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Muhammad Wasim
Aga Khan University Karachi

Mehr Musani
The Aga Khan University, Karachi

Hasan Salman Siddiqi
Aga Khan University, Karachi

Saara Muddasir
Aga Khan University Karachi

Bushra Amin
The Aga Khan University, Karachi

See next page for additional authors

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Authors

Muhammad Wasim, Mehr Musani, Hasan Salman Siddiqi, Saara Muddasir, Bushra Amin, and Fazal Manzoor Arain

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TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPUS SCLEROSIS: PREVALENCE, ETIOLOGY, AND TREATMENT OPTIONS WITH HERBAL MEDICINES

Muhammad Wasim[1], Mehr Musani[1], Hasan Salman Siddiqi[1], Saara Muddasir[1], Bushra Amin[1], Fazal Manzoor Arain[1]
[1]Department of Biological and Biomedical Sciences, The Aga Khan University, Karachi

Correspondence Author: Fazal Manzoor Arain *Department of Biological and Biomedical Sciences, The Aga Khan University, Karachi* ***Email:*** *fazal.arain@aku.edu*

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ABSTRACT

Background and objectives:
Epilepsy is a neurological disorder in which the patient suffers with two or more unprovoked seizures. It is one of the most common neurological disorders worldwide, affecting more than 70 million people. Currently various modes of effective treatments are available, but still there are many cases that remain drug resistant. Hence, there is a need to explore herbal medications for the treatment of drug resistant epilepsy.

Methods:
Recent reviews and research articles (2000-2022) from PubMed and Google Scholar have been explored.

Review:
Based on etiology, there are six categories of epilepsy: Genetic, Structural, Metabolic, Immune, Infectious, and Unknown epilepsy. Temporal lobe epilepsy with hippocampus sclerosis (TLE-HS) is one of the most common forms of structural epilepsy. Even though several new anti-epileptic drugs (AEDs) have been discovered, but the treatment of some cases, especially TLE-HS remain resistant to them. Surgery is one of the most effective treatment options for TLE-HS; however, this usually results in memory deficits, and occasionally, intracranial hematoma, delayed hydrocephalus, subdural empyema, and visual field defects in patients.

Conclusion:
Hence, to overcome drug resistance, new pharmacological and herbal therapies are required. Animal trials are first step in the development of new drugs, to study toxicity and efficacy of proposed drugs. Many herbs have anticonvulsant activity but remain an under-explored treatment option for epilepsy. Further research on herbal extracts as a possible treatment for epilepsy needs to be conducted.

Key words: Animal model; Epilepsy; Herbal therapies; Neurological disorders; TLE-HS

INTRODUCTION

Epilepsy is a disorder in which two or more unprovoked seizures occur; it is a non-communicable disease which effects people of all ages.[1-3] It is a major public health issue with severe physical and psychological consequences, including traumatic injury, mental health disorders, and premature death.[4] Being a common chronic disorder, it affects 1% - 3% of the population worldwide.[5] Around 70 million people have this disease, and 80% of those people belong to developing countries; hence it is the most common neurological disorder worldwide.[6-8] The main cause of seizures is the imbalance of neuronal excitation and inhibition which leads to excitatory overload in the brain. Hence, glutamate and Na+ channel activity increases while gamma-aminobutyric acid (GABA) and K+channel activity decreases which are only proposed mechanism associated with epilepsy to date.[9, 10] However, for better management of epileptic patients there is a need to explore other mechanisms as well. Although effective antiepileptic drugs (AEDs) are available, treatment is limited in refractory cases in developing and other nations, due to limited resources for the diagnosis and treatment.[4]

Prevalence of epilepsy is quite high in developing countries as compared to developed countries. Overall, the incidence of epilepsy is 81.7:100,000 in developing countries while 45:100,000 in developed countries.[4,11] It has also been reported that, epilepsies with unknown etiology and with generalized seizures had the highest prevalence.[12] The incidence rate of sudden unexpected death of epileptic patients is also high (1.4:1000), indicating an alarming situation.[13] The estimation, of prevalence, and incidence of epilepsy varies worldwide due to several factors like differences in measurement of age and sex, socioeconomic and demographic conditions, and clinical characteristics such as etiology and seizure

types. According to International League Against Epilepsy (ILAE), the etiology of epilepsy might be due to abnormalities in genetic, structure, infectious, metabolic, immune, and unknown reasons.[14] The focus of this review is on Temporal Lobe Epilepsy with Hippocampal Sclerosis (TLE-HS) and the role of herbs in its management.

METHODS

For this review article, old and recent review/research articles (2000-2022) from PubMed and Google Scholar have been included regarding epilepsy, animal model to induce TLE-HS, and articles with herbal treatment for the improvement of TLE-HS patients.

REVIEW AND DISCUSSION

Epilepsy is classified by ILAE into different types with respect to seizures like focal seizures, generalized seizures, combined generalized and focal seizures, and epileptic spasms.[15,16] Seizures can be caused by different factors, with several signs and symptoms such as temporary confusion, loss of consciousness, muscle stiffness, feeling of fear, anxiety, uncontrollable jerking movements of arms and legs, and even sudden unexpected death has also been reported [6, 7, 17-19].

However, according to ILAE, seizures are classified into three main types. If a seizure involves the entire brain, it is called a generalized seizure and it is further divided in six subtypes. On the other hand, if a seizure occurs in a particular segment of the brain, it is a focal seizure. Focal seizures are further divided into three subtypes. Finally, if there is dispute regarding the type of seizure, i.e., generalized, or focal, it is declared as epileptic spasms. [2, 16, 20] Overall comprehensive classification of epilepsy with respect to seizure types and its etiology is shown in Figure 1.

