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A review on natural products with anticonvulsant activity

[*1] Abubakar US, [2] Binta IK, [3] Amina MJ, [4] Muhammad S, [5] Fatima A, [6] Ukwubile CA
[1-5] Bioresources Development Centre, Kano. National Biotechnology Development Agency (NABDA), Abuja, Nigeria
[6] Department of Science Laboratory Technology (Biology Unit), Federal Polytechnic, Bali, Taraba State, Nigeria

Abstract
The need for new anticonvulsant drugs with greater efficacy and novel mechanisms of action becomes necessary; this is due to the fact that the current therapy with modern anticonvulsant drugs is associated with many side effects and approximately 30-40 % of the patients continue to have seizures with current antiepileptic drugs therapy. Medicinal plants are known for their anticonvulsant activities, and current interest in traditional medicine has led to rapid development and studies of many plants employed by various ethnic groups for the management of epilepsy. The present work summarized some medicinal plants and natural products with anticonvulsant activities. Also, the screening models, seizure inducing factors and the potential mechanisms underlying the anticonvulsant effects have been reported.

Keywords: epilepsy, medicinal plants, natural products and traditional medicine

Introduction
The term epilepsy is collectively designated for a group of chronic central nervous system disorders characterized by spontaneous occurrence of seizures generally associated with the loss of consciousness and body movements (convulsions) [1].

Epilepsy has been considered as the second neurological disorder and has no age, racial social, sexual or geographical boundaries. From many studies around the world, it has been estimated that the mean prevalence of active epilepsy is approximately 8.2 per 1,000 of the general population, while in developing the mean prevalence is more than 10 per 1,000. Thus, it is likely around 50 million people in the world have epilepsy [1].

The current therapy of epilepsy with modern anti epileptic drugs (AEDs) is associated with side effects, dose-related and chronic toxicity and approximately 30-40 % of the patients continue to have seizures with current antiepileptic drugs therapy. Thus, the need for new AEDs (especially from plants) with greater efficacy and novel mechanisms of action to serve as alternate therapy for the treatment of resistant epilepsy is necessary, these facts motivate researchers to develop novel approaches to treat epilepsy, for example, to discover new antiepileptic constituents from herbal medicines [2].

Medicinal Plants with Anticonvulsant Activity
The history of drug discovery showed that plants are highly rich sources in the search for new active compounds. Many synthetic drugs owe their origin to plant based complementary medicine [3, 4]. Medicinal plants were known for their anticonvulsant activity, and current interest in traditional medicine has led to rapid development and studies of many remedies employed by various ethnic groups of the world. Table 1 summarized the list of some medicinal plants which have been tested or reported for anticonvulsant properties [5].

Table 1: Some Plants Reported to Possess Anticonvulsant/Antiepileptic Property

Medicinal Plant	Family	Parts used
Cissus sicyoides	Vitaceae	Aerial part
Passion flower	Passifloraceae	Leaves and flower
Rosa domescana	Rosaceae	Flower
Argyreia speciosa	Convolvulaceae	Leaves
Drosera burmannii	Droseraceae	Whole plant
Echium amoenum	Boraginaceae	Flower
Glycerriza glabra	Fabaceae	Root
Oscimum sanctum	Lamiaceae	Leaves
Pongamia pinnata	Papilionaceae	Leaves
Berberis vulgeris	Berberidaceae	Leaves
Clerodendrum infortunatum	Verbenaceae	Leaves
Echium amoenum	Boraginaceae	Flower
Butea monosperma	Fabaceae	Flower
Valeriana officinalis	Valerianaceae	Roots
Saussurea lappa	Asteraceae	Roots
Cymbopogon winterianus	Poaceae	Leaves
Taxus wallichiana	Taxaceae	Whole plant
Nardostachys jatamansi	Valerianceae	Root
Dorstenia arifolia	Moraceae	Rhizome

Among those plants tested and confirmed to possess anticonvulsant activity, the active constituents are yet to be found, for those where the active components are known, they belong to different classes of phytoconstituents [6, 7].

