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Herbal Anticonvulsant Agents: A Brief Review

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ABSTRACT

Epilepsy is one of the most frequent neurological afflictions in men characterized by excessive temporary neuronal discharges resulting in uncontrolled convulsion. Inflict more than 60 million people worldwide. Epilepsy can be defined as a group of disorders characterized by abnormal electrical activity in the brain leading to altered behavior which may manifest as a change in a person's consciousness, movement or actions. These physical changes are called epileptic seizures. Epilepsy is therefore sometimes called a seizure disorder. Seizures mean a paroxysmal abnormal discharge at the high frequency. The research for perfect antiepileptic compound with more selective activity and lower toxicity continues to be an area of intensive investigation in medicinal chemistry. Moreover many side effect are reported in many patient treated with present available antiepileptic drugs (AEDs).In India studies have reported the prevalence rate of epilepsy varying from 1720 to 9800 cases per million population. The anticonvulsant activity of furanocoumarins, coumarin mixture and the essential oil obtained from the fruits of Heracleum crenatifolium was examined against maximal electroshock (MES)-induced seizures in mice. Bergapten showed significant anticonvulsant activity. Despite the optimal use of available antiepileptic drugs (AEDs), many patients with epilepsy fail to experience seizure control and other do so only at expense of significant toxic side effect. This review describes new herbal anticonvulsant agents representing various structures for which the precise mechanism of action is still not known. Here we are providing the review of herbal anticonvulsant agents, which seem to be effective when evaluated for their anticonvulsant activity.

KEY WORDS: Herbal anticonvulsant agents, epilepsy, seizure, GABA, Ethosuximide.

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TABLE CONTENTS

1. INTRODUCTION

Epilepsy is a very common disorder, characterized by seizures, which take various forms & result from episodic neuronal discharges, the form of the seizure depending on the part of the brain affected. Epilepsy is a chronic disorder of the brain that causes a tendency to have recurrent seizures. Two or more seizures must occur before a person can receive the diagnosis of epilepsy, also known as a seizure disorder. It's not uncommon for children to have a single seizure especially associated with a high fever and an estimated one in 10 people will experience a seizure at some time in life. There are five broad categories of epileptic seizures, the subtype and their characteristics are summarized in Table 1. A global campaign against epilepsy conducted by World Health Organization (WHO) in partnership with International Bureau for Epilepsy (IBE) and International League against Epilepsy (ILAE) suggested that around 1% of world population at any time (about 50 million people worldwide) is affected with this neurological disorder.[1,2]

Table1: Types of epileptic seizure.[4]

Sr.No.	Seizure Types	Symptoms
1	**Generalized Seizures**	**Produced by the entire brain**
a)	Tonic Clonic	Tonic rigidity of extremities, massive Clonic jerking, onset at any age.
b)	Simple Absence	Sudden loss of consciousness up to 30 sec Clonic jerking of eyelids.
c)	Myclonic jerking	Sudden Violent contraction of extremities, onset 5-20years.
d)	Atonic/Akinetic	Sudden loss of muscle tone lasting 10-60sec,onset 1-5 years.
2	**Partial Seizure**	
a)	Simple Seizure	Convulsant confined to single limb or muscle.
b)	Complex Seizure	Confused behavior, loss of consciousness, last for several minutes.

1.1 Mechanism of action: Mechanism of action of anticonvulsant agent can be divided in three main categories as shown in Fig.1 and is described as follows.[2, 3]

