# ANTIEPILEPTIC AND MOLECULAR DOCKING - BASED APPROACHES

**K. POOJA**

**20PCH012**

**Dissertation work submitted to the**
**Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore – 641043,**
**Tamil Nadu, India.**

**In partial fulfilment of the requirements for the**
**Master's Degree in Chemistry**

**May 2022**

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25/5/2022
Signature of the
Supervisor

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Signature of the
Head of the Department

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# CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF ABBREVIATION AND ACRONYMS

| Abbreviation or Acronym | Expansion |
|---|---|
| AED | AntiEpileptic Drug |
| SV2A | Synaptic Vesicle 2A |
| FTIR | Fourier - Transform InfraRed Spectroscopy |
| UV | UltraViolet Visible Spectroscopy |
| ADME | Adsorption, Distribution, Metabolism and Excretion |
| GPCR | G- Protein coupled Receptor |
| E Total value | Energy Total Value |

# 1.INTRODUCTION

*" Nature itself is the great Medicine- Hippocrates "*

It's a standard fact that Herbal treatments are fine compared to other treatments. It has minimum facet results compared to different treatments and hence can remedy several ailments like diabetic, epilepsy, kidney problems, stroke, paralysis etc. Epilepsy is one of the most common disorders of the brain, affecting 60 million people global in accordance to epidemiological studies ***(*Husain *et al., 2010;* Scheurer and Pedley*, 1990).***Epilepsy takes one of the leading places among neurological diseases, which greatly affects life quality and life expectancy ***(*El kayal *et al.,2019).***It is observed that most of the antiepileptic drugs, which are in scientific use are neither linked with any specific web page of motion nor with a recognized mechanism of motion ***(*Bialer *et al., 2010).*** Many AEDs show off their potency by way of many possible mechanisms of motion.With available marked antiepileptic drugs (AEDs) complete control of seizures is not achieved till date and also these drugs are associated with a wide range of side effects ***(*Desaubry *et al., 1995).*** Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness***( mayoclinic.org).***

Epilepsy occurs as a result of ordinary electrical activity originating in the brain. Brain cells communicate by means of sending electrical alerts in an orderly pattern. In epilepsy, these electrical indicators end up abnormal, giving upward shove to an "electrical storm" that produces seizures. These storms might also be inside a precise section of the Genius or be generalized, depending on the type of epilepsy ***(*Melinda Ratini*, 2020).***

The causes of epilepsy are divided into the following categories: structural, genetic, infectious, metabolic, immune and unknown. Examples include:

- Brain injury from prenatal or perinatal motives (e.g. a loss of oxygen or trauma in the course of birth, low shipping weight);
- Congenital abnormalities or genetic stipulations with associated brain malformations;

- An intense head injury;
- A stroke that restricts the quantity of oxygen to the brain;
- An infection of the Genius such as meningitis, encephalitis or neurocysticercosis,
- Certain genetic syndromes; and
- Brain tumor ***( WHO.org)***

There are several types of epilepsy such as Photosensitive Epilepsy, Benign Rolandic Epilepsy, Lennox Gastaut Epilepsy, Juvenile Myoclonic Epilepsy, Abdominal Epilepsy and Absence Seizures. Most human beings can manipulate epilepsy. A therapy diagram will be primarily based on severity of symptoms, your health, and how the body replies to remedy, such as,

**1.Antiepileptic drugs** (anticonvulsant drugs, antiepileptic drugs): These drugs may reduce the number of seizures. In some people they get rid of seizures.

**2.**To be effective, the medicine must be taken as prescribed. "**Vagus Nerve Stimulator**", This device is placed surgically under the skin of the breast and electrically stimulates nerves passing through the neck. This will help prevent seizures.

**3.Ketogenic diet:** More than half of people who do not respond to drugs benefit from this high-fat, low-carb diet.

**4.Brain surgery**: Areas of the brain that cause seizure activity can be removed or altered.

**5.Herbal treatment:** Another best way to treat epilepsy is herbal treatments.

Some of the Antiepileptic drugs which are commonly prescribed by doctors are, valproic acid, Stiripentol, phenytoin, carbazemin, Diazepam etc. But these drugs has some potential side effects such as fatigue, dizziness, skin rash, poor coordination,memory problems etc. Worldwide, 65 million people have epilepsy. That includes about 3 million people in the United States, the place where 150,000 new cases of epilepsy are identified each year. As many as 500 genes may relate to epilepsy in some way. For most people, the threat of developing epilepsy until age 20 is about 1 percent. Having a mother or father

with genetically linked epilepsy raises that hazard to 2 to 5 percent. For human beings over age 35, a leading cause of epilepsy is stroke. For 6 in 10 people, the purpose of a seizure can't be determined. Between 15 to 30 percent of youngsters with mental disabilities have epilepsy. Between 30 and 70 percent of human beings who have epilepsy additionally have depression, anxiety, or both. Sudden unexplained death influences about 1 percent of humans with epilepsy. Between 60 and 70 percent of humans with epilepsy reply satisfactorily to the first anti-epilepsy drug they try. About 50 percent can stop taking medicines after two to 5 years without a seizure.One-third of human beings with epilepsy have uncontrollable seizures because they haven't found a remedy that works. More than half of human beings with epilepsy who don't reply to treatment decorate with a ketogenic diet. Half of adults who try a modified Atkins food regimen have fewer seizures ***(*Ann Pietrangelo*, 2018).***

Antiepileptic medications are used to treat epilepsy by increasing the activity of gamma aminobutyric acid (GABA) and lowering the activity of voltage-gated ion channels. Around 30% of epileptic individuals do not respond to standard therapies. Furthermore, they are affected by their side effects and interactions. As a result, the search for newer antiepileptic medications from natural sources is a fascinating topic, as numerous phytochemical groups, such as saponin and flavonoids, are known to have antiepileptic action***(*Ahmed *et al.,2021).***

Epilepsy is a seizure that appears to have no apparent cause, but it is caused by a neurological system anomaly that causes epileptic and non-epileptic seizures such as hypoglycemia, fever, hypotension, migraine, and many other conditions. The main causes of patient discontent are 1-2 medication side effects. As a result, further research is needed to reduce drug adverse effects and improve treatment quality ***(*Parisa *et al.,2020).***

***Considering the aforesaid lacunae in epilepsy research and the need for safe and effective drugs, this project is aimed at a herbal redress via the usage of herbal compounds.***

## 1.1 Objective

a. Ability to know about, how to work with some software like SWISSADME, CHEMSKETCH, HEX, OPENBABEL etc.

b. To gain knowledge about many medicinal plants with chemical constituents used for antiepileptic treatments.

c. To gain knowledge about commercial drugs which are commonly used by patients for antiepileptic treatments.

d. To gain knowledge about some traditional medicines which are used to treat some diseases like epilepsy, seizures, nerves disorder and convulsant etc.

e. To analyze various herbal plants chemical constituents and find compounds which have the same property as commercial antiepileptic drugs, but it has less side effects and is more effective.

f. To determine the drug protein interaction of Commercial antiepileptic and egg protein using FT-IR spectrophotometer and UV single drop nano spectrophotometer .

g. To determine the drug protein interaction of select organic compounds and egg protein using FT-IR spectrophotometer and UV single drop nano spectrophotometer .

# 2.REVIEW OF LITERATURE

As a first step to research 15 plants which are traditionally used as herbal medicines to cure epilepsy were identified. An extensive literature survey was conducted to explore the chemical constituents present in the plants and its so far reported biological and pharmacological properties.

In Andhra pradesh, Palamaner district, Virupakshipuram village herbal decoctions are administered to people affected by seizures,epilepsy,stroke and brain fever etc. Throughout India too few herbal medicines are given for control of epilepsy.

## 2.1 Review of literature pertaining to studies on antiepileptic properties of plants compounds

Alternative methods for the treatment of epilepsy have recently gained prominence. The goal of this study was to see if quercetin, catechin, and kaempferol have antiepileptic properties. Experiments in vivo and in silico were carried out to learn more about them. Possibilities for treatment Pentylenetetrazole was given at a dose of 25 mg/kg per day for a week. 4 weeks after the rats were given epilepsy, they were given behavioral tests. Rat brain slices were studied and histologically analyzed. Kaempferol binding affinities. In silico studies were used to evaluate quercetin and catechin. Kaempferol, the maximum binding affinity was discovered with quercetin and catechin. Protein from synaptic vesicle 2A (SV2A), which is similar to levetiracetam (LEV) ***(*Hammad *et al.,2021).***

Study performed in rats and mice, the anticonvulsant activity of the ethanol extract of *Caesalpinia pulcherrima (L.) Sw., Fabaceae,* leaves was tested against maximum electroshock (MES) and pentylenetetrazole (PTZ) caused seizures at doses of 200 and 400 mg/kg, i.p. For comparison, diazepam (3 mg/kg, i.p.) was utilized as a conventional anticonvulsant medication ***(*Dinesh *et al.,2009)***.

Studies conducted on *Bacopa monnieri*, a plant that has been used for millennia as a memory enhancer, anti-inflammatory, analgesic, antipyretic, sedative, and antiepileptic drug. In multiple laboratories, the plant, extract, and isolated bacosides (the principal active

components) have been thoroughly examined for their various biological effects ***(*Srivastava *et al.,2009)***.*

*Drosera burmannii Vahl* was used to test the anticonvulsant effect. The antiepileptic effect of alcoholic and aqueous extracts of the whole plant of *Drosera burmannii* was tested in mice after they were given the drug pentylenetetrazole (PTZ). Up to a dose of 300mg/kg body weight, alcoholic and aqueous extracts were shown to have no toxic symptoms or mortality ***(*Gauthaman *et al.,2009)***.

The anticonvulsant efficacy of chloroform extract of *Nelumbo nucifera* was examined in mice using the maximum electroshock (MES) and (PTZ) techniques. The tonic extensor convulsion elicited by MES was significantly decreased by Nelumbo nucifera at a dosage of 120 mg/kg ***(*Joshi *et al.,2011).***

On electrically and chemically produced seizures, researchers tested the antiepileptic effects of aqueous and ethanol extracts of *Alangium salvifolium* leaves (AEAF and EEAF). The anticonvulsant effect of aqueous and ethanol extracts of *A. salvifolium* leaves (250 and 500 mg/kg) on MES and PTZ induced seizures in mice was investigated. The use of AEAF and EEAF (250 and 500 mg/kg, respectively) reduced the duration of MES-induced seizures and protected rats from PTZ-induced tonic seizures ***(*Balakrishnan *et al.,2010).***

Brahmi Ghrita's CNS activities were investigated. Reduced attentiveness, spontaneous locomotor activity, and reactivity were seen in the formulation. It also reduced the behavioral effects of d-amphetamine, improved the pain threshold, and potentiated the pentobarbitone-induced sleep ***(*Achliya *et al.,2005).***

Author Performed the In vitro studies on antiasthmatic, analgesic and anticonvulsant activities of the medicinal plant *Bryonia laciniosa.Linn*. Anticonvulsant activity was evaluated by a MES induced seizure test. The results indicated that 70% alcoholic extract of *Bryonia laciniosa* increased the anticonvulsant activity ***(*Reddy *et al.,2010).***

In mice, extracts of *Plectranthus barbatus* leaves were tested for anticonvulsant activity. These leaves are used to treat seizures, and the extract was given orally at doses of 1, 10, 30, and 100 mg/kg. They discovered that the *P. barbatus* extract exhibited potent

anticonvulsant properties when used to treat strychnine-induced convulsions ***(*Luciana *et al.,2010).***

In rats, the fruits of *Terminalia chebula retz*. were found to have anticonvulsant activity against MES and PTZ-induced seizures. In MES-induced seizures, the ethanolic and aqueous extracts demonstrated substantial (p0.01) action. Thus, ethanolic extracts of *Terminalia chebula Retz.* fruits have anticonvulsant properties ***(*Maheshwar *et al.,2010).***

Anticonvulsant investigations on *cochlospermum tinctorium* and *paullinia pinnata* extracts in laboratory animals were conducted. These findings reveal that both extracts have antiepileptic effects that are dosage dependent and control 70% of seizures ***(*Maiha *et al.,2009).***

Apigenin demonstrated strong anticonvulsant activity (P0.01) and repaired the memory loss caused by kainic acid (P0.05), according to the findings. Apigenin also enhanced the number of alive neurons in the hilus substantially (P0.001). Apigenin inhibited the release of cytochrome c (P0.01) in immunohistochemistry, implying an inhibitory action in the intrinsic apoptotic pathway. These findings show that apigenin improves memory by acting as an anticonvulsant and neuroprotector ***(*Paria *et al.,2019).***

Vitamins and meals have been tested in clinical trials for their anti-epileptic properties. Vitamins B1 and E, in particular, have demonstrated to be effective. Antiepileptic foods include 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, and opium poppy ***( Nilkalji et al.,2012).***

Anticipated the anticonvulsant action of chloral carboxamides - products of chloral condensation with carboxylic acid amides - using the computer software PASS. All of the connections used in the structure analysis were gathered previously, and the structures were taken from the SciFinder database. Using the GUSAR programme, acute toxicity in rats was investigated by intravenous and oral modes of administration. For each structure, calculated LD50 values have been provided. They have chosen leaders that have been tested for Lipinski compliance ***(Pavlo et al.,2017).***

Ocimum species are used to treat problems of the central nervous system (CNS). Due to its anticonvulsant properties, it is used in numerous parts of the world. Seizures are a symptom of epilepsy, which is a persistent illness. In around one out of every three patients with epilepsy, seizures are resistant to therapy with currently available anticonvulsant drugs (AEDs) focuses on the investigation of ocimum as an antiepileptic medication (AED) due to its unique anticonvulsant properties ***(*Chhaya *et al.,2013).***

In the *Cameroonian pharmacopeia,* a decoction made from the stem bark of Psychotria camptopus (Rubiaceae) is used to treat neurological disorders such as epilepsy ***(*Alliance *et al.,2021).***

*Albizia amara* has phytochemical components with pharmacologically important properties. Using pilocarpine-induced seizures in albino rats, we screened the phytochemical constituents and investigated their potential anticonvulsant activity. The extract contained flavonoids, alkaloids, saponins, tannins, and sterols, according to the qualitative phytochemical screening. The extract (400 mg/kg i.p.) prolonged the time to beginning of seizure (latency) and considerably reduced the duration of the seizure, according to the anticonvulsant activity assessment. Furthermore, the extract reduced mortality during the first 24 hours of observation. In addition, an in silico research was carried out to estimate the likely mechanism of action. Budmunchiamine A, 1, 2-benzenedicarboxylic acid, mono (2-Ethylhexyl) ester, hexadecanoic acid methyl ester, and hexadecanoic acid methyl ester were found to have the biggest contribution to activity ***(*Ahmed *et al.,2021).***

Some herbal plants and their active constituents which are used for epilepsy are given in Table 1

**Table 1: Active constituents in herbal plants used for Epilepsy treatment**

| S NO | NAME OF THE HERBS | FAMILY | CHEMICAL CONSTITUENTS | REFERENCE |
|---|---|---|---|---|
| 1 | *Ginger* | Zingibraceae | Phenylpropanoid, Gingerol | ***(* Nilkalji *et al.,2012)*** |
| 2 | *Lady's slipper* | Orchidaceae | Phenoanthrenequinones, Alkeloids | ***(* Nilkalji *et al.,2012)*** |
| 3 | *Skull cap* | Lamiaceae | Lignan, Tanin, Scutellonin | ***(* Nilkalji *et al.,2012)*** |
| 4 | *Kava* | Kawakava | Kavin variegatum | ***(* Nilkalji *et al.,2012)*** |
| 5 | *Flaxseed oil* | Linaceae | Alpha linolenoic acid, lignin | ***(* Nilkalji *et al.,2012)*** |
| 6 | *Geranium* | Geraniaceae | 2,4,6-Hydroxyethylbenzoate | ***(* Nilkalji *et al.,2012)*** |
| 7 | *Lindera* | Lauraceae | Proanthocynidin, Tannin, Trimer | ***(* Nilkalji *et al.,2012)*** |
| 8 | *Gatu kala* | Apiaceae | Triterpinoids | ***(* Nilkalji *et al.,2012)*** |

| | | | | |
|---|---|---|---|---|
| 9 | *Betony* | Lamiaceae | Phenylethamide, Glycosides, Tannin | ***(* Nilkalji *et al.,2012)*** |
| 10 | *Ginseng* | Araliaceae | Gincenoside, Phenezoside | ***(* Nilkalji *et al.,2012)*** |
| 11 | *Lily of the Valley* | Lily | Geraniol | ***(* Nilkalji *et al.,2012)*** |
| 12 | *Vitellaria paradoxa* | sapotaceae | Bassic acid, catechin, quercetin | **(E. Ngo Bum *et al.,2011)*** |
| 13 | *Bryophyllum pinnatum* | crassulaceae | Quercetin, rutin, luteolin, steroids. | **(E. Ngo Bum *et al.,2011)*** |
| 14 | *Datura stramonium* | Solanaceae | atropine, daturadiol, hyoscymine | **(E. Ngo Bum *et al.,2011)*** |
| 15 | *Flacourtia indica* | Salicaceae | Catechin, tannins, quercetin | **(E. Ngo Bum *et al.,2011)*** |

Some of the traditional plants which are used to treat epilepsy by intake in the form of decoction are mention in table 2

