ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

Epilepsy and Associated Comorbidities: Role of Phytomedicines in Epilepsy Management

Simran Sekhon*, Neeraj Kumar
[1]Shri Guru Ram Rai University School of Pharmaceutical Sciences Dehradun, Uttarakhand, India

Running Title: Epilepsy and comorbidities: Implication of Phytomedicines

***Corresponding author:** Address for correspondence
Simran sekhon
B.pharm
Shri Guru Ram Rai University School of Pharmaceutical Sciences Dehradun, Uttarakhand
Email id: sekhonasimran0606@gmail.com
Contact no. 8791128846

ABSTRACT
Epilepsy is the most dynamic of the neurological disorders, with seizures being the most common symptom. Treatment of seizure occurrence and frequency is more than just an epilepsy treatment option. Treating epilepsy comorbidities in addition to seizures would, in fact, improve epileptic patients' quality of life. When compared to the general population, epileptic patients have higher levels of psychiatric comorbidities. Anxiety, cognitive impairment, and depression are major comorbidities. However, there's also a correlation between neuroinflammation, autism and epilepsy in the brain. The suppression of ϒ-aminobutyric acid (GABA), which causes an imbalance in inhibitory and excitatory neurotransmitters is a major pathological cause of epilepsy. Other factors, such as heredity, as well as treatment with older generation antiepileptic medicines, have been investigated and found to play a role in the development of comorbidities. Medicinal plants with therapeutic potential have grabbed the interest of many researchers, scientists, and doctors, in addition to the available AED treatment strategies. Phytomedicines are secondary metabolites found in plants with therapeutic potential that can be employed in the treatment of diseases and their associated comorbidities. By doing so, the current review paper concludes the related comorbidities of epilepsy, their pathological aetiology, and the hunt for a molecule with therapeutic potency and limited side effects from medicinal plants.

KEYWORDS
Co-morbidities, Antiepileptic, Seizures, Phytomedicines, flavonoids.

1. INTRODUCTION
Epilepsy is a chronic, recurrent neurological illness characterised by unpredictable obtrusions known as "seizures" that affects more than 70 million individuals worldwide from all ethnic backgrounds. Epilepsy is a complicated condition that often involves the synchronized aberrant discharge of intracranial neurons.[1] Various pathologies have indeed been proposed possible causes of epilepsy, via an imbalance between the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and the excitatory neurotransmitter (GLUTAMATE) being the most significant. Other variables, such as neuromodulators that co-occur with neurotransmitters, however, play a significant role in both primary and secondary epilepsy.[2] On the other hand, brain stroke, central nervous system infections, neurodegenerative disorders, protracted seizures such as complex seizures, and status epilepticus account for 40% of epilepsy cases.[3] Epilepsy is the most common disorder in the world, with active instances of 6.38 per 1,000 people (95 percent confidence interval 5.57-7.30), and lifetime prevalence of epilepsy estimated to be around 7.60 per 1,000 people (95 percent confidence interval 6.17-9.38). According to a recent meta-analysis, the incidence and prevalence of epilepsy is higher in developing nations than in industrialised nations.[4] According to a research published by the World Health Organization (WHO), Epilepsy is a serious medical condition in which the frequency of seizures varies greatly from one person to the next. Various antiepileptic medications are on the market that aim to restore the balance between GABA and glutamate by either increasing GABA levels or lowering glutamate release. There are other AEDs that target various ion channels, including as Na+ and Ca2+, as well as newer medicines whose actions are still unknown. However, present AED treatments are based on symptomatic relief, or ictogenesis (the expression of seizures), rather than epileptogenesis (the long-term development of disease producing seizures), leading to the conclusion that we do not have any, prominent treatment for epilepsy.[5]

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

1.1 DEFINITION AND CLASSIFICATION

SEIZURES

A transitory development of signs and/or symptoms related to abnormal excessive or synchronised neuronal activity in the brain" is how seizures are defined. ILAE recently modified this definition, and it hasn't been altered yet[5]. The ILAE's 2017 seizure categorization system was based on the beginning of seizures and was separated into three types: (1) focal seizures, (2) generalised seizures, and (3) unknown onset seizures. Focal seizures are defined as seizures that originate in only one hemisphere or portion of the cortex and are classed as either awareness retained or impaired. In old terminology, focal aware seizures were called "simple partial seizures," whereas focal impaired episodes were called "complicated partial seizures." Generalized seizures affect both hemispheres, resulting in reduced consciousness, as compared to focal seizures, which have both motor and non-motor onsets. Not all areas of the brain are engaged in generalized seizures, and the seizures are also not symmetric. Generalized seizures involve absence seizures.[6]

EPILEPSY

Epilepsy is defined as a condition in which the brain produces recurring seizures with a frequency that varies from patient to patient. Epilepsy is diagnosed when two unprovoked seizures occur within 24 hours of each other, and the brain produces seizures with varying frequency due to any pathologic cause.[7] Epilepsy is characterized mostly based on clinical seizure types and data obtained from an EEG (Electroencephalogram). There are four major types of epilepsies, according to the 2017 ILAE classification: (1) focal seizures (2) generalized seizures (3) combined generalized and focal seizures (4) The answer is unknown. Both types of seizures and discharges in the EEG are present in combined focal and generalised epilepsy. When there isn't a lot of knowledge on the many varieties of epilepsy, it's labelled as unknown.[8] Epilepsy is categorised into three categories based on the cause: idiopathic, acquired, and cryptogenic. Idiopathic epilepsies are those with no anatomical brain abnormalities and no EEG history. These are usually thought to be hereditary and manifest themselves during childhood. Acquired epilepsies are defined as structural lesions with EEG data. Cryptogenic symptoms are those that have an unknown cause.[9]

1.2 ETIOLOGY OF EPILEPSY

Epileptogenesis is the gradual development and extension of tissues that cause epileptic seizures. Epileptogenesis at the cellular and molecular level refers to the events that occur after brain damaging insults cause changes at the molecular and cellular level, resulting in unprovoked seizures.[10] In 2016, a study showed that 977 genes are responsible with epilepsy. Ion channels, transporters, and enzymes are all regulated by these genes. Other genes are responsible for syndromes with significant features such as epilepsy and epilepsy-causing neurodevelopmental gene.[11] GABA and GLUTAMATE are two main neurotransmitters that have been studied in epilepsy. Hyperexcitation is caused by the inhibition of GABA over glutamate release, resulting in a GLUTAMATE/GABA imbalance. During epilepsy, glutaminergic mechanisms occur, resulting in higher extracellular glutamate levels and enhanced glutamate receptor upregulation, resulting in hyperexcitability. GABA is an inhibitory neurotransmitter, and a mutation in GAT-1 that causes GABA reuptake from synapses is responsible for epilepsy [12] Inflammation in the brain is a key factor in epilepsy. Brain traumas, strokes, and status epilepticus trigger inflammatory cascades in the brain, which result in seizures. In epileptic patients, glial cells, mostly astrocytes and microglia, play a crucial role in activating different receptors such as Toll-like receptors (TLR) and further activating other immune mediators, culminating in the production of recurrent seizures.

