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Review

The importance of botanical treatments in traditional societies and challenges in developing countries

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ABSTRACT

Epilepsy is one of the most common neurological conditions worldwide, with many affected persons found in Asia, Latin America, and sub-Saharan Africa. Relatedly, the large majority found in these regions does not receive the appropriate therapy with antiepileptic drugs (AEDs), stemming from various reasons among which are lack of access to AEDs, social stigma, and negative cultural attitudes. The presence of epilepsy resistant to the available AEDs coupled with the frequent AED side effects has further fueled the widespread and growing use of botanicals as alternative therapy in several traditional societies in these developing countries since people with epilepsy (PWE) consider them as safe and effective. There have, however, been few botanicals that have been examined for their pharmacological activities related to traditional uses, and there is hardly any conclusive evidence regarding their efficacy in humans or knowledge about the exact mechanism(s) of action. This review discusses some botanical treatments that have been used for epilepsy in developing countries and the challenges faced.

This article is part of a Special Issue entitled "Botanicals for Epilepsy".

1. Introduction

Epilepsy is a common neurological disorder that affects around 70 million people worldwide; with over 85% of the people with epilepsy (PWE) living in developing countries found in Asia, Latin America, and sub-Saharan Africa [1]. Regrettably, most developing countries are former colonies and are characterized by low economic development, low life expectancy, and high rates of poverty and disease [2]. The developing countries constitute some of the poorest in the world and rely heavily on development assistance for health, most of which is aimed at treating communicable diseases and not noncommunicable ones like epilepsy. While the bulk of PWE is found in developing countries, it is also in these regions that the large majority (90%) does not receive the appropriate AED therapy [3,4]. There are several reasons for this stemming from the following: scarcity of trained health workers, poor accessibility to AEDs, lack of diagnostic support facilities, social stigma, and cultural beliefs and attitudes [5,6]. Furthermore, it is estimated that approximately 30–40% of all PWE have seizures resistant to the available AEDs with similar numbers frequently affected by AED side effects [7].

This situation implies that many PWE may not seek biomedical treatment for their epilepsy [8] and have propelled a renewed interest in researchers in developing innovative means to treat epilepsy through the discovery of new antiepileptic medications from herbal medicines [9]. Herbal medicines or botanicals have also become quite popular, since PWE consider them as safe and effective [10].

1.1. Botanical treatments and traditional societies

According to the World Health Organization (WHO), it is estimated that 80% of the population in developing countries continues to rely on medicinal plant preparations to meet their basic health care needs [11]. Herbal medicines are derived from herbs and herbal materials. The herbs include the leaves, flowers, roots, bark, fruit, seed, stems, or other plant parts that are usually taken in the form of teas, infusions, decoctions, and/or tablets or used as creams/ointments prepared by an herbalist [12]. The herbal materials not only comprise herbs, but also include dried ground powder, plant extracts, resins, fixed oils and essential oils. A phytomedicine has been defined 'as a medicine derived from plants in their original state and standardized for use in a dosage regimen' [13].

Abbreviations: AEDs, antiepileptic drugs; AC/AE, anticonvulsant/antiepileptic; CBD, cannabidiol; CUC, cow's urine concoction; CYP450, cytochrome P450 system; $GABA_A$, gamma amino butyric acid type A; GAP, good agricultural practice; MES, maximum electroshock; NMDA, N-methyl-D-aspartate; PTZ, pentylenetetrazole; TCM, traditional Chinese medicine; THC, delta-9-tetrahydrocannabinol; TKM, traditional Korean medicine; PWE, people with epilepsy.

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Botanicals constitute herbal materials, in some instances with either algae, microscopic fungi, and/or their combinations. Hence, botanicals include plants and plant products that contain active ingredients found in some parts of plants or other plant materials or combinations and are developed to be used as drugs for treating various ailments [12].

Plants have been used since prehistoric times as medicinal remedies utilized in numerous ways to alleviate pain and cure different illnesses. Knowledge concerning the healing properties of herbs has been safeguarded over the centuries as far back as over 5000 years ago when clay tablets were used by the ancient Sumerians [14] and the time of the revered texts found in the Hindu and Chinese cultures [15]. The use of herbs as medicinal remedies has been fostered over the centuries through personal experimentation, storytelling, and practicing of local customs and folk tradition.

Typically, the respective traditional societies would identify the healing properties of certain medicinal plants and communicate this information to successive generations. The benefits of one society would be passed on to another, which in turn would improve the old properties and unearth new ones, continuing until the present day. Traditional societies are often referred to as those with a tendency to focus on the past rather than the future through the preservation of certain indigenous customs and, often, ancient cultural practices [16]. They are small-scale societies (a few dozen to a few hundred people) which have weak political leadership, with membership based principally on relationships and roles influenced primarily by age, gender, and status.

By virtue of residing for thousands of years in forests or in close proximity to forests, many traditional societies have gathered broad knowledge on medicinal plants and their properties. The use of botanicals has survived for many thousands of years in different forms in these traditional societies and in all cultures all over the world [17]. Botanical medicine serves as an important component of various traditional and modern medical systems and therapies. Some examples include traditional Chinese medicine (TCM), aromatherapy, naturopathy, homeopathy, flower essence therapy, and Ayurveda in Indian medicine.

In many developing countries, the use of botanicals plays a very important role in meeting the primary health care needs of the population, with Africa and Asia noted to be among the continents with many users [18].

1.2. Botanical treatments in conventional medical care

In the modern medical system over the last few decades, some drugs have been developed from plants that have used botanical ingredients, including artemisinin from *Artemisia annua* for treating malaria [19], cardiac glycosides from foxglove (*Digitalis purpurea*) used in heart failure [20], and Isoamylene guanidine obtained from *Galega officinalis* from which the synthetic biguanide metformin is obtained to treat diabetes mellitus [21]. In this regard, the classically-trained medical profession is increasingly realizing the importance and effectiveness of botanical medicine.

The widespread use of botanicals in PWE could be attributed to disillusionment with conventional medical care, ease of physical accessibility, low cost, cultural acceptability — being more relevant to their belief systems – and efficacy against certain types of ailments compared to modern medicines. There has been an increased supplementation of conventional medical care with alternative means by a large number of patients [11,18] more often times than not, without consultation with a medical practitioner [22,23]. By far, the most popular supplements taken by PWE are those considered to be from natural products, that is, herbal or botanical sources [10]. Unfortunately, there is substantial disagreement concerning the efficacy of these botanical supplements in the treatment of PWE. The cause of the disagreements stems from the lack of controlled studies reporting efficacy data for many of these botanicals, with most information in the form of anecdotal reports. The challenge, however, is how to evaluate these therapies systematically in PWE, as well as the developing countries where they are commonly used, so that any true benefit and any risks to the individual with epilepsy are accurately reported.

