

**Integrating alternative and complementary medicine in the management of epilepsy and its
comorbidities in low- and middle-income setting**

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Highlights

- The practice of Traditional/alternative and Complimentary Medicine (TCM) in the management of epilepsy and its associated comorbidities is very widespread in many low and middle countries, driven in part by cultural beliefs about the causation, misperceptions about the illness and non-response to modern treatment
- There is no conclusive evidence from randomised controlled trials that TCM products are effective in seizure control, nor what active ingredients and harms are associated with their use
- Regulation of TCM by health authorities are warranted owing to their expanding use locally and globally
- There is urgent need to invest in building knowledge base for TCM products for epilepsy care, to promote their integration into health care systems

Abbreviations

ILAE (international league against epilepsy); LMIC (low- and middle-income countries); TCM (traditional/alternative and complementary medicine); WHO (world health organization)

Key words

Epilepsy and mental health care; low- and middle-income countries; traditional/alternative and complementary medicine; health care systems, anti-seizure medications

Abstract

Traditional/alternative and complementary medicine (TCM) encompasses products, practices and practitioners that do not form part of conventional treatment and are not an integral part of the main health care systems. They are very common in the management of epilepsy and mental health conditions, particularly in low- and middle-income countries (LMIC). For instance, in population survey in Africa, over 70% of people with epilepsy had visited a traditional health practitioner before the survey, with similarly high estimates reported in Asia and South America. Accessibility, cultural appropriateness/alignment, non-response to conventional (biomedical) medicine, and exercise of control over one's treatment were some of the reasons TCM preferred over conventional medicine. There is also emerging evidence that TCM products administered alone or together with anti-seizure medications result in improvement in seizure control, psychiatric comorbidities, electroencephalographic findings, and quality of life. Most of the convincing evidence is from biological-based therapies for example, multivitamin supplementation, ketogenic diet and cannabidiol extracts. Mind-based therapies e.g. Yoga and whole-body systems therapies e.g. Ayurvedic and Traditional Chinese Medicine have also generated interest in epilepsy care. There is a paucity of effectiveness studies of these therapies in LMIC such as Africa, where capacity to take these products through clinical trials is limited. There are however serious concerns on reliability of reported findings because of inadequate randomization, and small sample sizes, and concerns on quality and safety owing to lack of standardization of bioactive compounds, accidental or intention botanical substitution of products and unhygienic handling. There is growing interest in TCM worldwide because of its economic potential, concerns and safety and quality and potential for integration into the health care systems. There is urgent need to develop and implement national TCM policies and programmes aimed at expanding the knowledge base and providing guidance on regulatory and quality assurance standards. However, LMIC continue to lag in implementation of these policies and guidelines, especially the areas of research and development and regulation of TCM practice. Working with stakeholders, countries are advised to assess their own national situations in relation to TCM, and then develop practical solutions to accommodate these approaches. For instance, surveying benefits and risks of TCM in the management of epilepsy in

the local context and using this to promote appreciation of a role for TCM, which will ease integration into the main health systems.

1.0 Introduction

Epilepsy remains the most serious neurological disorder in terms of disability adjusted life years and years of life lost[1]. It affects over 70 million worldwide most of whom live in low- and middle-income countries (LMIC)[2]. These settings have a collection of risk factors that are known to increase the burden for epilepsy, including birth complications related to home deliveries, brain infections and head injuries particularly following road traffic accidents. Most of these risk factors are preventable through simple public health interventions, which can eliminate up to 30% of epilepsy[3]. Most of the causes for epilepsy are unknown, but new data is emerging to support the important contribution of genetics in both generalised and focal epilepsies from many LMIC settings[4]. People with epilepsy experience more serious physical, psychiatric and psychosocial health challenges including epilepsy stigma, which complicates management, increasing the treatment gap[5].