**Table: 2 Antiepileptic plants used for decoction**

**(Ngo Bum *et al., 2011)***

| SNO. | Name of the plant | Parts used for decoction |
|---|---|---|
| 1 | *Annona muricata* | Fresh leaves |
| 2 | *Annona senegalensis* | Dried leaves |
| 3 | *Bidens pilosa* | Fresh leaves |
| 4 | *Bryophyllum pinnatum* | Fresh leaves |
| 5 | *Citrus sinenis* | Fresh leaves |
| 6 | *Clerodendron thomsoniae* | Dried leaves |
| 7 | *Daniellia oliveri* | Dried barks |
| 8 | *Datura stramonium* | Dried fruit |
| 9 | *Detarium microcarpum* | Dried roots |
| 10 | *Euphorbia hirta* | Fresh plant |
| 11 | *Flacourtia indica* | Dried bark |
| 12 | *Hymenocardia acida* | Fresh leaves |
| 13 | *Jatropha gossypiifolia* | Dried leaves |
| 14 | *Khaya senegalensis* | Dried leaves |
| 15 | *Mentha cordifolia* | Fresh leaves |
| 16 | *Prosopis Africana* | Dried leaves |
| 17 | *Ricinus communis* | Fresh leaves |
| 18 | *Securidaca longepedunculata* | Dried roots |
| 19 | *Senna singueana* | Dried roots |
| 20 | *Terminalia glaucescens* | Dried roots |
| 21 | *Tetrapleura tétraptera* | Dried barks |
| 22 | *Trichilia emetica* | Fresh roots |
| 23 | *Vitelaria paradoxa* | Fresh leaves |

Pilocarpine administration intraperitoneally increased lipid peroxidation and decreased antioxidant enzymes such as catalase, superoxide dismutase, and glutathione reductase. The administration of naringenin (20 mg/kg body weight and 40 mg/kg body weight) to mice reduced lipid peroxidation significantly. The glutathione concentration as well as all of the antioxidant enzymes evaluated showed considerable improvement. In the case of behavioral parameters, naringenin was found to reduce seizure severity. All of these improvements were backed up by histology findings, which demonstrated a significant reduction in neuronal damage.In their trial, the larger dose of naringenin was more potent and efficacious than the conventional medicine (sodium valproate) ***(*Sheeba *et al.,2017).***

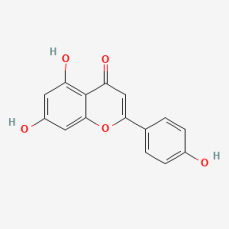
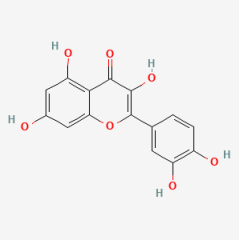
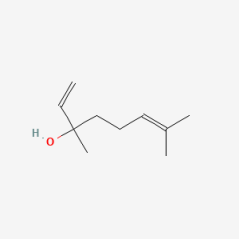
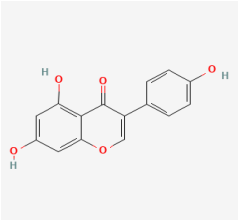
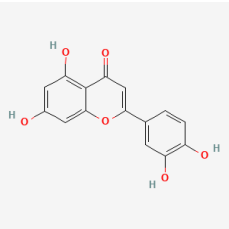
In ovariectomized rats challenged with pentylenetetrazole (PTZ) 90 mg/kg i.p., the potential neuroprotective impact of genistein, a phytoestrogen, was studied at dosages of 5, 10, 20, and 40 mg/kg p.o. PTZ caused convulsions, elevated oxidative stress, apoptosis, and histological changes when given systemically. Pretreatment with genistein delayed the start of seizures, lowered the length of seizures, improved the oxidative stress profile, decreased estrogen receptor expression, decreased apoptosis, and improved the histopathological pattern. Overall, the most protective benefits were seen with genistein dosages of 10 and 20 mg/kg. Finally, the current research reveals that genistein has neuroprotective properties against PTZ-induced seizures. Its estrogenic, antioxidant, and/or anti-apoptotic characteristics could explain these effects ***(*Amr *et al.,2017).***

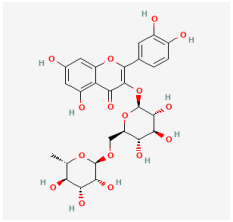
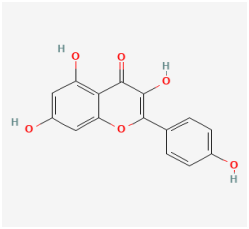
Flavonoids have structures that are comparable to benzodiazepines and act as anti-epileptics via regulating the GABA-Cl-channel complex. There are several flavonoids that can be utilized to treat epilepsy via various receptor signaling pathways. Tanshinone IIA is a hydrophobic ketone found in the *Salvia miltiorrhiza* plant. Glycosides have been shown to be effective in the treatment of epilepsy. Paeoniflorin (PF) works as an antiepileptic by blocking gluten-induced Ca2+ influx, activation of the metabotropic Glu receptor 5 (mGluR5), membrane depolarization, and neuronal death ***(*Li-ying *et al.,2021).***

Natural drugs used to treat epilepsy by regulating neurotransmitters and synaptic functions are given below table 3,

**Table 3 Natural drugs used to treat epilepsy**

***(*Li-ying *et al.,2021)***

| Natural Drugs | Compounds | Chemical Structure | Mechanism |
|---|---|---|---|
| *Matricaria chamomilla L*.<br>(Chamomile) | Apigenin |  | Curbing benzodiazepine agonist. |
| *Bupleurum chinense*<br>(Umbelliferae) | Quercetin |  | Influencing ionotropic GABA receptors. |
| Green tea *(Camellia sinensis(L*.)Kuntze) | Linalool |  | Improving $Na^+$ channels. |
| Soybean *(Glycine max (L.))* | Genistein |  | Affecting both cell-mediated and humoral components of the adaptive immune system. |
| *Eclipta prostrate L*.<br>(Asteraceae) | Luteolin |  | Inhibiting oxidative stress. |

| | | | |
|---|---|---|---|
| *Sophora japonica L*.<br>(Fabaceae) | Rutin |  | Improving epileptoid action. |
| *Achillea millefolium L.*<br>(Yarrow) | Kaempferol |  | Inhibition of DNA topoisomerase I enzyme. |

The phytoconstituents studied, showed promise as anticonvulsants while also being less hazardous. In the published investigations, a few of the phytoconstituents examined (e.g. diterpene phytol, -caryophyllene, CBD, and berberine) had no effect on behavioral characteristics such as locomotion and muscle coordination. The medicinal plants have the potential to be a gold mine for antiepileptic drugs that are both safer and more effective ***(*Jaskiran *et al.,2020).***

Kaempferol content in our daily foodstuff are given in table 4,

**Table: 4 Kaempferol content in foodstuff**

***(*Muhammad *et al.,2020)***

| | **Food/plant Beverages** | **Quantity** |
|---|---|---|
| Kaempferol | Strawberry | 5-8 mg/Kg |
| | Gooseberry yellow | 16 mg/Kg |
| | Gooseberry red | 19 mg/Kg |
| | Onion leaves | 832 mg/Kg |
| | Black tea | 118 mg/Kg |
| | Green chilli | 39 mg/Kg |
| | Papaya shoots | 453 mg/Kg |
| | Brinjal | 80 mg/Kg |
| | Pumpkin | 371mg/Kg |
| | Carrot | 140mg/Kg |
| | White radish | 38 mg/Kg |
| | Beans | 14 mg/Kg |

| | | |
|---|---|---|
| | Broccoli | 72 mg/Kg |
| | Cauliflower | 270 mg/Kg |

The protective efficacy of a poly herbal extract containing *Withania somnifera Dunal, Bacopa monnieri, Chlorophytum borivillianum, Curcuma longa, Glycyrrhiza glabra,* and *Terminalia arjuna* against seizures generated by the Maximal Electroshock Seizures method in rats was investigated. The experimental animals showed a considerable reduction in the time it took to restore their righting reflex. The levels of biogenic amines including dopamine, serotonin, and nor-adrenaline in the forebrain region were also measured, and the extract-treated animals showed a considerable level of repair. Its putative mechanisms include inhibition of prostaglandin synthesis and the monoamine oxidase enzyme, as well as a decrease in calcium ion influx (**Balamurugan *et al.,*2009).**

*Valeriana officinalis*: Valeriana officinalis and passionflower active components may increase the inhibitory activity of benzodiazepines binding to GABA receptors, resulting in severe side effects***.*** *Withania somnifera*: A poly herbal extract containing Withania somnifera Dunal, a medicinal plant utilized in several neuroprotective Ayurvedic treatments, as well as five other medicinal plants, was tested for its ability to prevent seizures caused by the MES method. These medicinal herbs have been used in the treatment of epilepsy ***(*Mohammad Asif *2013).***

Pentylenetetrazole, strychnine, and MES caused seizures in mice were examined using the saponins rich fraction (SFG) derived from *Ficus platyphylla* stem bark. SFG protected mice from seizures caused by pentylenetetrazole and strychnine, as well as delaying the development of myoclonic jerks and tonic seizures. SFG did not protect mice from the most severe electroshock convulsions. SFG did not stop spontaneous discharges caused by 4- aminopyridine in a neonatal rat brain slice model of tonic–clonic epilepsy, nor could it modify chloride currents in cultured cortical cells via the GABAA receptor channel complex. In these cultured neurons, however, it was able to non-selectively decrease

excitatory and inhibitory synaptic traffic, as well as prevent persistent repetitive firing and spontaneous action potential firing cells. It most likely works by obstructing voltage- gated sodium channels ***(*Syeda *et al.,2015).***

The flavonoids in *Rosa damascena* can reduce the latent periods of the onset of convulsions as well as the severity of seizures in rats in a dose-dependent manner, possibly through GABAA receptors **(kheirabadi *et al*.,2008).**

Pentylenetetrazole-induced seizures were avoided by the hexanoic portion of *Rubus brasiliensis*. The presence of a benzodiazepine-like principle in the fraction suggested that GABAA receptors were involved. The reversal of anxiolysis in rodents elicited by lumozenil, a selective GABA–A– benzodiazepine receptor antagonist, further supports its participation ***(*Nogueira *et al.,*2000).**

*Panchagavya Ghrutham*, a polyherbal ayurvedic formulation containing *Glycerrhiza glabra, Acorus calamus, and panchagavya* - the five products of the cow, namely milk, ghee (clarified butter fat), curd, urine, and dung - protected mice from tonic convulsions induced by maximal electroshock seizures and slightly prolonged the phases of seizure activity induced by Pentylenetetrazole ***(*Anupama *et al.,*2009).**

Antiepileptic and neuroprotective properties were found in polyphenolic antioxidants Apigenin-8-C-glucoside and Chlorogenic acid. Free radical quenching via increased antioxidant enzyme activities (SOD, catalase, and GSH) and inhibition of the expression of epileptic and neurodegenerative mediators such as Grin1, Grm1, and Grm5 may be linked to the antiepileptic actions of Apigenin-8-C-glucoside and Chlorogenic acid.These findings support the use of dietary polyphenols Apigenin-8-C-glucoside amd chlorogenic acid as neuroprotective agents in the treatment of epileptic sequelae ***(*Smilin *et al.,2016).***

Naringenin is a flavonoid with a number of extraordinary biological outcomes in the central fearful system. As mentioned, naringenin has neuroprotective, reminiscence enhancing, anti-inflammatory and antioxidant effects. Objectives: In this study, we investigated consequences of naringenin on pentylenetetrazole and maximal electroshock-induced seizures in mice.Naringenin was administered at doses of 50, a hundred and 200 mg/kg intraperitoneally in two fashions of seizure. Thirty minutes after extraordinary doses

of naringenin, phenytoin or diazepam and vehicle, the animal obtained pentylenetetrazole or cutting-edge stimulus through an electroconvulsiometer.In maximal electroshock model, naringenin 200 mg/kg reduced the length of hind limb tonic extension. In the pentylenetetrazole seizure model all doses of naringenin elevated the latency for convulsion and latency for Straub's tail; however, only naringenin 200 mg/kg confirmed significant discount in duration of myoclonic seizure. According to the results, naringenin showed substantial anticonvulsant and neuroprotection pastime in two pentylenetetrazole and electroshock models of convulsion in mice and these results may be mediated by means of antioxidant properties, agonist pastime on GABAA receptors and weakening of glutamate transmission ***(*Mohammad *et al.,2017).***

Flavonoids are a type of natural ingredient found in plants that has a variety of pharmacologic effects, including anti seizure capabilities. They discovered that chrysin could prevent tonic–clonic seizures caused by PTZ by blocking central benzodiazepine (BZD) receptors. Apigenin, which has one extra hydroxyl group on ring B than chrysin, may help to shorten the time it takes for PTZ-induced convulsions to start. Wogonin is produced by adding a methoxy group to the C-8 position of chrysin, and it has the potential to greatly reduce convulsions caused by PTZ and electroshock ***(*Hui *et al.,2014).***

*Tapinanthus globiferus* is often referred to as an all-purpose herb for the therapy of stroke and epilepsy. The present study investigates the anticonvulsant impact of methanolic leaf extract, lively fractions, and lupeol (isolate) of *Tapinanthus globiferus* in mice as well as the underlying mechanisms. Following phytochemical research of T. globiferus, preliminary assays were performed to evaluate MLE-induced toxic effect and behavioral changes. The pentylenetetrazol (70 mg/kg, i. p.)-induced seizure was once evaluated in mice that had been pre- treated orally with car 10 mL/kg, MLE (4, 20, or one hundred mg/ kg), fractions (F1 to F6), lupeol 10 mg/kg or diazepam (3 mg/ kg). Methanolic leaf extract preserved neuron viability as well as the relative organ weight, and hematological and biochemical parameters. The behavioral endpoints, neuromuscular coordination, and sensory response parameters published a dose-dependent impact of methanolic leaf extract. This extract, energetic fractions, lupeol, and diazepam potentiated the hypno- sedative effect of the barbiturate and attenuated PTZ-induced acute seizure.

This antiseizure impact used to be completely reversed with the aid of flumazenil two mg/kg (benzodiazepine website online antagonist). Altogether, the benzodiazepine site-mediated anticonvulsant effects of methanolic leaf extract, active fractions, and lupeol corroborate regular application of *T. globiferus* against epilepsy ***(*Christianah *et al.,2020).***

There are around 25 to 30 herbal plants used to treat epilepsy by traditional treatments.They are, *Cannabis sativa, Zizyphus jujuba, Valeriana officinalis, panar ginseng, flacourtia indica, Ricinus communis, Securidaca longepedunculata, Senna singueana, Terminalia glaucescens, Pimpinella anisum, cinnamomum camphora, zingiber officinalis, lavandula officinalis, origanum vulgare, ocimum basilicum, citrus sinensis, Cymbopogon flexuosus, centella asiatica* etc.

It is important to note that some commercial AED drugs may prevent seizures in one person but not in another. Also, even when a person finds the right drug, it may take some time to find the ideal dosage. Maximum people prefer Antiepileptic drugs. But it has more side effects. So I prefer herbal treatments to cure epilepsy. Because it has minimal side effects. So I analyze some plants which are used in herbal medicine to treat epilepsy.

Some of the Antiepileptic and anticonvulsant phytochemical compounds mention in the below flowsheet,

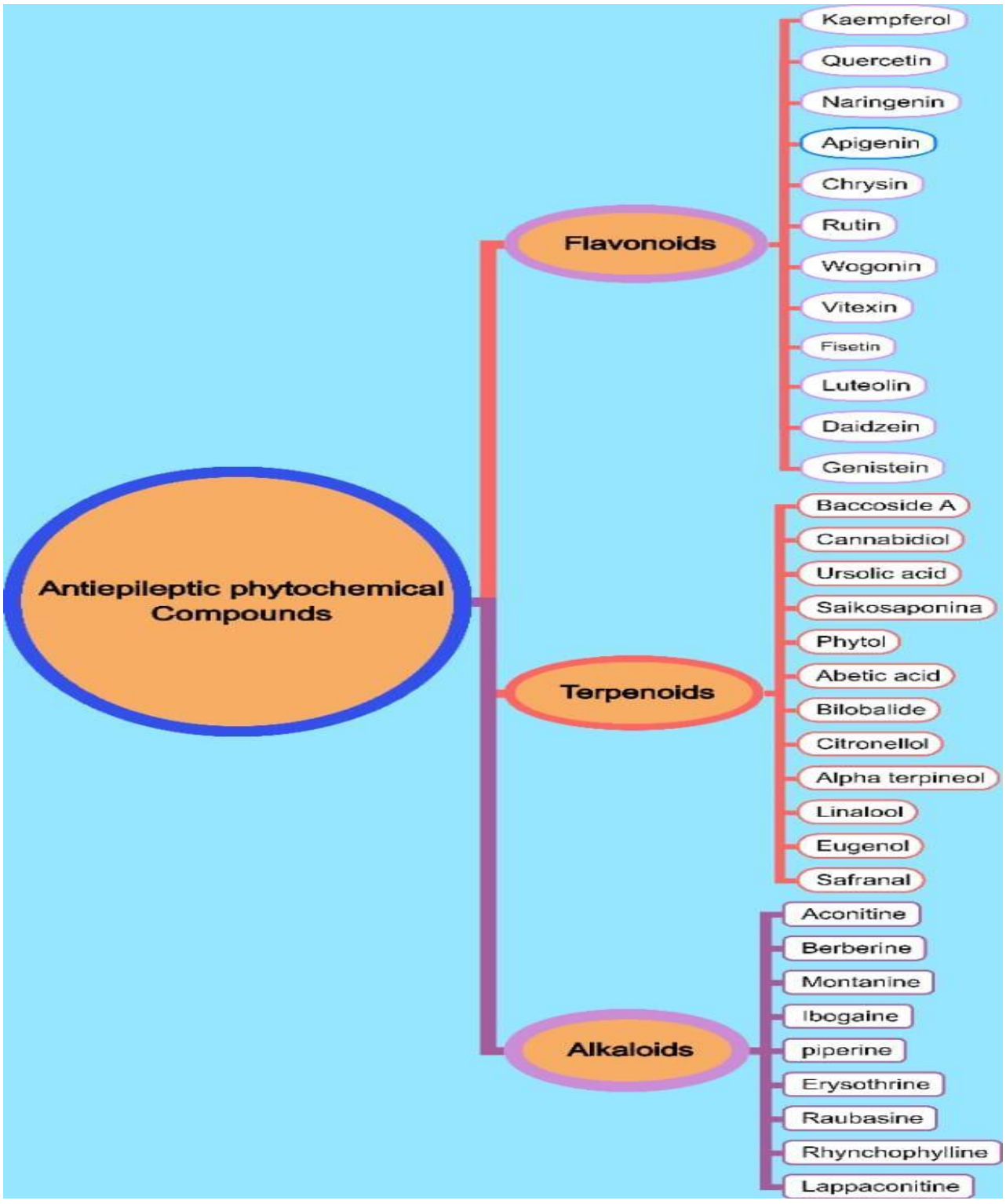



**Fig 1: Antiepileptic and anticonvulsant phytochemical compounds**

## 2.2 Commercial Herbal Antiepileptic drugs

Some of the marketed herbal medication with antiepileptic activity are given in table 5

