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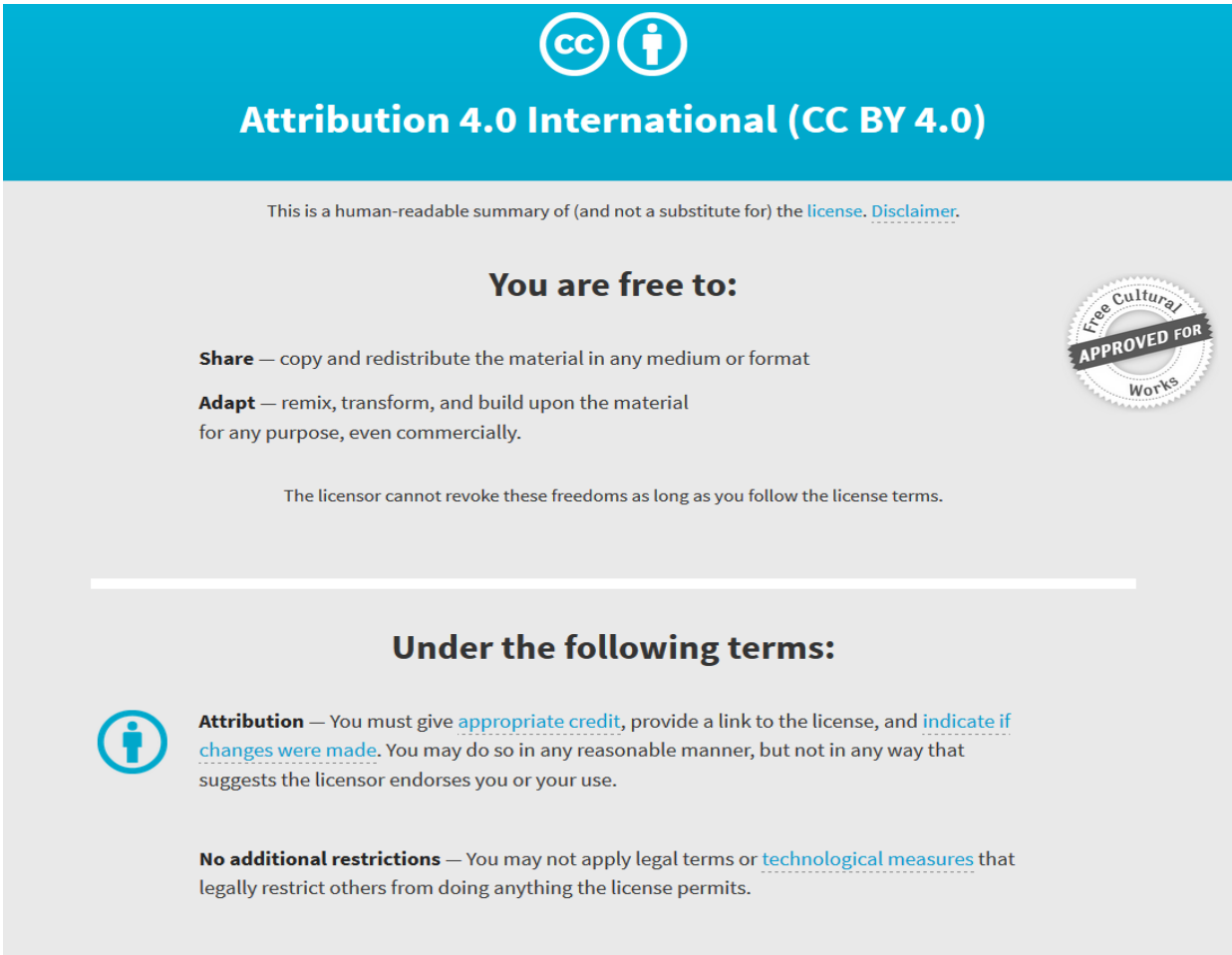
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Review Article