1.3 DIAGNOSIS AND TREATMENT

Epilepsy is diagnosed solely by eye witnessing and a combination of signs and symptoms of seizures experienced. Non-epileptic occurrences should be excluded because misdiagnoses are typical and can be very harmful. The electroencephalogram (EEG) is used to distinguish between focal and generalized seizures, although it does not identify epilepsy. Epileptiform discharges could be used to diagnose epilepsy. Computerized scanning and customized EEG, as well as long-term videography, may aid in epilepsy diagnosis. Other methods, including as MRI, reveal a 20% lesion in epileptic individuals when used in conjunction with an epilepsy regimen. However, detecting neuronal antibodies can also be used to diagnose unknown epilepsy, although this method is only used when other diagnostic procedures have failed and individuals are expressing signs and symptoms.[13]

There are currently 25 epilepsy drugs available, all of which are designed to manage seizures with minimal side effects and improve quality of life. Epilepsy therapy is governed by the signs, symptoms, and types of seizures, as well as their frequency, as assessed by the diagnostic technique. The recovery rate from seizures in epileptic patients who have been on medication since the beginning of their epilepsy is much higher. However, some patients develop resistance to medications and therapy, resulting in inadequate or non-existent epilepsy treatment. AEDs that are currently accessible have substantial side effects and are linked to additional comorbidities such as cognitive impairment. Patients' quality of life suffers as a result of poorly managed epilepsy under certain circumstances. Surgery is another epilepsy treatment option; however, it should only be used if non-invasive treatment and medication have failed.[9,14]

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

1.4 COMORBIDITIES IN EPILEPSY

Comorbidity implies the existence of two conditions at the same time, with a higher frequency of incidence than the general incidence rate in the population. Epilepsy comorbidities are frequent, and their presence improves the condition while also impacting medical costs and patient quality of life. Patients with epilepsy, at any stage of the disease or treatment, face mental, cognitive, and medical comorbidities, which can occur alone or in combination.[15] In the population with temporal lobe epilepsy, the prevalence rate of epilepsy connection with a psychiatric condition is around 20-50 percent, and individually 80 percent. This rate is much higher than the overall population rate (10-20%). Variation in results depends on different methods of investigation as well as the definition of prevalence along with their meanings (cumulative prevalence, punctual prevalence, lifelong prevalence).[16] The greatest risk associated with epileptic patients is comorbidity assessment, which is independent to therapy with currently available antiepileptic drugs. There are various chronic risk factors linked to epilepsy, including mental comorbidities (depression, anxiety, cognitive impairment, psychosis), which are divided into three categories: (1) neurobiological, (2) psychosocial, and (3) pharmaceutical variables.[17]

2. EPILEPSY INDUCED COGNITIVE IMPAIREMENT

Cognitive impairment is a heterogeneous disorder that affects 70-80 percent of epileptic patients. Cognitive impairment is characterized as a learning problem with varying degrees of dysfunction. Long-term epilepsy patients and pharmacoresistant epileptic patients are especially vulnerable to cognitive deterioration. Mood disorders and cognitive impairment in epileptic patients are frequently underdiagnosed, which is a major cause for concern.[24] As a result, treating cognitive damage is just as important for epileptic patients as treating seizures. As a result, cognitive impairment alters the biochemical environment of the brain, acting as a marker and contributing to the recurrence of frequent seizures. Epilepsy is a network disease with multiple comorbidities since Cognitive impairment and mood disorders have a tri-directional interaction with seizures.[25] When compared to the normal rate, epilepsy becomes more complicated with Cognitive impairment. With epilepsy, the typical rate of Cognitive impairement is around 0.6-17.5 percent, which is similar to Alzheimer's disease. According to a cohort research, people with Alzheimer's disease are 17 times more likely to suffer seizures than the general population. However, because symptoms arise considerably later than the neurodegenerative process in the brain, early diagnosis of these processes is challenging.[26]

2.1 MECHANISM OF COGNITIVE IMPAIRMENT IN EPILEPSY

Role of seizures

Induction of seizures, which has a variety of etiological reasons, could be a cause of neurocognitive impairments in epileptic patients due to focal or global brain dysregulation. As a result, various aetiologies have been identified, such as a mutation in the (STXBP1) gene that causes genetic disorders such as infantile epileptic encephalopathy, Rett syndrome, and Angelman syndrome. Seizures also disrupt brain development, particularly in children, causing anatomical alterations such as cortical malformation or hypoxic-ischaemic damage. Excessive excitatory neurotransmitter release (GLUTAMATE), as well as lactic acidosis in seizures, can induce cognitive impairment. The etiologies of Lysosomal Storage Disease's dysregulation of mitochondrial function are also being explored in the concomitant condition of epilepsy. The severity of cognitive impairment is determined by the stage of brain development at which seizures occur. Seizures primarily damage the developing brain rather than the adult brain, making it more sensitive to synaptogenesis, apoptosis, and the concomitant scenario of cognitive impairment, according to various research. However, other studies believe that a developing brain is sufficient for seizure resistance, whereas an adult brain is more likely to suffer cognitive dysfunctions.[27,28].

Role of ion channels

Due to the presence of distinct ion channels in distinct parts of the brain, the hereditary aetiology of epilepsy primarily targets ion channels, resulting in a dysregulated brain network. Ion channel function, particularly Na+, K+, and T type Ca+ channels, is altered in chronic epilepsies. Mutations in the gene (SCNIA) encoding the sodium channel's type-1 alpha subunit (NAv1.1) in neurons have been linked to epileptic encephalopathies. These mutations cause Purkinje cells to fire less GABA, resulting in epileptic patients' cognitive impairment. Inhibition of the NAv1.1 channel, according to Nicola et al. research, could improve cognitive performance in patients.[27,29]

Role of antiepileptic drugs

Antiepileptic medications (AEDs) reduce neuronal extricability by balancing neurotransmitters and enhancing ion channel function, lowering seizure production and impairing cognition. However, the mechanism underlying the negative impacts of reduced cognition is still being researched and understood. The literature therefore shows how a decrease in neuronal excitability caused by a change in neurotransmitter reduces seizure generation, resulting in a negative influence on patients' cognitive abilities. As a result, it was determined that the effects of AED on brain functioning are far more complex than simply lowering neuronal excitability. Long-term use of an AED, particularly in youngsters, increases the risk of cognitive damage. Benzodiazepines and barbiturates are the most common antiepileptic medications with memory and attention side effects.[28,30] Lamotrigine, levetiracetam, lacosamide, and perampanel are some of the first-choice treatments from a

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

neuropsychological standpoint. The observed AED adverse effect of cognitive impairment is reversible, meaning it goes away when the drug is completely stopped or the dose is reduced. These effects can be irreversible on the growing brain, particularly in youngsters, resulting in low I.Q. and learning difficulties.[31]

3. EPILEPSY INDUCED ANXIETY

Anxiety is a common and significant burden comorbid disorder among all epilepsy patients, although it receives little attention in comparison to depression and other comorbid illnesses. Its lifetime prevalence is believed to be 20.8 percent, although some publications claim it can be as high as 50 percent. Untreated anxiety can have a negative impact on epilepsy and worsen the prognosis of the disease. Patients with epilepsy-induced anxiety experience adverse effects from antiepileptic drugs, have poor seizure control, and have a reduced overall health-related quality of life. These individuals are more likely to have suicidal thoughts and attempt suicide.[18] People with epilepsy are more likely to suffer from Generalized Anxiety Disorder (GAD), a subtype of anxiety. There is still a need for a proper anxiety screening tool. The Hospital Anxiety and Depression Scale (HADS), on the other hand, has been shown to be a reliable instrument for detecting anxiety in epilepsy patients. The MINI (mini-international Neuropsychiatric Interview) is a standard collection of questions for detecting psychotic condition.[19]

3.1 PATHOPHSIOLOGY OF ANXIETY IN EPILEPSY

In epilepsy, the origin of anxiety is currently unclear. Various ideas on the source of anxiety in epilepsy have been proposed, including psychological, neurobiological, and aggregation hypotheses. Unpredictable seizure generation and its consequence on social humiliation generates behavior modifications and social phobias, according to psychological theory. According to the neurobiological idea, the amygdala is the source of anxiety in epileptic patients. The right side of the amygdala was increased in adults with anxiety as a comorbid condition, according to neuroimaging. In youngsters, the left amygdala was shown to be larger. Individual kids with epilepsy and a tendency to have comorbid anxiety condition are affected by parental psychiatric history or mood and behaviour disorder, according to familial or genetic theory.[20]