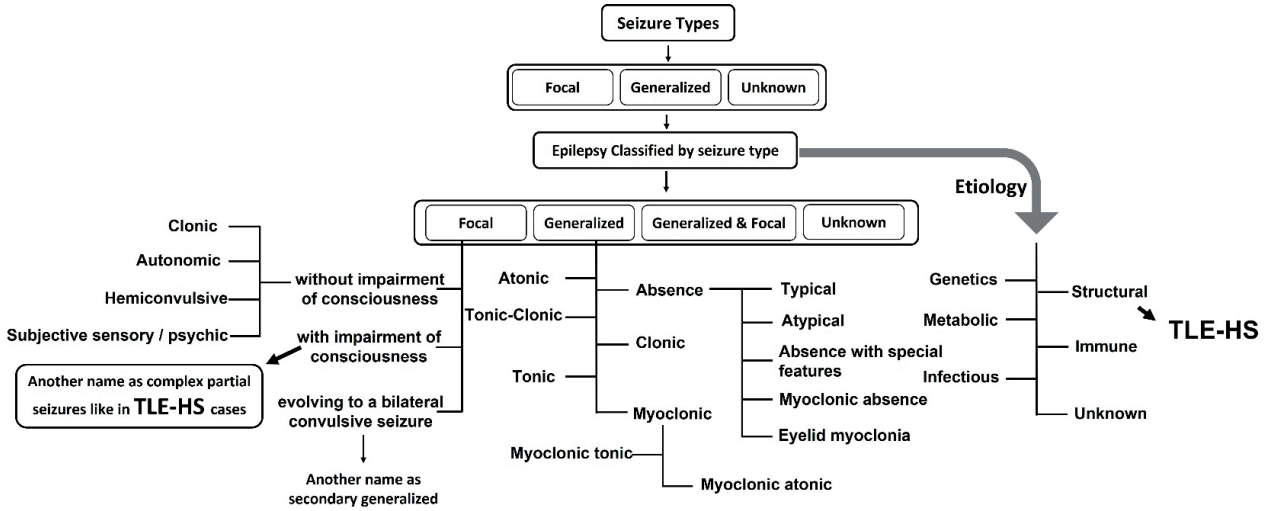

Figure 1: Classification of epilepsy based on seizure types and etiology. TLE-HS has been highlighted with enlarge bold text.

Classification of seizure type is important because it enables us to identify a specific region of the brain, which may facilitate in early diagnosis. Exact classification of epilepsy provides vital information including natural history, prognosis, diagnostic testing, therapeutics options, and helps to facilitate health care professionals. Hence, seizure type provides meaningful information even when the epilepsy cannot be classified. Sometimes, diagnosis of epilepsy might be confused with pseudo-seizures, syncope, migraine, cerebrovascular disease, movement, and sleep disorders.[5, 14]

Based on treatment, all the epileptic patients mainly fall into two broad categories: 1) patients who respond to the anti-epileptic drugs (AEDs), and their seizures are well controlled, 2) patient who do not respond to AEDs (drug resistant), and their seizures are not controlled.[2] In focal seizure epilepsy, the most common type of epilepsy is TLE-HS.[21] In this review article the use of animal models and development of treatment options for TLE-HS will be discussed in further detail.

Temporal Lobe Epilepsy (TLE)

The etiology of TLE is extensive and can be caused by different factors like genetics, birth defect, structural, tumors, traumatic brain injuries, vascular anomalies, cryptogenic and infectious. TLE needs to be differentiated from other diagnosis like migraine, psychiatric disorders, nonepileptic seizures, and syncope.[22] TLE accounts for around 66% of epileptic patients, making it the most common form of epilepsy, and among them around 71% of TLE patients are drug resistant.[21, 23, 24] TLE is further classified in two types: Mesial TLE (mTLE) and Neocortical TLE (nTLE).[25] It has also been reported that around 80% of TLE patients fall in the mTLE category.[21] mTLE is mostly observed in adult patients, in which seizures originate from the medial side of temporal lobe (mostly including a sclerosed hippocampus), leading to TLE-HS. nTLE originates from the outer part of temporal lobe, and this type of TLE is rare and mostly caused by genetics or lesions such as birth defect, tumor, blood vessel abnormality or other abnormalities in the temporal lobe. Thus, to overcome drug resistance in TLE-HS, development of effective pharmacological and herbal medicines is required.

Anti-epileptic Drugs (AEDs)

Several drugs have been introduced for the treatment of epilepsy. Phenytoin was the first AED used in 1938 to control seizures and epilepsy.[26] The new era in the development of drugs started in 1974 when novel chemical entities were introduced for the treatment of epilepsy. To date, more than 28,000 chemical entities against epilepsy have been screened worldwide.[26] Till now, AEDs are the keystone for the treatment of epilepsy, and globally, 27 licensed AEDs are used which confirmed that AEDs are the most common medications.[27] After the development of several drugs with different mechanisms of action, some drugs are used as first line treatment for status epilepticus like; lorazepam, midazolam, and diazepam, while some are used as second line treatment for epilepticus, for example, phenytoin, phenobarbital, valproate, lacosamide, and levetiracetam.[28]

Moreover, in TLE-HS cases, drug combinations were given for effectivity, but such combinations fail to terminate seizures completely.[26] Approximately, 30% of the overall epileptic patients show poor response against AEDs.[19] Hence, even though several AEDs are available in the market, the need to overcome drug resistance which requires a thorough understanding of pathophysiology of epileptic TLE-HS patients. For this purpose, animal models play a vital role.

