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BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF PHYSIOLOGY

INVESTIGATION OF ANTIEPILEPTIC ACTIVITY OF *ALLIUM SCHOENOPRASUM L.* EXTRACTS IN DIFFERENT MODELS OF EXPERIMENTAL EPILEPSY

MASTER OF SCIENCE

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BOLU, AUGUST - 2021

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Dana ZAQZOUQ

ABSTRACT

INVESTIGATION OF ANTIEPILEPTIC ACTIVITY OF *ALLIUM SCHOENOPRASUM L.* EXTRACT IN DIFFERENT MODELS OF EXPERIMENTAL EPILEPSY

MSC THESIS
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BOLU, AUGUST 2021
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Epilepsy is a chronic clinical disorder that affects approximately 1% of the world population. Treatment is aimed to prevent seizure activity. Therefore, it is suggested that developing new treatment strategies that can intervene in epileptogenesis will make important contributions to epilepsy treatment. This thesis aimed to reveal the potential anti-epileptic effects of *A. schoenoprasum l*, known as chives, which is one of the recommendations of the famous medical doctor Avicenna to find new compounds and develop new treatment strategies accordingly. Two different epilepsy models were used to study the potential antiepileptic effects of A. schoenoprasum l. The first epilepsy model was induced by intracortical injection of 500 IU penicillin. The second epilepsy model was induced injecting pentylenetetrazol (PTZ) at the dose of 60 mg intraperitoneally (i.p.). In the penicillin model the animals were given *Allium schoenoprasum l.* extract (200 or 400 mg/kg i.p.) after penicillin was applied and electrocortical activity was recorded for 120 min. In the PTZ model the animals were given *Allium schoenoprasum l.* extract at doses of 200 or 400 mg/kg orally for 7 days, after which the PTZ was applied, and tonic-clonic seizures were video recorded. A. schoenoprasum l. did not significantly change either the spike frequency or amplitude in the penicillin epilepsy model. Although it did not change the seizure score in the PTZ epilepsy model it reduced the death rate and significantly decreased the tonic-clonic seizure duration. The result suggests that A. schoenoprasum l. may have antiepeileptic effects when applied chronically.

KEYWORDS: *Allium schoenoprasum l.*, ECOG, Antiepileptic drugs, Seizure, Therapy

ÖZET

FARKLI DENEYSEL EPİLEPSİ MODELLERİNDE *ALLİUM SCHOENOPRASUM L.* EKSTRESİNİN ANTİEPİLEPTİK ETKİLERİNİN ARAŞTIRILMASI
YÜKSEK LİSANS TEZİ
DANA ZAQZOUQ
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
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Epilepsi, dünya nüfusunun yaklaşık %1'ini etkileyen kronik bir klinik bozukluktur. Tedavi genellik nöbet aktivitesini önlemeyi amaçlamakta olup epileptogeneze müdahale edebilecek yeni tedavi stratejilerinin geliştirilmesinin epilepsi tedavisine önemli katkılar sağlayacağı düşünülmektedir. Bu tezin amacı frenk soğanı olarak da bilinen ve modern tıbba ışık tutan ünlü tıp doktoru İbn Sina'nın epilepsi için önerdiği tedaviler arasından olan *A. Schoenoprasum L.* bitkisinin antiepileptik etkilerinin araştırılmasıdır. A. schoenoprasum l. bitkisinin potansiyel antiepeileptik etkileri iki farklı epilepsi modelinde araştırıldı. Birinci modelde epilepsi 500 IU penisilinin intrakortikal enjeksiyonu ile oluşturuldu. İkinci modelde epilepsi 60 mg/kg pentilentetrazolün (PTZ) intraperitoneal (i.p.) enjeksiyonu ile oluşturuldu. Penisilin modelinde hayvanlara Allium schoenoprasum l. ekstresi (200 veya 400 mg/kg i.p.) ve penisilin verildikten sonra 120 dakika elektrokortikal aktivite kaydı yapıldı. PTZ modelinde ise Allium schoenoprasum l. ekstresi 200 veya 400 mg/kg dozda 7 gün boyunca oral olarak verildikten sonra PTZ uygulandı ve tonik-klonik nöbetler video kaydı ile izlendi. A. schoenoprasum l. Penisilin modelinde spike frekansı veya amplitüdünde önemli bir değişikliğe neden olmadı. PTZ modelinde ise nöbet skorunda bir değişikliğe neden olmamakla birlikte ölüm oranını azalttı ve tonik-klonik nöbet süresini anlamlı olarak kısalttı. Sonuçlar A. schoenoprasum l.'nin kronik olarak uygulandığında antiepileptik etkilerinin olabileceğini göstermektedir.

ANAHTAR KELİMELER: Allium schoenoprasum l., Anti epileptik ilaçlar, Nöbet, Tedavi

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LIST OF ABBREVIATIONS AND SYMBOLS

AEDs : Antiepileptic drugs

AMPA : α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ANT-DBS : Anterior nucleus of the thalamus- Deep brain stimulation

ALDH7A1 : Aldehyde Dehydrogenase 7 Family Member A1

BBB : blood-brain barrier

CAM : Complementary and alternative medicine

CNS : Central Nervous System

CT : Computed tomography

CSF : Cerebrospinal fluid

DBS : Deep brain stimulation

ECOG : Electrocorticography

EEG : Electroencephalogram

EPSP : Excitatory postsynaptic potentials

FDA : US Food and Drug Administration

fMRI : Functional magnetic resonance imaging

FS : Febrile Seizures

GABAA : γ-Aminobutyric acid type A

INH : Isonicotinic acid hydrazide

ILAE : International League Against Epilepsy

MRI : Magnetic resonance imaging

MRS : Magnetic Resonance Spectroscopy

MEG : Magnetoencephalography

NMDA : N-methyl-D-aspartate receptor

NGS : Next generation sequencing

IPSP : Inhibitory postsynaptic potentials

PET : Positron emission tomography

PS : Provoked Seizure

PTZ : Pentylenetetrazole

SPECT : Single-photon emission computerized tomography)

SEEG : Stereoelectroencephalography

SS : Single Seizure

SUDEP : sudden unexpected death

TLE : Temporal lobe epilepsy

VNS : Vagus Nerve Stimulation

WES : Whole exome sequencing

WGS : Whole genome sequencing

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1. INTRODUCTION

Epilepsy is thought to affect 1% of the world's population, making it a significant public health issue (1). Current epilepsy treatment is aimed at preventing seizure activity, but it does not cure epilepsy. Therefore, it is suggested that developing new strategies that can intervene in epileptogenesis will make important contributions to epilepsy treatment (2). The basic strategy in the treatment of epilepsy, which still does not have a rational treatment, is aimed at preventing symptomatic and seizure activity with the help of some anticonvulsant drugs rather than eliminating the condition that causes epilepsy (3). Enlightening the basic mechanisms of epilepsy will make important contributions to the prevention and treatment of the disease (4). In order for epilepsy to become more understandable, appropriate experimental models with similar clinical features should be created in the investigation of epileptogenesis (5). Significant advances have been made in the treatment of epilepsy with the development of new antiepileptic drugs (AEDs). Despite the abundance of available medications, most of the seizures cannot be controlled (6). In addition, the fact that AEDs have common side effects limits their use in epilepsy treatment (7). For these reasons, there was a need to develop new and more effective ingredients. Research in recent years has turned to the medicinal properties of plants because this is a natural source, believed to have reduced side effects and financial advantages (8). In recent years, scientists and pharmaceutical companies have focused their attention on phytochemical research of herbal flora, with the goal of discovering new herbal compounds with the potential to treat a variety of diseases with minimal or no side effects. The Chives (Allium schoenoprasum) could be a promising source for developing new treatments for deadly diseases. Undoubtedly, this genus has a wide spectrum of characteristics, as indicated by practically all ancient records of herbal therapy. As a result, their popularity, dependability, and vast demands from the pharmaceutical sectors have skyrocketed.(9)

A. scorodoprasum subsp. *Rotundum*, an *Alliaceae* subspecies, is a medicinal and aromatic plant that grows wild in many places throughout the world, including our own. The Allium species are the most diverse and distinctive members of the Alliaceae family, which includes over 800 species, 15 subspecies, and 72 sections. They are found all around the planet, but notably in the northern hemisphere.

Thiosulphate and organosulphur compounds are abundant in Allium plants, and they play a significant role in cell biochemistry. These plants offer protection against a wide range of disorders, including cancer, obesity, cardiovascular disease, diabetes, hypercholesterolemia and hypertension(10)

Plants used by the public offer a great chance to develop new antiepileptic regimens. Numerous types of herbs have been studied to treat epilepsy and prevent seizure effectiveness. Abu Ali al-Husayn ibn Abd Allah ibn Sina, also known as Ibn Sina and known in English by his Latinized name Avicenna, was an Iranian who spoke Persian, Muslim polymath, and the foremost physician and Islamic philosopher of his time, who lived from c. 980 AD in Bukhara, Khorasan, to 1037 AD in Hamedan, Iran. Avicenna published around 450 treatises on a variety of topics, of which approximately 240 have survived, with 40 of them focusing on medicine. The Canon of Medicine, his most famous medical book, was a staple medical text in many Islamic and European universities until the early eighteenth century. Avicenna constructed a medical system based on his own personal experiences as well as Islamic medicine, Galen's medical system, as well as traditional Persian, Mesopotamian, and Indian medicine. Avicenna is regarded as one of the forefathers of early modern medicine.(9)

It is thought that the possible positive results obtained in these ways will contribute to the developments in epilepsy treatment. Indeed, nature has long been a rich supply of pharmaceuticals, with many new drugs sourced from nature, particularly those of plant origin. Because Avicenna was a prominent scientist and physician with amazing views and experiences, we believe it is worthwhile to study his recommended epileptic therapies and to conduct further scientific studies based on his proposed epilepsy treatments (9)

It is reported by Ibn Sina that herb like Allium schoenoprasum l. is one of the useful herbs for the treatment of epilepsy. Anticonvulsant effectiveness of other plants scanned for the work has been shown in studies. However, as a result of our literature scans, we found no study investigating the antiepileptic properties of the Allium schoenoprasum l. species. We believe that anticonvulsant activity will be present in these extracts of this species, that have yet to be studied, in the field of epilepsy. For this purpose, Effects of Allium schoenoprasum l. on seizure activity has been investigated in experimental epilepsy models with Pentylenetetrazole and Penicillin.

Even though various epileptic syndromes differ pathophysiologically, they appear to share ictogenesis-related traits such as enhanced neuronal excitability and synchronization. Evidence suggests that changes in synaptic functioning and neuronal intrinsic features are prevalent mechanisms generating hyperexcitability. As mutations of genes encoding ion channels were recently discovered in some forms of human epilepsy, progress in the field of molecular genetics offered grounds in favor of this concept. When a group of neurons fires too quickly and for too long, epileptic seizures occur. There is a sustained increase in neuronal excitability in all epileptic syndromes. The causes of abnormal cellular discharges include trauma, oxygen deprivation, malignancies, infection, and metabolic disturbance. About half of epilepsy patients, however, do not have a definite pathophysiology cause. (11)

Pentylenetetrazole, an antagonist of the GABAA receptor, is one of the most used proconvulsant agents to create an experimental epilepsy model (16). In general, PTZ acts by binding to GABAA receptors linked to postsynaptic Cl- channels, which are the binding site of picrotoxin, by receptor blockade (12)and by reducing the effect of GABA and other inhibitory neurotransmitters and facilitating the depolarization of neurons (13). The inverse relationship between PTZ and GABA has been demonstrated in different experimental studies. PTZ can be used to develop both acute and chronic animal epilepsy models. A PTZ injection at a threshold dose (60 to 100 mg / kg, i.p. or s.c.) causes myoclonic jerk, tonic-clonic seizures in rodents (14).

Penicillins are one of the oldest antibiotic classes still commonly utilized in clinical practice, penicillins have a long history of use. When used against sensitive organisms, they are very potent and highly effective bactericides. Amoxicillin, piperacillin, ticarcillin, ampicillin, amoxicillin, and oxacillin have all been linked to neurological and psychological side effects such as confusion, disorientation, myoclonus and seizures, as well as non-convulsive status epilepticus (NCSE) and encephalopathy Whatever its concentration in cerebral fluid, penicillin G has the highest epileptogenic potential (CSF)(15)

2. GENERAL INFORMATION

2.1. Epilepsy definition

Epilepsy is a long-term medical condition that happened as a result of sudden abnormal, excessive and uncontrolled electrical activity in the brain (16) “Epilambanein”, in the Greek language used to refer to “Epilepsy” which means seizure (17). It is used to refer to situations that involve movement or sensory spasms that occur periodically within a certain range. Epilepsy occurs from time to time when abnormal electrical discharges are repeated, the normal electrical activity of the brain arises as millions of simple electrical charges pass through nerve cells of the brain, which spreads along to the rest of the body. It is a nerve condition that may develop days, months, or many years after the cortex has been damaged. It's possible that a small number of defective neurons causes nearby or related neurons to be destroyed over time as a result of frequent, repetitive electrical impulses. When the network of aberrant neurons becomes large enough, it becomes capable of nourishing an excessive firing pattern for at least many seconds which we call a seizure. This hyper excitable network of neurons is the seizure center that can affect a person's consciousness, body movement, and sensations for a short period of time, and therefore epilepsy is sometimes called a spastic disorder. Among the causes of epilepsy, there are opinions suggesting the excess of elements such as zinc and copper in the brain (16) sometimes triggers this neurological disorder resulting in two or more unprovoked seizures to a person within an interval of more than 24 hours apart “Unprovoked” or “not justified” means the seizures didn’t occur due to an apparent cause, such as alcohol withdrawal, heart problems, or hypoglycemia(9)

Epilepsy, according to the World Health Organization (WHO), which is characterized by frequent seizures, affects around 70 million people worldwide. The phrase seizure (derived from the Latin sacire, which means "to seize" or "take possession of") refers to the act of seizing, is an irregular electrical activity in the brain that can result in a range of signs and symptoms that describes the clinical manifestation of a group of neurons in the cerebral cortex firing abnormally, excessively, and hypersynchronously. (18,19) means brief periods cause a variety of involuntary movement signs and symptoms that could include a segment of the body (partially) or the entire body (generalized), and are occasionally accompanied by loss of awareness and control of bowel or bladder function (20). The communications in

the brain between nerve cells and regulation between each other's activities is through electrical signals, seizures occur when this electrical activity is abnormally transmitted and the exchange between cells is not organized (17).

2.2. History of epilepsy

It is one of the oldest diseases, dating back 2000-3000 years, and had described by distant ancient cultures. Despite its long history and broad prevalence, epilepsy is veiled in myth and prejudice, which can only be overcome with considerable difficulty. The goal here is to narrate the early thoughts about epilepsy in ancient cultures, and to shed light on the historical gradation of epilepsy description. The term epilepsy is derived from the Greek verb "epilambanein", which means to be seized and overwhelmed by surprise or attack. So, epilepsy refers to a state of remission, a seizure, or an attack (21)

Epilepsy was well-known throughout the world's history. The earliest mention of epilepsy is given to the Sumerian, Babylonian, Assyrian, and Akkadian civilizations, which formed in Mesopotamia (the ancient name for Iraq) between 2000 and 3000 B.C. Ancient Akkadian manuscripts from 2000 BC contain the first documented description of epilepsy, with the author describing a condition comparable to epileptic episodes in a patient. His neck was cocked to the left, his hands and feet were stiff, his eyes were wide open, and his mouth was secretly spewing foam. The illness was diagnosed as "antasubbu," which means "a hand of sin from the God of the Moon."(21)

In the British Museum's Babylonian collection, there is a stone from the Babylonian series (1067–1046 BC). In this stone, epilepsy was called Sakikku ("English translation: "All Diseases"), miqtu ("translating to "the falling disease") and it described various signs for the diagnosis, treatment, and prognosis of epilepsy. Epilepsy was once thought to be caused by demons, evil spirits, and ghosts, and generalized seizures characteristics, the king Hammurabi also referred to epilepsy in his legislation (1790 BC). A person with epilepsy was not allowed to marry or testify in court, and a slave might be returned, and the money reimbursed if it was determined that he had bennu within a month after purchase. "Bennu" is another term for epilepsy, according to researcher Marten Stol (21).

Hippocrates, the "father of medicine" and the prevalent physician in the classical Greek period (480-323 BC), believed that diseases were derived from nature rather than from the gods, in his book "On the Sacred Disease "(400 BC). He

mentions that epilepsy occurs in the brain when too much mucus enters the bloodstream and is not of divine nature. Hippocrates was also the first to attempt a scientific approach to the study of epilepsy by proposing causes and treatments. He suggested that weakened brain function and history genetics play a role in the cause of epilepsy, that it is a disease that affect the brain and is not a sacred disease, and this is one of the most important original contributions to the history of medicine (22)

The commencement of scholarly opinions regarding the earliest thoughts of seizures and epilepsy occurred during the Hippocratic and post-Hippocratic eras, and precise descriptions of epilepsy ranged greatly between the numerous scientists of the time, causing a conflation of epilepsy and mental illnesses (23)

Ibn-Sina, a Persian physician (known as Avicenna (980-1037 AD) in the Western terms), contributed to the topic of epilepsy in his magnificent book "Al-Qanun fi al-Tibb" during the golden age of Islam in the Middle East (The Law on Medicine). He believed that the variation in seizure types was due to (the brain, stomach, spleen, The term "maraaqq" refers to a membrane structure in the abdomen, and the whole body). He described seizures that appear with changes in mood ("to a state of depression" and distraction accompanied by reactions Violent) and neuropsychiatric impairment prior to episodes such as severe anxiety and excitement(24)

Many myths and incorrect beliefs regarding epilepsy have existed since ancient times, and they have resulted in rejection, denial of education, and isolation in various parts of the world, which vary from society to society and from age to era (21).

It was believed that epilepsy is an infectious disease. People used to spit on someone who had an epileptic seizure and refused to use the same plate. And in the Middle Ages, when the clergy and church councils separated the inhabited from the believers because they believed that the possessed would defile sacred things and infect common dishes and cups (25). They were warning people not to talk or shower with patients who had seizures, because it was like a disease transmitted through the evil breath (21).

Finally, despite the development that the scientific and medical side has reached today, a large number of people from many different social levels, from the rich and the poor, women and men, the educated and the illiterate, are quick to seek

healing from the shrines, saints, witches, and charlatans before specialists and doctors, making the disease worse, and treatment more difficult.

2.3. Epidemiology

Epilepsy is one of the most common chronic disease of the Central Nervous System (CNS) that has an impact on people of all ages, race, and social classes. Heterogeneity of clinical features of seizures is one of the problems encountered during epidemiological data detection in epilepsy. Cases do not refer to the physicians because patients sometimes hide their condition, or it may be skipped due to discontinuation of treatment. Standardized definitions and the absence of a correct diagnosis is another problem (20). Until the 1960s, early epilepsy studies were conducted in the tertiary referral center, this leads people to believe that epilepsy is a chronic, progressively incurable disease with a very small chance of treatment. (26)

Since, many epidemiological data from developed and resource-poor countries have been published, but methodological differences, a lack of standardized categorization, case problems, certainty, and diagnostic accuracy all contribute to differences in research results, diagnosing epilepsy heterogeneity. (26)

Epilepsy accounts for a large proportion of the world's disease burden, about 70 million people worldwide are affected (20), 75% of them lives in resource-poor countries with little or no access to medical services and treatment (26). At a given time, the estimated percentage of the general population who suffers from epilepsy (i.e., persistent seizures or requiring treatment) is between 4 and 10 per 1,000 people (20)

Globally, nearly 5 million people are diagnosed with epilepsy each year. It is estimated in developed countries that 49 people are diagnosed with epilepsy for every 100,000/year people. In low- and middle-income countries, this number can raise to 139/100,000. This could be attributed to an increased risk of contracting endemic diseases like malaria or neurocysticercosis; a high rate of road traffic injuries; birth-related injuries; and changes in medical infrastructure, preventive health care programs, and available care. Epilepsy patients make up over 80% of the population in low- and middle-income nations. (20)

2.4. Incidence studies

The incidence of epilepsy in developed countries is about 50/100,000 people (range 40−70/100,000/year), while the incidence of epilepsy is usually higher in resource-poor countries. The range of 100-190 is 15/100,000/year, although many factors may cause this difference, research shows that people from socioeconomically deprived backgrounds are at higher risk for occurrence of epilepsy. Close to 90% of epilepsy cases worldwide are found in developing regions(20,27)

2.5. Prevalence

The prevalence is a calculation of the epilepsy patients in a population at a certain moment or within a specified time interval. Prevalence represents a complicated interaction between several elements, such as morbidity, death, or disease remission (27)

Studies have shown that in high income countries, the prevalence of active epilepsy is 4 to 10/1000, although most studies have concluded that the prevalence of active epilepsy is 4-7/1000 cases. The prevalence of active epilepsy in 50 years was determined at 10-year durations and ranged from 2.7/1000. It also increased from 2.7 per 1000 in 1940 to 6.8/1000 in 1980. (26)

Lifelong prevalence of seizures (risk of non-febrile seizures at certain times) average life span is between 2% and 5%. Most morbidity studies have shown that men with epilepsy are more common than women in both developed and underdeveloped countries. However, such discrepancies are uncommon in resource-poor countries. The average yearly incidence of epilepsy was 50.7% per100,000 for males and 46.2 percent per 100,000 for females, according to a comprehensive evaluation of incidence studies. The rate of occurrence also varies substantially with age. (24)

Research in the industrialized world always shows a bimodal distribution with high incidence in the first year of life and early childhood, while at puberty it is relatively reduced. The incidence rises lest between the ages of 20 and 40, with a steady increase after the age of 50, the largest increase is in people over 80 years old. There is indication that the elderly have a greater rate of epilepsy than children. (26)

Epilepsy is less common in Africa, but studies from Asia (particularly China and India) found rates comparable to those in Western nations, despite differences

in incidence and prevalence rates within regions in the same country. According to several research, that rates are higher in rural than in urban areas (26)

There is a domination of partial versus generalized seizures in most developed countries: National General Practice Study of Epilepsy (59% vs. 39%), Rochester Study (57% vs. 40%), Umeå Study (Sweden) (68% vs 16%) and CAROLE Study (France) (46.2% vs. 31.9%). Partial seizures occurred in 55% of patients, in contrast, generalized seizures accounted for 45% was found in a systematic review. In the Rochester study, seizures are common in the first five years and the occurrence is similar between the ages of 6 and 24, with at least partial episodes twice as common in adults at 24 years. While in the resource-poor countries research has found a greater prevalence of people with generalized seizures (80.5% in Pakistan and 65.4% in Turkey)(26)

2.6. Etiology of Epilepsy

There are many causes that disturb the normal activity of the neurons resulting in seizures. This means that disorder in neurotransmitters (the nerve signaling chemicals) or their functions or in the neural network in the brain can lead to epilepsy. Two conditions can cause an excess in the neuronal activity either through a high level of excitatory neurotransmitters which will increase neuronal activity or it could be a low level of inhibitory neurotransmitters that lead to a low activity of neurons in the brain (28)

GABA (gamma-amino butyric acid) the main inhibitory neurotransmitter in the CNS, is responsible for reducing the excitatory of neurons. Some drugs can alternate GABA in the brain or change the brain's responses to it (26). GABA is considered the key to epilepsy because of its abundance in the brain, its hyperpolarization and inhibition ability of all neurons. (29)

Since the cell membrane plays a major rule in generating electrical impulses in the neuron, research have shown that if there is any defection in the molecules that moving in and out of the membrane or if the mechanism for cell nourishment and repair of the membrane has been disrupted may lead to epilepsy (26). In some situations the changes in glia (non-neuronal brain cells) which have a role in regulation of the chemical concentration in the brain lead to neuronal signaling being affected (30)

2.6.1 Genetic factors:

Genetic abnormalities have a strong link to epilepsy, genes control the individual's seizures and seizures threshold. Some types of epilepsy can be traced from specific gene abnormalities. It was found that more than 500 genes play a role in this illness. If the genes which are responsible for ion channels "the gates" that regulate neuron signaling and the flow of ions in/out of cell membrane is defected. Also if a gene (which is coded for a protein cystatin B) is missing this will lead to a type of epilepsy called "myoclonus epilepsy" (28).

