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Herbal Remedies and Innovative Therapies for the Management of Epilepsy
Short Running Title: "Herbal and Innovative Therapies for Epilepsy"

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ABSTRACTS

Epilepsy is one of the most widespread non-communicable neurological conditions, impacting individuals throughout all age ranges. There are roughly 50 million epileptics worldwide, with 80 percent of instances occurring in poorer nations owing to an inability to obtain therapies due to their high cost and scarcity. Alternatively, the term may be employed to characterize the percentage of individuals with active epilepsy who do not receive appropriate medical care. Synthetic epilepsy medications are costly, take a long time to show symptoms, are prone to drug combinations, and may have serious side effects. Numerous synthetic medications are like Diazepam, Valproate, Phenytoin (PHT), and other medications are used to treat epilepsy. These medications feature newer side effects in addition to a wider range of efficacy.Currently, patients in industrialized and developing nations are treated with herbal remedies and innovative methods to manage seizures, prevent side effects from antiepileptic medications, or maintain overall health. These include gene therapies, stem cell therapy, Vagus nerve stimulation, Deep brain stimulation, ketogenic diet therapy, Biodegradable nanoparticles, Nasal spray etc. which are some of the innovative treatments for epilepsy that are currently available. Patients are using herbal medicines to control their seizures, reduce the negative effects of antiepileptic drugs, or preserve general health in both developed and developing countries. Because they have less adverse effects, using herbal medications as an adjuvant to treat epilepsy appears to be more useful and is becoming more and more popular.

Keywords: Epilepsy, seizures, antiepileptic drugs, gene therapies, Biodegradable nanotechnology, herbal medication.

I. INTRODUCTION

The primary feature of epilepsy, a persistent condition affecting the central nervous system (CNS), is aberrant electrical activity in the neurons of the hippocampal and cortical regions. Over 50 million individuals worldwide suffer with epilepsy, and the World Health Organization (WHO) reports that over 5 million new cases are diagnosed with the condition each year (1,2). Approximately 50 cases of epilepsy per 100,000 people live in industrialized countries, compared to 139 occurrences per 100,000 in low-income countries(3).

These days, epilepsy is regarded as one of the most dangerous neurological disorders, among the many common and incapacitating neurological diseases (4).According to this definition, epilepsy is a long-term change in the central nervous system that is typified bya disruption in the electrical activity of neurons. This imbalance causes a variety of repeated, unpredictable seizures that, depending on their severity, may result in the death of neurons in specific brain regions (5). Head trauma, brain tumors, strokes, infections such as meningitis or encephalitis, birth abnormalities, and occasionally even changes in blood sugar or sodium levels can also cause epilepsy (6).The brain region from which epileptic seizures originate, individual variability, and additional variables can all influence the frequency and extent of seizures. Falls, drowning, burns, and untreated protracted seizures account for a significant portion of epilepsy-related death causes (7).

The most recent definition of epilepsy, according to the International League Against Epilepsy (ILAE), describes it as a neurological illness marked by any of the following characteristics:

is a neurological disorder marked by any one of the following characteristics:

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- At least two reflexive seizures that happen more than 24 hours apart and are not provoked.
- Having at least one unprovoked (or reflex) seizure with a high probability of subsequent seizures over the next ten years.
- Seizures that match a recognized epilepsy condition. A brief period of signs and/or symptoms brought on by abnormally high or coordinated brain neuronal activity is known as an epileptic seizure (8).

Types of seizures-

There are two primary categories of seizures: focal seizures and generalized seizures (9,10).

1. Generalized Seizures:

These seizures occur across the brain and impact both hemispheres. There are symptoms and anomalies in the EEG on both sides.

- Convulsive Seizures: Grand mal seizures are among the bilateral motor activity seizures that can occur with or without loss of consciousness.

Myoclonic
Tonic-clonic
Tonic
Clonic

- Nonconvulsive Seizures:These typically involve absence or petit mal seizures, which impair awareness but do not involve motor signs.

2. Partial seizures:

They have a unilateral localized origin in the brain, but may spread to small or large area, or to the whole brain. Focal origin may be evident clinically, or may be detected in the EEG.

- Simple partial seizures, often known as "Focal motor" seizures, that are typically unilateral and cause no loss of consciousness.
- Complex partial (typically impaired consciousness; "psychomotor" seizures; psychic symptoms with odd behaviour stereotypes)
- Partial seizures that result in secondary generalization; these can be simple or complex partial seizures (6).

Epilepsy is difficult to classify since many theories exist based on factors such as the focus of the seizures, age at beginning, and coexisting medical conditions. The World Health Organization defined epilepsy as secondary or idiopathic.In Idiopathic epilepsies cause of seizures is not identified but secondary epilepsiesmay be due to brain tumor, brain infections or cranial traumatisms (11). Medical professionals can administer antiepileptic medications (AEDs) based on these classifications, which are customized based on the age and kind of epilepsy of the patient.

Majority of the people diagnosed with epilepsy may experience no seizures with appropriate antiepileptic drugs. Interestingly, 30% of individuals experience seizures that do not go better with medicine. Nearly 90% of epilepsy cases are said to occur in developing nations since there are insufficient antiepileptic treatments on the market, they are expensive, and the side effects of the drugs that are now accessible are unfavourable (12).Researchers are concentrating on herbal medicine and innovative medicines to treat different types of epilepsy because of these characteristics and the therapeutic gap (13). Recent studies on herbal remedies for epilepsy have gained substantial global attention (14). Owing to their wide applicability and numerous pharmacological benefits, herbal therapies, or phytoconstituents, are recognized as crucial elements of traditional medical systems and are extensively utilized worldwide. Nature provides an abundant diversity of both biological and chemical resources.Worldwide, herbal medicines are extensively utilized because of their broad range of applications, high therapeutic efficacy, and little side effects. Numerous therapeutic plants have been investigated for their potential to treat seizures (15).This review aims to thoroughly examine recent advancements in epilepsy treatment, particularly highlighting groundbreaking therapies and innovative methodologies that bring new hope to individuals struggling with drug-resistant epilepsy. Key among these are gene therapies, miRNA, the integration of nanotechnology with nasal spray delivery to the brain, gene transfer-based therapies, and stem-cell-based therapies.These innovative treatments for epilepsy represent promising avenues currently accessible. Thus, herbal remedies and novel therapies stand as alternative forms of treatment for individuals afflicted by epilepsy (16).

NATURAL REMEDIES FOR MANAGEING EPILEPSY WITH HERBAL PLANTS:

The most common complementary and alternative medicine method nowadays is the use of herbal remedies, which are crucial to the treatment of epileptic seizures and side effects from antiepileptic drug use. Herbal medicine is utilised

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in developed countries to treat seizures and minimize the negative effects of antiepileptic drugs. Herbal therapy is used worldwide as a clinical treatment for epilepsy by both traditional and contemporary western medicine. Numerous herbal treatments have been studied in the literature that is currently available. Since it is impossible to include every herbal remedy for epilepsy in a single publication, our study has analysed a few popular herbal remedies.