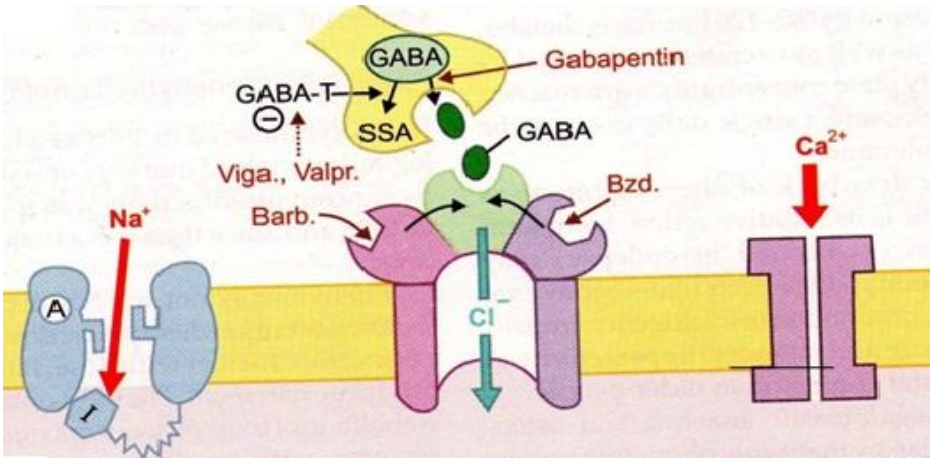


Figure 1: Mechanism of action of anticonvulsant agent[1]

1.1.1. Prolongation of sodium channel inactivation: Many drugs preferentially block the Na+ channel that remain open due to repetitive neuronal firing, they block the use dependent or voltage dependent Na^+ Channel. The higher the frequency of the firing the greater is the block. De polarization of neuron increases the proportion of the Na^+ channel in the inactivated state. Antiepileptic drugs bind preferentially to channels in this state, preventing them from returning to the resting state, and thus reducing the number of functional channels available to generate action [potentials.

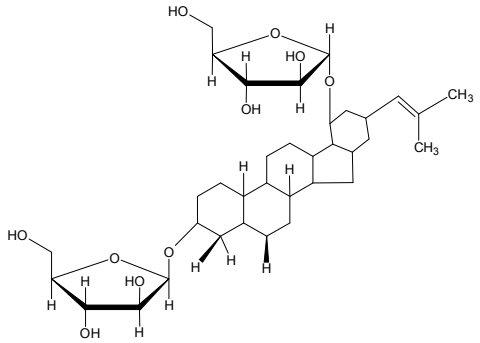
1.1.2. Facilitation of GABA mediated Cl^- action: GABA, gama aminobuteric acid is the principle inhibitory neurotrasmiter in the mammalian brain. It has been estimated that approximately 40% of synapses in the CNS are GABAergic. GABA is synthesized by the enzyme glutamic acid decarboxylase which acts on glutamate and removes the gamma carboxyl group as CO to produce GABA. Examples of drugs are Benzodiazepines, Barbiturates, Tigabine, Valproate, Zonisamide etc.

1.1.3. Inhibition of T-type calcium current: Ethosuximide is a major drug used for the treatment of absence seizures. It inhibits the low threshold Ca^{++} current carries by Type Ca^{++} channels. Type Ca^{++}current are responsible for generation of the thalamic cortical in petit mal attack. Inhibition or reduction of the low threshold T-type Ca^{++} channels therefore could account for the seizure specie therapeutic action of ethosuximide. Example of other drugs is Valproate, Zonisamide etc.

2. LITERATURE SURVEY [5-20]

Dinesh Kumar et. al., performed the anticonvulsant effect of the ethanol extract of Caesalpinia, pulcherrima (L.) Sw., Fabaceae, leaves against maximal electroshock (MES) and pentylenetetrazole (PTZ) induced seizures in rats and mice at dose levels 200 and 400 mg/Kg, i.p. respectively. Diazepam (3 mg/kg, i.p.) was used as a standard anticonvulsant drug for Comparison.[5]

