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## The treatment of epileptic seizures: the potential of Malaysian medicinal plants

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**ABSTRACT:** Epileptic seizures result from excessive brain activity and may affect sensory, motor and autonomic function; as well as, emotional state, memory, cognition or behaviour. Effective anti-epileptic drugs (AEDs) are available but have tolerability issues due to their side effects. Medicinal plants are potential candidates for novel AEDs, as many are traditional epilepsy remedies. Malaysia is a megadiverse country, with many endemic plants serving as a large pool of potential candidates for the development of local herbal products. The large variety of flora makes Malaysia a prime location for the discovery of medicinal plants with anti-convulsive potential. This review lists 23 Malaysian medicinal plants, of which four are used traditionally to treat epilepsy, without any scientific evidence. A further eight plants have no known traditional anti-epileptic use but have scientific evidence of its anti-epileptic activity. The remaining 11 plants possess both traditional use and scientific evidence. Thus, this review identified several potential candidates for the development of novel AEDs or enhancing current ones; as well as identified an imbalance between traditional use and scientific evidence. In addition, this review also identified several limitations in the reviewed studies and provided additional information to facilitate the design of future studies.

**Keywords:** epilepsy; traditional use; anti-epileptic potential; natural products;

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## 1. INTRODUCTION

Epileptic seizures are described as a short-term occurrence of several signs and/or symptoms because of abnormally superfluous or concurrent activity in the brain. In contrast, epilepsy is a group of neurological disorders characterised by the lasting tendency to spawn epileptic seizures. The International League Against Epilepsy (ILAE) in 2014, defined epilepsy as a brain disease which fulfils one of three conditions. The first condition is having two or more unprovoked or reflex seizures which occur more than 24 hours apart. The second condition is the occurrence of one unprovoked or reflex seizure with the possibility of subsequent seizures being similar to the general recurrence risk of at least 60%; after two unprovoked seizures occurring during the next 10 years. The final condition is the diagnosis of epilepsy syndrome [1]. Epilepsy is a serious Central Nervous System (CNS) disorder, as the global prevalence of epilepsy is approximately 1 in 100 people according to Holland [2]. However, the prevalence of epilepsy in developing countries such as Malaysia tends to be higher than in developed countries. For example, approximately 198 903 out of 23 522 482 Malaysians (~1%) were diagnosed with epilepsy in 2004 [3]. The uneven distribution of the global epilepsy burden has resulted in almost 80% of people with epilepsy living in developing world regions; with 75% of them not receiving treatment, even though successful epilepsy treatments are available [2].

While the cause of epilepsy may not always be known, there are anti-convulsant drugs available for symptomatic treatment. These drugs are also known as anti-epileptics and are typically divided into 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generations, but have comparable efficacies. Several anti-epileptic drugs (AEDs) commonly used to treat epilepsy today, include lamotrigine and vigabatrin [4]. The older generation of AEDs which are used in combination with newer AEDs include drugs such as phenytoin, phenobarbital and valproate [5]. Side effects from the older generation of AEDs range from drowsiness and nausea to delirium and hepatotoxicity, as well as other idiosyncratic reactions; whereas newer

generation drugs have side effects ranging from headache and dizziness to liver failure and weight loss [5]. Although the side effects of AEDs are largely dependent on the individual, it is also dose-dependent and worsens when multiple AEDs are used concurrently. This is unfortunate as multiple AEDs are often prescribed concurrently in high doses in an attempt to eliminate seizures [6]. Thus, while the efficacy of the AEDs used today is proven, there is still a need for the discovery of novel AEDs with fewer side effects. Currently available AEDs also do not always wholly cure epilepsy, as the seizures can reoccur even after several years without incident; regardless of whether treatment was discontinued [7].

Medicinal plants may provide important clues in the search for novel AEDs, as several drugs which affect the CNS have been developed from medicinal plants. For example, research in this area has yielded medicinal plant-derived drugs such as reserpine [8] from the dried root of *Rauwolfia serpentina* (Indian snakeroot), which was used in the past to treat mental illnesses such as schizophrenia. The plant itself has also been used for the traditional treatment of insanity [9]. *Valeriana officinalis* (Valerian) is another example of a medicinal plant which has been used to treat epilepsy and in more contemporary settings for the treatment of insomnia, stress and anxiety [8, 10]. In addition to valerian, several other medicinal plants have been traditionally used to treat epilepsy in various communities around the world [11-13]. The ability of plants to affect the human CNS is the result of the secondary metabolites which are synthesised by plants. Among the more important of these secondary metabolites are alkaloids, tannins, flavonoids and phenolic compounds [14]. The potential of traditional medicines is perhaps increasingly recognised as more novel treatments for a variety of ailments are developed from them.

