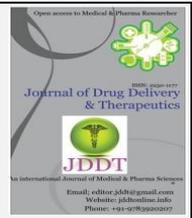


Available online on 15.02.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Review Article

Review on anti-epileptic activity of seaweed *Ecklonia cava*

Samiat Abimbola Owoalade*², Diana Moria Martin Lou², Kashikant Yadav², Sumitra Poudel²

Karnataka college of pharmacy, Campus # 33/2, Thirumenahalli, Hegde Nagar Main Road, Yelahanka Hobli, Bangalore North, Bengaluru, Karnataka 560064, India.

ABSTRACT

The Present study was undertaken to investigate the Anticonvulsant activity of sea weed extract of *Ecklonia cava* on electrically and chemically induced seizures in wistar rat. The methanolic seaweed extract was studied for its anticonvulsant activity by using experimental paradigms like Maximal electroshock-induced seizures (MES). Expected to exhibited protection against tonic convulsions induced by MES in wistar rats. Objective of these studies were designed to screen the antiepileptic activity of the seaweed *Ecklonia cava* in experimental laboratory animals.

Keywords: Antiepileptic Activity, *Ecklonia cava* (E.C), seizures, Flexon, Hind Limb Extension, Electroencephalography (EEG)

Article Info: Received 14 Dec 2018; Review Completed 29 Jan 2019; Accepted 01 Feb 2019; Available online 15 Feb 2019



Cite this article as:

Owoalade SA, Martin Lou DM, Yadav K, Poudel S, Review on anti-epileptic activity of seaweed *Ecklonia cava*, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):425-432 <http://dx.doi.org/10.22270/jddt.v9i1-s.2335>

*Address for Correspondence:

Samiat Abimbola Owoalade, Karnataka college of pharmacy, Campus # 33/2, Thirumenahalli, Hegde Nagar Main Road, Yelahanka Hobli, Bangalore North, Bengaluru, Karnataka 560064, India.

1. INTRODUCTION

Convulsion dated back to centuries, it has always been recorded in history but thought to be a spiritual attack or demonic possession.¹ The oldest description of epilepsy was about 2000 B.C. The Code of Hammurabi (an old Babylonian code) state this as a reason a purchased slave may be returned to previous master for a refund. Patients were believed to be under the influence of moon god and hence exorcisms were performed. Around 800-900B.C, Purnavasu Atreya described epilepsy as loss of consciousness.² This important description was carried forward into the ayurvedic text Charaka Samhita about 400 BC.³

In ancient times, the Greek had a rather contradictory view about convulsion, they thought of it as a form of spiritual possession, but they also associated the condition with genius and divinity. One of the names they gave to it was the "sacred disease"⁴ Hence it appearance within Greek mythology, it was associated with the goddesses of the moon Selene and Artemis, who was believed to afflict those that are wrongdoers or upsets them. The Greeks thought that important figures such as Julius Ceasar "the emperor" and Hercules "the mighty" had the disease.⁶ The notable exception to this divine and spiritual view was that of the school of Hippocrates. In the fifth century BC, Hippocrates rejected the idea pertaining to the disease being caused by the super naturals. In his landmark work, "the sacred disease" he proposed that epilepsy was not divine in origin and instead was a clinical condition and treatable originating within the brain. He also accused those attributing a sacred

cause to the disease of ignorance through a belief in superstition and magic. He proposed that hereditary was important as a cause, described worse outcomes if the disease presents at an early age, added a note of the physical characteristics as well as the social shame associated with it. Instead of referring to it as the *sacred disease*, he used the term *great disease*, giving rise to the modern term *grand mal*, used for tonic-clonic seizures.⁵ Despite such beautiful work detailing the physical origins of the disease, at the time his view was not accepted. Evil spirits continued to be blamed until at least the 17th century.