**Table: 5 Marketed herbal medication for Epilepsy**

***(*Vyawahare *et al.,*2007)**

| S. No | BRAND NAME | Mfg. COMPANY | INGREDIENT |
|---|---|---|---|
| 1 | APSA | IMIS | Withania somnifera, Hemamakshika Blasma, Rajatha Blasma, Extract of Rasona Vacha, Atimadhura, Mandukaparni, Kushta, Jatamansi, ParasikaYavani, Brahmi, Shatavari, Kushmanda, Sarpagandha, Triphal, Jeeraka, Krishana Beeja, Shirisha Beeja, Guduchi And Apapajitha |
| 2 | Ned forte | Charak | Akika Bhasma, Mass Extracts Of Yashthimadhu, Brahmi, and Vacha. |
| 3 | Zandopa | Zandu | Mucuna Pruriens. |
| 4 | Raswatarishta | Baidyanath | Brahmi, Shatavar, Vidara, Haritaki, Ushri, Sontha, Saunf, Nishoth, Laung Papal, Vacha, Kust, Ela, Ashvagandha, Bahera, Giloe, Vidanga, Dachini, Dhataki, Jaggery (Gud). |
| 5 | Chaturbhuj Ras | Baidyanath | Ras Sindoor, Kasturi, Swarna Blasma, Manashila and Hartal, Ghrit Kumari |
| 6 | Chaturmukha Ras.(with gold) | Baidyanath | Parad, Gandhak, Lauha, Bhasma, Abhrak, Bhasma, Swarna Bhasma |

## 2.3 Review of literature pertaining to studies on antiepileptic properties of chemical compounds:

A group of new isatin aroyl hydrazone (5a-e and 6a-e) was synthesized and evaluated for their anticonvulsant activities. The (Z)-configuration of compounds was proven by way of 1 H NMR. In vivo studies the usage of maximal electroshock (MES) and pentylenetetrazole (PTZ) models of epilepsy in mice published that whilst most of compounds had no impact on chemically-induced seizures at the greater dose of one hundred mg/kg however showed vast protection towards electrically-induced seizures at the lower dose of 5 mg/kg. Certainly, N-methyl analogs have been determined to be the most positive compounds, displaying 100%protection at the dose of 5 mg/kg. Protein binding and lipophilicity (logP) of the selected compounds were additionally determined experimentally. In silico critiques of isatin aroyl hydrazone compounds showed acceptable ADME parameters, and drug-likeness properties. Distance mapping and docking of the selected compounds with exceptional targets proposed the viable action of them on VGSCs and GABAA receptors ***(*Saeed *et al.,2021).***

A collection of novel quinoxaline derivatives linked to a pyridine moiety through phenylamino or phenoxy residue was once synthesized and evaluated as candidate anticonvulsants. The synthesis used to be performed through reaction of 2,3-dichloroquinoxaline (1) with an equimolar amount of 4-aminoacetophenone to give compound two which is regarded as an necessary synthon for the development of a pyridine ring via several synthetic routes. Some compounds have been synthesized through formation of the intermediate unsaturated compounds which, in turn, were allowed to react with malononitrile to provide the corresponding alkyl pyridines (8-17). Compounds 18-21 have been synthesized via a one-pot simple response between 2, the appropriate aldehyde, and malononitrile in sodium alkoxide solution. Moreover, they can be synthesized through the response of compound two and arylidene malononitrile in sodium alkoxide. The phenoxy analogues were organized with the aid of response of 1 with 4-hydroxyacetophenone or 3-hydroxybenzaldehyde to give 22 and 27, respectively. These compounds, in turn, were allowed to react with malononitrile and the perfect carbonyl compound in presence of sodium alkoxide in a one-pot response approach to supply the

target compounds. Biological assessment of the organized compounds showed that some of them are potent anticonvulsant agents. The distinct synthesis, spectroscopic and biological statistics are reported ***(*Magda *et al.,2003).***

Biological mechanism attributing mutations in KCNQ2/Q3 effects in benign familial neonatal epilepsy (BFNE), an uncommon shape of epilepsy and as a result neglected. It offers a possible goal for antiepileptic drug discovery. In the present work, a pharmacophore-based 3D-QSAR mannequin was generated for a sequence of Pyridine and pyrimidine benzamides possessing KCNQ2/Q3 opening activity. The pharmacophore model generated carries one hydrogen bond donor (D), one hydrophobic (H), and two aromatic rings (R). They are the indispensable molecular write-up detailing estimated binding efficacy of excessive affinity and low affinity ligands for KCNQ2/Q3 opening activity. Furthermore, it has been validated by the usage of a biological correlation between pharmacophore hypothesis-based 3D-QSAR variables and useful fingerprints of openers accountable for the receptor binding and additionally by way of docking of these benzamides into the validated homology model. Excellent statistical computational equipment of QSAR mannequin such as properly correlation coefficient (R2>0.80), greater F cost (F > 39), and exquisite predictive strength (Q2> 0.7) with low standard deviation (SD advise that the developed mannequin should be used for prediction of antiepileptic endeavor of newer analogs. A preliminary pharmacokinetic profile of these derivatives was additionally carried out on the basis of QikProp predictions ***(*Ruchi *et al.,2016).***

Six novel N-aryl-4-(1,3-dioxoisoindolin-2-yl) benzamide analogues were synthesized and anti-seizure efficacy was investigated. The way of interaction between the GABAA receptor and synthetized drugs was investigated using docking methods. NMR and mass spectroscopy were used to confirm the structures of all produced substances. After an hour of pentylenetetrazole administration, the latency time and mortality rate were assessed individually. Synthesized chemicals and thalidomide interact with the GABAA receptor in a comparable shape, according to a docking research. The testing and docking results showed that the most active molecule (N-(3-4-dimethylphenyl)-4-(1,3-dioxoisoindolin-2-yl) benzamide which contains a 3,4-dimethylphenyl residue, improved

the length of seizure inhibition threshold when compared to thalidomide ***(*Parisa *et al.,2020).***

Picrotoxin as an anticonvulsant was the subject of the research, which accounts for around 1% of the world's disease burden. In actuality, a number of synthetic antiepileptic medications are available; nevertheless, their effectiveness does not apply to the full population affected by this illness. Furthermore, side effects and medication interactions are significant limitations to its therapeutic value. They have summarized the present herbal antiepileptics and their research advances in this overview ***(*Vyawahare *et al.,2007)***.

New anticonvulsant drugs have been described, which represent diverse structures for which the particular mechanism of action is still unknown. Many of the compounds discussed in this review were investigated using the Antiepileptic Drug Development Program of the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke of the National Institutes of Health in the United States. Sulfonamides, amino acids, amides (vinyl GABA analogues, N-benzyl amides, 2,6-dimethylaniline, carboxamides, hydroxy amides, alkanolamides); heterocyclic agents (aryl alkyl) imidazoles, pyrrolidin-2,5-diones, lactams, semi-thiosemicarbazones, thiadiazoles, quina These new structural classes of compounds may prove valuable in the creation of new medications and the design of future targets ***(*Malawa *et al.,2005)***.

### 2.4 Commercial Antiepileptic drugs

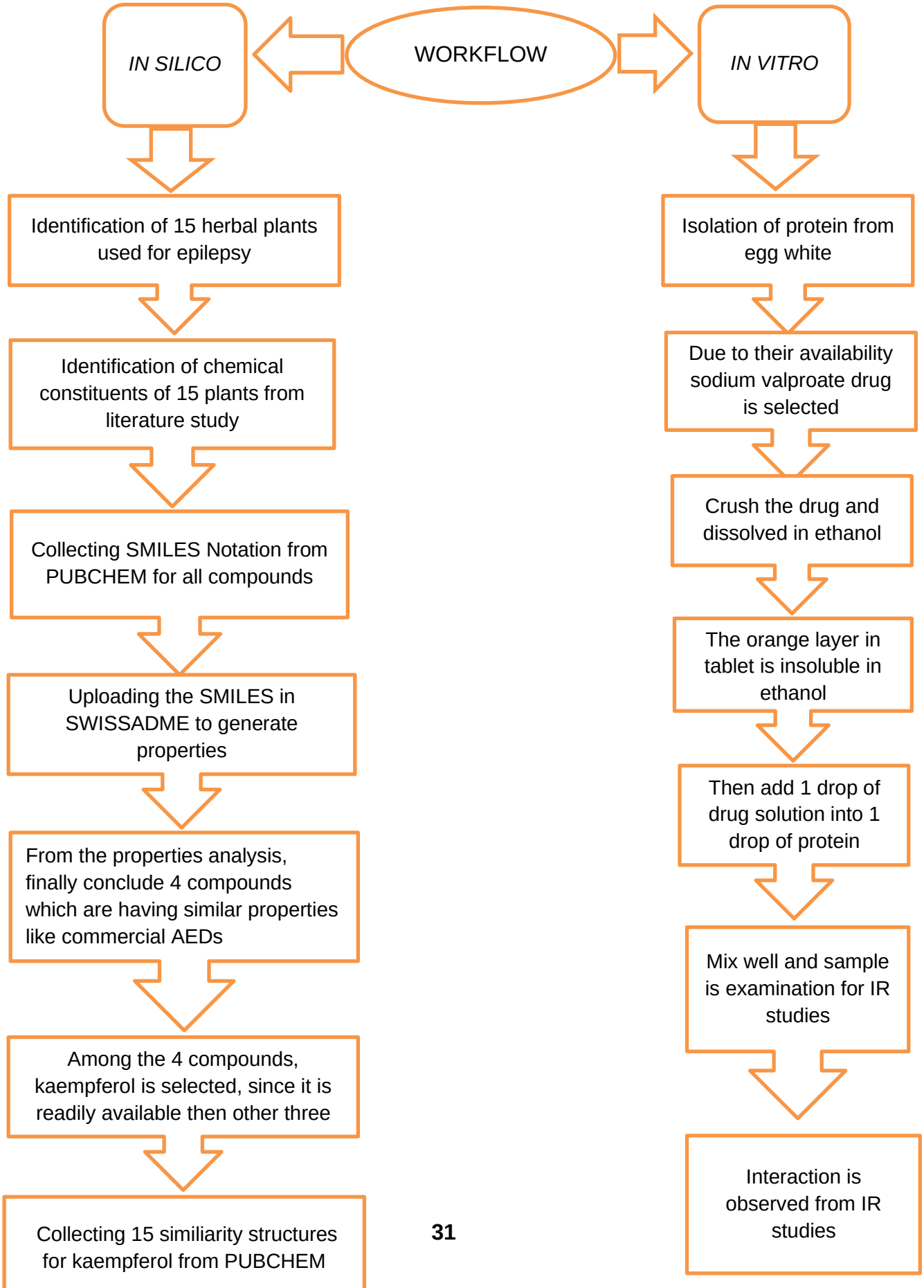
Available commercial Antiepileptic drugs with their mechanism of action, clinical application and adverse effects are given below in table 6.

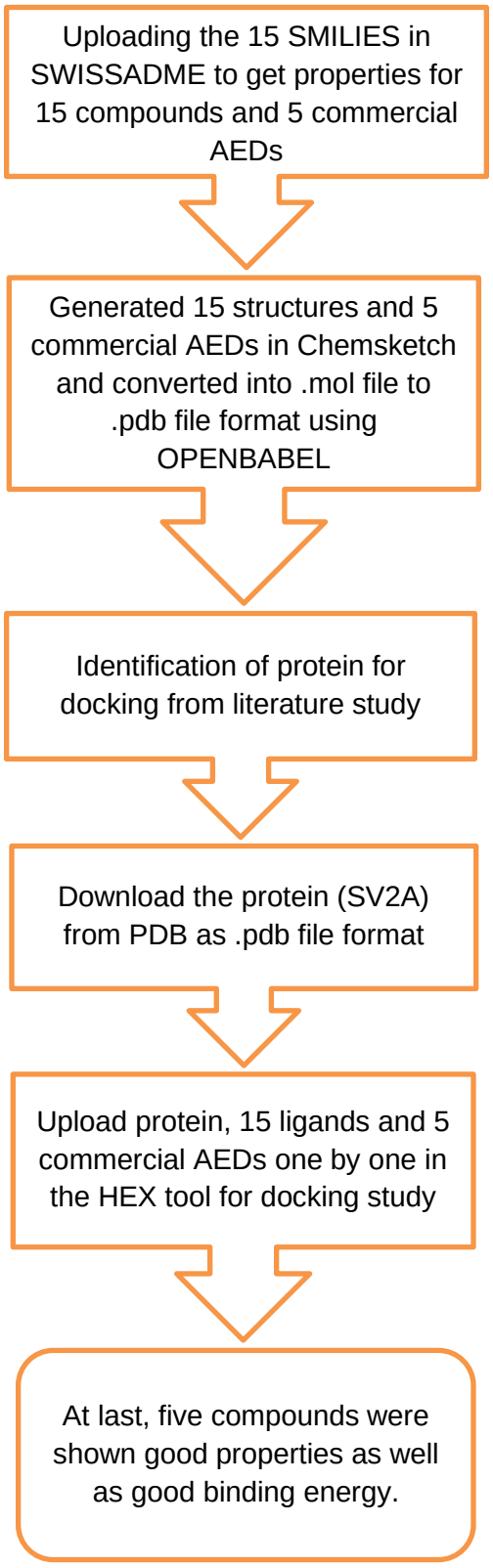
**Table: 6 Commercial antiepileptic drugs with mechanism, application and adverse effect *(*Syeda *et al.,2015)***

| Drug | Mechanism of action | Clinical Application | Adverse effect |
|---|---|---|---|
| Phenytoin | Blocks high frequency firing of neurons through action on voltage gated sodium ion channels. | Partial seizures and generalized tonic clonic seizures. | Ataxia, diploma, nystagmus, coarsening of facial features gingival hyperplasia, hirsutism, skin rashes, Steven's-Johnson syndrome, agranulocytosis, Atlantic anemia, teratogenicity. |
| Diazepam | Potentiates GABAA responses | Status epilepticus and seizure clusters | Sedation, lethargy, drowsiness, dizziness, behavioral disturbances in children, hypersalivation |
| Valproate | Blocks high frequency firing of neurons and modifies amino acid metabolism | Generalized seizures, partial seizures, absence seizures and myoclonic seizures | Tremor, weight gain, dyspepsia, peripheral edema, pancreatitis, hair loss, thrombocytopenia, polycystic ovaries, Stevens–Johnson syndrome, hepatotoxicity, |
| Tiagabine | Blocks GABA reuptake in forebrain by selective blockade of GAT-1 | Partial seizures | Dizziness, lethargy, tremor, nervousness, emotional changes |
| Stiripentol | Enhancement of inhibitory, GABAergic neurotransmission | Dravet's syndrome | Loss of appetite, drowsiness, cognitive impairment, ataxia, diplopia, nausea, abdominal pain |

# 3.MATERIALS AND METHODS

The materials, software, equipment used in this study entitiled “Antiepileptic And Molecular docking - based Approaches”


WORKFLOW
IN SILICO
IN VITRO
Identification of 15 herbal plants used for epilepsy
Identification of chemical constituents of 15 plants from literature study
Collecting SMILES Notation from PUBCHEM for all compounds
Uploading the SMILES in SWISSADME to generate properties
From the properties analysis, finally conclude 4 compounds which are having similar properties like commercial AEDs
Among the 4 compounds, kaempferol is selected, since it is readily available then other three
Collecting 15 similiarity structures for kaempferol from PUBCHEM
Isolation of protein from egg white
Due to their availability sodium valproate drug is selected
Crush the drug and dissolved in ethanol
The orange layer in tablet is insoluble in ethanol
Then add 1 drop of drug solution into 1 drop of protein
Mix well and sample is examination for IR studies
Interaction is observed from IR studies


Uploading the 15 SMILIES in SWISSADME to get properties for 15 compounds and 5 commercial AEDs
Generated 15 structures and 5 commercial AEDs in Chemsketch and converted into .mol file to .pdb file format using OPENBABEL
Identification of protein for docking from literature study
Download the protein (SV2A) from PDB as .pdb file format
Upload protein, 15 ligands and 5 commercial AEDs one by one in the HEX tool for docking study
At last, five compounds were shown good properties as well as good binding energy.

## 3.1 General

Structures are drawn by using Chemsketch tool, Docking study carried by using HEX, ADME property study carried by using SWISSADME tool.

### 3.1.1 Equipment and instruments used

Centrifuge machine, IR spectrometer and Sonnicator.