Malaysia is a Southeast Asian country and one of only 17 countries designated megadiverse by Mittermeier R. A. in an attempt to highlight how certain countries are critical in ensuring the continuity of a major

proportion of the world's biological diversity due to their inherent abundance in living organisms [15, 16]. Malaysia boasts an estimated 12 500 species of flowering plants together with an additional 185 000 species of fauna; with a significant proportion being endemic to the region's tropical forests [17]. The sheer variety of Malaysian flora thus makes it likely that the country also boasts a significant number of medicinal plants which affect the human CNS on sheer probability alone. Thus, in the search for novel drugs to treat CNS disorders, Malaysian medicinal plants could be an excellent starting point. Another reason to further examine Malaysian medicinal plants for the treatment of CNS disorders is that some Malaysian medicinal plants such as *Orthosiphon stamineus* (Misai kucing) have been traditionally used by Southeast Asians to treat epilepsy through the consumption of a herbal tea prepared from the leaves of this plant [18]. If this search is successful, the local availability of plant source material could also make these novel AEDs more affordable and available to Malaysians. This is important because middle-income countries such as Malaysia tend to have lower availability of AEDs and even when available, the AEDs tend to cost the equivalent of several days wages for the lowest paid government worker [19].

However, whilst there is at least one review describing the scientific validation of various Malaysian medicinal plants for a variety of traditional uses [20]; to our knowledge, there has not been a review with a focus on the traditional use of Malaysian medicinal plants for the treatment of epilepsy and the results of scientific investigations into the anti-convulsive properties of those Malaysian medicinal plants. Thus, the following article aimed to review the currently available literature to provide a non-exhaustive list of Malaysian medicinal plants which have the potential to be developed into novel AEDs. The list was subdivided into three sections, the first of which being Malaysian medicinal plants only used in traditional epilepsy treatment, but without any experimental evidence on its anti-convulsive properties. The second section focused on Malaysian medicinal plants with

experimental evidence for anti-convulsive activity but are not used traditionally to treat epilepsy. The final section highlighted Malaysian medicinal plants with both traditional use and experimental evidence.

## 2. METHODS

### 2.1 Search technique

As the definition of a Malaysian medicinal plant can be somewhat vague (Native versus introduced species), this review utilised a list of Malaysian medicinal plants (As of June 2017) given under the 'Malaysian Herbal Monograph' subsection of the 'Medicinal Herbs & Plant Database' section of the Global Information Hub on Integrated Medicine (Globinmed) website at <http://www.globinmed.com>. This organisation was chosen as it is supported by the Commonwealth countries as well as being approved and funded by the Malaysian government. The information on the Globinmed website was also contributed by a variety of both local Malaysian and international sources, further adding credibility to the website. Using the list of Malaysian medicinal plants, the search of literature was conducted to determine if the plant is traditionally used for the treatment of epilepsy and its anti-convulsive properties have been experimentally determined. Google Scholar was the sole database used for this review due to the relatively large number of Malaysian medicinal plants listed on the Globinmed website; which approximately 50 at the time of this review. This is because the time and human resources available were insufficient to conduct a query of multiple databases for a more systematic review with an acceptable degree of practicality. The time frame of the articles was not restricted due to the possibility of missing out on information. The search terms used were the scientific name of a Malaysian medicinal plant together with each of the following keywords individually: epilepsy, anti-convulsive, seizures and traditional.

### 2.2 Study selection and exclusion/inclusion criteria

From the generated search results from Google Scholar, patents and citations were excluded due to insufficient information for evaluation and comparison.

From the remaining search results, only articles published in the English language were considered. Abstracts of symposiums and conferences, books as well as patents were excluded due to insufficient information for evaluation and comparison. Articles which were irrelevant to the Malaysian medicinal plant, epilepsy or anti-convulsant screening were excluded.

### **3. MALAYSIAN MEDICINAL PLANTS USED TRADITIONALLY FOR EPILEPSY TREATMENT, WITHOUT EXPERIMENTAL EVIDENCE**

#### **3.1 Review outcomes**

After reviewing available literature, four plants were found to have been used in the traditional medicinal system of various countries. A summary of the plant's review outcome is given in Table 1 at the end of the review. These plants lack experimental evidence of their efficacy, and thus further scientific investigations should be conducted to help bridge this research gap. Experimenters should also consider the traditional route of administration when assessing the anti-convulsive potential of a plant. For example, a plant may be inhaled, implying that any active constituents are absorbed via the nasal route. Thus, an experiment which utilises the oral route of administration may give a false negative result for anti-convulsive ability due to the first pass effect.

#### **3.2 List of Malaysian medicinal plants used traditionally for epilepsy treatment, without experimental evidence**

##### **3.2.1 *Melastoma malabathricum* L.**

*Melastoma malabathricum* L roots are used as a mouthwash for the traditional treatment of epilepsy and toothache [21].

##### **3.2.2 *Moringa oleifera* Lam.**

*Moringa oleifera* Lam. roots are mixed in equal parts with orange peels to make a compound spirit for the traditional treatment of epilepsy [22].

##### **3.2.3 *Orthosiphon aristatus* (Blume) Miq.**

*Orthosiphon aristatus* (Blume) Miq. leaves are brewed into a tea to serve as a traditional remedy for ailments such as epilepsy [18].

##### **3.2.4 *Pandanus amaryllifolius* Roxb.**

*Pandanus amaryllifolius* Roxb oil extracted from the leaves has been used traditionally to treat epilepsy [23].