In far Ancient Rome, people neither ate nor drank with the same pottery as that used by someone who was affected.⁷ People of the time would spit on their chest believing that this would keep the problem from affecting them. According to Apuleius and other ancient physicians, in order to detect epilepsy, it was common to light a piece of gagates, whose smoke would trigger the seizure.⁸ Occasionally a spinning potter's wheel was used, perhaps a reference to photosensitive epilepsy.⁹

In most cultures back then, persons with epilepsy have been stigmatized, shunned, or even imprisoned; in the salpetriere, the birthplace of modern neurology, Jean-Martin Charcot found people with epilepsyside-by-side with the mentally ill, those suffering from chronic syphilis, and the criminally insane.¹⁰ In ancient Rome, epilepsy was known as the *morbus comitalis* ('disease of the assembly hall') and was seen as a curse from the gods. In northern Italy, epilepsy was once traditionally known as Saint Valentine's malady.¹¹

In west Africa, before the arrival of colonial masters, it was believed that epilepsy is as a result of being cursed by the gods, patients were thought to have an invincible lizard within their body that wiggles once in a while. whenever it wiggles, patient experience seizure, and without vomiting this "lizard" patient will continue to suffer from this disease, and can only be vomited if patient appeases the gods with a sacrifice of goat head, palm oil or whatever the gods asked for.

In the mid-1800s, the first effective anti-seizure medication, bromide, was introduced.¹² The first modern treatment, phenobarbital, was developed in 1912, with phenytoin coming into use in 1938.¹³

Convulsion arises due to sudden excessive and rapid discharge of cerebral neurons in the grey matter of the brain. It has been observed that presently available antiepileptic drugs are unable to control seizure effectively in as many as 25% of the patients.¹⁴⁻¹⁶ Epilepsy is a chronic neurological condition characterized by the recurrent, unprovoked seizures. An epileptic seizure, occasionally referred to as a "fit", is defined as a transient symptom of "abnormal excessive or synchronous neuronal activity in the brain". It can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. Sometimes it is not accompanied by convulsions but a full body "slump", where the person simply will lose control of their body and slump to the ground. It is the most common neurological disorders affecting people across all nationalities.¹⁷ The word epilepsy is derived from the Greek verb "*epilamvanein*" (to be seized, "to be taken hold off", or "to be attacked" indicating that the person having a seizure is possessed" or at least out of control.^{18,19} Epilepsy includes a group of heterogeneous and diverse conditions. The terms epilepsy and seizure are not synonymous and the distinction must be made clear. A seizure is an abnormal behavior (with symptoms or signs) resulting from abnormal discharges of cortical neurons and it is an observable phenomenon that is finite in time. It also refers to chronic conditions characterized by recurrent seizures.²⁰ Common causes of epilepsy include Hereditary, transient ischemic attack (TIA) (stroke), Traumatic brain injury, congenital brain defects, phenylketonuria.^{21,22} Epilepsy is one of the most common chronic neurological disorder with a worldwide prevalence of 0.5 - 5%. Approximately, 45-100 million people worldwide suffer from active epilepsy. In India, prevalence of epilepsy varies between 4.15 and 7.03 per 1000 population. The results from India were higher, and reached 60.0 per 100 000 person-years. Epilepsies are generally analyzed gradually taking into details these points;

-First cause or etiology.

-Observation manifestation.

-Location in the brain where the seizures originate.

-Identifiable medical syndromes.

-Events that triggers the seizures.^{23,24}

It has been observed that presently available antiepileptic drugs are unable to control seizure effectively in as many as 25% of the patients. A variety of different electrical or chemical stimuli can easily give rise to a seizure in any normal brain.²⁵

The current antiepileptic drugs in use such as oxcarbazepine, gabapentine, tiagabine, topiramate, levetiracetam, lamotrigine, felbamate and fosphenytoin have drawbacks such as

- Limited spectrum not enough to cover the range of the disease
- Drug interactions with oral contraceptives.

Three drugs of these gabapentine, lamotrigine and topiramate are approved for use in adults with partial seizure or without generalization. Felbamate and lamotrigine have potential of significant side effects. fosphenytoin and lamotrigine is parent pro-drug of phenytoin that is more tolerable than parenteral phenytoin.²⁶ Therefore, this is not surprising that the currently used antiepileptic drugs fail to provide satisfactory seizure control and toxicities associated with these drugs can further compromise quality of life while drug-drug interactions may complicate clinical management.