Animal Models of Temporal Lobe Epilepsy

In the modern research era, pre-clinical trials with most appropriate animal models offer an opportunity to reproduce human diseases with nearly similar symptoms.[29, 30] Animal models give us a chance to understand the pathophysiology of epilepsy.[31, 32] Choosing a correct animal model is critical and important because age, strain, weight, and gender play vital roles in the development of a model of epilepsy. Precise and carefully controlled variables may facilitate to obtain a reliable animal model of TLE-HS with reduced mortality and variability in behaviors.[31] Moreover, gender-specific male rats are mostly used, to minimize the variations on seizures and behavior to avoid hormonal variability. Furthermore, it has been shown that male rats are more sensitive against chemicals to produce seizures as compared to female rats.[33]

Environmental factors also effect on epilepsy research, for example the way animals are handled, housing conditions (temperature and humidity, and duration of light-dark cycle), components of feed.[31] Hence, for reliable and reproducible outcomes, it is recommended to practice internationally acceptable protocols.

In some models of epilepsy chemical compounds are used to induce seizures, for example kainic acid and pilocarpine, which then go on to produce symptoms and structural changes in the animal brain close to human TLE-HS.[31] Furthermore, pilocarpine induces TLE-HS, with rapid seizure induction and neuronal loss in short time. It also has lower mortality rate compared to the kainic acid model. Another drug, pentylenetetrazol (PTZ) is used to induce seizures. PTZ is a GABA receptor antagonist, is used to create a common chemically- induced seizure model but not an epileptic model.[34] However, lithium-pilocarpine is the best known model of epilepsy for the past three decades which is discussed below.

Lithium-Pilocarpine model

With respect to same pathological conditions as human and low mortality rate, lithium Pilocarpine is the best model for experiments because it induces structural modification in brains of laboratory animals, especially in rats.[9,35] The development of Lithium-Pilocarpine model occurs in three different stages: 1) induction of status epilepticus for approximately one hour, 2) start of latent period (during which structural changes in the brain occur), and 3) establishment of chronic period (life-long spontaneous seizures).[30,33,36,37] All three stages may occur in pilocarpine model without Lithium. When pilocarpine is administered, cell damage occurs initially in the dentate granule cells and hilus, followed by

neuronal degeneration in hippocampus in a short time (3 hours) with severe pathological changes.[31,38] Moreover, soon after the injection of pilocarpine, numerous nuclei of the thalamus and the amygdala are severely damaged.[31] Hence, pilocarpine without Lithium model is more severe with respect to the level of intensity and the time course of neuronal loss. The main drawback to use pilocarpine alone is the high mortality rate as animals do not survive during or after status epilepticus stage. To reduce the damaging neuropathological effects, lithium is used 24-hour ahead of low-dose pilocarpine injection, which helps to reduce neuronal loss and mortality.

Lithium is widely used as a mood stabilizer in depression and frequently used for the treatment of chronic neurodegenerative diseases.[32,33,35,39] Recently, it is reported that lithium-pilocarpine model does not just reduce the mortality but also reduced status epilepticus induction and morbidity.[30,31,33,37] Furthermore, to reduce the severe effects of pilocarpine, methylscopolamin-bromide can be injected 30 minutes prior to pilocarpine. In some experiments, diazepam was given to reduce mortality.[40, 41] Induction of lithium does not change experimental results, as in lithium-pilocarpine model that shows similar behavioral abnormalities, EEG activity, and histopathological changes as observed in pilocarpine model. But mortality rate significantly decreased to 7%, which ensures that this model is effective over pilocarpine model alone[33,40,] as shown in Figure 2. So, TLE-HS model should be used to study drug resistant and development of effective pharmacological and herbal therapies for such cases.