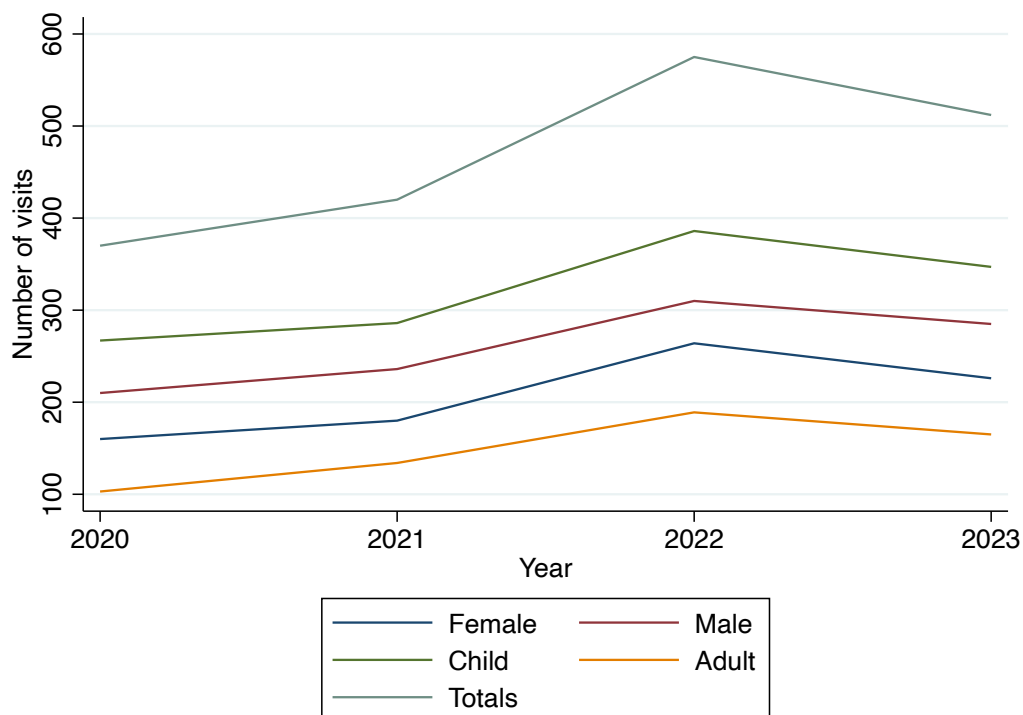
The epilepsy treatment gap can be as high as 90% in some LMIC settings, and this could be even higher if is comprehensively characterised to including those not diagnosed, who cannot start care; those on anti-seizure medications but are not achieving optimal levels; those who cannot access non-pharmaceutical options e.g. epilepsy surgery and those preferring traditional/alternative and complementary medicine (TCM)[5]. The main causes of the epilepsy treatment gaps are cultural beliefs, lack of public awareness, lack of skilled health care workers, limited access to essential anti-seizure medications and other non-pharmaceutical options, and lack of prioritisation of epilepsy by health policy makers[6]. These treatment gap challenges are dire in LMIC, where, for instance, there are no specific epilepsy care laws and regulations, despite ratification of epilepsy-related resolutions by the World Health Assembly comprising the member states[7]. Consequently, the rights of people with epilepsy continue be violated including denial of access to care and equal opportunities for participation in employment and education. Comprehensive care, delivered by multidisciplinary health care teams, should include health care and social and educational services to addresses the complexity, chronicity and multimorbidity nature of epilepsy[8]. Furthermore, integrated models of care that are person centred and follows a life-approach and should promote self care, facilitate telehealth, and embrace communication[7].

There are serious misconceptions about the causes and nature of epilepsy by both the community and health care workers in many LMIC settings[9], which deters people from seeking epilepsy care. Therefore, people with epilepsy will first consult traditional health practitioners, who in Kenya are thought to be more acceptable in terms of availability, time spent with the patients, comprehensible explanations of the disease and modalities of payments. This delay in seeking biomedical treatment was associated with complication of epilepsy, severe that may not easily respond to initiated treatment [10]. Educational interventions have been utilised to address misperceptions or animistic beliefs about epilepsy, but these are often ineffective because they are logistically difficult to sustain in the longterm[11], and presence of intellectual disability may in some people with epilepsy impedes comprehension[12]. The old generational antiseizure medications that are readily available in these settings, tend to have less responsiveness against some epilepsy syndromes and their comorbidities[13], often complicated by concomitant infection[14], are associated with more adverse drug reactions deterring adherence to treatment[15], and can interact with other medications including TCM[16]. Ensuring access to newer antiseizure medications, in order to reduce adverse drug reactions and interactions with TCM. One such ASM is levetiracetam which has been included in the new World Health Organization (WHO) model list for essential medications because of predictable pharmacokinetics, and less propensity for protein binding and interactions with other medications including traditional and alternative medications[17].