Even in people without family history of epilepsy, the overlapping of numerous genetic and emergency variables can induce seizures; people may have a newly formed aberration, or mutation, in an epilepsy-related gene. This explains why external stimuli including light signaling streaks, alcohol consumption, sleeplessness, and temperature can cause or trigger genetic epilepsy(28,31).

Research also show that some people have an active abnormal version of gene that responsible for resistance to drugs, which explain why anticonvulsant drugs are useless in some cases. Additionally abnormalities in the genes that are associated with the control of development areas in the brain which develop before birth could cause epilepsy (28)

2.6.2 Poisoning:

Brain damage from other disorders caused due to lead, carbon monoxide and other poisons exposure, are known to trigger epilepsy, as well as exposure to street drugs or overdoses of antidepressant medications. Lack of sleep is also a powerful excitatory to seizures, which is why epilepsy patients should take care of their sleep schedule. Excessive consumption of alcohol or some drugs such as "heroin, cocaine etc." may cause seizures. In addition, insecticides, herbicides and artificial fertilizers if used by farmers, if used excessively and without the use of masks and protective clothing to prevent toxic effects are known to affect farmers. (28)

2.6.3 Acquired etiology:

- Any kind of brain damaged can develop epilepsy such as

1. Brain tumors.
2. Alcoholism.
3. Alzheimer's disease.
4. Reduction in the supply of oxygen (cerebrovascular, heart attack, strokes)
5. Parasitic infection (Neurocysticercosis) caused by the pork tapeworm Taenia solium.
6. Infections in the CNS may cause seizures, as the microbes inside the brain injure the brain cells. Common infections are: Cerebral abscess, cerebral tuberculosis, cerebral meningoencephalitis, encephalitis, and meningitis.
7. Head injury, (Often a violent traffic accident causes an internal hemorrhage or a skull fracture with deep wounds, they are usually accompanied by loss of consciousness and vomiting, and these accidents may cause an initial seizure in the first days of the accident, which may recur months or years later, and in this last case, epilepsy arises in the affected person)
8. Maternal infections, poor nutrition and oxygen deficiencies in fetus development.(28,30)

To summarize most epileptic seizures are idiopathic or cryptogenic, the remainder are linked to head injury, infections, and other identifiable problems.(30)

2.7. Epilepsy pathophysiology

The physiopathology of epilepsy remains unclear. A seizure can be conceptualized as when the normal balance between excitement (glutamate) and inhibition (γ-aminobutyric acid (GABA)) of the brain neurotransmission is somehow destroyed (32). This imbalance can be caused by changes in brain function at many levels, and it can be genetic (from genes and subcellular signalling pathways to the entire neuronal network) or acquired. (33)

In the epileptic cell population as result of collective anatomic or physiological neuronal changes, excitability may be facilitated in a network-dependent way, maybe accompanied by a decrease in inhibitory effects, e.g. due to selective loss of inhibitory neurons An example of neural changes leading to greater excitability is Mossy Fiber Sprouted (MFS).(11)

There are three main mechanisms involved, glial cells (especially Astrocyte dysfunction), an increase in excitatory amino acids (such as glutamate) and the reduction of inhibitory amino acids (mainly GABA) (34)

Astrocytes are provided with a mechanism to sense and respond to neural activity. Recent research has demonstrated that astrocytes play an important physiological role in the central nervous system, such as synchronization of neuronal firing, ion homeostasis, neurotransmitter uptake, glucose metabolism and vascular tone regulation. Astrocytes have been known to be responsible for hemostatic function including removal of neuronal K+ release and glutamate from the extracellular environment, and there is abundant connectivity through gap junctions that allow them to reallocate the elevated K + from sites of excessive neuronal activity to sites of lower extracellular K + concentration. So glial cells play a role in both propagation and stopping of seizures (35)

Seizures occur in the forebrain, where the cerebral cortex and thalamus are the main components. One of the elements of the cerebral cortex usually associated with seizures, especially in human patients, is the hippocampus. (18)

The gray matter in the cerebral cortex is a relatively thin layer of no more than a few millimeters in size arranged on the surface. The separation of nerve cell bodies (which make up the gray matter) from the axial processes (which make up the white matter) allows space to be preserved using shorter axon processes(18)

The generation of an action potential is the basic response of a neuron to be stimulated, which leads to depolarization along the axon and release of neurotransmitters at the axon terminal. The action potential is an all or nothing response and in an epilepsy patient the goal is to avoid the hyper-excitable state that can caused from increased excitation, decreased inhibition, a change in the voltage-gated ion channels or a change in the intracellular or extracellular ion concentrations towards a more depolarized state. (18)

In the CNS the main neurotransmitters include glutamate, gamma-aminobutyric acid (GABA), norepinephrine, serotonin, acetylcholine, dopamine, histamine and some other hormones. Among them, glutamate is the main excitatory neurotransmitter, and GABA is the main inhibitory neurotransmitter. It was found that the reinforcement of glutamate or the use of glutamate receptor agonists has been proven to increase seizure activity, while the use of glutamate antagonists reduces seizure activity. There are many subtypes of glutamate receptors, which can

be divided into ionotropic type (receptors form an ion channel pore) or metabolized type (receptors are indirectly linked with ion channels through signal transduction mechanisms, such as G proteins). The main ionotropic glutamate receptors include AMPA, Kainite and NMDA receptors, and all Na + and K + permeable. NMDA receptors are also permeable to Ca++ (mediated by Mg++), and this is the mechanism which is responsible for the excitatory nerve activation. (18)

As mentioned earlier GABA is the main inhibitory CNS neurotransmitter and There are three main GABA receptors: GABA(A) (postsynaptic ligand gated ion channel) and GABA(B) (presynaptic metabotropic G-protien coupled recepter) and recently identified GABA(C) type (form ligand-gated chloride ion channels), GABA(C) receptors are believed to be oligomeric protein complexes composed of five subunits in a pentameric arrangement (36) . Any stimulation of GABA(A) receptors makes them permeable to Cl− ions in to move into the cell, this influx hyper-polarize the cell and makes it more stable or less able to depolarize and reach the threshold to generate an action potential. Therefore barbiturates (drugs that acts as a central nervous system depressant) and benzodiazepines (GABAA receptor agonists) can reduce seizure activity. GABA(B) due to their presynaptic location restrict neurotransmitter release, therefore GABA(B) receptors agonists may reduce a seizure activity and hyper-excitable state (18) as shown in figure 2.1

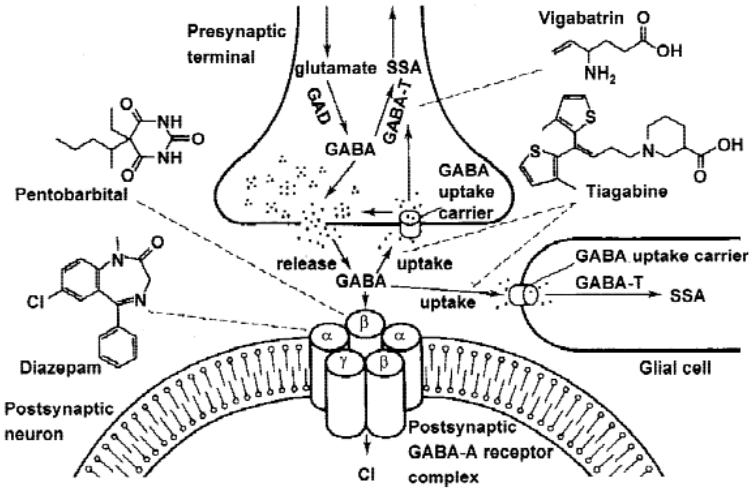
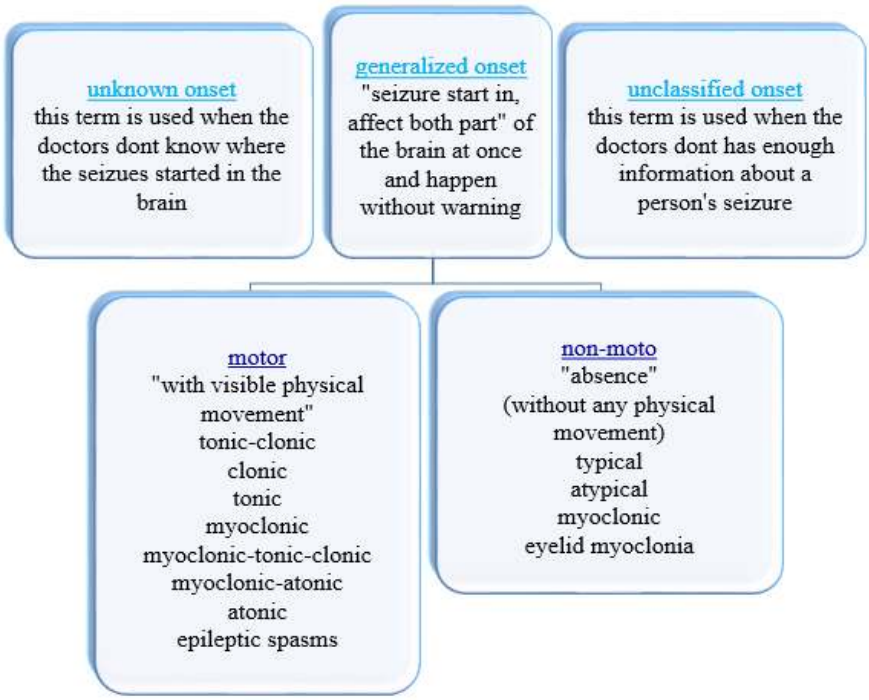


Figure 2.1 γ -Aminobutyric acid (GABA)ergic synapse. (37)

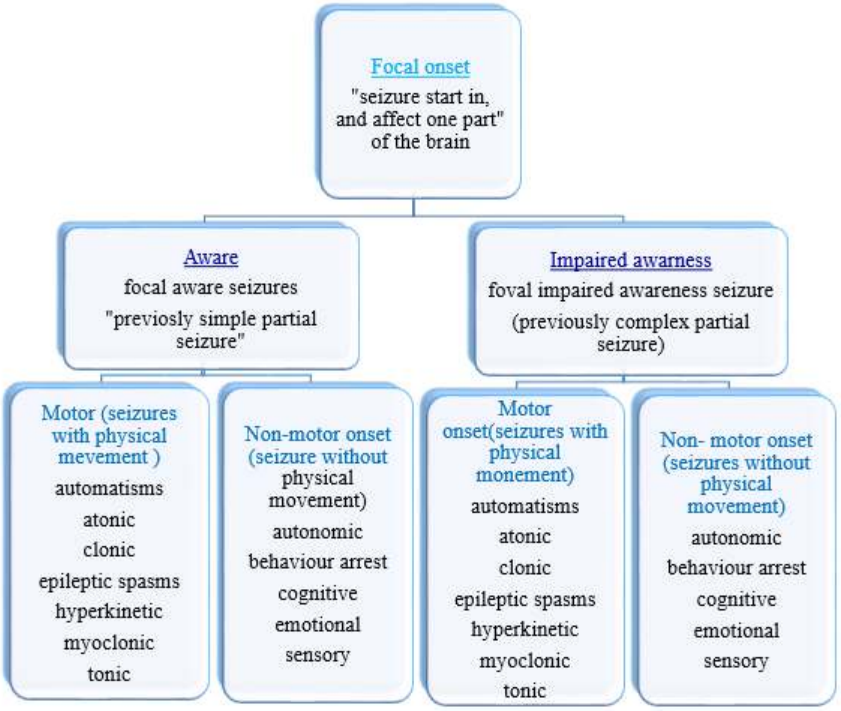
2.8. Classification of epilepsy

In order to facilitate communication between doctors, basic sciences and clinical sciences a universal vocabulary, epileptic seizures have been classified into formats. Classification of Epileptic Seizures in 1981 of the International Epilepsy Association (ILAE) Clinical and Electroencephalographic was a widely accepted classification(38,39) Figure 2.2 and figure 2.3.

As ILAE updates the seizure classification, it is vital that healthcare professionals and epilepsy patients understand the new classification and how to use the new terminology. We have become accustomed to many commonly used seizure vocabularies, such as grand mal, petit mal and partial seizures, as general terms to refer to any major or minor seizures(26,39,40).



2.2. Figure: Frame work for classification of generalized, unclassified and unknown epilepsy according to ILAE(39)



2.3. Figure: Frame work for classification of focal epilepsy according to ILAE(39)

2.9. Semiology (Signs and symptoms)

The Key signs and symptoms of seizures (semiology) are used to classify seizures that are focal or generalized from onset or an undetermined onset (40). The symptoms and manifestations of an epileptic seizure vary according to its type. The seizure may be preceded by some indications of the coming epileptic seizure. Seizures are classified into focal or generalized, according to clinical features and EEG results. (41)

Generalized seizure starts in and spreads through both sides of the cerebral cortex, to produce a motor (with visible physical movement) and non-motor (absence of the physical movement) response. A partial seizure that spreads to a part of the brain according to where it started, is also characterized by the presence of either movement, sensitivity, sensory or psychological symptoms (42)

Epileptic seizures are characterized by the appearance of some epileptic signs that precede the convulsive stage which indicates that the seizure is about to occur. These signals depend on where the electrical activity is released in the lobes of the Cerebrum. These signs appear in the form of a feeling of dizziness, anxiety, fear, and in some cases numbness in the limbs, midline including the perioral region (e.g.,

chin, lips, gums, tongue, throat), numbness or loss of the ability to speak and abnormal body movements, commonly cited as a sensation of tingling, warmth, tension, or electrical current (42)

In some cases, these signs appear as a feeling of hunger, nausea, or a sense of auditory hallucinations (hearing strange noises or hearing speech in the environment), or visual hallucinations (seeing strange things). In some cases, the person may smell abnormal odors, or feels disturbances in his awareness of things, such as doing unusual activities, making uncontrolled movements, and going places without remembering.(40,42)

Epilepsy semiology can be defined as the clinical signs or manifestations before (pre-ictal), during (ictal), or after (post-ictal) a seizure. Some people can be aware that the seizure is going to occur before it happens which is called “prodrome” and it’s not part of the seizure such as fever, illness, lack of sleep, lack of compliance, reflex, photosensitivity, and hyperventilation. (42–45)

The ictal phase may start with (Ictal Onset or Aura), which are brief focal signs or symptoms (a four- warning) and it can be the first symptoms of the seizure. The patient may still conscious and aware of what is going on during this stage of the seizure, while others have no aura or warning, thus they will lose consciousness or awareness immediately away. Aura can sometimes occur without any additional symptoms, which is known as a "simple partial seizure" (42–45)

During (ictal onset /aura) patient can have some of body changes like feeling hot, cold, or sweaty, looking pale, feeling dizzy. And he might have some change in senses like headache, numbness, tingling, or feelings like an electric shock in part of their body; or seeing flashing lights. An aura may include smells, emotions, or psychological experiences, such as a feeling of déjà vu or an out of body experience. (42–45)

The ictal phase which is (the middle of a seizure) is the time when visible symptoms started till the seizure activity in the brain stops. During this phase the patient will experience loss of thoughts and awareness, memory lapses, unable to talk, making nonsense or garbled sounds, and display stiffness in muscles, twitching or jerking movement (in the face, arms, legs, or whole body). With tonic-clonic seizure the patient may have change in breathing, difficulty in swallowing, biting their tongue, losing control of the bladder and bowel. (42–45)

After the seizure ends the (Post-Ictal Phase) some patients recover immediately while others may take some minutes to hours to feel well feeling depending on the type of seizure and which portion of the brain has been affected. During this phase the patient may being slow in responding or not responding at all, memory loss, feeling" fuzzy", depressed or sad, scared and confused. The patient also will has some body changing like dizziness, headache, thirst, feeling weak, tiered and the need to sleep (42–45)

2.10. Diagnosis

Epilepsy diagnosis is difficult, especially in the early stages, and not straightforward and there is no single test that can be used to diagnose the condition, in addition, misdiagnosis is not entirely avoidable and can have severe consequences, because there are several other conditions that can produce behavioral abnormalities in people and be mistaken for epilepsy, such as (Vasovagal syncope, Cardiovascular syncope, non-epileptic attack disorder). Since the treatment always depends in an accurate diagnosis and to confirm the presence of epilepsy, some complementary tests must be conducted. These tests are considered the key to helping the physician identify the underlying cause of the patient epilepsy(33,46)

2.10.1. History of Epilepsy including medications or drug exposure

The key to helping the physician diagnose the underlying cause of epilepsy is based on finding out what happens to the patient before, during and after the seizures. Medical history, neurological, general physical examination and any additional medical disorders, such as those caused by a head trauma, a brain infection (like meningitis), or a stroke, will be investigated as part of the diagnosis, such as tuberous sclerosis, can also cause epilepsy. However, for the majority of patients, there are no obvious causes for their epilepsy and sometimes they can't remember anything about what happened, therefore having a family member record details regarding a seizure can assist the doctor in confirming that it was a seizure and determining the type. (33)

In order to diagnose epilepsy, physicians can perform developmental and behavioral tests on their patients to consider their motor ability, cognition, strength, sensation, reflexes, walking, intellectual capacity and behavior. These tests also give information to doctor which helps identify the type of epilepsy the patient has.(46)

2.10.2. Blood test

Alongside these tests' laboratory evaluations are complementary, such as fasting blood glucose, serum calcium, serum FTA-ABS, serum electrolytes, CBC, kidney function studies, and liver function tests. (47,48)

These tests can warn the doctor if there is any electrolyte imbalance, kidney, or liver disfunctions. (49)

Physicians sometimes want to conduct laboratory studies from serum samples when diagnosing epilepsy to determine whether epilepsy is caused by metabolism or genetics. They are also used to identify problems that may cause seizures, such as infections, poisoning, diabetes, and anemia. Some researchers recommend routine measurement of some serum parameters, such as glucose, calcium, magnesium and urea, to assess the cause of epilepsy and diagnose whether there is epilepsy (49)

2.10.3. Genetic Testing:

Epilepsy is a syndrome with a wide range of phenotypes, and genetic abnormalities in the genome are thought to be the underlying cause in 70 to 80 percent of cases. There is a lot of phenotypic interfere between mutations in different genes associated with epilepsy syndromes (50)and since the identification of the first gene that cause epilepsy in 1995, more than 500 genes that associated with epilepsy have been detected, such as ion channels encoding genes(e.g. the voltage-gated sodium channel), the genes that are involved in the synaptic vesicle cycle and in different metabolic pathways (e.g. glucose transport or vitamin B6), as well mutations in neurotransmitter receptors such as GABAA. (50)

Because epilepsy is a complicated disorder, the differences between each technique affect the ability to create a diagnosis as well as the ability to accurately detect of the genetic etiology of the disorder. With 70 to 80 percent of epilepsy cases having a genetic cause, there are now hundreds of genes associated with epilepsy syndromes that can be analyzed using next generation sequencing (NGS) such as targeted gene panels, whole exome sequencing (WES) and whole genome sequencing (WGS). (50)

Several ethical and psychosocial issues must be considered before the test begins and each test has its own consideration. Individuals and their families can benefit from genetic counseling while deciding whether to undergo genetic testing.

It can also influence treatment decisions by assisting individuals in understanding the risks of recurrence for future children. (31)

According to studies, using next-generation sequencing (NGS) to determine the genetic basis for detected epilepsy would lead to adjustments and improvements in patients' treatment options. Because the therapy and treatment of epilepsy is focused on regular intake of pyridoxine (vitamin B6), this has previously been recognized through the discovery of ALDH7A1 variants. (50)

Regrettably, genetic epilepsies don’t belong to the rule of one-gene-one-disease. Although many epileptic genes are linked to one or more common symptoms, one gene can cause multiple syndromes, and one syndrome can be linked to multiple genes. (31)

2.10.4. Electroencephalography (EEG)

In evaluating a patient with probable epilepsy, electroencephalography is the most significant and common diagnostic test. It can aid in the diagnosis of epilepsy as well as the classification of the underlying epileptic syndrome. (51)

An EEG is a recording of electrical activity of the brain. It can detect irregular electrical activity such focal spikes or waves (which are indicative of focal epilepsy) or diffuse bilateral spike waves (associated with epilepsy in general with generalized epilepsy). It is preferable to include a routine EEG for both awake and sleep states because the spread of epileptic form abnormalities differs in these different states of consciousness. Hyperventilation and photo stimulation are activation procedures performed during an EEG to increase the productivity of epileptic activity. (33)

Even when they are not suffering an epileptic seizure, people with epilepsy frequently notice variations in their normal brain wave pattern. Although the EEG can be highly useful in detecting epilepsy, it is not completely reliable because some patients can have normal brain wave patterns following a seizure. An EEG should be performed as soon as feasible after the patient's first seizure. Because brain activity differs during sleep and during the day, it's preferable to do the test on the patient while they're sleeping.(51)

2.10.5. Brain Scans

Radiography is one of the important methods of epilepsy diagnosing. The main role of radiography in epilepsy is to identify any structural abnormalities or diseases and to aid the patient's treatment protocol. Radiological data play an important role, especially in patients who have been presumed to have undergone surgery, in determining the diagnosis and monitoring the disease. (33) Figure 2.3. The most commonly used brain scans are:

CT (computed tomography) which is a kind of X-ray that creates detailed images of internal organs and tissue; it can identify abnormalities like scar tissue tumors, malformed blood vessels and any problem in the spinal fluid circulation. (33)

PET (positron emission tomography) sugar or small amounts of radioactive glucose is injected intravenously to create detailed image of the brain tissue to view the blood flow and brain cells activity, which gives an idea of where local seizure occurs, namely the areas that use less sugar. (33)

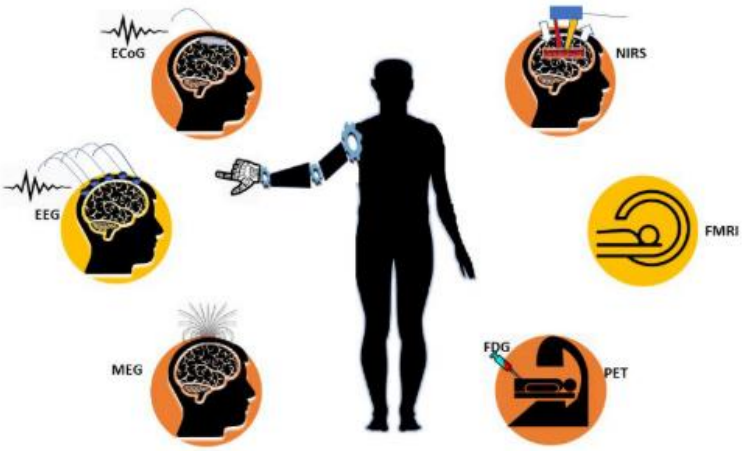
MRI (magnetic resonance imaging) which can provide the most detailed and accurate image of the brain. It is a magnetic field and radio waves create a computerized two- or three-dimensional image that can detect defects in the brain's biochemical processes, and with near-infrared spectroscopy, a technique that can detect oxygen levels in brain tissue. (33)