CURRENT STATUS OF EPILEPSY IN MALAYSIA AND WAY AHEAD

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ABSTRACT

Epilepsy is the third most common neurological disorder, following stroke and Alzheimer's disease with the highest frequency of newly identified cases occurring among children and adults. About 50 million people worldwide have epilepsy, and nearly 80% of epilepsy occur in developing countries including Malaysia. In Malaysia, epilepsy is still a highly misunderstood and a number of studies explored the poor understanding of the illness. Epilepsy patients have the serious impact on quality of life. Both individuals and families of the patients have an appalling experience. Another factor is cost of AEDs which is very high. It is a burden for both patients and their families to meet the costs. There is a significant need persists to develop an accessible, cost effective, efficacious and less toxic antiepileptic drugs. Natural products used in traditional herbal medicine can be an important source for the search of novel anti-epileptogenic compounds. A number of plants used in traditional medicine have shown to possess anticonvulsant activity. Malaysia is rich in medicinal plants. Attempts have been made in the past to explore the effectiveness of some medicinal plants for the treatment of epilepsy, but the rationale for selection of plants was not justifiable and hence they failed to get a hit. Some of the Malaysian plants are used by traditional healers in the treatment of epilepsy, but their therapeutic effectiveness is not being scientifically explored. This review focused to enlighten the status of epilepsy and research required for the Malaysian medicinal plants for the treatment of epilepsy.

Keywords: Epilepsy, Malaysia, Impact on quality of life, Medicinal plants, Anti-epileptics.

INTRODUCTION

Epilepsy is a disorder defined as chronic unprovoked recurrent seizures that occur when there is a sudden intense electrical impulse outburst in the brain [1]. The abnormal brain activity causes epileptic seizures (symptom) which are seen as episodic disturbances in movement, consciousness or feeling [2, 3]. These seizures can be both brief and confined (partial) to certain muscles in the body or prolonged and generalized throughout the body. The frequency of these epileptic seizures also varies from once per year to several in a day. Epileptic patients also exhibit other temporary symptoms such as loss of awareness and sensations, disturbances in mental function and manifestation of mood disorders. The risks of epilepsy development can vary from brain tumors to gene mutations in the brain to systemic disorders such as infections, dehydration and hypertension [3].

According to a 2012 survey done by the Center for Disease Control and Prevention (CDC) in USA, about 2.3 million adults were diagnosed with active epilepsy while an estimate of 1.7 million adults were having inactive epilepsy (diagnosed but no seizures for almost 12 months) [4]. The World Health Organization (WHO) on the other hand, believes that approximately 50 million people worldwide are suffering from epilepsy [1]. They also believe that almost 80% of these reported cases originate from developing countries including Malaysia. The reason for this could be because developing countries lack the resources needed to treat epilepsy as well are more prone to the risks of epilepsy such as infections.

Current review emphasizes on status of epilepsy in Malaysia with respect to understanding of the illness, impact on sleep in children and adults and quality of life of the individuals. The review also discusses the possible options, efforts and directions required for the development of novel antiepileptic drugs using the traditional knowledge of medicinal plants of Malaysia. This will also contribute to the knowledge of new drug discovery of AEDs, which will be cost effective and easily accessible.

Epilepsy in Malaysia : myths and understandings

Malaysia is a multiethnic country which is made up by three major ethnic groups where Malays emerged as the majority, followed by Chinese and Indians. Several surveys have been completed in certain

districts or populations in Malaysia to assess the concept of understanding and attitudes towards epilepsy.

In Malaysia, epilepsy is still a highly misunderstood illness and patients are often dodged by the public [5]. In this region, epilepsy is still considered as condition due to mythic causes, such as demonic possession [6]. The more recurrent a person's epileptic seizures are, the more likely he or she will be exposed to derision and humiliation. Epileptic patients make up 1% of the overall Malaysian population [7].

Taking care of the well-being of epileptic patients is one of the main fields that identified by government. As an initiative, the government started setting up the tertiary referral centers in Malaysia. The well-being of the patients was evaluated in one particular tertiary referral center. This particular center is situated in a northern-eastern peninsular Malaysia and it is serving a population that has a lower socioeconomic status. The national effort to tackle epilepsy is considered low and is restricted to certain tertiary education institutions. They are conducting public surveys and also promoting public awareness through events organized by different societies. The studies have covered the assessment of the Malay population in Kelantan [8]. On Malaysian Public university students [6] and the assessments which were done in 2010 covered the Chinese population in urban areas of peninsular Malaysia. The surveys have found that there is a frequent use of traditional treatment among the respondents [9]. The outcomes of those surveys also provided important information for the better planning of the future health education program in Malaysia [10].

Besides that, a latest consensus guideline on the management of epilepsy in Malaysia was published in the year 2010. The guidelines were prepared by the collaborative work between the Epilepsy Council of the Malaysian Society of Neurosciences and Malaysian Epilepsy Society. They involved Malaysian local specialists covering from family physicians, internists, pediatricians, neurologists, to all relevant health care providers pertaining to the management of epilepsy. The guidelines created to also provide the updates for the use of generic drugs and Pharmacogenetics aspect of the drugs. All the recommendations in the guidelines were updated based on the most recent publications as well as the expert opinions of the panel [11].