### **4. MALAYSIAN MEDICINAL PLANTS WITH ONLY EXPERIMENTAL EVIDENCE FOR ANTI-CONVULSIVE ACTIVITY**

#### **4.1.1 Screening for anti-convulsive compounds**

To screen for anti-convulsive compounds, there must first be a way of replicating human epileptic seizures in animal models. Nearly all scientific investigations in this review utilised the rodent model of epilepsy, possibly because rodents are widely used both today and in the past for similar experiments because of their genetic similarity to humans [24]. However, one scientific investigation utilised zebrafish larvae (*Danio rerio*) as their animal model. Two frequently utilised approaches to inducing seizures in animal models are chemoconvulsants and electrical brain stimulation [25]. This review found that the two most common methods used to screen for anti-convulsive properties are via the chemoconvulsant pentylenetetrazole (PTZ) and maximal electroshock (MES). Other less commonly used chemoconvulsants were pilocarpine, strychnine, bicuculline, picrotoxin and kainic acid.

#### **4.1.2 Review outcomes**

After reviewing available literature, eight plants were found to have been experimentally proven to have anti-convulsive properties. A summary of the plant's review outcome is given in Table 1 at the end of the review. In some instances, despite the lack of use as a traditional epilepsy remedy, the authors decided to test the anti-convulsive properties of several plants experimentally; with various justifications. In other cases, the plant was determined indirectly to possess anti-convulsive properties, as it contains one or more

**Table 1.** List of Malaysian medicinal plants together with their traditional use in epilepsy treatment and experimental evidence of anti-convulsive activity

Scientific Name; Common Name; Malay Name	Family	Distribution	Traditional Use in Epilepsy Treatment	Experimental Evidence for Anti- Epileptic Activity	Mechanism of Anti-Epileptic Action	Major Active Constituent	Ref.
<i>Andrographis paniculata</i> (Burm.f.) Wall. ex Nees; King of Bitters; Hempedu Bumi	Acanthaceae	Asia, the West Indies and Central America	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• The extract is a sedative and possesses brain function altering activities in rodents</li> <li>• Antagonises PTZ and MES triggered seizures</li> </ul>	<ul style="list-style-type: none"> <li>• Downregulates functions of the benzodiazepine site of GABA<sub>A</sub> receptors</li> <li>• The site is involved in stress-triggered physiological responses</li> </ul>	Andrographolide	[26, 27]
<i>Carica papaya</i> L.; Papaya; Betik	Caricaceae	Tropical and warmer subtropical regions	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• Leaves smoked for central stimulation</li> <li>• Protects against PTZ and MES triggered seizures</li> </ul>	Increases neuronal recovery time by decreasing K <sup>+</sup> permeability	Carpaine	[28]
<i>Centella asiatica</i> (L.) Urb.; Asiatic Pennywort; Pegaga	Apiaceae	Southeast Asia and some subtropical regions	Ayurvedic literature recommends daily fresh juice of <i>Centella asiatica</i> with honey, garlic juice in oil and powdered root of wild asparagus with milk	<ul style="list-style-type: none"> <li>• Extract is anxiolytic</li> <li>• Prevents PTZ induced ATPase inhibition in different brain regions</li> </ul>	<ul style="list-style-type: none"> <li>• ATPase inhibition possibly increases neuronal excitability by altering the influx and efflux of cations</li> </ul>	Asiaticoside	[29-31]
<i>Cinnamomum verum</i> J.S. Presl.; Cinnamon; Kayu Manis;	Lauraceae	Many tropical and subtropical regions on all continents	Used internally as a herbal remedy in 16 <sup>th</sup> and 17 <sup>th</sup> century central Europe	<ul style="list-style-type: none"> <li>• Both the whole plant and bark extract delayed the onset of PTZ and MES induced convulsions</li> <li>• Recovery time also significantly reduced</li> </ul>	Possibly by the eugenol in cinnamon essential oil suppressing both epileptiform activity and spreading depression in rats; likely via inhibition of synaptic transmission	Cinnamaldehyde	[32-35]
<i>Clinacanthus nutans</i> Lindau; Sabah Snake Grass; Belalai Gajah	Acanthaceae	Southeast Asia and South India	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• The leaves contain the flavonoid vitexin</li> <li>• Vitexin increases the onset time of PTZ induced seizures</li> </ul>	<ul style="list-style-type: none"> <li>• Vitexin may be a ligand for the benzodiazepine receptors</li> <li>• Exerts its effects through the GABA<sub>A</sub>-benzodiazepine receptor complex</li> </ul>	Vitexin	[36, 37]