There are concerted efforts to address the epilepsy treatment gaps in LMIC, including the popular demonstration projects led by international partners eg WHO and International League Against Epilepsy (ILAE) in supporting National health systems in identifying and responding to epilepsy care needs[18]. Investigator led public health interventions for addressing the treatment gap ought to follow community model/approaches particularly building capacity for the healthcare workforce, provision of antiseizure medications, and community epilepsy awareness[19]. Multi-pronged community-based public interventions were applied in populations on the rural Kenyan coast around 2020 and resulted in increased visits of patients with epilepsy using an outpatient epilepsy clinic on the Kenyan coast (Figure 1). Few other interventions have focused on improvement of stewardship for antiseizure medications,

specifically efficacy of treatment, adherence to treatment and tolerance to treatment [20]. The WHO has recently published the first global report on the burden of epilepsy and sustained response required from policy makers, the technical brief on key information about epilepsy and recommendations to improve outcomes to policymakers and other stakeholders; and an intersectoral global action plan on epilepsy and other neurological disorders for improving brain health and neurology services worldwide, using a comprehensive, and multisectoral coordinated response[21]. In these reports, revising and updating policies and regulations on non-communicable diseases, by removing special exclusions, and integrating primary helthcare for epilepsy, for instance, into mainstream health care system, can ensure access to care, to provide mechanisms for oversight of health care systems and to promote rights of people with epilepsy. While many of these efforts encourage partnerships between stakeholders in improving brain health, they do not highlight the role and practice of TCM in improving the epilepsy treatment gap, and advancing universal health coverage for epilepsy care[22].

Figure 1. Absolute number of incident visits to a community outpatient epilepsy clinic in rural Kenya following multipronged community-based public health interventions



The aim of this paper is threefold: (i) to discuss the concepts, extent and reasons associated with use of TCM in epilepsy; (ii) to provide practical examples of use of alternative and complementary medicine in epilepsy care based on empirical evidence in the literature, and (iii) outline the future prospects of integration of TCM into routine epilepsy care and regulatory aspects of its practice.

2.0 The concept of traditional/alternative and complementary medicine

There is no one single operational definition for TCM as many differ across studies, with few following guidelines from National Center for Complementary and Integrative Health (<https://www.nccih.nih.gov/about>). Understanding the definition of conventional medicine which is also referred to as Western medicine, biomedicine, scientific medicine, or modern medicine, is the first step in appreciating TCM. Briefly, conventional is the care delivered by specialists or primary health care providers using drugs, psychotherapy, radiation, technology or surgery, and often use empirical evidence to improve the best available clinical expertise[23]. TCM are health care practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant health-care system of a country. It encompasses medical treatments, therapies, practices, and products that are used outside of the that are used outside of conventional allopathic medicine. The definition of TCM is complicated by wide range of practices and beliefs arising from multiple histories, traditions, and philosophies, with some referring to it as conventional education and practice system[24]. For instance, what was considered conventional medicine in the medieval times e.g. cure of diseases by letting out of excess blood has shifted to be alternative medicine[25]. The accumulation of empirical evidence and the advancement of scientific discoveries has also influenced the choice of medicine e.g. the understanding of anatomy and physiology has rendered the attribution of diseases to supernatural causes irrelevant[25].

3.0 Extent of use of traditional/alternative and complementary medicine

Usage of TCM is on the rise worldwide, despite the challenges with limited empirical evidence and lack of replication of findings on their effectiveness and safety. For instance, in a population-based study of epilepsy conducted in Kenya, over 70% reported having used

traditional medicine before embarking on biomedical treatment[26]. The high usage of TCM is also reported in Asia and South America[27]. In these LMIC, it was not possible to establish the time when these patients engaged traditional health practioners in relation to when they visit the biomedical practioners, or if the TCM and conventional medications were used concurrently, which can increase possibility of drug-drug interaction. The usage of TCM is much lower in high income countries, for example it was 24% in a Swiss health survey[28]. In Switzerland, osteopathy, neuropathy and hypnosis are the most common methods, and many of these can be eligible for insurance cover if administered by a certified physician[28]. In Norway, 62% of people with headaches had used TCM particularly acupuncture and chiropractic[29]. Available reports indicate that the acceptance for TCM is highest for family medicine and in mental and neurological disorders and is lowest in surgical practice[27]. However, efforts to TCM into mental health care in South Africa faced resistance from the specialists and primary health care workers[30]. Similar observations were made in Kenya, where primary health care workers could not consider collaborating with traditional healthcare practitioners because they are unqualified and promote use of dangerous concoctions[31]. The use of TCM is common practice for epilepsy and mental health disorders as separate conditions, but the same treatment principles can be applied when these two are co-occurring or a comorbid in one patient, if consideration for drug-drug interactions are respected.