With this positive thought, various herbal medicines have been tried in the past for their potent anticonvulsant properties. There are various models for epilepsy and to determine the effects of the chemicals for the same. Physical and chemicals models are used for the experimental evaluation of the same, chemicals like PTZ, picrotoxin, strychnine and INH-isoniazid are reproducible laboratory animal models for preclinical evaluation of the potential drug for epilepsy.²⁷ Hence, during the race against epilepsy, we turn to natural products. Ayurveda is the knowledge of healthy living and not merely confined to the treatment of diseases or disorders. It is an ancient and holistic system of diagnosis and treatment involving nutrition, hygiene and rejuvenation originating in India more than 5000 years ago.²⁸

Therefore, we studied the properties of the drugs which were reported for many other activities but not scientifically proven so we chose sea weed *Ecklonia cava*. It was reported for various CNS activities. The initiation of seizure is associated with high frequency burst of action potential (AP), i.e. caused by long lasting depolarization of the neuronal membrane triggered by a large influx of calcium ions into cells.²⁹ Although, vast number of drugs were introduced for the treatment of epilepsy, still there is a need for an ideal antiepileptic agent with properties like broad spectrum activity, rapid onset of action, least side effects, good oral bioavailability and low cost.^{30,31}

In recent years, calcium channel blockers have been found to suppress seizures induced by a variety of chemical or physical stimuli.³² Physiological studies have emphasized the possible roles of calcium ion flux on the paroxysmal discharges associated with seizure activity.^[33] Hence calcium channel blockade may be important in preventing seizure spread. In neurons showing intrinsic burst firing, signaling epileptic activity there is massive influx of Ca²⁺ associated with the paroxysmal depolarizing shift (PDS) and hence the influx of extracellular Ca²⁺ into neurons is considered to be an important feature in triggering epileptic activity.³⁴ Anticonvulsants such as phenytoin, barbiturates and benzodiazepines may act in part by inhibition of calcium influx and thus alter PDS.³⁵ The above findings suggest that in refractory epilepsy, treatment with conventional antiepileptic drugs combined with agents that modify calcium ion modulation, as add on therapy, may provide better seizure control.³⁶ According to WHO, Epilepsy is the world's most common serious disorder of the brain.^{37,38} As reported, it is the second most common chronic neurological condition seen by neurologists. *Ecklonia cava* was subjected to anti-convulsive and sleep-inducing effects in mice with picrotoxin-induced seizure. Utilizing the phlorotannin-rich fraction (PTRF) from *E. cava* generated depressive effects in the CNS by positive allosteric therefore presents an attractive target for treatment of neuropsychiatric disorders