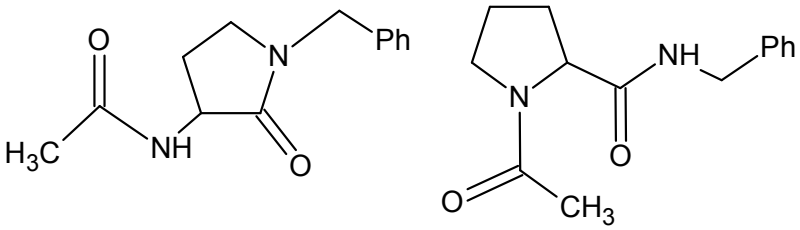
Srivastava, et. al ., performed the study on Becopa moniera, used for centuries as a memory enhancing, anti-inflammatory, analgesic, antipyretic, sedative and antiepileptic agent. The plant, extract and isolated bacosides (the major active principles) have been extensively investigated in several laboratories for their different biological activities.[6]



Bacosaponin A

N. S. Vyawahare et al., performed the study on Picrotoxin as anticonvulsant, which accounts for about 1% of the world's burden of diseases. A number of synthetic antiepileptic drugs are available in practice, however their effectiveness does not hold true with the entire range of population suffering from this disorder. Moreover the side effects and the drug interactions are major restrictions in its clinical utility. In this overview they have summarized the current herbal antiepileptic and their research advancements.[7]

Barbara Malawska, et al., described new anticonvulsant agents, which representing various Structures for which the precise mechanism of action is still not known. Many of the compounds presented in this review have been tested according to the procedure established by the Antiepileptic Drug Development Program of the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke, National Institute of Health, USA. The newer agents include sulfonamides, amino acids, amides (analogs of vinyl GABA, N-benzylamides, 2,6-dimethylanilides,carboxyamides, hydroxyamides, alkanoamides); heterocyclic agents (aryl alkyl) imidazoles, pyrrolidin-2,5-diones,lactams, semi-thiosemicarbazones, thiadiazoles, quinazolin-4(3H)-ones,2,5-disubstituted 1,2,4-thadiazoles, xanthones, derivatives of Isatin) and enaminones. These new structural classes of compounds can prove useful for the design of future targets and development of new drugs.[8]



Gauthaman K et al,. performed the anticonvulsant effect of Drosera burmannii Vahl. The antiepileptic activity of the alcoholic and aqueous extracts of the whole plant of Drosera burmannii was examined against pentylenetetrazole (PTZ) induced seizures in mice. It was found that alcoholic and aqueous extracts up to a dose of 300mg/kg body weight, did not show any toxic manifestations or death.[9]

Joshi M. K., et al performed the anticonvulsant activity of chloroform extract of *Nelumbo nucifera* was investigated by studying the effects on seizures induced by maximal electroshock (MES) and (PTZ) methods in mice. *Nelumbo nucifera* with dose of 120 mg/kg show significant activity reduced the tonic extensor convulsion induced by MES.[10]

Balakrishnan N. et al,. performed the antiepileptic activity of aqueous and ethanol extracts of the leaves of Alangium salvifolium (AEAF and EEAF) on electrically and chemically induced seizures. The aqueous and ethanol extracts of the leaves of A. salvifolium (250 and 500 mg/kg) were studied for its anticonvulsant effect on MES induced seizures and PTZ induced seizures in mice. AEAF and EEAF (250 and 500 mg/kg) shows significantly reduced the duration of seizures induced by MES as well as protected animals from PTZ induced tonic seizures.[11]

Achliya G. S., et al,. performed the evaluation of CNS activity of Bramhi Ghrita. The formulation exhibited reduced alertness, spontaneous locomotor activity and reactivity. It also antagonized the behavioral effects of d-amphetamine, potentiated the pentobarbitone induced sleep and increased the pain threshold.[12]

Reddy J. et al, performed the In vitro studies on anti asthmatic, analgesic and anticonvulsant activities of the medicinal plant *Bryonia laciniosa.Linn.* Anticonvulsant activity was evaluated by MES induced seizure test. The results indicated that 70% alcoholic extract of *Bryonia laciniosa* increased the anticonvulsant activity.[13]