## 3.2 Selection and preparation of ligands

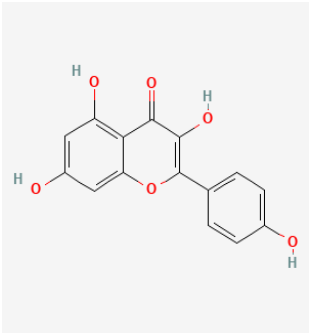
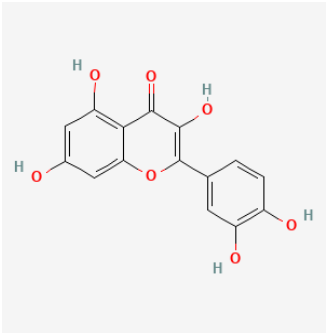
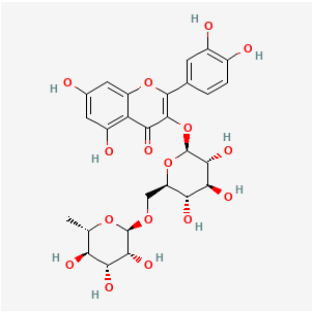
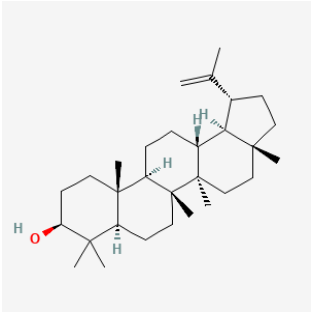
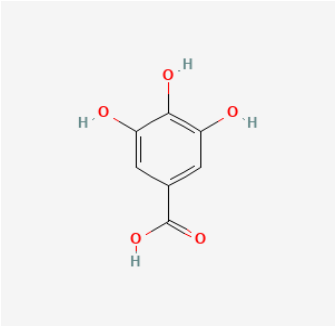
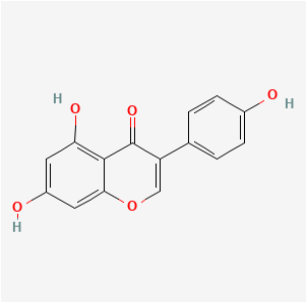
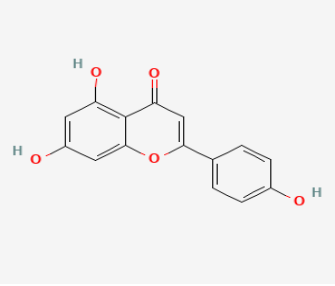
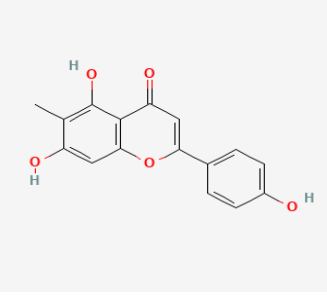
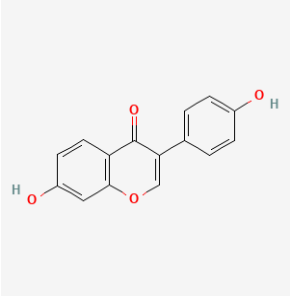
Using a "similarity structure" search, naturally accessible phytochemical compounds are gathered from pubchem. Chemsketch professional software was used to create two-dimensional chemical structure of ligands, which were saved in mol file format. Then by using OPENBABEL software, mol file format is converted into pdb file format because Docking software is accepted only in the pdb file format.

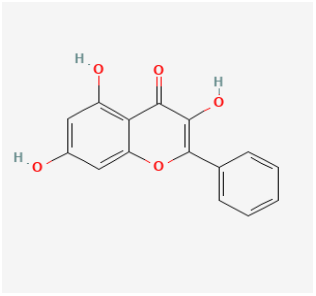
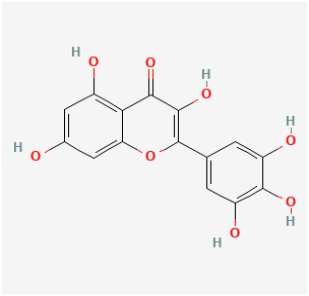
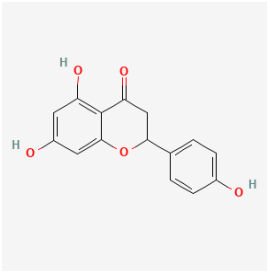
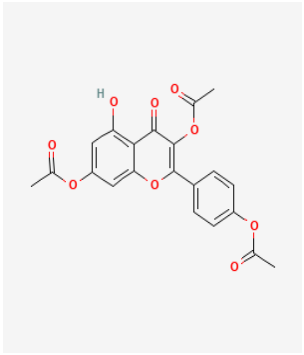
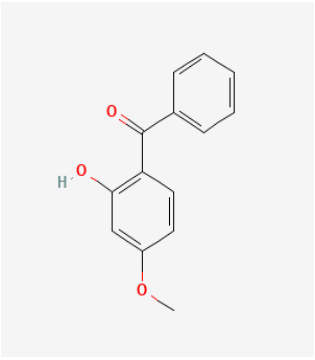
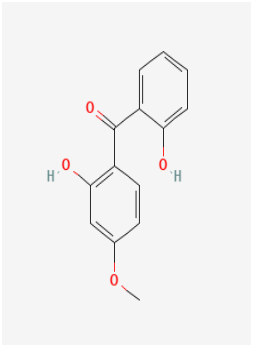
## 3.3 Structures

The 15 compounds are listed below table 7;

Kaempferol (1), Quercetin (2), Rutin (3), Lupeol (4), Gallic acid (5), Genistein (6), Apigenin (7), 6-Methyl Apigenin (8), Daidzein (9), Galangin (10), Myricetin (11), Naringenin (12), Kaempferol 3,4,7 triacetate (13), Oxybenzone (14), Dioxybenzone (15).

**Table 7: Structures for this study**

| | | |
|---|---|---|
| 1.  | 2.  | 3.  |
| 4.  | 5.  | 6.  |
| 7.  | 8.  | 9.  |

| | | |
|---|---|---|
| 10.  | 11.  | 12.  |
| 13.  | 14.  | 15.  |

( Source : PUBCHEM)

### 3.3.1 Standard compounds

In this study, standard compounds used are commercial antiepileptic drugs such as,

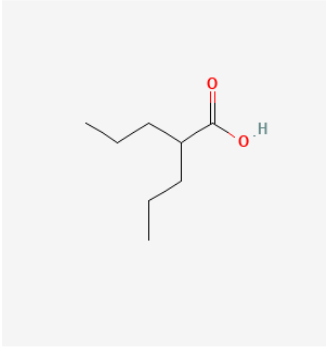
a.Valproic acid

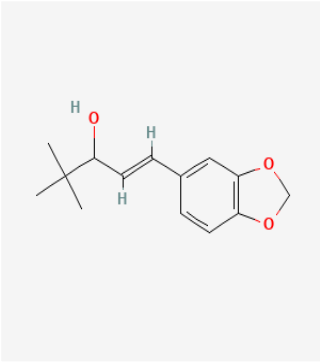
b. Stiripentol

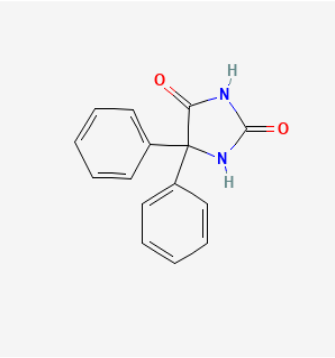
c. Phenytoin

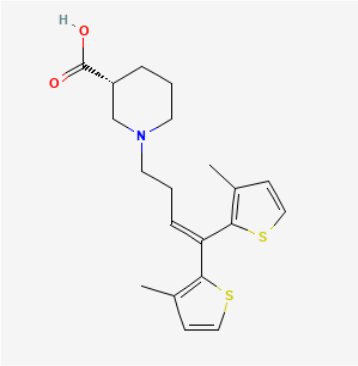
d.Tiagabine

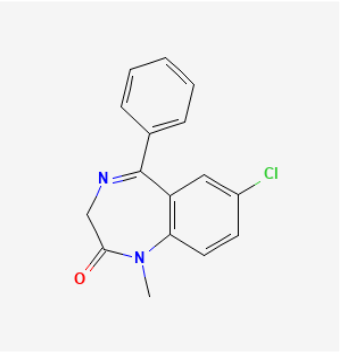
e. Diazepam

a. 

b. 

c. 

d. 

e. 

## 3.4 Selection of Proteins

Proteins are selected from some articles collected from scifinder software, and the proteins are downloaded from PDB software. Selected protein SV2A.

## 3.5 Prognostication of ADME Property

ADME properties of these compounds are studied by using the SWISSADME tool. Some of the ADME properties such as iLOGP, XLOGP3, WLOGP, MLOGP, CYP2C19 inhibitors, logKp, Bioavailability, Lead Likeness, GI Absorption etc.

## 3.6 Prognostication of LIPINSKI RULE OF FIVE

Lipinski rule of five states that,

1.Molecular weight should be <500.

2. Lipophilicity should be <5.

3. H - bond Donors should be <5.

4. H - bond Acceptors < 10.

5. Rule violations <2.

This rule helps to investigate if a chemical molecule with a specific pharmacological or biological activity has chemical and physical qualities that would lead to it becoming a potential orally active.

## 3.7 Analysis of Constituents in Antiepileptic Plants

There are around 25 to 30 herbal plants used to treat epilepsy by traditional treatments.They are, *Cannabis sativa, Zizyphus jujuba, Valeriana officinalis, panar ginseng, flacourtia indica, Ricinus communis, Securidaca longepedunculata, Senna singueana, Terminalia glaucescens, Pimpinella anisum, cinnamomum camphora, zingiber officinalis, lavandula officinalis, origanum vulgare, ocimum basilicum, citrus sinensis, Cymbopogon flexuosus, centella asiatica* etc.

## 3.8 Prognostication of Molecular Docking

These compounds are docked with protein SV2A by using an HEX software tool.

## 3.9 Prognostication of Bioactivity Properties

The SMILES Notation of Compounds under study copied and pasted in the molinspiration software and clicked bioactivity properties. The properties like GPCR ligand, Ion channel modulator, kinase inhibitors, Nuclear receptor ligand, Protease inhibitors and Enzyme inhibitors for 5 compounds.

- Molecules with the highest activity score have the highest probability to be active
- If the bioactivity score is more than 0.0, then the molecule will be active

- If the bioactivity score is between - 5 and 0.0, then the molecule will be moderately active
- If the bioactivity score is less than -5.0, then the molecule will be inactive

### 3.10 Isolation of protein from egg white

- First, Take fresh egg and gently put hole and collect the white portion along in a clean and dry beaker
- Then, Take small portion from that beaker into a small clean test tube, and diluted the egg white with distilled water then homogenized
- The other components of egg white were removed through centrifugation
- The clear upper portion is protein and stored in a cooled place

## 3.11 Sodium valproate in solvent

Take one tablet of 200mg sodium valproate dissolved in 6 ml of ethanol, stirred well using glass rod. Here there is one orange layer which is coated in a tablet, that layer cannot be dissolved. Then slightly keep the sample in Sonnicator for 15 mins for complete dissolve.

## 3.12 Protein with commercial AED

Take 1ml of protein and add 1 ml of sodium valproate solution into it. Without shaking or any disturbance, samples were kept safe and tested for interaction study by using FTIR.

# 4.Results and Discussion

The results of the study on" Antiepileptic and Molecular Docking Based Approaches" and relevant discussions are presented in the following pages.

## 4.1 Results of ADME properties

### Commercial drugs

- For this study, 5 commercial Antiepileptic drugs were chosen on the basis of patients used.They are Diazepam, Sodium valproate, Phenytoin, Tiagabine and Stiripentol
- All the five drugs had molecular weight below 500. So all the drugs obeys the Lipinski rule. They were shown below in table 8

**Table: 8 Physicochemical properties of commercial AEDs**

| Molecule | Canonical SMILES | Formula | MW |
|---|---|---|---|
| Valproic acid | CCCC(C(=O)O)CCC | C8H16O2 | 144.21 |
| Stiripentol | OC(C(C)(C)C)C=Cc1ccc2c(c1)OCO2 | C14H18O3 | 234.29 |
| Phenytoin | O=C1NC(=O)NC1(c1ccccc1)c1ccccc1 | C15H12N2O2 | 252.27 |
| Tiagabine | OC(=O)C1CCCN(C1)CCC=C(c1sccc1C)c1sccc1C | C20H25NO2S2 | 375.55 |
| Diazepam | Clc1ccc2c(c1)C(=NCC(=O)N2C)c1ccccc1 | C16H13ClN2O | 284.74 |

**Table :9 Physicochemical properties of commercial AEDs**

| Molecule | #Heavy atoms | #Aromatic heavy atoms | Fraction Csp3 | #Rotatable bonds | #H-bond acceptors |
|---|---|---|---|---|---|
| Valproic acid | 10 | 0 | 0.88 | 5 | 2 |
| Stiripentol | 17 | 6 | 0.43 | 3 | 3 |
| Phenytoin | 19 | 12 | 0.07 | 2 | 2 |

| | | | | | |
|---|---|---|---|---|---|
| Tiagabine | 25 | 10 | 0.45 | 6 | 3 |
| Diazepam | 20 | 12 | 0.12 | 1 | 2 |

From the above table 9, three drugs have the least number of H - bond acceptors, so these drugs show better action than the other two drugs.

**Table: 10 Physicochemical properties, iLOGP and XLOGP3 properties of commercial AEDs**

| Molecule | #H-bond donors | MR | TPSA | iLOGP | XLOGP3 |
|---|---|---|---|---|---|
| Valproic acid | 1 | 42.34 | 37.3 | 1.99 | 2.75 |
| Stiripentol | 1 | 67.53 | 38.69 | 3.13 | 4.16 |
| Phenytoin | 2 | 77.5 | 58.2 | 1.65 | 2.47 |
| Tiagabine | 1 | 111.63 | 97.02 | 3.48 | 2.65 |
| Diazepam | 0 | 87.95 | 32.67 | 2.68 | 2.99 |

Table 10 reveals that, Phenytoin and Tiagabine have higher value of TPSA, Hence these drugs have high drug transport tendency.

**Table: 11 Lipophilicity and ESOL Log S properties of commercial AEDs**

| Molecule | WLOGP | MLOGP | Silicos-IT Log P | Consensus Log P | ESOL Log S |
|---|---|---|---|---|---|
| Valproic acid | 2.29 | 1.96 | 1.6 | 2.12 | -2.14 |
| Stiripentol | 2.73 | 2.25 | 3.15 | 3.08 | -3.98 |
| Phenytoin | 0.9 | 2.01 | 2.42 | 1.89 | -3.3 |
| Tiagabine | 4.66 | 3.32 | 6.41 | 4.11 | -3.74 |
| Diazepam | 2.39 | 2.67 | 4.12 | 2.97 | -3.87 |

From the table 11, The drug Tiagabine shows high Lipophilicity value, Hence it has high off target binding. (Increase in Lipophilicity, increase in off target binding).

**Table: 12 water solubility properties of commercial AEDs**

| Molecule | ESOL Solubility (mg/ml) | ESOL Solubility (mol/l) | ESOL Class | Ali Log S | Ali Solubility (mg/ml) |
|---|---|---|---|---|---|
| Valproic acid | 1.05E+00 | 7.30E-03 | Soluble | -3.19 | 9.35E-02 |
| Stiripentol | 2.47E-02 | 1.06E-04 | Soluble | -4.68 | 4.89E-03 |
| Phenytoin | 1.28E-01 | 5.06E-04 | Soluble | -3.34 | 1.16E-01 |
| Tiagabine | 6.87E-02 | 1.83E-04 | Soluble | -4.34 | 1.72E-02 |
| Diazepam | 3.87E-02 | 1.36E-04 | Soluble | -3.34 | 1.30E-01 |

From the above results (table 12), shows all the 5 drugs are readily aqueous soluble, Hence they can approach the target easily.

**Table : 13 water solubility properties of commercial AEDs**

| Molecule | Ali Solubility (mol/l) | Ali Class | Silicos-IT LogSw | Silicos-IT Solubility (mg/ml) | Silicos-IT Solubility (mol/l) |
|---|---|---|---|---|---|
| Valproic acid | 6.48E-04 | Soluble | -1.67 | 3.07E+00 | 2.13E-02 |
| Stiripentol | 2.09E-05 | Moderately soluble | -2.93 | 2.75E-01 | 1.17E-03 |
| Phenytoin | 4.61E-04 | Soluble | -5.62 | 6.07E-04 | 2.40E-06 |
| Tiagabine | 4.59E-05 | Moderately soluble | -4.94 | 4.35E-03 | 1.16E-05 |
| Diazepam | 4.57E-04 | Soluble | -6 | 2.83E-04 | 9.95E-07 |

From table 13, Stiripentol and Tiagabine are moderately soluble, Thus they have less action when compared to the other three drugs**.**

**Table : 14 Silicos-IT class and pharmacokinetics properties of commercial AEDs**

| Molecule | Silicos-IT class | GI absorption | BBB permeant | Pgp substrate |
|---|---|---|---|---|
| Valproic acid | Soluble | High | Yes | No |
| Stiripentol | Soluble | High | Yes | No |
| Phenytoin | Moderately soluble | High | Yes | No |

| | | | | |
|---|---|---|---|---|
| Tiagabine | Moderately soluble | High | No | Yes |
| Diazepam | Poorly soluble | High | Yes | No |

The above table reveals that, all the drugs are transported actively, because they have high gastro intestinal (GI) absorption.

**Table : 15 pharmacokinetics properties of commercial AEDs**

| Molecule | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|---|---|---|---|---|---|
| Valporic acid | No | No | No | No | No |
| Stiripentol | Yes | No | Yes | Yes | No |
| Phenytoin | No | No | No | No | No |
| Tiagabine | No | Yes | Yes | No | No |
| Diazepam | Yes | Yes | Yes | Yes | Yes |

Table 15 explains, valproic acid doesn't hold any inhibitors as well as easy availability and low cost. Hence this drug is taken for in vitro studies.

Diazepam holds all the above-mentioned inhibitors, so it can be used as standard for in silico studies.

**Table: 16 Drug Likeness properties of commercial AEDs**

| Molecule | log Kp (cm/s) | Lipinski #violations | Ghose #violations | Veber #violations | Egan #violations |
|---|---|---|---|---|---|
| Valporic acid | -5.23 | 0 | 1 | 0 | 0 |
| Stiripentol | -4.78 | 0 | 0 | 0 | 0 |
| Phenytoin | -6.09 | 0 | 0 | 0 | 0 |
| Tiagabine | -6.71 | 0 | 0 | 0 | 0 |
| Diazepam | -5.91 | 0 | 0 | 0 | 0 |

From table 16, The LIPINSKI violation for all the drugs are zero, They are perfectly fit under the LIPINSKI rule.