Bacopa monnieri(Bramhi)

Bacopa monnieri is known for its purported cognitive-enhancing properties and is used in traditional Indian herbal medicine. It is a traditional ayurvedic drug used to treat epilepsy and other neurological disorders. Its antipyretic, analgesic, anti-inflammatory, memory-enhancing, and antiepileptic properties date back hundreds of years. Phytoconstituents such as triterpenoid, saponins, alkaloids, and their bacosides, which are present in various preparations of Bacopamonnieri, are responsible for the improvement in nerve impulse transmission.Extracts from Bacopa monnieri demonstrate antiepileptic effects by targeting specific regions of the brain. Furthermore, studies involving rats treated for epilepsy and PTZ have utilized these extracts (17). The anticonvulsant properties of ethanolic extracts of Bacopa monnieri were evaluated in albino rats across various convulsion models.(18,19).

Taxus wallichiana(Himalayan yew)

It has long been practiced to use Taxus wallichiana, or Himalayan yew, for a variety of medical purposes, like bronchitis, asthma, and ailments associated with inflammation but most notably the treatment of epilepsy. A wide variety of phytoconstituents, such as taxoids, lignans, steroids, and flavonoids, are thought to contribute to the plant's pharmacological activity. Among these, taxol, a well-known diterpenoid, has attracted a lot of interest due to its possible medicinal uses (20). Several animal models of epilepsy, including the maximal electroshock seizure (MES) model and the pentylenetetrazol (PTZ) produced seizure model, have been used in preclinical research to assess the anticonvulsant effects of Taxus wallichiana (21). Based on the plant's demonstrated potential to alter neurotransmitter systems and lessen seizure severity, these investigations validate the plant's traditional use and lay the groundwork for future pharmaceutical research (22).

Argemone mexicana (Mexican poppy)

Mexican poppy, or Argemone mexicana, have long been used in medicine to cure a variety of conditions, such as microbiological infections, skin conditions, and jaundice. The plant's abundance of phytoconstituents, which support its pharmacological qualities, includes flavonoids, phenolic compounds, and alkaloids (berberine, protopine, sanguinarine, and chelerythrine) (23). Preclinical investigations have demonstrated the potential of Argemone mexicana in the treatment of epilepsy. Its antiepileptic qualities were evaluated using conventional paradigms for assessing the effectiveness of anticonvulsants, namely the maximum electroshock (MES) model and the rodent pentylenetetrazole (PTZ)-induced seizure model. The plant's neuropharmacological mechanisms involving glutamatergic and GABAergic pathways are likely responsible for the encouraging outcomes these models have demonstrated, suggesting the plant's potential to influence seizure activity. According to these results, Argemone mexicana has long been used to treat epilepsy, and more research is necessary to completely understand its therapeutic potential (24).

Magnolia grandiflora(Evergreen magnolia)

Magnolia grandiflora, commonly known as the Southern Magnolia/ Evergreen mangnolia, has been traditionally utilized in various medicinal applications, including the treatment of anxiety, depression, and epilepsy. Its therapeutic potential is attributed to a diverse array of phytoconstituents such as magnolol, honokiol, and alkaloids, which exhibit significant neuroprotective and anticonvulsant properties (25). The effectiveness of Magnolia grandiflora extracts has been evaluated in research on the treatment of epilepsy using a variety of animal models. Notably, deciphering the plant's anticonvulsant processes has been made possible by models notably the one generated by pentylenetetrazol (PTZ), the one induced by maximal electroshock seizure (MES), and the one induced by kainic acid. There is now scientific support for the traditional usage of Magnolia grandiflora in the treatment of epilepsy as studies have shown that these phytoconstituents can alter neurotransmitter systems and lower oxidative stress (26).

Cestrum nocturnum(Night-blooming jasmine)

Night-blooming jasmine, or Cestrum nocturnum, has long been used for its therapeutic benefits throughout many cultures, most notably in the management of epilepsy. The plant's abundance

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of flavonoids, alkaloids, tannins, saponins, and essential oils are among the phytoconstituents that support its medicinal properties. Extracts from cestrum noctrunm have been demonstrated to possess anticonvulsant qualities in experimental forms of epilepsy(27).The incidence and severity of seizures can be significantly reduced by these extracts, according to animal studies, particularly those that use rodent models such as the maximal electroshock seizure (MES) model and the pentylenetetrazol (PTZ)-induced seizure model. These findings point to potential mechanisms involving the modulation of ion channel functions and neurotransmitter systems. These results suggest that Cestrum nocturnum might be a useful natural supplement or alternative for treating epilepsy, and they call for more investigation to identify the active ingredients and clarify how they work (28).

Zizyphus jujube (Chinese date)

Jujube, also known as Zizyphus jujube, is a plant that is widely used for its therapeutic qualities. Its abundance of phytoconstituents, which include flavonoids, saponins, and polysaccharides, has been linked to these benefits. These substances show a range of pharmacological properties, including neuroprotective, anti-inflammatory, and antioxidant properties. Notably, the possibility of using jujube to treat epilepsy has been investigated (29).Studies reveal that the fruit extract of Ziziphus jujube, which is hydroalcoholic, can lessen seizures in rats that are brought on by maximum electroshock (MES) and pentylenetetrazol (30). Jujube extracts have been shown in preclinical research to lower seizure frequency and severity in rodent models of epilepsy; this effect is probably attributed to the modulation of GABAergic neurotransmission and antioxidant processes. This implies that jujube may function as an adjunctive therapeutic agent in the treatment of epilepsy, providing a safer and more natural substitute for traditional antiepileptic medications with fewer adverse effects (31).

Ficus platyphylla(Fig)

Ficus platyphylla, a medicinal plant indigenous to various regions in Africa, has garnered significant attention for its therapeutic potential in epilepsy management. The phytoconstituents of Ficus platyphylla include flavonoids, alkaloid,saponins, and tannins, which are believed to contribute to its anticonvulsant properties (32). These bioactive compounds exhibit a broad spectrum of pharmacological activities, including neuroprotective, antioxidant, and anti-inflammatory effects. In preclinical studies, extracts from Ficus platyphylla have demonstrated efficacy in reducing seizure frequency and severity, potentially through the modulation of neurotransmitter systems and ion channel activities. The proposed model of epilepsy treatment with Ficus platyphylla involves the inhibition of excitatory neurotransmission and enhancement of inhibitory pathways, thereby stabilizing neuronal membranes and preventing hyperexcitability (33). This multifaceted approach underscores the plant's promise as a complementary or alternative therapeutic agent in epilepsy management. This multifaceted approach underscores the plant's promise as a complementary or alternative therapeutic agent in epilepsy management (34).