MRS (Magnetic Resonance Spectroscopy) can analyze the molecular components of tissue in a particular area of the brain, which helps to differentiate if the patient has seizure or another condition like stroke or metabolic disorder. (33)

fMRI (Functional magnetic resonance imaging) measure changes in oxygen and blood flow (called *blood oxygen level dependence" BOLD"*) to a specific area of the brain while a person performs specific repetitively tasks, like reading a short passage and speaking little words so the doctor can determine essential areas in the brain that are responsible for language, memory or motor functions. (33)

SPECT (Single-photon emission computerized tomography) is a new type of brain scan that detects blood flow in certain areas in the brain during or after the seizure. The results are displayed as a picture on a computer monitor with various color that shows different level of blood flow. (33)

MEG (Magnetoencephalography) detects the dynamic electromagnetic signals which are generated by the neurons to allow doctors to observe brain activity and locate epileptic dipoles, while MEG is similar in concept to EEG, it does not need electrodes and it can detect signals from deeper in the brain than an EEG does.(33)



2.4 Figure: Various imaging methods that contribute to the development of the mind-machine interface in a clockwise direction from the upper right angle: near-infrared spectroscopy (NIRS), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetic EEG (MEG), Electroencephalography (EEG), and electroencephalography (ECoG). (33)

2.11. Treatment of epilepsy

The major objective of the treatment is to ensure normal and suitable life for epilepsy patients with less mental and physical disabilities. It is in the first place prophylactic (aims to prevent seizure recurrence) and provide a complete seizure control whenever this is possible, most studies focused on seizure frequency while seizure severity is also important because it is the way to prevent extra harm and aim to achieve a better quality of life for the patient if it is under control.(52)

Epilepsy is the reason for the most illness related absences from schools and work, and it can also affect normal social and life activity like driving, pregnancy, travelling or sport. Over the years seizures can also lead to physical injuries, burns, head trauma, bone fractures and fatal accidents (e.g., drowning). However, the most concerns are the risk of sudden unexpected death (SUDEP), so it is important to

decide which kind of treatment will be primarily suitable and correct for the patient according to the type of seizure, possible etiology, correct classification of the type of epilepsy and the recurrence of the seizure. Additional considerations must be taken when deciding which type of treatment is best like other medications, effect on patient's lifestyle, patient's preference, with the aim to minimize interference with the daily activities of the patient (52). Many patients believe that their seizures are provoked by external or internal stimuli, despite the fact that Avicenna's suggestions were provided in reference to seizure triggering elements that occur spontaneously without apparent instigating reason in most persons. Some of these etiological elements, such as sleep deprivation, excessive alcohol intake, premature awakening, psychological stress, prolonged fasting, physical weariness, and photic stimulation, have been extensively described in recent research (9). Knowing what circumstances can cause seizures will help you better comprehend how some people have managed to avoid them. Patients with epilepsy should avoid triggering factors for seizures, including as drinking, overfeeding, sleep deprivation, and oversleeping, according to Avicenna. In the current literature, overfeeding and oversleeping have not been recognized or examined as possible seizure triggering variables.(9)

Some people need treatment for life while others may stop if the seizure disappears over time. There are two types of treatment:

2.11.1. Pharmacological Treatment

FDA anti-epileptic drugs(AEDs): Following the second epileptic seizure, AED therapy is usually recommended and most patients can be treated with AEDs once a diagnosis of epilepsy is confirmed, but if it's not confirmed that the patient has epilepsy more evaluation should be taken, symptoms of epilepsy in most patients can be successfully treated with one or more antiepileptic drugs (which can provide satisfactory control or sometimes total relief of seizures) (53,54). Although AEDs do not prevent or cure the significant behavioral, cognitive, and somatic problems present in many epileptic patients, they do help to improve their quality of life. (55)

The AED treatment plan for the patient's seizure type should be individualized to the type of seizure, epileptic syndrome, co-medication and co-morbidity, age, gender, the patient's lifestyle, and the person's and their family's and/or careers' preferences (56)

It's not always required to initiate the therapy when a single seizure occurred, the decision to start long-term therapy with AEDs should be taken from a specialized physician in seizure management (56). It is recommended that a single AEDs(monotherapy) should be the first step of pharmacological treatment (57). When the monotherapy is un-successful, doctors will recommend combination therapy. Figure 2.4 explain the epilepsy treatment pathway.

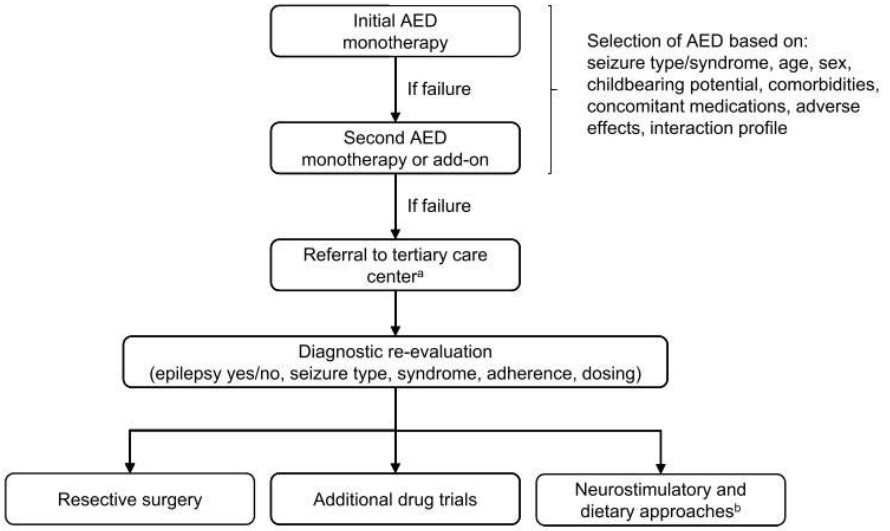


Figure 2.5: Epilepsy treatment pathway(54)

Antiepileptic drugs aim to control seizures completely without any long-term safety issues (such as teratogenicity, hypersensitivity reactions or organ toxicity). Since the 1980s there have been more than 15 antiepileptic drugs providing more choices, even epilepsy specialists, however, have their doubts, it is difficult to choose the best drug for each patient, because each medication has its advantages and limitations (55) Table 2.1

Table 2.1: Characteristics of major antiepileptics (54,55)

Drug	Mechanism of action	Main uses	Adverse effect
Carbamazepine	Na+ channel blocker	First-line treatment for tonic-clonic seizures with a focal, generalized onset.	Blood dyscrasias, headaches, hyponatremia, metabolic bone disease, nausea, nystagmus, rash (human leukocyte antigen testing may be relevant), somnolence, and vomiting
Gabapentin	Ca2+ blocker	Hepatotoxicity has not been observed in clinical trials. Use with a focal insert for focal and generalized seizures.	Ataxia, dizziness, somnolence No
Lamotrigine	Na channel blocker	For focal and generalized seizures, this is the first-line treatment.	skin rashes and headaches
Levetiracetam	SV2A (synaptic vesicle membrane protein) modulation	Intravenous first-line treatment for focal and generalized seizures with focal onset, as well as myoclonic seizures. Hepatotoxicity has not been observed in clinical trials. For new onset focal seizures, it's as effective as carbamazepine.	• Dizziness. • Headache. • Irritability. • Sleepiness.
Oxcarbazepine	Na+ channel blocker	First line drug for focal and generalized seizures with focal onset	Ataxia, diplopia, dizziness, headache, hyponatremia, nausea, rash, sedation, vertigo Acute
Topiramate	Multiple (GABA potentiation, glutamate, (AMPA) inhibition, and Na and Ca channel blocking)	First line drug for focal and generalized seizures. No clinical heptotoxicity	dizziness, diarrhea and feeling sick
Valproate	Voltage-gated sodium channels blocker and increased brain (GABA).	First line drug for myoclonic, absence, generalized-onset tonic clonic seizures	Dizziness, headache, tremor, abnormal color vision, myoclonus, and bruxism

Treatment objectives, medication adherence, and AED side effects should be reassessed at least once a year, with special emphasis paid to seizure frequency, drug effects, preconception counseling, and the necessity for referral to specialized facilities for persistent symptoms (55). Figures 2.6 illustrate the mechanisms that various of AEDs drugs use to inhibit glutamate activation of brain cells.

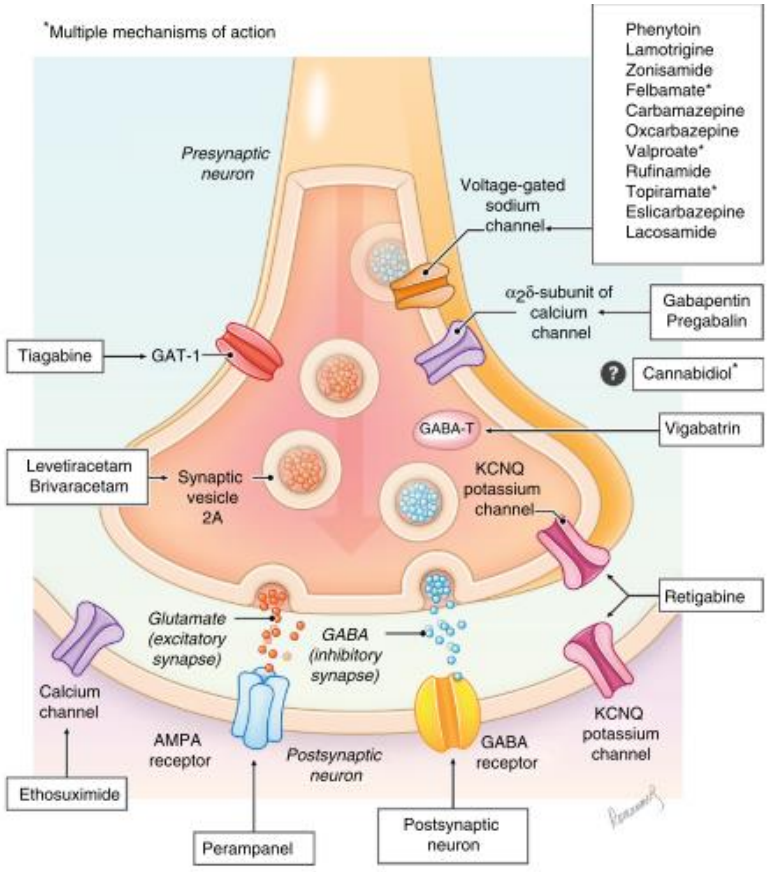


Figure 2.6: Multiple mechanisms of action for AED drugs (58)

Drug resistance epilepsy is one of the main problems that can be considered as a challenge in epileptic treatment with AEDs, however the real reasons and mechanism for this is unknown. The patient will count as having drug resistant epilepsy if at least two trials of selected anti-epileptic drugs and doses did not bring sustained remission according to ILAE-resistant epilepsy standards and if the seizures don't stop within a year. The failure of at least six anti-epileptic medicines may be required to diagnose absolute drug resistance, because even if two to five

drugs fail to control seizures, when other anti-epileptic drugs are given, about 17% of patients will become seizures free (55)

Additionally in patients with temporal lobe epilepsy (TLE), drug resistance is a particular problem, where seizures originate in the temporal lobe, the area of the brain most likely to cause epilepsy(53)

The transporter theory, target hypothesis, network hypothesis, genetic variation hypothesis, and intrinsic severity hypothesis are some of the current theories. These, however, are insufficient to explain how human epilepsy develops resistance (55), so other strategies of treatment must also adopted :

2.11.2. Non-pharmacological Treatment of Epilepsy

2.11.2.1 Surgical Intervention:

If tests reveal that seizures are caused by a dysfunction in a small area of the brain that may be removed without serious effects, some test will be done before surgery such as (brain scans, EEG). The seizures may not stop directly after surgery, the patient may need to keep taking AEDs for 1-2 years. The patient may have some complications after surgery like problems in memory, mood or vision, neurologic deficits, or some medical complications (intracerebral infections, cerebrospinal fluid leak, aseptic meningitis) which may improve over time or maybe permanent. (56)

Patients with focal epilepsy have many zones that overlap; this overlap is considered when calculating the surgical resection limits. The irritative zone is the cortical area that can create epileptic form activity, whereas the ictal-onset zone is the cortex region implicated in seizure formation. The epileptogenic region is quite complex and is also considered the area of seizure occurrence that may generate the ictal onset of a seizure in the future. This differentiation of the current ictal-onset region from the potential seizure start area is important, in cases where a recurrence of the seizure occurs months to years after the excision of the seizure start area. (59)

If seizure semiology, non-invasive scalp EEG, and coherence imaging show a clear epileptic zone (EZ) in a surgically accessible location, an excision or other targeted surgery can be conducted with fair confidence. However, when there is conflicting evidence or many potential foci or proximal cortex, intracranial electrode implantation and surgical mapping of the seizure onset location can help with further treatment planning (59). In Stereoelectroencephalography (SEEG) the epileptic zone concept is different, as its identification is a necessary step in the preoperative

investigation (60). It is a different strategy in which depth electrodes are inserted through holes drilled in the skin to detect precise stereotactic coordinates in the brain. SEEG has been used in some European centers for a long time, and it is gaining popularity in North America, supported by the advent of stereotaxic robotic assistance and increasing evidence of safety, without the need for catheter angiography, with low rates of hemorrhage, infection and other clinically significant complications.(59)

In ECOG, it is best to retrospectively define the epileptogenic zone after surgery as apart of the cortex that is necessary and sufficient for initiation of seizures and whose removal is necessary to completely cancel the happening of seizures.(60)

2.11.2.2 Ketogenic Diet:

The ketogenic diet is an effective treatment for epilepsy, particularly in children with refractory epilepsy. Although the mechanism by which diet reduces seizures is unclear, acetone ketone body has anticonvulsant action and may play a role in seizure control (57). It should not be used as the last treatment option but should be provided early in the treatment flow chart. In some cases, such as glucose transporter 1 (GLUT1) deficiency, but in certain mitochondrial disorders, this is the first-line treatment (54)

The ketogenic diet has been used successfully to treat people with intractable epilepsy since the 1920s. It’s a diet with high fat but low carbohydrate and protein content, providing enough protein for growth, but not meeting all the body's metabolic needs from carbohydrates (57). In this case, energy comes from the oxidation of fatty acids in the mitochondria. Glucose is an important energy source for the human brain, fatty acids can’t be used because they can’t cross the blood-brain barrier (BBB). On the other hand, during the ketogenic diet, the glucose is partially replaced by ketone bodies as fuel for the brain. Basically, the ketone body is converted into Acetyl-CoA, which then enters the brain to produce energy.

On the other hand there are many negative effects such as include gastrointestinal symptoms (vomiting, diarrhea, abdominal pain), metabolic abnormalities (hyperuricemia, hypocalcemia, decreased amino acid levels, acidosis), renal calculi, and cardiac abnormalities (cardiomyopathy and prolonged QT interval)(56)

2.11.2.3 Vagus Nerve Stimulation (VNS)

The US Food and Drug Administration (FDA) approved VNS as an adjuvant therapy in the treatment of medically (who are difficult to treat with antiepileptic drugs) intractable partial epilepsy in people aged 12 years old and older who have no chance for epilepsy resective surgery, or for whom surgery was ineffective, and include adults whose epilepsy is predominantly focal (with or without secondary generalization) or generalized seizures(57). A battery-powered stimulator is implanted with wires around the left vagus nerve and connected to a programmable pacemaker during this procedure. Its mechanism is unknown; however, it is most likely caused by afferent activity that blocks the electrical circuits in the brain that trigger seizures. Furthermore, VNS causes an increase in the excretion of the inhibitory neurotransmitter GABA in the cerebrospinal fluid (CSF) (56).

When the device is activated, it has been shown to reduce seizure frequency in adults and children, but it does not always completely control seizures. It has also shown mild and mostly temporary stimulation-related side effects that are different from common AED side effects, such as a hoarse voice, sore throat, and cough. This happens once every 5 minutes and lasts 30 seconds.(54)

2.11.2.4 Emerging Treatments

- **Deep brain stimulation**:

The DBS of the anterior nucleus of the thalamus (ANT-DBS) is another neurostimulation method that has shown long-term success in drug-resistant patients (54). It is bilateral stimulation of the anterior nuclei of the thalamus (ANT). It works in a similar way to VNS, only the device is implanted in the chest and is connected to cables that flow directly into the brain. By altering electrical signals in the brain, electrical pulses delivered through these connections can help to prevent seizures. Because DBS is a relatively new surgery that is rarely utilized, it is not yet established how effective it is for epilepsy. There are also some major hazards linked with it, such as brain hemorrhage, depression, and memory issues. (56)

- **Responsive neuro stimulation:**

The lead for this recently authorized technology is implanted directly into the epileptic area, which can be cortical or subcortical, unlike the vagus nerve stimulator. The neuro stimulator administers electrical stimulation to the target epileptic area in response to aberrant electrical activity. Pain at the implant site, infection at the implant site, headache, and paresthesia are all possible side effects. (56)

2.11.2.5 Investigational Therapies

Obviously, the status of refractory epilepsy represents a major problem. As a result, as a new method of epilepsy treatment, different directions, acupuncture, TCM, cannabis, melatonin, vitamin supplementation, and yoga are just a few examples (56), stem cell-based cell therapy and gene therapy are being intensively studied. (53)(56)

- cell therapies based on own stem cells can benefit by providing the following platforms:

1. Cell replacement, in which the transplanted cells are used to repair the neural network by replacing deformed neurons.
2. Trophic support, in which the transplanted cells are used to promote the survival and endogenous repair of the affected neurons.
3. Ex gene therapy, neurons derived from stem cells used for transplantation are genetically modified; such as modified neurotransmitters and neurotrophic factors.(53)

- Transplantation of GABA Releasing Cells

Through transplantation of immortalized cells (which are genetically modified)in to pre-existing neural area to produce (GABA), thereby to increase GABAergic transmission, which can restore the proposed defect that has been shifted towards excitation processes (owing to the loss of GABAergic neurons, which is common in epileptic areas)(53)

- Transplantation of Adenosine- Releasing Cells

This depends on Adenosine Gene Therapy to increase local adenosine levels and can be a way to dampen glutamate excitatory transmission and cause seizures to stop. An alternative trend is to implant adenosine-releasing cells into dysfunctional brain regions. Several research have shown that this strategy is effective, as it has shown that cell culture from various sources, including mouse embryonic stem cells, human multiple sclerosis cells, and immortal fibroblasts, designed to release adenosine, are able to suppress spontaneous chronic seizures.(53)

2.12. EEG and ECOG

Brain mapping and invasive recording technology is an important electrophysiological instrument in preoperative evaluation and surgical treatment of patients with epilepsy, in which electrodes are placed on the skull or inside the brain

to record its activities. Either outside of surgery or during surgery, cerebral cortical mapping can be performed (60,61)

Transmembrane currents are produced by neuronal activity in the brain and can be detected in the extracellular media. Potentials are formed by the electrical potential difference between inside and outside of the cell, they gather in the cortex and spread to the scalp from the structures surrounding the brain. Synaptic transmembrane current is considered the main contributor of the extracellular signal, thus high-intensity recordings of neural activity, along with newly created data-processing software and computational modeling, can shed light on neurons' cooperative behavior, the average of their synaptic inputs, and their spiking outputs, and can improve knowledge of how these processes contribute to extracellular signaling. The main advantage of the extracellular field recording approach is that it was used to analyze neural network activity rather than a variety of other methods, the biophysics associated with these measurement methods is understood very well. This enabled the creation of a repeatable and quantitative mathematical model that explained how the transmembrane current produced the electric potential record.(62)

EEG & EcoG is used widely and effectively to diagnose epilepsy and maintain its importance in guiding diagnosis and treatment.