Robert K. O. et al, performed the ethanolic extraction and phytochemical screening of two nigerian herbs on pathogens isolated from wound infections. The Microbiological analysis of wound specimens, using the streak-plate technique, revealed the presence of bacteria involving in descending order of prevalence *Klebsiella* spp (25.4%), *Staphylococcus aureus* (24.1%), *Pseudomonas* spp (18.2%), *Escherischia coli* (18.0%), and finally *Streptococcus pyogenes* (14.1%).[14]

Govind P. et al, presented a review on pharmacological activities of *ocimum sanctum* (tulsi). *Ocimum sanctum* Linn is medicinal herb used in the indigenous system of medicine. OS has a variety of biological pharmacological activities such as antibacterial, antiviral, antifungal, antimalarial,

anthelmentic, antidiarrhoeal, analgesic, antipyretic, antiinflammatory, antiallergic, antihypertensive, cardioprotective, central nervous system (CNS) depressant, memory enhancer, antihypercholesterolaemic, hepatoprotective, antidiabetic, antiasthmatic, antithyroidic, antioxidant, anticancer, chemopreventive, radioprotective, immunomodulatory, antifertility, antiulcer, antiarthritic, adaptogenic / antistress, anticataract, antileucodermal and anticoagulant activities.[15]

Badrul M. A., Haque M. E. et al., Performed antioxidant and anti-inflammatory activities of the leaf extract of *brassica nigra.* Crude ethanolic extract of *Brassica nigra* was studied to detect the chemical compounds as well as to evaluate the antioxidant and anti-inflammatory activities. *Brassica nigra* was found to contain 2.04 mg/g of quercetin in flavonoid assay. Total antioxidant capacity of the extract was found to be 97.08 mg/g of ascorbic acid. *Brassica nigra* showed IC 50 value of 63.09 g/ml.[16]

Luciana C. B. F., Carlos C. C. et al,. Evaluated the anticonvulsant activity of extracts of plectranthus barbatus leaves in mice. These leaves are useful in treatment of seizure and the extract was administered orally at 1, 10, 30, and 100 mg/kg. they reported that the *P. barbatus* extract had marked anticonvulsant activity against strychnine-induced convulsions.[17]

Maheshwar G. H, Deshpande S.V. et al., performed anticonvulsant activity of fruits of *terminalia chebula* retz. against MES and PTZ induced seizures in rats. The ethanolic and aqueous extracts showed significant ($p<0.01$) activity in MES induced seizures. Thus ethanolic extracts of fruits of *Terminalia chebula Retz* . possess the anticonvulsant activity.[18]

Maiha, B. B., Magaji, M. G. et al., performed the anticonvulsant studies on *cochlospermum tinctorium* and *paullinia pinnata* extracts in laboratory animals. These results shows that the antiepileptic effect of both the extract are dose dependent and control 70 % of seizure.[19]

3. Examples of herbal Anticonvulsants

Valerian is currently one of the most popular orthodox antispasmodic medications in Russia and Germany according to Daniel Mowrey author of Herbal Tonic Therapies. It is its anticonvulsant action that has been useful in treating epilepsy. Valerian was used in the First World War to prevent shell shock in front-line troops. Valerian is a great herb to discuss here because it is classified as a tonic herb. It can regulate and balance opposite extremes. Recent research has shown it to be a sedative but more research has reported it can also stimulate in a way as to improve coordination, increase concentration and energy.[20] This tonic nature of Valerian allows it to depress or stimulate where necessary depending on the current needs of the nervous system. Another way Valerian has been

characterized by clinical studies is that it has neurotropic effects directly on higher centers of the central nervous system. One of the most remarkable aspects of Valerian is the almost total lack of toxicity, even with long term use. Clinical studies have proven the antispasmodic action of **Lobelia**. Historically it has been used to treat epilepsy.

Chinese Ginseng, perhaps the most famous medicinal plant of China, is considered a tonic to whole body and has folk use for this condition.