Passiflora incarnata (Passionflower)

Passionflower, or Passiflora incarnata, is a plant whose therapeutic qualities have attracted a lot of interest. It is very useful for treating epilepsy. This plant's therapeutic potential is attributed to its abundance of many phytoconstituents, such as glycosides, alkaloids(like harman and harmaline) and flavonoids(such as chrysin, vitexin, and isovitexin)(35). Research has indicated that these substances have anticonvulsant qualities, which suggests that Passiflora incarnata is a promising option for the treatment of epilepsy. In the suggested epilepsy treatment model, GABAergic neurotransmission is modulated. The flavonoids raise brain GABA (gamma-aminobutyric acid) levels, which calms neuronal excitability and lowers seizure frequency. Moreover, it has been demonstrated that alkaloids such as harman and harmaline inhibit monoamine oxidase, potentially stabilizing mood and brain activity even further (36). Clinical and preclinical trials support the inclusion of Passiflora incarnata in comprehensive treatment regimens for epilepsy since they demonstrate the plant's effectiveness in reducing seizure frequency and intensity (37).

Zingiber officinale(Ginger)

Zingiber officinale, commonly known as ginger, is extensively employed in traditional medicine for its wide array of therapeutic benefits. The rhizome of this plant is rich in phytoconstituents such as gingerols, shogaols, paradols, and zingerone, which contribute to its anti-inflammatory, antioxidant, and neuroprotective properties (38). Recent studies have highlighted the potential of Zingiber officinale in the management of epilepsy, a neurological disorder characterized by recurrent seizures. The anticonvulsant effects of

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ginger are attributed to its ability to modulate neurotransmitter activity, reduce oxidative stress, and inhibit neuroinflammation. Experimental models of epilepsy, such as the pentylenetetrazol (PTZ) and kainic acid (KA) induced seizure models, have demonstrated that ginger extracts can significantly reduce seizure frequency and severity (39). These findings suggest that Zingiber officinale could serve as an adjunctive therapy in epilepsy treatment, offering a natural and holistic approach to seizure management (40).

Scutellariabaicalensis (Baikal skullcaps)

Baikal skullcap, also called Scutellariabaicalensis, is an ancient remedy that is used intensively for its neuroprotective, antioxidant, and anti-inflammatory qualities (41, 42). Its abundance in phytoconstituents, such as wogonin, baicalin, baicalein, and oroxylin A, is primarily accountable for its medicinal potential. These flavonoids have noteworthy pharmacological effects, especially when considering neurological conditions like epilepsy (43, 44). Investigation has indicated that S. baicalensis possesses anticonvulsant properties through altering GABAergic neurotransmission, decreasing oxidative stress, and blocking inflammatory pathways. Baicalein and wogonin, by increasing GABA receptor activation and reducing neuronal hyperexcitability, have been demonstrated in animal models of epilepsy to reduce seizure susceptibility and intensity. This implies thatScutellariabaicalensis could serve as a complementary therapeutic agent in epilepsy management, providing a multi-faceted approach to mitigate seizure activity and improve neurological health (45, 46).

Some other herbal plants are:

Plant Name	Parts Used	Uses	References
Passiflora incarnata (passionflower)	Aerial parts	Sedative, anticonvulsant	SoulimaniR et al., 1997. (43)
Valeriana officinalis (Valerian)	Roots	Sedative, antispasmodic	Cropley M et al., 2017. (44)
Withaniasomnifera (Ashwagandha)	Roots, Leaves	Anticonvulsant, Adaptogen	Ulkarni S K et al., 2008. (45)
Centella asiatica (Gotu Kola)	Whole plant	Neuroprotective, Anticonvulsant	Brinkhaus B et al., 2000. (46)
Cannabis sativa (Cannabis)	Leaves, flowers	Anticonvulsant, reduces seizures frequency	Devinsky O et al., 2014. (47)
Glycyrrhiza glabra (Licorice)	Roots	Anti-inflammatory, Neuroprotective	Beshbishy A M et al., 2020. (48)
Curcuma longa (Turmeric)	Rhizomes	Anti-inflammatory, Anticonvulsant	Vaibhav K et al., 2013. (49)
Piper nigrum (Black Papper)	Fruits	Enhances bioavailability of other treatments, Anticonvulsant	Sudjarwo S A et al., 2017. (50)
Zingiber officinale	Rhizomes	Anti-inflammatory, Anticonvulsant	Ali B H et al., 2003. (51)
Rauwolfia serpentina	Roots	Anticonvulsant	Akhondian J et al., 2011. (52)
Scutellarialateriflora	Aerial Parts	Anticonvulsant, Neuroprotective	Awad R et al., 2003 (53)
Melissa officinalis	Leaves	Sedative, reduces seizure frequency	Cases J et al., 2011 (54)
Piper methysticum (kava)	Roots	Sedative, muscle relaxant, anticonvulsant	Grunze H et al. 2001. (55)

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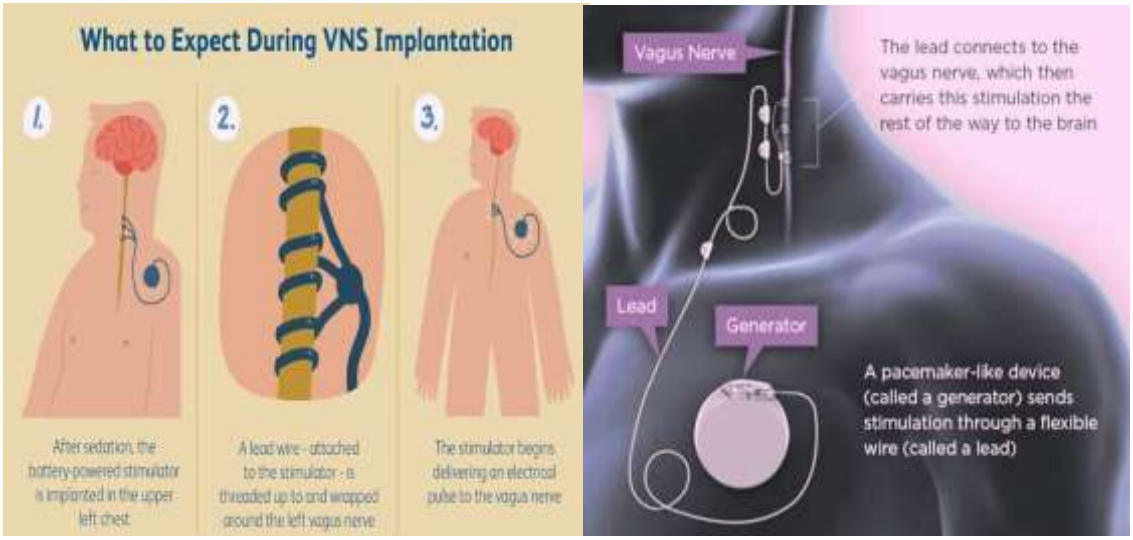
INNOVATIVE STRATEGIES FOR MANAGING EPILEPSY

Despite standard treatments including antiepileptic drugs and, in extreme circumstances, surgery, epilepsy—a neurological disorder marked by recurring seizures resulting from aberrant brain electrical activity—presents difficulties (56). But new therapeutic options are emerging as a result of medical research breakthroughs, providing a means of relief for individuals who find traditional treatments unsatisfactory or unsuccessful.Here is a following innovative procedure that are now being used to expand the range of treatment possibilities(57,58).