Neurobiological crosslink with comorbid anxiety in epilepsy

The imbalance between various neurotransmitters such as serotonin, -aminobutyric acid (GABA), norepinephrine, dopamine, and neuropeptide Y (NPY) that are hypothesised to play a key role in the generation of anxiety in epileptic patients is the focus of neurochemical aspects of epilepsy-induced anxiety.[21] Flumazenil's affinity to Benzodiazepine receptors is reduced in panic disorder, reducing receptor availability in specific brain locations. In temporal lobe epilepsy patients, a decrease in BDZ receptors develops, resulting in a common cause for both epilepsy and anxiety. The amygdaloid nucleus is the most important structure studied in the disease of anxiety from a neuroanatomical standpoint. This set of nuclei is in charge of data exchange and processing, which is subsequently passed on to the efferent system, which mediates cognitive, emotional, multi-autonomic, and endocrinological components that play a role in anxiety responses. Seizures in the right amygdala's basolateral nuclei not only generate limbic complex partial seizures, but they also affect anxiogenic behaviours, resulting in anxiety.[22] Xinjian et al., through his experimental data, concluded the presence of anxiety-like behaviour in epileptic mice by evaluating the population of GABAergic neurons subtypes like Parvalbumin protein (PP) a calcium-binding protein and two others like SOM and NPY (Neuropeptide Y). The results of the immunofluorescence experiment showed that all of the markers were reduced, resulting in angiogenic behaviours in mice. The concentration of GAD67, an enzyme involved for the generation of GABA, was shown to be lower in the hippocampus of epileptic mice.[23]

4. EPILEPSY INDUCED PSYCHOSIS

The psychotic condition is a common or serious comorbidity in epilepsy patients. The interrelationship between these two diseases has piqued the interest of not just scientists and clinicians, but also artists and novelists. Epidemiological research provided a reliable estimate of the prevalence of psychotic disorders in epilepsy patients. Meta-analysis or systemic studies revealed that approximately 2-7 percent of epileptic patients suffer with psychosis. While gender has no bearing on the disease, age does, and it is more common in persons with long-term epilepsy. On the other hand, research have revealed that the presence of psychotic condition differs across epilepsies. When opposed to a generalised form of epilepsy, temporal lobe epilepsy (60%) or extratemporal epilepsy (54%) have a higher incidence of psychotic condition, resulting in a distinct pathophysiology. Uncontrolled seizures, neurodevelopmental problems, a history of status epilepticus, and a history of psychotic disorders are all associated with an increased risk of psychotic disorders.[41,42] The most devastating forms of psychosis are preictal and postictal psychosis. Interictal psychosis is a type of psychosis that develops outside of the context of epilepsy. Many times, likely psychosis is overlooked by physicians in epileptic patients, and many times, cohort studies are excluded owing to a lack of knowledge of the symptoms. Electronic health data and patient history, on the other hand, have become a viable alternative in cohort studies.[43]

4.1 CLASSIFICATION OF PSYCHOTIC DISORDER IN EPILEPSY

Psychotic disorders in epilepsy are characterised as ictal, postictal, or interictal based on the timing of symptomatic manifestation following the onset of seizures. After a seizure, interictal psychosis develops in the

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

absence of distinct consciousness. It happens in people with epilepsy who are 14-15 years old, and the cause could be the use of an AED, as well as anatomical and functional changes in the brain as a result of seizure genesis in epilepsy. In epilepsy, it is the most well-known psychotic condition.[44] Within a week of having seizures or a series of seizures, postictal psychosis develops. Hallucinations, delusions, and confusion have been observed, but awareness and orientation are preserved. These psychotic episodes may last a few days or weeks and eventually fade away on their own. PPI affects 10% of the population, primarily those with pharmacoresistant epilepsy (TLE).[45]

4.2 PATHOLOGY OF PSYCHOTIC DISORDER INDUCTION IN EPILEPSY

Neuroanatomical studies-Role of neurotransmitters

The pathogenic cause of psychosis is studied via dopamine circuitry, which is well-known. TLE patients exhibit hallucinations and delusions, according to clinical investigations. Indeed, parvalbumin interneuron loss, as well as hyper responsibility of the mesolimbic dopamine (DA) System, could be a contributing factor. In mesial TLE, Dopamine binding affinity to D2/D3 receptors in the striatum is diminished, resulting in cortical hyper-excitability, whilst D2 receptors work antiepileptically and D1 receptors operate stringently in lowering the seizures threshold. As a result, low dopamine levels in the prefrontal cortex cause pinning in epilepsy and psychotic diseases.[41,45,46] In psychotic illness patients with epilepsy, altered dopamine levels are the most commonly utilised models in the research of schizophrenia, resulting in decreased hippocampal volume when compared to epilepsy controls. A sample from patients with POE (psychosis of epilepsy) showed a decrease in tail, body volume, but not in the head of the hippocampus.[47] Second, the dominant concept underpinning psychosis is glutaminergic dysfunction. Increased expression of Brain-derived neurotrophic factor (BDNF), GluN2B-containing NMDA receptor, and postsynaptic density proteins 95 (PSD-95) in the CA3 subregion of the post-mortem brain of a patient with schizophrenia, resulting in increased synaptic strength and transmission of glutaminergic transmission molecules. Enhanced levels of BNDF and other proteins were found in hippocampus autopsy, implying increased glutamate signalling as the cause of hyperexcitability.[48] Autoimmunity also plays a significant role in POE for the reasons stated above. Encephalitis caused by synaptic autoantibodies eventually affects NMDA, GABA-B, AMPA, voltage-gated potassium channels (VGKC), and other cellular proteins such as CASPR2 and LG11. 65 percent of persons with NMDAR antibodies had behavioural and psychotic problems, according to the study. These antibody productions are being investigated in the context of NMDA receptor hypofunction in schizophrenia. These also reduce NMDAR expression in the neuronal hippocampus, resulting in an increase in glutamate concentration extracellularly, leading to a rise in glutamate levels (POE). The breakdown of the Blood-Brain Barrier (BBB) caused by seizures, which is caused by receptor failure, ion channel malfunction, and an inflammatory process, causes antibodies from the peripheral to enter the CNS, worsening the condition.[49]

Role of antiepileptic drugs

AED adds to the genesis of psychosis, in addition to the various reasons postulated above as to the origin of psychotic illnesses in epilepsy. There are various disagreements on the role of AED, with some writers claiming that it is related to a specific AED while others claiming that even stopping the first therapy results in the existence of psychotic symptoms in the long run. To investigate the effects of AED, Noguchi et al. conducted a case-control research with 30 patients with psychosis and 212 adult patients with partial epilepsy as the control group. With newer antiepileptic medicines such as zonisamide and phenytoin, polytherapy of AED causes psychosis in 80% of the psychotic group and 46% of the control group.[50] Second-generation antiepileptic medications are more commonly known for their psychotic adverse effects than older antiepileptic medicines. AEDs such as gabapentin, zonisamide, topiramate, tiagabine, lamotrigine, levetiracetam, and gabapentin have a high rate of psychosis. The development of psychosis is unrelated to the AED dose; even a lower dose increases the risk of psychosis.[51]

5. EPILEPSY INDUCED NEUROINFLAMMATION

Seizures are caused by inflammatory processes in the brain, which are triggered by traumatic brain injuries. Due to the hyperexcitability generated by seizures in epilepsy, these activities result in formation and release of numerous inflammatory mediators, mostly from brain resident cells-astrocytes and microglia. Neuroinflammation is a natural process that helps the brain maintain homeostasis, but it may also be maladaptive, causing cellular malfunction in epilepsies, pain, and stress.[32] According to biochemical tests, epileptic patients who have a poor response to AED and are resistant to the medication have multiple inflammatory pathways active. The presence of interleukins-1, Toll-like receptors (TLRs), Tumour Necrosis Factor (TNF-), and Cyclooxygenase-2 (COX-2) in experimental models on animals revealed the presence of inflammatory cascades in epilepsy.[33] These inflammatory mediators have the potential to serve as biomarkers for a variety of epilepsies. Pro-epileptogenic mechanisms are implicated in the development of post-traumatic epilepsy (PTE). Traumatic brain damage is the primary cause of Chemokines, Cytokines, and IL-6 activation, which aggravates the illness and manifests as PTE. The inflammatory cascade was found to play a role in the development of more frequent seizures in animals with pharmacoresistant epilepsy. In neocortical epilepsy,