This article reviews the literature and highlights the importance of botanicals for epilepsy in various traditional societies in the developing countries situated in Asia, Latin America, and sub-Saharan Africa and the present day challenges encountered in this field.

2. Methods

In this review, the term 'botanicals' denotes the products derived from plants or parts of plants. These include the following: herbs, herbal materials, botanicals, botanical drugs, and phytomedicines [12].

2.1. Search strategy

Data and relevant information were obtained through a search of the PubMed database using free text and Medical Subject Headings terms for all articles published in English from the 1st of January 1980 through the 24th of January 2015. The search included the following terms: seizures, epilepsy, fits, convulsions, anticonvulsant, proconvulsant, phytomedicines, herbs, herbal treatments, herbal medicines, herbal medications, botanicals, botanical drugs, complementary therapies, alternative therapies, and traditional medicines relevant to developing countries. In addition, because of a scrutiny of the reference sections of all relevant studies or reviews, a manual search of key journals and abstracts from the major annual meetings in the field of epilepsy was done. The procedure was concluded by checking with the commercial search engines Google Scholar and Bing for any missing publications.

3. Botanicals in developing countries and mechanisms of relevance to epilepsy

Botanicals for epilepsy in developing countries are usually obtained from traditional healers/practitioners [24] with patients in some situations combining this treatment with the conventional therapy of AEDs [25]. The patients often consider this habit very acceptable since the use of herbal preparations is considered natural and has been part of the culture passed down through successive generations.

Furthermore, in general, it is alleged that when botanicals are administered properly and in specified therapeutic dosages, they can be effective, can result in fewer side effects for most patients than pharmaceutical drugs, can help some people to better control their seizures, and are, by and large, less expensive than prescription pharmaceutical drugs. There have, however, been no standardized tests that compare the safety and efficacy of botanicals to those of AEDs to confirm these assumptions.

The benefits of the use of botanicals in treatment of ailments may be subtle or dramatic, depending on the preparation used and the illness being addressed. Botanical medicine, however, has been noted to be especially beneficial when administered to help with chronic ongoing symptoms [26], which may explain its popular use in PWE. A few examples illustrating some of the documented botanicals with anticonvulsant properties described in the literature and used in epilepsy in in vivo/in vitro studies in different developing countries are, hereby, presented.

3.1. Africa

Sub-Saharan Africa is rich in both biological and cultural diversity and endowed with a wide variety of indigenous plant species. Medicinal plants from Africa serve as a principal reservoir of phytochemicals for pharmaceutical drug development [27].

Unlike in other regions such as Asia using Ayurveda, in Africa, there is no specific practiced traditional medical system, with local healers

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often employing varied methods to diagnose and treat the respective ailments using a unique assortment of botanicals.

The use of botanicals is practiced throughout the African continent and widely accepted as a helpful therapy for virtually all ailments, including epilepsy [28].

There is current support for the recording and international standardization of medicinal plants from Africa, which has been spearheaded by the Association for African Medicinal Plants in an effort to unite medicinal researchers in Africa under one umbrella [29].

Among the Yoruba-speaking people of Nigeria, there has been reported use of a traditional herbal concoction prepared from leaves of tobacco, garlic and basil; together with lemon juice, rock salt, and bulbs of onion, which are soaked in the base of cow's or human urine for differing periods as treatment for childhood convulsions irrespective of cause [25]. In animal studies, "Cow's urine concoction (CUC)" has been noted to cause excitement in low doses and convulsion and/or death in higher doses [30]. Over fifty chemical compounds have been isolated from CUC, the key ones being the following: phenyl acetic acid, benzoic acid, thymol, and nicotine, and CUC is believed to exert its effect on the skeletal muscle via the release of acetylcholine [31]. Despite this preparation being discouraged because of the toxicity of several of the components of the concoction [32], it is still being practiced in the 21st century [33].

In the West African savannah and forest areas of Ghana, Ivory Coast, Nigeria, Senegal, Togo, and Cameroon, plant extracts of the deciduous trees of *Millettia thonningii* (Leguminosae) (*M. thonningii*) and *Securidaca longepedunculata* Fres (Polygalaceae) (*S. longepedunculata*) and the herb *Ocimum sanctum* Lam (Lamiaceae) (*O. sanctum*) are used to treat various diseases like epilepsy, insomnia, and headaches [33]. It has been suggested that the anticonvulsant properties of *M. thonningii* are mediated by inhibition of the *N*-methyl-D-aspartate (NMDA) receptors while those of *O. sanctum* and *S. longepedunculata* work via excitation of the glycine receptors. All the extracts from these plants show evidence of promising anticonvulsant efficacy against generalized tonic–clonic/partial seizures and generalized clonic seizures [34].

In Guinea-Bissau (Western Africa), many of the ethnic groups attribute neurologic illnesses in general and epilepsy in particular to possessions by evil spirits or to witchcraft. This delays correct diagnosis and treatment. Traditional healers play a very important role in the delivery of health services, especially in the rural areas. The treatment provided involves drinking of herbal remedies and bathing in decoctions or infusions made with specific roots and leaves [35]. Among the medicinal plants commonly used for treatment of epilepsy and convulsions are two indigenous African shrubs, namely, *S. longepedunculata* Fresen (Polygalaceae) and *Uvaria chamae* (P. Beauv) (Annonaceae) [36].

Among the Karanga people in south-central Zimbabwe (Southern Africa), an extract from the roots of the shrub *S. longepedunculata* Fresen (Polygalaceae) is drunk as an herbal epilepsy medicine [37]. The individual bioactive compound in this preparation and its mode of action in epilepsy are not confirmed. However, it has been noted to have, in addition, antimalarial [38], analgesic, antiinflammatory, and hypoglycemic [39] activities.

In the Iringa community in the Southern highlands of Tanzania in East Africa, extracts of *Diospyros fischeri* Gurke (Ebenaceae) roots, a traditional remedy for epilepsy, were noted to inhibit pentylenetetrazole (PTZ)-induced convulsions in mice [40]. Pentylenetetrazole is a central nervous system convulsant believed to act at the γ-aminobutyric acid type A ($GABA_A$) receptor [41]. This finding supports the rationale for its traditional use in epilepsy in the Tanzanian community and suggests that *D. fischeri* extract may have the capacity to manage absence seizures as is typical of drugs which inhibit PTZ-induced seizures and raise the threshold for the production of electrically induced seizures [42]. There is, however, more work to be done to determine the potential benefits of the specific compound(s) from these extracts in the treatment of epilepsy. The $GABA_A$-benzodiazepine receptor plays a role in sedation as well as in seizures, suggesting other possible uses for these compound(s) [43].