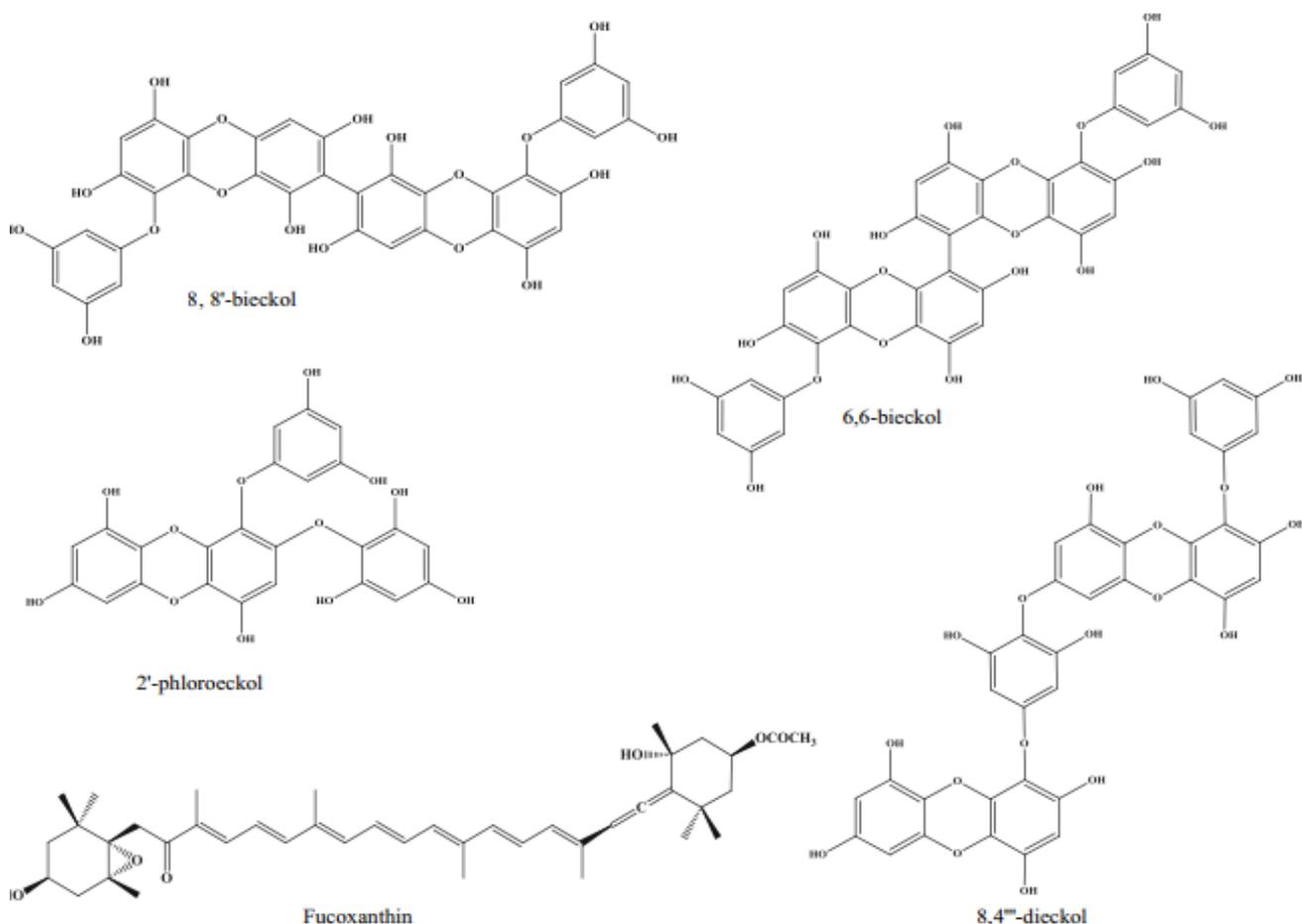
including anxiety and insomnia.^{39,40} Infact, due to its numerous health benefit Ecklonia Cava has been intended to be transplanted via artificial reef, as the extinction of this sea weed will affect future researches.⁴¹⁻⁴⁴