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

Leah and join in the year 2019 resulted in an increase in the translocator protein 18 kDa (TSPO). These proteins were discovered on overexpressed microglia and reactive astrocytes and were found to be a sign of neuroinflammation. The results of the study showed that 9 out of 11 individuals had an elevated protein level after PET scanning.[34,35]

5.1 AETIOLOGY BEHIND NEUROINFLAMMATION IN EPILEPSY

Role of proinflammatory mediators

Proinflammatory cytokines such as IL-6, IL-1, and TNF-, as well as their receptors, are expressed at a reduced level by brain cells such as astrocytes and microglia in normal conditions. Accordingly, these mediators have a variety of functions: (1) they aid in neuronal development, cell survival, and neurogenesis; (2) they modulate voltage-gated, receptor-coupled ion channels as well as neurotransmitter receptors, which control pruning, transmission, and plasticity in the adult brain. Apart from that, IL-1 is involved in the production of excitatory currents via NMDA-mediated Ca2+ ions or by downregulating the astrocytic glutamate transporter (GLT-1), which increases glutamate and ATP release. Inhibitors of IL-6 and IL-1, such as Ca2+, K+, and Na+, on the other hand, block the current created through them.[36,37]

Role of DAMP, TLR-4, and HMGB1

The alarmin or harmful chemicals generated by dead or necrotic cells are known as danger-associated molecular pattern (DAMP). The nonhistone chromatin confined protein High mobility group box 1 protein (HMGB1) is an excellent example of DAMP. HMGB1 translocation in neurons and glial cells is enhanced during seizure genesis. HMGB1 was shown to play a role in seizures, as evidenced by the fact that intra-cerebrovascular injection of mice increased seizure generation and severity.[38] Toll-like receptor-4 (TLR4) is a required receptor for HMGB1 binding. Binding of HMGB1 and TLR-4 activates a number of additional signalling pathways, including NF-B activation, which leads to the production of chemokines and cytokines, resulting in neuroinflammation.[39] Quercetin inhibited HMGB1-TLR-4 signalling and the NF-B pathway in experimental animals, effectively controlling seizure production. In a cell model of epilepsy generated by coriaria lactone, Yanbu et al. found that stimulated cells had higher levels of HMGB1 and TLR-4 expression than intractable epileptic brain tissues. HMGB1 suppression may reduce neuroinflammation, resulting in fewer seizures.[40]

6. EPILEPSY INDUCED DEPRESSION

Emotional problems, depression, anxiety, aggressive behaviour, and memory impairment are all prevalent mental symptoms of temporal lobe epilepsy (TLE). Mood is influenced by the presence of explicit emotions, but it is also linked to cognitive mindsets, behavioural predispositions, and autonomic nerve system circumstances. Mood has a significant impact on an individual's ability to adjust to a variety of natural situations. Around 350 million people have been influenced all across the world.[68]Patients with epilepsy are prone to depression. Its prevalence is much higher than in the all-inclusive community, and it can reduce personal happiness and even lead to suicide, which increases epileptics' death rate.[69] At least 33% of patients with dynamic epilepsy suffer from a considerable reduction in enthusiastic well-being. According to Barbara Braszczok et al, depression episodes in epilepsy are the most well-known co morbidity, affecting between 11 and 62 percent of epileptic patients.[68,70]

6.1 PATHOLOGY OF EPILEPSY INDUCED DEPRESSION

Role of AED

Anti-epileptic medications' side effects include fatigue, sleep disturbance, weight gain, and cognitive problems, despite the fact that some anti-epileptic medications have a positive psychotropic profile. Carbamazepine, gabapentin, lacosamide, lamotrigine, pregabalin, and valproate are some of them. Acute depression may be linked to the start of treatment with phenobarbital tiagabine, topiramate, or vigabatrin. Medications such as levetiracetam and zonisamide have been linked to negative psychotropic effects.As a result, it is critical to specify what form of depression is being investigated, and it is estimated in epilepsy. Andersohn et al. published a case control study with 44300 epileptic patients who were given anti-epileptic medicines. The use of topiramate, levetiracetam, vigabatrin, and tiagabine was linked to an increased risk of depression and a threefold rise in the risk of suicidal behaviour, according to this study.[70,71]

Role of neurotransmitter

Several neurotransmitters have been associated to epilepsy and depression, including dopamine, glutamate, nor adrenaline, GABA, acetylcholine, and serotonin. In clinical investigations, many of these neurotransmitters have been associated to epileptic seizures and mental depression.Apart from typical neurotransmitters, there are a variety of additional chemicals and systems to consider. Despite the fact that they've been related to epilepsy or depression on their own, they should be looked at more in the context of comorbidity.

Neuroinflammation

One of the most common comorbidities of temporal lobe epilepsy is depression, which has a significant detrimental impact on TLE patients' quality of life (TLE). Anhedonia, or the inability to feel pleasure, and despair have been found in post-SE animals, as well as disruption of the hypothalamic-hypophyseal-adrenocortic (HPA) axis and serotonergic rape-hippocampal transmission. One aspect that may contribute to

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

depression in TLE patients is hippocampal tissue inflammation, particularly elevated interleukin-1 (IL-1) signalling.Activation of hippocampal IL-1 and its receptor (IL-1R) has been connected to epileptogenesis pathways, and has been recognised as a characteristic of TLE in both clinical and experimental contexts.[72,73] Both clinical and experimental research have shown that IL-1 and other inflammatory cytokines can disrupt the HPA axis and produce depression.[74,75] In particular, the disruption of the HPA axis (a neuroendocrine characteristic of depression).[76] Epilepsy-induced depression may result from direct activation of hippocampus IL-1 signalling.[77]

Neurotrophins

Neurotrophins, particularly brain-derived neurotrophic factor (BDNF) and its receptor, TrkB, are thought to play a role in depression and epilepsy, as well as medium therapeutic effectiveness. In fact, persons with epilepsy.[78] and depression have lower levels of BDNF, which can be corrected with antidepressant medication.[79] TrkB and BDNF are also involved in epilepsy and depression models. After animal testing, hippocampus BDNF over-expressions, for example, reduced the severity of spontaneous seizures, demonstrating that BDNF signals were beneficial in anticonvulsants.[80] Mice expressing the negative regulator form of TrkB showed delayed spontaneous seizures and a pro-convulsant effect of TrkB signalling, whereas mice expressing the positive regulator form of TrkB showed delayed spontaneous seizures and a pro-convulsant effect of TrkB signalling. BDNF and TrkB were also tested in rodent depression models. Exercise that is antidepressant or anticonvulsant enhances BDNF expression.[81]

7. EPILEPSY INDUCED AUTISM

Epilepsy and autism are two frequent neurodevelopmental disorders that are linked. Despite the fact that it is a well-studied topic, effective treatment for comorbid conditions is still missing. The prevalence of autism in epilepsy ranges from 2.7 percent to 46.4 percent, which is significantly greater than any other comorbidity. In addition to intellectual handicap, lower socioeconomic position, female sex, adult age, and a family history of autism may all play a role.[52] Both epilepsy and ASD are complex illnesses that are associated to a variety of neurodevelopmental issues such as learning and behaviour, anxiety, depression, and cerebral palsy. Treatment for epilepsy is no longer solely focused on reducing seizure frequency, but also includes cognitive, neurologic, and psychosocial modifications.[53] Both epilepsy and ASD have a considerable influence on patients' quality of life, particularly in youngsters, which adds stress and hardship to families.[54]