<i>Curcuma longa</i> L.; Turmeric; Kunyit	Zingiberaceae	India, Southeast Asia and tropical regions	Used as a traditional medicine against seizures	<ul style="list-style-type: none"> <li>• Both curcumin and turmeric oil decreased PTZ induced convulsions in zebrafish larvae</li> <li>• Seizure resistance in mice also increased, requiring a greater amount of PTZ to trigger all behavioural endpoints</li> </ul>	<ul style="list-style-type: none"> <li>• Unknown; possibly related to the neuroprotective effect of turmeric oil through the suppression of oxidative DNA damage and lipid peroxidation.</li> <li>• May also modulate neuronal excitability through modulation of Ca<sup>2+</sup> influx</li> </ul>	Curcumin	[38, 39]
<i>Cymbopogon citratus</i> (DC.) Stapf; Lemongrass; Serai	Poaceae	Tropical and warm sub-tropical regions	Tea made from the leaves is used for its anti-convulsive properties in Brazilian folk medicine	<ul style="list-style-type: none"> <li>• The essential oil delays PTZ induced clonic seizures and prevents MES induced tonic extensions</li> <li>• Possibly due to the synergism of multiple compounds</li> </ul>	<ul style="list-style-type: none"> <li>• Interferes with the seizure threshold and/or blocks the propagation of seizures via interaction with GABAergic neurotransmission</li> <li>• Other pathways such as the glycinergic pathway may also be involved</li> </ul>	Citral	[40]
<i>Elaeis guineensis</i> Jacq.; African Oil Palm; Kelapa Sawit	Arecaceae	West Africa, Southeast Asia, Central America and the West Indies	Powdered or decocted roots are used orally for the treatment of epilepsy	<ul style="list-style-type: none"> <li>• Palm kernel nut oil and octanoic acid alone both significantly delayed the onset of strychnine-induced seizures in rats</li> <li>• Octanoic acid, thiazoles and pyrrolidine in palm kernel nut oil may be responsible</li> </ul>	Unknown	Palmitic Acid	[41, 42]
<i>Etilingera elatior</i> (Jack) R.M.Smith; Torch Ginger; Bunga Kantan	Zingiberaceae	Indonesia, Malaysia, southern Thailand and in tropical and subtropical regions worldwide	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• Contains curcumin, which delays the onset and reduces the severity of pilocarpine-induced seizures</li> <li>• The occurrence of status epilepticus significantly decreased by curcumin pre-treatment; onset also delayed</li> </ul>	<ul style="list-style-type: none"> <li>• Unknown; possibly related to the neuroprotective effect of turmeric oil through the suppression of oxidative DNA damage and lipid peroxidation</li> <li>• May also modulate neuronal excitability through modulation of Ca<sup>2+</sup> influx</li> </ul>	1,1-dodecanediol diacetate	[38, 39, 43]

<i>Hibiscus sabdariffa</i> L.; Roselle; Asam Belanda	Malvaceae	Tropical Regions	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• Reportedly used to treat epilepsy</li> <li>• Methanolic extract provides significant dose-dependent protection from strychnine and PTZ induced seizures in mice</li> <li>• Methanolic extract was more effective in reducing the number of PTZ induced seizures, as compared to strychnine-induced seizures</li> </ul>	<ul style="list-style-type: none"> <li>• May modulate frequency and duration of GABA mediated Cl<sup>-</sup> channel openings to counteract PTZ</li> <li>• May influence synthesis of the inhibitory neurotransmitter glycine at neuronal synaptic vesicles to counteract strychnine</li> </ul>	Hibiscus acid	<a href="#">[44]</a>
<i>Kaempferia galanga</i> L.; Kencur; Cekur	Zingiberaceae	India, southern China, Southeast Asia and Northern Australia	Rhizomes are used as a traditional Indian medicine for the treatment of epilepsy	<ul style="list-style-type: none"> <li>• Contains the monocyclic monoterpene <math>\alpha,\beta</math>-epoxy-carvone (EC), which protects against PTZ and MES induced convulsions</li> <li>• EC delays the development of picrotoxin-induced convulsions and protects against the convulsions</li> </ul>	<ul style="list-style-type: none"> <li>• EC modulates the GABAergic system at a location other than the benzodiazepine site of GABA<sub>A</sub> receptor</li> <li>• May protect through its antioxidant effect</li> <li>• May reduce neuronal excitability by blockading voltage-dependent Na<sup>+</sup> channels</li> </ul>	Ethyl p-methoxycinnamate	<a href="#">[45, 46]</a>
<i>Melastoma malabathricum</i> L.; Malabar melastome; Senduduk	Melastomataceae	Tropical Asia, Polynesia and Australia	Roots are used as a mouthwash	No experimental evidence found for anti-epileptic activity	Unknown	Ellagic Acid	<a href="#">[47]</a>

<i>Morinda citrifolia</i> L.; Great Morinda; Mengkudu	Rubiaceae	Many tropical regions	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• Fruit juice widely used traditionally for many different illnesses</li> <li>• Fruit extract reduces the duration of the various phases of MES induced epileptic seizures in rats</li> <li>• Also, it significantly reduces the time needed for recovery from MES induced seizures</li> </ul>	<ul style="list-style-type: none"> <li>• Increases the level of brain monoamines, possibly by inhibiting monoamine oxidase</li> <li>• Serotonin raises the threshold of PTZ induced seizures</li> <li>• The monoamines noradrenaline and dopamine inhibit the release of the excitatory neurotransmitter glutamate</li> </ul>	Octanoic Acid	<a href="#">[48]</a>
<i>Moringa oleifera</i> Lam.; Drumstick Tree; Merunggai	Moringaceae	Many tropical and subtropical regions	Root extract is inhaled  A spirit is made from equal parts of the root and orange peels	No experimental evidence found for anti-epileptic activity	Unknown	Oleic acid	<a href="#">[22, 49]</a>
<i>Myristica fragrans</i> Houtt; Nutmeg; Pala	Myristicaceae	Perhumid or humid tropical regions	The dried seed kernel (nutmeg) has been traditionally used to treat epilepsy in many countries	<ul style="list-style-type: none"> <li>• Oil has a rapid, but short-lived anti-convulsive action</li> <li>• Dose-dependent anti-convulsive activity against MES induced hind limb tonic extension as well as PTZ and bicuculline-induced tonic seizures</li> <li>• Delayed onset of strychnine induced hind limb tonic extensor jerks</li> <li>• Proconvulsant at high doses</li> </ul>	Unknown; Possibly affects GABA mediated neurotransmission and interacts with neuronal Na <sup>+</sup> channels	Sabinene	<a href="#">[50]</a>
<i>Ocimum basilicum</i> L.; Saint-Joseph's-wort; Selasih	Lamiaceae	Widespread in Asia, Africa as well as Central and Southern America	Used as a folk remedy for epilepsy	<ul style="list-style-type: none"> <li>• Essential oil protects against death and reduces the occurrence of convulsions in response to PTZ, picrotoxin and strychnine</li> <li>• Latency time for induced convulsions also increased by the essential oil</li> </ul>	<ul style="list-style-type: none"> <li>• Similar to that of barbiturates or benzodiazepines</li> <li>• Possesses multiple mechanisms of action and displays broad anti-convulsive activity</li> </ul>	Linalool	<a href="#">[51, 52]</a>