2.12.1 EEG (Electroencephalography)

Electroencephalography (EEG) is one of the oldest and most widely used methods of examining the electrical activity of the brain (62) figure 2.7. The cerebral cortex is the brain’s outermost layer, and it is thought to be in charge of knowledge, perception, memory, thinking, emotions, actions, and behaviors. Electrical impulses between neurons change numerous times in the 10 ms (0.01 s) range in cortical processes. The only generally available tool with sufficient temporal resolution to track these rapid dynamic changes is electroencephalography (EEG). EEG provides a comfortable, although often obfuscated, “window into the mind,” allowing electrical processes at the brain’s surface to be examined.(63)

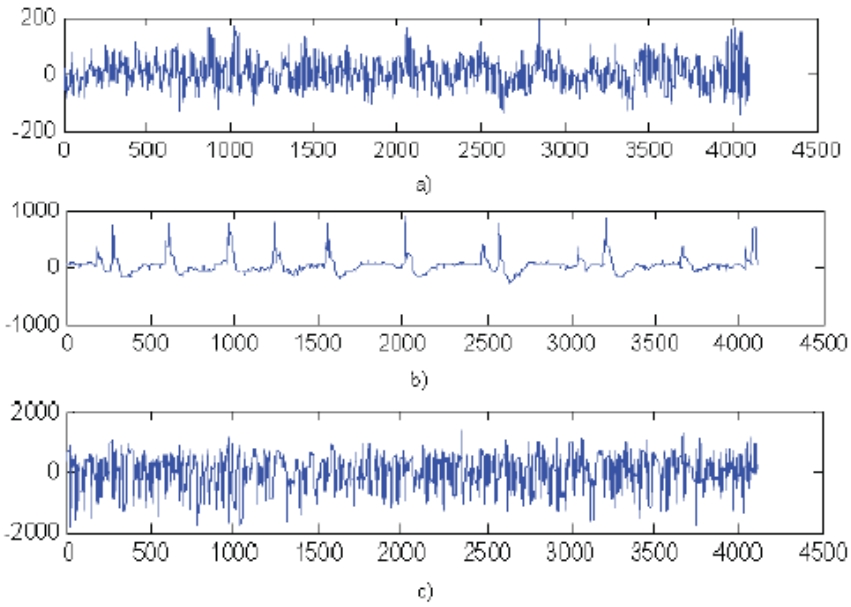


Figure 2.7: EEG signals: a) Normal; b) pre-ictal; c) Epilepsy. (60)

EEG is a non-invasive tool for monitoring the electrical signals in the brain that are linked to various perceptual processes. It is made up of electrodes put on the scalp that record electrical signals of low strength that flow through the neural network of the brain.(64). Due to the non-invasive connections placed on the scalp, the EEG is able to take samples from a wider areas around the skull. (64)

Use electrodes with a diameter usually in the range of 0.4-1 cm to record human EEG and use a specific paste to stick it to the scalp, cover or net. The EEG recording procedure is non-invasive, safe, and painless. To improve electrical contact a special gel between the electrode and the scalp will be applied. The wires from the scalp electrodes are connected to a special EEG machine with an amplifier to enhance the original scalp signal, which is usually in the range of 5–200 mV(63)

The EEG Electroencephalogram (EEG) measures the electricity and records the biological currents of the scalp in the brain. In the cortex the pyramid neurons are parallel to each other and perpendicular to the dendritic tissue of the cortex surface to generate large extracellular currents that can be recorded as EEG from the scalp. This test is frequently used to detect the type and source of seizures. For example, an EEG can show the source of the abnormal activity in the brain and can help to differ between generalized or focal seizures. EEG is only helpful in diagnosis if it detects typical patterns of epilepsy. (65)

The 10/20 system is used to determine the usual position of scalp electrodes for classic EEG recording. The distance in percentages of the range 10/20 between Nasion-Inion and fixed positions is at the core of this method. Frontal pole (Fp), central ©, parietal (P), occipital (O), and temporal (T) poles are the names given to these sites. The electrodes in the center are denoted by the subscript z. (which stands for zero). Odd numbers are utilized in the left hemisphere, whereas even numbers are used in the right(61), as shown in figure 2.8

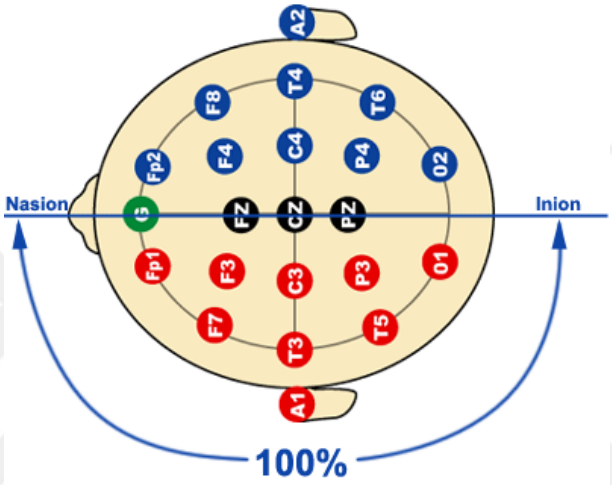


Figure 2.8: shows 10/20 System of electrode placement(66)

Brain waves recorded on EEG were divided into 4 classes as alpha, beta, theta, and delta shown in figure 2.8. Brain waves are formed by the synchronization of synaptic activity remaining as a result of the algebraic sum of excitatory (EPSP) and inhibitory postsynaptic potentials (IPSP) and are printed with the help of the recording electrode on the surface. EPSPs of neuronal structures close to the cortex surface form the positive parts of the EEG waves. In addition, superficial IPSPs contribute to the formation of the positive parts of the EEG waves and the negative parts of the deep ones as shown in Figure 2.9 (65)

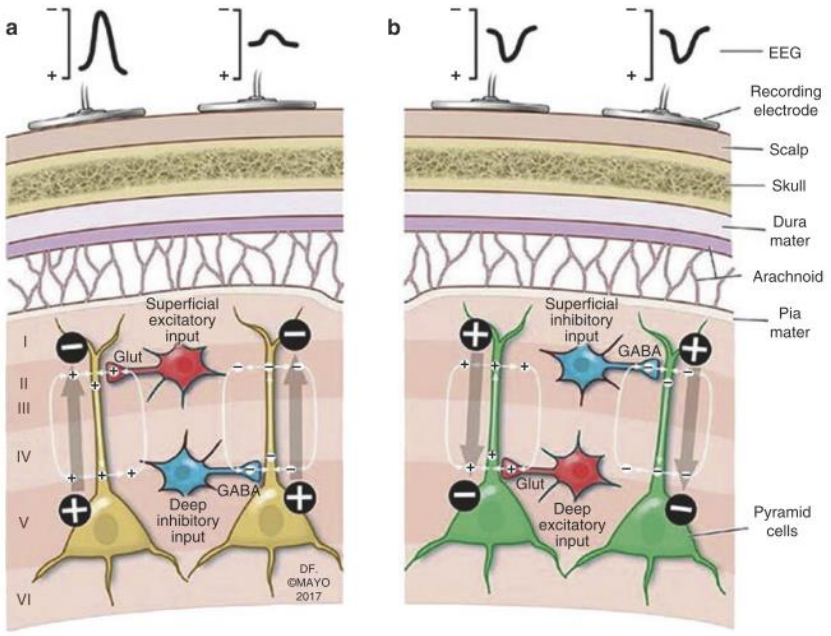


Figure 2.9 : This is an image of a scalp Positive (downward) deflections are due to deep excitatory inputs, while negative (upward) deflections are due to surface excitatory inputs.(65)

1- **Alpha Waves** are rhythmic waveforms with a frequency between 8-13 Hz per second. Although these waves are the strongest measured in the occipital region, they are also observed in the parietal and frontal areas of the scalp. Their amplitude is usually about 50 µV. They are found on the EEG of awakening young adults in a peaceful resting state, and the alpha rhythm disappears during deep sleep, opening eyes, receiving sensory stimulation or mental distress. Instead, instability, lower voltage and high frequency activity are observed. This event is called Alpha blockade or desynchronization(65,67)

2- **Beta Wave** is rhythmic activity with a frequency higher than 13 Hz and lower than 80 Hz per second. Its amplitude is 10-20 µV. It is recorded mainly from the parietal and frontal areas of the brain during the specific activation of these parts in brain. Attention focus, mental work, processing of sensory information occurs in the rapid eye movement phases of specific sleep (67)

3- **Theta Waves** have a frequency of 4-7 Hz per second. Its amplitude is 20-100 µV. Although it is observed especially in the parietal and temporal regions of children, it may also occur in emotional stress conditions such as frustration in

some adults. It is physiological in sleep in adults, and pathological in awake adults(67)

4- **Delta Waves** contain all waves of the EEG with frequency less than 3.5 per second. Its amplitude is 20-200 μV. They occur in very deep sleep (during the 3rd and 4th stages of deep rhythm), childhood (from birth to one year), and severe organic brain damage. Therefore, delta waves can occur strictly in the cortex independently of activities in the lower regions of the brain, also in the presence of sub-cortex damages, if there is extensive harm, also seen in metabolic encephalitis and hydrocephalus. In the frontal area in adults, and in children it is more prominent in the occipital region(65,67)

In table 2.2 and figure 2.10 shows different types of normal brain waves in electroencephalogram and frequencies

Table 2.2: Frequencies and Amplitude of brain waves(68)

Wave name	Frequency (Hz)	Amplitude(μV)
Alpha	8-3	2-10
Beta	13-30	1-5
Delta	0.5-4	20-200
Theta	4-8	5-100

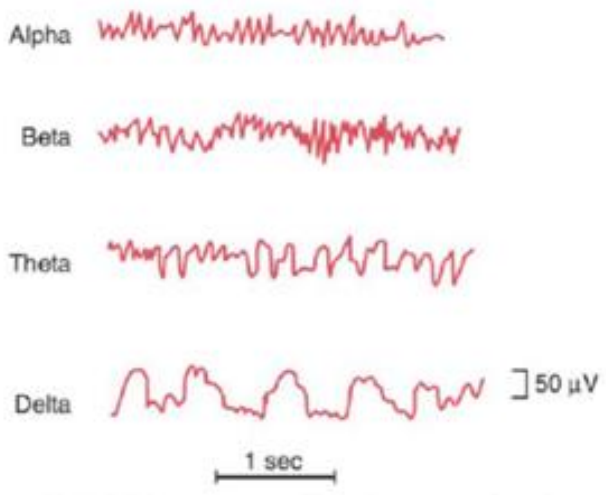


Figure 2.10: Different types of normal brain waves in an electroencephalogram(67)

2.12.2 Electrocorticography (ECoG):

ECoG was initially used primarily for patients with brain malignancies. It was previously thought that the electrophysiological changes detected surrounding brain tumors were caused by damage to nearby cortical areas rather than structural lesions. Since its introduction at the Montreal Institute of Neurology in the 1930s, electrocardiography (ECoG) has been widely used in epilepsy surgery. Penfield and Jasper described several successful examples in which ECoG was utilized to detect epileptic lesions. Since then, epilepsy surgical evaluation has focused on better understanding and identifying the numerous epilepsy sites.(60)

ECoG is a partially invasive process of recording the electrical activity in the brain by electrodes which have direct contact with the cerebral cortex or the surface of the brain. An electrocorticogram (ECoG) is a trace of brain waves generated by a device used to detect and record brain waves, which could confirm the location and extent of epileptic tissue because it's records electrical activity directly from the surface of the cerebral cortex during surgery. ECoG is performed after the preoperative evaluation of epilepsy, and after surgical removal of the epileptic cortex, to assess the completeness of the treatment.

Neurosurgeons can use EEG to identify motor, sensory, and linguistic functions to avoid during surgery by electrically stimulating a single electrode. Therefore, ECoG gives the opportunity to map important functional areas in the brain, thereby providing a safety margin for neurosurgeons to successfully resection(69,70).

A small subdural grid electrode set of platinum, silver, or stainless steel of 10-15 mm is placed in a soft, flexible silicone plastic strip with 8-16 connections for ECoG recording. These strips can be placed on the cortex's direct surface or introduced from the craniotomy's edge to the neighboring lateral, inferior, and medial cortical surfaces. Wires link the contacts in the strip to the EEG equipment. The tape recorder works in the same way as the EEG machine. ECoG records are often made up of solely interictal discharges, which might contain spikes and sharp waves. The best technique to confirm epileptic cortex is to record electrogram seizures with ECoG. However, due to the short recording time (less than 1 hour), they are rarely captured (69,70).

Due to the fact that they record directly from the brain surface, ECoG machines have several advantages over chronic invasive EEG recordings (recordings

obtained from surgical placement of electrodes on cortical surfaces during prolonged video monitoring) because they detect a large number of interictal abnormalities that do not appear on a routine scalp EEG (69). Some of ECoG advantages are:

- There is flexibility in placing the recording and stimulating electrodes within the exposed cortex and adjacent areas. If the placement of the electrodes leads to conflicting results or no results, they can be moved and replaced easily (69)
- Records can be made before and after the different stages of resection, and the presence or absence of epileptiform activity after resection can be determined. (69)
- ECoG research also provides an opportunity to map important functional regions of the brain. (69)
- A shorter recording time and only one procedure are possible with ECoG, compared to chronic invasive recording (one for placement of electrode, one for removal and ablation).(69)
- Finally, ECoG is cheaper than chronic invasive EEG research and there is no standard electrode placement protocol. Therefore, the abnormality is only seen in the area where the strip electrode is placed(69)
- Clinically, it has become a more prominent method for examining cortical processes. Subdural grid or strip electrodes that are flexible and densely spaced can improve the spatial resolution of the recorded electric field (5 mm2).(62)

In theory, the ECoG study could have the drawback of extending the duration of operation and cortical exposure by around 90 minutes. The fact remains that this hasn't been proven. This can be stressful for youngsters, especially those who are still growing.(69)

2.13. Experimental Epilepsy Models

Although epilepsy affects millions of people of all ages throughout the world, the complicated processes of seizures in temporal lobe epilepsy and other forms of epilepsy are still poorly understood in human clinical research. It is therefore vital to employ animal models that are suitable. Models that mimic the natural history of epilepsy have been created. Electric-behavioral seizures can produce chemical, molecular and anatomical alterations. These experimental models can provide partial understanding and close insight into seizure mechanisms, overall brain function and consciousness, and animal models of epilepsy will continue to advance the progress

of both epilepsy and neurophysiology research.(71,72) There are two broad reasons for using experimental models of epilepsy. The first is the development of new treatments, especially the screening of compounds as potential antiepileptic drugs (AED), because current available drugs are ineffective in controlling seizures in around one third of patients, as well being associated with side effects which prevent the progress of treatment. The second is to discover the pathophysiological mechanisms that cause seizures, through studying the changes that occur in the brain before and after epilepsy developed (72,73). The development of several models of experimental epilepsy in animals clearly helps to study specific brain regions that can cause convulsions, and also helps study the mechanisms and actions of epilepsy drugs, because it's not possible to identify these changes in human tissues for ethical reasons. In order to develop experimental animal models of epilepsy, animals are usually selected according to epilepsy type that we need to study, each model has its advantages and disadvantages, unfortunately, many epilepsy syndromes, especially in pediatrics, still lack effective animal models (72,74). In addition to that there is no animal model of epilepsy that can fully represent this disease, because under the term of "epilepsy" there is a group of cases which is classified(74)

As with all disease models these conditions must be fulfilled: (i) the etiology and mechanism of human disease, (ii) the phenotypic characteristics of human disease (exhibits the same physiology, behavior, or genetic phenotype) and EEG characteristics (69)(iiii) clinically visible treatment response (responds to the same therapy). (75)

Rodents are an important species for epilepsy research as well as neurodevelopmental and biomedical research. This is related to their small size and ability to multiply rapidly in captivity.(75)

Seizures are classified by some researchers based on epileptic models instead of humans. There are three categories in which to categorize experimental models. Reflex epilepsy and idiopathic epilepsy are three types of experimental seizures that are caused by chemical convulsions or electrical stimulation.(76)

All seizures fall into one of three categories. First there are partial seizures, which can be divided into simple partial seizures and complex partial seizures. 2. There are several subtypes of generalized seizure: the tonic seizure (grand mal), the clonic seizure (petit mal) and the status epilepticus. 3. Seizures that are not classified.

(76) In experimental epilepsy research, animal models have been developed based on the following classifications:

2.13.1 Simple partial:

2.13.1.1 Penicillin

This is the most frequently and commonly used model for causing partial epilepsy rapidly and simply with pharmacological agents. Since penicillin was found via neurosurgery while it was being given to the brain to prevent infection, it has become a prevalent antibiotic. An electrode inserted in the region of the mouse's cortex records repeated interictal spikes within a few minutes, similar to interictal spikes recorded from the cortex of a human. A cortical area is affected by epilepsy when penicillin is injected into neocortex tissue. When it came to answering questions about epilepsy's neurological underpinnings, the penicillin epilepsy model (PE) was undoubtedly the most useful tool. Seizure activity prevalence can also be estimated using this technique. One of the advantages of the penicillin-induced epilepsy model is that it can be administered intraperitoneally, intramuscularly, intravenously, or intracortically. (74,76)

In the field of experimental epilepsy research, the PE model is one of the most useful acute models. Acute partial epilepsy EEG recordings are also available. Penicillin-induced epilepsy begins locally but expands to cause generalized epilepsy.(76)

2.13.1.2 Bicuculline, Picrotoxin, Strychnine

Bicuclline is an alkaloid putative blocker of GABA, it shows mechanisms that affect the spread of Ca2+ and blockage of K+ channels that lead to disinhibition of neurons, although its mechanism is not clear it was used also as an anticonvulsant, the brain metabolism in bicuculline-induced early-stage lead to generalized tonic-clonic seizures and give greatest effect if it is in neocortex and synaptic related regions (73). Five percent bicuculline applied to the temporal cortex of cats causes paroxysmal depolarization after a few seconds, while one or two hours of bicuculline-induced epilepsy in rats results in alterations to the frontal and parietal cortices of the hippocampal nucleus. (74,76)

Picrotoxin is a poisonous crystalline plant compound, in particular, it was discovered in the fruit of "Anamirta cocculus". (76)

Strichnine is a poisonous alkaloid that is derived from the seeds of the nux vomica tree (Strichnos nuxvomica) and related plants. It functions as a non-competitive inhibitor of glycine, which it blocks.

Specifically, pecculin, picotoxin, and strychnine function as antagonists of the inhibitory neurotransmitter GABA, causing epilepsy. Bicuculline or picrotoxin, GABAA antagonists, dramatically boost dopaminergic neuron stimulation.(76)

There are neurotoxic effects linked with the GABA Abstinence Model, which is a focal epilepsy model established by injection of GABA into the motor cortex.(74)

2.13.2 Simple partial, chronic

2.13.2.1 Cortically implanted metals:

- Alumina hydroxide: - is an implantation of minerals in the brain to generate a simple, recurrent "automatic" partial seizure and they considered the best endorsed and most realistic models of epilepsy. The prototype for this group of models is the alumina hydroxide gel model. After the injection spontaneous and recurring attacks similar to simple partial seizures in humans generally begins in 1 to 2 months and last for several years, and an episodic development into secondarily generalized tonic-clonic seizures.(76)
- Cobalt: - In animals, Chronic or subacute recurrent seizures can be caused by cobalt implantation in the cortex. 2-3 weeks following the establishment of cobalt foci in the rat motor cortex, GABA receptors were observed to be reduced. Anatomical variations in white or gray matter outside of areas of cobalt-induced MR signal loss further revealed that there was no substantial brain injury in the one-sided cobalt model.(76)
- Intravenously injected mineral salts (zinc, copper, manganese, iron) can cause epileptic seizures in some people. Na+ and K-ATPase membrane pumps are believed to be blocked by these minerals.(76). By injecting 10 µl of zinc sulfate into the rabbit hippocampus a chronic model of experimental epilepsy (as complex partial, simple partial, secondary generalized seizures “clinically or electro-physiologically) can be established in rabbits but not in rats(which spontaneous seizures can be generated by aluminum model), also in the oxygen and glucose deprivation model of Zn2 + trans-synaptic transport, Ca-A / K channels were expected to have a late role in neuronal damage.(76). High concentrations of zinc

(Zn2+) (>100 mM) contribute to the death of neurons during seizure, in addition, there is evidence that zinc-induced seizures can cause SE (status epilepticus). Certain subsets of the hippocampus's GABAA receptors have been demonstrated in studies to be inhibited by Zn2 +(74)

Many voltage-dependent ion channels have been found to be modulated by Zn2+ (including GABA, NMDA, AMPA, and kainate-type glutamate receptors). In parturition cortical projections, Zn2+ may have a role in selective cell death, and maybe excitatory toxicity, of GABAergic projections, according to these results.(74)

2.13.2.2 Cryogenic injury

For the cryogenic or frozen lesion model, there is no need for exogenous medicines to be injected into the brain, which can result in partial seizures. In either case, seizures start within hours and last for a few days. The lesion is generally accompanied by a significant amount of cerebral edema.(76)

2.13.3 Complex Partial Complex

Usually come from the limbic lobe, which includes the amygdala, hippocampus, and sometimes the temporal neocortex or extratemporal regions.

2.13.3.1 Kainic acid

This is a glutamate analog and a promoter of the of the putative excitatory neurotransmitter, glutamate receptor and AMPA /kainate receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) class agonist for glutamate receptors, which was first isolated from seaweed (Digenea Simplex) (72,76). As another mechanism, mRNA of the GABAB receptors in Hp as well as GABAB in granular cells of Hp may decrease.(74)

KA was found to have a powerful excitatory action on rat cortical neurons by Shinozaki and Konishi in 1970, whether it was applied directly to the amygdala (Am), hippocampus (Hp), striatum, or the substantia nigra, or injected intraventricularly. In all cases, it produced epileptic convulsions in rats. (74)

This model is used to produce chronic or acute epilepsy by administering KA at doses ranging from 4 mg/kg to 15 mg/kg lasting for hours with typical behavioral episodes beginning with squinting spells, followed by head nods and jerking, about one hour after the injection, rats shows repeated motor seizures and falls before entering a state of epilepsy that can last for hours, followed by a latent seizure-free period of weeks, followed by spontaneous recurrent focal seizures that begin between 3 and 4 weeks after the onset of the first episode. (72).

Human temporal lobe epilepsy shares many similarities with this mouse model. Examples include hippocampal sclerosis and sprouting mossy fibers. This means that the KA model can be used to research the underlying mechanisms of epilepsy generation because it resembles many of the phenotypic aspects of human temporal lobe epilepsy. Another side effect of KAI injections is the development of parenchymal necrosis in the afflicted area due to a large swelling of the astrocytes surrounding nerve cells and blood vessels. (76)

On the other hand, the cell death reported in TLE chemotaxis models is more severe and extensive than what is observed in TLE patients.(72)

2.13.3.2 Tetanus neurotoxin (TeNT)

Tetanus is a disease produced from the gram-positive bacteria, *Clostridium tetani bacillus*, which produce Tetanic toxin which internalized by the neurons in a ganglioside (74)(76).

Tetanic toxin was initially employed in 1962 to cause chronic epileptic seizures. Seizures are dose dependent and characterized by myoclonic jerks in the front extremities (76). Studies indicate that the toxin interferes with presynaptic release of inhibitory neurotransmitters, as administration of tetanus toxin in Hp results in seizures associated with coma, which is considered a chronic condition of epilepsy (74). Myoclonic seizures in the front limbs and generalized tonic-clonic seizures in some rats are common. (76). A disadvantage of tetanus toxin injections that it did not report any immediate clinical effects: no early epileptic case, nor hippocampal sclerosis. After about a week the animals began to have spontaneous seizures, that were repeated intermittently for period of 6–8 weeks. The absence of hippocampal sclerosis means that the tetanus toxin with in the hippocampus is non localized temporal lobe epilepsy, which is a major clinical problem (73)

Following intra-hippocampal injection, tetanic toxin is thought to disinhibit GABAergic activities, with a particular preference for inhibiting inhibitory neurons. Axons in the outer molecular layer of the dentate gyrus may indicate that dendrites of granule cells are being rebuilt. Tetanic toxin can induce chronic partial seizures in rats as an epilepsy model. In addition to these features, this model of epilepsy shares many similarities with the human epilepsy model of axons in the dentate gyrus (74). Tetanus toxin (TeNT) a zinc protease selective for Vesicle Associated Membrane Protein (VAMP) or synaptobrevin (a group of small, integral membrane proteins of synaptic vesicle that is mostly involved in vesicle fusion in the presynaptic end of

the neuron), in rats it is reported selectivity for VAMP2. Intra-hippocampal TeNT causes a chronic model of temporal lobe epilepsy (TLE) (77). A suggested action mechanism of the toxin consists of the blockage of exocytosis(74)

2.13.3.3 Kindling

Kindling is a process in which repeated low-intensity electrical stimulation to different parts of the brain enhances the electrical excitation of the brain until an epileptic seizure is triggered (72). Electrical stimulation of the amygdala is the most common way to trigger it, but it can also be triggered by activation of the hippocampus, perirhinal cortex, or piriform cortex. Rats of different ages and strains have varied rates of kindling in different brain areas. These wires are inserted in the amygdala or any other brain location to generate this model. Daily electrical stimulation droppers are applied via the electrodes until the animal heals from surgery (76). An after-discharge threshold stimulation is then applied daily until the animal suffers stage 5 convulsions (72). The development of behavioral seizures by kindling was classified into the following five stages: (1) mouth and facial clonus, (2) head nodding, (3) forelimb clonus, (4) rearing, and (5) rearing and falling (78). Also using a low dose of chemical convulsant or excitatory chemicals through repeated stimulation could produce kindling (72). Seizures in kindling model originate from the site of stimulation and then spread to other areas with repeated stimulation the clinical phenotype of partial seizures with secondary generalization. (72). Sorting the kindling shows that hyperactive neurogenesis realigns the brain by activating glutamate receptors and other messenger systems as well as neurotrophic factors and proteins. In various brain regions, including the hippocampal CA1 area, GABA-mediated inhibition fails more often. (74).

Kindling is a popular model for studying TLE (Temporal Lope Epilepsy) processes. The fundamental advantage of the kindling is that it may be used to activate a specific area of the brain in a regulated manner in order to explore its role in seizure development and epileptogenesis (epilepsy formation). The kindling model is frequently employed in preclinical studies of AED efficacy. In order to analyze the anticonvulsant impact of the medication, rats that have been fully agitated are given the medication and its effectiveness in preventing seizures is evaluated. This is done by administering a medication during the kindling process (before each stimulus) and measuring its efficiency in inhibiting the kindling (72).