Animals Models for Testing Anticonvulsant Drugs
A number of animal models have been developed in the search for more effective and more tolerable anticonvulsant drugs. In fact, the models employed in the early stage of anticonvulsant drug discovery are highly predictive of subsequent efficacy in easy to manage generalized and partial epilepsy [8]. The animal models more employed are;

1) Leptazole induced seizure
2) Maximal electroshock induced seizure

3) Metrazole induced seizures
4) Picrotoxin induced convulsion
5) Pilocarpine induced convulsion
6) Pentylenetetrazole induced convulsion
7) Strychnine induced seizures

However, maximal electroshock, picrotoxin and pentylenetetrazole induced convulsion models continue to represent the three most widely used animal seizure models employed in the search for new anticonvulsant drugs [9].

An ideal epilepsy model is the one that reflects similar pathophysiology and phenomenology to human epilepsy. Seizures should evolve spontaneously after a post-insult latent period or in a developmental time frame consistent with the human condition [10]. Similarly, the ideal model should display a pharmacological profile that is resistant to at least two of the existing anticonvulsant drugs [11].

Considering the heterogeneous nature of seizure disorders in humans, the complexity of the seizure phenotypes and the syndromes involved; it is highly unlikely that one animal model will ever predict the full therapeutic potential of an investigational anticonvulsant drug. Therefore, investigational anticonvulsant drugs are currently evaluated in a battery of syndrome specific model systems. As specific models are developed and the drugs they identify are validated clinically, they are then integrated into the existing discovery process to better identify potentially antiepileptic therapies [8].

Chemical Kindling Model for Testing Anticonvulsant Drugs

Kindling model has been widely studied as a tool for understanding chronic epileptogenesis and for testing anticonvulsant drugs with a potential for treating complex partial seizures. However, this model is too laborious for use as a primary screening procedure, yet it is clear that it consistently identifies compounds with therapeutic potential in complex partial seizures [12].

Natural Products with Anticonvulsant Activity

The present work summarizes several kinds of natural compound with anticonvulsant or antiepileptic activities; this includes alkaloids, coumarins, flavonoids, saponins and terpenoids. The screening models, the seizure inducing factors, the effective dose and the potential mechanisms underlying the anticonvulsant or antiepileptic effects have also been reported.

1. Alkaloids

Aconitum alkaloids are a series of diterpene alkaloid neurotoxins that interact with the voltage-dependent Na^+ channel. Because this channel has an exceptional relationship with neuronal excitability, the effect of aconitum alkaloids on the central nervous system, especially their potent antiepileptiform activity was investigated *in vitro*. The study revealed that benzoyl ester may be an important active center for this kind of anticonvulsant property. Most of the aconitum alkaloids tested have shown a significant inhibition of the epileptiform activity, except those without benzoyl ester side chain [13].

Also, there are many other kinds of alkaloids that have been reported with anticonvulsant activities; this include

1) Isoquinoline alkaloids such as berberine [14], montanine [15] and tetrahydropalmatine [16].
2) Indole alkaloids such as ibogaine [17].
3) Piperidine alkaloids such as piperine [18].
4) Amide alkaloids such as piplartine [19].
5) Tetracyclic oxindole alkaloids such as rhynchophylline and isorhynchophylline [20].
6) Aporphine alkaloids such as nantenine [21].
7) Erythrine byproducts such as erysothrine [22], (+)-erythravine, (+)-11-a-hydroxyerythravine [23] and raubasine [24].

2. Coumarins

Coumarins are a group of plant derived polyphenolic which possess a wide range of pharmacological activities. Esculetin is a coumarin which could significantly decrease seizure induced by electroshock, and it exerted anticonvulsant effect probably through the GABAergic neuron [25].

Compared with bergapten that contained a C-5 substituent, isopimpinellin and byakangelicol both possess a substituent at the C-8 position; therefore, they showed much stronger anticonvulsant activities than bergapten [26].

3. Flavonoids

Chrysin is flavonoid reported to prevent the expression of tonic clonic seizures induced by pentylenetetrazole induced convulsion through central benzodiazepine receptors [27]. Apigenin which bears one more hydroxyl group on ring B than chrysin, could reduce the latency in the onset of picrotoxin-induced convulsion convulsions [28]. A methoxy group added to the C-8 position of Chrysin produced Wogonin, which significantly blocked convulsion induced by pentylenetetrazole induced convulsion and electroshock [29].