Vagus Nerve Stimulation (VNS)

The science of neurostimulation has advanced significantly with the widespread use of vagus nerve stimulation therapy for epilepsy management.Approved for use in treating epilepsy across all age groups and types of seizures, VNS therapy involves implanting a device that delivers electrical impulses to the vagus nerve—a nerve extending from the brain to the abdomen. This stimulation is designed to modify brain activity, potentially reducing both the frequency and severity of seizures. Key components of the VNS therapy system include a bipolar VNS lead, a programming wand with compatible software for a handheld device, a tunneling tool, handheld magnets, and a pulse generator. The generator stimulates the vagus nerve through the lead, while the software enables the programming wand to adjust stimulation parameters by interfacing with the generator, which is shown in figure1(59, 60).

Despite its recognized efficacy in managing seizures, Vagus Nerve Stimulation (VNS) therapy offers additional benefits such as improved sleep quality, enhanced emotional well-being, reduced frequency of hospital admissions, and the prospect of minimizing medication reliance. The modulation of VNS intensity remains a pivotal aspect, allowing for personalized adjustments to mitigate potential side effects while optimizing seizure control. Furthermore, the flexibility to adapt stimulation levels throughout the day and night, coupled with the capacity to administer heightened stimulation in anticipation of seizures, underscores the complementary nature of VNS treatment when integrated with conventional anti-seizure pharmacotherapy (61, 62).



(Figure 1: It shows how to implant and how to work a vagus nerve stimulator to modify brain activity to control epilepsy.)

Deep brain stimulation (DBS)

Deep Brain Stimulation (DBS) involves the use of implanted electrodes to deliver controlled electrical impulses to deep regions of the brain, serving as an invasive neurosurgical technique as shown in figure 2. It is typically recommended for individuals who are not suitable candidates for conventional surgery and who suffer from difficult-to-treat focal epilepsies. Approved by the FDA, stimulation of specific areas such as the anterior thalamus and the ictal onset zone has shown significant and sustained reduction in

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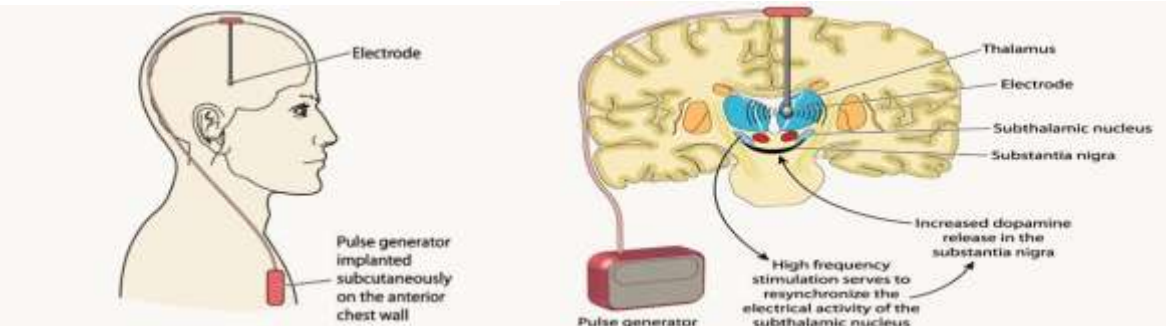
seizures (63, 64). Numerous patients' quality of life can be improved by DBS, as clinical studies have shown it can significantly reduce both the frequency and severity of seizures. In order to improve the efficacy and safety of DBS for the treatment of epilepsy, ongoing research attempts to optimize stimulation parameters and target areas(65,66,67).



(Figure 2: It shows the function of Deep Brain Stimulator in the particular region of the brain)

Responsive neurostimulation (RNS)

Responsive neurostimulation (RNS) represents a groundbreaking approach in the treatment of epilepsy, particularly for patients who do not respond adequately to conventional therapies such as medications or respective surgery. RNS technology involves the implantation of a neurostimulator device within the brain, which continuously monitors neural activity. When the device detects abnormal electrical patterns indicative of an impending seizure, it delivers targeted electrical pulses to disrupt these patterns and prevent the seizure from occurring. This real-time, responsive intervention is designed to address epileptogenic activity as it arises, thereby minimizing seizure frequency and severity (68). According to studies, RNS can help patients with focal epilepsy reduce their seizure frequency significantly and may be a good option if their epileptogenic zones are difficult to treat.Additionally, RNS has the potential to offer insights into the neural dynamics of epilepsy, contributing valuable data for ongoing research (69). The system is customizable, allowing for adjustments based on the patient's evolving neurological profile, which enhances its efficacy over time. While RNS does not cure epilepsy, it significantly improves the quality of life for many patients by providing better control over their seizures and reducing the debilitating effects associated with the condition (70).

Gene therapy

Growing pre-clinical data indicates gene therapy may be an effective treatment for a considerable proportion of epileptic individuals for whom no other therapies are working.In addition to introducing healthy gene variations into cells, gene therapy also involves gene editing and modifying the activity of already-existing genes(71). Approaches to epilepsy that use gene therapy can be broadly classified into two groups: those that focus on the mechanism(s) responsible for generating seizures, and those that target the gene defect in genetic forms of the condition (72, 73).

During gene therapy, target cells are exposed to exogenous nucleic acids in order to modify gene expression. These large, negatively charged macromolecules are often delivered using carriers, also known as vectors (74). Mechanism of gene therapy are given below in figure 3.The blood-brain barrier (BBB) poses a significant challenge in epilepsy treatment by impeding genetic vectors from entering the brain through the bloodstream. The choice of transgenes, promoters, and viral vectors are only a few of the factors that need to be taken into account when using gene therapy in clinical settings(75, 76, 77).