In addition, this model allowed researchers to evaluate the effectiveness of various antiepileptic medicines, and the brain structures that are involved with epileptic activity (74), it has proved valuable; for example, it played a key role in recognizing levetiracetam's potential as an AED (73). And because the electrical stimulation, the other side effects of chemical models can be controlled, and this is another advantage of this model (74). Also EEG recording during different stages of kindling provides that experimental animals exhibit a generalized development and morphological change similar to that found in human patients with secondary generalized partial seizures (74)

Unfortunately, kindling is a time-consuming and expensive technique that involves long periods of handling and stimulation treatments, as well as technical restrictions that require meticulous electrode placement, as well as the risk of losing or destroying the chronic implants (72). The model's fundamental flaw is that it requires a large number of stimuli and more than 90 stage 5 seizures before 40 percent of stimulated rats suffer spontaneous seizures. After 30 stage 5 convulsions, cell death in the hippocampus can be observed, but the level of damage is not equal to that seen in epileptics.(71)(72)

2.13.4 Generalized tonic-clonic seizures

2.13.4.1 Genetic

Because idiopathic epilepsy has a hereditary component, researchers attempted to create models of genetically abnormal strains of animals; and there are no acceptable animal models for recurrent generalized primary tonic-clonic seizures because idiopathic epilepsy includes a hereditary component, according to researchers. Aspects such as the need for specific types of accelerated stimuli or other non-epileptic deficiencies make each of these models different from the clinical grand mal case.(76)

2.13.4.2 Photo-Sensitive Baboon Model (PAPIO PAPIO)

Photosensitive epileptic seizures occur in Senegalese Papio papio baboons following stroboscopic stimulation at 25 cycles per second for 20 to 30 seconds. These seizures are considered a model for generalized seizures in humans. Papio papio seizures can be characterized by generalized mioclonic paroxysmal discharges, depending on their sensitivity. Some drugs, according to studies in the pharmacology field, increase photosensitivity, whereas others, which boost

GABAergic activity, are anticonvulsant. In this model, drugs such as barbiturates, benzodiazepines, and sodium valproate were evaluated and proven to prevent seizures in these primates.(74)

2.13.4.3 Audiogenic seizures Model

According to Smith, mice are susceptible to auditory seizures. Sound stimulation of 102 to 131 decibels causes seizures (dB). This model exhibits audiogenic convulsions of the generalized seizure type, while partial epilepsy affecting the temporal lobe is the second group of seizures. When exposed to the sound of a fire alarm, mice (day 14 after birth) suffer uncontrollable seizures that terminate in tonic-clonic convulsions.(74)

2.13.4.4 Epilepsy mice (El)

A genetic model of deposited sensory temporal lobe epilepsy is the mouse. When administered similar stimulation to adults, all adult mice that were given rhythmic vestibular stimulation (such as tossing and spinning) during development will have tonic-clonic disorders. Seizures have three stages: prodromal, convulsive, and postictal (79). For example, chewing and drooling may occur as a result of seizures in this model. Clinically complex partial epilepsy is resembled by electrical discharges in limbic areas deep in the brain. Interictal secretions are produced by the parietal cortex, notably the hippocampus, according to EEG study. To put it another way, these mice suffer temporal lobe epilepsy.(76)

2.13.4.5 Genetically epilepsy-prone rats

Mice genetically predisposed to epilepsy are one of the most popular models of genetic epilepsy. Seizures in this breed were thought to be caused primarily by auditory stimulation until it was discovered that heat, electric shocks, pentylenetetrazol and bicuculline can also trigger seizures.(76)

2.13.4.6 Electrical stimulation

Using electrodes placed on the cornea or ears, electrical stimulation of the brain induces motor convulsions that vary in intensity based on the stimulus density. Tonic-clonic convulsions are caused by high electrical currents ranging from 25 mA to 150 mA at 50 Hz for 2 ms. Convulsive crises can be caused in mice by applying 45-mA current through the ocular electrode for 0.2 seconds). Behavior caused by electric shocks changes last for at least 28 days, and mice models may show an anticonvulsant effect when injected with GABA(74)

Animal models of electrical stimulation-induced seizures have the advantage of mimicking epileptogenic features in a healthy brain while maintaining a low mortality rate and remarkable reproducibility. Furthermore, unlike seizures generated by chemical convulsants, post-epileptic alterations caused by electrical stimulation can be studied even when the cause of the epilepsy is unknown. However, electrical stimulation modeling of seizures does not offer cell type specificity in the brain. Additionally, stimulation protocols can be expensive and difficult when used in chronic studies (71). This model was used to discover fenitoin, which reduced epileptic activity by 50%. Following that, numerous antiepileptic medicines, including carbamazepine and valproic acid, were investigated using this model. In this model Lamotrigin plus oxcarbazepine reduced seizures by 50%. (74)

Electroshock-induced seizures: One of the most researched models of electrical stimulation is seizures generated by electric shock (ES). Because it only needs to be applied once, there is no need for stereotaxic electrode insertion. There are two types of ES: minimal ES and maximal ES.(71)

Minimal ES is a typical myoclonic seizure model that can be induced with ocular electrodes by applying electricity. This disorder is marked by a lightning reflex and shaking motions of the face and front limbs. Minimum ES may generalize as stimulus intensity increases.(71)(76)

Maximal electroshock (MES) is the best studied animal model and the most beneficial for seizures. This model is often used to study the development of antiepileptic drugs. MES show extension and flexion of the posterior limb, followed by phimosis(76)

2.13.4.7 Chemical convulsant

There are many chemicals can induced generalized seizures if they administrated systematically such as Pentylenetetrazol, strychnine, allyglycine, penicillin, bemegride, picrotoxin, bicuculline, homocysteine (76). By using chemo-convulsants spontaneous recurrent seizures can be generated in rodents. These models can simulate temporal lobe epilepsy (TLE), and the 'clinical history' should match the human counterpart, including precipitated primary injury to the hippocampus and/or temporal lobe (for example, the status epilepticus [SE]), a latent period between injury and the occurrence of spontaneous seizures, and chronic manifestations of spontaneous seizures (partial seizures and usually tonic-clonic seizures).(71)

2.13.4.8 Pentylenetetrazol

(PTZ) is a model of epilepsy induction that is analogous to primary tonic-clonic epilepsy in human's model. (71). It is one of chemicals that often used to study the development of antiepileptic drugs. PTZ is a tetrazole derivative with consistent convulsive actions in mice, rats, cats and primates, when given by injection (76). A 0.85 percent PTZ solution given intracerebrally at a volume of 0.01 mL per kilogram of body weight, or intraperitoneally in doses ranging from 20 to 300 mg/kg. Small front-limb clonic convulsions or short vibration periods can be detected in mice. Axon growth is found to be increased in the interior section of the CA3 layer of the Hp in PTZ-induced epilepsy. PTZ-induced epilepsy is caused by raising the voltage in the voltage-gated potassium channel, one of the causes. Specifically, PTZ blocks GABAA receptors. It is considered a selective GABA agonist (means it cause loss of GABA-mediated inhibition which leads to hyper-excitability) and originally a model for absence epilepsy.(74)

Pentylenetetrazol's effect on neuronal ion channels has been the subject of several research. The depolarization of the cell is caused by calcium and sodium inflow, according to a 1987 study. A conclusion has been drawn that pentylenetetrazol acts on calcium channels, causing calcium channels to lose selectivity and conduct sodium ions as a result of these interactions.(80)

2.13.4.9 Systemic penicillin as a tonic-clonic model Penicillin

Injections of penicillin have been shown to cause abrupt seizures. Myoclonus generalized tonic-clonic seizures, and encephalopathy have been linked to high systemic doses of penicillin in humans, according to studies. Patients who receive an intravenous dose of more than 20 million units per day are more likely to develop encephalopathy in the hospital, especially if they have concurrent renal failure that keeps their blood-brain barrier permeable. It has been observed that penicillin injections cause widespread convulsions in cats.(76)

2.13.4.10 Other inhibitory antagonists

There are a number of other common systemic convulsants, such as, allyglycine, methionine sulfoximine, bicuculline, bemegride, picrotoxin and strychnine. (76)

Bemegride (Megimide) is a glutarimide derivative that operates similarly to PTZ. A clonic seizure can be induced with this drug. It is also used to induce focal epilepsy. Picrotoxin and bicuculline, which cause partial seizures when applied

locally, cause generalized clonic and tonic-clonic seizures when given systemically.(76)

Strychnine i.v. injection can generalize a potent generalized seizure model can be. It interacts with GABA-benzodiazepine receptors (which are part of the GABA receptor complex on postsynaptic nerve end), also it has an important action as noncompetitive inhibitor of glycine receptor (which is a brainstem and spinal cord's inhibitory neurotransmitter) (76)

2.13.4.11 Metabolic derangements

Many metabolic abnormalities, such as hypoglycemia, hypoxia, uremia, medication withdrawal, and excessive temperature, can cause seizures. Because they commonly result in other central nervous system disorders in the used model, these cases were not often beneficial for researching the mechanisms of epilepsy. However, three metabolic diseases have been used in a few generalized seizure studies. Hypercapnia and hyperbaric oxygen.

Hyperthermic seizures caused by an increase in body temperature in immature rodents by a hot current result in multiple neurons in separate regions of the limbic system, and a large proportion of neurons in the central nucleus of the amygdala and layer of pyramidal cells in the hippocampus are affected by CA3 and CA1 24 hours after seizures (73). Animal models of febrile seizures at approximately 41°C show typical behavioral seizures consisting of facial mechanism, wet canine jerks, myoclonic jerks and tonic flexion of the body causing neurological injury to the limb structures(72)(71)

Hypoxia model: A brief and repetitive tonic-clonic seizures can be induced by exposure the immature rodents to air with low oxygen concentration. Neonatal hypoxic encephalopathy is a human relevance, and it used to AED screening, long-term consequences, and epileptogenesis mechanisms (71)

2.13.5 Generalized absence seizures

2.13.5.1 Thalamic stimulation

Thalamic reticular nucleus is composed of a thin strip of cells that wraps around the thalamus's rostral, lateral, and dorsal sides. (81), and they are able to affect large areas of the cortex. In the mediastinal thalamus and intraplate, stimulation can cause EEG waves to disappear or to become abnormally high or low. The hypothalamus and brain play a role in the generation of absence. Epilepsy is still a subject of investigation. Petit mal patients are rarely treated with thalamic

stimulation since it requires chronic electrode implantation and continuous stimulation during the test.(76)

2.13.5.2 Bilateral cortical foci

Bilateral cortical foci models that generate petit mal depends in that the absence epilepsy caused by cortical defect. Dilute convulsants such as estrogen, PTZ, and penicillin can cause bursts when applied to wide portions of the cat's brain. It is possible to build the same model in rhesus monkeys. (76)

2.13.5.3 Systemic penicillin

The injection of Penicillin G (Benzylpenicillin) intramuscularly in a cat caused frequent periods of lethargy, gazing, myoclonus and facial and mouth twitching as well as occasional progression to generalized tonic-clonic seizure activity. Approximately one hour after injection, seizure activity begins and continues intermittently for six to eight hours. There are many types of EEG spike wave morphologies in the EEG, most of which originate from a normal backdrop. When penicillin is administered to extensive portions of the cortex, SW EEG discharges can result (which originate cortically in this model)(76)

2.13.5.4 Intraventricular opiates

When administered in small doses, it is believed that morphine sulfate acts as an anticonvulsant, but in excessive doses it can cause clonic convulsions in rodents. After opiates enter the ventricle, EEG behavioral patterns can be classified using complex partial or absence epilepsy models.(76)

2.13.6 Status epilepticus

Single seizures lasting more than five minutes or numerous seizures occurring within a five-minute period at short enough intervals without the person returning to normal between them are considered status epilepticus by medical professionals. When given in significant quantities to mice, some chemical convulsions capable of generating seizures, such as flurothyl, bicuculline, and PTZ, can cause epilepsy.(76)

2.13.6.1 Lithium-pilocarpine

Pilocarpine is a muscarinic acetylcholine receptor agonist, resulting in seizures that accumulate in limbic SE. In this study, mice are pre-treated with lithium chloride. Pilocarpine is administered at least 20 hours after the ingestion of the drug. AEDs that are effective against complex partial seizures in individuals can prevent spontaneous seizures in the pilocarpine model. (76). The structural damage and

subsequent development of spontaneous recurrent seizures are identical to those of human complex partial seizures, and the EEG pattern progresses in a manner that is extremely similar to human epilepsy (71)**.** Neuron loss and death occur in lithium-pilocarpine-treated adult rats, and hippocampus damage can be seen in the CA1 and CA3 pyramidal cell layers, as well as the dentate gyrus's hilus. (76)

2.13.6.2 Cobalt-homocysteine

Another drug combination that can cause status epilepticus in animals is focal cobalt with systemic homocysteine, whereas homocysteine can cause significant tonic-clonic seizures on its own. For seizures that occur regularly, this model gives a focus.(76).

2.14. Ethnopharmacological relevance

Medicinal plants are nature's gift to humans to make a healthy life free from disease, and to play a vital role in maintaining our health. They are believed to be the safest and proven elixir in treating various diseases (82). There is growing interest in industry, academically, and health sciences in medical and aromatic plants. Medical traditions of ancient civilizations such as those in China, India, Africa and South America have a large stock of plants in their pharmacopoeia that are still used throughout Southeast Asia. Consequently, a very high percentage of the world's population depends on medicinal and aromatic plants for their treatment. Western medicine is also already responding, across Europe and the USA, schools of medicine, pharmacy and health are increasingly offering phytotherapy training. (83). In fact, plants are used to treat a variety of ailments in both humans and animals, and this tradition dates back as far as human existence itself. Globally, roughly 80 percent of people get their primary health care from non-conventional sources, such as herbal sources. In addition to being an important part of the local culture, medicinal herbs have international appeal. Herbs are found in abundance around the world. There is sufficient evidence of increased demand for medicinal plants as a result of the global trend toward enhancing "quality of life" (82). Seizures are brief behavioral changes caused by the rhythmic and synchronous discharge of a group of neurons in the central nervous system (84) and when the primary issue in the treatment of seizures and epilepsy is the need for long-term, continuous, and multi-drug treatment, which can lead to the development of numerous adverse effects, such as drug resistance, and a lack of access to more effective treatment approaches As a result, it is necessary

to pay attention to traditional medicine and herbal medications in order to develop low-risk drugs with minimal side effects (85).

The use of complementary and alternative medicine (CAM) is growing, notably among epileptic patients. Most consumers believe that herbal medicine, one of the most prominent kinds of complementary and alternative medicine, is safe and effective. Many epilepsy patients turn to CAM treatment as a supplement of their medical regimen. On the other hand, there are many disadvantages of using herbs, for instance they may contain neurotoxic ingredients that can cause seizures. As a direct consequence of their intrinsic proconvulsant properties, heavy metal contamination, and effects on the cytochrome P450 enzyme system and P-glycoprotein metabolism, many herbs can increase your risk of seizures when used unsupervised. They may also contain undeclared amounts of conventional medicines (86) Herb–drug interactions may be difficult to predict.

Finally, the herbs may affect the effectiveness of AED through affecting the absorption, distribution, metabolism and excretion (86). Because of its varied climate and large number of biological zones, Turkey's East Anatolia boasts a diverse flora. This flora diversity provides a plentiful supply of medicinal plants, which have long been used by Anatolian tribes, and hence accounts for the region's exceptional medical folk knowledge. Plants are historically used by the majority of Turkish people who live in rural areas, mostly for nutrition and medicinal purposes. Traditional uses of plants for medical purposes have piqued the interest of researchers in our country in recent years (87). There are many plants utilized by the common populace in Turkey for diverse reasons, and their biological functions have yet to be fully discovered. Medical plants are increasingly being used in alternative treatments due to their numerous therapeutic properties and low cost. Because such plants are extensively utilized in public medicine, it is critical to do scientific research on their impact on health.

Herbal, traditional, and experimental medicines are prepared by extracting and processing medicinal plants. Correct and timely collection of a medicinal plant for experimental purposes, validation by an expert, proper drying and grinding are all part of the notion of medicinal plant preparation. Extracting the biologically active component is then followed by fractionating it and isolating it, as needed. As a first step, preparing medicinal plants for experimental purposes is critical to the success of any research project.(88) Before and during flowering, many herbal

medicine researchers have demonstrated that harvesting stage affects the amount of phenolic content and antioxidant activity of the plant. (89) The quality and quantity of biologically active components must be extracted and determined before herbal medicines may be used safely and effectively. herbal medicines, unlike pharmaceutical medications manufactured from single molecules, require precise identification of the plant species and the selection of appropriate parts for usage. (90)Therefore the failure to find a significant effect from this extract could indicate that there may be an error in the way the plant was collected or extracted.

The Allium vegetable chive (Allium scorodoprasum L.) is one of these commonly used medicinal plants. It is an alternative plant used to improve shelf life, boost nutritive content, and for its health effects, in addition to its use as food by the general population. More research is needed to determine its components and biological activity, as well as its application as a natural preservatives and in alternative medicine to replace artificial antioxidants (91).

Allium species have been known to exist throughout recorded history. At this time, there is also a growing interest in studying other Allium species. Avicenna constructed a medical system based on his own personal experiences as well as Islamic medicine, Galen's medical system, and ancient Persian, Mesopotamian, and Indian medicine. Avicenna mentions A. schoenoprasum L. as one of the oldest epilepsy therapies (9). Many epidemiological studies have suggested that some natural foods, such as A. schoenoprasum L., can help to avoid the development of many diseases. They've been proven to have a wide range of pharmacological effects, including tumor cell growth inhibition and chemoprevention (92).

2.13.1 *Allium Scorodoprasum L*

Allium is an attractive perennial aromatic flowering herbaceous plant that belongs to one of the major monocot genera. Allium species have long been utilized in both culinary and medicinal applications. In Turkey, it's also known as wild garlic or wild leek. There are around 600 species of Allium L. in the genus Allium. Other species in the section schoenoprasum that are significant for human nutrition include A. cepa L. (onion), A. sativum L. (garlic), A. schoenoprasum L. (chives), A. Chinese L. (scallion), A. ascalonicum L. (shallot), A. ampeloprasum L. (leek), and A. hookeri L. (hookeri) (hooker chive) (10,93–96) .

History and cultural importance: For at least 5,000 years, members of the Allium family have been grown in the Middle and Far East. Several documents, pictures, and skeletal remains attest to the use of these plants as diets, religious objects, and remedies. These plants have been revered for millennia for their use in seasoning food, medicinal capabilities, and religious rites in several parts of the world (97,98)

In food Alliums (particularly onions and garlic) were highly esteemed as foods in ancient China, Egypt, and India. In Sumeria four thousand years ago, onions and leeks were commonly utilized in cooking. Both the leaves and the blooms can be eaten. The blossoms are mostly used in salads, while the leaves are widely utilized in European cuisine. The flavor is similar to onions, although it's a little lighter. Garlic in Chinese, suan, is written as a single sign, according to Hyams1, indicating that it was widely used at the time of its invention. Radishes, onions, and garlic were staple foods for the workmen who built the Great Pyramid at Ghiza according to Greek historian Herodotus (about 450 B.C.). Chives leaves are used as a tasty garnish in soups, cooked dishes, salads, and even as a sandwich stuffing. It can be used at any time in the kitchen. Salted chives are kept for winter use in Siberia. It is a permanent culture that grows on almost all soils that aren't too poor or too dry. The presence of garlic oil gives chives their peppery flavor. It has a high concentration of vitamin C, carotin, and calcium (98,99). It's a key component in East Anatolia's Van Herb cheese as shown in figure 2.11, the Aegean region's körmen salad, roasted körmen, körmen mücver, körmen börek, and körmen halva, and Sivas's körmen pilav. Quarcetin, luteolin, apigenin, and hyperon are just a few of the flavonoids found in it. This plant's tubers are reported to have antibacterial, antifungal, antioxidant, and antiviral properties. Its antibacterial, antihypercholesterolemic, antihyperlipidemic, antihyperpertansive, hepatoprotective, diuretic, and anticancer properties have all been described (91).

Figure 2.11: Van Herb Cheese.(91)

In religion, an eastern tradition says that once Satan emerged from Eden after man's fall, onions grew in his right footprint and garlic in his left one. Following this, the role of alliums in religious beliefs and behaviors was clearly established. Throughout the Third and Fourth Dynasties, onions were used as sacred sacrifices in Ancient Egypt (2800 to 2100 B.C.). They were found in mummified remains in the pelvic regions, thorax, and eyes, flattened against the ears and positioned along the legs and feet. In the thoracic cavity, flowering onions were frequently discovered. Garlic was also employed as payment in ancient Egyptian and Middle Eastern cultures, with 15 pounds of garlic being used to purchase a healthy slave circa 2,500 BC. Followers of Moses lauded the gastronomic joys of garlic over manna in the Old Testament.(98)

In medicine, twenty-two garlic treatments were contained in the Codex Elsers, an Egyptian medical papyrus that dates back to around 1500 B.C. A major Indian medical literature, the Charaka-Samhita, which was composed in the first century a.d. but was based on sources dating back at least five centuries, associated both garlic and onion with a wide range of medicinal benefits He said they had diuretic properties as well as digestive tract, eye, and heart health benefits, as well as antirheumatic properties. For rheumatism, hemorrhoids, ulcers, and loss of appetite, Pliny the Elder (79 A.D.) devised 61 garlic-based remedies. As a result, he recommended that 28 different disorders may be treated using onion extract. As well as erasing stress, it amplifies any existing chest and head pain. (98). In the Middle Ages and beyond, the writings of dioscorides, Pliny, Hippocrates, and Galen had a profound impact on medicine. GENUS ALLIUM is specifically mentioned as a

treatment for jaundice in St. Hildegard von Bingen's "Physica" from the 11th century. Garlic's antitoxic qualities and efficiency against internal worms were emphasized by herbal doctors Paracelsus and Lonicerus (1564) five centuries later. Mattiolus advised using garlic to treat stomach chills, colic, and flatulence in 1626. A collection of 19th century (mostly) American herbal treatments and home cures includes alliums prominently. Anticoagulants, antiseptics, anti-inflammatory agents, anticancer agents, carminatives, sedatives, poultices, vermifuges, hair restorers, and veterinary goods were all made with alliums (98). In Turkey the bulbs of this plant are reported to have antibacterial, antifungal, antioxidant, and antiviral properties. Antiseptic, diuretic, hypotensive, wound healer, and laxative are some of its pharmacological properties. It is used to treat problems associated to age, cardiovascular disease, and liver disease as a protector. Some persons with sensitive stomachs may experience discomfort if they utilize bulbs directly. Its young leaves are utilized in the same way that onions are. Externally, it is utilized as a local abscess treatment. (91)

Apart from being utilized as ethnomedicine, Allium schoenoprasum L. (family Amaryllidaceae) has a lot of culinary value. The anti-inflammatory, anticancer, antioxidant, anthelmintic, and antihypertensive properties of chives have been validated by scientific research. Despite the presence of Sulphur and phenolic compounds, flavonoids, saponin, and steroidal glycosides in phytochemical studies, further rigorous research to uncover bioactive molecules is required. Allium species have been used as vegetables and spices for ages, as well as being appreciated as ornamentals and ethnomedicine for the prevention of numerous ailments. (93)