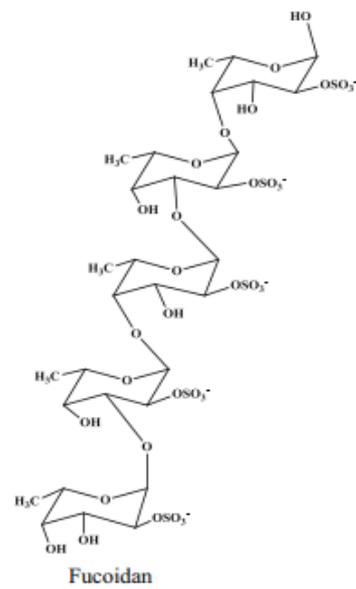
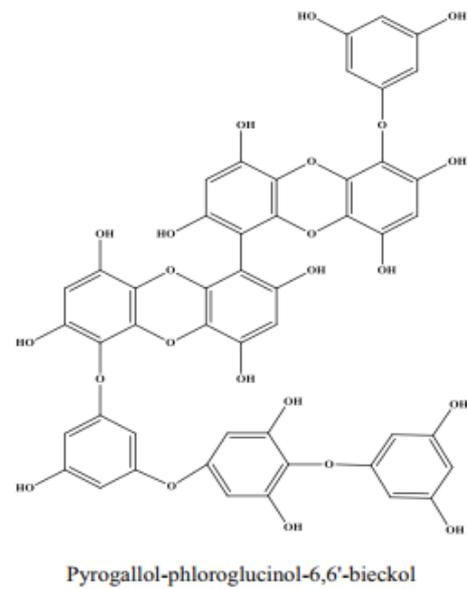
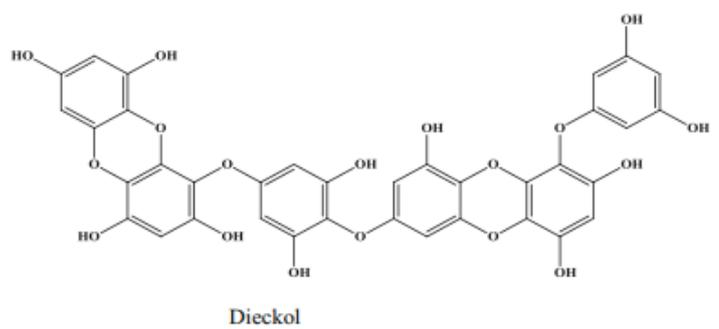
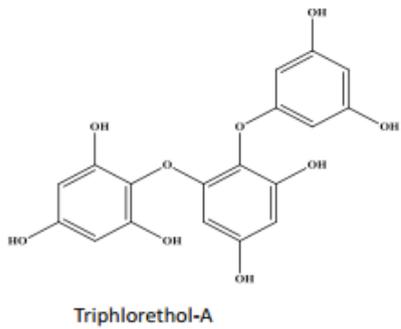
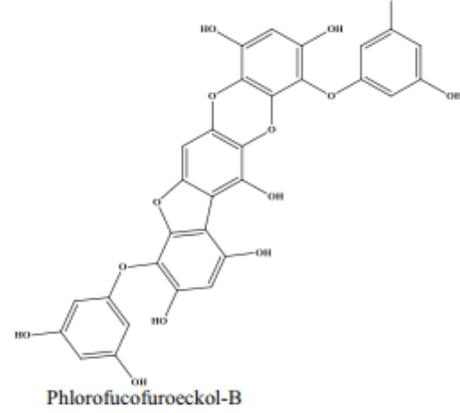
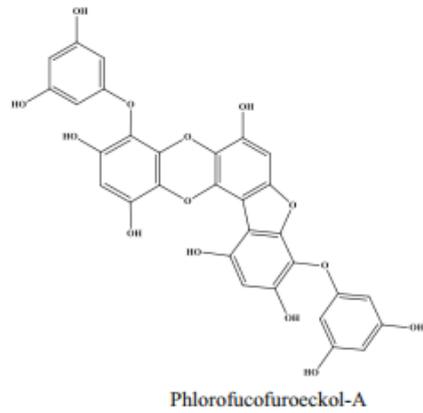
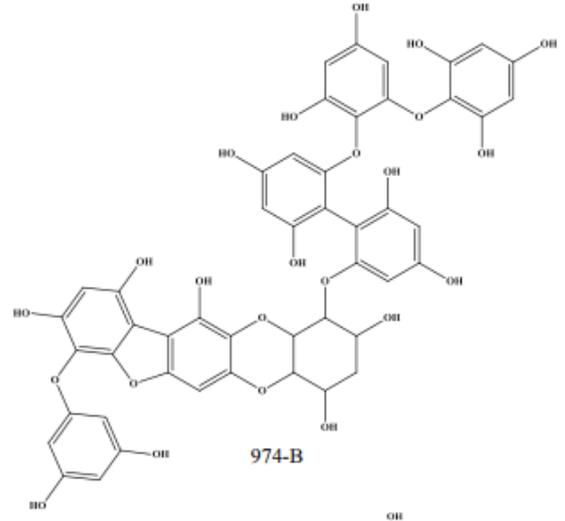
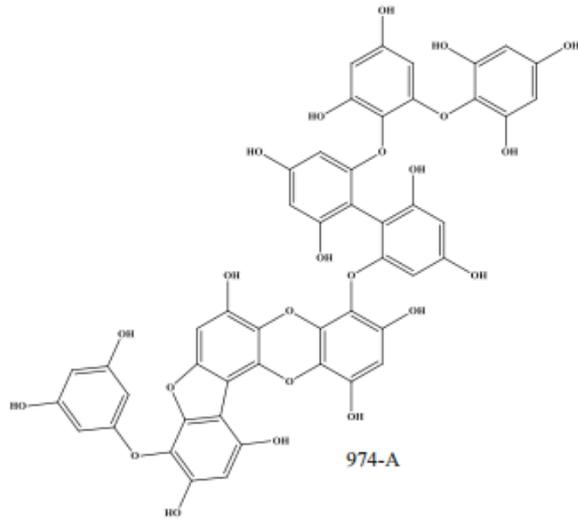
The total phenolic content of *E. cava* extract has been found the highest among the 50 marine plant extracts examined.⁴⁵ EC a brown alga, also known as “sea trumpet,” is an edible, perennial, and abundant seaweed distributed in Japan and the southern coast of Korea and has been used as a seasonal vegetable in coastal areas. This grows in sea water at a water depth of 5–25 m in the sublittoral zone, along the coasts of Korea ⁴⁶, and it is produced plentifully in the Jeju Island of Korea for commercial purposes. *E. cava* has a variety of bioactive compounds and derivatives such as phlorotannins, sulphated polysaccharides, peptides, carotenoids, and fucidans.^{47,48}