7.1 PATHOLOGICAL CAUSE: EPILEPSY-AUTISM

Epilepsy mimics the symptoms of AUS, resulting in the discovery of a shared underlying cause for both. Epilepsy and autism may both be caused by a genetic mutation that alters synaptic functioning and brain development. Genetic, environmental, immunological, and metabolic variables may cause neurodevelopmental abnormalities that affect the structure and function of the brain, resulting in excitatory/inhibitory circuit imbalance and hyperexcitability.[55]

GABAergic dysfunction-Excitation/inhibition imbalance

A post-mortem of human brain tissues revealed a reduced amount of glutamate decarboxylase, number of GABAergic neurons, ligands binding to GABAA receptors, and lowered GABA levels in patients with autism and epilepsy, implying a comparable pathophysiology. In both ASD and epilepsy patients, brain imaging such as MRI revealed lower grey/white matter volumes.[55,56]

Role of genetics

Understanding the genetic condition involved is one of the most researched approaches to determine the exact relationship between epilepsy and ASD. Previous research has found that the gene connected to ASD and behavioural problems is also linked to the origin of epilepsy. These researches are mostly concerned with shared pathways or processes, protein-protein interactions, co-expression, and another network that links epilepsy and ASD. Tuberous sclerosis is a rare genetic condition that has been linked to autism spectrum disorder (ASD) and epilepsy. Intractable epilepsy, cognitive impairments, infantile spasm, and learning disabilities are some of the neurodevelopmental impacts of TSC. The majority of those affected have mutations in the Tsc1 and Tsc2 genes, which induce accelerated cell proliferation and tumour formation. Early onset seizures linked to TSC are mostly linked to ASD generation. A retrospective research found that 40 percent of 103 individuals had ASD and had frequent seizures.[57,58,59]

8. PHYTOMEDICINE IN THE MANAGEMENT OF EPILEPSY AND INDUCED COMORBIDITIES

Treatment of neurological disorders is crucial from the standpoint of entire body system control, including neurotransmitter and hormone secretion. Due to its severe side effects, comorbidities, and drug resistance difficulties, AED is not often the ideal treatment for epilepsy.[60] People increasingly employ herbal medications as a primary treatment method for many ailments since they are less expensive and have less adverse effects. Herbal medications were traditionally used mostly in China, Europe, Iran, and America. Among other countries, Chinese herbal medicine treatment for epilepsy are the most prevalent.[61] As a result, due to the existence of

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

drug-like qualities and fewer side effects, a variety of medicinal plants with important phytoconstituents are utilised in the treatment of epilepsy. Alkaloids, Glycosides, Polyphenols (Flavonoids, Tannins, Phenolics), Saponins, and Terpenoids are among the secondary metabolites found in the plant. These phytochemicals are in charge of protecting plants from microbial illness and pest infestation. They are also known as phytomedicinal because they exhibit therapeutic efficacy and drug-like qualities. Medicinal plants and their usefulness in epilepsy and comorbidities, as well as the phytoconstituents that are mostly responsible, are discussed in (Table-1).[62]

Uses of flavonoids in Epilepsy

Flavonoids have shown significant effects in many experimental models for neurological illnesses such as Alzheimer's, Parkinson's, ischemic strokes, and epilepsy. Modulation of the -aminobutyric acid (GABA) receptor, mitochondrial dysfunctions, and management of anti-inflammatory and antioxidant levels through modifying GSH (glutathione), MDA (malondialdehyde), and cytokines are all part of the system. Preclinical investigations have revealed antiepileptic benefits that have yet to be confirmed in clinical trials. Flavonoids such as quercetin, apigenin, and naringenin penetrate the Blood-Brain Barrier, allowing them to act as antioxidants and anti-inflammatory agents in a variety of CNS illnesses.[63] The pharmacological action of quercetin is mediated by its accumulation in rat brain tissues; 50 mg/kg of quercetin reduced oxidative stress in rats caused by the chronic forced swim method.[64] Seizures reduce the brain's powerful antioxidant potential, causing an increase in free radical production and oxidative stress, as well as cellular protein damage. Flavonoids, according to researchers, have a structure that is similar to that of benzodiazepines, and hence may have similar effects.[65] Naringenin and kaempferol both had effects on drug-resistant animals with focal epilepsy.[66] Naringenin was more susceptible and had greater effects. Inhibition of p-glycoprotein-mediated AED efflux or reversal of its interference was done in combination with flavonoids such as -epigallocatechin gallate, kaempferol, quercetin, and silymarin. This dual combination of flavonoids showed a good result, increasing its potential in drug-resistant epilepsy therapy.[67]

CONCLUSION

Epilepsy is a comorbid disorder that affects the medical, cognitive, and psychiatric functioning areas of the brain, posing significant diagnostic and treatment challenges. Psychological comorbidities are more common in epileptic patients than in the general population. Anxiety, depression, cognitive deficits, psychosis, autism, and neuroinflammation are examples of co-morbidities that have a same aetiology and so co-occur. Future study should focus on the structural and functional mechanisms involved in the comorbid state of neuronal circuits in the limbic brain, as well as receptors, ion channels, genetics, and neurotransmitters, which revolutionise our understanding of epilepsy. Understanding the basis of epilepsy and comorbidities is thus an essential step in epilepsy treatment and diagnosis. In the end, medical treatment and care decisions affect one's quality of life. Psychiatric comorbidity appears to be the rule rather than the exception for people with epilepsy, and as a result, comprehensive care necessitates a focus on mental health.

CONFLICT OF INTEREST

Authors have none to declare.

ACKNOWLEDGMENT

We would like to acknowledge the Sri Guru Ram Rai University School of Pharmaceutical Sciences Dehradun, Uttarakhand for providing the infrastructure and support.

REFERENCES

1. Shi Y, Zhang L, Teng J, Miao W. HMGB1 mediates microglia activation via the TLR4/NF-κB pathway in coriaria lactone induced epilepsy. Molecular medicine reports. 2018 Apr 1;17(4):5125-31.
2. Raut D, Bhatt LK. Evolving targets for anti-epileptic drug discovery. European Journal of Pharmacology. 2020 Sep 18:173582.
3. Yin YH, Ahmad N, Makmor-Bakry M. Pathogenesis of epilepsy: challenges in animal models. Iranian journal of basic medical sciences. 2013 Nov;16(11):1119.
4. Garg K. Prevalence of Major Mental and Neurological Disorders in India. Neurology India. 2021 Mar 1;69(2):302.
5. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel Jr J, Forsgren L, French JA, Glynn M, Hesdorffer DC. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

6. Varnado S, Price D. Basics of modern epilepsy classification and terminology. Current Problems in Pediatric and Adolescent Health Care. 2020 Nov 3:100891.

7. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, Tomson T, Hauser WA. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010 Apr;51(4):671-5.

8. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-21.

9. Anwar H, Khan QU, Nadeem N, Pervaiz I, Ali M, Cheema FF. Epileptic seizures. Discoveries. 2020 Apr;8(2).

10. Pitkänen A, Ndode-Ekane XE, Lapinlampi N, Puhakka N. Epilepsy biomarkers–Toward etiology and pathology specificity. Neurobiology of disease. 2019 Mar 1;123:42-58.

11. Ma MG, Liu XR, Wu Y, Wang J, Li BM, Shi YW, Su T, Li B, Liu DT, Yi YH, Liao WP. RYR2 mutations are associated with benign epilepsy of childhood with centrotemporal spikes with or without arrhythmia. Frontiers in Neuroscience. 2021 Apr 7;15:244..

12. Carvill GL, McMahon JM, Schneider A, Zemel M, Myers CT, Saykally J, Nguyen J, Robbiano A, Zara F, Specchio N, Mecarelli O. Mutations in the GABA transporter SLC6A1 cause epilepsy with myoclonic-atonic seizures. The American Journal of Human Genetics. 2015 May 7;96(5):808-15.

13. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. The Lancet. 2019 Feb 16;393(10172):689-701.

14. Niriayo YL, Mamo A, Kassa TD, Asgedom SW, Atey TM, Gidey K, Demoz GT, Ibrahim S. Treatment outcome and associated factors among patients with epilepsy. Scientific reports. 2018 Nov 26;8(1):1-9.

15. Seidenberg M, Pulsipher DT, Hermann B. Association of epilepsy and comorbid conditions. Future neurology. 2009 Sep;4(5):663-8.

16. Bragatti JA, Torres CM, Isolan GR, Bianchin MM. Psychiatric comorbidities of epilepsy: a review. J Neurol Neurophysiol. 2011;2:10-20.

17. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-21.

18. Pham T, Sauro KM, Patten SB, Wiebe S, Fiest KM, Bulloch AG, Jetté N. The prevalence of anxiety and associated factors in persons with epilepsy. Epilepsia. 2017 Aug;58(8):e107-10.

19. Wang Z, Luo Z, Li S. Anxiety screening tools in people with epilepsy: a systematic review of validated tools. Epilepsy & Behavior. 2019 Oct 1;99:106392.

20. Mula M. Pharmacological treatment of anxiety disorders in adults with epilepsy. Expert opinion on pharmacotherapy. 2018 Nov 22;19(17):1867-74.

21. Paudel YN, Lisgaras CP, Lim KS, Shaikh MF. Epilepsy and Comorbidities: Towards unraveling the common underlying mechanisms. Neuroscience Research Notes. 2018 Oct 14;1(3):1-4.

22. Kimiskidis VK, Valeta T. Epilepsy and anxiety: epidemiology, classification, aetiology, and treatment. Epileptic disorders. 2012 Sep;14(3):248-56.

23. Zhu X, Yao Y, Li X, Dong J, Zhang A. Alteration of GABAergic signaling is associated with anxiety-like behavior in temporal lobe epilepsy mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2019 Jul 13;93:141-8.

24. Jackson-Tarlton CS, Whatley BP, Kasheke GD, Pohlmann-Eden B, Omisade A. A prospective pilot study of cognitive impairment and mood in adults with first seizure, new-onset epilepsy, and newly diagnosed epilepsy at time of initial seizure presentation. Epilepsy & Behavior. 2020 Nov 1;112:107359.

25. Pohlmann-Eden B, Aldenkamp A, Baker GA, Brandt C, Cendes F, Coras R, Crocker CE, Helmstaedter C, Jones-Gotman M, Kanner AM, Mazarati A. The relevance of neuropsychiatric symptoms and cognitive problems in new-onset epilepsy—current knowledge and understanding. Epilepsy & Behavior. 2015 Oct 1;51:199-209.

26. Beghi, Ettore, Massimiliano Beghi. Epilepsy, antiepileptic drugs and dementia.Current opinion in neurology vol. 33,2 (2020): 191-197.

27. Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. Nature Reviews Neurology. 2016 Aug;12(8):465.

28. Kim EH, Ko TS. Cognitive impairment in childhood onset epilepsy: up-to-date information about its causes. Korean journal of pediatrics. 2016 Apr;59(4):155.

29. Masala N, Pofahl M, Haubrich AN, Nikbakht N, Bohmbach K, Henneberger C, Golcuk K, Kelly T, Beck H. Targeting aberrant dendritic integration to treat cognitive comorbidities of epilepsy. bioRxiv. 2020 Jan 1.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

30. Barr WB. Understanding the cognitive side effects of antiepileptic drugs: can functional imaging be helpful?. Epilepsy currents. 2019 Jan;19(1):22-3.

31. Helmstaedter C, Witt JA. Anticonvulsant drugs and cognition. NeuroPsychopharmacotherapy. 2020:1-2.

32. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nature Reviews Neurology. 2019 Aug;15(8):459-72.

33. Mahfoz AM, Shahzad N. Neuroinflammation impact in epileptogenesis and new treatment strategy. Behavioural pharmacology. 2019 Dec 1;30(8):660-74.

34. Dickstein LP, Liow JS, Austermuehle A, Zoghbi S, Inati SK, Zaghloul K, Zanotti-Fregonara P, Theodore WH. Neuroinflammation in neocortical epilepsy measured by PET imaging of translocator protein. Epilepsia. 2019 Jun;60(6):1248-54.

35. Mukherjee S, Arisi GM, Mims K, Hollingsworth G, O'Neil K, Shapiro LA. Neuroinflammatory mechanisms of post-traumatic epilepsy. Journal of neuroinflammation. 2020 Dec;17(1):1-1.

36. Vezzani A, Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. Neuropharmacology. 2015 Sep 1;96:70-82.

37. Leal B, Chaves J, Carvalho C, Rangel R, Santos A, Bettencourt A, Lopes J, Ramalheira J, Silva BM, da Silva AM, Costa PP. Brain expression of inflammatory mediators in mesial temporal lobe epilepsy patients. Journal of neuroimmunology. 2017 Dec 15;313:82-8.

38. Ravizza T, Terrone G, Salamone A, Frigerio F, Balosso S, Antoine DJ, Vezzani A. High mobility group box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy. Brain, behavior, and immunity. 2018 Aug 1;72:14-21.

39. Andersson U, Yang H, Harris H. High-mobility group box 1 protein (HMGB1) operates as an alarmin outside as well as inside cells. InSeminars in immunology 2018 Aug 1 (Vol. 38, pp. 40-48). Academic Press.

40. Shi Y, Zhang L, Teng J, Miao W. HMGB1 mediates microglia activation via the TLR4/NF-κB pathway in coriaria lactone induced epilepsy. Molecular medicine reports. 2018 Apr 1;17(4):5125-31

41. Maguire M, Singh J, Marson A. Epilepsy and psychosis: a practical approach. Practical neurology. 2018 Apr 1;18(2):106-14.

42. Agrawal N, Mula M. Treatment of psychoses in patients with epilepsy: an update. Therapeutic advances in psychopharmacology. 2019 Jul;9:2045125319862968.

43. Josephson CB, Jetté N. Psychiatric comorbidities in epilepsy. International review of psychiatry. 2017 Sep 3;29(5):409-24.

44. Adachi N, Akanuma N, Fenwick P, Ito M, Okazaki M, Ishida S, Sekimoto M, Kato M, Onuma T. Seizure activity and individual vulnerability on first-episode interictal psychosis in epilepsy. Epilepsy & Behavior. 2018 Feb 1;79:234-8.

45. Kanner AM, Scharfman H, Jette N, Anagnostou E, Bernard C, Camfield C, Camfield P, Legg K, Dinstein I, Giacobbe P, Friedman A. Epilepsy as a network disorder (1): what can we learn from other network disorders such as autistic spectrum disorder and mood disorders?. Epilepsy & Behavior. 2017 Dec 1;77:106-13.

46. Butler T, Weisholtz D, Isenberg N, Harding E, Epstein J, Stern E, Silbersweig D. Neuroimaging of frontal–limbic dysfunction in schizophrenia and epilepsy-related psychosis: toward a convergent neurobiology. Epilepsy & Behavior. 2012 Feb 1;23(2):113-22.

47. Allebone J, Kanaan R, Maller J, O'Brien T, Mullen SA, Cook M, Adams SJ, Vogrin S, Vaughan DN, Connelly A, Kwan P. Bilateral volume reduction in posterior hippocampus in psychosis of epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2019 Jun 1;90(6):688-94.

48. Nakahara S, Adachi M, Ito H, Matsumoto M, Tajinda K, van Erp TG. Hippocampal pathophysiology: commonality shared by temporal lobe epilepsy and psychiatric disorders. Neuroscience journal. 2018;2018.

49. Pollak TA, Nicholson TR, Mellers JD, Vincent A, David AS. Epilepsy-related psychosis: a role for autoimmunity?. Epilepsy & Behavior. 2014 Jul 1;36:33-8.