Among the 5 drugs, The Bioavailability score is high for valproic acid, Hence it has taken to in vitro studies, shown in below table 17,

**Table: 17 Drug Likeness and medicinal chemistry properties of commercial AEDs**

| Molecule | Muegge #violations | Bioavailability Score | PAINS #alerts | Brenk #alerts | Lead Likeness #violations | Synthetic Accessibility |
|---|---|---|---|---|---|---|
| Valproic acid | 1 | 0.85 | 0 | 0 | 1 | 1.28 |
| Stiripentol | 0 | 0.55 | 0 | 0 | 2 | 3.23 |
| Phenytoin | 0 | 0.55 | 0 | 1 | 0 | 2.28 |
| Tiagabine | 0 | 0.55 | 0 | 0 | 1 | 3.98 |
| Diazepam | 0 | 0.55 | 0 | 0 | 0 | 3 |

From the above five commercial Antiepileptic drugs, Diazepam has benzodiazepine, which is naturally present in herbal plants. Compounds which are used for this study are also phytoconstituents. Hence diazepam is chosen as standard.

**Compounds under study (Molecules 1 to 15)**

The below mentioned molecules were given in the table 7

**Table: 18 Physicochemical properties for compounds under study**

| Molecule | Canonical SMILES | Formula | MW |
|---|---|---|---|
| Molecule 1 | Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O | C15H10O6 | 286.24 |
| Molecule 2 | Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O | C15H10O7 | 302.24 |
| Molecule 3 | Oc1cc(O)c2c(c1)oc(c(c2=O)OC1OC(COC2OC(C)C(C(C2O)O)O)C(C(C1O)O)O)c1ccc(c(c1)O)O | C27H30O16 | 610.52 |
| Molecule 4 | CC(=C)C1CCC2(C1C1CCC3C(C1(C)CC2)(C)CCC1C3(C)CCC(C1(C)C)O)C | C30H50O | 426.72 |
| Molecule 5 | OC(=O)c1cc(O)c(c(c1)O)O | C7H6O5 | 170.12 |
| Molecule 6 | Oc1ccc(cc1)c1coc2c(c1=O)c(O)cc(c2)O | C15H10O5 | 270.24 |
| Molecule 7 | Oc1ccc(cc1)c1cc(=O)c2c(o1)cc(cc2O)O | C15H10O5 | 270.24 |

| | | | |
|---|---|---|---|
| Molecule 8 | Oc1ccc(cc1)c1cc(=O)c2c(o1)cc(c(c2O)C)O | C16H12O5 | 284.26 |
| Molecule 9 | Oc1ccc(cc1)c1coc2c(c1=O)ccc(c2)O | C15H10O4 | 254.24 |
| Molecule 10 | Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccccc1 | C15H10O5 | 270.24 |
| Molecule 11 | Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1cc(O)c(c(c1)O)O | C15H10O8 | 318.24 |
| Molecule 12 | Oc1ccc(cc1)C1CC(=O)c2c(O1)cc(cc2O)O | C15H12O5 | 272.25 |
| Molecule 13 | CC(=O)Oc1ccc(cc1)c1oc2cc(OC(=O)C)cc(c2c(=O)c1OC(=O)C)O | C21H16O9 | 412.35 |
| Molecule 14 | COc1ccc(c(c1)O)C(=O)c1ccccc1 | C14H12O3 | 228.24 |
| Molecule 15 | COc1ccc(c(c1)O)C(=O)c1ccccc1O | C14H12O4 | 244.24 |

From table 18, except molecule 3, all other molecules have molecular weight less than 500. Hence those molecules obey the LIPINSKI rule.

**Table: 19 Physicochemical properties for compounds under study**

| Molecule | #Heavy atoms | #Aromatic heavy atoms | Fraction Csp3 | #Rotatable bonds | #H-bond acceptors |
|---|---|---|---|---|---|
| Molecule 1 | 21 | 16 | 0 | 1 | 6 |
| Molecule 2 | 22 | 16 | 0 | 1 | 7 |
| Molecule 3 | 43 | 16 | 0.44 | 6 | 16 |
| Molecule 4 | 31 | 0 | 0.93 | 1 | 1 |
| Molecule 5 | 12 | 6 | 0 | 1 | 5 |
| Molecule 6 | 20 | 16 | 0 | 1 | 5 |
| Molecule 7 | 20 | 16 | 0 | 1 | 5 |
| Molecule 8 | 21 | 16 | 0.06 | 1 | 5 |
| Molecule 9 | 19 | 16 | 0 | 1 | 4 |
| Molecule 10 | 20 | 16 | 0 | 1 | 5 |
| Molecule 11 | 23 | 16 | 0 | 1 | 8 |
| Molecule 12 | 20 | 12 | 0.13 | 1 | 5 |
| Molecule 13 | 30 | 16 | 0.14 | 7 | 9 |
| Molecule 14 | 17 | 12 | 0.07 | 3 | 3 |
| Molecule 15 | 18 | 12 | 0.07 | 3 | 4 |

Results of table 19, shows molecule 3 has 16 H - bond acceptor, and doesn’t obey Lipinski’s rule

**Table: 20 Physicochemical, ILOGP and XLOGP3 properties for compounds under study**

| Molecule | #H-bond donors | MR | TPSA | iLOGP | XLOGP3 |
|---|---|---|---|---|---|
| Molecule 1 | 4 | 76.01 | 111.13 | 1.7 | 1.9 |
| Molecule 2 | 5 | 78.03 | 131.36 | 1.63 | 1.54 |
| Molecule 3 | 10 | 141.38 | 269.43 | 2.43 | -0.33 |
| Molecule 4 | 1 | 135.14 | 20.23 | 4.68 | 9.87 |
| Molecule 5 | 4 | 39.47 | 97.99 | 0.21 | 0.7 |
| Molecule 6 | 3 | 73.99 | 90.9 | 1.91 | 2.67 |
| Molecule 7 | 3 | 73.99 | 90.9 | 1.89 | 3.02 |
| Molecule 8 | 3 | 78.95 | 90.9 | 2.26 | 3.38 |
| Molecule 9 | 2 | 71.97 | 70.67 | 1.77 | 2.47 |
| Molecule 10 | 3 | 73.99 | 90.9 | 2.08 | 2.25 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 11 | 6 | 80.06 | 151.59 | 1.08 | 1.18 |
| Molecule 12 | 3 | 71.57 | 86.99 | 1.75 | 2.52 |
| Molecule 13 | 1 | 104.44 | 129.34 | 3.4 | 2.84 |
| Molecule 14 | 1 | 64.83 | 46.53 | 2.43 | 3.79 |
| Molecule 15 | 2 | 66.85 | 66.76 | 2.25 | 3.43 |

Table 20 reveals that, molecule 3 and 11 has H -Bond donors is more than 5. Hence molecule 3 and 11 does not obey LIPINSKI rule completely, So, for this study molecule 3 and 11 is not selected**.**

**Table: 21 Lipophilicity and ESOL Log S properties for compounds under study**

| **Molecule** | **WLOGP** | **MLOGP** | **Silicos-IT Log P** | **Consensus Log P** | **ESOL Log S** |
|---|---|---|---|---|---|
| Molecule 1 | 2.28 | -0.03 | 2.03 | 1.58 | -3.31 |
| Molecule 2 | 1.99 | -0.56 | 1.54 | 1.23 | -3.16 |
| Molecule 3 | -1.69 | -3.89 | -2.11 | -1.12 | -3.3 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 4 | 8.02 | 6.92 | 6.82 | 7.26 | -8.64 |
| Molecule 5 | 0.5 | -0.16 | -0.2 | 0.21 | -1.64 |
| Molecule 6 | 2.58 | 0.52 | 2.52 | 2.04 | -3.72 |
| Molecule 7 | 2.58 | 0.52 | 2.52 | 2.11 | -3.94 |
| Molecule 8 | 2.89 | 0.77 | 3.02 | 2.46 | -4.23 |
| Molecule 9 | 2.87 | 1.08 | 3.02 | 2.24 | -3.53 |
| Molecule 10 | 2.58 | 0.52 | 2.52 | 1.99 | -3.46 |
| Molecule 11 | 1.69 | -1.08 | 1.06 | 0.79 | -3.01 |
| Molecule 12 | 2.19 | 0.71 | 2.05 | 1.84 | -3.49 |
| Molecule 13 | 2.94 | 1.24 | 3.44 | 2.77 | -4.12 |
| Molecule 14 | 2.63 | 1.99 | 2.92 | 2.75 | -3.97 |
| Molecule 15 | 2.34 | 1.41 | 2.43 | 2.37 | -3.81 |

From table 21, molecule 4 has high lipophilicity value, Hence it is highly off target binding. It is also proven in molecular docking studies, (I.e) Binding energy for molecule 4 is -253.04 as shown in table 32.

**Table: 22 Water solubility properties for compounds under study**

| Molecule | ESOL Solubility (mg/ml) | ESOL Solubility (mol/l) | ESOL Class | Ali Log S | Ali Solubility (mg/ml) |
|---|---|---|---|---|---|
| Molecule 1 | 1.40E-01 | 4.90E-04 | Soluble | -3.86 | 3.98E-02 |
| Molecule 2 | 2.11E-01 | 6.98E-04 | Soluble | -3.91 | 3.74E-02 |
| Molecule 3 | 3.08E-01 | 5.05E-04 | Soluble | -4.87 | 8.30E-03 |
| Molecule 4 | 9.83E-07 | 2.30E-09 | Poorly soluble | -10.22 | 2.58E-08 |
| Molecule 5 | 3.90E+00 | 2.29E-02 | Very soluble | -2.34 | 7.86E-01 |
| Molecule 6 | 5.11E-02 | 1.89E-04 | Soluble | -4.23 | 1.59E-02 |
| Molecule 7 | 3.07E-02 | 1.14E-04 | Soluble | -4.59 | 6.88E-03 |
| Molecule 8 | 1.68E-02 | 5.89E-05 | Moderately soluble | -4.97 | 3.06E-03 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 9 | 7.51E-02 | 2.95E-04 | Soluble | -3.6 | 6.41E-02 |
| Molecule 10 | 9.39E-02 | 3.48E-04 | Soluble | -3.79 | 4.33E-02 |
| Molecule 11 | 3.14E-01 | 9.88E-04 | Soluble | -3.96 | 3.50E-02 |
| Molecule 12 | 8.74E-02 | 3.21E-04 | Soluble | -3.99 | 2.77E-02 |
| Molecule 13 | 3.14E-02 | 7.61E-05 | Moderately soluble | -5.21 | 2.52E-03 |
| Molecule 14 | 2.46E-02 | 1.08E-04 | Soluble | -4.46 | 7.89E-03 |
| Molecule 15 | 3.78E-02 | 1.55E-04 | Soluble | -4.51 | 7.50E-03 |

Even though molecule 4 has good binding and lipophilicity properties, From results of table 22 it is shown that molecule 4 has poor solubility.

**Table: 23 Water solubility properties for compounds under study**

| **Molecule** | **Ali Solubility (mol/l)** | **Ali Class** | **Silicos-IT LogSw** | **Silicos-IT Solubility (mg/ml)** | **Silicos-IT Solubility (mol/l)** |
|---|---|---|---|---|---|
| Molecule 1 | 1.39E-04 | Soluble | -3.82 | 4.29E-02 | 1.50E-04 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 2 | 1.24E-04 | Soluble | -3.24 | 1.73E-01 | 5.73E-04 |
| Molecule 3 | 1.36E-05 | Moderately soluble | -0.29 | 3.15E+02 | 5.15E-01 |
| Molecule 4 | 6.05E-11 | Insoluble | -6.74 | 7.69E-05 | 1.80E-07 |
| Molecule 5 | 4.62E-03 | Soluble | -0.04 | 1.55E+02 | 9.10E-01 |
| Molecule 6 | 5.88E-05 | Moderately soluble | -4.4 | 1.07E-02 | 3.94E-05 |
| Molecule 7 | 2.55E-05 | Moderately soluble | -4.4 | 1.07E-02 | 3.94E-05 |
| Molecule 8 | 1.08E-05 | Moderately soluble | -4.79 | 4.64E-03 | 1.63E-05 |
| Molecule 9 | 2.52E-04 | Soluble | -4.98 | 2.64E-03 | 1.04E-05 |
| Molecule 10 | 1.60E-04 | Soluble | -4.4 | 1.07E-02 | 3.94E-05 |
| Molecule 11 | 1.10E-04 | Soluble | -2.66 | 6.98E-01 | 2.19E-03 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 12 | 1.02E-04 | Soluble | -3.42 | 1.04E-01 | 3.82E-04 |
| Molecule 13 | 6.10E-06 | Moderately soluble | -5.69 | 8.34E-04 | 2.02E-06 |
| Molecule 14 | 3.46E-05 | Moderately soluble | -4.42 | 8.62E-03 | 3.78E-05 |
| Molecule 15 | 3.07E-05 | Moderately soluble | -3.85 | 3.47E-02 | 1.42E-04 |

Among 15 molecules, molecule 4 is insoluble. Thus, from the results of table 22 and 23, it is evident that Molecule 4 cannot be taken for further studies.

**Table: 24 pharmacokinetics properties for compounds under study**

| Molecule | Silicos-IT class | GI absorption | BBB permeant | Pgp substrate |
|---|---|---|---|---|
| Molecule 1 | Soluble | High | No | No |
| Molecule 2 | Soluble | High | No | No |
| Molecule 3 | Soluble | Low | No | Yes |
| Molecule 4 | Poorly soluble | Low | No | No |

| | | | | |
|---|---|---|---|---|
| Molecule 5 | Soluble | High | No | No |
| Molecule 6 | Moderately soluble | High | No | No |
| Molecule 7 | Moderately soluble | High | No | No |
| Molecule 8 | Moderately soluble | High | No | No |
| Molecule 9 | Moderately soluble | High | Yes | No |
| Molecule 10 | Moderately soluble | High | No | No |
| Molecule 11 | Soluble | Low | No | No |
| Molecule 12 | Soluble | High | No | Yes |
| Molecule 13 | Moderately soluble | High | No | No |

| | | | | |
|---|---|---|---|---|
| Molecule 14 | Moderately soluble | High | Yes | No |
| Molecule 15 | Soluble | High | Yes | No |

Table 24 reveals, molecule 3, 4 and 11 has low Gastrointestinal (GI) Absorption. Hence these molecules were omitted for further studies.

**Table: 25 Pharmacokinetics properties for compounds under study**

| **Molecule** | **CYP1A2 inhibitor** | **CYP2C19 inhibitor** | **CYP2C9 inhibitor** | **CYP2D6 inhibitor** | **CYP3A4 inhibitor** |
|---|---|---|---|---|---|
| Molecule 1 | Yes | No | No | Yes | Yes |
| Molecule 2 | Yes | No | No | Yes | Yes |
| Molecule 3 | No | No | No | No | No |
| Molecule 4 | No | No | No | No | No |
| Molecule 5 | No | No | No | No | Yes |
| Molecule 6 | Yes | No | No | Yes | Yes |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 7 | Yes | No | No | Yes | Yes |
| Molecule 8 | Yes | No | No | Yes | Yes |
| Molecule 9 | Yes | No | No | Yes | Yes |
| Molecule 10 | Yes | No | No | Yes | Yes |
| Molecule 11 | Yes | No | No | No | Yes |
| Molecule 12 | Yes | No | No | No | Yes |
| Molecule 13 | Yes | No | Yes | No | Yes |
| Molecule 14 | Yes | Yes | Yes | No | No |
| Molecule 15 | Yes | No | Yes | No | Yes |

From the above table 25, we can say that for the Molecules 3 and Molecule 4, all the inhibitors were not present.

**Table: 26 Drug Likeness properties for compounds under study**

| Molecule | log Kp (cm/s) | Lipinski #violations | Ghose #violations | Veber #violations | Egan #violations |
|---|---|---|---|---|---|
| Molecule 1 | -6.7 | 0 | 0 | 0 | 0 |
| Molecule 2 | -7.05 | 0 | 0 | 0 | 0 |
| Molecule 3 | -10.26 | 3 | 4 | 1 | 1 |
| Molecule 4 | -1.9 | 1 | 3 | 0 | 1 |
| Molecule 5 | -6.84 | 0 | 2 | 0 | 0 |
| Molecule 6 | -6.05 | 0 | 0 | 0 | 0 |
| Molecule 7 | -5.8 | 0 | 0 | 0 | 0 |
| Molecule 8 | -5.63 | 0 | 0 | 0 | 0 |
| Molecule 9 | -6.1 | 0 | 0 | 0 | 0 |
| Molecule 10 | -6.35 | 0 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 11 | -7.4 | 1 | 0 | 1 | 1 |
| Molecule 12 | -6.17 | 0 | 0 | 0 | 0 |
| Molecule 13 | -6.8 | 0 | 0 | 0 | 0 |
| Molecule 14 | -5 | 0 | 0 | 0 | 0 |
| Molecule 15 | -5.35 | 0 | 0 | 0 | 0 |

Table 26 shows, All the molecules have LIPINSKI violation is 0 except molecule 3 and molecule 4.