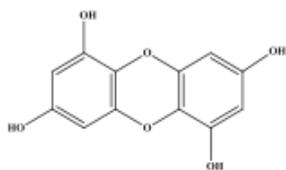
The genus Ecklonia (Lessoniaceae, Phaeophyceae), commonly called kelp, is abundant on the coasts of Japan and Korea. During the past few decades, Ecklonia species have received tremendous attention for their wide range of therapeutic properties and multiple health benefits, such as great nutritional value and being rich in vitamins, minerals, dietary fiber, proteins, and polysaccharides. Several novel functional ingredients with diversified biological activities have been isolated and possess antimicrobial, antiviral, hepatoprotective, cardioprotective, anti-inflammatory, neuroprotective, anticarcinogenic, immunomodulatory, hypolipidemic, antidiabetic, and antioxidant therapeutic

properties. The present review discusses the phytochemical, pharmacological, therapeutic, nutritional, and health benefits of different species of genus Ecklonia, as well as their use in the prevention of disease and maintenance of health. Brown algae have been used for thousands of years, but only in modern times have they been recognized to contain bioactive substances like polysaccharides, lipids, and polyphenols, with various pharmacological properties⁴⁹. Ecklonia is a genus of kelp (brown algae) belonging to the family Lessoniaceae that has an abundance of eckoltype phlorotannins. There are nine species: *Ecklonia biruncinata*, *Ecklonia brevipes*, *Ecklonia cava* (EC), *Ecklonia fastigiata*, *Ecklonia kurome* (EK), *Ecklonia maxima* (EM), *Ecklonia muratii*, *Ecklonia radiata* (ER), and *Ecklonia stolonifera* (ES)⁵⁰ EC, is an edible marine brown alga, also used as a food ingredient, animal feed, fertilizer, as well as a raw material in the production of fucoidan and phlorotannin. EC is also used as an herbal remedy in the form of an extract called Seanol, a polyphenolic extract, and Ventol, a phlorotannin-rich natural agent with two major constituents, phlorotannins and sterols.^[51] Ecklonia species are known to exhibit antioxidant, anti-inflammatory, antibacterial, anti-diabetic, anticancer, anti-photoaging, anti-HIV, anti-hypertensive, hepatoprotective, and anti-allergic activities.⁵²⁻⁶¹

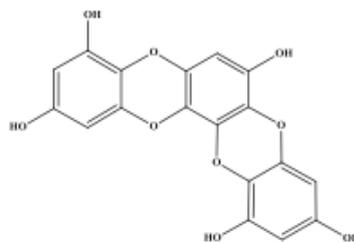
Below are some of the active phytochemical constituent in Ecklonia species, however *Ecava* reported has dieckol, eckol, triphlorethol-A, seapolynol. These are majorly constituent of phlorotannins and phloroglucinol.