<i>Orthosiphon aristatus</i> (Blume) Miq.; Cat's whiskers; Misai Kucing	Lamiaceae	Southern China, India, Southeast Asia and tropical Queensland	The leaves are brewed into a tea and taken as a traditional epilepsy remedy	No experimental evidence found for anti-epileptic activity	Unknown	Rosmarinic Acid	[53]
<i>Pandanus amaryllifolius</i> Roxb.; Fragrant Pandan; Pandan Wangi	Pandanaceae	Tropical areas of Southeast Asia	Oil from the leaves is effective against epilepsy	No experimental evidence found for anti-epileptic activity	Unknown	2-Acetyl-1-pyrroline	[54]
<i>Phyllanthus niruri</i> L.; Gale of the Wind; Dukung anak	Phyllanthaceae	All tropical and subtropical regions	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• Used in India to cure a wide range of ailments; no scientific data about anti-convulsive activity</li> <li>• Both ethanolic and aqueous extracts abolished MES induced seizures and mortality in rats</li> <li>• Both ethanolic and aqueous extracts increased the latency of PTZ induced seizures and prevented mortality in rats</li> </ul>	<ul style="list-style-type: none"> <li>• Unknown; possibly blockades voltage-gated Na<sup>+</sup> channels or antagonises NMDA effects to prevent MES induced seizures</li> <li>• Possibly also antagonises GABA<sub>A</sub> to prevent PTZ induced convulsions</li> <li>• May have antioxidant properties, which protects against PTZ and MES induced seizures</li> </ul>	Phyllanthin	[55]
<i>Piper Nigrum</i> L.; Black Pepper; Lada Hitam	Piperaceae	Tropical regions	Used in preparing Ayurvedic medicine to treat epilepsy	<ul style="list-style-type: none"> <li>• Extract significantly increases the time taken for the onset of PTZ induced clonic convulsions</li> <li>• The extract also reduces the duration of all MES induced convulsion stages and protects against MES induced mortality</li> </ul>	Unknown; possibly reduces T-type calcium ion currents, enhances GABA <sub>A</sub> receptor-mediated inhibitory neurotransmission and/or inhibits activation of NMDA to prevent PTZ induced seizures	Piperine	[33, 56]

<i>Syzygium aromaticum</i> (L.) Merr. & L.M.Perry; Clove; Cengkih	Myrtaceae	Tropical Asia, Zanzibar, Madagascar, Tanzania and Brazil	The plant and its essential oil are used as a traditional epilepsy treatment in Iran	<ul style="list-style-type: none"> <li>• The essential oil prolongs the onset of strychnine and picrotoxin-induced convulsions and reduces the duration</li> <li>• Mortality is also slightly reduced at high doses for PTZ and more significantly for picrotoxin-induced seizures</li> </ul>	Possibly potentiates the effects of the inhibitory neurotransmitters glycine and GABA by preventing the inhibition of their receptor sites by strychnine and picrotoxin respectively	Eugenol	[57, 58]
<i>Vitex negundo</i> L.; Chinese chastetree; Lemuni	Lamiaceae	Tropical regions	Root powder is taken 2-3 times daily to treat epilepsy	<ul style="list-style-type: none"> <li>• The sub-protective dose of leaf extract potentiates the activity of PHT on MES induced convulsions</li> <li>• High doses (1000 mg/kg) provide 50% protection against clonic convulsions and 24-hour mortality induced by PTZ</li> <li>• The number and duration of PTZ induced clonic seizures was also decreased</li> </ul>	Unknown; possibly increases levels of the inhibitory neurotransmitter, GABA	$\beta$ -caryophyllene	[11, 59]
<i>Zingiber zerumbet</i> (L.) Smith; Bitter Ginger; Lempoyang	Zingiberaceae	India, Sri Lanka, China and throughout Southeast Asia	No traditional use in epilepsy treatment found	<ul style="list-style-type: none"> <li>• Contains trace amounts of <math>\beta</math>-eudesmol which protects against MES induced convulsions and lethality; no effect on PTZ and picrotoxin-induced seizures</li> <li>• Combining <math>\beta</math>-eudesmol and PHT sub-effective doses produces an additive effect against MES induced seizures</li> </ul>	Unknown; possibly affects NMDA or GABA receptor channels	Zerumbone	[60, 61]