Taxonomy

Allium schoenoprasum l is a member of the section schoenoprasum of the genus *Allium*. The *Allium* genus was previously classified as belonging to the Alliaceae family (which includes more than 800 species, 15 subspecies and 72 sections), but according to the APG III (Angiosperm Phylogeny Group) classification, it is now classified as belonging to the Amaryllidaceae family and subfamily Allioideae. There are around 600 species of Allium L. in the genus Allium (93). Allium schoenoprasum subsp. gredense and Allium schoenoprasum subsp. latiorifolium are the two-known subspecies (100). The genus Allium is distinguished by a diverse variety of morphological and phytochemical forms, which is related to the samples' variety of geographical origins. The genus demonstrates remarkable

environmental adaptability, with species found from sea level to high mountains, and from desert environments to wetlands. In addition, polyploidy is remarkably common and the reported cell patterns differ in external morphology, anatomy, fertility and cytogenetic phytochemistry. It is a monocotiledonate perennial species, it is the tiniest and most widely distributed onion species. It contains the smallest edible species, A. schoenoprasum L. (often known as chives). The term "schoenoprasum" comes from the Greek words "skhonos" (which means "grass") and "prason" (means leek), the Latin word cepa is the source of the English term (chives) and the word chive comes from the French word cive. It's also known as Kashmiri garlic or Snow Mountain garlic. (93,99)

General morphological features: It produces dense clusters of thin cylindrical leaves in the spring and summer, as well as long hollow flower stems with globular heads, as depicted in Figures 2.12, 2.13, and 2.14. Thick grass-like perennial that forms bulbs and grows up to 20 cm tall. 2–3 cm long and 1 cm in diameter, the bulbs are thin and conical. 2-4 mm in diameter, the stems are hollowed out and tubular. Eatable green tubular leaves with sharp points have a mild onion flavor. They have a subtle purple hue to their flowers. Hermaph- rodite blossoms secrete nectar and have attractive umbels that attract bees, hoverflies, and butterflies (Lepidoptera) and pollinate them. Cold and scorching temperatures are no match for this plant, which thrives in dry, sunny conditions. It is recommended that seeds be germinated at temperatures of 3–5 °C, with 15 to 20 °C being optimal. It can be cultivated in a variety of soils, but the best soil is sandy loamy with a high organic matter content and a pH of 6–6.5. Chives can be propagated from seeds or by dividing clumps (93,98). This plant is native to Turkey's eastern and northern Anatolia regions. During the fifth and sixth months of the year, it is in full bloom. Between 0 and 1400 meters above sea level, this plant can be found in calcareous environments, clayey sloped slopes, lawns in rural areas, and on beaches and sands.(91)

Figure 2.12: Liliaceae/*Allium scorodoprasum L.* (101)

Figure 2.13. and 2.14: *Allium schoenoprasum L.* flowers (wild chives)(102)

A. schoenoprasum L is a common household herb in native areas, where it is produced as a garden crop and sold in grocery stores. Chives are utilized as a substitute for onion and garlic because they have similar physical and medicinal benefits. Because of its attractive ball-like lavender-colored umbels, it is used as an ornamental plant and in creative arrangements. It is normally served in modest portions and seldom as the main course, so there aren't many side effects, however

overconsumption might cause stomach issues. Chives have insect repellent characteristics, making them valuable in gardens for pest management. (93)

Geographic Distribution: Chives are thought to have originated in Siberai and spread throughout Asia, Europe, and North America including the Arctic. It is thought to have originated in Central Asia or the Mediterranean and spread as a wild plant over Europe up to 70 degrees latitude, across Middle Eastern and Northern Asia, and throughout Northern America up to the Arctic regions. Several times, the cultivated version appears to have been domesticated. There seemed to have been no strong selecting factors at work, and there is a lot of variety in the cultivated forms, as well as hybridization between cultivated and wild species. It has been used as a spice in Europe since at least the early Middle Ages. (95)

Chive leaves are used as a garnish. A. schoenoprasum (AS) is now grown in Austria, Canada, France, Germany, the United Kingdom, Italy, the Netherlands, and the United States of America. It grows at altitudes of 8000–11000 feet in the Western Himalayas of India, from Kashmir to Kumaon. (Figure 2.15)(93)

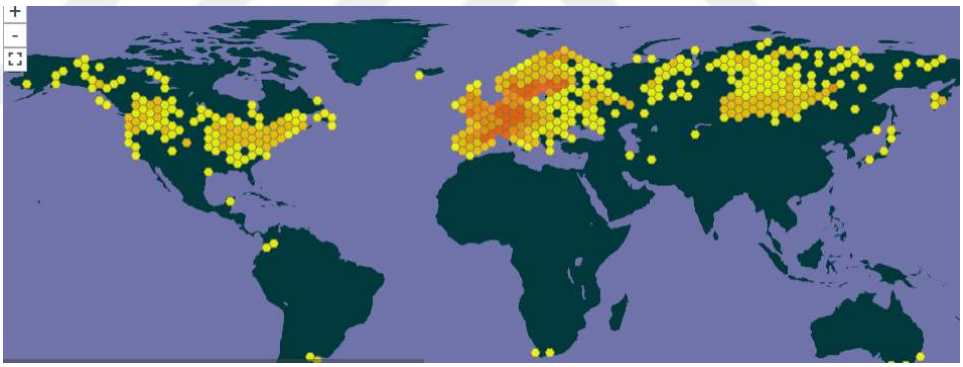


Figure 2.15: the distribution of A. schoenoprasum species all around the worldwide(103)

In Turkey, it can be found in the provinces of Adana, Osmaniye, Bolu, İstanbul, Mardin, Çankırı, Adıyaman, Ağrı, Ankara, Antalya, Artvin, Çorum, Erzincan, Erzurum, Eskişehir, Hatay, İzmir, Kayseri, Kırklareli, Konya, Kütahya, Kahramanmaraş, Muğla, Sivas and Trabzon. It is known as wild garlic, wild leek, körmen, sirmo and çatlangus as shown in figure 2.16.

Figure 2.16: Distribution of A. schoenoprasum L. over turkey, based on Vilayets (104)

Phytochemistry: Chives contain a wide range of phytochemical components that have been identified using a variety of spectroscopic and chromatographic techniques. (93)

- Phenolic compounds: Plants ranging in phenol content from 0.74 to 6.76 mg/g have been discovered in several investigations. Several plant parts (roots, stalk, and leaf) were evaluated for total phenol concentration; roots were determined to be a substantial source of phenolic compounds. A 70 percent ethanolic chives extract yielded P-coumaric acid (8.50 g/mL), ferrulic acid (37.16 g/mL), sinapic acid, and gallic acid (8.45 g/mL) as phenolic components. Rosmarinic acid, p-hydroxybenzoic acid, and protocatechuic acid were all found in abundance in the flower extract. The peroxidation of 1, 2-dilinoleoyl-sn-glycero-3-phosphocholine liposomes was discovered to be inhibited by rosmarinic acid. Allium porrum stem extract was shown to contain rosmarinic acid, a significant phenolic component with high antioxidant properties.(93,94)

- Flavonoids: Flavonoids in the Amaryllidaceae family include flavonols (quercetin, isoquercetin, rutin, and myricetin), flavanones (naringenin), and flavones (quercetin, isoquercetin, rutin, and myricetin), and flavones (quercetin, isoquercetin, rutin, and myricetin) (luteolin). Surprisingly, just one kind of flavonoid, flavonol, is reported in AS. Total flavonoids have been found in a variety of components of chives, including the bulb, stem, and the leaf. The most effective inhibitor of amylase was A. scorodoprasum stem extract. Rutin, eriodictyol, quercetin, and luteolin were among the flavonoids found in this extract. Many researchers have

demonstrated flavonoid-dependent inhibition of -amylase as well as hypothesized mechanisms of inhibition. (93,94)

- Anthocyanins: Chives also contain anthocyanin–flavonol complexes, which impact the plant's color. Anthocyanins are claimed to be present in the flowers and stem of chives in the form of 3-(6-malonylglucoside), (6-dimalonylglucoside), 3-(3-malonylglucoside), and 3-glucoside of cyanidin. (93)
- Fatty acids: Allium Schoenoprasum leaves have been shown to contain significant levels of fatty acids (Figure 2.17) such as linoleic acid (22.8–32.3%), linolenic acid (34.4–38.7%), and palmatic acid (24.5–25.9%).(93)
- Steroids: Four new spirostane glycosides, as well as four recognized steroidal saponins, have been discovered in research. Sitosterol, stigmasterol, campesterol, and cholesterol were also discovered in addition to spirostane steroids.(93)
- Sulphur compounds: Sulphur compounds, which are responsible for a variety of biological processes, are produced by plants in this genus. Methyl pentyldisulfide and pentylhydrodisulfide are two types of disulfides that have been isolated and discovered. These chemicals have a sweet onion fragrance and are essential scent components methyl-propyldisulphide, and dipropyldisuphide are sulphur compounds found in the green leaves of chives. N-propyl groups, methyl groups, and 1-propenl groups are the most common thiosulfinate compounds found in chives.(93)
- Essential oil: The presence of sulphur compounds in the volatile oil of Allium species is well known. In the literature, a significant amount of essential oil from chives has been recorded. The sulphur compounds found in chives essential oil (1-propenyl propyl disulphide, allyl methyl trisulfide, allyl propyl disulphide, allyl propyl trisulfide, diallyl sulphide, dimethyl disulphide, dimethyl tetrasulfide, dimethyl trisulfide, dipropyl disulphide, dipropyl tetrasulfide, methyl propyl trisulfide and propyl 1-(prop- ylthio) ethyl trisulfide), along with hydrocarbons (α-copaene and nonane), sesquiterpenes (alpha farnesene, borneol, caryophyllene, E-beta farnesene, selinene and sesquiphellandr- ene) and fatty acids (ethyl linoleate, ethyl linolenate, ethyl palmitate, methyl linolenate, methyl palmitate and palmitic acid) (93)

Nutritional Value of *Allium schoenoprasum*

Minerals	Value per gram
Calcium	92 mg
Iron	1.60 mg
Magnesium	42 mg
Phosphorus	58 mg
Potassium	296 mg
Sodium	3 mg
Zinc	0.56 mg
Copper	0.157 mg
Manganese	0.373 mg
Selenium	0.9 µg

Vitamins	Value per gram
Vitamin C	58.1 mg
Thiamin	0.078 mg
Riboflavin	0.115 mg
Niacin	0.647 mg
Pantothenic acid	0.324 mg
Vitamin B6	0.138 mg
Total Folate	105 µg
B-carotene	2612 µg
Vitamin A	4353 IU
Vitamin E	0.21 mg
Vitamin K	212.7 µg

Lipids	Value per gram
Total saturated fatty acids	0.146 g
Total monounsaturated fatty acids	0.095 g
Total polyunsaturated fatty acids	0.267 g
Phytosterols	9 mg

Amino acids	Value per gram
Tryptophan	0.037 g
Threonine	0.128 g
Isoleucine	0.139 g
Leucine	0.195 g
Lysine	0.163 g
Methionine	0.036 g
Phenylalanine	0.105 g
Tyrosine	0.095 g
Valine	0.145 g
Arginine	0.237 g
Histidine	0.057 g
Aspartic acid	0.303 g
Glutamic acid	0.677 g
Glycine	0.162 g
Proline	0.216 g
Serine	0.148 g

Figure 2.17: Nutritional value of Allium schoenoprasum(93)

Pharmacological activity of A. schoenoprasum L.

- The chive (A. schoenoprasum L.) is an herbaceous perennial plant easy to grow and nurture for its leaves which are utilized for both culinary and medicinal uses, Chives are a milder-flavored Allium species that are used as a condiment in meals. it has similar medicinal effects to garlic, though they are less potent, they are used to treat high blood pressure, sunburn, and sore throat pain, as well as antibacterial and antifungal agents. The antioxidant activity of A. schoenoprasum is one way by which it achieves these effects. It is the major ingredient in the Van herby cheese, a classic Turkish cheese. The leaves and bulb of A. scorodoprosum are used as spices and can be eaten raw or cooked. A. scorodoprosum was employed in folk medicine to manage diabetes and improve vision, to treat sunburn and sore throat pain in addition to culinary uses. Antibacterial, antifungal, antioxidant, and antiviral

activities were claimed for the tubers of A. scorodoprosum. Antimicrobial, anti-obesity, hepatoprotective, and anticancer properties of A. scorodoprosum have been identified in pharmacological research. Chives have antibacterial, especially antifungal, and antioxidant qualities that help the circulatory system by decreasing blood pressure. Flavonoids, vitamin C, and carotenoids are responsible for the pharmacological effects, in addition to other bioactive compounds such as polyphenols, dietary fibre and microelements. Worms, dog and snake bites, baldness, toothache, ulcers, excema and other skin ailments were treated with it, as well as birthmarks and leprosy. Since they produced gas, increased appetite, and provoked thirst, they were regarded to ratify the body's humors. The application of onion juice to the eye improved vision and protected against cataracts in the early stages of the disease when mixed with honey. (94,97,98,105)

- Antioxidant activity: Multiple acute and chronic disorders, including diabetes, cardiovascular, neurodegenerative, and renal diseases, are associated with oxidative stress. Due to an imbalance between oxidants (reactive oxygen species) and endogenous antioxidants, cell death might result. The possible antioxidant capabilities of chives and their numerous components have been determined using a variety of in vitro experiments. Its ease of use and quick turnaround time make it one of the most common free radical scavenging assays. (93)

- Antifungal activity: different fungus strains were inhibited by the A. schoenoprasum L. leaf extract such as (Penicillium gladioli, Botrytis cinerea, Botrytis paeoniae and Sclerotinia sclerotiorum)(93)

- Anthelminthic activity: In mice infected with Trichuris, chives powder (500 and 1000 mg/kg) for eight consecutive days reduced the number of worms in their intestines compared to untreated mice. This was not as effective as onion powder, which eliminated all worms from mice's intestines. Therefore, chives may have a modest antihelmintic action, or require a high dose to entirely eradicate parasites from the digestive tract.(93)

- Anti-inflammatory activity: Inflammation is the body's attempt to defend itself by removing damaging stimuli and allowing the healing process to begin. There are two types of inflammation: acute inflammation, which is described as an immediate regulated form, and chronic inflammation, which is described as a long-term regulated form. Chronic inflammation is a type of inflammation that occurs

over time and results in tissue necrosis. Autoimmune illnesses, malignancies, neurodegenerative illnesses, metabolic syndrome, and cardiovascular illnesses are only a few of the diseases and conditions that can be caused by uncontrolled inflammation. In rats, chive leaf extract has an anti-inflammatory action against turpentine oil-induced inflammation. (93) Only at the highest dose did extract lower phagocytic activity and index out of three dosages examined. The anti-inflammatory effects of A. schoenoprasum L. were aided by decreased phagocytosis and nitro-oxidative stress. (93) It's probable that phenolic and other chemicals are responsible for anti-inflammatory effects, but no research has been done too far to pinpoint the anti-inflammatory chemicals.(93)

- Antihypertensive activity: A study has confirmed that chives are an effective antihypertensive medicine. This is comparable to what a normal vasodilator would do (isosorbide dinitrate)(93).
- Anticancer activity: Leaf extracts inhibited the growth of subcutaneously grafted Ehrlich cancer in male BDF mice. (93) Human immortalized nontumorigenic keratinocyte cell line was inhibited by a 90 percent methanol extract of the flowers in an MTT cell proliferation assay (HaCaT) (93). Additional AS compounds were investigated for anticancer activity in human colon cancer cell lines as part of the investigation. Among male participants with prostate cancer in a Chinese community, researchers examined the relationship between prostate cancer incidence and consumption of Allium vegetables (garlic and other Allium vegetables, onions, chives and leeks). According to the findings of the study, men who consumed more than 10 grams of Allium vegetables per day (including chives) had a significantly lower risk of cancer than those who consumed less. (93) Additionally, consuming Allium vegetables, such as chives, may lessen the risk of stomach and esophageal cancer. Chives may have anticancer effects, according to these studies.(93)

3. MATERIAL AND METHODS

3.1. Plant Extract

Allium schoenoprasum L. (chives) which bought from a local market in Van province. The extraction process of the plant was carried out in the laboratory of the biology department of Bolu Abant İzzet Baysal University. The leaves were powdered after drying in an incubator at 40 °C without being exposed to the sun so that they do not lose their biological content and activity. Infusion technique was used for the extraction. Boiling water was added to powdered leaf samples (15%, w/v), kept in a water bath at 40°C for 18 hours and then centrifuged in refrigerated centrifuge (Nuve®) at 4 °C and 4100 rpm for 10 min to precipitate the plant parts. Supernatant portion was then vacuum filtered and then freeze-dried at -65 °C using ***lyophilizator*** (Christ®). Obtained powdered form extract was stored at -20 °C. Extraction yield was 17.97%. Extraction yield was calculated with the formula: Yield (%) = Weight of extract (g) / powdered plant material (g) × 100.(106) The extract powder is shown in Figure 3.1

Figure 3.1: The Allium schoenoprasum l. extract powder

3.2. Experimental animals

Animals were provided from BAIBU Experimental Animals Application and Research Center. The study used male rats of 2-4 months old Wistar albino strain,

each 200-250 grams. The animals were kept in Type IV cages in an environment with a constant temperature (24 ± 2 ° C) and humidity (55 ± 15%) until and during the study, at the BAIBU Experimental Animals Application and Research Center. Rats were allowed free access to standard rat food and water prior to testing.

3.3. Experimental Protocol

3.3.1. Epilepsy model induced by PTZ.

Pentetrazol known as also (Pentylenetetrazol) is an organic heterobicyclic compound and is a central nervous system convulsant that is used to induce epilepsy models. Its molecular formula is $C_6H_{10}N_4$, and molecular weight is 138.17g/mol (107).

PTZ is an antagonist for the gamma aminobutyric acid (GABA)-A receptor. It inhibits the function of inhibitory synapses, which results in increased neuronal activity. In animals, this regulation induces generalized seizures(108). PTZ induces all four behaviors: freezing, myoclonic twitches, clonic seizures, and tonic-clonic seizure (109). In laboratory animals the seizures induced by PTZ are the most commonly used early screening tests for characterizing potential anticonvulsant drugs. The PTZ test, on the other hand, is a reliable model for human generalized myoclonic and absence seizures (110).

In the epilepsy model induced by PTZ the animals were divided into 4 groups (n = 7, in each group). Control group was given p.o. (oral administration) 1 mg/kg physiological saline solution for 7 days. The second and the third groups received oral Allium schoenoprasum l. extract at doses of 200 and 400 mg/kg, respectively, for 7 days (100 mg of Allium schoenoprasum l. extract + 1 ml DMSO) (111).

On the 8^{th} day of the experiment the animals in the first three groups received SF or plant extracts respectively then after 60 min, they received 60 mg/kg PTZ intraperitoneally (i.p.). The animals in the fouth group received 5 mg/kg diazepam (i.p.) and 30 min later they were injected with, 60 mg/kg PTZ (i.p.) (105). Thirty minutes video recordings were taken after PTZ injection in all groups to determine tonic-clonic seizures. Groups are compared in terms of seizure score, seizure latency, seizure duration, and protection from seizure-related death (112–114). Seizure scoring is made according to the Racine scale (78). Racine scale is a numerical method to evaluate the seizure severity in experimental models of epilepsy, the higher the number, the more severe the seizure as shown in table 3.1

Table 3.1 Epileptic behavior stages according to Racine scale(115)

Phase	Behavioral Responses
Phase 0	No response (No behavioral change)
Phase 1	Immobility, eye closure, ear movement, mustache movement, sniffing movement
Phase 2	Adding head nod to more severe facial clonus
Phase 3	Clonus of one of the anterior extremities, myoclonic jerk is present, no rearing movement
Phase 4	Bilateral anterior extremity clonus, rearing movement
Phase 5	Falling on one side due to rearing and generalized clonic seizure
Phase 6	Death

The experimental groups were:

1. Group I (Control, saline, 1 ml / kg p.o.)
2. Group II (A. schoenoprasum l., 200 mg / kg p.o.)
3. Group III (A. schoenoprasum l., 400 mg / kg p.o.)
4. Group IV (Diazepam, 5 mg / kg i.p.)

3.3.2. Epilepsy model induced by Penicillin.

Penicillin G Potassium, an antibiotic, is used to induce experimental epilepsy as GABA blocker. Its molecular formula is $C_{16}H_{17}KN_2O_4S$ and molecular weight is: 372.48 g/mol (116).

Penicillins are one of the earliest antibiotic groups still used in clinical practice. They are highly effective against sensitive organisms and are bactericidal. Penicillin G has been related to confusion, disorientation, myoclonus, seizures, non-convulsive status epilepticus, and encephalopathy. Penicillin's neurotoxic effects were first seen following an intraventricular infusion of penicillin G, which caused myoclonic twitching.(15) Penicillin G when applied locally to the cortex can block GABAA receptors, so is used in experiments to simulate acute focal epilepsy models.It prevents GABA-mediated inhibitory control of major groups of pyramidal neurons because the vein from the cerebral cortex is most sensitive to penicillin-mediated epilepsy formation.(117) This model was chosen for its prevalence and effectiveness.

3.3.2.1 Surgical Procedure

2-month-old Wistar rats were divided into 4 groups (n = 7, in each group). Rats were first anesthetized by injection with ketamine (90 mg / kg i.m) and xylazine (5 mg / kg i.p.) then placed in the stereotaxy apparatus in which the Bregma and Lambda points of the head were at the same level. The scalp was applied in the rostro-caudal point, the cranium part over the left sensorimotor cortex was removed and the left cerebral cortex was exposed, as shown in figure 3.2.

500 IU penicillin (in a volume of 2.5 µl) was injected with a Hamilton micro-injector 1 mm deep into the left sensorimotor cortex. For intracortical injection Bragma was used as reference (AP = -1mm, L = 1.5mm) (118–120).

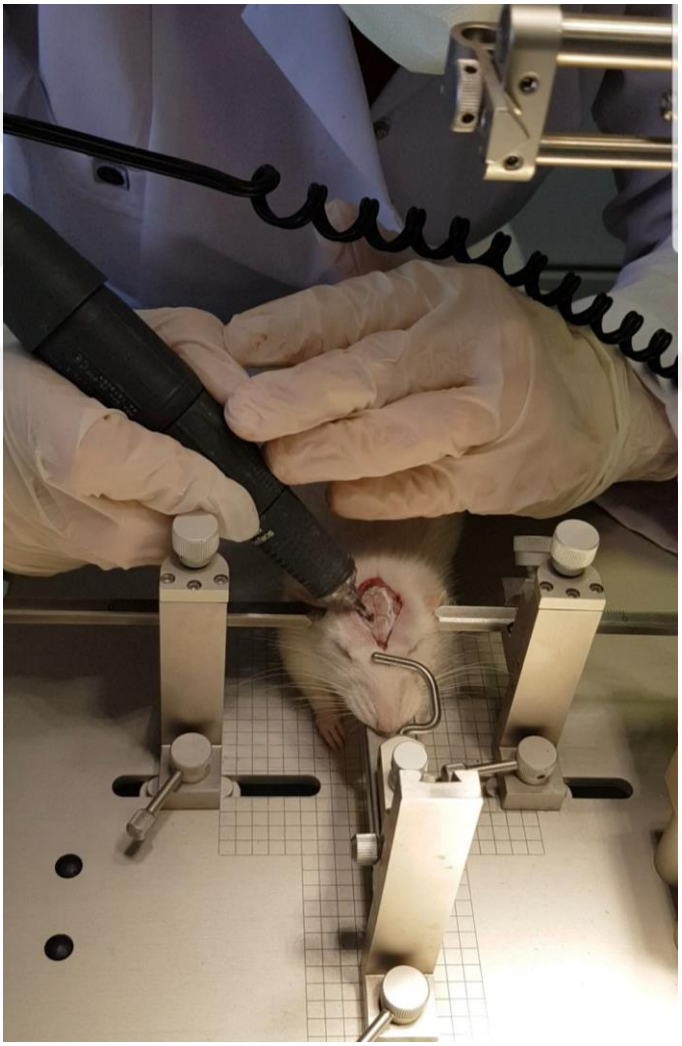


Figure 3.2: The opening of the scalp and the cranium part over the left sensorimotor cortex

3.3.2.2. Experimental groups

In the epilepsy model induced by penicillin the animals were divided into 4 groups. The control goup animals received i.p.(intraperitoneally) injection of saline. The second and third groups received 200 and 400 mg/kg i.p (intraperitoneally). injection of A. schoenoprasum l. exctract, recpectively. The fourth group received i.p. (intraperitoneally) injection of 5 mg/kg diazepam. All anmimals in the experimental groups were injected with 500 IU penicillin G potassium intracortically 30 minutes after the first injections.

