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Review Article

Conventional Epilepsy Treatments in Morocco and Recommendations for Future Research Directions: An Up-to-Date Review

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ABSTRACT

Epilepsy affects around 70 million people globally, with a high prevalence in low- and middle-income countries like Morocco. Rural populations face difficulties accessing treatment due to economic challenges, poor healthcare infrastructure, and social stigma. Over 20 clinically approved medications are used for treatment. This review explores conventional approaches to epilepsy treatment in Morocco, emphasizing the need for improved healthcare access and culturally sensitive interventions. The study was conducted through a comprehensive literature search across various databases, including ScienceDirect, Springer, PubMed, MDPI, Frontiers, and Hindawi. Keywords, such as "epilepsy," "mental disorder and seizures," "brain disorder," and "epilepsy treatment" were used to perform the search. The literature review revealed a rising prevalence of epilepsy, affecting individuals of all ages and representing 0.6% of the global disease burden, particularly in low- and middle-income countries. Causes include stroke, infections, genetic factors, and environmental influences. Conventional treatments, such as antiepileptic drugs (AEDs) and surgical interventions, are vital for seizure control, but many patients experience medication resistance and side effects. Surgical options remain underutilized due to misconceptions and access issues. In rural areas, reliance on traditional healers and medicinal plants like *Artemisia herba-alba* and *Mentha pulegium* for alternative therapies highlights a gap in epilepsy awareness and diagnosis. The review emphasizes the need to integrate traditional knowledge with modern medical practices and calls for interdisciplinary research and equitable distribution of treatment centres. Future efforts should prioritize culturally sensitive, cost-effective strategies to improve early diagnosis, treatment access, healthcare services, and public awareness for better epilepsy outcomes in Morocco.

***Keywords*:** Epilepsy, Conventional treatment, Antiepileptic drugs.

Introduction

Mental disorders constitute a serious burden on healthcare systems worldwide. Multiple endo and exogenous factors affect brain homeostasis resulting in functional perturbations, including epilepsy. Epilepsy is one of the most neurological disorders accompanied by various physical and psychological consequences, such as bodily injuries, recurrent seizures, mental health perturbations, and premature death.[1] The disorder is characterized by recurrent seizures accompanied by cognitive, neurobiological, and psychosociological consequences, which affect the quality of life of patients.[2] It affects approximately 70 million people of all ages, with the highest proportion registered in low- and middle-income regions, especially in rural zones.[3,4]
The lack of appropriate healthcare for patients with epilepsy is the main cause of its rise in underdeveloped countries, which may be tenfold more than in high-income ones.[5]

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Several factors, such as environmental and social differences, and local geographic regions, may strongly influence epilepsy prevalence. Low incomes and inadequate access to medical assistance and healthcare exacerbate the situation, contributing to higher rates of epilepsy in rural regions. These challenges make it difficult to accurately determine the true prevalence of the condition in these areas.[6] Furthermore, less knowledge, greater reliance on artisanal healers, and environmental exposure may explain the very high prevalence rate of epilepsy in rural regions. In Morocco, almost half of the population lives in rural areas, which are confronted with challenges such as economic vulnerability, lack of access to health care, the misconception of epilepsy, discrimination, and so on.[6] The prevalence of epilepsy in Morocco is estimated at 1.1%, with approximately 370,000 individuals affected. The mortality rate associated with epilepsy is estimated at 0.2%.[5] Several factors contribute to the prevalence of mental health disorders, including unfavourable geographic locations, a shortage of neurologists, and widespread misconceptions about epilepsy, often viewed as either contagious or a spiritual condition.[5,6] Furthermore, a recent study conducted in Arab countries evoked that epilepsy is a multifactorial chronic disease in origin, and the most common risk factors that induce epilepsy are family history of epilepsy, consanguinity, and perinatal infections or insults.
Managing the disease incurs high costs and often requires patients to travel to cities where neurologists are available, increasing the treatment burden. As a result, medicinal plants are gaining attention for their availability, safety, lack of side effects, and effectiveness. Despite advancements in epilepsy treatment, limited knowledge, and infrastructural challenges hinder accurate diagnosis and effective disease management. Additionally, 90% of individuals in low- and middle-income countries do not receive standard care.[7] One of the most fundamental challenges in drug discovery is understanding the

mechanism of action of a disease and how it is triggered in patients, given that the etiology of the disease is largely heterogeneous. Another major concern for the development of new antiepileptic drugs is the control of their adverse effects. The causative factors are a network of various abnormalities in multiple interconnected pathways that require individualization of treatment for each patient. Moreover, human interindividual variability induced by various genetic and environmental factors makes it difficult to develop effective early diagnosis, treatment, and prognostic assessment of diseases in a given population. Thus, pharmacogenetics and pharmacogenomics address the genetic basis of variable drug responses in patients.