50. Noguchi T, Fukatsu N, Kato H, Oshima T, Kanemoto K. Impact of antiepileptic drugs on genesis of psychosis. Epilepsy & Behavior. 2012 Apr 1;23(4):462-5.

51. Adachi N, Fenwick P, Akanuma N, Hara K, Ishii R, Okazaki M, Ito M, Sekimoto M, Kato M, Onuma T. Increased frequency of psychosis after second-generation antiepileptic drug administration in adults with focal epilepsy. Epilepsy & Behavior. 2019 Aug 1;97:138-43.

52. Strasser L, Downes M, Kung J, Cross JH, De Haan M. Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis. Developmental Medicine & Child Neurology. 2018 Jan;60(1):19-29.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

53. Tuchman R. What is the relationship between autism spectrum disorders and epilepsy?. InSeminars in pediatric neurology 2017 Nov 1 (Vol. 24, No. 4, pp. 292-300). WB Saunders.

54. Milovanovic M, Radivojevic V, Radosavljev-Kircanski J, Grujicic R, Toskovic O, Aleksić-Hil O, Pejovic-Milovancevic M. Epilepsy and interictal epileptiform activity in patients with autism spectrum disorders. Epilepsy & Behavior. 2019 Mar 1;92:45-52.

55. Bozzi Y, Provenzano G, Casarosa S. Neurobiological bases of autism–epilepsy comorbidity: a focus on excitation/inhibition imbalance. European Journal of Neuroscience. 2018 Mar;47(6):534-48.

56. Sierra-Arregui T, Llorente J, Minguez PG, Tønnesen J, Peñagarikano O. Neurobiological Mechanisms of Autism Spectrum Disorder and Epilepsy, Insights from Animal Models. Neuroscience. 2020 Oct 1;445:69-82.

57. Buckley AW, Holmes GL. Epilepsy and autism. Cold Spring Harbor perspectives in medicine. 2016 Apr 1;6(4):a022749.

58. Peng J, Zhou Y, Wang K. Multiplex gene and phenotype network to characterize shared genetic pathways of epilepsy and autism. Scientific reports. 2021 Jan 13;11(1):1-6.

59. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. The Lancet Neurology. 2015 Jul 1;14(7):733-45.

60. Kaur I, Sharma S, Bhardwaj K. Wonders of Phytomedicine in the management of neurological disorders. European Journal of Molecular & Clinical Medicine. 2020 Dec 23;7(7):2899-914.

61. Liu W, Ge T, Pan Z, Leng Y, Lv J, Li B. The effects of herbal medicine on epilepsy. Oncotarget. 2017 Jul 18;8(29):48385.

62. Shakya AK. Medicinal plants: Future source of new drugs. International Journal of Herbal Medicine. 2016;4(4):59-64.

63. Kwon JY, Jeon MT, Jung UJ, Kim DW, Moon GJ, Kim SR. Perspective: therapeutic potential of flavonoids as alternative medicines in epilepsy. Advances in Nutrition. 2019 Sep 1;10(5):778-90.

64. Ishisaka A, Ichikawa S, Sakakibara H, Piskula MK, Nakamura T, Kato Y, Ito M, Miyamoto KI, Tsuji A, Kawai Y, Terao J. Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats. Free Radical Biology and Medicine. 2011 Oct 1;51(7):1329-36.

65. Diniz TC, Silva JC, Lima-Saraiva SR, Ribeiro FP, Pacheco AG, de Freitas RM, Quintans-Júnior LJ, Quintans JD, Mendes RL, Almeida JR. The role of flavonoids on oxidative stress in epilepsy. Oxidative medicine and cellular longevity. 2015 Oct;2015.

66. Copmans D, Orellana-Paucar AM, Steurs G, Zhang Y, Ny A, Foubert K, Exarchou V, Siekierska A, Kim Y, De Borggraeve W, Dehaen W. Methylated flavonoids as anti-seizure agents: Naringenin 4′, 7-dimethyl ether attenuates epileptic seizures in zebrafish and mouse models. Neurochemistry international. 2018 Jan 1;112:124-33.

67. Ferreira A, Santos AO, Falcão A, Alves G. In vitro screening of dual flavonoid combinations for reversing P-glycoprotein-mediated multidrug resistance: Focus on antiepileptic drugs. Food and Chemical Toxicology. 2018 Jan 1;111:84-93.

68. Elger CE, Johnston SA, Hoppe C. Diagnosing and treating depression in epilepsy. Seizure. 2017 Jan 1;44:184-93.

69. Tao K, Wang X. The comorbidity of epilepsy and depression: diagnosis and treatment. Expert review of neurotherapeutics. 2016 Nov 1;16(11):1321-33.

70. Błaszczyk B, Czuczwar SJ. Epilepsy coexisting with depression. Pharmacological Reports. 2016 Sep;68(5):1084-92.

71. Rider FK, Danilenko OA, Grishkina MN, Kustov GV, Akzhigitov RG, Lebedeva AV, Gekht AB. Depression and epilepsy: Comorbidity, pathogenetic similarity, and principles of treatment. Neuroscience and Behavioral Physiology. 2018 Jan;48(1):78-82.

72. Bartfai T, Sanchez-Alavez M, Andell-Jonsson SI, Schultzberg M, Vezzani A, Danielsson E, Conti B. Interleukin-1 system in CNS stress: seizures, fever, and neurotrauma. ANNALS-NEW YORK ACADEMY OF SCIENCES. 2007 Oct;1113:173.

73. Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, Ravizza T, Perego C, De Simoni MG. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. Epilepsia. 2002 Jun;43:30-5.

74. Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. Brain, behavior, and immunity. 2003 Feb 15;17(1):119-24.

75. Leonard BE. HPA and immune axes in stress: involvement of the serotonergic system. Neuroimmunomodulation. 2006;13(5-6):268-76.

76. Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. Ageing research reviews. 2005 May 1;4(2):141-94.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

77. Parsadaniantz SM, Dauge V, Roques BP, Kerdelhue B. Acute intrahippocampal injection of human interleukin-1β stimulates the anterior pituitary POMC transcription and increases plasma levels of ACTH and corticosterone in the male rat. Neuroendocrinology. 1999;69(2):77-87.

78. Binder DK, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing?. Trends in neurosciences. 2001 Jan 1;24(1):47-53.

79. Borges G, Degeneve A, Mullen W, Crozier A. Identification of flavonoid and phenolic antioxidants in black currants, blueberries, raspberries, red currants, and cranberries. Journal of agricultural and food chemistry. 2010 Apr 14;58(7):3901-9.

80. Paradiso B, Zucchini S, Su T, Bovolenta R, Berto E, Marconi P, Marzola A, Mora GN, Fabene PF, Simonato M. Localized overexpression of FGF-2 and BDNF in hippocampus reduces mossy fiber sprouting and spontaneous seizures up to 4 weeks after pilocarpine-induced status epilepticus. Epilepsia. 2011 Mar;52(3):572-8.

81. Li N, He X, Zhang Y, Qi X, Li H, Zhu X, He S. Brain-derived neurotrophic factor signalling mediates antidepressant effects of lamotrigine. International Journal of Neuropsychopharmacology. 2011 Sep 1;14(8):1091-8.

82. Kumar R, Arora R, Agarwal A, Gupta YK. Protective effect of Terminalia chebula against seizures, seizure-induced cognitive impairment and oxidative stress in experimental models of seizures in rats. Journal of ethnopharmacology. 2018 Apr 6;215:124-31.

83. Mishra P, Mittal AK, Rajput SK, Sinha JK. Cognition and memory impairment attenuation via reduction of oxidative stress in acute and chronic mice models of epilepsy using antiepileptogenic Nux vomica. Journal of Ethnopharmacology. 2021 Mar 1;267:113509.