In South Africa, several plants are used by traditional healers to treat mental and neurological illnesses, specifically epilepsy, depression, age-related dementia, and debilitative mental disorders. However, among these plants, only a small number have been scientifically evaluated. Examples comprise the ethanol leaf extracts of the *Searsia* species (Anacardiaceae), including *Searsia dentata* and *Searsia pyroides* which act as possible antagonists of NMDA-type glutamate receptors. These plants have a clinical potential for developing into an efficient treatment for epilepsy since they are believed to combine one or more $GABA_A$ agonists with one or more NMDA antagonists [44].

In South Africa, some traditional communities make use of an ancient Northern Sotho multi-ingredient remedy for epilepsy, '*Sehlare sa Seebana*', which consists of aqueous and ethanol extracts of six plants: *Acrotome inflata*, *Aptosimum indivisum*, *Asparagus suaveolens*, *Barleria bolusii*, *Commiphora marlothii*, and *Sesamum triphyllum*. This remedy was tested in the $GABA_A$–benzodiazepine receptor-binding assay and found to show good dose-dependent activity, especially with the ethanol extract of all six plants in combination [45].

3.2. Asia

Approximately 35,000 to 70,000 plant species have been used for medicinal purposes worldwide [46], and of these, about 6,500 species are found in Asia [47].

In India, the utilization of plants for medicinal purposes has traditionally been used as the principal form of medicine by indigenous people of varied ethnic groups for the management of numerous illnesses affecting people and their animals. There are approximately 84 million indigenous people in India also known as 'Scheduled Tribes', though their self-preferred term is Adivasi (literally "original inhabitants") [48]. The Adivasis comprise approximately 8% of India's population, and each has their own distinctive culture, religious rites, food habits, and valuable knowledge of herbal medicine [49,50], which they continue to practice in their local communities.

In the indigenous communities of Bhoxa, Tharu, and nomadic Gujjars of the sub-Himalayan region of Uttarakhand, India, a total of 24 plants were claimed to possess anticonvulsant/antiepileptic (AC/AE) properties [51]. Each of these communities had their commonly used specific plants. The Bhoxa community mostly utilized *Ricinus communis* L. and *Datura stramonium* L., while the nomadic Gujjar community preferred *Martynia annua* L., *Bacopa monnieri* (L.) Wettst., and *R. communis* L. None of the Tharu community's favored species for the treatment of epilepsy, however, was similar with those of other indigenous communities, namely, *Allium sativum* L., *Asparagus racemosus* Willd., and *Achyranthes aspera* L.

Notably, one-third of these plants were being reported for the first time as useful in the treatment of epilepsy in these communities; however, less than half (38%) had been evaluated for their pharmacotherapeutic properties. This provides a rationale for establishing detailed research projects on indigenous plants and their derivatives with suspected anticonvulsant properties as a means to provide new regimens for epilepsy or other diseases of the CNS.

Ficus religiosa (L.), commonly known as the sacred tree '*Peepal*', belonging to the family Moraceae, is a large perennial tree, found throughout the plains of India. The plants of *F. religiosa* have been used in traditional Indian medicine for managing about 50 types of disorders including epilepsy, asthma, gastric problems, diarrhea, diabetes, inflammatory disorders, infectious disorders, and sexual disorders [52].

The methanolic extract of its fruits has been shown to have anticonvulsant activity in a dose-dependent manner against maximum electroshock (MES) and picrotoxin-induced convulsions in mouse models with no neurotoxic effects. It is suspected that the antiepileptic effect of *F. religiosa* extract might be mediated via modulating serotonin-dependent GABAergic and/or glutamatergic neurotransmission [53].

Despite experimental studies having justified the traditional medicinal use of *F. religiosa*, it is complicated to duplicate the results and

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pinpoint the actual bioactive compounds involved based on all these poorly described crude extracts used in these pharmacological studies. There is, thus, a need to standardize and identify the bioactive compounds in *F. religiosa*. The outcome of these studies will further develop the existing therapeutic potential of *F. religiosa* and provide a platform to test its potential clinical use [54].

In Bangladesh, the 'Santals' are considered one of the largest traditional with an estimated 100,000 people belonging to twelve clans [55]. They are spread out in the northern part of Bangladesh, are animistic nature-worshippers, and are believed to be descendants of the Austric-speaking Proto-Australoid race. The 'Santals' heavily rely on medicinal plants for the treatment of a variety of ailments owing to their tradition and inability to afford the western medicines. Each clan has traditional medicinal practices that are quite distinct. In one study done among the Soren clan to gather information on their use of medicinal plants, it was noted that there were 53 plant species distributed into 32 families. These varied plant species are used by the Soren traditional healers to treat more than 35 ailments. For the treatment of epilepsy, approximately 20 ml of juice obtained from fresh leaves of *Sesbania grandiflora* (L.) Pers. (Leguminosae) is taken with powdered black peppers twice daily for 15–20 days [55]. This plant however has not been validated using modern scientific techniques, unlike *Justicia adhatoda* used by the Sorens for treatment of asthma [56] and the gastroprotective effects of *Benincasa hispida* used in Soren traditional medicine for treatment of colic pain and flatulence [57]. There is, hence, a necessity to further scientifically explore *S. grandiflora* and other medicinal plants used by the Soren healers in a bid to develop drugs that are more effective than western drugs against a variety of ailments and which may have lesser or no side effects.

Ayurvedic medicine is a traditional East Indian healing system in which treatment is individualized and does not solely depend on the patient's presenting condition. Ayurveda is a Sanskrit term implying "science of life". Ayu signifies "life" or "daily living"; veda denotes "knowing". Ayurveda is the science of balance embracing both the spiritual and physical aspects of healing. It claims that a healthy person is one who has balance in his physiology (*doshas* or humors—fluids that circulate in the body), balanced digestive abilities (*agni*), balanced tissues (*dhatus*), balanced excretion (*malas*), and a content soul, sense, and mind. In Ayurveda, epilepsy is called '*apasmara*', meaning loss of consciousness of the body. Impairment of *Vata dosha* is believed to be the main imbalance responsible for epilepsy, while *Kapha* and *Pitta* imbalances may be contributory. Blocked channels are thought to be responsible for deteriorated nutrition of the brain or nerve blockage. Ayurvedic medicine strives to treat epilepsy by clearing out the channels of the heart and the mind that may be blocked by the excess of *doshas*. This unblocking of the channels is aided by the use of various concoctions and purgatives which act as drugs. The drugs are made from oils and *ghee* (purified butter also known as "*ghrtas*") often cooked with different herbal (botanicals) and animal products. For epilepsy, these are taken orally, applied externally, or by means of eye and nasal applications as part of the treatment [58].