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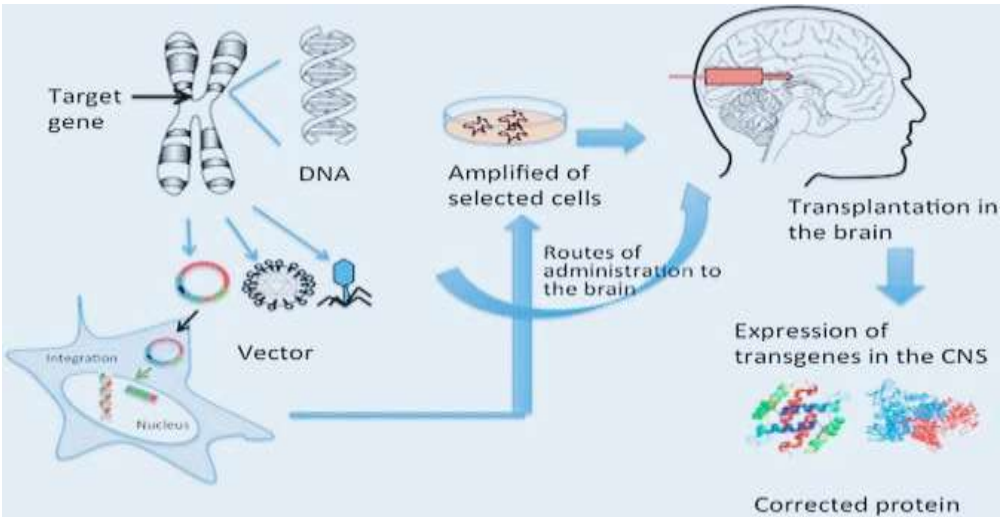

(Figure 3: This figure shows the mechanism of gene therapy)

Stem cell therapy

Stem cells are immortal, self-renewing, and able to differentiate into multiple cell types.There are several sources of stem cells, including tissues from foetuses, adults, and embryos. Neurological conditions like epilepsy, spinal cord damage, and stroke are possibilities for treatment with many types of stem cells, much like other diseases(78, 79). Recurrent seizures are linked to the depletion of inhibitory GABAergic interneurons. Thus, to improve inhibitory synaptic function and lower the incidence of spontaneous seizures, injured interneurons may be replaced with GABAergic precursors during transplanting(80, 81). Currently, progenitors derived from the medial ganglionic eminence (MGE), generated either from human induced pluripotent stem cells or foetal brains, have demonstrated exceptional efficacy in treating epilepsy, particularly temporal lobe epilepsy, in a groundbreaking manner.In order to improve inhibitory synaptic neurotransmission, medial ganglionic eminence cells migrate widely, develop into GABAergic interneurons, and integrate well into the hippocampus area of the brain. The best donor cell type for MGE progenitors appears to be pluripotent cells since they don't present any ethical issues and work well with patient-specific cell treatment for epilepsy that isn't genetic(82, 83, 84).

Biodegradable nanoparticles

Epilepsy, due to its complex etiopathogenesis, necessitates a variety of therapeutic approaches. While antiseizure medications are highly effective in managing seizures, their narrow therapeutic index and numerous drug interactions pose significant challenges for their widespread application. The blood-brain barrier (BBB) serves as both a physical and metabolic shield, safeguarding the brain's microenvironment and regulating the exchange of nutrients and xenobiotics. In this context, nanoparticles (NPs) offer a promising strategy to circumvent the BBB and achieve therapeutic concentrations of antiseizure medications (ASMs) (85, 86). The application of biodegradable nanoparticles in epilepsy treatment is gaining traction owing to their ability to penetrate the BBB, improve brain targeting, minimize side effects, and enable sustained drug release. These nanomaterials can be engineered to degrade upon reaching the target site while remaining stable at non-target sites, eventually breaking down into non-toxic byproducts within the body. The primary types of biodegradable nanoparticles include lipid nanoparticles and polymeric nanoparticles (87).

Ketogenic diet therapy

Antiseizure medications (ASDs) are the primary treatment for most individuals with epilepsy. However, 30% of patients find ASDs ineffective. In such cases, nonpharmacological therapies, including a glutamate-reduced diet and ketogenic diet therapy (KDT), are considered (88). The ketogenic diet is a high-fat, low-carbohydrate plan that mimics the effects of hunger and is an alternate non-pharmacological treatment for those with drug-resistant epilepsy.When conventional drugs fail, nutritional therapy becomes necessary for patients with drug-resistant epilepsy. This dietary approach, beneficial for both adults and

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children, involves high-fat, low-carbohydrate diets (89, 90).

Ketogenic diet therapy is the first line of treatment for conditions like glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency. It should be administered to children who do not respond well to anti-epileptic drugs (AEDs) (91, 92). The therapeutic scope of KDTs is broader than that of medications as they inhibit vesicular glutamate transport, modulate metabolism by reducing mitochondrial ATP synthesis and glycolysis, activate ATP-sensitive potassium channels to decrease neuronal excitability, elevate polyunsaturated fatty acids, and reduce reactive oxygen species through mitochondrial dissociation. Consequently, KDTs not only diminish neuronal hyperexcitability but also offer neuroprotective effects by addressing cellular energy deficiencies and protecting against epilepsy-induced brain damage.(93, 94).

Cannabidiol therapy (CBD)

Cannabidiol (CBD) therapy has emerged as a promising avenue in the realm of epilepsy treatment, offering a novel approach to managing this complex neurological disorder. Through its interactions with the endocannabinoid system, CBD exerts potential anticonvulsant effects, thereby mitigating seizure activity. Clinical trials and observational studies have underscored its efficacy in reducing seizure frequency and severity, particularly in patients with refractory epilepsy syndromes such as Dravet syndrome and Lennox-Gastaut syndrome. Moreover, CBD demonstrates a favourable safety profile, with limited adverse effects compared to traditional antiepileptic drugs (95). However, challenges persist in optimizing dosing regimens and elucidating its mechanisms of action. Collaborative efforts among researchers, healthcare professionals, and regulatory bodies are imperative to further explore the therapeutic potential of CBD in epilepsy treatment, ensuring evidence-based practice and patient-centered care. This synthesis draws upon seminal research articles, clinical trials, and expert consensus statements in the field, providing a comprehensive overview of the current understanding and future directions of CBD therapy in epilepsy management(96, 97).

These all above innovative methods provide an alternative for individuals with epilepsy, especially those unresponsive to conventional therapies or who endure significant adverse effects from medications. Nevertheless, comprehensive research is essential to thoroughly ascertain their effectiveness, safety, and enduring impact.

II. CONCLUSION

Antiepileptic medication adverse effects may be more detrimental to a patient's quality of life than seizure frequency because even very effective AEDs can have significant side effects when their effectiveness is zeroed out.The adverse effects of synthetic medications could require the use of an alternate therapy for epilepsy management. One alternative for managing and treating epilepsy may be herbal remedies, which have less adverse effects than synthetic medications. Innovative methods are needed for epilepsy treatment to be successful. Numerous novel approaches to treating epilepsy are presently under investigation, including as deep brain stimulation, vagus nerve stimulation, stem cell therapies, and gene therapies etc. Each of them has a few benefits and drawbacks. However, it is evident that these unique and novel treatment options are gradually gaining popularity as potential alternatives to traditional epilepsy therapeutic procedures, especially as more preclinical studies are conducted.