PTZ – Pentylenetetrazol, MES – Maximal Electroshock,  
GABA –  $\gamma$ -Aminobutyric Acid,  
NMDA – N-Methyl-D-Aspartate,  
ATP – Adenosine Triphosphate,  
PHT – Phenytoin

compounds which have been experimentally proven to be anti-convulsive. The findings of this section thus refute the notion that the search for novel drugs should focus entirely on traditionally used medicinal plants due to the better odds of discovering a compound with the desired effect. This is because doing so could lead to potentially useful medicinal plants being overlooked simply because they are not known to be traditionally used to treat the ailment or disease of interest.

## 4.2 List of Malaysian medicinal plants with only experimental evidence for anti-convulsive activity

### 4.2.1 *Andrographis paniculata* (Burm.f.) Wall. ex Nees

*Andrographis paniculata* (Burm.f.) Wall. ex Nees plant extract has been scientifically studied for its anti-convulsive potential due to its sedative and rodent brain function altering activity. The study found that it antagonises PTZ and MES induced seizures in rodents, when given daily at a 200 mg/kg oral dose for 10 days [56].

### 4.2.2 *Carica papaya* L.

*Carica papaya* L. was scientifically examined by Gupta, Wambebe [28] to determine the anti-convulsive activity of *Carica papaya* L. leaf extract, as the leaves are smoked for their stimulant effect. They found that *Carica papaya* L. leaf extract injected intraperitoneally at a dose of at least 50 mg/kg, protected rats from PTZ induced seizures. The leaf extract also protects against MES induced convulsions at a dose of 200 mg/kg via the intraperitoneal route.

### 4.2.3 *Clinacanthus nutans* Lindau

*Clinacanthus nutans* Lindau contains vitexin [37], which when given intracerebroventricularly in at least a 50 µM/kg dose, has been experimentally proven to delay the onset of PTZ induced seizures in rats [36].

### 4.2.4 *Etligeria elatior* (Jack) R.M.Smith

*Etligeria elatior* (Jack) R.M.Smith contains curcumin [62], which has been experimentally found to prolong the onset and reduce the severity of seizures induced with pilocarpine when given intraperitoneally at 50

mg/kg to rats [38]. Curcumin also decreases the occurrence of kainic acid induced status epilepticus (prolonged or repeated seizures without a recovery in between) and prolongs its onset in rats [43].

### 4.2.5 *Hibiscus sabdariffa* L.

*Hibiscus sabdariffa* L. has been found by Kulkarni *et al.* [44] to reduce the number and duration of seizures induced via PTZ and strychnine, in mice when given a 200 mg/kg intraperitoneal dose of methanolic dried leaf extract from this plant.

### 4.2.6 *Morinda citrifolia* L

*Morinda citrifolia* L fruit extract has been experimentally found to reduce the duration and recovery time of MES induced seizures in rodents given 200 or 400 mg/kg of the extract orally for 15 days [63].

### 4.2.7 *Phyllanthus niruri* L.

*Phyllanthus niruri* L. was the subject of an experiment was conducted by Manikkoth, Deepa [55] on the rationale that the plant is used in India to cure a wide range of ailments. The experiment found that both ethanolic and aqueous extracts at a concentration of 70 mg/kg given orally for 10 days, abolishes MES induced seizures in rats; as well as increased the latency of PTZ induced seizures.

### 4.2.8 *Zingiber zerumbet* (L.) Smith

*Zingiber zerumbet* (L.) Smith contains β-eudesmol in trace quantities [61]. β-eudesmol protects against MES induced convulsions and lethality in rats, either alone or together with phenytoin at sub-effective doses of both compounds [60].

## 5. MALAYSIAN MEDICINAL PLANTS WITH BOTH TRADITIONAL USE AND EXPERIMENTAL EVIDENCE FOR ANTI-CONVULSIVE ACTIVITY

### 5.1 Review outcomes

After reviewing available literature, 11 plants were found to have both been used in the traditional medicinal system of various countries and were experimentally proven to have anti-convulsive properties. A summary of the plant's review outcome

is given in Table 1 at the end of the review. The combination of these two factors suggests that these plants are prime candidates in the search for novel AEDs.

## **5.2. List of Malaysian medicinal plants with only experimental evidence for anti-convulsive activity**

### **5.2.1 *Centella asiatica* (L.) Urb.**

*Centella asiatica* (L.) Urb. fresh juice mixed with honey, garlic juice in oil and powdered root of wild asparagus with milk, is recommended in Ayurvedic literature to be taken daily for the treatment of epilepsy [29]. This plant has also been experimentally proven to prevent the inhibition of ATPase in the rat brain by PTZ when given a 200 mg/kg dose orally for 7 days. This prevents the neuronal excitability and seizure vulnerability increase associated with the altered electrochemical gradient [30] which otherwise would otherwise result.