Two Ayurvedic herbal remedies believed to be effective for epilepsy are *Siddharthaka ghrita* and *Saraswatarishta*. The latter herbal remedy has 21 different ingredients, some of which have been incorporated in the marketable Cerebrex® capsules, a medicinal preparation produced from the European Institute for Scientific Research on Ayurveda [58]. Some of the constituents of *Saraswatarishta* include Brahmi (*B. monnieri*), Shatavari (*A. racemosus*), Vidari (*Pueraria tuberosa*), Usheera (*Vetiveria zizanioides*), and Shunti — ginger (*Zingiber officinalis*) [59].

BR-16A (Mentat®) is a remedy containing certain important Ayurvedic ingredients such as *B. monnieri* (*jalbrahmi*), *Centella asiatica* (*mandookaparni*, *brahmi*), *Withania somnifera* (*ashwagandha*), *Evolvulus alsinoides* (*shankhapushpi*), and many others and is commonly used in combination with AEDs in current Indian medical practice [60]. Conversely, from the review of literature, Ayurvedic medicines are not endorsed as main-stay or add-on therapy in PWE; nonetheless, they have the potential to form the basis of future new AEDs [58]. Notably, most, if not all, of these medicines have not been scientifically or clinically proven to cure or help PWE and are generally recommended because of the patient's belief in their efficacy.

China boasts as having one of the earliest records of botanical medicine, namely the *Pen T'Shao Kang Mu* (The Great Herbal), compiled in the Ming dynasty (1368–1644 AD) by Li Shih Chen (1518–1593 AD). This book includes descriptions of almost 2000 different kinds of herbal medicines as well as minerals and animal products, and today [61], China is the leading producer of herbal medicine [62]. With respect to epilepsy, the *Huang Di Nei Ching* (The Yellow Emperor's Classic of Internal Medicine) was the first known document on epilepsy, supposedly authored by a group of physicians around 770–221 BC. The concept of epilepsy in this book was restricted to generalized convulsive seizures with the treatment grounded on the principles of "Yin Yang Wu Xing," which is comprised of herbs, acupuncture, and massage [63].

In traditional Chinese medicine, herbs are often given in combination for the management of seizures. The purpose of this approach is to get the best out of all the constituents of the herbal combinations utilized by focusing on various points of action as well as reducing unfavorable side effects. The Chinese herb 'tian ma' has had one of its constituents vanillin and its symbiotic fungus '*Armillaria mellea*' demonstrated to have AED properties [64] and may, in the future, be developed into AEDs. Other traditional Chinese herbal remedies that have been proposed for use in epilepsy with doubtful efficacy and unknown mechanism of action include the combination treatments of *saiko-keishi-to* and *sho-saiko-to* (identified by Japanese names). The components of these remedies include varying proportions of Asian ginseng root (*Panax ginseng*), Asian skullcap root (*Scutellaria baicalensis*), ginger root (*Zingiber officinale*), peony root (*Paeonia lactiflora*), licorice root (*Glycyrrhiza glabra*), pinellia root (*Pinellia ternata*), thorowax root (*Bupleurum falcatum*), cassia bark (*Cinnamomum cassia*), and jujube fruit (*Ziziphus jujuba*) [65,66]. Following animal studies, it has been suggested that this Chinese herbal mixture may prevent seizures by actions on calcium flux or by modifying cyclic nucleotides in neurons [67].

A systematic review of 71 studies to evaluate the scientific evidence backing the utility of herbal Chinese formulas in epilepsy treatment noted that over 135 individual herbs were used singly or in assorted combinations [68]. Regrettably, despite a considerable number of publications on Chinese herbal medicine for epilepsy care, Cochrane reviews show that there is no evidence to support its use in these patients [69]. There is a need to foster more research in this area applying strict research methodology and using uniform herbal combinations to determine which is most efficacious.

The practice of traditional Chinese medicine was introduced to Korea with Buddhism and was further developed and practiced to give rise to traditional Korean medicine (TKM) [70]. The main components of TKM consist of medicinal treatment, Sasang constitutional medicine, and acupuncture. Sasang constitutional medicine was created using the principles of Korean medical tradition [71] and is a unique theory that suggests that the human being's response to herbal medications varies according to the person's physiological, psychological, and physical characteristics, which also in turn determine the body structure. It marks out four distinct body structure types, namely, *Taeyangyin* (TY type), *Tae-eumin* (TE type), *Soyangyin* (SY type), and *Soeumin* (SE type) [71]. This implies that certain herbal remedies may work well with certain body types but cause adverse reactions in others.

Korean traditional herbs have been used medicinally to treat illnesses for thousands of years. *Scuttellaria baicalensis* (Lamiaceae) is one of the most important medicinal herbs in traditional Korean medicine. The flavonoids from *S. baicalensis* have been demonstrated to exert anticonvulsive effects in chemically induced and MES-induced seizures in mice or rat models through binding to the $GABA_A$ receptors [72].

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The outcomes of clinical studies using TKM are, however, questionable. One study conducted among children to determine the clinical outcomes associated with the combined use of TKM and conventional AEDs, compared to AEDs alone, found that the latter group used fewer AEDs and had more seizure-free patients than in the TKM combination group [73].

Among some of the other botanicals used in the Asian continent and documented in the epilepsy literature, besides *Gastrodia elata* (tian ma), are as follows: *Arisaema japonicum*, *Scolopendra subspinipes*, *Acorus calamus*, and *Poria cocos* [74].

3.3. Latin America

The Mayans, Aztecs, and Incas are one of the ancient civilization empires that existed in Central and South America before the discovery of America by Columbus. Whereas these empires were demolished, traces of traditional societies following ways of life broadly similar to those of their ancient ancestors exist to date in some of the regions spanning from modern-day Mexico to Chile.

The Aztecs and Incas believed epilepsy to be related to supernatural and religious causes and, in addition to using magic therapy, utilized several botanical medicines prescribed by their physicians who had extensive empiric knowledge of medicinal plants. While these plant names have been documented, the related pharmacologic and chemical data have not been evaluated [75].