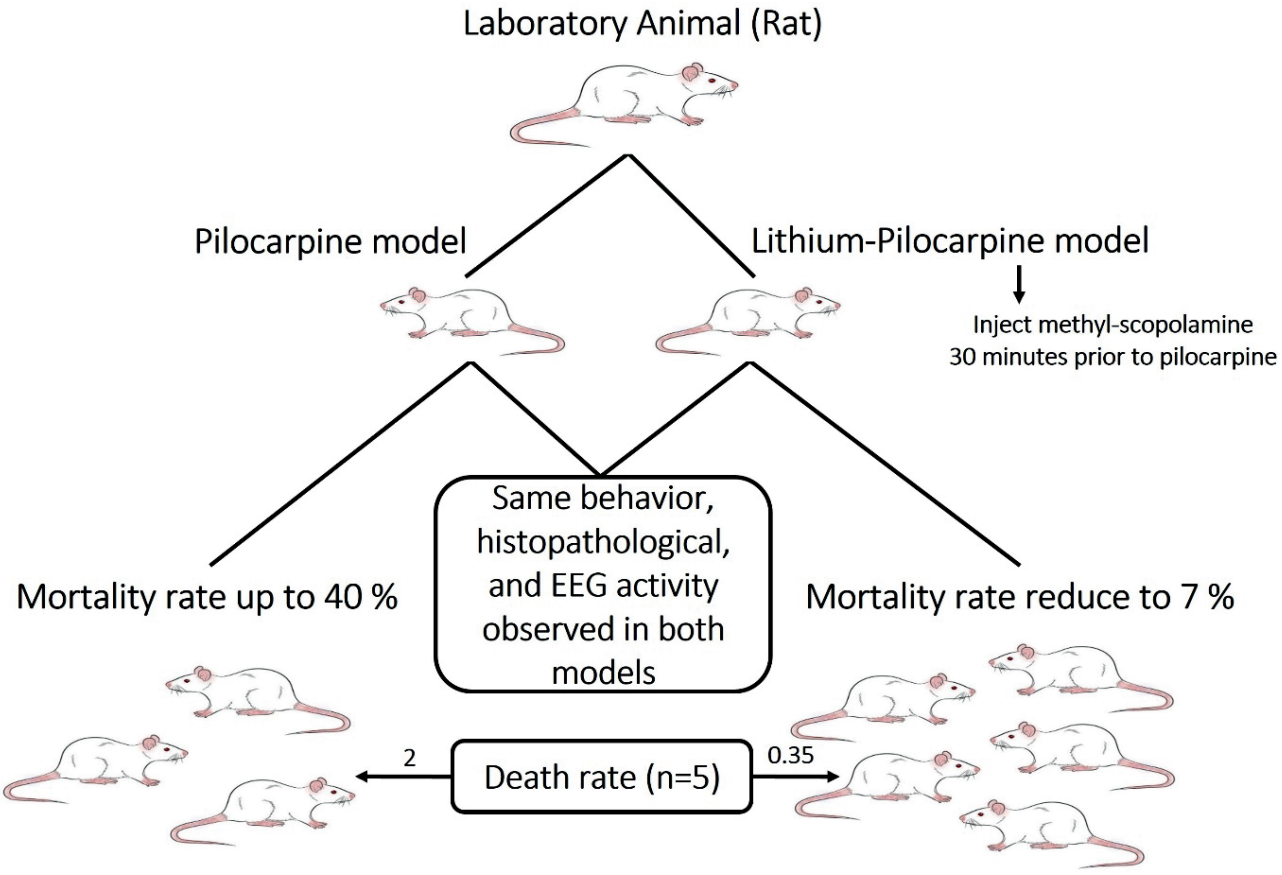

Figure 2: This figure shows advantage of using lithium-pilocarpine model as compared to pilocarpine alone. Advantage of Li-Pi is the higher survival of post treatment which allows other treatment to be conducted.

Extended survival rate increases hope for scientists and neurologists to develop new therapeutics and effective drugs for epilepsy.[31] Several interpretational techniques can be used for detailed examination of TLE-HS cases as discussed below.

Experimental Interpretation Techniques

Use of laboratory animals is a fundamental need for the welfare of humankind because they show similar behavior in experiments as humans.[31,42] Handling of laboratory animals is not an easy task, especially to record or observe seizures with behavioral changes. Such observations can be monitored for the clinical assessment through Magnetic Resonance Image (MRI) and Electroencephalography (EEG), and especially through video-EEG. [1,43,44]

MRI helps in the diagnosis of mTLE in a better way because in mTLE condition, hippocampal sclerosis or scarring that occurs in the temporal lobe can be easily observed through MRI.[45] EEG is commonly used as a clinical tool for the monitoring of seizures. EEG may help to recognize different inherited metabolic and mitochondrial disorders because seizures have been frequently observed especially if seizures occur in early stage of life.[2] EEG is a highly tedious, laborious, and time-consuming method for neurologists to identify seizures.[17, 46] As continued analysis is required for the interpretation of results, hence, it is necessary to use video-EEG so that the scientists can determine when status epilepticus starts and when it stops.[31,47] Additionally, other stages like latent and chronic periods can also be determined through video-EEG. Such techniques are essential for the interpretation of experiments especially the MRI and video-EEG which can help to understand disease pathophysiology and behavioral changes in epileptic models in a continues manner.[23,43,44,48,49.] Figure 3 represents vital interpretation techniques with their basic steps and requirements. A proper diagnosis after the interpretation through such techniques, treatment can be initiated. Different treatment options are available for epileptic patients which are discussed below.

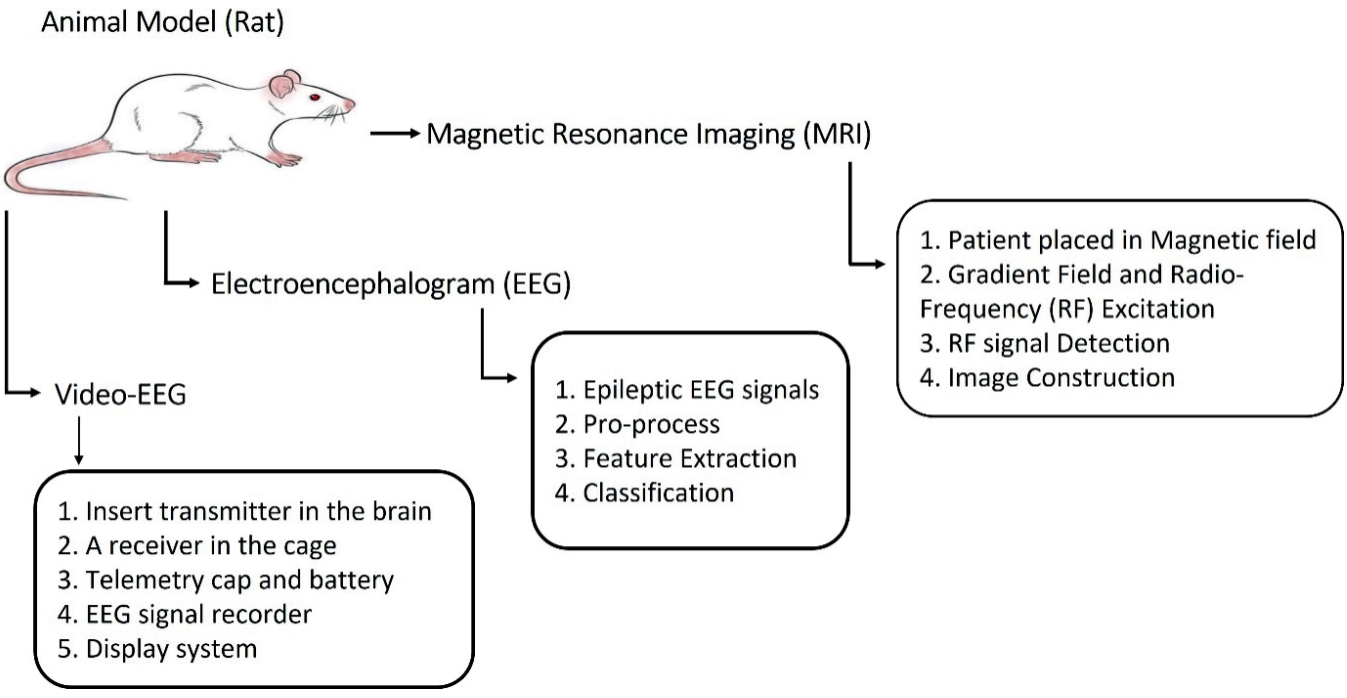

Figure 3: Data interpretation techniques. Data acquired from MRI, EEG, and video EEG for the detailed in-depth analysis of pathophysiological and behavioral changes in animal model.

