absence seizures. The traditional system of medicine is slow acting as compared to modern synthetic drugs, as it involved the administration of crude preparations. Therefore, the

| Table 3: Effect of ethanol root extract and ethyl acetate fraction on locomotor activity |
| Groups | Dose mg/kg, p.o | Actophotometer score in 10 min |
|--------|-----------------|------------------------------|
| Control | —               | 317.42±7.40                  |
| Diazepam | 4 mg/kg, i.p.  | 120.16±11.14**               |
| Crude ethanol extract | 200 | 309.42±2.13                 |
| Ethyl acetate fraction | 100 | 270.51±2.51**               |
|  | 200              | 236.73±1.82*                 |
|  | 300              | 219.35±1.27*                 |

*P<0.05; **P<0.01 vs. control; Dunnet’s test

| Table 4: Effect of ethanol root extract and ethyl acetate fraction in pentobarbital induced sleeping time |
| Pentobarbitone (40 mg/kg, i.p.) 30 min Post treatment of the vehicle and drugs | Onset of action (min) | Duration of action (min) |
|-----------------------------|----------------------|-------------------------|
| Control                     | 5.85±0.47            | 128.50±0.17             |
| Ethanol extract (p.o.)      | 5.12±0.46            | 135.91±0.71*            |
| 200 mg/kg                   | 6.16±0.93            | 150.24±1.16*            |
| 600 mg/kg                   | 6.03±1.15            | 203.65±0.61**           |
| Ethyl acetate fraction (p.o.) | 6.23±2.17          | 153.71±1.72*            |
| 100 mg/kg                   | 5.67±1.62            | 165.45±0.38*            |
| 300 mg/kg                   | 5.93±2.13            | 177.41±0.32**           |

*P<0.05; **P<0.01 vs. control; Dunnet’s test

| Table 5: Effect of ethanol extract and ethyl acetate fraction in rotarod test |
| Groups (vehicle 6 ml/kg p.o.) | Time spent on revolving rod (sec) |
|-----------------------------|--------------------------|
| Control                     | 327.08±14.82             |
| Diazepam (4 mg/kg, i.p.)    | 167.81±1.75**            |
| Ethanol extract()           |                          |
| 200 mg/kg                   | 315.52±11.31             |
| 600 mg/kg                   | 309.16±3.61              |
| Ethyl acetate fraction (p.o.) | 299.15±4.85             |
| 100 mg/kg                   | 307.13±4.39              |
| 200 mg/kg                   | 304.56±3.87              |
| 300 mg/kg                   | 301.44±6.31              |

*P<0.05; **P<0.02 vs. control; Dunnet’s test
results obtained by preliminary phytochemical screening carried out in the present study showed the presence of steroids, flavonoids, tannins, and carbohydrates in crude ethanol extract and flavonoids and tannins in ethyl acetate fractions, respectively.

It is worthwhile to isolate the bioactive principles, which are responsible for these activities; the process has commenced in our laboratory. These findings justify the traditional use of this plant in the control and/or treatment of convulsions and epilepsy as the plant is unexplored yet.

CONCLUSION

It can be concluded from the study that ethyl acetate fraction of roots of *F. strobilifera* possesses anticonvulsant activity. The anticonvulsant effects of these root extracts may be *via* non-specific mechanisms. However, extensive studies are needed to evaluate the precise mechanism(s) active principles, and the safety profile of the plant as a medicinal remedy for convulsive disorders. The present study will help the industry to develop herbal medicine in the treatment of convulsion with fewer side effects. In future, the development of formulation by these plant constituents will give good anticonvulsant drug at a lower cost.

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