Among the Maya Tzeltal, a community of approximately 250 inhabitants found in the Upper Chiapas in Mexico, epilepsy is believed to be caused by spirits [76]. Epilepsy here is referred to as *tub tub ik'al* (which means a "person that breathes anxiously or shocking"). In this community, epilepsy is known to be incurable; however, certain herbs are administered to ameliorate the condition. The biological names of these herbs are not known but locally are called *kaxlam tunim* and *cheneh pox sbil* [76]. With regard to administration, seeds from these plants are combined and mixed with cold water and ingested daily for one week.

Similarly, for the Kamayur'a, native group living in Matto Grosso state in Brazil, the etiology of epilepsy is attributable to spiritual or supernatural causes. Here, epilepsy is called *teawurup* (which means *armadillo*'s disease). Apart from a ritual cleansing act in which tobacco is smoked over the body of the patient with epilepsy, the witchdoctor goes into a trance in which the responsible sprits inspire him regarding which herbs or roots to use for treatment. The Kamayur'a use the roots of the plants *tsim'o* (*Serjania cuspidata*) and *wewur'u* to make a decoction which can be drunk, applied to the eyes, or used to induce vomiting for adults with epilepsy, while for children, the sap from the plant called *kamarapalap* is rubbed onto the skin of the child by the witchdoctor as he makes certain prayers [76].

Whereas epilepsy has been recognized as a unique health condition by many of these traditional societies, and these native cultures have developed a system of orally transmitted knowledge about epilepsy based on magic-religious traditions, much of the knowledge of the ancient pre-Columbian physicians is missing. It is important that the biological names of these recommended herbs be identified and the anticonvulsive efficacy of these herbs be evaluated.

Cannabis sativa L. is the species name for the annual herbaceous cannabis plant which belongs to the Cannabaceae family. Since ancient times, *C. sativa* has been utilized as a drug to treat a number of diseases in countries from Asia, Africa, and Latin America. Three subspecies of the genus *Cannabis* are recognized (*C. sativa*, *Cannabis indica*, and *Cannabis ruderalis*) [77]; however, *C. sativa* and *C. indica* are the two most widely known and cultivated species.

The medicinal use of *Cannabis* as an anticonvulsant dates back to early civilizations including ancient China and India [78,79]. *Cannabis sativa* subspecies originated in the equatorial countries of Colombia, Mexico, Jamaica, South Africa, Thailand, and South East Asia [80]. The *Cannabis* plant produces over 100 well-characterized C_{21} terpenophenolic compounds known as phytocannabinoids, all of which have been found to have unique medicinal properties [81,82]. Each subspecies of *Cannabis* contains different ratios of phytocannabinoids, which together are believed to work synergistically to provide its therapeutic effects.

The most researched phytocannabinoid is delta-9-tetrahydrocannabinol (THC), which is the major psychoactive ingredient [83]. In addition to having antiepileptic effects, it has euphoric, stimulant, muscle-relaxing, antidepressant, and analgesic actions. Cannabidiol (CBD) is the other main phytocannabinoid and is the major nonpsychoactive ingredient in *Cannabis* [84]. Cannabidiol lessens the psychoactive effects of THC and, in addition, has sedative and analgesic effects.

There are reports of *C. Sativa* herbal preparations utilizing the leaves, seed, or bark to treat epilepsy by various indigenous communities of India, specifically the sub-Himalayan region of Uttarakhand [85], and the states of Himachal Pradesh [86], and Uttar Pradesh [87].

In a placebo-controlled study conducted in South Africa [88], twelve patients with frequent seizures unresponsive to conventional AEDs were randomized into two groups to receive either sunflower oil plus 100 mg CBD daily or sunflower oil alone for four weeks. There was no statistically significant difference between the two groups, and the authors attributed this to the severity of the participants' brain injuries and their epilepsy.

In another placebo-controlled study conducted in Brazil [89], cannabidiol (CBD) was administered to fifteen adult patients with epilepsy whose seizures were unresponsive to epilepsy treatment. One group of eight patients received 200–300 mg of CBD daily in addition to their usual AEDs, while the others received a placebo. Despite improvements in 50% of the patients in the intervention arm, the results were inconclusive and were limited by small sample size and methodological problems.

Larger, well-powered, randomized, double-blind, controlled trials of phytocannabinoids used in human epilepsy are virtually nonexistent in the developing world. Most research data from the developed world at present are mainly comprised of anecdotal reports of beneficial effects seen in individual case studies [90], small-scale open-label studies, and surveys [91,92]. More recent anecdotal reports of high-ratio CBD: THC medical marijuana have claimed efficacy, but the studies were not controlled [91,93]. There are no reliable data presently on the efficacy of cannabinoids as treatment for epilepsy [94].

Intriguingly, the effect of phytocannabinoids on seizure activity in animal models is complex. In most research on animal models, THC has shown conflicting results [95], exhibiting both proconvulsant and anticonvulsant effects depending on dose, type of epilepsy, and other factors. In contrast, research using many acute animal seizure models has conclusively shown that CBD can act as a strong anticonvulsant [95,96] without the risk of exacerbating seizures and, in addition, with neuroprotective and anti-inflammatory effects.

The lack of stereo-specificity implies that the mechanism of action of phytocannabinoids in epilepsy may not solely be due to a single receptor interaction but probably a result of serotonin, GABA, acetylcholine, or prostaglandin system involvement [97]. Some of the proposed antiepileptic mechanisms of CBD include effects on the orphan G-protein-coupled receptor 55 (GPR55) reducing presynaptic calcium release [98], activation of the transient receptor potential (TRP) of vanilloid type-1 cation channel (TRPV1) [99], agonistic action on the 5-HT_{1a} (serotonin) receptor [100], or potentiation of the $\alpha 3$ and $\alpha 1$ glycine receptors [101].

Considering the pre-clinical evidence and the lack of well-designed clinical studies and long-term safety information, there currently is disagreement amongst clinicians about the use of medicinal cannabis for the treatment of epilepsy. There is an urgent need for large, randomized, placebo-controlled clinical trials to establish efficacy and safety and, also, to explore the possible mechanisms of the

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antiepileptic activity of the phytocannabinoids and other constituents of *C. sativa* L.

A summary of the botanicals mentioned in this review, their families, geographical distribution, the utilized plant parts, and proposed mechanisms of action (if reported) are shown in Table 1.

4. Safety issues on the use of botanicals

In many developing countries, the favorable cultural attitudes towards botanicals and the distrust of western drugs lead to viewing botanicals as generally safe and effective [28]. The assumption of safety

Table 1
A summary of some of the selected botanicals used for epilepsy treatment in developing countries and proposed mechanisms of action.