The experimental groups are:

1. Group I (Control, saline 1 ml/kg i.p. + Penicillin 500 IU)
2. Group II (A. schoenoprasum l. 200 mg / kg i.p. + Penicillin 500 IU)
3. Group III (A. schoenoprasum l. 400 mg / kg i.p.) + Penicillin (500 IU)
4. Group IV (Diazepam 5 mg / kg i.p. + Penicillin 500 IU)

3.3.2.3. Electrocorticogram (ECoG) Recordings

For electrophysiological recording, the positive electrode was placed 2 mm anterior to Bregma and 3 mm posterior to the negative electrode and the grounding electrode was attached to the ear. In summary, as described in previous studies (118,119), basal electrical activity was recorded for 15 minutes. Afterwards, the extract of Allium schoenoprasum l. was injected in doses of 200 or 400 mg / kg then after 30 minutes the penicillin injection was given and recording continued for another 120 minutes, after which the experiment was terminated. In the recordings, the frequency, amplitude, and latency of epileptic discharges were analyzed as shown in Figure 3.3.

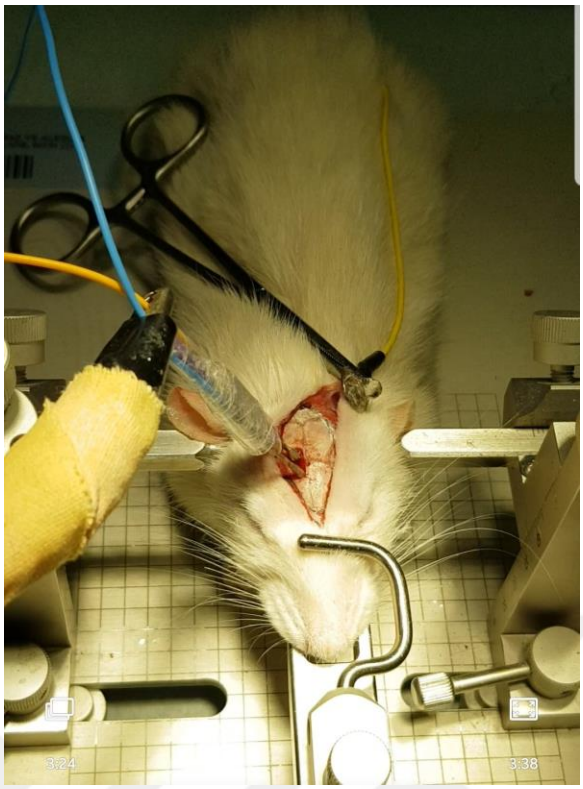


Figure 3.3.: An image during recording of a rat with recording electrodes placed on the surface of the somatomotor cortex.

The Lab Chart Reader program was used to obtain ECoG recordings. Representative images taken at the time of recording after penicillin injections in the experimental groups are given in the figures 3.4, 3.5, 3.6, 3.7.

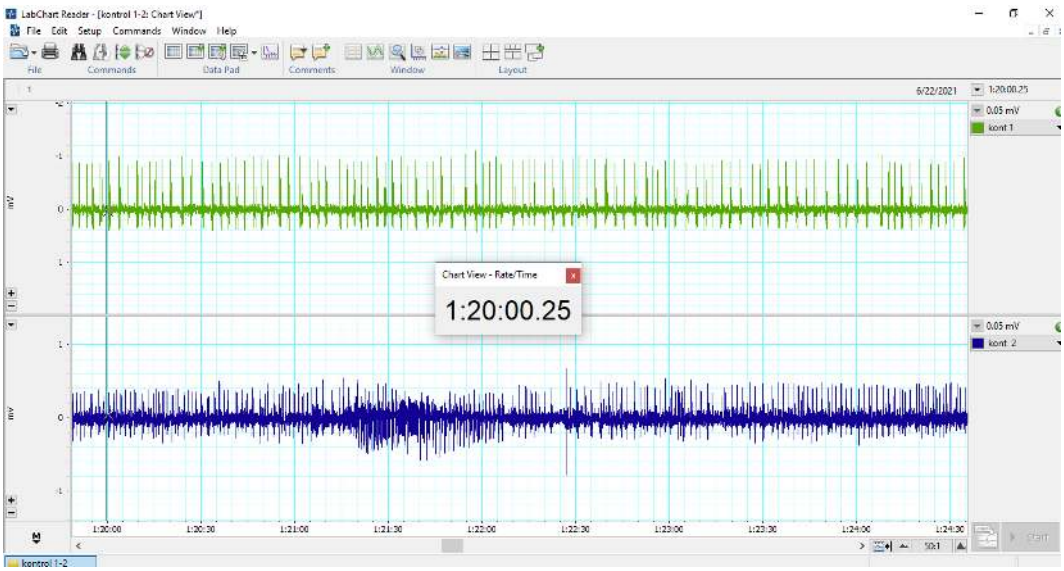


Figure 3.4. A representative recording at the time of epileptic activity in the control group

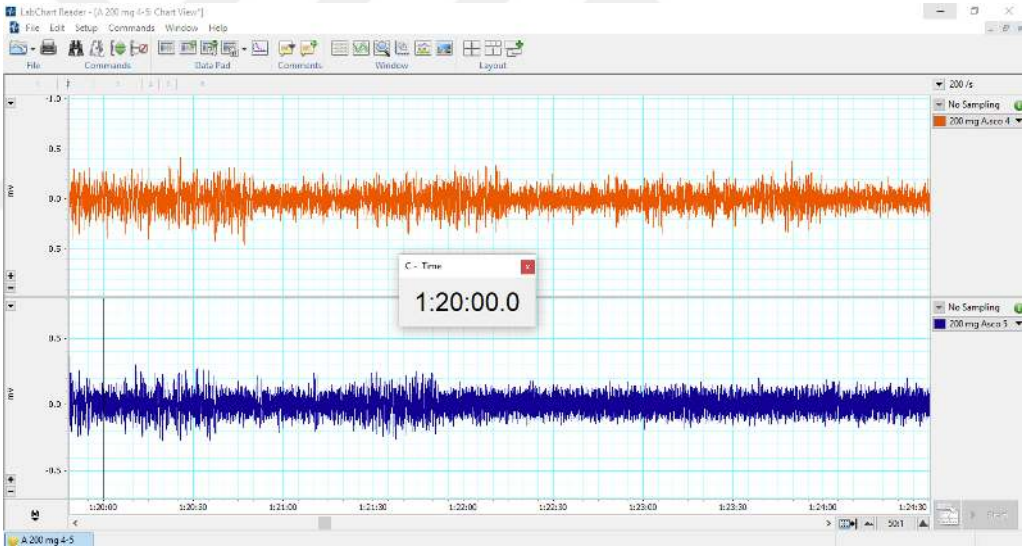


Figure 3.5. A representative recording at the time of epileptic activity in the 200 mg/kg of A. schoenoprasum group

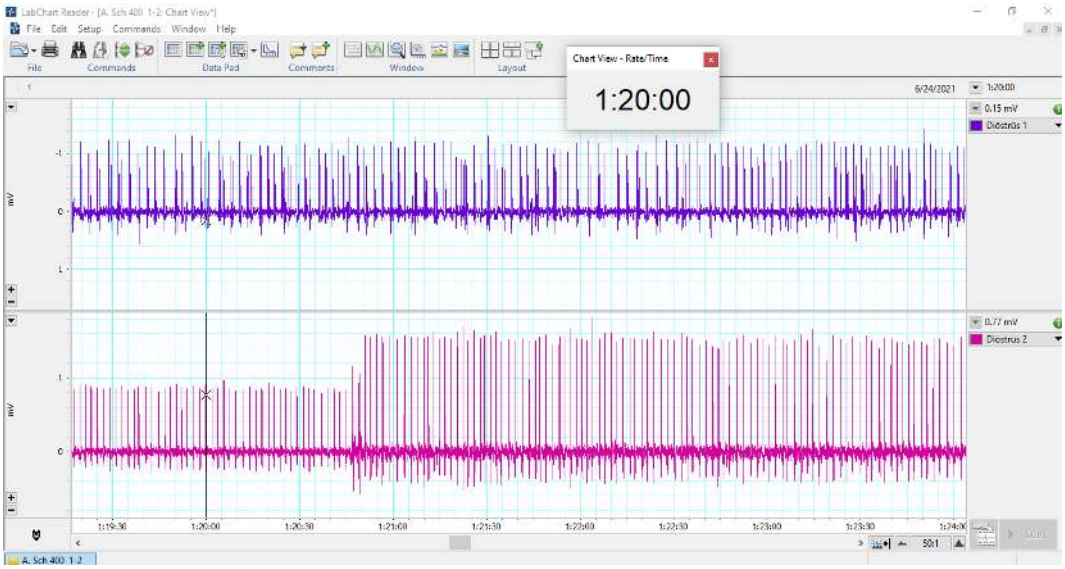


Figure 3.6. A representative recording at the time of epileptic activity in the 400 mg/kg of A. schoenoprasum group

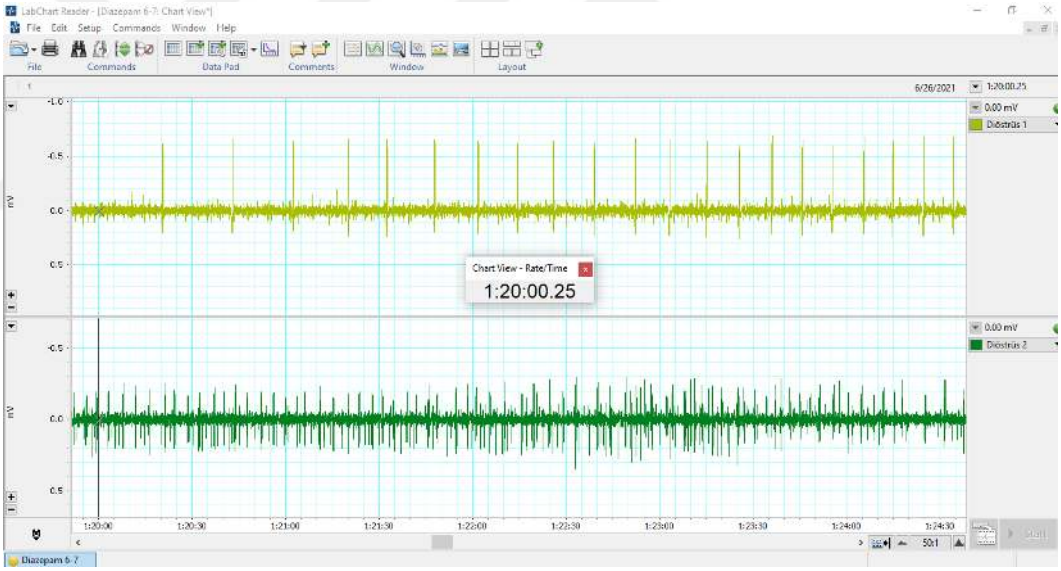


Figure 3.7. A representative recording at the time of epileptic activity in the Diazepam group (it is better to use an

3.4. Statistical Analysis

Since the data were not normally distributed, the non-parametric Kruskal-Wallis H test was used, and different groups determined by post-hoc Dunn test. SPSS 22.0 was used as a statistics program. P <0.05 was considered statistically significant. Data of the control groups were compared to data of groups treated with the plants extracts and to data of the positive control groups.

4. RESULTS

4.1. Results of the penicillin-induced epilepsy model

In the penicillin-induced epilepsy model, the groups were compared in terms of latency time, spike amplitude and spike frequency.

4.1.1. Effects of A. schoenoprasum on the latency time

Descriptive statistics of latency times in the penicillin-induced epilepsy model are given in Table 4.1.

Table 4.1. Descriptive statistics of latency times (second) in penicillin-induced epilepsy model.

Groups	n	Mean	SD	min.	max.	p
Control	7	199,54	56,72	129,6	253,2	0,124
A. schoenoprasum 200 mg/kg	7	227,59	287,90	4,33	850,80	
A. schoenoprasum 400 mg/kg	7	82,97	4,46	78,0	89,4	
Diazepam	6	354,10	156,43	79,2	513,0	

As can be seen from Figure 4.1. there was no statistically significant difference between the groups in terms of the latency times of penicillin-induced seizures.

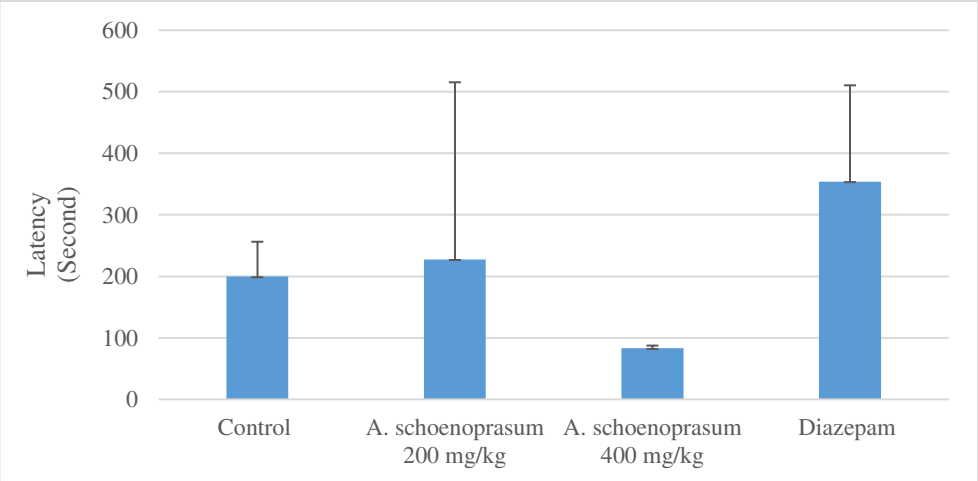


Figure 4.1. Comparison of latency times in penicillin-induced epilepsy model. The error bars in the figure represents the standard deviation.

4.1.2. Effects of A. schoenoprasum on the spike amplitude

The difference between the Diazepam group and the A. schoenoprasum 400 mg/kg group was statistically significant in terms of spike amplitude between 0-5, 6-10, 11-15, 96-100, 101-105, 106-110, 111-115 and 116-120 minutes after penicillin. The difference between Diazepam group and A. schoenoprasum 200 mg/kg group is statistically significant in terms of spike amplitude between 91-96 and 111-115 minutes (Figure 4.2.). A. schoenoprasum in both 400 and 200 mg/kg doses did not cause any significant change on the pike amplitude.

Descriptive statistics of spike amplitudes obtained from the recording after penicillin application are shown in Table 4.2.

Table 4.2 Descriptive statistics of spike-amplitude (mV) obtained from recordings after penicillin injection.

Time (minute)	Control		A. Schoenoprasum 200 mg/kg		A. Schoenoprasum 400 mg/kg		Diazepam		p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
0-5	0,73	0,28	0,66	0,40	1,08	0,45	0,48	0,33	**0,006***
6-10	1,92	1,52	0,83	0,60	1,44	0,56	0,83	0,52	**0,039***
11-15	1,16	0,65	1,01	0,71	1,57	0,66	0,78	0,46	**0,042***
16-20	1,08	0,21	1,25	0,90	1,58	0,59	0,77	0,53	0,097
21-25	1,02	0,30	1,44	0,83	1,65	0,47	0,80	0,57	0,119
26-30	1,04	0,32	1,33	0,77	1,61	0,47	0,78	0,53	0,171
31-35	1,02	0,36	1,27	0,66	1,60	0,42	0,75	0,52	0,174
36-40	1,08	0,67	1,18	0,59	1,62	0,52	0,81	0,45	0,295
41-45	1,23	1,04	1,08	0,51	1,50	0,41	0,81	0,43	0,301
46-50	1,08	0,31	1,11	0,47	1,43	0,33	0,64	0,46	0,175
51-55	0,92	0,33	0,98	0,41	1,38	0,30	0,58	0,44	0,104
56-60	0,81	0,35	1,02	0,34	1,35	0,31	0,57	0,45	0,067
61-65	0,82	0,37	0,99	0,28	1,27	0,29	0,55	0,43	0,084

66-70	0,78	0,36	0,90	0,32	1,20	0,27	0,52	0,40	0,071
71-75	0,82	0,43	0,86	0,32	1,28	0,30	0,54	0,41	0,050
76-80	0,82	0,49	0,77	0,26	1,22	0,29	0,52	0,38	0,067
81-85	0,88	0,58	0,74	0,30	1,24	0,42	0,56	0,37	0,077
86-90	0,82	0,52	0,74	0,25	1,26	0,47	0,55	0,38	0,071
91-95	0,80	0,52	0,71	0,23	1,22	0,50	0,54	0,37	**0,044***
96-100	0,67	0,41	0,68	0,27	1,23	0,54	0,52	0,38	**0,019***
101-105	0,63	0,39	0,68	0,26	1,15	0,55	0,51	0,35	**0,023***
106-110	0,62	0,36	0,68	0,27	1,19	0,60	0,52	0,37	**0,013***
111-115	0,67	0,33	0,66	0,20	1,11	0,53	0,47	0,36	**0,008***
116-120	0,63	0,31	0,75	0,38	1,02	0,42	0,48	0,32	**0,024***

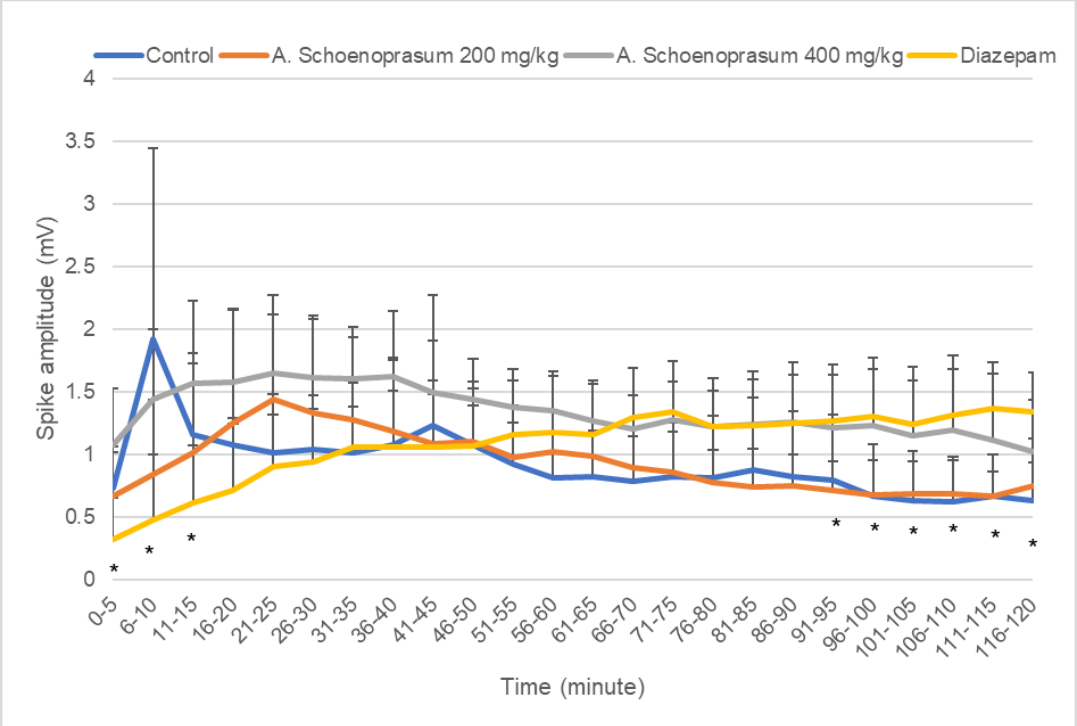


Figure 4.2. Comparison of spike-amplitude (mV) obtained from recording after penicillin injection. * p< 0,05, when Diazepam group is compared to the Control group.

4.1.3. Effects of A. schoenoprasum on the spike-wave frequency

As seen in Figure 4.2, there is a statistically significant difference between the diazepam group and the control and A. schoenoprasum 400 mg/kg groups in terms of spike-wave frequency between 0-5 minutes. While 400 mg/kg A. schoenoprasum significantly increased the spike frequency for the first 5 min diazepam caused a significant decrease. 400 mg/kg A. schoenoprasum did not cause any significant change durinf the remaining 115 minutes while 200 mg/kg A. schoenoprasum exctarct did mot show any effect on the spike frequency for 120 minutes. Descriptive statistics of spike-wave frequency obtained from the recording after penicillin application are shown in Table 4. 3.

Table 4. 3. Descriptive statistics of spike-wave frequency (number/min) obtained from recording after penicillin injection.