The present study aimed to review and discuss current literature and recent data on epilepsy, focusing on conventional approaches used to manage the disorder in Morocco.

Materials and Methods

The present study was prepared using scientific articles published in various databases, including ScienceDirect, Springer, PubMed, MDPI, Frontiers, and Hindawi. Various keywords were used for the article search, including "epilepsy," "mental disorder and seizures," "brain disorder," and "epilepsy treatment." Articles for this review were selected based on their scientific rigour and relevance.

Results and Discussion

Prevalence, causes, and risk factors of epilepsy.

All age groups are predisposed to epilepsy, with a peak in the elderly. As a chronic disorder, the clinical manifestations of epilepsy are characterized by seizures, recurrent episodic attacks, and psychiatric consequences.[8] The ageing process is generally accompanied by dysfunction of different systems, including brain function, which can be associated with an elevated frequency of epilepsy. The older population is more susceptible than the younger population due to various factors, including ageing, stress, and environmental influences.[8–10] It is classified as the third most common disease affecting older people after stroke and dementia.[4] The ageing process is an important factor in epilepsy and brain disorders. A study by de la Court *et al*. (1996) found that the prevalence rate increased with ageing with a value of 7 per 1000 individuals aged 55 to 65 years and 12 per 1000 individuals aged 85 to 94 years.[11] Other evidence showed that epilepsy affects 1% of persons aged over 65 years.[12,13]

In Morocco, several factors affect the accurate determination of epilepsy prevalence and the age groups impacted, including illiteracy and ignorance, which hinder access to healthcare. Furthermore, it is considered a spiritual disease, thereby requiring traditional healers.[5,14] Epilepsy affects people of all ages with 0.6% of the global burden illness, with a prevalence of 0.8% in North America,[15] 1.129% in Africa,[16] 0.23% in the Arab world,[17] 1.1% in West Africa, 0.6% in Asia,[2] and 0.83% in India.[18] It is observed that epilepsy prevalence varies significantly globally, particularly across developed and undeveloped countries. Epilepsy rates increase with age, with elderly individuals experiencing approximately twice the prevalence seen in young adults.[19] The older patients with acquired epilepsy suffer from other brain disorders, including neoplastic, cerebrovascular, or other brain lesions known to generate seizures.[20] The causes of epilepsy were categorized by the International League Against Epilepsy (ILAE) into structural, genetic, infections, metabolic, immune, and unknown causes.[21]

Pathophysiology of epilepsy

Epileptogenesis is the process of transforming a normal neuronal network into a hyperexcitable one. This transformation often occurs following brain damage or disease, leading to the generation of seizures that are closely correlated with the extent of the injury. Permanent discharge of a group of neurons could be due to multiple factors, including tumours, metabolic derangements, infections, brain damage, and oxygen deprivation.[22] Mounting evidence has shown that the majority of older patients suffering from acquired epilepsy have neoplastic, cerebrovascular, and other brain disorders that cause seizures.[20] Despite scientific progress, clinical assessment, and imaging advancement, 25-50% of persons with epilepsy remain undiagnosed correctly with unknown etiology.[19] Genetic factors are implicated in the pathogenesis process. Scientific progress in sequencing technologies has found that multiple gene mutations are involved in the occurrence of brain disorders by perturbing channel function (ion channels and non-ion channels), dysfunction of the electrical pulse, as well as signal transmission of neurones.[23,24]

Treatment of epilepsy

A brain disorder is a common neurological condition caused by an imbalance between excitatory and inhibitory processes, resulting in unwanted seizures despite optimal medication.[25] The treatment of epilepsy consists of numerous modalities, including anti-seizure drugs, surgery, and complementary alternative medicine. The choice of provider is strongly influenced by multiple factors, including the nearest provider or the provider suggested by friends or neighbours, treatment costs, and so on.