### **5.2.2 *Cinnamomum verum* J.S. Presl.**

*Cinnamomum verum* J.S. Presl. has been internally used to treat epilepsy during the Renaissance [32]. Both the whole plant and bark extract have been experimentally found to delay the onset of PTZ, and MES induced convulsions, as well as reduce the recovery period in rats when given 250, 500 and 750 mg/kg of the extracts orally [33, 34].

### **5.2.3 *Curcuma longa* L.**

*Curcuma longa* L. has been used outside the kitchen as a traditional treatment for seizures and contains curcumin as the major compound [64]. Scientific experiments have determined that both curcumin and turmeric oil decreases the convulsions induced by PTZ in zebrafish larvae, and increased resistance to PTZ induced convulsions in mice. Bisabolene sesquiterpenoids in the plant also contribute to the anti-convulsive effect of the plant [39].

### **5.2.4 *Cymbopogon citratus* (DC.) Stapf**

*Cymbopogon citratus* (DC.) Stapf is used by Brazilians to treat epilepsy using a traditional tea made from the leaves of this plant [65]. The essential oil of this plant has been experimentally found to delay PTZ induced

clonic seizures and prevent the tonic extensions induced by MES when given orally to mice at 0.5 and 1.0 mg/kg concentrations [40].

### **5.2.5 *Elaeis guineensis* Jacq.**

*Elaeis guineensis* Jacq. roots are powdered or decocted by the people of Togo, for oral administration to treat epilepsy [66]. Palm oil has also been experimentally found to delay the onset of strychnine induced seizure in rats [41].

### **5.2.6 *Kaempferia galanga* L.**

*Kaempferia galanga* L. rhizomes are traditionally used in the Ayurvedic medicine system to treat epilepsy [46]. The monoterpene  $\alpha,\beta$ -epoxy-carvone (EC) in the essential oil of this plant possesses anti-convulsive properties and has been experimentally proven to provide a dose-dependent protection against PTZ, MES and picrotoxin-induced seizures when injected into rodents [67].

### **5.2.7 *Myristica fragrans* Houtt**

*Myristica fragrans* Houtt dried seed kernel is known as nutmeg and is traditionally used outside kitchens, to treat epilepsy [68]. The essential oil of this plant protects against MES, PTZ and bicuculline-induced seizures, as well as delays the effect of strychnine-induced seizures, when given intraperitoneally to mice at a 50, 100 and 200  $\mu$ L/kg dose. However, a 300  $\mu$ L/kg dose seems to increase susceptibility to chemoconvulsants [50].

### **5.2.8 *Ocimum basilicum* L.**

*Ocimum basilicum* L. is utilised in countries such as Egypt and Thailand for the treatment of epilepsy [51]. Essential oil from *Ocimum basilicum* L. cultivated in Egypt produces a dose-dependent reduction in the occurrence and mortality rate of seizures in mice when injected intraperitoneally at a 0.2, 0.4, 0.8 or 1.2 mg/kg concentration. The time taken for the convulsions to occur was also increased, although the anti-convulsive activity of the essential oil was 2-3 times more effective against PTZ and picrotoxin as compared to strychnine [51].

### 5.2.9 *Piper Nigrum* L

*Piper Nigrum* L is commonly used in the traditional Ayurvedic medicinal system for the treatment of epilepsy [69]. An extract made from the whole plant has been found to delay the onset of PTZ induced seizures when given orally to rats at a 500 mg/kg concentration. The same concentration also reduces the duration and mortality rate of MES induced seizures [33].

### 5.2.10 *Syzygium aromaticum* (L.) Merr. & L.M.Perry

*Syzygium aromaticum* (L.) Merr. & L.M.Perry oil and the plant itself are used by Iranians for the traditional treatment of epilepsy [58]. An experiment has found that the essential oil of this plant can delay the onset and reduce the duration of strychnine and picrotoxin-induced convulsions when given intraperitoneally to mice at 0.025, 0.05 and 0.1 ml/kg concentrations [57].

### 5.2.11 *Vitex negundo* L.

*Vitex negundo* L. powdered roots are used for the traditional treatment of epilepsy by the Indians [11]. The efficacy of this plant in the treatment of epilepsy has been experimentally verified by Tandon and Gupta [59], as they determined that an extract of the leaves protects against the convulsions and mortality induced by PTZ, but only when given to mice orally at a high concentration of 1000 mg/kg. The extract also reduced the number and duration of the PTZ induced seizures, but there was no significant effect on MES induced seizures alone. This plant has also been experimentally proven to potentiate other drugs, including AEDs [59].

## 6. DISCUSSION

This review identified 23 Malaysian medicinal plants, of which four are used traditionally to treat epilepsy, without any scientific evidence. A further eight plants have no known traditional anti-epileptic use but have been experimentally proven to possess anticonvulsant activity, although in the case of *Etlingera elatior* (Jack) R.M.Smith and *Zingiber zerumbet* (L.) Smith, the scientific evidence was indirect as the researchers tested a compound known to be present in the Malaysian medicinal plant rather than an extract of the

plant itself. The remaining 11 plants possess both traditional use and scientific evidence. Despite the success of researchers in directly demonstrating the anticonvulsive properties of 17 plants (Excluding *Etlingera elatior* (Jack) R.M.Smith and *Zingiber zerumbet* (L.) Smith) in this review, these results cannot be easily applied to humans as the animal models used by the authors of those 17 papers are not animal models of epilepsy per se, but seizures. The reason for this lies in the definition of epilepsy itself, as epilepsy is characterised by multiple unprovoked seizures or the increased susceptibility to seizures [1]. Certain chemoconvulsants and electricity induce acute seizures in animals, without resulting in the spontaneous recurrent seizures found in true epileptics [70]. Thus, the medicinal plant extracts and essential oils which were tested in the 17 papers have only been proven to possess anti-convulsive properties in acute seizure models, but this provides no information regarding their effects on chronic epilepsy models.