Time (minute)	Control		A. Schoenoprasum 200 mg/kg		A. Schoenoprasum 400 mg/kg		Diazepam		p
	Mean	Stand. dev.	Mean	Stand. dev.	Mean	Stand. dev.	Mean	Stand. dev.	
0-5	39,50	34,41	40,00	43,23	82,57	32,56	0	0	**0,001***
6-10	146,67	68,56	111,29	108,84	151,86	57,39	72,33	35,86	0,183
11-15	199,33	79,04	133,71	132,00	153,00	36,87	158,17	31,34	0,813
16-20	175,67	58,67	152,43	124,90	168,86	57,56	180,33	32,53	0,917
21-25	182,67	64,11	166,43	114,07	182,71	78,41	151,50	47,51	0,911
26-30	185,00	87,59	168,00	100,17	164,86	74,00	164,17	53,36	0,986
31-35	170,00	63,41	153,29	91,11	182,86	90,44	171,00	69,18	0,896
36-40	166,83	74,69	151,14	85,39	179,14	88,49	175,83	83,84	0,931
41-45	162,33	80,44	148,14	80,72	169,14	94,62	168,17	70,00	0,984
46-50	154,83	80,58	139,00	72,71	173,86	86,41	164,33	63,55	0,875
51-55	146,33	87,64	142,00	75,59	165,00	66,80	168,17	67,58	0,753
56-60	146,50	89,24	143,71	72,52	153,00	47,98	164,00	60,76	0,873

61-65	147,00	92,23	143,43	75,50	154,14	51,68	153,33	54,72	0,831
66-70	149,83	95,92	139,43	69,72	151,71	50,10	157,83	52,23	0,868
71-75	144,33	91,35	139,86	76,15	144,71	46,62	160,00	48,57	0,966
76-80	148,17	101,52	141,14	75,33	153,43	54,67	166,67	43,98	0,931
81-85	137,17	106,61	134,71	65,91	158,86	58,67	173,67	38,60	0,617
86-90	141,33	114,29	133,57	60,37	146,29	48,99	171,00	41,94	0,836
91-95	149,00	129,13	131,57	57,03	147,57	48,66	166,00	46,47	0,844
96-100	135,00	116,11	131,86	59,45	136,86	46,42	175,33	40,29	0,475
101-105	133,83	122,25	128,29	59,97	140,71	55,93	166,67	40,37	0,502
106-110	137,17	124,73	132,00	53,00	137,57	53,05	157,67	37,95	0,603
111-115	115,17	89,72	129,86	51,79	131,86	52,65	168,67	39,98	0,421
116-120	96,83	69,92	40,00	43,23	125,57	49,08	141,17	49,04	0,160

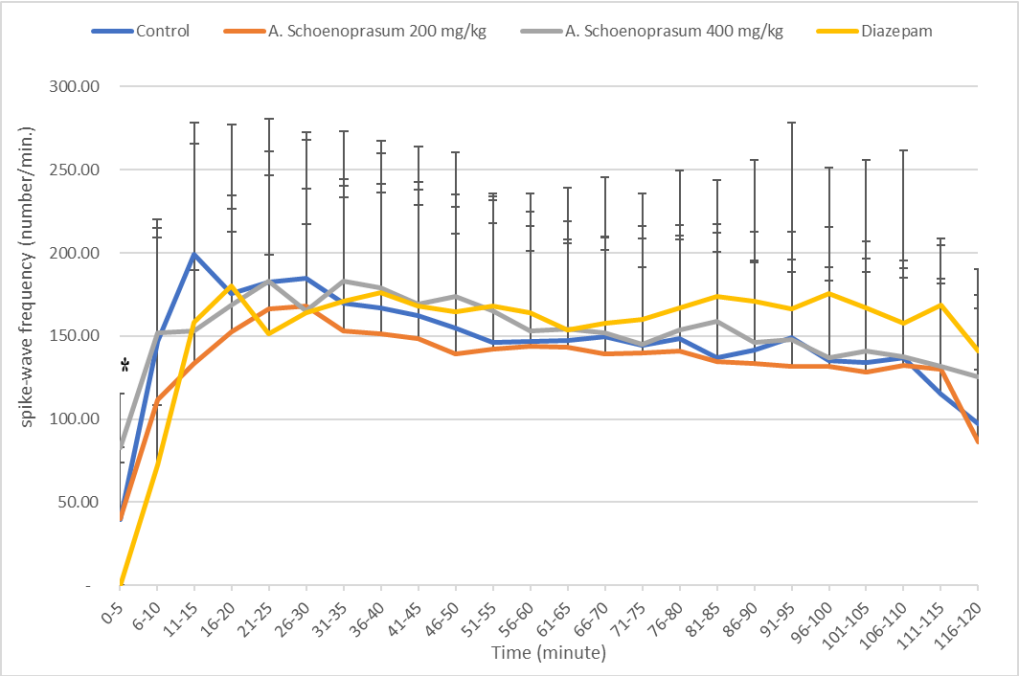


Figure 4. 3. Comparison of spike-wave frequency (number/min) obtained from recording after penicillin injection. * p< 0,05, when the Diazepam group is compared to the Control group.

4.2. Results of the PTZ-induced epilepsy model

In the PTZ-induced epilepsy model, groups were compared in terms of seizure score, protection from seizure-related death, time to first myoclonic jerk, and tonic-clonic seizure duration.

4.2.1. Effects of A. schoenoprasum on the seizure scores

Descriptive statistics of seizures evaluated according to the Racine scale in the PTZ-induced epilepsy model are given in Table 4.4.

While the difference between the diazepam group and the control group was statistically significant, there was no difference between the other two groups in the comparison with the Control group in terms of the mean scores obtained from the Racine scale.

Table 4. 4. Descriptive statistics of seizure scores according to Racine scale

Group	n	Mean	SD	min	max	p
Control	**7**	5,57	,535	5	6	**0,003**
A. schoenoprasum 200mg/kg	**7**	5,14	,690	4	6	
A. schoenoprasum 400mg/kg	**7**	4,71	,756	3	5	
Diazepam	**7**	1,86	2,410	0	5	

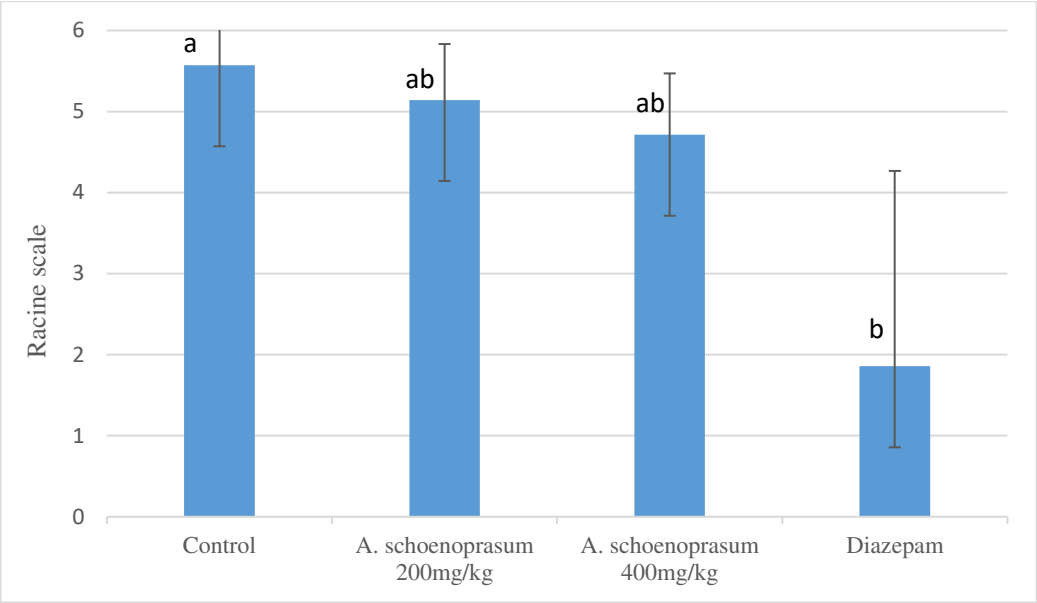


Figure 4.4 Comparison of groups according to seizure score.

a, b: The difference between groups with different letters is statistically significant. The error bars in the figure represent the standard deviation value.

4.2.2. Effects of A. schoenoprasum on the death rate due to seizures

While no death was observed in the subjects in the post-seizure A. schoenoprasum 400mg/kg and diazepam groups, there were 4 deaths in the control group and 2 deaths in the A. schoenoprasum 200mg/kg group (Table 4.5).

Table 4.5. Descriptive statistics on protection from seizure-related death.

a: $p > 0.05$ (non-significant compared to control), b: $p = 0.005$ (significant compared to control)

Group	n	Protection from death	
		n	%
Control	**7**	**3**	43
A. schoenoprasum 200mg/kg	**7**	**5**	71 [a]
A. schoenoprasum 400mg/kg	**7**	**7**	100 [b]
Diazepam	**7**	**7**	100 [b]

4.2.3. Effects of A. schoenoprasum on the time of first myoclonic jerk

Descriptive statistics of the groups according to the time of first myoclonic jerk are given in Table 4.2.2. Since only 3 of the animals in the diazepam group showed myoclonic jerks, they were not included in the comparison.

Table 4.6 Descriptive statistics of the groups according to the time of the first myoclonic jerk (second)

Group	n	Mean	Stand. dev.	min	max	p
Control	7	88,86	22,29	67	127	0,855
A. schoenoprasum 200mg/kg	7	104,43	83,79	5	249	
A. schoenoprasum 400mg/kg	7	136,29	174,44	34	561	
Diazepam	3	99,33	11,15	87	117	

As can be seen from Figure 4.5, there was no statistically significant difference between the groups according to the time of first myoclonic appearance after PTZ application.

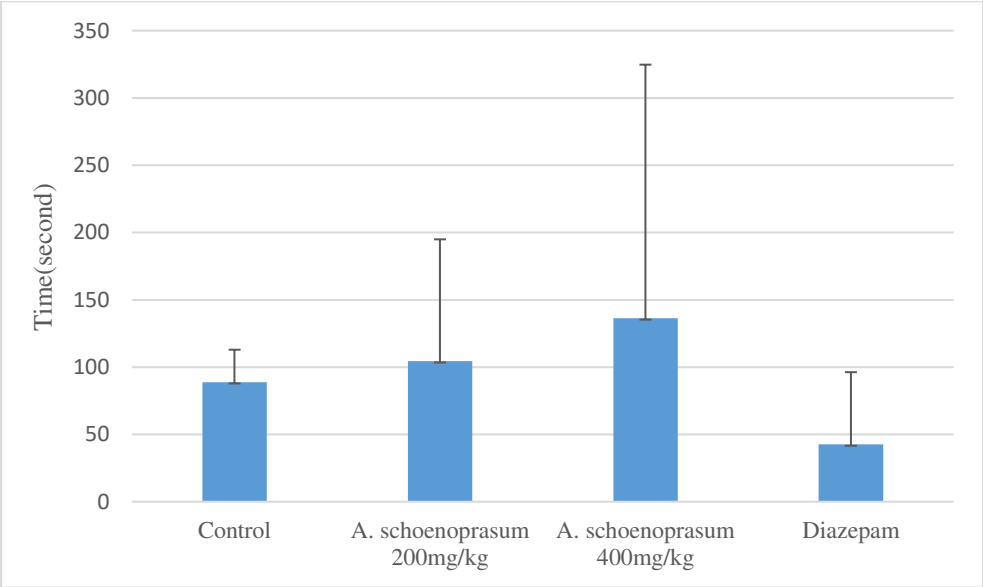


Figure 4.5: Comparison of groups according to first myoclonic jerk time

* The bars in the figure represent the standard deviation value.

4.2.4. Effects of A. schoenoprasum on the tonic-clonic seizure duration

The tonic-clonic seizure duration was significantly longer in the control group compared to the other groups. While the seizure duration in the A. schoenoprasum 200mg/kg group was significantly shorter than the control group, it was longer than the diazepam group. There was no significant difference between the A. schoenoprasum 400 mg/kg group and the diazepam group. Both 400 and 200 mg/kg A. schoenoprasum extract significantly reduced the tonic-clonic seizure duration compared to the contrıl group.

Table 4.7: Descriptive statistics according to tonic-clonic seizure duration in seconds

Group	n	Mean	Stand. dev.	min	max	p
Control	7	88,86	24,08	67	127	**0,001**
A. schoenoprasum 200mg/kg	7	44,57	14,51	27	72	
A. schoenoprasum 400mg/kg	7	18,00	10,91	0	30	
Diazepam	7	6,43	11,60	0	29	

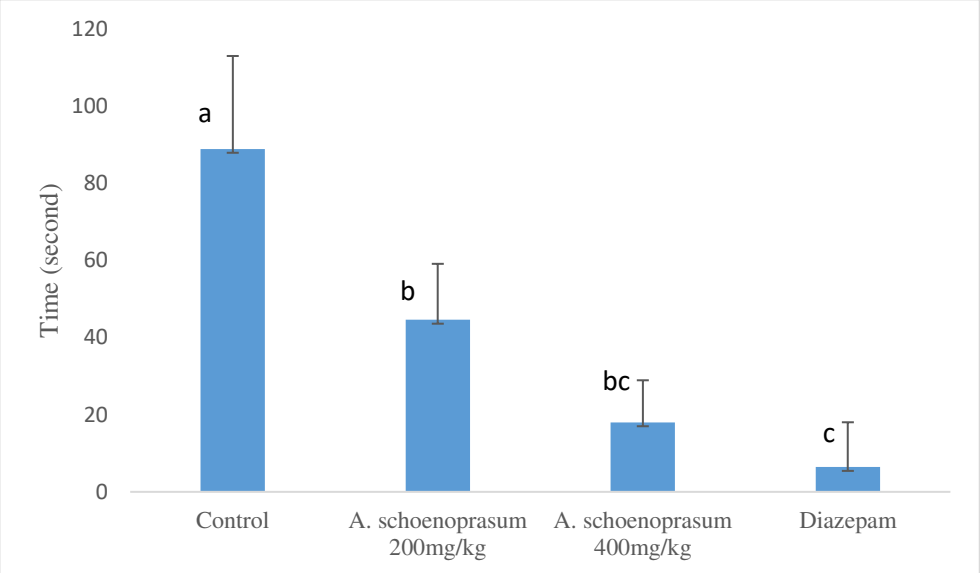


Figure 4.6. Comparison of groups according to tonic-clonic seizure duration

a, b, c: The difference between groups that received different letters is statistically significant. (The bars in the figure represent the standard deviation value).

5. DISCUSSION

Epilepsy is a common chronic neurologic condition characterized by recurring spontaneous seizures in diverse parts of the brain. Many studies have attempted to find the pathogenetic process of epilepsy, however the problem remains unsolved. In general, epilepsy develops as a result of excessive excitation in one or more brain areas, resulting in uncontrolled and improperly synchronized electrical discharges in the brain neural networks. These events are most likely caused by increased glutamate and/or decreased GABA release. (121)It is an important public health problem increasing day by day, which affects individuals both physically and psychologically, decreasing their quality of life, often putting restrictions on their daily activities and in addition incurring medical costs. This in turn has an effect on other members of their family and wider society. The seizure is a temporary behavioral change due to the simultaneous and rhythmic output of neurons in the central nervous system which needs long-term, continuous, and multi-medicinal treatment. This is a central point of treatment which can sometimes lead to the development of various side effects such as drug resistance and lack of access to more effective treatment procedures (8). As a result, research in recent years has turned to plants as an important source of pharmacueticals, focusing on the natural characteristics of herbal and traditional medicine to develop more effective, low-risk drugs with fewer side effects. (122)

Because of their diverse medicinal characteristics and affordability, medical plants are increasingly being used in alternative treatments. Such plants are already widely used in public health, therefore scientific research on their effects on health is vital (85). Many epidemiological studies have suggested that some natural foods, can aid in the prevention of a variety of diseases. They've been shown to have a variety of therapeutic effects, including the inhibition of tumor cell development and chemoprevention. (92) Her some examples about the effectiveness of the different kind of herbs in different epilepsy induced models.

PTZ-induced convulsions were successfully treated with plant extracts from the Annonaceae, Asteraceae, Lam and Verbenacea families in 78.3 percent of the 21 studies done. Five of the plants studied showed excellent anticonvulsant effectiveness against PTZ, PIC, or INH-induced seizures (Flacourteria indica,

Ricinus communis, Securidaca longepedunculata, Senna singueana and Terminalia glaucescens).(122)

In a previous study, the spike/wave frequency in the brain was lowered in a penicillin-induced epilepsy model when an extract of Salvia Miltiorrhiza was employed. Female control group amplitude was substantially greater (P 0.05) than male control group amplitude after 20 minutes of recording activity. There was a significantly greater latency to the initial spike/wave in the male SmE-treated and control groups compared to the males in the female groups. (121)

A previous study on the extract of Allium cepa L., (which is in the same species as the plant in this research) significantly shortened the duration of the tonic convulsion in electrically generated seizures at all doses. At 50mg/kg and 200mg/kg doses, it delayed the onset of tonic convulsion in the PTZ-induced seizure. Allium cepa extract has an anticonvulsant effect, particularly in MES-induced seizures, and could be a useful alternative for convulsion treatment. This observation helps to explain why herbalists use it to treat convulsions. (123)

In an in-vitro DPPH free radical scavenging model, methanolic extracts of Allium cepa and Allium sativum were found to have excellent antioxidant capabilities. A combination of herbal extracts of A. calamus, A. cepa and A. sativum was evaluated for anticonvulsant properties using the Isoniazid (INH) induced seizure model. The anti-seizure effect was evaluated for a fraction containing β-Asarone as a major component. The experimental data show that a fraction containing β-Asarone (101 mg/kg) and its combination with A. cepa (300 mg/kg) possessed 100 % protection in the INH induced seizures (100 mg/kg) whereas the combination of β-Asarone (101 mg/kg) with A. sativum (300 mg/kg) exhibited 50 % protection, indicating that A. sativum decreases whereas A. cepa potentiates the anticonvulsant activity of β-Asarone. The combination of Methanolic extracts of all three plants was also found to possess mild anticonvulsant effects. (124)

In another study, mice treated with low, medium, and high dosages (100, 200, and 400mg/kg) of Allium cepha bulb extract showed significant increases in the threshold for clonic and tonic convulsions, 66.66, 83.33, and 83.33 percent of the control group's convulsions were prevented by diazepam (5mg/kg), while 80mg/kg s.c. injections of PTZ (80mg/kg) resulted in 100 percent protection.(125)

One of the medical plants which is often used as therapeutic herb is the Allium vegetable commonly known as chives (Allium scorodoprasum L.). It is an alternate plant that is utilized to extend shelf life, raise nutritional value, and improve health, in addition to being eaten as a salad vegetable. Research has shown that the quantities of free thiols, mainly in the bulbs, indicate a high antioxidant capacity of the plant and is also beneficial for lipid peroxide balance in tissues (91)

In addition to culinary uses, chives were used in traditional medicine to manage diabetes and improve vision, as well as to alleviate sunburn and sore throat irritation. Pharmacological studies have discovered that A. scorodoprosum has antimicrobial, anti-obesity, anti-hypertensive, hepatoprotective, diuretic, and anticancer effects. (94,97,98,105)

The study is the first of its kind on the antiepileptic effects of Allium schoenoprasum l. The aim is to reveal the potential anti-epileptic effects of the herb, according to previous studies have shown that it is effective in a variety of neurological and non neurological disease as following, in an investigation on the effect of Allium schoenoprasum L. (known as Sirmo in Turkey) against acrylamide toxicity in rats, it was observed that Allium schoenoprasum L. has benefits against oxidative stress caused by acrylamide toxicity. (126)

Another investigation of the antioxidant and cytoprotective effects of an ethanol extract of Allium schoenoprasum l. in carbon tetrachloride-induced liver injury in rats showed that it had a dose-dependent liver-protective effect against CCL4-induced liver toxicity. (127)

Also, according to the recommendations of the famous 10th century doctor Avicenna, whose guidance is still relevant for modern medicine, for the treatment of epilepsy, to find new compounds in the treatment of epilepsy and develop new treatment strategies accordingly. Research into the antiepileptic activity of plants using two different epilepsy models (Penicillin and PTZ induced models) will provide new information to the literature in terms of epilepsy treatment and plant properties.

In our study, focal epilepsy was produced in rats by penicillin G administration. In the ECOG recordings the 4 groups were compared in latency time, spike amplitude and spike frequency. In terms of latency times, there was no difference between the groups. The Allium schoenoprasum l. extract at 200 and 400

mg/kg did not show any effect in term of spike amplitude, while in terms of the spike wave frequency an effect was observed in the 0-5 minutes compared to the diazepam group. However, when looking at the difference in patterns of activity between the groups there does appear to be evidence of a slight negative effect from the Allium schoenoprasum l. extract on the spike frequency at the beginning of the epilepsy. One of the obvious observations was the inability of the diazepam to reduce the spike amplitude and decrease the spike frequency.

As it showed in a study that diazepam terminates brief but not prolonged seizures in young Naive rats, the dosage of diazepam that stopped seizures in 5 minutes was not effective in stopping seizures in 60 minutes in all age groups. This decrease in efficacy could be seen as early as 15 minutes following the onset of the seizure.(128)

It was shown that individual and combination intracerebroventricular injections of crocin and diazepam reduced penicillin-induced epileptiform activity in a previous study, penicillin was administered intracortically (i.c.) to rats anesthetized with urethane and electrocorticographic (ECoG) recordings were taken to measure epileptiform activity. Diazepam icv injections at 10 g increased the latency time to the beginning of the first spike wave and lowered spike wave frequency. (129)

when diazepam was injected into the hippocampus at one of four possible doses, followed by bicuculline methiodide 5 minutes later. Diazepam suppressed spikes and ictal events in a dose dependent manner. At 100 mM, diazepam reduced spikes from 678±128 to 87±35 for a 15 min segment. (130)

In this study after each PTZ injection, seizures were observed for 30 minutes. In this model descriptive statistics of seizures were evaluated according to the Racine scale. While there was no significant difference between the two A. schoenoprasum groups in terms of the mean scores obtained from the Racine scale, there is an overall lower score than the control group, again indicating that these plant extracts are having some effect.

The plant extract was observed to decrease the mortality in PTZ-induced seizures, where there was no death in the 400 mg/kg of the A. schoenoprasum group and 100% of the group survived from the seizure-related death, and only 2 deaths in the A. schoenoprasum 200 mg/kg group (71% of the rats rurvived) while there were 4 deaths in the control group. There was no noticeable effect between the groups

according to the time of first myoclonic appearance, but once again the mean results showed that the plant extracts did give a slightly longer delay in the timing of the seizure.

Most significant results are in the tonic-clonic seizure duration in the A. schoenoprasum 200mg/kg group, which was significantly shorter than the control group. Furthermore the 400 mg/kg group of Allium schoenoprasum was almost as effect as the Diazepam in reducing the length of these seizures.

No electrophysiological investigation into the antiepileptic activity of Allium schoenoprasum l. by any induced epilepsy models was found in the literature, therefore the results of this research could not be compared. It is thought that the findings obtained in this study, in which we analyzed the changes in latency, epileptiform activity spike-wave frequency and amplitudes electrophysiologically, will make an important contribution to the literature.

6. CONCLUSION AND RECOMMENDATIONS

As a result of the study, In the PTZ (Pentylenetetrazole) induced model, the plant extract was observed to decrease the mortality, especially the 400 mg/kg of A. schoenoprasum. Most significant results are in the tonic-clonic seizure duration in the A. schoenoprasum 400 mg/kg group, which was significantly shorter than the control group and was not significantly different from the Diazepam group. 400 mg/kg A. schoenoprasum extract also significantly reduced the tonic-clonic seizure duration compared to the control group but it was longer than the Diazepam group.

For penicillin induced model, 200 and 400 mg/kg the Allium schoenoprasum l. extract did not show any effects on spike amplitude. However, there was a negative effect on the spike frequency only during the first 5 minutes after epilepsy induction. The extract did not show any effect between 6-120 minutes on the spike frequency, so there appears to be a slight adverse effect of the Allium schoenoprasum l. extract on the spike frequency at the beginning of the penicillin-induced epilepsy.

A. schoenoprasum extract appers to have antiepileptic effects since it decreased the tonic-clonic seizure duration and decreased seizure-related death in the PTZ-induced epilepsy model. However its antiepileptic effects were not observed in the penicillin-induced epilepsy model.

Epilepsy is a complex pathophysiological process involving several pathways, which contributes to the complexity of herbal medicine's effects on the condition. For future research, big samples, multi-center, double-blind, randomized, controlled clinical studies are still required.

Herbal medicines, unlike pharmaceutical medications manufactured from single molecules, it requires precise identification of the plant species and the selection of appropriate parts for usage, so correct way, the timely collection, drying methods, can affect greatly in the amount of biological content and activity in many types of herbs. Therefore, we suggest considering these reasons in the collection process of herbal plants for the purpose of medical research.

Finally, the medicinal plant extract of our experiment deserves additional studies in terms of its mechanism of antiepileptic effect in PTZ-induced epilepsy model. Furthermore, the active elements in the herbal medicine extract should be thoroughly investigated which ingredient is effective in that extract. An herbal medicine database should also be established in the future

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