84. Mehla J, Reeta KH, Gupta P, Gupta YK. Protective effect of curcumin against seizures and cognitive impairment in a pentylenetetrazole-kindled epileptic rat model. Life sciences. 2010 Nov 20;87(19-22):596-603.

85. Pahwa P, Goel RK. Ameliorative effect of Asparagus racemosus root extract against pentylenetetrazol-induced kindling and associated depression and memory deficit. Epilepsy & Behavior. 2016 Apr 1;57:196-201.

86. Ngoupaye GT, Bum EN, Daniels WM. Antidepressant-like effects of the aqueous macerate of the bulb of Gladiolus dalenii Van Geel (Iridaceae) in a rat model of epilepsy-associated depression. BMC complementary and alternative medicine. 2013 Dec;13(1):1-8.

87. Taiwe GS, Tchoya TB, Menanga JR, Dabole B, De Waard M. Anticonvulsant activity of an active fraction extracted from Crinum jagus L.(Amaryllidaceae), and its possible effects on fully kindled seizures, depression-like behaviour and oxidative stress in experimental rodent models. Journal of ethnopharmacology. 2016 Dec 24;194:421-33.

88. Moto FC, Arsa'a A, Ngoupaye GT, Taiwe GS, Njapdounke JS, Kandeda AK, Nkantchoua GC, Omam Omam JP, Pale S, Kouemou NE, Ayissi Mbomo ER. Anxiolytic and antiepileptic properties of the aqueous extract of Cissus quadrangularis (Vitaceae) in mice pilocarpine model of epilepsy. Frontiers in pharmacology. 2018 Jul 17;9:751.

89. Naderi N, Akhavan N, Ahari FA, Zamani N, Kamalinejad M, Shokrzadeh M, Ahangar N, Motamedi F. Effects of hydroalcoholic extract from Salvia verticillata on pharmacological models of seizure, anxiety and depression in mice. Iranian journal of pharmaceutical research: IJPR. 2011;10(3):535.

90. Addae JI, Pingal R, Walkins K, Cruickshank R, Youssef FF, Nayak SB. Effects of Jasminum multiflorum leaf extract on rodent models of epilepsy, motor coordination and anxiety. Epilepsy research. 2017 Mar 1;131:58-63.

91. Potraj B, Ahamed SM, Narasimha S, Suhas DS, Vijayakumar S. Deciphering the role of Bixin isolated from Bixa orellana L., in epileptic and psychotic experimental models in rod en ts. Manipal Journal of Pharmaceutical Sciences. 2019;4(2):15-22.

92. Nandal, N., & Nandal, N. (2019). BSCQUAL: A Measuring Instrument of Service Quality for the B-Schools . International Journal of Psychosocial Rehabilitation, Vol. 23, Issue 04, 1574-1589

93. Gupta G, Kazmi I, Afzal M, Rahman M, Saleem S, Ashraf MS, Khusroo MJ, Nazeer K, Ahmed S, Mujeeb M, Ahmed Z. Sedative, antiepileptic and antipsychotic effects of Viscum album L.(Loranthaceae) in mice and rats. Journal of ethnopharmacology. 2012 Jun 14;141(3):810-6.

94. Chitra KK, Babitha S, Durg S, Thippeswamy BS, Veerapur VP, Badami S. Anti-epileptic and anti-psychotic effects of Ipomoea reniformis (Convolvulaceae) in experimental animals. Journal of Natural Remedies. 2014 Jul 1;14(2):153-63.

95. Sandhya T, Sowjanya J, Veeresh B. Bacopa monniera (L.) Wettst ameliorates behavioral alterations and oxidative markers in sodium valproate induced autism in rats. Neurochemical research. 2012 May;37(5):1121-31.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

96. Kim P, Park JH, Kwon KJ, Kim KC, Kim HJ, Lee JM, Kim HY, Han SH, Shin CY. Effects of Korean red ginseng extracts on neural tube defects and impairment of social interaction induced by prenatal exposure to valproic acid. Food and chemical toxicology. 2013 Jan 1;51:288-96.

97. Golechha M, Bhatia J, Ojha S, Arya DS. Hydroalcoholic extract of Emblica officinalis protects against kainic acid-induced status epilepticus in rats: evidence for an antioxidant, anti-inflammatory, and neuroprotective intervention. Pharmaceutical biology. 2011 Nov 1;49(11):1128-36.

98. Golechha M, Sarangal V, Bhatia J, Chaudhry U, Saluja D, Arya DS. Naringin ameliorates pentylenetetrazol-induced seizures and associated oxidative stress, inflammation, and cognitive impairment in rats: possible mechanisms of neuroprotection. Epilepsy & Behavior. 2014 Dec 1;41:98-102.\

99. Drion CM, van Scheppingen J, Arena A, Geijtenbeek KW, Kooijman L, van Vliet EA, Aronica E, Gorter JA. Effects of rapamycin and curcumin on inflammation and oxidative stress in vitro and in vivo—in search of potential anti-epileptogenic strategies for temporal lobe epilepsy. Journal of neuroinflammation. 2018 Dec;15(1):1-1.

Table 1: Epilepsy and induced comorbidities treatment through various plant and their phytoconstituents in experimental models of epilepsy.

COMORBIDITY	INDUCER/MODEL	PLANT/PHYTOCONSTITUENT	COMMENT	REFERNCES
EPILEPSY INDUCED COGNITIVE IMPAIRMENT	PTZ induced seizures, MES induced seizures in rats. **Behavioural assessment**: Elevated plus maze, Passive avoidance test and open field test	*Terminaliachebula*- Chebulic acid, Chebulagic acid. *Nux vomica*-Brucine, Strychnine *Curcuma longa*- curcumin, quercetin.	Reduces seizure and seizure induced cognitive impairement.	82,83,84
EPILEPSY INDUCED DEPRESSION	PTZ induced seizures test. **Behavioural assessment:** Passive shock avoidance paradigm, Tail suspension test. Pilocarpine induced seizures **Behavioural assessment:** Forced swim test, Open field test.	*Asparagus racemosus* – rutin, kaempferol and quercetin. *Gladiolus dalenii* – Kaempferol, apigenin *Crinum jagus* - Kaempferol	Reduced seizures and induced depression in mice and Wistar rats.	85,86,87
EPILEPSY INDUCED ANXIETY	PTZ induced seizures. MES induced seizures **Behavioural assessment:** Elevated plus maze test, Open field test, and Light dark test and Rota rod treadmill.	*Cissus quadrangularis* -kaempferol, quercetin. *Salvia verticillate*: β-carotene, linolic acid. *Jasminum multiflorum*-Quercetin-3-O-rutinoside, kaempferol	Reduced seizures, anxiety and altered behavioural parameters of anxiety	88,89,90
EPILEPSY INDUCED PSYCHOSIS	PTZ induces seizures test, MES induced seizures test Ionized induced seizures. **Behavioural assessment:** Apomorphine-induced stereotyped, Apomorphine-induced climbing.	*Bixa Orellana*- Bixin *Viscum album*- naringenin, quercetin *Ipomoea reniformis* – Caffeic,p-coumaric and ferulic acid	Reduces seizures and psychotic behaviour in rats and mice	91,92,93
EPILEPSY INDUCED AUTISM	Valproic acid induced test. **Behaviour assessment:** Elevated plus maze test, Social Behaviour in Adolescent Period, Social Behaviour in Adulthood Period, Locomotor activity, and Open-field locomotor activity.	*Bacopa monnieri* – Quercetin *Korean red ginseng*	Reduced behavioural parameters of autism and induced seizure.	94,95
EPILEPSY INDUCED NEUROINFLAMMATION	KA induced Status epilepticus. PTZ induced seizures test. Brain analysis by ELISA SE induction with intracranial electrodes. In Vitro- astrocytes cell culture	*Emblica officinalis* –quercetin, kaempferol, emblicanin *Naringin* *Curcumin*	Reduced seizures and decreased level of interleukins-6 and TNF-α in rats.	96,97,98