REFERENCES

[1]. Scheuer M L, Pedley T A.The evaluation and treatment of seizures. The new England journal of medicine. 1990. 323. 21.

[2]. Kumar S, Madaan R, Bansal G. Plant and plant products with potential anticonvulsant activity-A review. Pharmacognosy communications. 2012. 2. 3-4.

[3]. Adams M, Schneider S V, Kluge M, Kessler M. Hamburger M. Epilepsy in the renaissance: A survey of remedies from 16th and 17th century. German herbals J ethanopharmacol. 2012. 143. 1-13.

[4]. Fraser D A. New drugs for the treatment of epilepsy. Clinical biochemistry. 1996. 29. 97-110.

[5]. Sucher N J, Carles M C. A pharmacological basis of herbal medicines for epilepsy. Epilepsy and behaviour. 2015. 52 part -B (52-B). 308-318.

[6]. Shashi K P. Kumar M, Kumar A. Herbal and synthetic approaches for the treatment of epilepsy. International journal of nutrition, pharmacology, neurological diseases. 2014. 4 (1). 43-52.

[7]. Macdonald R L, Kolly K M. Antiepileptic drug mechanism of action. Epilepsia. 1995. 36 (soppl). 52-12.
[8]. Jangra M K, Yadav A K, Shashi K P. Herbal and synthetic approaches for the treatment of epilepsy. Pharmacology and neurological disease. 2014. 4.
[9]. Barrientos E 4, Barragan -Galvez J C, Hidalgo-Figueroa S. Neuropharmacological effects of the dichloromethane extract from the stems of A.ochroleuca sweet(Papaveraceae) and it's active compound dihydrosangurine. Pharmaceutical. 2023.16.1175.
[10]. Tripathi K D. Essentials of medical pharmacology. Jaypeebrothers'medical publishers (P) ltd. 2019. 8. 438.
[11]. Bonilla L, EsteruelasG, Ettcheto M. Biodegradable nanoparticles for the treatment of epilepsy: from current advances of future challenges. Epilepsia.2021.4.
[12]. Kaur T, Manchanda S, Saini V. Efficacy of anti-epileptic drugs in the treatment of tumour and it's associated with epilepsy: an in vitro perspective. Karger medical and scientific publishers. 2016. 1. 33-43.
[13]. Auditeau E, Chassagne F. Herbal medicine for epilepsy seizures in Asia, Africa and Latin America: a systematic review. Journal of ethnopharmacology. 2019. 234.119-153.
[14]. Leonti M, Verpoorte R. Traditional mediterranean and European herbal medicines. Journal of ethnopharmacology. 2017. 227. 161-167.
[15]. Mohammad, Asif. Anticonvulsant potential of some medicinal plants and their beneficial properties. CellmedOrthocellularmedicine and pharmaceutical association. 2013. 3. 27.1-27.13.
[16]. Farrelly M A, Vlachou S, GrintzalisK. Efficacy of Phytocannabinoids in epilepsy treatment: novel approaches and recent advances. International journal of environmental research and public health. 2021. 18. 3993.
[17]. Komali E, VenkataramaiahCh, Rajendra W. Antiepileptic potential of bacopa monnieri in the rat brain during PTZ-induced epilepsy with reference to cholinergic system and ATPases. Journal of traditional and complementary medicine. 2021. 11. 137-143.
[18]. Kaushik D, Tripathi A, Ganachari M. Anticonvulsant activity of bacopa monniera in rodents. Brazilian journal of pharmaceutical sciences. 2009. 4. 45.
[19]. Mathew J, Balakrishnan S, Antony S. Decreased GABA receptor in the cerebral cortex of the epileptic rats: effect of Bacopa monnieri and Bacoside-A. journal of biomedical science. 2012. 25.
[20]. Kumar S. Phytochemistry and pharmacology of Taxus wallichiana. Journal of Ethnopharmacology. 2015. 160. 59-78.
[21]. Singh A. Anticonvulsant activity of Taxus wallichianaZucc in experimental animal models. Journal of Ethnopharmacology. 2012. 140. 211-216.
[22]. Tripathi Y C. Himalayan Yew: a potential source of anti-epileptic drugs.Pharmacognosy Reviews. 2014. 8.15. 97-105.
[23]. Sharma A, Jain A & Sharma S.Pharmacological properties of Argemone mexicana: A review. Journal of Ethnopharmacology. 2019. 234. 121-135.
[24]. Raj S, Singh S & Sharma A. Anticonvulsant potential of Argemone mexicana: Mechanistic insights and preclinical evidence. Journal of Ethnopharmacology. 2018. 210.238-246.
[25]. Kim J H. Neuroprotective effects of magnolol and honokiol: Potential therapeutic roles in neurodegenerative diseases.Phytotherapy Research. 2017. 31. 31-39.
[26]. Li X, Duan X, Yang Y & Han S. Neuroprotective Effects and Mechanisms of Magnolia grandiflora Extracts in Epileptic Models. Neurochemical Research. 2020. 45. 2514-2526.
[27]. Alam M A, Subhan N, Rahman M M, Uddin S J, Reza H M, Sarker S D.Effect of natural products on drug-resistant epilepsy. Frontiers in Pharmacology. 2021. 12. 632426.
[28]. Perez-Saad H, Buznego M T.Behavioral and antiepileptic effects of acute administration of the extract of the plant Cestrunumnocturnum Linn (Lady of the night). Epilepsy and behaviour. 2008. 12. 366-372.
[29]. Ghorbani A, Esmaeikizadeh M. Pharmacological properties of Zizyphus jujube in the traditional and modern