**Table: 27 medicinal chemistry properties for compounds under study**

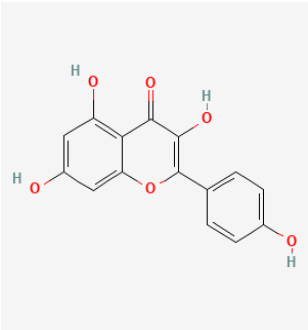
| **Molecule** | **Bioavailability Score** | **PAINS #alerts** | **Brenk #alerts** | **Leadlikeness #violations** | **Synthetic Accessibility** |
|---|---|---|---|---|---|
| Molecule 1 | 0.55 | 0 | 0 | 0 | 3.14 |
| Molecule 2 | 0.55 | 1 | 1 | 0 | 3.23 |
| Molecule 3 | 0.17 | 1 | 1 | 1 | 6.52 |

| | | | | | |
|---|---|---|---|---|---|
| Molecule 4 | 0.55 | 0 | 1 | 2 | 5.49 |
| Molecule 5 | 0.56 | 1 | 1 | 1 | 1.22 |
| Molecule 6 | 0.55 | 0 | 0 | 0 | 2.87 |
| Molecule 7 | 0.55 | 0 | 0 | 0 | 2.96 |
| Molecule 8 | 0.55 | 0 | 0 | 0 | 3.06 |
| Molecule 9 | 0.55 | 0 | 0 | 0 | 2.79 |
| Molecule 10 | 0.55 | 0 | 0 | 0 | 3.12 |
| Molecule 11 | 0.55 | 1 | 1 | 0 | 3.27 |
| Molecule 12 | 0.55 | 0 | 0 | 0 | 3.01 |
| Molecule 13 | 0.55 | 0 | 1 | 1 | 3.69 |
| Molecule 14 | 0.55 | 0 | 0 | 2 | 1.8 |
| Molecule 15 | 0.55 | 0 | 0 | 1 | 1.87 |

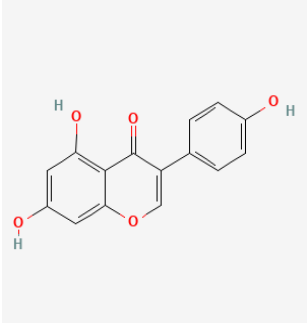
Table 27 shows, All the molecules have bioavailability score 0.55 as similar as standard drug diazepam except molecule 3 and 5.

The ADME properties of the above discussed 15 compounds have been compared with the properties of diazepam commercial drug. Among The 15 compounds, based on similarity, 5 compounds were identified.

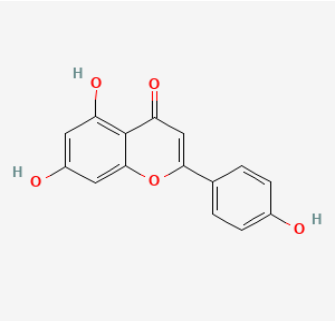
Those 5 compounds structures were mentioned below,



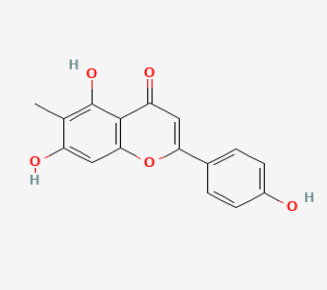
Kaempferol



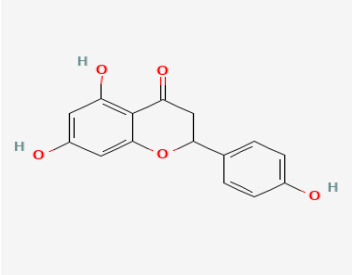
Genistein



Apigenin



6-Methyl apigenin



Naringenin

The 7 similar properties of 5 compounds, were compared with Diazepam commercial drug as tabulated below in table 28,

**Table: 28 Compared ADME properties with commercial drug Diazepam**

| Properties | Diazepam | Genistein | Apigenin | 6-Methyl Apigenin | Kaempferol | Naringenin |
|---|---|---|---|---|---|---|
| **Formula** | C16H13ClN2O | C15H10O5 | C15H10O5 | C16H12O5 | C15H10O6 | C15H12O5 |
| **MW** | 284.74 | 270.24 | 270.24 | 284.26 | 286.24 | 272.25 |
| **#HEAVY ATOMS** | 20 | 20 | 20 | 21 | 21 | 20 |
| **ESOL Class** | soluble | Soluble | soluble | soluble | soluble | soluble |
| **GI absorption** | High | High | high | high | high | High |
| **CYP3A4 inhibitors** | Yes | Yes | yes | yes | yes | Yes |
| **CYP1A2 inhibitors** | Yes | Yes | yes | yes | yes | Yes |
| **CYP2D6 inhibitors** | Yes | Yes | yes | yes | yes | No |
| **logKp (cm/S)** | -5.91 | -6.05 | -5.8 | -5.63 | -6.7 | -6.17 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Lipinski#violations** | 0 | 0 | 0 | 0 | 0 | 0 |

The properties of the compounds and the standard are comparable. **GI absorption and other parameters are also comparable**

## 2.LIPINSKI Rule Of Five

Above five compounds obeys the LIPINSKI rule of five are tabulated below,

**Table: 29 Compounds under study, obeys LIPINSKI rule**

| **Compounds** | **Molecular weight (g/mol) <500** | **Lipophilicity (MLog p) <5** | **H- bond donors <5** | **H - bond acceptors <10** | **Rule violations <2** |
|---|---|---|---|---|---|
| Kaempferol | 286.24 | -0.03 | 4 | 6 | 0 |
| Apigenin | 270.24 | 0.52 | 3 | 5 | 0 |
| 6 - methyl apigenin | 284.26 | 0.77 | 3 | 5 | 0 |
| Genistein | 270.24 | 0.52 | 3 | 5 | 0 |
| Naringenin | 272.25 | 0.71 | 3 | 5 | 0 |

Above 5 compounds showing more drug likeness properties. So, This study suggested that these 5 compounds give better remedy to treat epilepsy.

## 3. Constituent Analysis in Antiepileptic Plants

Among these plants this study found that linalool is a common constituent in many plants which are used in epilepsy treatment. This show in below table 30,

**Table: 30 Constituents of various herbal antiepileptic plants**

| NAME OF THE PLANTS | CHEMICAL CONSTITUENTS |
|---|---|
| Cinnamomum Camphora | Linalool(1), cineole(2), safrole(3), borneol(4), nerolidol(5). |
| Zingiber officinale | Shogaols(6), paradols(7), quercetin(8),nerolidol(5), geraniol(9), limonene(10), zingerone(11), beta-bisabolene(12), alpha-curcumene(13), zingiberene(14), alpha-farnesene(15), beta-sesquiphellandrene(16),linalool(1). |
| Lavandula officinalis | Cineole(2), borneol(4), camphor(17), terpinen-4-ol(18), linalool(1), linalyl acetate(19), alpha-bisabolol(20), alpha-terpineol(21), beta-farnesene(22). |
| Origanum vulgare | Carvacrol(23), thymol(24), linalool(1), gamma-terpinene(25), p-cymene(26), beta-caryophyllene(27), germacrene D(28). |
| Ocimum basilicum | Rosmarinic acid(29), sinapic acid(30), ursolic acid(31), eugenol(32), cubenol(33), bornil acetate(34), alpha-bergamotene(35), alpha-copaene(36), alpha-bisabolol(20), linalool(1), eucalyptol(37), beta-farnesene(22), methyl eugenol(38). |
| Citrus sinensis | Myrcene(39), limonene(10), alpha-pinene(40),linalool(1). |
| Cymbopogon flexuosus | Citral-a(41), citral-b(42), geranyl acetate(43), linalool(1). |
| Pimpinella anisum | Anethole(44), estragole(45), methyl chavicol(46), p-anisaldehyde(47), gamma-himachalene(48), linalool(1). |
| Valeriana officinalis | Valerian(49), valerianine(50), valerenic acid(51), valerenal(52), valepotriates(53), terpene valeranone(54), linalool(1). |
| Centella asiatica | Asiaticoside(55), quercetin(8), kaempferol(56), campesterol(57), brahmoside(58), madecassic acid(59), linalool(1), myrcene(39), asiatic acid(60), limonene(10). |

## 4.Molecular Docking

In this study, standard drugs such as Diazepam, valproic acid, Tiagabine, phenytoin and stiripentol are docked with protein SV2A (PDB ID: 4V11) and the E total value obtained are tabulated below.

**Table: 31 Docking results for commercial AEDs**

| Drugs | E total value |
|---|---|
| Valporic acid | -149.80 |
| Diazepam | -222.79 |
| Phenytoin | -211.58 |
| Tiagabine | -236.62 |
| Stiripentol | –205.11 |

Among these five commercial drugs, this study takes diazepam as standard because they contain plant compound benzodiazepine. The docking image shown below fig 2.

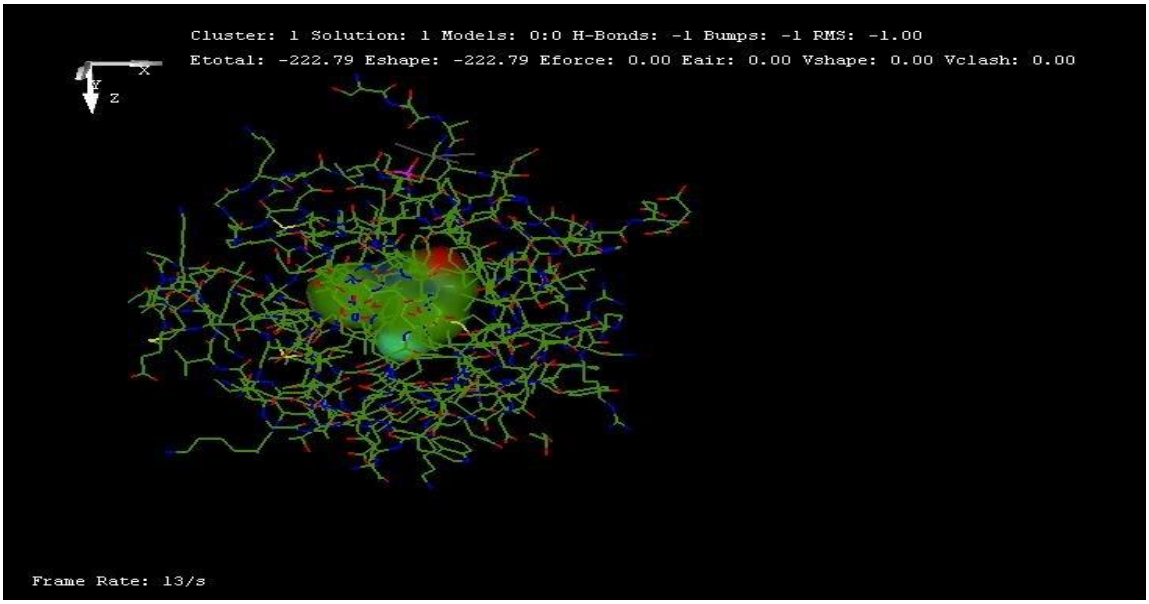



**Fig 2: Binding of protein (SV2A) and Diazepam**

Then the 15 compounds were docked with same protein SV2A were tabulated below,

**Table: 32 Docking results for compounds under study**

| Compounds | E total value |
|---|---|
| 6-methyl apigenin | -204.89 |
| Apigenin | -199.79 |
| Daidzein | -199.60 |
| Dioxybenzone | -203.75 |
| Galangin | -207.29 |
| Gallic acid | -155.18 |
| Genistein | -209.26 |
| Kaempferol 3,4,7 triacetate | -256.13 |
| Kaempferol | -214.04 |
| Lupeol | -253.35 |
| Myricetin | -222.31 |
| Naringenin | -229.45 |
| Oxybenzone | -193.35 |
| Quercetin | -218.02 |
| Rutin | -293.70 |

Compounds having lower E total value, binding will be more effective. So, E total value of these compounds are compared with E total value of diazepam commercial drug.

Apigenin, Genistein, kaempferol, Naringenin and 6- methyl apigenin show more effective binding properties. Their binding images are shown below,