Botanical name	Family	Country	Part of the plant used	Proposed mechanism of action from in vivo and in vitro studies	References
Achyranthes aspera	Amaranthaceae	India	Root	Enhanced ($GABA_A$) receptor-mediated inhibitory neurotransmission	[51,127]
Acorus calamus	Araceae	China, India	Rhizome, root	NR	[74,128]
Acrotome inflata	Lamiaceae	South Africa	Entire plant	$GABA_A$–benzodiazepine receptor potentiation	[45]
Allium sativum	Amaryllidaceae	India	Bulb	$GABA_A$ receptor agonist	[129]
Aptosimum indivisum	Scrophulariaceae	South Africa	Leaves	$GABA_A$–benzodiazepine receptor potentiation	[45]
Arisaema japonicum	Araceae	China	Tuber	NR	[74]
Asparagus suaveolens	Asparagaceae	South Africa, Kenya, Tanzania, Malawi, Mozambique, Namibia, Botswana, Zimbabwe	Stems, root	$GABA_A$–benzodiazepine receptor potentiation	[45]
Asparagus racemosus	Asparagaceae	India, Sri Lanka	Aerial parts, roots	NR	[51,58]
Bacopa monnieri	Scrophulariaceae	India	Leaves	Enhanced ($GABA_A$) receptor-mediated inhibitory neurotransmission	[58,60,130]
Barleria bolusii	Acanthaceae	South Africa	Aerial parts	$GABA_A$–benzodiazepine receptor potentiation	[45]
Bupleurum falcatum	*Apiaceae*	China	Root	NR	[65,66]
Cannabis sativa	Cannabaceae	India, China, Brazil, South Africa	Seeds, bark, leaves, entire plant	Activation of GPR55 receptor; activation of TRPV1 receptor; potentiation of $5\text{-}HT_{1a}$ receptor; activation of $\alpha 3$ and $\alpha 1$ glycine receptors	[98–101]
Centella asiatica	Apiaceae	Nigeria, India, Brazil, Indonesia	Leaves	Potentiates an increase in cerebral levels of GABA	[60,128,131]
Cinnamomum cassia	Lauraceae	China, Indonesia, India	Bark	NR	[65,66]
Commiphora marlothii	Burseraceae	South Africa, Botswana, Zambia, Zimbabwe	Leaves	$GABA_A$–benzodiazepine receptor potentiation	[45]
Datura stramonium	Solanaceae	India, Nepal	Leaves, fruits, seeds, roots	NR	[51]
Diospyros fischeri	Ebenaceae	Tanzania	Roots, bark	Enhancement of the $GABA_A$ receptor inhibitory effects	[40,41]
Evolvulus alsinoides	Convolvulaceae	India, Nigeria, Senegal, Cameroon, Sri Lanka	Entire plant	Enhancement of the $GABA_A$ receptor inhibitory effects	[60,132]
Ficus religiosa	Moraceae	India	Fruit, leaves	Enhancement of the $GABA_A$ receptor inhibitory effects	[52–54]
Gastrodia elata	Orchidaceae	China	Root	NR	[74]
Ginkgo biloba	Ginkgoaceae	China	Leaves, stem	Prevents reduction in GABA levels through potentiation by bilobalide of glutamic acid decarboxylase (GAD) activity	[133]
Glycyrrhiza glabra	Leguminosae	China, Korea	Rhizome, roots	Enhanced ($GABA_A$) receptor-mediated inhibitory neurotransmission	[65,66]
Martynia annua	Martyniaceae	India, Mexico	Leaves, roots	Enhanced ($GABA_A$) receptor-mediated inhibitory neurotransmission	[51,134]
Millettia thonningii	Leguminosae	Ghana, Central Africa, Ivory Coast, Nigeria, Senegal, Togo, Cameroon	Seeds	Antagonists of NMDA receptors; activation of GABA receptors in the GABAA receptor complex	[33,34]
Ocimum sanctum	Lamiaceae	Ghana, Central Africa, Ivory Coast, Nigeria, Senegal, Togo, Cameroon	Entire plant	Activation of glycine receptors; activation of GABA receptors in the $GABA_A$ receptor complex	[33,34]
Paeonia lactiflora	Ranunculaceae	China, India	Root	NR	[65,66]
Panax ginseng	Araliaceae	China, Korea	Root	NR	[65,66]
Pinellia ternate	Araceae	China	Tuber	NR	[65,66]
Poria cocos	Polyporaceae	China	Stalk	NR	[74]
Pueraria tuberosa	Leguminosae	India, Nepal	Tubers	NR	[58,135]
Ricinus communis	Euphorbiaceae	East Africa, India, Nigeria	Root, bark, fruit, leaves, seeds, flowers	Interfering with GABA, glutamate mechanism	[51,136]
Scolopendra subspinipes	Scolopendridae	South Korea	Entire plant	NR	[74]
Scutellaria baicalensis	Lamiaceae	China, Korea	Root	$GABA_A$ receptor agonist	[65,66,73,137]
Searsia dentata	Anacardiaceae	South Africa	Leaves	Antagonists of NMDA-type glutamate receptors; $GABA_A$ receptor agonist	[44,138]
Searsia pyroides	Anacardiaceae	South Africa	Leaves	Antagonists of NMDA-type glutamate receptors; $GABA_A$ receptor agonist	[44,138]
Securitaca longepedunculata	Polygalaceae	Guinea-Bissau, East Africa, Ghana, Ivory Coast, Nigeria, Senegal, Togo, Cameroon, Zimbabwe	Root	Activation of glycine receptors; activation of GABA receptors in the $GABA_A$ receptor complex	[33,34,36,37]
Serjania cuspidata	Sapindaceae	Brazil	Root	NR	[76]

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Table 1 (*continued*)

Botanical name	Family	Country	Part of the plant used	Proposed mechanism of action from in vivo and in vitro studies	References
Sesamum triphyllum	Pedaliaceae	South Africa, Angola, Botswana, Zimbabwe, Mozambique, Swaziland	Seed	$GABA_A$–benzodiazepine receptor potentiation	[45]
Sesbania grandiflora	Leguminosae	Bangaladesh, India	Leaves, flowers	NR	[55]
Uvaria chamae	Annonaceae	Guinea-Bissau, Senegal, Gambia, Cameroon	Roots, leaves	NR	[36]
Vetiveria zizanioides	Poaceae	India	Roots	Facilitation of chloride ion channel as well as inhibition of calcium channel	[58,139]
Withania somnifera	Solanaceae	India, Ethiopia	Root	Enhancement of the $GABA_A$ receptor inhibitory effects	[60,140]
Zingiber officinale	Zingiberaceae	India	Rhizome	NMDA receptor antagonist; $GABA_A$ receptor agonist; presence of the following phytoconstituents: phenylpropanoid, gingerol	[65,66,141]
Ziziphus jujuba	Rhamnaceae	China, Korea	Fruit, seeds	NR	[65,66]