Treatment options with herbal therapies

Different treatment options are available to effectively treat epilepsy like AEDs, surgery, and diet therapies (e.g., ketogenic diet) to control or terminate seizures.[18, 50-52] But TLE-HS (AEDs resistant cases) is the most frequent condition of epilepsy that is referred to the surgical centers by neurologists and family practitioners for complete termination of seizures.[53] Outcome of the surgery are positive in 50-73% patients of TLE[1], but often results in memory deficits, and occasionally, intracranial hematoma, delayed hydrocephalus, subdural empyema, and visual field defects in operated patients.[54] So, there is a need to explore herbal treatments for the treatment of TLE-HS cases as shown in Figure 4.

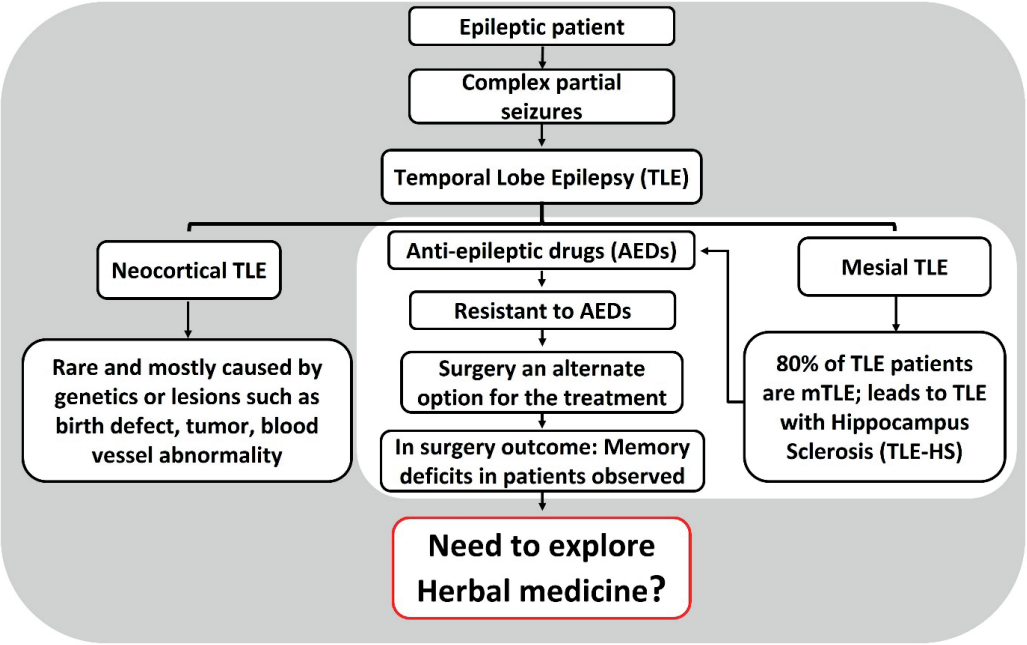

Figure 4: Possible treatment option for TLE-HS patients. Current treatment options are limited, hence herbal extracts need to be explored as a treatment option for TLE-HS.

Herbal medicine is the area that remains under-explored, though having a great potential to effectively treat epilepsy. Data has been reported with different herbs with potential to control/ terminate seizures, yet clinical studies have not been performed. Herbs have been used as traditional medicines for several decades in almost all the developed and developing countries. Many preclinical studies have been reported using epileptic models by giving herbs (anticonvulsant activity) for the treatment of epilepsy as listed in Table 1.[55-67]

Several herbs have been tested in various animal models like Maximal Electroshock (MES) administered, and treated with pentylenetetrazol (PTZ), kainic acid and picrotoxin. However, the efficacy of herbal extract treatment in pilocarpine-induced model of TLE-HS has not been well studied. It has been reported that Chinese herbs with anti-epileptic effects have the potential of effective treatment against epilepsy. Numerous herbal medicines, such as Ginkgo biloba and Huperzia serrata, have been reported to have antiepileptic or anti-convulsant effects.[57] It has also been reported that apigenin (a plant extract) has protective effect on memory-deficit induced by kainate-induced TLE-HS model a [68] Moreover, a herbal compound Danshen has been used for the treatment of TLE and cognitive deficit, and shown to have improving results; however, combined administration of Danshen with carbamazepine was shown to be more effective in controlling seizures, protection against cognitive impairment and inhibition of hippocampal neuronal loss in TLE.[69] Although, there are several reports of herbs with anticonvulsive effects, a large-scale experimental evidence and randomized controlled clinical trials are required to confirm their antiepileptic effects with outcomes. As listed in Table 1, most of the reported data used PTZ (a GABAA receptor antagonist) model to induce seizures, but this is not a virtuous model for the development of new therapies because in the PTZ model only seizures occur, not the disease epilepsy, and this model can only be used for initial screening of AEDs.[34]

Table 1: Herbs having anticonvulsant activity analyzed with different seizure models (PTZ, MES, Kainic acid and Picrotoxin)