Impact on sleep

The effect of epilepsy on sleep behaviors of Malaysian children with epilepsy was also studied by Malaysian researchers. Comparison was made between children with epilepsy and their siblings in order to conclude the elements which are associated with greater sleep disturbances. Several key findings include, the severity of the epileptic disorder is associated with the sleep disturbances. They also found that, the epileptic children were having a higher prevalence of co-sleeping and more sleep disturbances than their healthy siblings. It was observed that children with epilepsy have difficulty in the initiation and maintenance of the sleep and experiences sleep-wake transition disorders. These findings are very useful in developing exhaustive protocols for the care of children with severe epilepsy [12].

Impairment in life quality of adult epilepsy patients is also influenced by sleep disturbance. A cross-sectional study was done to measure quality of life for Malaysian epileptic patients with obstructive sleep apnea and the effect of obstructive sleep apnea treatment at the Neurology Clinic of the Hospital University Sains Malaysia. In this context, two sets of questionnaires namely Epworth Sleepiness Scales (ESS) and the Malay version of Quality of Life in Epilepsy patients (QOLIE-31) were used for these assessments on a total of 180 enrolled participants. Several important findings were discovered at the end of the study. In brief, the worry of seizure is significantly higher in the patients whom had diagnosed positive for obstructive sleep apnea and the group also exhibiting lower scores for life quality index. The study also showed that the medication does affect the quality of life of the Malaysian patients; specifically, it helps emolliating the seizure worry and improving their cognitive functioning [13].

Impact on employment

Researchers also study the impact of epilepsy on employment was also recently done in Malaysia. A study was conducted in 250 subjects suffering from epilepsy. The study has identified several different indicators such as the age of onset, total score in seizure severity scale, the responsiveness to first antiepileptic drug as significant predictors of unemployment in epilepsy patients. The findings also highlighted that epilepsy has impact on employment in Malaysia, as there is a high prevalence of unemployment among epileptic patients [14].

Impact on quality of life

The predisposition of the frequent strikes of epileptic seizures and the poor reliance attention on medicines are eventually affecting the quality of life of the patients in Malaysia [15]. Researchers in Hospital Kuala Lumpur also conducted a study on the aspects of socioeconomic and psychological impact on the quality of life in Malaysian patients. The study has concluded the significance of those aspects in association with quality of life of Malaysian epileptic patients [16]. The importance of seizure control for a better quality of life in Malaysian patients is confirmed in that study. The findings also highlighted that the medication effect is among least influencing factors towards the quality of patients' life [17].

Although Malaysia is a multi-ethnic society, the findings of the surveys which covered only two major groups, namely Malays and Chinese have come to the quite similar conclusion. As there is still a considerable number of respondents maintained a negative attitude and had poor knowledge on the causation and treatment of epilepsy [8, 10].

Current epilepsy therapy

Current treatment options for epilepsy treatment include anti-epileptic drugs (AEDs) and brain surgery. On an average, epileptic patients are prescribed with 1.51 AEDs where 54.3 percent of the patients on monotherapy and 45.7 percent on polytherapy. Drugs from first line therapy like sodium valproate are most frequently used followed by carbamazepine and lamotrigine [18]. Newer drugs are also commonly used which includes Lamotrigine (Brand: Lamictal), Tiagabine (Brand: Gabitril) and lamotrigine, topiramate (Brand: Topamax) tiagabine, etc. AEDs help to gradually decrease the frequency and severity of epileptic seizures and have been proven to

have an efficiency rate of 60-70% in all treated epilepsy cases [1, 19]. AEDs have different mechanisms of action that enable efficient epilepsy treatment which includes blocking the sodium channels, enhancing GABA-mediated chloride currents, blocking T-calcium currents and blocking the glutamate mediated currents [19]. In other words, AEDs are used to enhance the inhibitory action on neurons (hyperpolarization) and inhibit the excitatory action on neurons (depolarization) and therefore controlling the abnormal electrical impulses in the brain. However, despite its efficiency, AEDs are often associated with many adverse effects such as skin rash, drowsiness, ataxia, bleeding gums, hyperplasia and even osteoporosis (long-term usage) [3, 19]. Moreover, some patients do not react to AEDs effectively and therefore are subjected to brain surgery instead, which is more costly and has a high risk of resulting in further complications.