There are several types of TCM as outlined by the National Cancer Institute Office of Alternative and Complementary Medicine (<https://www.cancer.gov/about-cancer/treatment/cam>). Mind body therapies such as Yoga and meditation help relation body and mind. Biological based practices such as dietary supplements and herbs can enhance healing or improve physiological function. Manipulative and body-based practices such as reflexology and chiropractic involve stimulating parts of the body e.g. spine. Energy healing is premised on the belief that energy flows through the body, and that for healing this should be balanced by placing hands on the person akin to therapeutic healing. Whole body healing systems that have been practiced and changed over time in different parts of the world and includes traditional healing including Chinese medicines such as acupuncture, Ayurvedic medicine, homeopathy and naturopathy. Table 1 shows the description for each TCM.

Table 1. Types of TCM as adapted from the National Cancer Institute, Office of Complementary and Alternative Medicine (<https://www.cancer.gov/about-cancer/treatment/cam>)

Type of TCM	Subtypes	Description
Biological-based therapies	Vitamins	Micronutrients the body needs in small amounts to function and stay healthy
	Diet Supplements	products added to the diet that may be enriched for ingredients such as minerals, and herbs
	Botanicals/Herbs/Spices	Part of plants or extracts of plants. Examples include cannabis, herbs and spices such as turmeric or cinnamon
	Special foods/diets	meal plans that control the intake of certain foods or nutrients e.g. ketogenic diet and gluten-free diet
Mind-body therapies	Meditation	focused breathing or repetition of words or phrases to quiet the mind and lessen stress
	Biofeedback	mind-body technique used to control some of your body's functions, such as your heart rate, breathing patterns
	Hypnosis	a waking state of awareness, (or consciousness), in which a person's attention is detached from immediate environment and is absorbed by guided inner experiences such as feelings, cognition and imagery
	Yoga	ancient system of practices used to balance the mind and body through stretches and poses, meditation, and controlled breathing
	Tai Chi	a form of gentle exercise and meditation that uses slow sets of body movements and controlled breathing
	Imagery	Palming imagery involves imagination of colours that cause more relaxations eg light blue, while guided imagery is whereby an expert instructs one to imagine desirable or peaceful scenes eg beaches, swimming pools.
	Creative outlets	Calming oneself using interests such as art, music, or dance
Manipulative & body-based	Massage	soft tissues of the body are kneaded, rubbed, tapped, and stroked
	Chiropractic therapy	Mechanical manipulations of the joints and spine to relieve pain and discomfort

	Reflexology	Application of pressure to different part of the body (the feet, hands, and ears) to relive stress or pain for instance.
Energy healing	Reiki	A biofield therapy in which an attuned therapist places their hands on or near the client's body and sends healing energy
	Therapeutic touch	manipulation of the spine, joints, and skeletal system
Whole medical systems therapies	Ayurdelic medicine	Seeks to treat epilepsy by unblocking the channels of the heart and the mind that may be clogged by the excess of doshas or humors.
	Traditional Chinese Medicine	Uses combinations of herbal and animal products to balance between two forces called yin and yang and then keep a person's spiritual, emotional, mental, and physical health in check
	Acupuncture	Chinese medicine that involves stimulating certain points on the body to promote health
	Naturopathic medicine	a system that avoids drugs and surgery. It is based on the use of natural agents such as air, water, or others such as herbal products, and aromatherapy to help the body heal itself

Several reasons drive the increase in popularity of use of TCM worldwide, but it is difficult to identify the most relevant because the choice often depend on time, setting, disease, and individual patient[32]. For instance, social networks in LMIC are important influences of TCM use, while in HIC this influence may come from a contact from within the health care system[33]. In many LMIC, the TCM is considered as culturally appropriate because it aligns well with their values, beliefs e.g. religion, and lifestyle, and therefore they are also likely to be recommended by relatives, and members of the community. Interventions to strengthen educational and health systems that promote the use of biomedical medicine may therefore be viewed by some as deterrent to the use of TCM. Further the mystery behind the mechanisms of action of the concoctions, aligns well with the -myths, and superstitions associated with the disease in some communities[34]. Also, seeking epilepsy care from traditional health practitioners who are widely accepted in some communities[35], will be perceived as less stigmatizing by some. In rural Kenya the interaction of people with epilepsy and a traditional healers was so crucial in influencing the decision whether to seek biomedical care, because the