Countries	Herbal Medicine	Seizure Model	References
Africa	Gladiolus dalenii, Acanthus montanus, Alchornealaxiflora, Hyptisspicigera,MicroglossapyrifoliaKuntze, Piliostigmareticulatum, and Voacangaafricana	PTZ and MES	55, 56
China	Ganoderma lucidum, Gastrodiaelata, Uncariarhynchophylla, Acoritatarinowii, Paeonia lactiflora, Bupleurum chinense, Ziziphus jujuba, Pinelliaternata, Paeonia suffruticosa, Stephania tetrandra, Cistanchedeserticola, Corydalis yanhusuo, Salvia miltiorrhiza, and Skullcap	PTZ, Kainic Acid, and MES	55, 57
Europe	Cannabis, Passiflora invarnate, Skullcap,Paeonia, and Viscum album	PTZ and MES	55, 58
India	Zizyphus jujube, Zingiber officinale, Marsilea quadrifolia, Moringa oleifera, and Viscum album	PTZ and MES	55, 59-61
Iran	Paeonia officinalis, Bryonia alba, Lavandula stoechas, Ferula persica willd, Ferulaasafoetida, Coriandrum sativum, Caesalpinia bonducellaroxb, Ferulagummosaboiss, Cuscutaepithymummurray, Cedrus deodara loudon, and Origanum majorana	PTZ, Picrotoxin, and MES	55, 62, 63
Pakistan	Taxus wallichianaZucc, black pepper, Anaphalistriplinervis	PTZ	55, 64-67
USA	American hellebore, betony, Blue cohosh, Kava, Mistletoe, Mugwort, Pipsissewa, Skullcap, and Valerian	PTZ and MES	55

PTZ: pentylenetetrazol, MES: Maximal Electroshock

Lithium-pilocarpine model is more effective with respect to seizure induction and low mortality rate, and this model shows the same stages (status epilepticus, latent period, and chronic seizures) as observed in human epileptic patients. But there are very few experiments on this model particularly to check the efficacy of herbs. As most of the AEDs are resistant to commonest form of epilepsy; TLE-HS, so, there is a need to develop herbal medicines for the treatment of epilepsy using lithium-pilocarpine model. For this purpose, efforts should be made by the scientists to overcome resistance through the development of new drug therapies using herbs.

Limitation

This review focuses on TLE-HS and possible herbal treatment, however, there is a need to explore genetic aspects as well as multiomics strategies for the early diagnosis and targeted treatment options for TLE-HS cases.

Future directions with herbal therapies

Although, several medical, immunological, surgical, and dietary therapies are available to control/ terminate seizureshowever surveys and research activities show that incidence of epilepsy is still quite high in population due to drug resistance, poor quality of health facilities, and diagnosis. [2, 18, 26, 27, 51, 68] Hence, further research on herbs is required for the treatment of epilepsy because numerous herbs have the potential (anticonvulsant activity) to control/ terminate seizures. Herbs can help in the development of new therapies after complete experimentation on animal models to overcome resistance. But currently, for the herbal experimentation, PTZ model is used which is not suitable due to lack of the spontaneous seizures activity as in chronic condition.[34] Thus lithium-pilocarpine model can be used to overcome such limitations. Hence, in future, large-scale experimentation on animal model and clinical studies should be done, to overcome drug resistance and development of effective herbal treatment for TLE-HS cases.

CONCLUSION

Epilepsy is a chronic neurological disorder affecting people of all ages. TLE-HS is the most common type of structural epilepsy. AEDs are available but epileptic patients with TLE-HS are mostly resistant to AEDs. It

has been reported that surgery can significantly reduce the number of seizures in patients, however, it can result in long lasting deficits for the patient. Hence, there is a need to explore herbal medicines as new treatment options for drug-resistant form of epilepsy. It is also important to use a suitable animal model for experimentation and interpretation and to explore herbs for the treatment of epilepsy using lithium-pilocarpine model. In this way, burden of epilepsy may be minimized from the society.

REFERENCES

1. Tellez-Zenteno JF, Hernandez-Ronquillo L. A review of the epidemiology of temporal lobe epilepsy. Epilepsy Res Treat. 2012;2012:630853.
2. Sirven JI. Epilepsy: A Spectrum Disorder. Cold Spring Harb Perspect Med. 2015;5(9):a022848.
3. Beghi E. The Epidemiology of Epilepsy. Neuroepidemiology. 2020;54(2):185-91.
4. Ba-Diop A, Marin B, Druet-Cabanac M, Ngoungou EB, Newton CR, Preux PM. Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa. Lancet Neurol. 2014;13(10):1029-44.
5. Shneker BF, Fountain NB. Epilepsy. Dis Mon. 2003;49(7):426-78.
6. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet. 2019;393(10172):689-701.
7. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med. 2011;365(19):1801-11.
8. Ullah S, Ali N, Khan A, Ali S, Nazish HR. The Epidemiological Characteristics of Epilepsy in the Province of Khyber Pakhtunkhwa, Pakistan. Front Neurol. 2018;9:845.
9. Amanlou A, Eslami F, Shayan M, Mortazavi P, Dehpour AR. Anticonvulsive evaluation and histopathological survey of thalidomide synthetic analogs on lithium-pilocarpine-induced status epilepticus in rats. Res Pharm Sci. 2021;16(6):586-95.
10. Fountain NB. Status epilepticus: risk factors and complications. Epilepsia. 2000;41 Suppl 2:S23-30.
11. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011;77(10):1005-12.
12. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303.
13. Saetre E, Abdelnoor M. Incidence rate of sudden death in epilepsy: A systematic review and meta-analysis. Epilepsy Behav. 2018;86:193-9.
14. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21.
15. Pack AM. Epilepsy Overview and Revised Classification of Seizures and Epilepsies. Continuum (Minneap Minn). 2019;25(2):306-21.
16. Milligan TA. Epilepsy: A Clinical Overview. Am J Med. 2021;134(7):840-7.
17. Liu G, Xiao R, Xu L, Cai J. Minireview of Epilepsy Detection Techniques Based on Electroencephalogram Signals. Front Syst Neurosci. 2021;15:685387.
18. Perucca P, Scheffer IE, Kiley M. The management of epilepsy in children and adults. Med J Aust. 2018;208(5):226-33.
19. Lai W, Du D, Chen L. Metabolomics Provides Novel Insights into Epilepsy Diagnosis and Treatment: A Review. Neurochem Res. 2022.
20. Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harb Perspect Med. 2015;5(6).
21. Fan J, Shan W, Yang H, Zhu F, Liu X, Wang Q. Neural Activities in Multiple Rat Brain Regions in Lithium-Pilocarpine-Induced Status Epilepticus Model. Front Mol Neurosci. 2019;12:323.
22. McIntosh WC, J MD. Temporal Seizure. StatPearls. Treasure Island (FL)2022.
23. Abarrategui B, Mai R, Sartori I, Francione S, Pelliccia V, Cossu M, et al. Temporal lobe epilepsy: A never-ending story. Epilepsy Behav. 2021;122:108122.
24. Hernández-Ronquillo L, Buckley S, Ladino LD, Wu A, Moien-Afshari F, Rizvi SA, et al. How many adults with temporal epilepsy have a mild course and do not require epilepsy surgery? Epileptic Disord. 2016;18(2):137-47.
25. Vinti V, Dell'Isola GB, Tascini G, Mencaroni E, Cara GD, Striano P, et al. Temporal Lobe Epilepsy and Psychiatric Comorbidity. Front Neurol. 2021;12:775781.
26. Sankaraneni R, Lachhwani D. Antiepileptic drugs--a review. Pediatr Ann. 2015;44(2):e36-42.
27. Johannessen Landmark C, Johannessen SI, Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs: current status and future