Conventional approaches to treating epilepsy

a) Medication treatment

Medication treatment is at present the pillar of epilepsy treatment. Several anti-seizure drugs have been available on the market in recent years, with around 30 currently accessible for the treatment of brain disorders.[26] Multiple chemical agents, including sodium valproate, carbamazepine, and phenobarbital, were the common drugs used to treat epilepsy.[27] Anti-seizure medications aim to improve quality of life by helping patients become seizure-free. The choice of suitable treatment is highly related to different factors, such as seizure type, epilepsy syndrome, other pathologies, and medication used to avoid any drug interaction.[28] The recurrence of seizures is used to evaluate the efficacy of epileptic drugs in clinical trials.

Numerous countries did not consider epilepsy to be a public health priority like other pathologies, such as diabetes, cardiovascular diseases, and cancer. The goal of epilepsy treatment is to achieve effective seizure control or a complete cure. Despite ongoing efforts to develop effective antiepileptic drugs, around 30 to 40% of epileptic patients are estimated to show resistance to these medications.[5,29,30] Untreated patients may have negative consequences in their lives. The discovery of new antiepileptic drugs has helped reduce drug interactions and the occurrence of convulsions, but they still fall short of completely treating the underlying brain disorder. Anti-epileptic drugs (AEDs) act differently by diverse mechanisms of action. Understanding these mechanisms constitutes an effective avenue to select medication for particular epilepsy patients.[31] Anti-epileptic drugs could be divided into different groups according to the target. These drugs primarily target the inhibitory synapse and include benzodiazepines, barbiturates, ganaxolone, stiripentol, felbamate (FBM), topiramate (TPM), and bromide.[31–33] Meanwhile, AEDs that act on excitatory synapses include topiramate, lamotrigine, phenobarbital, felbamate, valproate, gabapentin, and pregabalin.[31,34–38] Antiepileptic drugs (AEDs) primarily targeting excitatory synapses focus on NMDA receptors. Neurone depolarization is mediated by presynaptic voltage-gated calcium channels (Ca_V), which facilitate the influx of calcium ions and then cause the synaptic release of neurotransmitters.[31] Antiepileptic drugs block the activity of these channels by binding the subunit of Cav named $\alpha 2\gamma 1$ protein.[34,39] Conversely, AEDs inhibit synapses by targeting post-synaptic GABAA and GABAB receptors.[31] These drugs activate the receptors without GABA or by potentializing the impact of GABA.[32] Antiepileptic drugs (AEDs) are classified based on their mechanisms of action, including those that primarily affect voltage-gated channels, GABA, NMDA, and AMPA receptors, and neurotransmitter release modulators (Table 1).[40]

Despite the scientific progression of epilepsy drug discovery, 20-30% of patients suffering from epilepsy still experience seizures, even if multiple antiepileptic agents are used to handle the pathology.[43] The resistance occurrence is highly associated with several factors, such as inappropriate dose, seizure type, early start of epilepsy, seizure frequency, and genetic factors.[44,45] The AEDs' long-term administration and dosage could be the main reason for side effects.[46–48] Chemical drugs induce oxidative stress with serious deleterious effects surpassing antioxidant defence systems.[49]

Table 1: Mechanisms of action of different antiepileptic drugs

Drug name	Synapse	Target	Effect	Reference
Ketamine Felbamate Sodium valproate Topiramate Lamotrigine Phenobarbital	Excitatory synapse	N-methyl-D-aspartate (NMDA) receptor α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptor	Inhibit influx of sodium and trigger postsynaptic excitation	[41]
Gabapentin Pregabalin Lamotrigine Levetiravetam Phenobarbital		Presynaptic voltage-gated calcium channels (Ca_V)	Inhibit membrane depolarization then glutamate release	[41,42]
Benzodiazepines Barbiturates Vigabatrin tiagabine	Inhibitory synapse	γ-aminobutyric acid (GABA) receptors A and B	Induce hyperpolarization of post-synaptic neurons Enhance the influx of chloride into the postsynaptic cell	[41]
Lamotrigine Lacosamide		Voltage-gated sodium channels	Block sodium channels	