4. Saponins

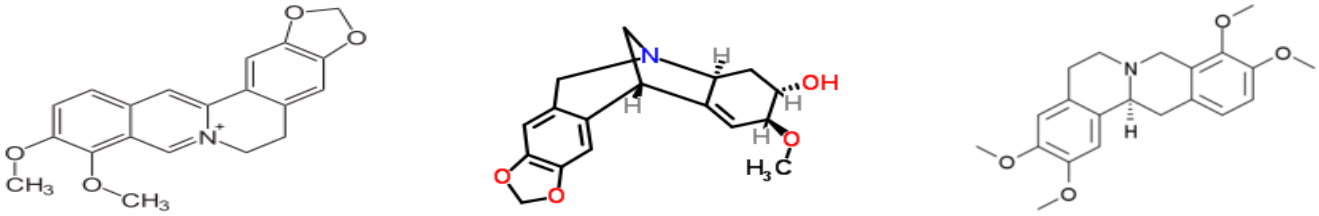
Cynanchum otophyllum (also known as Qingyangshen) is one of the most important medicinal plant species used in southwestern part of China to treat epilepsy. A product based on *Cynanchum otophyllum* extract has already been developed by the Yunnan Baiyao Group together with the Kunming Institute of Botany, Chinese Academy of Sciences. Recent studies have demonstrated that Otophylloside A and Otophylloside B, two C-21 steroidal saponins are its main active constituents that exhibit anticonvulsant activities [30, 31].

Apart from the pure compounds, some saponin extracts are considered nowadays as potential bioactive agents in treating epilepsy. To test the anticonvulsant activity of extracts from different parts of American Ginseng, seizures were induced in rats by Kainic acid, pilocarpine, or pentylenetetrazole induced convulsion. Only a partially purified extract that concentrates the Rb1 and Rb3 ginsenosides (Rb extract) showed significant effect [32]. The anticonvulsant effects of the saponin fraction obtained from *Astragalus mongholicus* on acute pentylenetetrazole induced convulsion was tested; and the results showed that the saponin components were useful in the treatment of convulsive disorders, although their action mechanisms remain unclear. Also, saponin rich fraction of *Ficus platyphylla* stem bark demonstrated anticonvulsive effects on pentylenetetrazole and strychnine induced seizures

in vivo, but failed to protect mice against maximal electroshock induced convulsion test; neither abolished the spontaneous discharges induced by 4-amino pyridine *in vitro* [33].

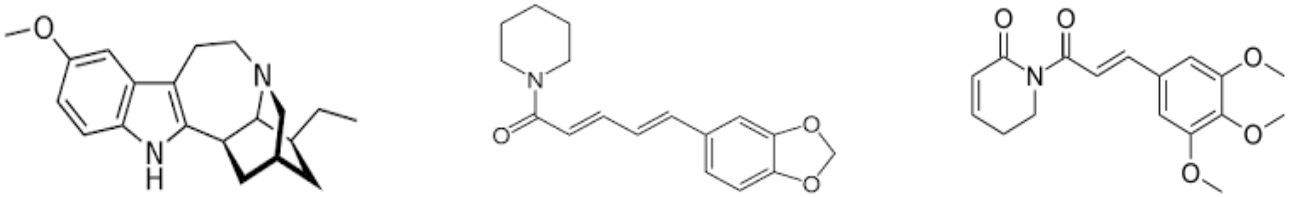
5. Terpenoids

Terpenoids are now under investigation for multiple pharmaceutical functions including anticonvulsant activities. Most of these compounds are monoterpenes. Citronellol, an acyclic monoterpene alcohol, existed in essential oils of many aromatic plants, and showed protective effects against pentylenetetrazole, picrotoxin and maximal electroshock induced seizures in mice. Some diterpenes and their derivatives also exhibited good anticonvulsive effects in preclinical experiments. Phytol could reduce pilocarpine induced seizures probably by modulating other systems neurotransmitters rather than the GABAergic system [34].