NR = not reported.

may not be based in reality; some natural compounds may cause life-threatening adverse effects as is seen in seizures in PWE being exacerbated with the ingestion of herbal stimulants containing ephedrine (*Ephedra sinica* or *ma huang*) [102]. Another demonstrated example involves the ingestion of Hyssop herbal tea derived from the herb hyssop, which is an essential oil. This herbal tea is believed to be safe, however, it can be toxic when taken in excessive doses with some of the constituents of hyssop oil thought to aggravate seizures [103]. *Ginkgo biloba* nuts [104] and Chinese *ginseng* [105] have also been suggested to be proconvulsant. Ginkgo seeds contain a seizure-promoting neurotoxin called 4-methoxypyridoxine (MPN) [106] (also termed as "Ginkgotoxin") that indirectly inhibits $GABA_A$ formation.

The CYP450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug–drug interactions that can cause unanticipated adverse reactions or therapeutic failures. The older generation AEDs like carbamazepine, phenobarbital, and phenytoin commonly used in developing countries are potent inducers of CYP450 enzyme activity by increasing enzyme synthesis. Typically, there is a delay before enzyme activity increases, depending on the half-life of the inducing drug. It is, hence, possible that, for a drug like phenobarbital (a CYP450 enzyme inducer with a very long half-life [107] which can occur up to one week after the initiation of the drug), there may be altered pharmacokinetics, efficacy, and safety issues when coadministered with herbal remedies. Garlic, Echinacea (various Echinacea species), mugwort (Artemisia species), and St. John's wort are some of the botanicals reported to interact with the cytochrome P450 system (CYP450) in the liver and could, hence, alter the pharmacokinetics of hepatically metabolized AEDs [105].

This situation poses a potential risk of developing herbal–drug interactions, toxicity, or, in certain instances, death [102]. Besides, patients already on AEDs enhance their risk of toxicity by ingesting botanicals that may also compromise AED activity [108,109]. Drug–herbal interactions have been demonstrated for some herbal preparations and AEDs, for example *Shankpushpi*, an Ayurvedic medication, which interacts with phenytoin, lowering its serum levels and, thus, increasing the likelihood of seizures [108]. Similarly, Mentat (BR16A) [110], another Ayurvedic medication, when administered with phenytoin, suppresses the latter's metabolism and, when given with carbamazepine, increases its bioavailability [109].

In many developing countries, the regulations concerning the manufacture or utilization of botanicals differ, with some countries having nonexistent policies on this issue. The absence of a regulatory body to assess the quality or safety of botanicals, in accordance with accepted standards of good agricultural practice (GAP), augments the risk of having potentially contaminated botanicals. For example, heavy metals (lead, mercury, and/or arsenic) [111] (which may induce seizures) as well the presence of some conventional medicines [112] have been isolated in some Ayurvedic products. Other contaminants may include chemical toxins, radioactive substances, or microorganisms [18].

In addition, variation in the manufacturing processes implies that many of these botanicals may have wide-ranging amounts of the active component in each completed product, yet the consistency in composition and biologic activity of botanicals is a significant prerequisite for their safe and effective use. This is a concern that is often not taken into consideration by the prescribing physician or by the patient consuming a particular botanical [74].

In developed countries, it has been observed that patients were less likely to share information with their western-trained physicians regarding their use of botanicals concurrently with conventional medications if they believed the botanicals were safe [113]. Earlier studies done in developed countries noted that less than one in three patients with epilepsy revealed to their physicians that they were also taking complementary and alternative medication in addition to AEDs [22,114,115].

While the actual percentage of patients sharing similar information in developing countries is not clear, this evidence means that a large percentage of physicians may be uninformed by their patients of their complementary treatment with botanicals. Consequently, physicians should proactively ask patients whether they are taking botanicals or other pharmacologically active substances in order to assess the potential safety risks and possibility of untoward effects on AEDs and to be able to advise their patients accordingly.

5. Challenges in the use of botanicals

The international interest in herbal medicine is on the rise [10], and this has steered the commercial growth of medicinal plants, with a few, however, still picked from the wild. This may explain why today, based on the estimates of the WHO, as many as 80% of the world's population rely on traditional medicine for their primary healthcare needs [11]. The challenge is to ensure sustainable management of this resource in order to meet the growing demand, with the hovering threats of deforestation, environmental degradation, and global warming. In addition, as these botanicals are subjected to climate change and overexploitation, their genetic diversity is in peril. This calls for clear policies and strategies for their protection and sustainable use.

Although the rich indigenous knowledge on the medicinal use of plants has been relatively well documented, in some traditional societies, there is generally lack of documentation of ancestral knowledge on traditional plant medicines, especially with the younger generations. This information is often passed solely through oral communication from the knowledgeable elders or ordinary people through the family line with lack of any written documents. In some communities, this knowledge transfer is based on gender (preferably males) [116] and

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shrouded in secrecy [117]. However, there is a potential threat to the existing knowledge on botanicals being wiped out with the growing influence of a more western way of living, adaptation of modern agricultural practices destroying botanical environments, migration of the younger generations to urban areas creating a knowledge–practice gap coupled with their diminished interest to learn and practice this art [118], and the increasing availability of conventional medicines. This implies that unless urgent conservation measures such as ethnobotanical studies are instituted, there may be a loss of valuable knowledge of medicinal plants of several indigenous communities.

While there has been considerable study of botanicals in animal models of epilepsy, there is a paucity of consistent and reproducible efficacy data in humans which should preclude any recommendations regarding the use of most botanical treatments for epilepsy. Many of the studies suffer from flawed methodologies including lack of proper controls, or randomization of subjects, small numbers of study subjects, and the absence of meticulous monitoring of the results of the interventions. This situation contributes to the delay in understanding their mechanisms of action (which is not known for many botanicals) and the lack of information on the precise dosage [119] and, hence, their recommendation for use in epilepsy.