Research indicates that oxidative stress plays a significant role in the onset and progression of various diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease.[50,51] Due to their high oxygen consumption, neurons generate elevated levels of free radicals during signal transmission.[50] The excessive concentration of reactive oxygen species (ROS) and reactive nitrogen species (RNS) poses potential toxicity to neurones. In this context, the scientific research community emphasizes the need to develop new medications to address neuronal overexcitation, regulate glial cell activity, manage oxidative stress, and combat chronic inflammation.[52] Recently, encapsulation has emerged as a promising approach to enhance the efficiency of medication delivery.[53,54] The encapsulation of lamotrigine in dehydroascorbic acid (DHAA) and polyethylene glycol (PEG) to form DHAA-PRG-poly-LysB showed promising effects by scavenging free radicals and enhancing anti-oxidation, inflammation persistency, and over-excitation of neurones.[52] Overall, the combination strategy of antiepileptic drugs (AEDs) could enhance their therapeutic effects effectively and improve neuronal tissue protection.

b) Surgical treatment

Surgical intervention is regarded as the second option for treating epilepsy, particularly in individuals with focal epilepsy, through procedures such as amygdalohippocampectomy.[55] This surgical technique can eliminate seizure occurrence or reduce antiepileptic drug resistance in approximately 80% of patients.[55] The ability to control seizures and enhance patients' quality of life compared to medical management of epilepsy has been scientifically demonstrated.[56] Surgery can improve the quality of life by reducing the risk of early mortality and is considered safe and cost-effective.[57] The most effective management of epilepsy is closely tied to accurately diagnosing medication resistance and selecting the optimal surgical treatment option.[58] In Africa, epilepsy surgery is initiated in numerous African countries, such as the Republic of South Africa, Morocco, Tunisia, and Algeria.[16] The costs of epilepsy surgery were estimated at 3,411 to 4,500 USD.[16] Neurosurgery in Morocco was initiated in the first half of the 20th century by French doctors, especially Dr. R. Acquaviva, who founded modern neurosurgery as an independent surgical specialty in Morocco.[59] Since 2005, surgical interventions for epilepsy have been initiated, with a total of fifty-one patients undergoing surgery.[60] Several factors contribute to the underutilization of epilepsy surgery as a treatment option, including perceptions of the procedure, attitudes toward it, and gaps in knowledge. Furthermore, patients receive different medications from numerous healthcare professionals throughout their treatment.[57]

Epilepsy treatment centres expand to other cities to bring services closer to patients. In a study conducted by Souirti *et al*.,[58] at the University Hospital Centre, Hassan II of Fez, it was reported that 57% of patients obtained seizure freedom (Engel Class I). The study also demonstrated that surgical resection can liberate 70-90% of patients suffering from epilepsy medication resistance from seizure recurrence.[58,61,62] Pre-surgical assessment necessitates a comprehensive set of tools to accurately diagnose the brain disorder. Additionally, the operational evaluation requires multidisciplinary teams and convenient access to healthcare, which has been recently limited by the emergence of the coronavirus.

c) Complementary and alternative medicine

Since ancient times, natural products have been widely utilized to manage the different nutritional and pharmaceutical needs of humans of different civilizations. Several natural remedy descriptions appeared in ancient writings and date back to the Paleolithic age (60,000 years ago).[63] Natural products are gaining prominence as safe and effective remedies for treating various conditions, including nervous system disorders.[64] Despite the progress of the discovery of new medications, medicinal herbs are more used to treat brain disorders.[65] The study by Rutebemberwa *et al*.,[56] reported that epilepsy patients seek treatment from five main types of providers as their first point of contact: health centres (35.4%), hospitals (21%), neighbours or friends (12.8%), churches or mosques (11.8%), and traditional healers (10.5%). In another study conducted by Danesi and Adetunji,[67] reported that African traditional medicine was highly used to treat epilepsy with a percentage of 47.6%. In another study conducted in Morocco, 75% of

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participants reported having consulted traditional healers at least once.[16] Similar findings have been reported in several studies conducted in various countries, including Ghana, South Africa, and Ethiopia.[68–70] Numerous plants are used in Morocco to treat epilepsy, such as *Artemisia herba-alba* Linnaeus, *Chrysanthemum coronarium* Linnaeus, *Tetraclinis articulata* Linnaeus, *Retama monosperma* (L.) Boiss, *Retama raetam* Linnaeus, *Marrubium echinatum* Linnaeus, *Mentha pulegium* Linnaeus, *Allium cepa* Linnaeus, *Myristica fragrans* Linnaeus, *Coffea arabica* Linnaeus, *Solanum tuberosum* Linnaeus, *Aloysia citrodora* Linnaeus.[64] Two major factors attract patients to traditional healers and natural products, including poor knowledge of epilepsy and low income, which highly delay healthcare consultation for the proper diagnosis and treatment.[16] In Morocco, several traditional practices were used to treat epilepsy, such as exorcism, rituals lasting all night, reading the Quran, and blessed amulets.[16,63] Table 2 presents different natural remedies used to treat epilepsy in several countries.