local healers provide explanations for the disease that resonates with cultural perspectives of the members of the community[9, 35]. Lack of access to quality conventional medicines may encourage people with epilepsy to use of TCM, especially if they cannot afford the medications, or when the old generation anti-seizure medications readily available in many not be effective for the epilepsy syndrome or associated with side effects. These patients will revert easily to TCM through the traditional health practitioners they made initial contacts with before they switched to modern medicine. Failure to respond to anti-seizure medications or the associated adverse drug reactions can result in disappointment with conventional medicine or with trained or specialist health care workers[9]. Somatic and psychiatric comorbidity of epilepsy impact on response to treatment, particularly if the choice of treatment does not consider the possibility of induction of seizures by some antidepressants, for example, and drug-drug interaction. These chronic comorbid conditions require prolonged treatment, which many patients cannot cope with, resulting in sampling of TCM as last a last resort or for hope. Some patients will prefer TCM because it offers more control over treatment decisions and others because it is less invasive[9], compared, for example, to epilepsy surgery.

Barriers to use of TCM have been identified including the incomplete understanding of the scientific basis of TCM action, concerns about safety and efficacy, unhygienic practice in product preparation[36], and financial implications due to non-coverage by insurance[37]. The lack of scientific evidence for TCM is related to reduced capacity to conduct and translate research findings and the institutional culture of disinterest in TCM study and research[38]. While TCM is being practiced in some mainstream healthcare systems from Asia, there is low levels of awareness among health care workers[39], with many discouraging its use in countries like the United States[37]. Many TCM products are also not patentable and continue to be viewed with suspicion by pharmaceutical companies and wide society[40]. Some of these barriers could be addressed through education initiatives, promotion of collaborations between TCM stakeholders and academic or research institutions, advocacy for increased funding towards TCM research, and bridging the epistemological differences e.g. acceptability of clinical trials of products by TCM[41].

4.0 Role of biological-based therapies and epilepsy care

Like other anti-seizure medicines, TCM of proven quality, safety, and efficacy, can contribute to the goal of ensuring that all people with epilepsy have access to care. Biological-based therapies are the leading TCM for the management of epilepsy. Supplementation with multivitamins and folic acid has consistently reduced seizures frequency particularly in childhood epilepsy[42, 43]. It is helpful to establish low levels of for the vitamins and folic acid to avoid induction of seizures with supplementation[44]. Prolonged use of phenytoin and phenobarbital can lower levels of folate and vitamin B[45]. Melatonin is effective in control of myoclonic and nocturnal seizures[46], perhaps through improved sleep quality[47]. Probiotic supplementation was safe and effective in reducing seizures in patients with refractory epilepsy[48], suggesting that there is a gut microbiota role in epilepsy[49].

Ketogenic diet is arguably the most common form of special foods or diet used in control of refractory epilepsy particular in children, that leverages on upregulation of neuroprotective chemical messengers such as gamma-aminobutyric acid and monoamines by ketone bodies resulting from intake of ketogenic diets[50]. In findings pooled from 8 randomized controlled trials, children with epilepsy using ketogenic diet were 6 times more likely to experience a 50% or more reduction in seizures, compared with controls[50]. There are anecdotal or case reports of other forms of special foods/diets associated with improvement in seizures control includes Mediterranean diet (high in plant-based foods and seafood)[51]; elimination/gluten-free diet which excludes inflammatory food such as wheat and cow's milk[52]; and Feingold diet (eliminates natural salicylates and artificial colors and flavors)[53].

There are hundreds of botanicals or herbs being used for seizure control, with very few recommended for mainstream care for seizures, due to incomplete understanding of underlying mechanisms and limited evaluation of efficacy in clinical trials[54]. The extracts of *Gladiolus dalenii*, which are commonly used in Africa, have anticonvulsant effects against pentylenetetrazol-induced seizures [55], while *Bryonia alba*, which utilizes benzodiazepine-like mechanisms, is common in Iran, Asia [56]. Herbal medicines such as the American and Mistletoe (*Viscum sp*) are used in epilepsy management of epilepsy in the US despite that there

is no data on their clinical efficacy[57]. Cannabidiol products which acts through the endocannabinoid receptors in the brain and can impact the gut microbiome, improves seizures and developmental status of children with epilepsy[58]. In fact, use of cannabidiol in the Sesame oil formulations has been approved in the US for the treatment of refractory Dravet and Lennox–Gastaut syndrome, and tuberous sclerosis in young children[59].