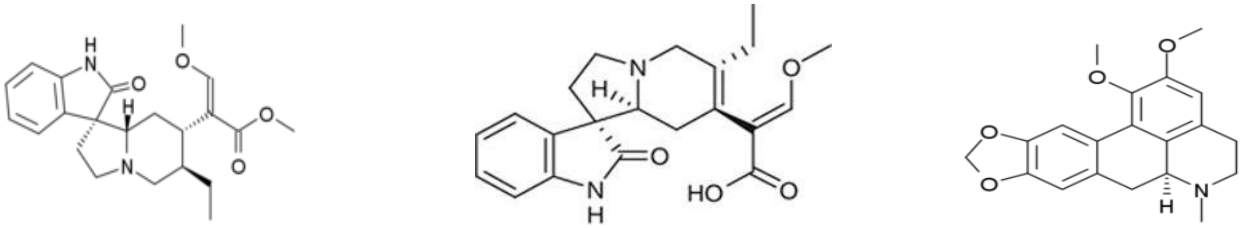
Berberine Montanine Tetrahydropalmatine

Fig 1: Chemical Structure of Natural Products with Anticonvulsant Properties



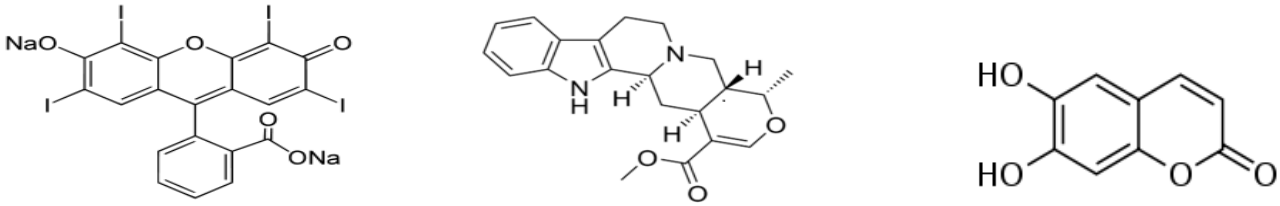
Ibogaine Piperine Piplartine

Fig 2: Chemical Structure of Natural Products with Anticonvulsant Properties



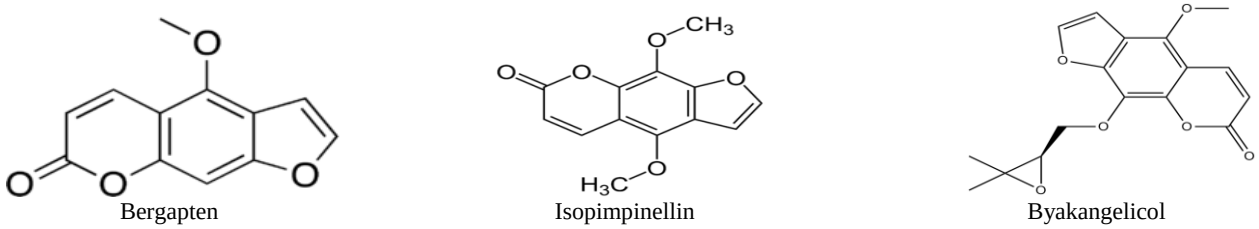
Rhynchophylline Isorhynchophylline Nantenine