Mistletoe has a historical use for epilepsy. Hippocrates claimed it was highly effective remedy for the spleen and some modern European physicians believe treating the spleen may be beneficial in epilepsy. Sir John Colbatch, an english physician in 1720 wrote a small publication titled "The Treatment of Epilepsy by Mistletoe". There has been confusion about the toxicity of this herb but paying attention to the correct botanical and current safety warnings, the herb can safely be used.[21]

Motherwort was used to calm epileptics during the 17th century and now is used as a nerve tonic and sedative. Current evidence has confirmed its benefits as a cardiotonic and hot-water extracts also show sedative and anti-epileptic effects in animals.[22]

Mugwort extracts have been injected into laboratory animals confirming its sedative effects so researchers conclude it is possible the herb could be beneficial for epilepsy. Mugwort has been used for this condition.

Sage is famous throughout history in many different cultures as a miracle herb. A constituent in a Chinese variety Salvia militiorrhiza may become the source of a new tranquilizing agent but without the side-effects of Valium. Valium and Librium are benzodiazepines which are widely prescribed since 1960 to treat epilepsy. Benzodiazepines act on the central B_2 receptors in the central nervous system. The herb compound also interacts with the central B_2 receptors.[23]

Scullcap has always been known as a mild and safe nervine. Traditionally it has been used for delirium tremens, St. Vitus' dance, convulsions, seizures, hysterical states, lockjaw, tremors and epilepsy.

Blue Vervain is worth mentioning here after reading old American herb doctors tales of their successes with stubborn cases of epilepsy. Blue Vervain is another wonderful herb nervine use by many cultures all over the world. It is an American Indian remedy for several diseases including nervous afflictions.[24]

Black Cohosh is so highly recommended in numerous respected publications. Herbs have a balancing effect on our systems allowing the use of these kind of relaxing herbs mentioned above, to be used during the day without excessive drowsiness.

Every year about 2.5 million new cases are added to these data, some herbal anticonvulsant agent along with their family and their chemical constituents are presented in Table 2.

Table 2: List of Herbs for Epilepsy [25].

Sr.No.	NAME OF THE HERBS	FAMILY	CHEMICAL CONSTITUENTS
1	*Ginger*	Zingibraceae	Phenylpropanoid,gingerol
2	*Ladys slipper*	Orchidaceae	Phenoanthrenequinones,alkeloids
3	*Skull cap*	Lamiaceae	Lignan,tannin,scutellonin
4	*Kava*	Kawakava	Kavin Variegatum
5	*Flax seed oil*	Linaceae	Alpha-linolenoic acid,lignin
6	*Geranium*	Geraniaceae	2,4,6-hydroxyethylbenzoate
7	Lindera	Lauraceae	Proanthocynidin,Tannin,trimer
8	Gatu kala	Apiaceae	Triterpinoids,
9	Betony	Lamiaceae	Phenylethamide,glycosides,tannin
10	Ginceng	Araliaceae	Gincenoside,phenezoside
11	Lily of the valley	lily	Geraniol,citranellol

Vitamins and foods have been clinically studied for their beneficial effects on epilepsy. Vitamins especially B_1 and E have shown good results. Foods that are clinically classified as antiepileptic are: asparagus, carob, wheat, been nut, white lupine, Chinese cabbage, soybean, chives, buffalo gourd,

groundnut, butternut, almond, opium poppy, tomato, Italian stone pine, chaya, cowpea, black bean, pignut hickory, white mustard.