The other barrier to the use of botanicals in epilepsy is the lack of definite and complete information about the composition of extracts. Thus, it is challenging to reproduce any experimental results and pinpoint the precise bioactive compound involved. Consequently, phytochemical standardization should be a prerequisite as well as the bioactivity-guided identification of bioactive compounds. Furthermore, the chemical composition of the preparations varies according to several factors, such as the botanical species, used chemotypes, the structural part of the plant used (seed, flower, root, leaf, etc.), and the mode of preparation. The storage conditions should also be taken into consideration: for example, the facilities used, exposure to sunlight, level of humidity, and the duration of storage. The growth situation of the plant such as the type of ground, time of harvest, and the delineated geographical area in which the plant species has been grown may also affect the composition of the preparation. As such, situations employing poor quality control measures may result in inconsistent effects for certain botanicals.

The use of botanicals for the treatment of epilepsy in traditional societies often finds its basis on magical, religious/cultural beliefs or popular experience. Almost one quarter of patients in Tanzania were noted to consult a traditional healer as their first referral point before going to a modern health care facility [120]. Another study surveying the capital city of Tanzania, Dar-es-salaam, found that over 100 traditional healers were managing epilepsy [121], demonstrating the significance and acceptability of their services. While the popular use of botanicals may indicate general safety, the specific efficacy of these treatments and when to use them are not clear. To date, no clear guidelines exist for the use of botanicals by patients on AEDs. The WHO, however, is involved in developing definitive guidelines for the methodology of clinical research and the evaluation of the effectiveness of botanicals [11].

As noted above, it has been observed that PWE use botanicals in conjunction with their AEDs [25,120,121]. The combinations of these botanicals with AEDs, though not competently studied, may lead to reduced control of seizures and increased risk of adverse drug reactions [122]. Unfortunately, the patient's perception on the concurrent use of these treatments and possible side effects is limited and underscores the need to educate patients and their caregivers.

The safety of long-term use of most botanicals is undetermined [123]. However, in the short term, there have been reports of accidental herbal toxicity in developing countries stemming from a lack of pharmaceutic quality control in harvesting and preparation and the general opinion that these preparations are nontoxic [124]. What is glaringly absent and needs to be addressed, especially in the developing world, is the necessity of creating broad screening methods to identify the particular toxins involved as well as identifying effective interventions.

Another bottle neck in the use of botanicals is the lack of universal GAP [125] implementation in developing countries. The adoption of GAP is essential to systematically regulate the whole process of production, controlling the quality of botanicals in order to ensure consistent quality and safety of medicinal plants or herbal preparations. For example, the quality of some TCM has been questioned following the use of substandard planting and processing techniques, finding disproportionate pesticide residue and poor quality of TCM herbs [126]. This has led to inconsistent quality and variable effects of Chinese-made TCM products.

It is important that means to address these challenges be developed (See Table 2). A list of possible strategies that could be adopted as guiding principles on future directions to solve these challenges is outlined in Table 3.

Table 2
Salient points on the importance of botanical treatments in developing countries and their challenges.

1. The use of botanical treatments is popular in PWE, however, it faces the threat of extinction with the rise of modernization.
2. There is lack of decisive information regarding efficacy, long term safety, and exact mechanism(s) of action of many botanical treatments used in PWE.
3. Certain botanical treatments have proconvulsant properties or may modify AED metabolism calling for the use of validated scientific studies to determine the composition of these extracts.
4. The consistent quality and safety of botanical treatments in general are hindered by a deficiency of implementation of good agricultural practices.
5. No clear evidence-based guidelines exist on the use of botanical treatments by patients on antiepileptic treatment.

PWE = people with epilepsy; AEDs = antiepileptic drugs.

6. Conclusions

Over the past few decades, the use of botanicals in epilepsy continues to be employed by several traditional societies in developing countries. This practice has substantially been enhanced by the population's desire for treatment that is viewed as harmless, natural, readily accessible, culturally acceptable, economically affordable, and efficacious. Whereas this supposition may not be wholly true in view of case reports depicting safety issues with some of these botanicals, it is important that the indigenous knowledge on these botanicals be preserved.

At present, there is a paucity of definitive and consistent information regarding efficacy and a lack of knowledge about exact mechanism(s) of action and appropriate dosing. These are important shortcomings and, in large part, could explain why there is considerable uncertainty regarding the effectiveness of botanicals and their recommendation for use in epilepsy.

There is, therefore, a need to scientifically study the safety and efficacy of the available botanical products recommended for use in epilepsy by local healers in these societies. The identification of the individual bioactive natural products and illustration of their exact mechanisms of action may pave the way for the development of potential inexpensive treatments to reduce the epilepsy treatment gap in developing countries. Furthermore, this may also provide new treatments for epilepsy, especially in PWE with drug-resistant seizures.

Whereas there are active in vivo and in vitro studies in many developing country regions for which botanical preparations have shown positive anticonvulsant properties, there is insufficient evidence, based on currently available data, to recommend the use of any particular botanical product to treat epilepsy. The task now is to await the future results of carefully conducted clinical studies using botanicals to illuminate the next steps in this controversial arena.

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Table 3
Proposed strategies for further development of botanical treatments in developing countries.

1. Involvement of humanitarian foundations in supporting well controlled randomized control trials geared at identifying relatively unprofitable but inexpensive and readily available botanical treatments.
2. Development of strong research collaboration networks on epilepsy treatment between traditional healers using botanical treatments and western doctors using evidence-based medicine.
3. Documentation and information sharing among the different developing country regions using a central data base in which botanical treatments showing promise in epilepsy treatment are selected for further development into possible drugs.
4. Drug companies to venture and invest more finances in the development of future drugs from the botanical treatments used in PWE that have shown efficacy in the respective developing country regions.
5. Setting up of collaborative networks of developing country regions with western countries to develop comprehensive screening methods to identify the particular toxins involved in selected botanical treatments as well as creating suitable antidotes.
6. Development of simple information brochures utilizing pictures and common names in the respective languages of the different developing country regions showing which botanicals may exacerbate seizures and should be avoided in PWE.
7. Setting up of model centers of excellence to promote good agricultural practices in each of developing country regions to ensure consistent quality and safety of medicinal plants or herbal preparations.
8. Development of clear evidence-based guidelines for the use of botanicals by PWE on conventional antiepileptic treatment.
9. Development of sustainable infrastructure in developing country regions to isolate the active compounds in the varied botanicals with antiepileptic effects that can also be used as training sites on the use of botanicals in epilepsy.
10. Creation of more publicity using the digital media, international conferences, billboards, and other culturally appropriate means on the importance of botanical treatments in developing country regions.

PWE = people with epilepsy.

Author contributions

AKM conceptualized the study and wrote and approved the final manuscript.

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Conflict of interests

The author declares that she has no conflict of interest. She confirms that she has read the Journal's position on issues involved in ethical publication and affirms that this report is consistent with those guidelines.

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