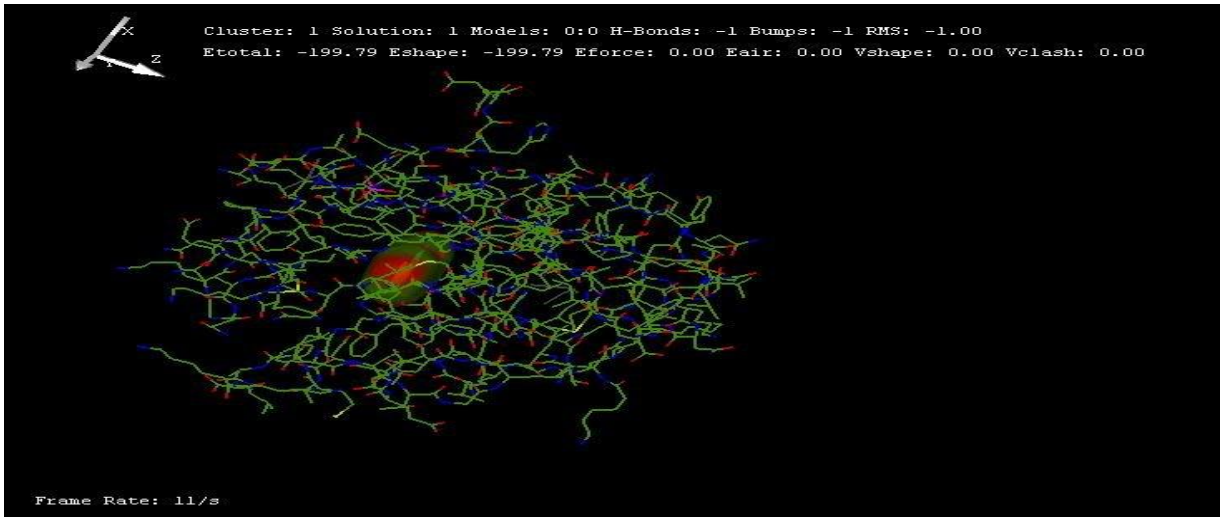



**Fig 3 Binding of protein (SV2A) and Apigenin**

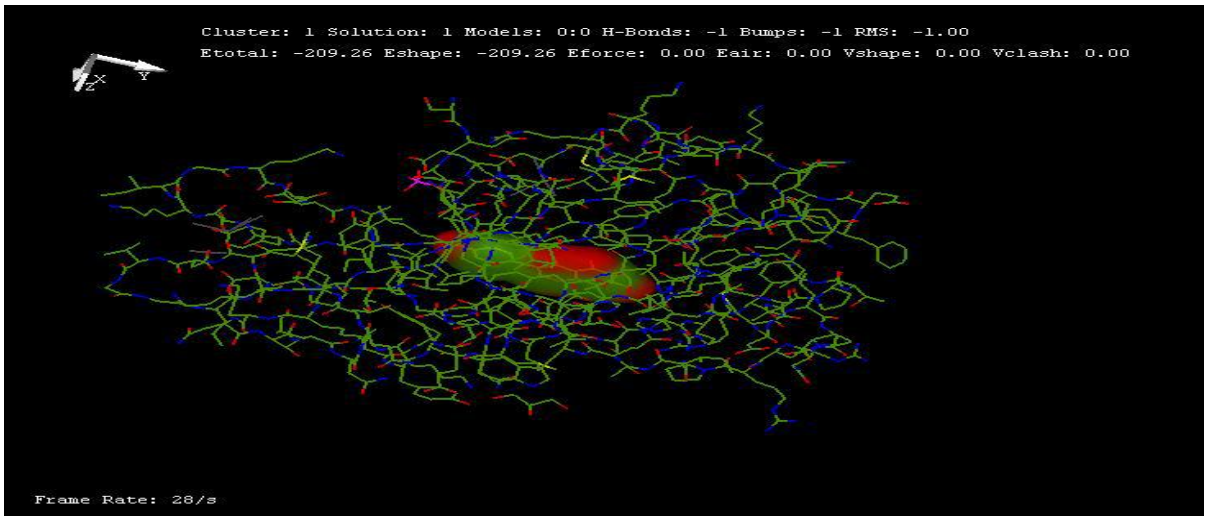



**Fig 4 : Binding of protein (SV2A) and Genistein**

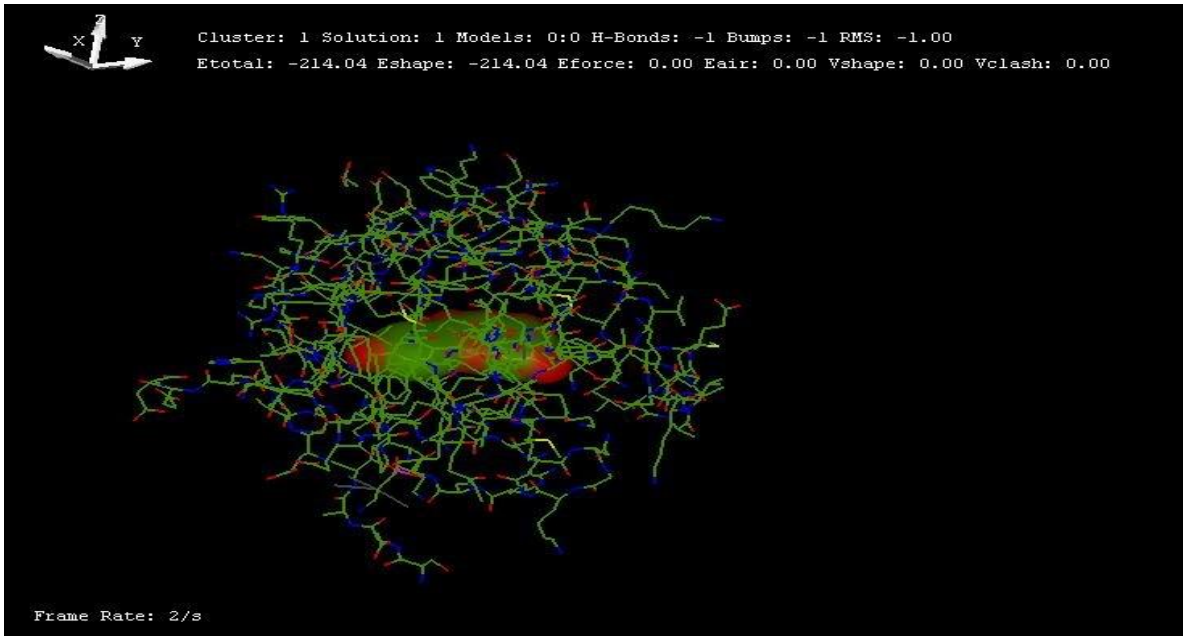



**Fig 5: Binding of protein (SV2A) and kaempferol**

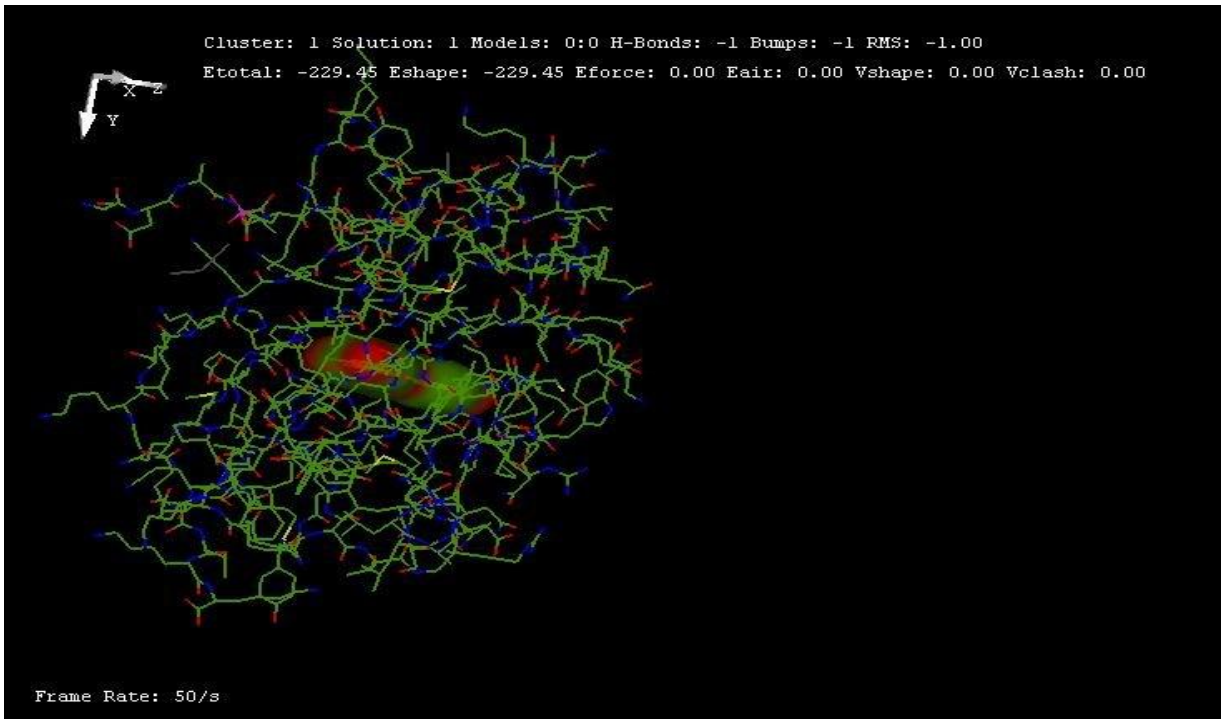



**Fig 6 Binding of protein (SV2A) and Naringenin**

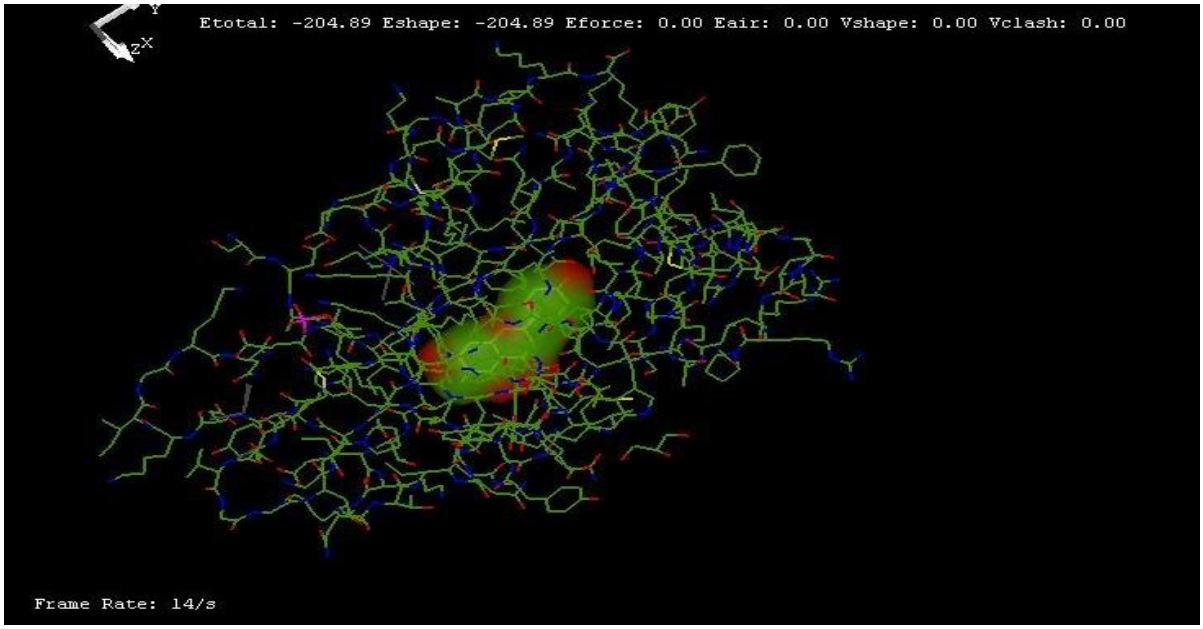
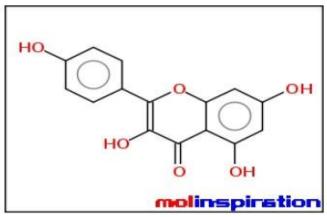



**Fig 7: Binding of protein (SV2A) and 6- methyl apigenin**

## 5.Bioactivity properties

molinspiration Calculation of Bioactivity Scores

originalSMILES
C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
miSMILES:
C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Kaempferol




Molinspiration bioactivity score v2021.03

| | |
|---|---|
| GPCR ligand | -0.10 |
| Ion channel modulator | -0.21 |
| Kinase inhibitor | 0.21 |
| Nuclear receptor ligand | 0.32 |
| Protease inhibitor | -0.27 |
| Enzyme inhibitor | 0.26 |

Get data as text (for copy / paste).

Get 3D geometry BETA

**Fig 8: Bioactivity score of kaempferol**

- Here in this molecule, kaempferol, GPCR ligand value is between -5 to 0.0.(I.e )GPCR ligand = -0.10. Hence, kaempferol is a moderately active compound for GPCR ligand
- The value of protease inhibitor is -0.27, thus it is moderately active for protease inhibitors

- The value of enzyme inhibitor is 0.26, which is active for enzyme inhibitors

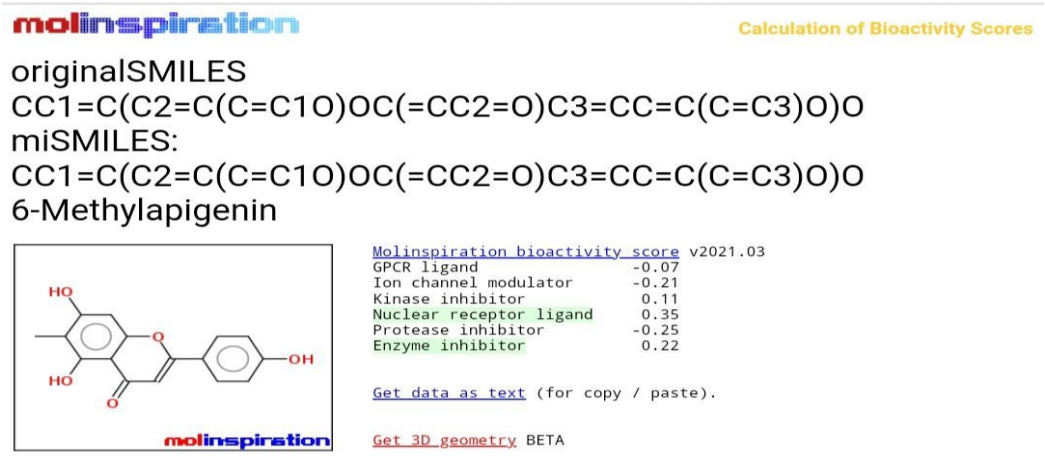



**Fig 9: Bioactivity score of 6-methyl apigenin**

- Here in this molecule, 6 - Methyl Apigenin, GPCR ligand value is between -5 to 0.0.(I.e )GPCR ligand = -0.07 Hence, 6 - Methyl apigenin is a moderately active compound for GPCR ligand
- The value of protease inhibitor is -0.25, thus it is moderately active for protease inhibitors
- The value of enzyme inhibitor is 0.22, which is active for enzyme inhibitors

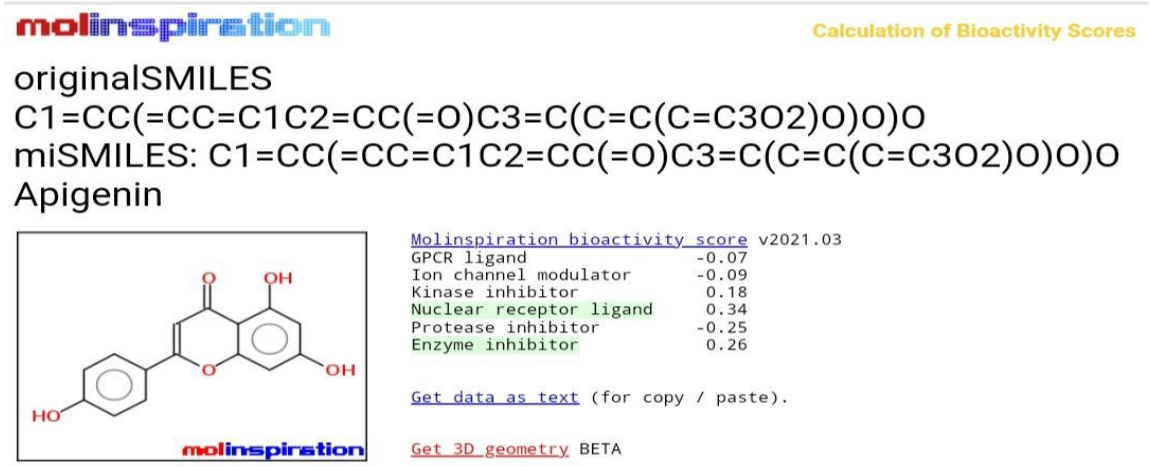



**Fig 10: Bioactivity score of Apigenin**

- Here in this molecule, Apigenin, GPCR ligand value is between -5 to 0.0.(I.e )GPCR ligand = -0.07, Hence, Apigenin is a moderately active compound for GPCR ligand
- The value of protease inhibitor is -0.25, thus it is moderately active for protease inhibitors
- The value of enzyme inhibitor is 0.26, which is active for enzyme inhibitor

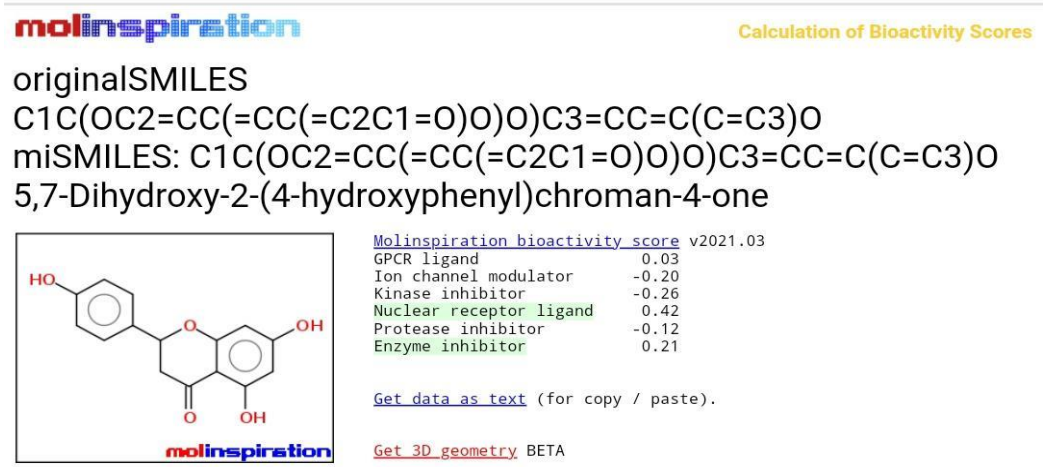



**Fig 11: Bioactivity score of Naringenin**

- Here in this molecule, Naringenin, GPCR ligand value is more than zero( I.e) GPCR ligand = 0.03, Hence, Naringenin is an active compound for GPCR ligand
- The value of protease inhibitor is -0.12, thus it is moderately active for protease inhibitors
- The value of enzyme inhibitor is 0.21, which is active for enzyme inhibitors

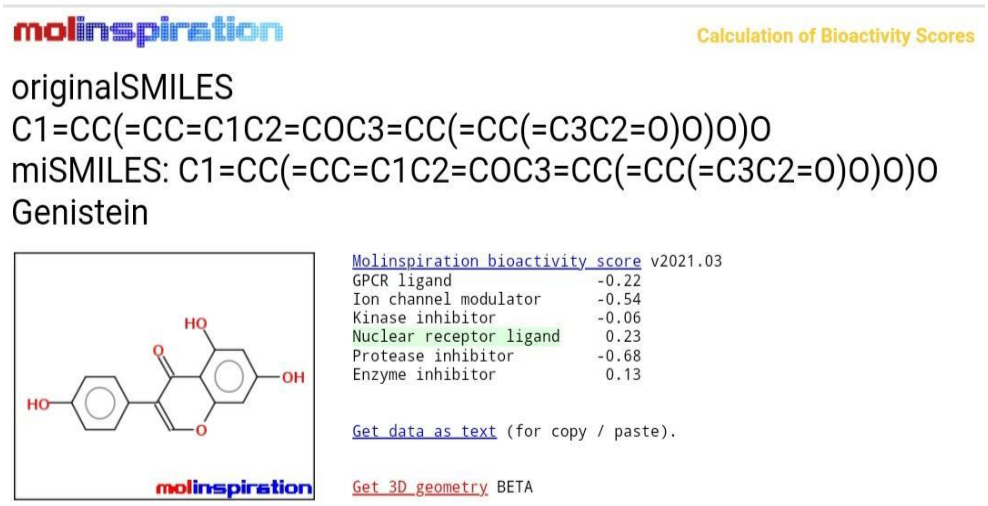



**Fig 12: Bioactivity score of Genistein**

- Here in this molecule, Genistein, GPCR ligand value is between -5 to 0.0. ( I.e) GPCR ligand = - 0.22, Hence, Genistein is a moderately active compound for GPCR ligand
- The value of protease inhibitor is -0.68, thus it is moderately active for protease inhibitors
- The value of enzyme inhibitor is 0.13, which is active for enzyme inhibitors

## 6. Drug protein interaction study

The interaction between drug sodium valproate and egg protein can be determined using the FTIR spectrum.