Table 2: Different traditional remedies used to treat epilepsy in different traditional medicines

Medicine	Name	Formulation	Effect	Reference
Traditional Chinese Medicine	Chaihu Shugan decoction	*Paeonia lactiflora* *Bupleurum chinense* *Ligusticum wallichii* *Citrus aurantium* *Citrus reticulate* *Uncaria rhynchophylla* *Glycyrrhiza uralensis*	Upregulates the glutamate transporter (GLT-1) Upregulates the glutamate synthetase (GS) activity Reduces seizure frequency Exerts significant neuroprotective potency	80–83
	Tianma Gouteng decoction	*Gastrodia elata* *Uncaria rhynchophylla* *Gardenia jasminoides* *Poria cocos* *Scutellaria baicalensis* *Eucommia ulmoides* *Achyranthes bidentate* *Polygonum multiflorum*	Reduces the seizure frequency Alleviates symptoms of seizures	84,85
	Kangaxian capsules	*Gastrodia elata* *Pinellia ternate* *Acorus tatarinowii* *Bombyx mori* *Fritillaria cirrhosa* *Poria cocos* *Polygala tenuifolia* *Salvia miltiorrhiza* *Ophiopogon japonicus*).	Relieves clinical symptoms of epilepsy by increasing insulin-like growth factor 1(IGF-1) and brain-derived neurotrophic factor (BDNF) Controls the influx of calcium and reduces the NMDA receptor channel current	
	Taohong Siwu decoction	*Prunus persica* *Carthamus tinctorius* *Angelica sinensis* *Paeonia lactiflora* *Ligusticum wallichii* *Rehmannia glutinosa*	Treats epilepsy symptoms Reduces seizures recurrence	81
	Liujunzi decoction	*Panax ginseng* *Glycyrrhiza uralensis* *Atractylodes macrocephala Rhizoma* *Poria cocos* *Pinellia ternata*	Alleviates seizures	81
	Huazhuo Jiedu Shugan decoction	*Scutellaria baicalensis* *Gynostemma pentaphylla*	Inhibits epileptic seizures	86

		Radix bupleuri	Ameliorates cognitive and emotional	
		Rhizoma acori graminei	disorders	
		Lotus petiole	Regulates neuropeptide Y expression	
		Basil (Luo le)	Regulates the cyclic adenosine monophosphate (cAMP) signaling pathway	
Persian Medicine	*Terminalia chebula*	Fruit extract	Reduces seizure duration	87–91
	Anacyclus pyrethrum	Root extract	Increases the seizure threshold	
	Pipinella anisum		Acts as anticonvulsant agent	
	Laurus nobilis	Seed extract	Acts as anticonvulsant agent	
	Origanum majorana	Fruit extract	Reduces seizure duration	
		Aerial part extract		
Byzantine Medicine	*Hellebore*			92
	Scammony			
	Aloes			
	Clysters			
	Bloodletting			

The earliest written evidence of medicinal plant use is believed to have been found in Sumerian culture.[71] According to the literature, the Egyptians, Chinese, and ancient Greeks were among the earliest to use plants for treating ailments.[72] The establishment of the School of Medicinal Plants by Theophrastus was a pivotal moment in the advancement of research into the beneficial properties of medicinal plants.[72,73] The bioactive compounds in these medicinal plants are responsible for their scientifically proven anticonvulsant and sedative effects (Figure 1).[74–79] Kolawole *et al*. found that oral pretreatment of mice with crude extract of *Newbouldia laevis* leaves at different doses (160-600 mg/kg bw) significantly increased seizure latency and decreased seizure duration and mortality.[1] The authors found that this plant exhibited anticonvulsant effects mediated by GABAergic and opioidergic transmission systems.[1] In the same context, Bolanle *et al*. found that the phytocompounds extracted from *Jatropha curcas* exhibited considerable protective effects against convulsions induced in an animal model. Several phytoactive compounds are effective against convulsions as antiepileptic agents, including amentoflavone, oliganthin, epigallocatechin-3-gallate, phenytoin, and rutin.[1]