Demerits and cost of current therapy

Current therapeutic strategies for the treatment of epilepsy have designed to halt the seizure initiation and propagation rather than treating the root cause of the disease. As a result, none of the currently available anticonvulsant drugs are capable of preventing epilepsy. Gamma amino butyric acid (GABA) and Glutamate levels are well studied in epilepsy and considered as reliable biomarkers of epilepsy. The most common excitatory neurotransmitter in the brain, glutamate, has been implicated in both the initiation and propagation of seizures as well as brain damage that can occur following prolonged or repeated seizures. Gamma- amino butyric acid, the most common inhibitory neurotransmitter, usually suppresses seizure activity. Antiepileptic drugs prevent the metabolism of GABA or exhibit GABA mimetic effect [20, 21]. Current Antiepileptic Drugs (AEDs) are associated with side effects on cognition and behavior, dose related and chronic toxicity that involve virtually every organ system.

The cost of new AED, i. e. lamotrigine, oxcarbamazepine, felbamate, vigabatrine, gabapentin is 3-6 times higher than the conventional AEDs. In developing countries, the costs of new AED are up to 250% higher when converted into local currency. Most of the population usually does not have medical insurance and patients with epilepsy are among those with the lowest income, it is usually impossible for most of the patients to meet the costs [22, 23].

The need of the hour

There is pressing need to develop an accessible, cheap and adverse effect free drug to treat epilepsy. Natural products used in traditional herbal medicine can be an important source for the search of novel anti-epileptogenic compounds. A number of plants used in traditional medicine have shown to possess antiepileptic activity. The interest of researchers in medicinal plants as a natural source of medicine has noticeably increased in the past 20 years and particular attention has been given to substances which are used as folklore medicines for the development of drugs against various pharmacological targets [21, 24].

Many Asian plants thought to be useful in the treatment of neurological disorders have been identified to possess neuroactive properties. The herbal medicines have remarkable achievements in research and development which have received worldwide acceptance. Currently, phytochemicals extracted from higher plants, or their derivatives remain the mainstay of interventional strategy on pharmaceutical drugs [25, 26].

Natural products used in traditional herbal medicine can be an important source for the search of novel antiepileptogenic compounds. A number of plants used in traditional medicine have shown to possess anticonvulsant activity [26, 27]. Thus, researchers around the globe are focusing on exploring the anti-epileptic benefits of natural products mainly plants. Plants that are easily available and has a less costly extraction process. Plant source is also an interest of scientists as it looks promising for efficient epilepsy treatment that would be affordable for patients in developing countries. Besides that, the key goal of natural product usage in medications is to minimize the adverse effects associated with modern medicines as natural products especially plants are more in tune with our body pharmacology. In America, 24% of epileptic

patients in one tertiary care epilepsy clinic reported using complementary and alternative medicines (CAM) which includes herbal medicines instead of conventional treatments [28, 29]. People often refer herbal medicines (plants) as "healthy" [30].

Malaysian medicinal plants and hope for cure

Most of the medicinal plants are used by traditional healers living in rural areas and rarely used by urban population of the world. Urban population considers herbal medicines as their second choice as they have the impression that it as enchanter's therapeutics [31]. In recent years, there has been a remarkable rise in the interest of the scientific community to explore the biological actions of assertions made by traditional healers about medicinal herbs. They also accepted the folk medicine and their medicinal properties [32].

There are many species of plants all around the world, but the benefits of these plants have yet to be discovered by man. Malaysian natives are using plants as a treatment for epilepsy since generations, but they neither have the understanding of the pharmacokinetics nor the pharmacodynamics of the plant. Borneo region of Malaysia is like a treasure of medicinal plants. These plants include mustard seeds, *Anacyclus pyrethrum*, *Zizyphus jujuba*, *Benincasa hispida* and *Orchis mascula* [33]. Two plant species used by natives to treat epilepsy have promising outcomes and therefore require further investigations. These plant species are *Alstonia macrophylla* and *Amaranthus spinosus* [34, 35]. The former is a native plant in Malaysia and can also be found in the Bay Islands, India, while the latter is found distributed in tropical areas of America and throughout India [36, 37].