3.1 How often do persons with epilepsy take herbs:

U.S. and England studies shows up to 1 in 3 persons uses antiepileptic drugs. Herbs taken include ginseng, St. John's wort, melatonin, gingko biloba, garlic and black cohosh to treat seizures (<10%), other symptoms (20%), and general health (>70%). Currently available antiepileptic drugs(AEDs) provides adequate seizure control in many patient; still about 28-30% of patient are estimated to be poorly treated. Several newer drugs (such as pregabalin, stiripentol, lamotrigine, zonisamide, topiramate) as promising anticonvulsants. These drugs have proven to be effective in reducing seizure, whilst their therapeutic efficacy is overcome by some undesirable side effect such as headache, nausea, hepatotoxicity, anorexia ataxia, drowsiness, gastrointestinal disturbance and hirsutism. These observations affirm the further scope and need for the development of newer agent. The term "convulsion" is often used interchangeably with "seizure," although there are many types of seizure, some of which have subtle or mild symptoms instead of convulsions. Seizures of all types are caused by disorganized and sudden electrical activity in the brain.[26, 27]

3.2 Future prospectus for diagnosis and treatment of epilepsy:

It is quite pertinent that commonly available synthetic anticonvulsants do not adequately meet patient treatment demands.

1) Ketogenic diet- a highly fat, low carbohydrate diet developed with the advent of effective anticonvulsants. The mechanism of action is unknown. It is used mainly in the treatment of children with severe, medically intractable epilepsies.[28]

2) Electrical stimulation- A currently approved device is vagus nerve stimulation. Investigational devices include the responsive neurostimulation system and deep brain stimulation.[29]

3) Vagus nerve stimulation- The device stimulates the vagus nerve at pre-set intervals and intensities of current. Efficacy has been tested in patients with localization-related epilepsies.[30]

4) Responsive neurostimulator system (RNS)-It consists of a computerized electrical device implanted in the skull with electrodes implanted in presumed epileptic foci within the brain. The brain electrodes send EEG signal to the device which contains seizure detection software. When certain seizure criteria

are met, the device delivers a small electrical charge to other electrodes near the epileptic focus and disrupts the seizure.[31]

4. CONCLUSION

Epilepsy is serious brain disorder; drug which is used in treatment of epilepsy should have maximum effect for controlling seizure with lesser side effect. All AEDs available in market have some adverse side effect and leads to neuronal cell loss and, as it has been already mentioned, neuro degeneration may affect the protective activity of some antiepileptic drugs. Herbal anticonvulsant drug like Caesalpinia, pulcherrima, Becopa moniera, Drosera burmannii, Nelumbo nucifera and many more possess a remarkable anticonvulsant effect with lesser or no side effect. Hence present study needs a synthesis and formulation of combined extract of one or more novel herbal drugs to treat the seizure effectively.

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7. REFERENCES

1. Tripathi K D, Essentials of Medical Pharmacology', Jaypee Brothers, Medical publisher; New Delhi: 5th Edn 2004; 369-374.
2. Barar F S K, Essentials of Pharmacotherapeutics, 3rd Edn., S Chand and company ltd. New Delhi: 2005: 95-101.
3. Rang H P, Dale M M, Ritter J M , Pharmacology, Edinburg : Churchill Livingstone.199 - 201.
4. Foye W O, Principle of Medicinal Chemistry, 3rd Edn. Dader,Vargheese Publication house, Mumbai. 1989: 173-188.
5. Kumar D, Sing J., Anticonvulsant effect of the ethanol extract of Caesalpinia Pulcherrima (L.)Sw., Fabaceae, leaves, Revista Brasileira de Farmacognosia. Brazilian J. Pharmacog. 2009: 1410-1415.
6. Shikha S, Nidhi M, Bacopa monniera -a Future Perspective. Int. J. Pharm. Sci. and Drug Res. 2009:13: 154-157.