The number of scientific reports on natural products has remained high in recent decades, owing to their unique beneficial properties against various human brain disorders. The beneficial effects of natural products in the clinical treatment of epilepsy have been reported in several studies.[93–95] Natural products contain several phytocomponents with pleiotropic effects. Plants produce these compounds to counteract the harmful effects of abiotic and biotic agents.[96] Through chance discoveries and experimental tests, humans have uncovered the potential of these molecules to prevent and treat various diseases, including epilepsy.[94] Mounting evidence indicates that flavonoids exert effects similar to certain antiepileptic drugs (AEDs), such as benzodiazepines, due to their chemical structures.[97] Bioactive compounds act directly or indirectly by interacting with central nervous system receptors, such as γ-aminobutyric acid receptors type A (GABA R), and act as anticonvulsive agents to recover the physiologic excitability of neurones.[98] *In situ* assays using molecular docking revealed that phytocompounds interact efficiently with different targets, including NMDA, AMPA, carbonic anhydrase enzyme II, and voltage-gated sodium ion channels.[99] Chrysin, a flavonoid compound, inhibits the expression of tonic-clonic seizures.[100] Importantly, wagonin has been found effective in treating epilepsy without inducing sedation and myorelaxation, which are well-known side effects of AEDs.[98]

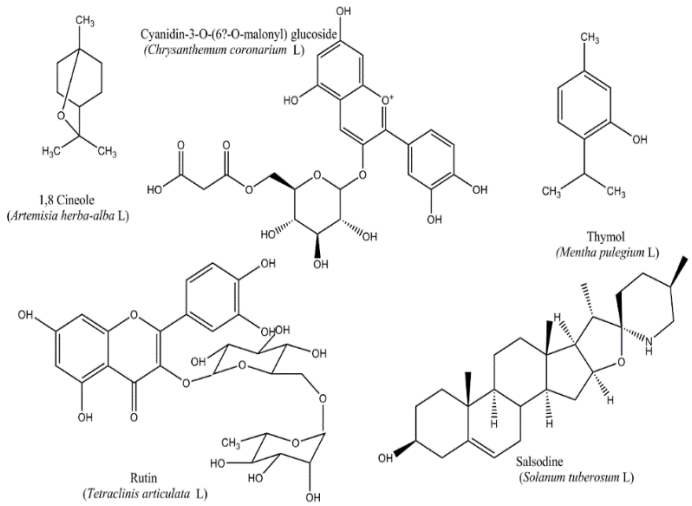

Figure 1: Chemical structures of natural compounds found in different medicinal plants with antiepileptic effect.

Recommendations for future research direction

Brain disorder is a serious condition that affects all age groups. It requires special care to improve the quality of life of patients and reduce the severity and morbidity of brain illness. Decision-makers are invited to integrate this pathology into the care basket lists, such as long-lasting ailments. Public awareness includes brain infections, head injuries, and ischaemic damage as reasons that could induce epilepsy. Additionally, establishing epilepsy centres in various regions and ensuring their equitable distribution across the country could enhance access to healthcare for patients and their families. Conversely, it is recommended to enhance and update the training of medical and paramedical healthcare professionals based on the latest medical research. Furthermore, establishing multiple epilepsy centres is preferable to facilitate researchers in developing new drugs and strategies to improve the quality of life for patients. In the past two years, the COVID-19 pandemic has adversely affected patients with epilepsy. Healthcare access was suspended during difficult times in the pandemic, which may have had unintended consequences.

It is recommended to establish multidisciplinary teams for epilepsy surgery evaluations and pre-surgical monitoring, which necessitate

adequate infrastructure. It is also advised that physicians consult the product information leaflet that comes with every medication packaging for details regarding the medication dosage and frequency. Furthermore, therapeutic monitoring of antiepileptic drugs represents a potential avenue for optimizing personalized medication therapy to avoid drug-resistant epilepsy and side effects.

Conclusion

This review underscores the importance of integrating traditional knowledge with modern medical practices, encouraging interdisciplinary research, and promoting the equitable distribution of epilepsy treatment centres. Future research should focus on developing culturally appropriate, cost-effective strategies to address epilepsy, improving early diagnosis, and expanding access to both conventional and alternative treatments. Expanding healthcare services, enhancing public awareness, and updating medical training are essential to improving outcomes for individuals with epilepsy in Morocco.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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