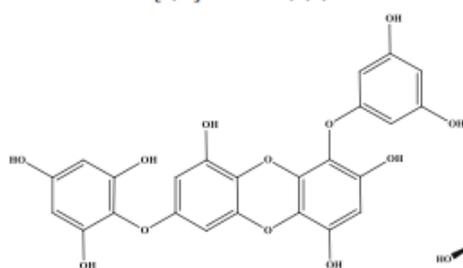




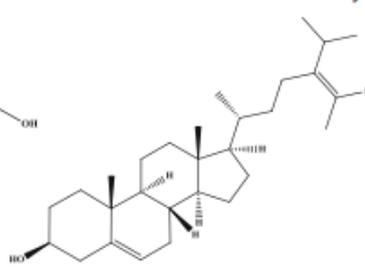
Dibenzo [1, 4] dioxine-2,4,7,9-tetraol



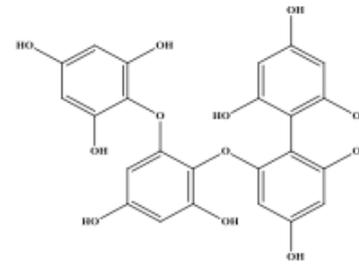
Dioxinodehydroeckol



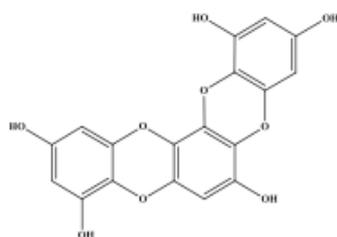
7-phloroeckol



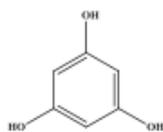
Fucosterol



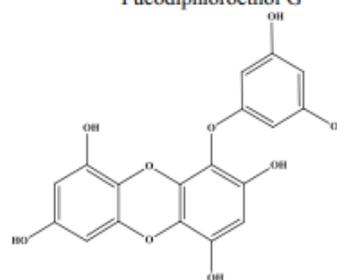
Fucodiphloroethol G



Eckstonolol



Phloroglucinol



Eckol

EC is also used as an herbal remedy in the form of an extract called Seanol, a polyphenolic extract, and Ventol, a phlorotannin-rich natural agent with two major constituents, phlorotannins and sterols.⁶²⁻⁷¹

Discussing about Epilepsy will not be complete without its classification,

CLASSIFICATION OF SEIZURES

A Partial seizure (Focal or local seizures)

a. Simple partial seizures: These have various manifestations, without impairment of consciousness. They may include convulsion confined to a single limb or muscle group (Jacksonian motor epilepsy), specific and localized sensory disturbances (Jacksonian sensory epilepsy) and other limited signs and symptoms depending upon the particular cortical area producing the abnormal discharge.

b. Complex partial seizures: These attacks result in confused behavior, with impairment of consciousness. They have a wide variety of clinical manifestations associated with bizarre generalized EEG activity during the seizure but with evidence of anterior temporal lobe focal abnormalities even in the interseizure period in many cases.

B. Generalized seizures (Convulsive or non-convulsive)

a. Absence seizures

i. Atypical absence seizures: Such attacks have a slower onset and cessation than is usual for absence seizures and are associated with a more heterogeneous EEG.

ii. Typical absence seizures: These seizures are brief and abrupt. The resultant loss of consciousness is associated with high-voltage, bilaterally synchronous, 3-per-second

spike-and-wave pattern in the EEG, usually with some symmetrical clonic motor activity varying from eyelid blinking to jerking of the entire body, sometimes with no motor activity.

b. Myoclonic seizures: These are isolated clonic jerks associated with brief bursts of multiple spikes in the EEG.

c. Clonic seizures: These are rhythmic clonic contractions of all muscles. They result in loss of consciousness and marked autonomic manifestations.