medicine: A Review. Iranian Journal of basic medical sciences. 2017. 20. 522-536.
[30]. Zhao Z, Wang W, Guo H, and Zhou D. Anticonvulsant effect of jujube (Zizyphus jujuba mill) in mouse models. Journal of Ethnopharmacology. 2013. 148. 510-514.
[31]. Wang B, Li W, Wang Y, TangJ.Neuroprotective Effects of Zizyphus jujuba in Epileptic Rats. Neuroscience Letters. 2017. 645. 78-82.
[32]. Elufioye T O, Agbedahunsi J M. Anticonvulsant effects of Ficus platyphylla stem bark in mice. Journal of Ethnopharmacology. 2004. 95. 371-375.
[33]. Mohammed A, Tanko Y, Okasha M A. (2007). Anticonvulsant activity of methanolic extract of Ficus platyphylla stem bark in laboratory animals. African Journal of Traditional, Complementary and Alternative Medicines. 2007. 4. 68-72.
[34]. Yakubu M T, Akanji M A, Oladiji A T. Aphrodisiac potential of the aqueous extract of Ficus platyphylla stem bark in male albino rats. Asian Journal of Andrology. 2005. 7. 399-404.
[35]. Dhawan K, Dhawan S, Sharma A. Passiflora: a review update. Journal ofEthnopharmacology. 2004. 94. 1-23.
[36]. Doyle N, Vines L, Curtis C. The Anticonvulsant Potential of Flavonoids from Passiflora incarnata. Journal of Medicinal Plant Research. 2020. 14. 234-245.
[37]. Ferreira M B, Santos J C, de Almeida R N. Phytochemical Analysis and Anticonvulsant Activity of Passiflora incarnata. Epilepsy &Behavior. 2021. 118. 107-907.
[38]. Sharma M, Jamwal S, Sharma A. Phytoconstituents of Zingiber officinale: An Overview on Their Role in Epilepsy Management. Phytotherapy Research. 2019. 33.2020-2027.
[39]. Mohd Yusof Y A, Abd Aziz N H, Abdul Rahman H S.Zingiber officinale: A Potential Antiepileptic Herb. Journal of Ethnopharmacology. 2018. 219. 112-123.
[40]. Alvi S S, Dar A, Ahmad A. The Neuroprotective Role of Ginger (Zingiber officinale) in Various Models of Epilepsy: A Systematic Review. Epilepsy Research 2019. 157. 106-220.
[41]. Li H B, Wong C C, Cheng K W, Chen F. Antioxidant properties in vitro and total phenolic contents in methanol extracts from medicinal plants. LWT-Food Science and Technology. 2008. 41. 385-390.
[42]. Zhou J, Zhou S. Antihyperglycemic and hypolipidemic effects of Scutellariabaicalensis extracts in db/db mice.Journal of Ethnopharmacology. 2012.139. 931-937.
[43]. Xie G, SchepetkinI A, Siemsen D W, Kirpotina L N, Quinn M T. Fractionation and characterization of biologically-active polysaccharides from Artemisia tripartite. Phytochemistry 85 (2013): 137-146.
[44]. Chen Y L, Cheng J T. Inhibitory effect of baicalin on calmodulin in diabetes-induced rats.Journal of Biomedical Science. 2003. 10.3. 353-362.
[45]. Lie W Ge T, Pan Z, Leng Y, Lu J, Li B. The effect of herbal medicine on epilepsy. Oncotarget. 2017. 8. 48385-48397.
[46]. Shashi P K, Jangra M K, Yadav A K. Herbal and synthetic approaches for the treatment of epilepsy. International journal of nutrition, Pharmacology, Neurological diseases. 2014. 4.
[47]. Soulimani R, Younos C, Jarmouni S, BoustaD. The calming and anti-anxiety effects of Passiflora incarnata L. in the rat. Phytotherapy Research. 1997. 11. 362-365.
[48]. Cropley M, Cave Z, Ellis J, Middleton R W. Effect of Cava and Valerian on human physiological responses to mental stress assessed under laboratory conditions. Phytotherapy Research. 2017. 31. 7-13.
[49]. Ulkarni S K, Dhir A. Withaniasomnifera: an Indian ginseng. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008. 32. 1093-1105.
[50]. Brinkhaus B, Lindner M, Schuppan D, Hahn E G. Chemical, pharmacological and clinical profile of the East Asian medical plant Centella asiatica. Phytomedicine. 2000. 7. 427-448.
[51]. Devinsky O, Cilio M R, Cross H, Fernandez-Ruiz J. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014. 55. 791-802.
[52]. Beshbishy A M, et al. Traditional uses, bioactive chemical constituents and pharmacological and toxicological activities of glycyrrhiza glabra L. (Fabaceae). Biomolecules. 2020. 10. 352.
[53]. Vaibhav K, Shrivastava P, Javed H, Khan A, Ahmed M E. Interactions of curcumin

with anti-seizure drugs in ameliorating seizures in pentylentetrazole-kindled rats. Phytotherapy Research. 2013. 27. 612-618.

[54]. Sudjarwo S A, Eraiko K, SudiraI W. Protective effects of Piperineon lead acetate-induced neurotoxicity in wistar rats. 2017. 20. 1227-1231.

[55]. Ali B H, Blunden G. Pharmacological and toxicological properties of Zingiber officinale (ginger). Food and chemical toxicology. 2003. 41. 627-631.

[56]. Akhondian J, Kianifar H R, KhajedalueeM, Tahri H. The effects of thymoquinone on intractable pediatric seizures (pilot study). Epilepsy Research. 2011. 93. 39-43.

[57]. AwadR, Arnason J T, Trudeau V, Bergeron C, Budzinski J W. Phytochemical and biological analysis of skullcap (scutellarialaterifloral): a medicinal plant with anxiolytic properties. Phytomedicine. 2003. 10. 640-649.

[58]. Cases J, Ibarra A, Feuillere N, Roller M. Pilot trial of Melissa officinalis L. leaf extract in the treatment of mild-moderate anxiety disorders and sleep disturbances. Mediterranean Journal of Nutrition and Metabolism. 2011. 4. 211-218.

[59]. Grunze H et al. Kava pyrones exert effects on neuronal transmission and transmembraneouscation currents similar to established mood stabilizers. Prog NeuropsychopharmacolBiol Psychiatry. 2001. 25. 1555-1570.

[60]. French J A, White H S, Klitgaard H, Holmes G L, Privitera M D. Development of new approaches for epilepsy: Unmet needs and opportunities. Epilepsia official journal of the international league against epilepsy. 2013. 54. 3-12.

[61]. Mesraoua B, Deleu D, Kullmann D M, Shetty A K, Boon P. Novel therapies for epilepsy in the pipeline. Epilepsy and behaviour. 2019. 97. 282-290.

[62]. Ghosh S, Sinha J K, Khan T, Devaraju K S, Singh P. Pharmacological and therapeutic approaches in the treatment of epilepsy. Biomedicines. 2021. 9. 470.

[63]. Fukuda M, Matsuo T, Fujimoto S, Kashii H, Kumada S, Ishiyama A. Vagus nerve stimulation therapy for drug-resistant epilepsy in children-A literature review. Journal of clinical medicine. 2024. 13. 780.

[64]. Gonzalez H F J, Yengo-kahn A, Englot D J. Vagus nerve stimulation for the treatment of epilepsy. Neurosurgery clinics. 2019. 30. 219-230.

[65]. Uthman B M, Wilder B J, Penry J K, Ramsay R E. Treatment of epilepsy by stimulation of the vagus nerve. Neurology. 1993. 43. 1338.

[66]. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. The lancet neurology. 2002. 1. 477-482.

[67]. Tobias L, Andrew P, Silvia N, Kenneth B. Deep brain stimulation in epilepsy. Journal of clinical neurophysiology official publication of the American clinical neurophysiology society. 2001. 18. 514-532.

[68]. Laxpati N G, Kasoff W S, Gross R E. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. 2014. 11. 508-526.

[69]. Matias CM, Sharan A, Wu C. Responsive neurostimulation for thetreatment of epilepsy. Neurosurg Clin N Am. 2019. 30. 231-242.