prospects. Expert Opin Drug Metab Toxicol. 2020;16(3):227-38.
28. Kim D, Kim JM, Cho YW, Yang KI, Kim DW, Lee ST, et al. Antiepileptic Drug Therapy for Status Epilepticus. J Clin Neurol. 2021;17(1):11-9.
29. Amin F, Dar AH, Osama K, Khan F, Mitha R, Tharwani A, et al. A species dependent response to the pro-epileptic drug pentylentetrazole in birds. Brain Res Bull. 2017;134:189-94.
30. Klitgaard H, Matagne A, Vanneste-Goemaere J, Margineanu DG. Pilocarpine-induced epileptogenesis in the rat: impact of initial duration of status epilepticus on electrophysiological and neuropathological alterations. Epilepsy Res. 2002;51(1-2):93-107.
31. Levesque M, Avoli M, Bernard C. Animal models of temporal lobe epilepsy following systemic chemoconvulsant administration. J Neurosci Methods. 2016;260:45-52.
32. Hong N, Choi YS, Kim SY, Kim HJ. Neuroprotective effect of lithium after pilocarpine-induced status epilepticus in mice. Korean J Physiol Pharmacol. 2017;21(1):125-31.
33. Curia G, Longo D, Biagini G, Jones RS, Avoli M. The pilocarpine model of temporal lobe epilepsy. J Neurosci Methods. 2008;172(2):143-57.
34. Kandratavicius L, Balista PA, Lopes-Aguiar C, Ruggiero RN, Umeoka EH, Garcia-Cairasco N, et al. Animal models of epilepsy: use and limitations. Neuropsychiatr Dis Treat. 2014;10:1693-705.
35. Suchomelova L, Baldwin RA, Kubova H, Thompson KW, Sankar R, Wasterlain CG. Treatment of experimental status epilepticus in immature rats: dissociation between anticonvulsant and antiepileptogenic effects. Pediatr Res. 2006;59(2):237-43.
36. Ahmed J, II, Che Has AT. The evolution of the pilocarpine animal model of status epilepticus. Heliyon. 2020;6(7):e04557.
37. Scorza FA, Arida RM, Naffah-Mazzacoratti Mda G, Scerni DA, Calderazzo L, Cavalheiro EA. The pilocarpine model of epilepsy: what have we learned? An Acad Bras Cienc. 2009;81(3):345-65.
38. Covolan L, Mello LE. Temporal profile of neuronal injury following pilocarpine or kainic acid-induced status epilepticus. Epilepsy Res. 2000;39(2):133-52.
39. Postnikova TY, Diespirov GP, Amakhin DV, Vylekzhanina EN, Soboleva EB, Zaitsev AV. Impairments of Long-Term Synaptic Plasticity in the Hippocampus of Young Rats during the Latent Phase of the Lithium-Pilocarpine Model of TemporalLobe Epilepsy. Int J Mol Sci. 2021;22(24).
40. Glien M, Brandt C, Potschka H, Voigt H, Ebert U, Loscher W. Repeated low-dose treatment of rats with pilocarpine: low mortality but high proportion of rats developing epilepsy. Epilepsy Res. 2001;46(2):111-9.
41. Dubey V, Dey S, Dixit AB, Tripathi M, Chandra PS, Banerjee J. Differential glutamate receptor expression and function in the hippocampus, anterior temporal lobe and neocortex in a pilocarpine model of temporal lobe epilepsy. Exp Neurol. 2022;347:113916.
42. Robinson NB, Krieger K, Khan FM, Huffman W, Chang M, Naik A, et al. The current state of animal models in research: A review. Int J Surg. 2019;72:9-13.
43. Zayachkivsky A, Lehmkuhle MJ, Dudek FE. Long-term Continuous EEG Monitoring in Small Rodent Models of Human Disease Using the Epoch Wireless Transmitter System. J Vis Exp. 2015(101):e52554.
44. Fonseca E, Quintana M, Seijo-Raposo I, Ortiz de Zarate Z, Abraira L, Santamarina E, et al. Interictal brain activity changes in temporal lobe epilepsy: A quantitative electroencephalogram analysis. Acta Neurol Scand. 2022;145(2):239-48.
45. Malmgren K, Thom M. Hippocampal sclerosis--origins and imaging. Epilepsia. 2012;53 Suppl 4:19-33.
46. Paul Y. Various epileptic seizure detection techniques using biomedical signals: a review. Brain Informatics. 2018;5(2):6.
47. Tacke M, Janson K, Vill K, Heinen F, Gerstl L, Reiter K, et al. The influence of information about the circumstances of EEG recordings on the ability to identify seizure patterns. Seizure. 2021;88:125-9.
48. Kerr WT, Zhang X, Hill CE, Janio EA, Chau AM, Braesch CT, et al. Epilepsy, dissociative seizures, and mixed: Associations with time to video-EEG. Seizure. 2021;86:116-22.
49. Blair RD. Temporal lobe epilepsy semiology. Epilepsy Res Treat. 2012;2012:751510.
50. Smith PEM. Initial Management of Seizure in Adults. N Engl J Med. 2021;385(3):251-63.
51. Johnson EL. Seizures and Epilepsy. Med Clin North Am. 2019;103(2):309-24.
52. Saxena VS, Nadkarni VV. Nonpharmacological treatment of epilepsy. Ann Indian Acad Neurol. 2011;14(3):148-52.
53. Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, et al. Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery. N Engl J Med. 2017;377(17):1648-56.
54. Mathon B, Navarro V, Bielle F, Nguyen-Michel VH, Carpentier A, Baulac M, et al. Complications After Surgery for Mesial Temporal Lobe Epilepsy