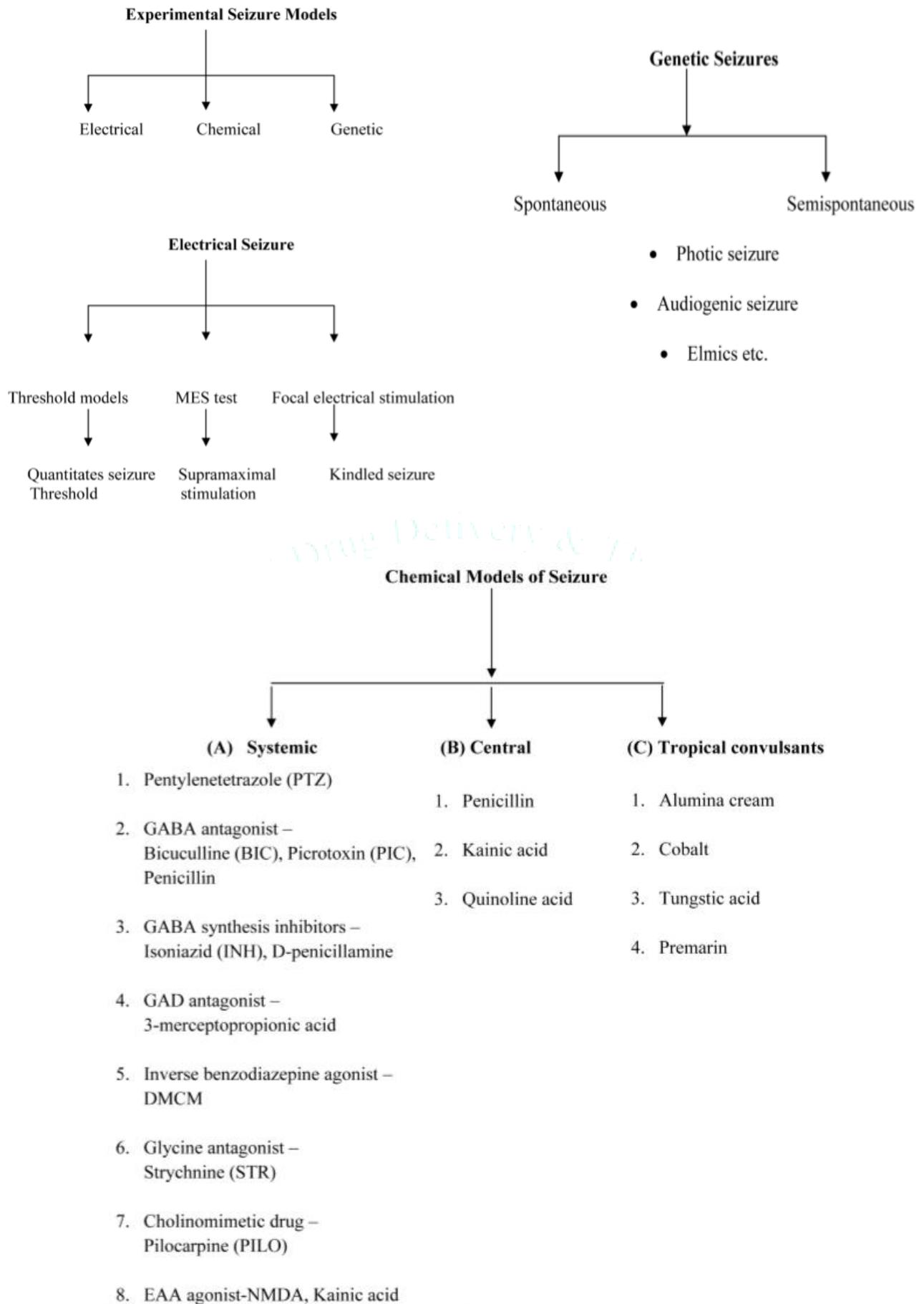
d. Tonic seizures: Tonic seizures are opisthotonus and result in a loss of consciousness and marked autonomic manifestations.

e. Tonic-clonic (grand mal) seizures: These are major convulsions, usually a sequence of maximal tonic spasms of all body musculature, followed by synchronous clonic jerking and a depression of all central functions.

f. Atonic seizures: These are characterized by loss of postural tone, sagging of the head and/or falling.⁷²⁻⁷⁴

EXPERIMENTAL MODELS USED FOR CONVULSION STUDIES

The induction of convulsion is an important step during this experimental procedure. There are various ways through which convulsion can be induced. Innumerable in vitro and in vivo models of seizures have been described over the years.^[75] The in vitro models include brain slices, monosynaptic system and neuronal culture. The in vivo models employ diverse animal species like mice, rats, guinea pigs, cats, dogs, monkeys etc. and use different physical and chemical/pharmacological stimuli to induce seizures.



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