[70]. Schulze-Bonhage A. Deep brain stimulation: A new approach to the treatment of epilepsy. DeutschesArzteblatt international. 2009. 106. 407-412.

[71]. Boon P, Vonck k, Herdt V D, Goethals M. Deep brain stimulation in patients with refractory temporal lobe epilepsy. Epilepsia official journal of the international league against epilepsy. 2007. 48. 1551-1560.

[72]. Bergey G K, Morrell M J, Mizrahi E M. (2015). Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015. 84. 810-817.

[73]. Fisher R S et al. Electrical stimulation of the brain for epilepsy: the state of art. Epilepsia. 2024. 55. 464-475.

[74]. Bergey, Gregory K N. Neurostimulation in the treatment of epilepsy. Experimental Neurology. 2024. 244. 87-95.

[75]. Kaur S, Kumar R, Singh A P, Singh A P, Malhotra M. Gene therapy: A review. International journal of medical, pharmacy and drug research. 2024. 8.

[76]. Street J S, Qui Y, Lignani G. Are genetic therapies for epilepsy ready for clinic? Sage journals. 2023. 23.

[77]. Bettegazzi B, Cattaneo S, Simonato M, Zucchini S. Viral Vector-based gene

therapy for epilepsy: What does the future hold? 2023. 28. 5-13.

[78]. Kanasty RL, Yin H, Eltoukhy AA, Vegas A J, Anderson D G. Non-Viral vectors for gene-based therapy. Nat rev genet. 2014. 15. 541-555.

[79]. Balagura G, Guglielmo A, Riva A, Iacomino M, Amadori E. Emerging treatment for progressive myoclonus epilepsies. Expert rev neurother. 2020. 20. 341-350.

[80]. Riva A, Golda A, Balagura G, Amadori E, Vari M S, Piccolo G. New trends and most promising therapeutics strategies for epilepsy treatment.Frontiers in neurology. 2017. 12.

[81]. Van Emde BW, Blume W, Elger C, Genton P, Lee P. Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005. 46. 1701–1702.

[82]. Goodarzi P, Aghayan H R, Soleimani M, Norouzi-Javidan A. Stem cell therapy for treatment of epilepsy. Acta medica Iranica. 2014. 52. 9.

[83]. Mesraoua B, Deleu D, Kullmann DM, Shetty AK, Boon P. Novel therapies for epilepsy in the pipeline. Epilepsy Behav. 2019. 97. 282–90.

[84]. Shetty AK, Upadhya D. GABA-ergic cell therapy for epilepsy: advanceslimitations and challenges. NeurosciBiobehav Rev. 2016. 62. 35–47.

[85]. Upadhya D, Hattiangady B, Castro OW, Shuai B, Kodali M. Human induced pluripotent stem cell-derived MGE cell graftingafter status epilepticus attenuates chronic epilepsy and comorbiditiesvia synaptic integration. Proc Natl Acad Sci USA. 2019.116. 287–296.

[86]. Perucca P, Scheffer IE, Kiley M. The management of epilepsy in children and adults. Med J Aust. 2018. 208. 226–233.

[87]. Marchi N, Granata T, Ghosh C. Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. Epilepsia. 2012. 53. 1877–1886.

[88]. Han H, Mann A, Ekstein D, Eyal S. Breaking bad: the structure and function of the blood-brain barrier in epilepsy. AAPS J. 2017. 19. 973–988.

[89]. Su S, Kang PM. Systemic review of biodegradable nanoparticles in nanomedicine. Nanomaterials. 2020. 10. 656.

[90]. Jabir N, Tabrez S, Firoz CK, Zaidi S, Gan S. A synopsis of nano-technological approaches toward anti-epilepsy therapy: present and future research implications. Curr Drug Metab. 2015. 16. 336–345.

[91]. Bonilla L, EsteruelasG, Ettcheto M, Espina M, Cano A. Biodegradable nanoparticles for the treatment of epilepsy: From current advances to future challenges. Epilepsia open the open access journal of the international league against epilepsy. 2021.5.12567.

[92]. Shegelman A, Carson K A, McDonald T J W, Diaz-Arias L A.The psychiatric effects of ketogenic diet therapy on adults with chronic epilepsy.Epilepsy and Behavior. 2021. 117. 107807.

[93]. Pinaffi-Langley A C da C, Dajani R M, Prater M C, M Nguyen H V. Dietary Nitrate from Plant Foods: A Conditionally Essential Nutrient for Cardiovascular Health.Advances in Nutrition. 2024. 15. 100158.

[94]. Kovacs Z, Brunner B, Ari C. Beneficial effects of exogenous ketogenic supplements on aging processes and age-related neurodegenerative diseases. Nutrients. 2021. 13. 2197.

[95]. Zhu H, Zhang Y, Kong C, Du J, Wu X, Qin H. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. Signal transduction and targeted therapy. 2022. 7.

[96]. Williams T J, Henry-Barron B J, Olieman J F,Duvekot J J, Vermeulen M J, Bannink N. Ketogenic diet therapy for epilepsyduring pregnancy: A case series. Seizure. 2017. 45. 198-201.

[97]. Lyons L, Schoeler N E, Langan D, Cross J H. Use of ketogenic diet therapy in infants with epilepsy: A systemic review and meta-analysis. Epilepsia. 2020.

[98]. Nisa Mughal Z U, Maalik A, Rangwala B S, Rangwala H S, Fatima H, Ali M. Glutamate-reduced diet and ketogenic diet for Pediatric Drug-Resistant epilepsy: A novel approach to treatment. Animals of medicine and surgery. 2024. 86. 2399-2401.

[99]. Perucca E. Cannabinoids in the treatment of epilepsy: Hard Evidence at last. Journal of Epilepsy Research. 2017. 7. 61-76.

[100]. Devinsky O, Cross H J, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. New England Journal of Medicine. 2014. 376. 2011-2020.
[101]. Thiele E A. Marsh E D, French J A, Mazurkiewicz-Beldzinska M, Benbadis S R, Joshi C. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double blind, placebo-controlled phase 3 trial. The Lancet. 2018. 391. 1085-1096.
[102]. López-García, M.A., Feria-Romero, I.A., Segura-Uribe, J.J., Escalante-Santiago, D., Orozco-Suárez, S. (2016). Gene Therapy in Epilepsy. In: Talevi, A., Rocha, L. (eds) Antiepileptic Drug Discovery. Methods in Pharmacology and Toxicology. Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-6355-3_10
[103]. Smith, Yolanda. (2022, November 26). What Does Deep Brain Stimulation Involve? News-Medical. Retrieved on July 04, 2024 from https://www.news-medical.net/health/What-does-deep-brain-stimulation-involve.aspx.
[104]. Kryshtopava, Maryna. (2017). Functional Magnetic Resonance Imaging Study of Central Neural System Control Of Voice, With Emphasis On Phonation In Women With Muscle Tension Dysphonia.