5.0 Role of whole-body system therapies in epilepsy care

Whole body medical systems therapies are fairly reported in the literature as feasible TCM approaches for improving epilepsy outcomes. Traditional (including Chinese) medicines are common in many settings including Asia and Africa. In Kenya for instance, epilepsy that was considered ordinary that is caused by demons, concoctions were used to control it, whereas non-ordinary epilepsy due to other causes herbs or extracts from Zebra hooves were used[31]. The Traditional Chinese therapy are holistic in that they combine dietary, animal products and herbal therapies with anti-seizure activity including anti-inflammation, antioxidation and regulation of neurotransmission[60]. A recent review highlighted over 30 botanicals and prescriptions that are common for Traditional Chinese therapy for epilepsy[61]. Traditional therapies would not be easily incorporated into routine treatment because of lack of standardized treatment, and incomplete understanding of the bioactive ingredients, which should be clarified in future clinical trial of efficacy and safety. Putative anti-convulsant effects of acupuncture have been tested in animal models, and likely involve the vagus nerve and its central connections and decrease of neuronal and inducible nitric oxide synthases[62]. Acupuncture combined with anti-seizure medications was associated with improved response to treatment and quality of life and reduced frequency of seizures and adverse effects in a systematic review of 17 experimental studies[63]. The studies however were of low quality, were from a single country (China), did not use a standardize protocol for acupuncture and were not well randomized, necessitated further evidence.

Ayurdelic medicine or simply Ayurveda is widely utilized in Asia, where herbal remedies such as *siddharthaka ghrita aswagandharistam* and *Saraswata rishta* are thought to have fewer adverse effects than ASM[64]. Treatment of epilepsy with Ayurveda to open the mind channels

using various concoctions and purgatives fried in oil and butter[65]. Despite extensive reference of epilepsy in the Ayurvedic literature[66], there are no good quality studies to inform use of this TCM as a standard treatment option for epilepsy. Naturopathic medicine includes homeopathy therapy and can overlap with other body-based or TCM options e.g. body-based TCM therapies described below, and biological-based TCM therapies described above, so long as patients abstain from other pharmaceutical medicines and surgery. Homeopathy with plant or animal products, that otherwise produce seizure-like symptoms in health people, are also used in epilepsy care. Improvement in seizure control and quality of life was reported in children with epilepsy that used homeopathic medicines such as *Calcarea carbonica*, *Ignatia amara*, *Natrum muriaticum* and Phosphorus[67]. However, anti-seizure medications are never withdrawn in some studies of naturopathic therapy using adjunctive nutritional supplementation[42], perhaps because the epilepsy is already refractory to treatment.

6.0 Role of mind and body therapies in epilepsy care

Mind and body therapies have been used to control seizures, and to improve psychiatric problems. Yoga can cause desynchronization, increased Gamma-aminobutyric acid levels and improved blood flow to the brain, which explains the reports of reduced seizure frequency (including normalization of EEG), and psychological distress in some clinical trials [68]. In a recent experimental study from India[69], Yoga was not only associated with seizure reduction and freedom but also with reduction in felt stigma (as measured with Kilifi stigma scale) and anxiety symptoms with improvement in cognitive function and quality of life. Reduction in seizures and improvement in EEG background has been reported following meditation and biofeedback[70, 71]. Hypnosis has been used to differential psychogenic non-epileptic seizures from epileptic seizures through hypnotic suggestion by trained physicians[72]. Hypnotherapy has been considered for psychogenic non-epileptic seizures, but findings from earlier trials were not promising[73].

Creative arts therapy improved depression and anxiety in patients with stroke[74], in whom seizures are common. Mental imagery, which is a form of weak perception[75], has been integrated within cognitive behavioural therapies, for management of depression and suicidal

behavior[76], which are often comorbid with epilepsy. Long-term treatment of people with epilepsy with music i.e. Mozart effect, induced a neurostimulation associated with reduction in seizure frequency and interictal epileptiform discharges on EEG[77]. Future trials should investigate if the calmness and happiness resulting from mental imagery creative arts studies would improve seizure frequency. However, many of these studies are of low quality in terms of being unblinded and uncontrolled and use of small numbers and different outcomes based on self-reports.