Fig 3: Chemical Structure of Natural Products with Anticonvulsant Properties



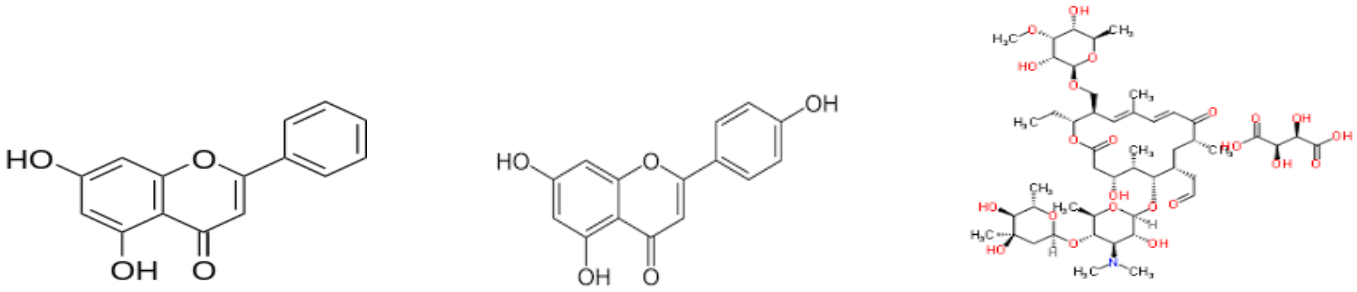
(+)-erythravine Raubasine Esculetin

Fig 1: Chemical Structure of Natural Products with Anticonvulsant Properties



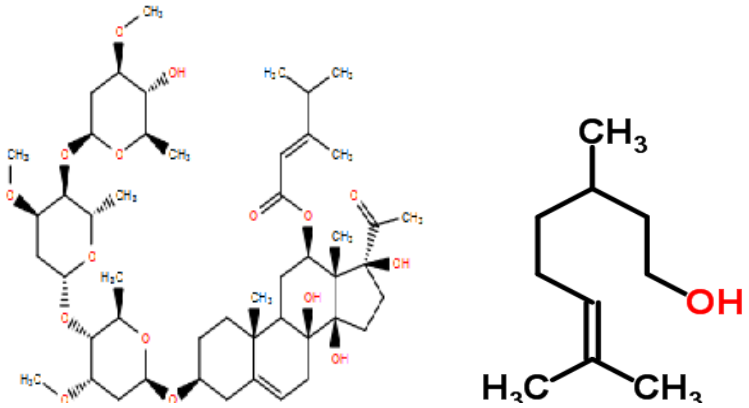
Bergapten Isopimpinellin Byakangelicol

Fig 1: Chemical Structure of Natural Products with Anticonvulsant Properties

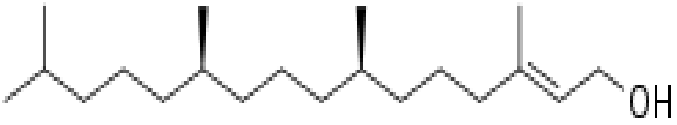


Chrysin Apigenin Otophylloside A

Fig 1: Chemical Structure of Natural Products with Anticonvulsant Properties



Otophylloside B Citronellol



Phytol

Fig 1: Chemical Structure of Natural Products with Anticonvulsant Properties

Conclusion

It can be concluded that studies with species from many families have been shown to have bioactive agents with anticonvulsant properties and understanding of the complex mechanism of epilepsy. It is evident that medicinal plants have the potential to be a rich source for discovering safer and more effective antiepileptic agents.

References

1. World Health Organization. Epilepsy: A Manual for medical and clinical officers in Africa, 2002.
2. Wickenden AD. Potassium channels as antiepileptic drug targets. Neuropharmacology, 2002; 43:1055-1060.
3. Howes MJR, Perry NSL, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. Phytother Res, 2003; 17:1-18.
4. Orhan I, Sener B, Choudhary MI, Khalid A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some Turkish medicinal plants. J Ethnopharmacol, 2004; 91:57-60.
5. Malvi RK, Biogoniya P, Sethi S, Jain S. Medicinal plants used in the treatment of epilepsy. IRJP. 2011; 2(2):32-39.
6. Chaturvedi AK, Parmar SS, Bhatnagar SC, Misra G, Nigam SK. Anticonvulsant and antiinflamatory activity of natural plant coumarins and triterpenoids. Res Commun Chem Path, 1974; 9:11-22.
7. Nsour WN, Lau CBS, Wong ICK. Review on phytotherapy in epilepsy. Seizure 2000; 9:96-107.
8. Smith M, Wilcox KS, White HS. Discovery of antiepileptic drugs. Neurotherapeutics. 2007; 4:12-17.
9. While HS, Woodhead JH, Wilcox KS, Stables JP, Kupferberg HJ, Wolf HH. Discovery and preclinical development of antiepileptic drugs. In: Levy RH, Mattson RH, Meldrum BS, Perucca E. eds. antiepileptic drugs. 5th ed. Philadelphia: Lippincott Williams & Wilkins. 2002, 36-48.
10. NIH, AES. The national institutes of health and American epilepsy society models II workshop, 2002.
11. Stables JP, Bertram E, Dudek FE. Therapy discovery for pharmacoresistant epilepsy and for disease-modifying therapeutics: Summary of the NIH/NINDS/AES Models II workshop. Epilepsia, 2003; 44:1472-1478.
12. Löscher W, Schmidt D. New horizons in the development of antiepileptic drugs: innovative strategies. Epilepsy Res., 2006; 69:183-272.