Alstonia macrophylla is a pantropical tree that belongs to the family Apocynaceae. Natives have used the barks and leaves of this plant to treat stomachaches, skin diseases and urinary infections. A research done in India showed that the plant had low anti-microbial activity, thus explaining their ability as an effective treatment [38]. This 5-10m high tree with its velvety leaves also has been used as an anti-inflammatory, sedative and relieves depression [39]. Thus, it is proven that this plant has an effect on the central nervous system and thus it is hypothesized that this may have an anti-epileptic property as well. Furthermore, in Nigeria, the root of the *Alstonia macrophylla* is commonly used as an antipsychotic to treat "madness" and epilepsy [40].

However, conclusive report of its benefit as an anti-epileptic has yet to be studied. It is believed that the amazing ability of *Alstonia macrophylla* as a medical treatment among the natives is due to its phytochemicals such as quebrachidine, vincamajine, alstomaline, dimethoxynareline, alstohentine, alstomicine and alstophyllal [41, 42].

As for the *Amaranthus spinosus* plant species, it comes from the family Amaranthaceae. It is a spinous weedy plant that has been used by natives as vegetable, animal feed and to treat hallucinations, leprosy, nausea, boils, diabetes and snake bites [37, 43]. This plant also has anti-inflammatory property as *Alstonia macrophylla*. *Amaranthus spinosus* is among the useful plants of west tropical Africa that can be used to treat epileptic seizures, especially in children [44].

Even though natives have used these plants as treatments for epilepsy, conclusive scientific evidence for their anti-epileptic property has yet to be recorded. In other words, there are enough experimental reports available for their efficacy to treat epilepsy, but experimental data has to be generated. Further research on this particular property may provide a more efficient treatment for epilepsy with possibly minimal to no side effects. In an attempt to develop novel antiepileptic drugs from medicinal plants, an approach is to be adopted which could combine traditional or experiential clinical knowledge of the substance by adopting reverse pharmacology approach [45].

Earlier attempts

A group of researchers investigated some of the interesting Malaysian plants for their antiepileptic potential. Plants screened were *Popowia odoardiDiels* (Annonaceae) (leaf and stem), *Artabotrys roseus Boerl* (Annonaceae) (bark), *Lit-sea lliptibacea*

Merr. (Lauraceae) (bark), *Decaspermum fruticosum Forst.* (Myrtaceae) (bark), *Dyera costulata (Miq.) Hook f.* (Apocynaceae) (leaf), and *Irvingia malayana Oliv* (Simaroubaceae) (leaf). They used electrophysiological and behavioral methods to screen these plants. They concluded that none of the plant extracts tested were active [46]. The main drawback of this study was that they have selected the plants randomly and not based on their traditional use. There was no rationale for the selection of these plants for their antiepileptic screening. Neither these plants are traditionally used by traditional healers nor any report related to them exists.

Selection criteria for a potential antiepileptic plant or natural product

In fact, several criteria of plant selection for antiepileptic drug research should be in place before taking the plant to the next level of research. One of the most tangible ways of plants selection for research studies, perhaps is picking up the medicinal plants, which are being used within the communities by traditional healers [47]. Often, this approach could lead to significant findings and this concept is being employed in India under the term "Reverse Pharmacology" [48]. Researchers can always refer to documentation of traditional medicinal plants usage in certain ethnic group as well as in the ancient system of medicines like Traditional Chinese Medicine (TCM) [49], Ayurveda [50] and other traditional medicines in Malaysia such as Malay traditional medicines [51, 52]. The reasons for selection should be based on traditional use for seizures or specifically the action targets in retrospect to known mechanisms of action that are relevant to epilepsy. Epidemiological observations could also be one of the options that can assist to identify the potential plants of anti-epileptic potential.

Eventually, there is a great need of discovering rather developing the Malaysian herbal medicine or drug for treating epilepsy. The rich diversity of medicinal plants in Malaysia is waiting to be explored by Malaysian researchers. The action should be immediate, with assurance that the planning and design of experiments should be much more comprehensive and logically sounds. The importance of this field of study shouldn't be ignored, but it should be nurtured further. As the fact that, there are tremendous promising outcomes and benefits in studying Malaysian local herbal medicines as most of them have been used since immemorial times and effectiveness are proven [53-55]. For instance, there are numbers of herbal extracts and compounds which are derived from three main streams of herbal therapies namely, Chinese, Japanese and Indian are being explored for their anti-epilepsy activities at the National Institute of Neurological Disorders and Stroke (NIH-NINDS) Anticonvulsant Screening Project (ASP) [56]. This further implies that the action of harnessing our own traditional knowledge should be fastened up which can result in creating more opportunities and benefits to our own communities.

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CONFLICT OF INTERESTS

Declared None.

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