7.0 Role of manipulative and body-based therapies in epilepsy care

Manipulative and body-based therapies are known relaxation and calmness, through stimulation of the parasympathetic nervous system, release of serotonin and dopamine or induction of cerebral waves similar to those of sleep[78]. In a clinical trial of people with refractory epilepsy on anti-seizure medications, reflexology massage of the foot and hands administered by relatives was associated with a reduction in seizure frequency[79]. There are not clinical trials on the role of massage in improving epilepsy outcomes, although available literature suggests that it can reduce anxiety[80], or improve outcomes for other neurological disorders such as migraines[81] and Parkinson disease[82]. There are anecdotal reports of chiropractic therapy improving epilepsy outcomes especially if the therapy involves correction of upper cervical vertebral subluxation[83, 84], but these suppositions should be established with well-designed studies. The accumulating evidence on neural correlates of manipulative and mind-based therapies[85], supports need to examine their role in improving outcomes in people with epilepsy, carefully documenting if any possibilities of exacerbation in seizures.

8.0 Role of healing energy approach in epilepsy care

There are few studies on use of energy healing in people with neuropsychiatric disorders, with the few available studies demonstrating reliable evidence in controlling depression and anxiety symptoms following Reiki therapy[86]. Reiki and touch therapy did not improve functional outcomes in people with stroke[87], and it is therefore unclear if there would be any benefits with its use in epilepsy patients. It is thought that energy healing is transferred from healer to the recipient patient, via quantal perceptive mechanisms[88]. Despite that the processes of

Reiki and therapeutic touch in healing is incompletely understood, hypothesis have been put forward that it is seen as a practice that can be easily integrated into nursing practice[89].

9.0 Safety and regulatory concerns for traditional/alternative and complementary medicine

There are concerns about use of TCM related to the lack of properly designed studies eg well powered clinical trials to establish efficacy and to detect adverse reactions in the short- and long-term, with little or no replication studies showing some effects. These adverse events should be graded according to specific products without generalising to the entire TCM practice. Designing randomised controlled trials for TCM can be complicated by challenges with inability to assess long-term adverse events, inclusion of heterogeneous cases, because of inaccurate diagnosis by traditional health practitioners; or by incomplete blinding situations where a placebo does not have same distinctive aroma (e.g. garlic-containing TCM products) as the TCM product. Since heterogeneous case definitions can mask evaluation of efficacy, accurate diagnosis in clinical trials of TCM can be ensured by promoting co-ordinated partnerships between biomedical health specialists and traditional health practitioners[90]. Governments would not engage in regulation of TCM that are not registered as medicines in national registries[91]. The response of conventional medicine is dependent on careful characterisation of the seizure semiology, yet few TCM studies described the epilepsy phenotypes. Some studies use combined herbal products without standardization, resulting in inter-variations in preparations[91], making it difficult to attribute side effects or effectiveness to any one bioactive compound. Many of the TCM are co-administered with anti-seizure medications, increasing the possibility of interaction. The consequences of interaction are either increased activity (leading to adverse drug reactions or decreased activity) or decreased activity (responsible for non-response)[92]. It also possible that these TCM products alters the function of cytochrome P450 enzymes and P-glycoproteins, which can affect ASM levels. The TCM products can be contaminated with heavy metals such as lead and mercury because of unhygienic handling, accidental or intentional botanical substitution and lack of quality control mechanisms, causing neurotoxicity and further exacerbation of seizures. There may be other harmful safety of concerns that are yet to be discovered, including the possibility some (e.g. homeopathic therapies) are proconvulsant.

10.0 Regulation and integration of TCM into health systems

Integration of TCM within the health systems of countries is faced with lots of regulatory, operational and scientific bottlenecks[93]. Many countries do not have the mechanisms to regulate and control TCM or herbal products, monitor TCM providers and regulate TCM advertising and claims. Technically, there is lack of expertise on TCM within the ministries of health and government agencies, and there no facilitated channels for collaborations between various TCM stakeholders nor clear plans on training the TCM providers. There is no supervised empirical research on efficacy and safety of TCM, for instance, because of lack of funding and under-appreciation of the sector. Nonetheless, in some health systems, TCM are recognised and are employed in all areas of health-care provision, including national drug policy, education curriculums, research and innovation, and insurance of treatment etc [93].

It is crucial that countries assess their own national situations in relation to TCM, and then come up with practical solutions to these realities, using ratified guidelines and best practices. Many countries from LMIC continue lag in implementation of these policies and guidelines, especially the areas of research and innovation and regulation of TCM practice[94]. One important resource is the WHO Traditional Medicine Strategy 2014-2023, which aims to harness the potential contribution of TCM in routine health care of member states, and promoting the safe and effective use of TCM through guided regulation[95]. This strategy also contributes to knowledge generation and policy formulations around TCM, quality assurance and regulated use of TCM, and use of TCM to promote universal health coverage.