Associated with Hippocampal Sclerosis. World Neurosurg. 2017;102:639-50 e2.
55. Liu W, Ge T, Pan Z, Leng Y, Lv J, Li B. The effects of herbal medicine on epilepsy. Oncotarget. 2017;8(29):48385-97.
56. Bum EN, Taiwe GS, Nkainsa LA, Moto FC, Seke Etet PF, Hiana IR, et al. Validation of anticonvulsant and sedative activity of six medicinal plants. Epilepsy Behav. 2009;14(3):454-8.
57. Lin CH, Hsieh CL. Chinese Herbal Medicine for Treating Epilepsy. Front Neurosci. 2021;15:682821.
58. Li P, Shen J, Wang Z, Liu S, Liu Q, Li Y, et al. Genus Paeonia: A comprehensive review on traditional uses, phytochemistry, pharmacological activities, clinical application, and toxicology. J Ethnopharmacol. 2021;269:113708.
59. Ingale SP, Gandhi FP. Effect of aqueous extract of Moringa oleifera leaves on pharmacological models of epilepsy and anxiety in mice. International Journal of Epilepsy. 2016;3(1):12-9.
60. Sahu S, Dutta G, Mandal N, Goswami AR, Ghosh T. Anticonvulsant effect of Marsilea quadrifolia Linn. on pentylenetetrazole induced seizure: a behavioral and EEG study in rats. J Ethnopharmacol. 2012;141(1):537-41.
61. Pahuja M, Kleekal T, Reeta KH, Tripathi M, Gupta YK. Interaction profile of Zizyphus jujuba with phenytoin, phenobarbitone, and carbamazepine in maximal electroshock-induced seizures in rats. Epilepsy Behav. 2012;25(3):368-73.
62. Bagheri SM, Sahebkar A, Gohari AR, Saeidnia S, Malmir M, Iranshahi M. Evaluation of cytotoxicity and anticonvulsant activity of some Iranian medicinal Ferula species. Pharm Biol. 2010;48(3):242-6.
63. Sahranavard S, Ghafari S, Mosaddegh M. Medicinal plants used in Iranian traditional medicine to treat epilepsy. Seizure. 2014;23(5):328-32.
64. Bukhari IA, Pivac N, Alhumayyd MS, Mahesar AL, Gilani AH. The analgesic and anticonvulsant effects of piperine in mice. J Physiol Pharmacol. 2013;64(6):789-94.
65. Nisar M, Khan I, Simjee SU, Gilani AH, Obaidullah, Perveen H. Anticonvulsant, analgesic and antipyretic activities of Taxus wallichiana Zucc. J Ethnopharmacol. 2008;116(3):490-4.
66. Basharat A. Distribution, morphology and medicinal uses of taxus baccata. Hamdard Medicus. 1997.
67. Ajaib M, Ishtiaq M, Bhatti KH, Hussain I, Maqbool M, Hussain T, et al. Inventorization of traditional ethnobotanical uses of wild plants of Dawarian and Ratti Gali areas of District Neelum, Azad Jammu and Kashmir Pakistan. PLoS One. 2021;16(7):e0255010.
68. Barba C, Cossu M, Guerrini R, Di Gennaro G, Villani F, De Palma L, et al. Temporal lobe epilepsy surgery in children and adults: A multicenter study. Epilepsia. 2021;62(1):128-42.
69. Jia C, Han S, Wei L, Dang X, Niu Q, Chen M, et al. Protective effect of compound Danshen (Salvia miltiorrhiza) dripping pills alone and in combination with carbamazepine on kainic acid-induced temporal lobe epilepsy and cognitive impairment in rats. Pharm Biol. 2018;56(1):217-24.

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Author's contribution:
Muhammad Wasim; concept, data collection, data analysis, manuscript writing, manuscript review
Mehr Musani; data collection, data analysis, manuscript writing, manuscript review
Hasan Salman Siddiqi; concept, data analysis, manuscript review
Saara Muddasir; data collection, data analysis, manuscript review
Bushra Amin; data collection, data analysis, manuscript review
Fazal Manzoor Arain; concept, manuscript review