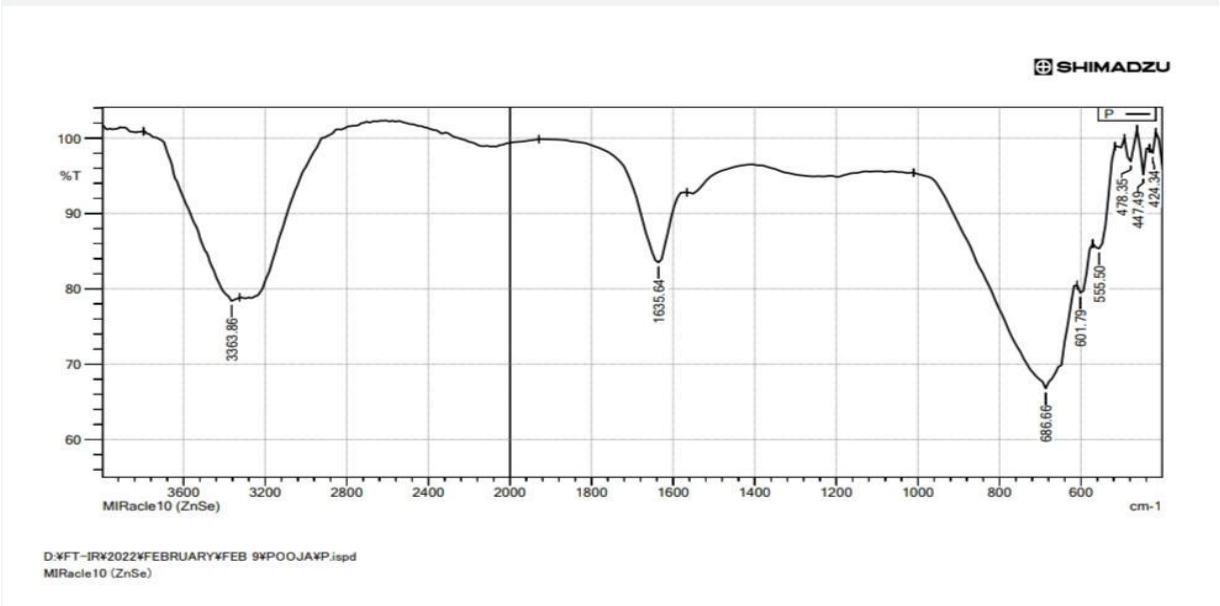



**Fig 13 FTIR spectrum of egg protein**

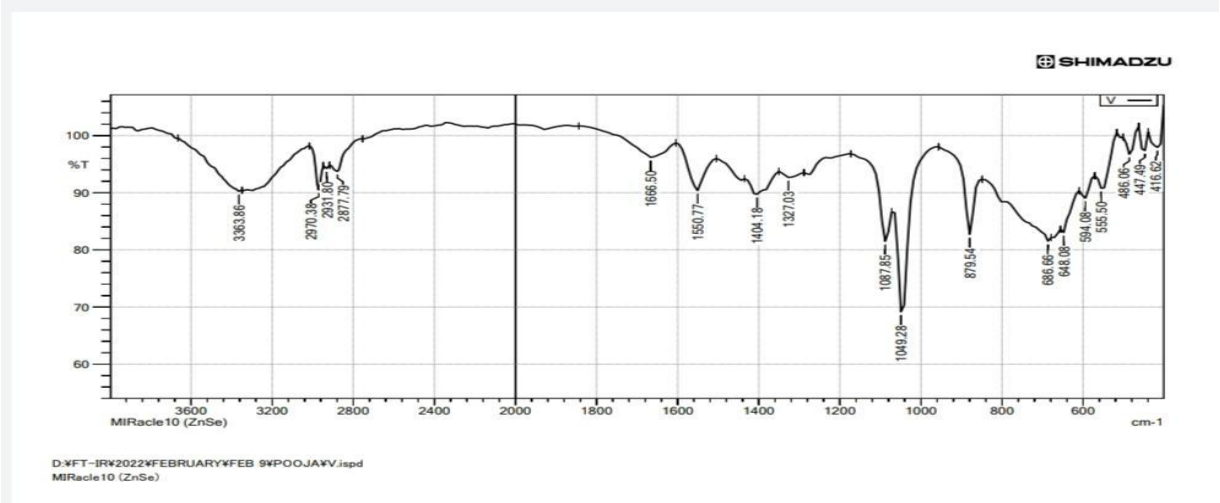



**Fig 14: FTIR spectrum of drug sodium valproate**

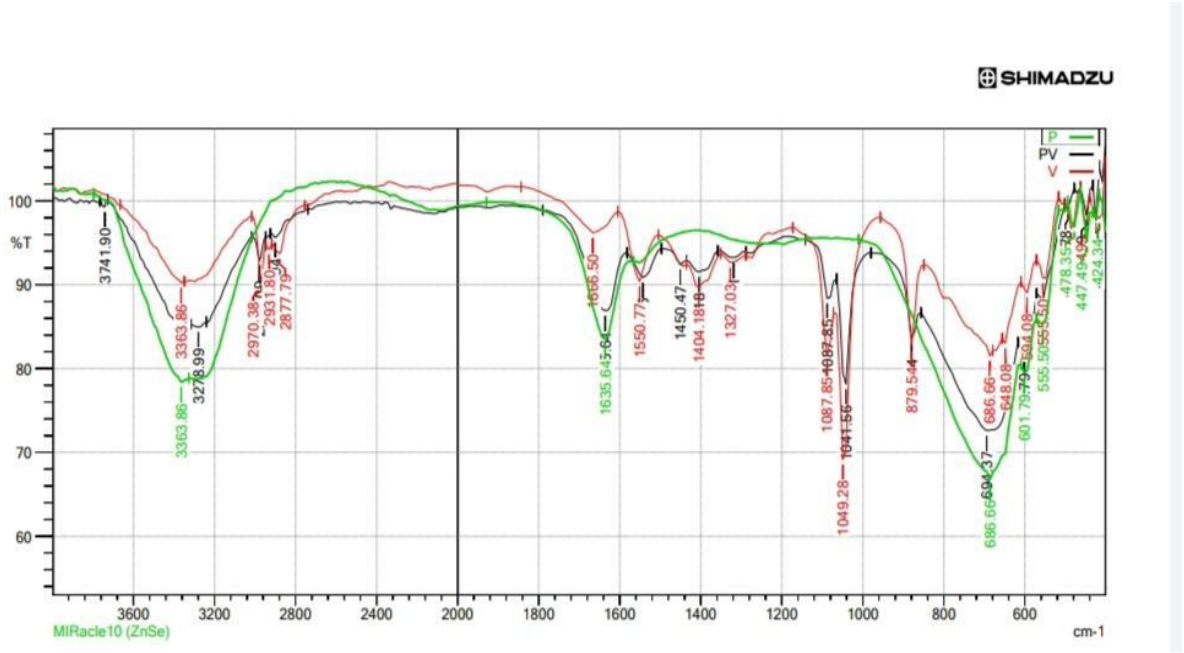



**Fig 15: FTIR spectrum of merged results of protein and drug**

Fig 15, shows the combined protein and drug peaks lie between the pure drug peak and the egg protein peak. Hence, This study confirms that, there is some interaction that takes place between drug and the protein.

# 5.SUMMARY AND CONCLUSION

- Commercial Antiepileptic drugs hold adverse effects, while consuming. To Overcome those problems, Herbal plants constituents were examined in this following work
- Identification of 15 herbal plants used for epilepsy and identify their chemical constituents. They contain around 52 chemical constituents
- Collecting SMILES of those compounds from PUBCHEM and then upload them to the SWISSADME tool to get ADME properties
- Compare the properties with commercial AEDs and shortlisted 5 compounds which have slightly same properties as like commercial AEDs
- Among those 5 compounds, kaempferol is taken because of its easy availability
- Again collecting 15 similar structures of kaempferol. Then collecting SMILES from PUBCHEM and generate ADME properties by using SWISSADME tool
- At the same time, 5 commercial AEDs are also selected based on widely used patients, costs and availability etc and generate ADME properties for these 5 drugs also
- Creating these 20 structures in the CHEMSKETCH tool and save as .mol file format. Then change into .pdb file format by using OPENBABEL tool for molecular docking purpose
- Selection of protein for molecular docking from literature study. The protein taken for this in silico study was SV2A. This protein was downloaded from Protein Data Bank as .pdb file format
- Then molecular docking was carried out by using HEX software and comparing the docking score with commercial drugs
- From the Results of docking and ADME properties, This study concludes 5 compounds hold Good as like as commercial AEDs. The 5 compounds were kaempferol, Naringenin, Apigenin, 6- methyl apigenin and Genistein
- Then for these 5 compounds, Bioactivity score study is also done by using the MOLINSPIRATION tool. All the 5 compounds show a good bioactivity score

- Up to this in silico study was carried out. The in vitro study was carried out by using egg protein and sodium valproate drug. These were selected on the basis of easy availability
- At first, isolate the protein from egg white by simple procedure (ie) Take egg white add distilled water and centrifuge it. Then take the upper clear portion protein
- Next, sodium valproate was dissolved in ethanol as a solvent. Since it was slightly undissolved, it was kept in the sonicator for 15 mins to get completely dissolved
- Then add sodium valproate into protein and without shaking or any disturbance, kept safe for IR studies
- From the IR results, This study concludes the interaction takes place between protein and drug

**Future work**

- From *in silico* studies, it was concluded that Kaempferol, Apigenin, Naringenin, 6-methylapigenin and Genistein has better antiepileptic properties among the 15 compounds taken under study
- Since, these compounds are naturally found in plants such as,
    - Kaempferol in Moringa leaves,
    - Apigenin, 6- Methyl apigenin and Naringenin inDried Parsley leaves
    - Genistein in Psoralea Corylifolia leaves
- So, this study can continue in future by making soup using the combination of the leaves of these 3 plants, which can be suggested as a better alternative for epilepsy treatment.

# 6. REFERENCE


- Ahmed, A.S., Mosab, Y.A., Mirghani, H.M., Hussam, E.A., Fadlalbaseer, A.E., Ahmed, A.A., Esraa, E., Ahmed, H.A., **2021**, Phytochemical, in vivo and in silico anticonvulsant activity screening of Albizia amara leave's ethanolic extract, *Hacettepe university journal of the faculty of pharmacy*, (41): 09-22

- Aliance, R.F., Maglore, K.N., Adeline, K.W., Francis, D.T.B., Appolinaire, K.D., Rodolphe, C., Pepin, A.N., Telesphore, B.N., **2021**, Anticonvulsant effects of the aqueous and methanol extracts from the stem bark of *Psychotria Camptopus Verdc.(Rubiacaea)* in rats, *Journal of Ethnopharmacology,* 272: 113955

- Amr, A.E., Esther, T.M., Mariane, G.T., Bassant, M.M.I., Nagwa, A.S., Amani, E.K., **2017**, Effects of genistein on pentylenetetrazole- induced behavioral and neuro chemical deficits in overiectomized rats, *Naunyn- Schmiedeberg's Arch Pharmacol*, 391: 27-36

- Anupama, K., Satyanarayana, S., Mukkanti, K., Khan, K.A., Kumar, K.P., **2009**, Anticonvulsant activity of Panchagavya Ghrutham: A polyherbal Ayurvedic formulation, *Journal of Pharmacy Research*, 2(5): 795-797

- Achliya, G. S., Wadodkar, S. G., **2005**, Evaluation of CNS activity of bramhi ghrita, *International Journal of Pharmacol.,* 1 (37): 33-36

- Asif, H., Mohd, R., Afroz, A., Ravinesh, M., Deepak, G., **2010**, Design, synthesis and pharmacological activities of novel N-1-2-(substituted phenyl)-4-oxo-1,3-thiazolan-3-yl-2,2-diphenyl-acetamides, *Int JPharm Sci Rev Res*, 5(2): 102-106

- Balakrishnan, N., Kumar, S.A., **2010**, Antiepileptic activity of alangium salvifolium leaf extracts, *Herbal Technology Industry,* 20-23

- Balamurugan, G., Muralidharan, P., Selvarajan, S., **2009**, Anti-epileptic activity of poly herbal extract from indian medicinal plants, *Journal of Scientific Reasearch*, 1(1): 153-59

- Christianah, A.E., Ana, L.G.F., Ane, E.Q.M., Iranse, O.S., Jose, L.R.M., Daniel, A.R., Gustavo, R.P., Elson, A.C., Mohamed, A.I., Jordan, K.Z., James, O.F., **2020**, Involvement of benzodiazepine site in the anticonvulsant activity of Tapinanthus globiferus against pentylenetetrazole- induced seizures in mice, *Planta Med*, 1209-1254

- El,K.W., Sergiy, Y.S., Sergiyv, Z., Amjad, A.S., Vadim, V.T., Sergiy, M.K., Natalya, D.B., Lina, O.P., Hanna, I.S., Victoriya, A.G., **2019**, Synthesis, in vivo and in silico anticonvulsant activity studies of new derivatives of 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)acetamide, *European journal of medicinal chemistry*, 19: 30612-9

- E.Ngo Bum, G.S. Taiwe, F.C.O.Moto, G.T. Ngoupaye, R.R.N. Vougat, V.D. Sakoue, C.Gwa, C.Dong, S.V. Rakotonirina, A. Rakotonirina**, 2011**, Antiepileptic medicinal plants used in traditional medicine to treat epilepsy, *Clinical and Genetic Aspects of Epilepsy*

- G.Smilin, B.A., U. Suryakala, Doulethunisha, S.S., P. Chandra, B., T. Sivasudha, **2016**, Expression pattern of NMDA receptors reveals antiepileptic potential of apigenin 8-C-glucoside and chlorogenic acid in pilocarpine induced epileptic mice, *Biomedicine and Pharmacotherapy*, 82: 54-64

- Gauthaman, K, Mohamed, S, **2009**, Anticonvulsant Effect of Drosera burmannii Vahl, Int. J. *Applied Research in Natural Products,* 3: 1-4

- Hammad, A., Mahtab, A.k., Syed, A.A.Z., Sajjad, M., **2021**, In silico and In vivo: Evaluating the therapeutic potential of kaempferol, quercetin and catechin to treat chronic epilepsy in a rat model, *Frontier in Bioengineering and Biotechnology*, 9: 754952

- Hui-Ling, Z., Jian, B.W., Yi, T.W., Bao, C.L., Cheng, X., Jing, H., Peng, L., **2014**, Medicinal compounds with antiepileptic/ anticonvulsant activities, *Epilepsia*, 55(1): 3-16

- Jaskiran, k., Paras, F., Mani, F., Meenu, M., Saurabh, S., Neha, S., Manish, V., Gopal, L.K., Dinesh, K.C., Kamal, D., Navneet, K., **2020**, Potential Antiepileptic phytoconstituents: An updated Review, *Journal of Ethnopharmacology*, 113565

- Joshi, M. K, Joshi, H.B., **2011**, Anticonvulsant activity of chloroform extract of Nelumbo nucifera, *International Journal of Pharmacy Research Development,* 3

- Kheirabadi, M., Moghimi, A., Rakhshande, H., Rassouli, M.B., **2008**, Evaluation of the Anticonvulsant Activities of Rosa damascena on the PTZ Induced Seizures in Wistar Rats, *Journal of Biological Sciences*, 8(2): 426-430

- Kumar, D., Sing, J., **2009**, Anticonvulsant effect of the ethanol extract of Caesalpinia Pulcherrima (L.)Sw., Fabaceae, leaves, *Revista Brasileira de Farmacognosia, Brazilian Journal of Pharmacog.* 1410-1415

- Li, Y.H., Mei,B.H., Ruo, L.L., Rong, Z., Lin, H.F., Lin, H., Feng, L., Xun, Y., Yong, L.H., Chun, J.W., **2021**, Natural medicines for the treatment of epilepsy: Bioactive components, Pharmecology and Mechanism, *Frontiers in pharmacology*, 12: 604040

- Luciana, C.B.F., Carlos, C.C., **2010**, Anticonvulsant activity of extracts of plectranthus barbatus leaves in mice, Evidence-Based Complementary and Alternative Medicine, 1 (1): ID 860153

- Magda, N.N., Magdy, M.G., Azza, R.M., **2003**, Synthesis and anticonvulsant activity of novel 2-and 3-[4-(trisubstituted pyridyl)-phenylamino]- and 2-[3- and 4-(trisubstituted pyridyl)-phenoxy]-quinoxaline derivatives, *Scientia pharmaceuticals*, 71: 9-17

- Maheshwar, G.H., Deshpande, S.V., **2010**, Anticonvulsant activity of fruits of terminalia chebula retz, against MES and PTZ induced seizures in rats, *Journal of Herbal Medicine Toxicology*, 4 (2): 123-126

- Maiha, B.B., Magaji, M.G., **2009**, Anticonvulsant studies on cochlospermum tinctorium and paullinia pinnata extracts in laboratory animals*, Nig, Journal of Pharmacy Science,* 8 (1): 102 – 108
- Malawska B., **2005**, New anticonvulsant agents, *Current Topics in Medicinal Chemistry*., 5: 1-6
- Mohammad A., **2013**, Anticonvulsant potential of some medicinal plants and their beneficial properties, *TANG[Humanites Traditional Medicines]*, 3(4): e27
- Mohammad, J.K., Saeed, S., Mohsen, R., Amir, S., Ahad, K., Gholamreza, H., **2017**, Evaluation of the effects of naringenin on pentrylenetetrazole and maximal electroshock-induced convulsions in mice, *Jundishapur Journal of natural pharmaceutical products*, 12(1): e31384
- Muhammad, A.S., Waqas, A., Haroon, K., Omar, C., Luciano, S., **2020**, kaempferol as a dietary anti-inflammatory agent: current therapeutic standing, *Molecules*, 25: 4073
- Nikalje, A.G., Altamash, A., Ghodke, M.S. ,**2012**, Herbal anticonvulsant agents: A brief review, *International Journal of research in pharmacy and sciences*, 2(3): 1-13
- Nogueira, E, Vassilieff, VS., **2000**, Hypnotic, anticonvulsant and muscle relaxant effects of Rubus brasiliensis. Involvement of GABAA-system, *Journal of Ethnopharmacology*, 70(3): 275-280
- Paria, H., Javad, F.B., Somaye, V., Farnaz, N., **2019**, Evaluation of the neuroprotective, anticonvulsant and congnition-improvement effects of apigenin in temporal lobe epilepsy: Involvement of the mitochondrial apoptotic pathway, *Iranian Journal of basic medical sciences,* 22: 752-758
- Parisa, K.M., Mehdi, A., Faezeh, S.H., Mahmood, B., Massoud, A., **2020**, Synthesis,in vivo and in silico studies of N-Aryl-4-(1,3-dioxoisoindolin-2-yl)benzamides as an anticonvulsant agent, *Pharmaceutical sciences*, 26(1): 38-44

- Pavlo, V.Z., Vadym, V.K., Ihor, O.P., Oxana, V.O., Alleksandr, V.K., **2017**, In silico prediction of anticonvulsant activity of N-(2,2,2,-trichloro-1-hydroxyethyl)alkyl carboxamides, *Journal of chemical and pharmaceutical sciences*, 10(3): 1102-1108

- Reddy, J., Gnanasekaran, D., **2010**, In vitro studies on antiasthmatic, analgesic and anticonvulsant activities of the medicinal plant Bryonia laciniosa.Linn, *International Journal of Drug Discovery,* 2: 01-10

- Ruchi, M., Pakhuri, M., Shubham, S., Bhanwar, S.C., Manish, S., **2016**, Pharmacophore modeling, 3D- QSAR and insilico ADME predictionof N-pyridyl and pyrimidine benzamides as potent antiepileptic agents, *Journal of Receptors and Signal Transduction*, 1217883

- Saeed, E., Mehdi, V., Fatemeh, K.K., Fatemehsadat, S.A., Maria, R., Majid, G., Mahmood, T., Patrick, H.M., Aidin, S., Hamid, I., Nematollah, A., **2021**, Synthesis, insilico, invitro and invivo evalutions of Isatin aroylhydrazones as highly potent anticonvulsant agents, *Bioinorganic Chemistry*, 112: 104943

- Sheeba, S., Muneeb, U.R., Nehida, T., Umar, A., Manzoor, U.R.M., **2017**, Effect of Naringenin (Aa naturally occurring flavanone) Against pilocarpine – induced status epilepticus and oxidative stress in mice, *Pharmacognosy Magazine*, 13: 154-60

- Shikha, S., Nidhi, M., **2009**, Bacopa monniera -a Future Perspective. *International Journal of Pharmacy Science and Drug Research,* 13: 154-157

- Syeda, N.F., Dr.S.Vasudevamurthy, N. Rajkumar, **2015**, A Review on phytoextracts with Antiepileptic property, *Journal of Pharmaceutical Sciences and Research*, 7(11): 994-1003

- Vyawahare, N.S., Khandelwal, A.R., Batra, V.R., Nikam, A.P., **2007**, Herbal anticonvulsants, *Journal of Herbal Medicine and Toxicology*, 1(1): 9-14

**WEBSITES**

WWW.WHO.org; WWW.mayoclinic.org