7. Vyawahare N S, Khandelwal A R, Herbal anticonvulsants. J. Herbal Med. Toxicology, 2007:1 (1): 9- 14
8. Malawska Barbara, New anticonvulsant agents, Current Topics in Medicinal Chemistry. 2005, 5:1-6.
9. Gauthaman K, Mohamed S, et al. Anticonvulsant Effect of Drosera burmannii Vahl, Int. J. Applied Res. in Nat. Prod. 2009: 3:1-4.
10. Joshi M K, Joshi Harsh B, et al. Anticonvulsant activity of chloroform extract of Nelumbo nucifera, Int. J. of Pharm. Res. Develop. 2011: 3.
11. Balakrishnan N, Kumar S A. et al. Antiepileptic activity of alangium salvifolium leaf extracts, Herbal Tech Industry.2010: 20-23.
12. Achliya G S, Wadodkar S G, et al. Evaluation of CNS activity of bramhi ghrita, Ind. J Pharmacol. 2005: 1 (37): 33-36.
13. Reddy J, Gnanasekaran D, et al. In vitro studies on anti asthmatic, analgesic and anti convulsant activities of the medicinal plant Bryonia laciniosa.Linn, Inter .J. of Drug Discovery. 2010: 2: 01-10.
14. Robert Kelechi O, Ferdinand C N, Uduak U. Ndubuisi-N. Ethanolic extraction and phytochemical screening of two nigerian herbs on pathogens isolated from wound infections. Inter, J. compre. Pharm. 2011: 2 (10):
15. Govind P, Madhuri S. et al., Pharmacological activities of *ocimum sanctum* (tulsi): a review, Inter. J. of Pharma. Sci. Rev. and Res. 2010: 5 (1):61-66.
16. Haque et al., Antioxidant and anti-inflammatory activities of the leaf extract of *brassica nigra.* Inter. J. Pharma.Ssci. & Res., 2011: 2 (2): 303-310.
17. Luciana C B F, Carlos C C, et al,. Anticonvulsant activity of extracts of plectranthus barbatus leaves in mice. Evidence-Based Complementary and Alternative Medicine. 2010: 1 (1): ID 860153.
18. Maheshwar G H, Deshpande S V, et al., Anticonvulsant activity of fruits of *terminalia chebula* retz, against MES and PTZ induced seizures in rats, J. Her. Med. Toxi. 2010: 4 (2):123-126.
19. Maiha, B B, Magaji, M G, et al., Anticonvulsant studies on *cochlospermum tinctorium* and *paullinia pinnata* extracts in laboratory animals. Nig, J. Pharm. Sci. 2009: 8 (1):102 – 108.
20. Blumenthal, Mark, et al. The Complete German Commission E Monographs. Austin: American Botanical Council. 1998: 104-5

21. Hoffmann, David, The Complete Illustrated Holistic Herbal. Shaftsbury, Dorsett: Element Books, 1996.
22. McGuffin, Michael, et al., Ed. American Herbal Products Association's Botanical Safety Handbook. Boca Raton: CRC Press, 1997.
23. Mowrey, D B, Herbal Tonic Therapies. New Canaan: Keats Publishing Co. 1993.
24. Murray, Michael T, The Healing Power of Herbs. Rocklin, CA: Prima Publishing. 1991.
25. Chavali kameswara R, Flora a gardener's encyclopedia, Om book service. 2004: (1,2) :133,459,631,849,1329,825.
26. Null, Gary. The Clinicians Handbook of Natural Healing. New York: Kensington Books. 1997.
27. Shook, Edward E. Advanced Treatise in Herbology. Beaumont, CA: Trinity Center Press. 1978.
28. Russo E, Constanti A, Topiramate hyperpolarizes and modulates the slow post stimulus AHP of rat olfactory cortical neurons in vitro. Br. J. Pharmacol, 2004: 141: 285-301.
29. Bialer M, Johannesen SI, Kupferberg H J, et al. Progress report on new antiepileptic drugs: a summary of the Seventh Eliat conference (EILAT VII). Epilepsy Research. 2004; 61:1-48.
30. MacDonald R L., Greenfild J., Mechanism of actions of new anti-epilptic drugs. Current Opinion in Neurology. 1997: 2: 121-8.
31. Sparreboom A, Cox M C, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. J. Clin. Oncol., 2004: 22: 2489-503.