13. Ameri A. Inhibition of rat hippocampal excitability by the aconitum alkaloid, 1- benzoylnapelline, but not by napelline. Eur J Pharmacol, 1997; 335:145-152.
14. Bhutada P, Mundhada Y, Bansod K. Anticonvulsant activity of berberine, an isoquinoline alkaloid in mice. Epilepsy Behav. 2010; 18:207-210.
15. Da Silva AFS, De Andrade JP, Bevilaqua LRM. Anxiolytic antidepressant-and anticonvulsant like effects of the alkaloid montanine isolated from hippeastrum vittatum. Pharmacol Biochem Behav. 2006; 85:148-154.
16. Lin MT, Wang JJ, Young MS. The protective effect of dltetrahydropalmatine against the development of amygdala kindling seizures in rats. Neurosci Lett. 2002; 320:113-116.
17. Chen K, Kokate TG, Donevan SD. Ibogaine block of the NMDA receptor:in vitro and in vivo studies. Neuropharmacology, 1996; 35:423-431.
18. Da Cruz GM, Felipe CF, Scorza FA. Piperine decreases pilocarpine-induced convulsions by GABAergic mechanisms. Pharmacol Biochem Behav, 2013; 104:144-153.
19. Felipe FCB, Sousa JT, Souza LEDO. Piplartine, an amide alkaloid from *Piper tuberculatum*, presents anxiolytic and antidepressant effects in mice. Phytomedicine, 2007; 14:605-612.
20. Kang TH, Murakami Y, Matsumoto K. Rhynchophylline and isorhynchophylline inhibit NMDA receptors expressed in xenopusoocytes. Eur J Pharmacol. 2002; 455:27-34.
21. Ribeiro RA, Leite JR. Nantenine alkaloid presents anticonvulsant effect on two classical animal models. Phytomedicine, 2003; 10:563-568.
22. Rosa DS, Faggion SA, Gavin AS. Erysothrine, an alkaloid extracted from flowers of *Erythrina mulungu* mart. Ex benth: evaluating its anticonvulsant and anxiolytic potential. Epilepsy Behav. 2012; 23:205-212.
23. Faggion SA, Cunha AO, Fachim HA. Anticonvulsant profile of the alkaloids (+)-erythravine and (+)-11-alpha-hydroxyerythravine isolated from the flowers of *Erythrina mulungu* martex benth (leguminosae-papilionaceae). Epilepsy Behav. 2011; 20:441-446.
24. Charveron M, Assie MB, Stenger A. Benzodiazepine agonist type activity of raubasine, a *Rauwolfia serpentina* alkaloid. Eur J Pharmacol. 1984; 106:313-317.
25. Woo TS, Yoon SY, DelaPena IC. Anticonvulsant effect of artemisia capillaris herba in mice. Biomol Ther. 2011; 19:342-347.
26. Singhuber J, Baburin I, Ecke GF. Insights into structure activity relationship of GABAA receptor modulating coumarins and furanocoumarins. Eur J Pharmacol. 2011; 668:57-64.
27. Medina JH, Paladini AC, Wolfman C. Chrysin (5, 7-di-OHflavone), a naturally ooccurring ligand for benzodiazepine receptors, with anticonvulsant properties. Biochem Pharmacol. 1990; 40:2227-2231.
28. Avallone R, Zanoli P, Puia G. Pharmacological profile of apigenin, a flavonoid isolated from *Matricaria chamomilla*. Biochem Pharmacol. 2000; 59:1387-1394.
29. Park HG, Yoon SY, Choi JY. Anticonvulsant effect of wogonin isolated from *Scutellaria baicalensis.* Eur J Pharmacol. 2007; 574:112-119.
30. Mu QZ, Lu JR, Zhou QL. Two new antiepilepsy compounds–otophyllosides a and b. Sci. Sin B. 1986; 29:295-301.
31. Zhou J. Bioactive glycosides from Chinese medicines. Mem Inst Oswaldo Cruz. 1991; 86:231-234.
32. Lian XY, Zhang TZ, Stringer JL. Anticonvulsant activity of ginseng on seizures induced by chemical convulsants. Epilepsia, 2005; 46:15-22.
33. Jalsrai A, Grecksch G, Becker A. Evaluation of the effects of *Astragalus mongholicus* bunge saponin extract on central nervous system functions. J Ethnopharmacol. 2010; 131:544-549.
34. Costa JP, Ferreira PB, De Sousa DP. Anticonvulsant effect of phytol in a pilocarpine model in mice. Neurosci Lett. 2012; 523:115-118.