Efforts to generate knowledge and national policies for TCM, should start with careful selection of TCM products where health authorities should invest in, since there are hundreds of these in use whose efficacy and safety is unknown. An important step towards achieving this is deliberately seeking to understand the specific nature of their national TCM sector, while acknowledging the crucial role it can play in the health-care system and establishing collection of valid and comprehensive baseline data from which to build on[93]. Government in partnership with stakeholders should invest and facilitate research and innovation into the various forms of TCM products, including those from other settings shown to be effective from

the literature[96]. This should employ randomised controlled trials for comparative effectiveness of the TCM products in different settings; with mixed method designs to appreciate the perspectives of the consumers, providers and stakeholders. Importantly, ministries of health should develop policies and regulation with a national and global perspective, using best practice approaches.

To regulate and control use of TCM and ensure safety and quality assurance, governments should come up with regulatory frameworks for both products, providers and consumers[91]. These can adopted, for instance, from the WHO's Good Manufacturing Practice, which advocates adherence to prescribed standards and quality during the product manufacturing process and marketing of the finished products [97]. A review of regulatory frameworks from 5 Asian countries[97], found a lack of robust evaluation of products before listing, limited partnership with research institutions in development process of products, and lack of investment in resources and technology for post marketing surveillance or pharmacovigilance. This quality control process should be informed by empirical data from within the country to reflect specific local and national needs. Such studies should also identify the active ingredients of the herbal medications as was done with the anti-malarial drugs. This works effectively when a multisectoral approach is followed in defining the modalities of practising TCM, while ensuring safety and efficacy. Monitoring and evaluating the progress of TCM practice using reference standards, from best practice guidelines or benchmarking from other countries, should be considered. Many LMIC can adopt regulatory frameworks or policies for TCM from other related countries with long history of TCM practice e.g. China, or from WHO good manufacturing practice[97], and recently Traditional Medicine Strategy 2014-2023 regulation[95] and Medicines and Healthcare products Regulatory Agency's yellow card for continuous documentation of adverse events from TCM[98]. Throughout the process ensuring that TCM practice complies with international treaties, which helps in addressing challenges such as inadequate domestication of legislative frameworks to suit local or national needs, ineffective sharing or communication of quality and safety information, and scepticism of TCM use within different cultures.

Integration of TCM into routine health care systems may accelerate realisation of universal health coverage within countries. Specifically, if TCM development and use is well regulated and safe and effective products made more accessible to populations who need them, this can advance principles of universal health coverage such as ensured access to quality health care without financial hardships[99]. There is emerging evidence that TCM, when included in universal health care plans, eases the pressure on the system and diminishes costs[22]. Focus should be placed on products on which there is empirical evidence on effectiveness, since they have the greatest potential for acceleration into phase IV trials, within ideal health system settings. Even as acceleration of TCM as standard treatment option for epilepsy is ongoing, efforts should be made to ease of the burden of payment from payment, by promoting their inclusion in insurance plans. Health authorities can then settle on models of integration of TCM into national health care system, premised on strategies such as understanding the environment and capacity of a health system, and population and political settings; consumer experiences with TCM to inform facilitated or consumer-led for example; and the integrated health systems model that works e.g. parallel, consultative, coordinated/facilitated, or fully integrated TCM practice[93] Involving consumers in this integration process, and clarifying that they are free to make informed choice about treatment modalities.

11.0 Conclusions and future directions

Practice of TCM in the management of epilepsy is widespread, particularly in LMIC settings, which is in part driven by traditional beliefs, social or family influences, personal preferences, disease factors e.g. chronicity and non-response to treatment and unavailability of antiseizure medications. There is no reliable evidence from randomised controlled trial that TCM products are effective in seizure control, nor what harms are associated with their use, because of limited properly designed clinical trials, lack of replication of studies showing effectiveness and poor mechanisms for quality assurance. These can be evaluated through future animal models and mixed methods studies including randomised controlled trials. Active ingredients for TCM products should be identified and tested in properly clinical trials because of their potential to strengthen the health care system in terms increasing access to medication and reducing costs of care. Even if many of these TCM are not registered for the management of epilepsy, their

regulation by authorities is warranted owing to their expanding use locally and globally and because some products may be harmful and should be monitored. Health authorities and agencies should invest in building knowledge base for TCM, strengthening its quality assurance and developing or adopting regulatory policies and frameworks that promotes integration of TCM products for epilepsy care into health care systems, to accelerate the realisation of universal health coverage for epilepsy and its associated comorbidities.

Declaration of competing interest

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