While most reviewed literature utilised the chemoconvulsant PTZ to induce seizures in their animal model, PTZ produces acute seizures rather than epilepsy. Other chemoconvulsants such as kainic acid and pilocarpine can induce spontaneous recurrent seizures, making them useful for chronic epilepsy models which may better mimic human epilepsy. A procedure known as kindling may also be performed to produce a chronic epilepsy model which is believed to approximate the development of human epilepsy [71]. Another way of producing a valid animal model of epilepsy is by using genetic seizure models in the form of seizure prone animals such as photosensitive baboons (*Papio papio*) and strains of audiogenic seizure-prone mice such as DBA/2J. These inbred, seizure-prone animals develop seizures when exposed to certain stimuli such as light or sound and are believed to more closely approximate human epilepsy [72]. Despite their advantages, adoption of genetic seizure models for the screening of anti-convulsive compounds is presently hampered by the scarcity of test animals and the lack of regular seizure frequencies [72].

While most reviewed literature relied on PTZ and MES to induce seizures and a handful of other reviewed literature used other chemoconvulsants, perhaps a more systematic approach to screening would facilitate the search for novel AEDs. This is because the mechanism by which seizures are induced in animal models are as varied as the methods for inducing them and thus certain medicinal plants may only prevent seizures induced using specific methods and not others. Hence, to avoid false negatives, a standardised series of tests should be conducted. All studies in this review were also found to be limited to the pre-clinical stage and conducted using only animal models of epilepsy. Although the studies proved the anti-convulsive ability of several medicinal plants, Malaysian medicinal plant derived AEDs have yet to be developed and tested in clinical trials. One reason for this could be the lack of toxicity studies to confirm the safety of the medicinal plants; as toxicity studies were very rarely conducted among the studies examined in this review. In the interests of standardisation, future toxicity studies of medicinal plants should be conducted based on the OECD Guidelines for the Testing of Chemicals or other similar guidelines. Standardising the toxicity study protocol will also allow the relative toxicities of different medicinal plants to be compared with each other, in addition to providing a reference dose for future studies. The medicinal plants with proven anti-convulsive properties have also yet to be tested in humans or even non-human primates, raising concerns about their efficacy and safety in humans; although arguably this may not be as relevant to traditionally used medicinal plants. This review also found that some medicinal plants exhibit synergistic effects with AEDs, rendering otherwise sub-protective doses of both the anti-convulsive plant and the AED, effective against convulsions. This raises the intriguing possibility of using medicinal plants to enhance existing AEDs rather than developing novel ones. This would allow a reduction in the therapeutic dose, thus reducing any dose-dependent side effects of AEDs and increasing tolerability in epileptic patients.

Another concern is that several studies utilised injections as their route of administration, which may not be desirable when the medicinal plant is developed into a novel AED, as AEDs are typically taken over an extended period. However, there were also studies which utilise the oral route of administration, which would be a highly desirable route of administration if developed into a novel AED. Besides, the experimental route of administration for a given Malaysian medicinal plant did not always correlate with the traditional route of administration. One possible explanation for this deviation is that not all the literature reviewed provided sufficient information on the traditional route of administration. For example, in the case of *Curcuma longa L.*, no information could be found in the literature regarding the traditional route of administration, beyond the fact that it is traditionally used as a treatment for seizures. Another possible explanation could be a difficult route of administration, which would make it difficult to implement using animal models. Some examples of this are *Centella asiatica (L.) Urb.*, which requires a complex blend of different ingredients and *Melastoma malabathricum L.* which must be used as a mouthwash. Another reason could be that of practicality as the experiments which utilised an oral dose typically required high doses or repeated exposure to have an anti-convulsive effect as compared to experiments which utilised injections.

For the Malaysian medicinal plants with a known traditional route of administration, the most popular route by far is the oral/enteral route. The popularity of the oral route of administration in traditional medicine is understandable due to its ease; although, from a scientific perspective, the bioavailability of the traditional medicine would vary widely from person to person depending on several factors such as gastrointestinal mobility. It also remains to be seen if the active substance in the traditional remedy can survive the extreme pH changes in the gastrointestinal tract without being inactivated before absorption. It is, however, possible that the active substance is

absorbed via the sublingual or buccal route rather than through the enteral route. This would avoid the first pass effect as well as facilitate a more rapid absorption of the active substance into the bloodstream. While this is the route of administration for *Melastoma malabathricum* L., further studies should be conducted to ascertain the actual traditional route of administration for the other Malaysian medicinal plants so that studies can be designed to mimic the traditional route of administration if need be. The only other known traditional route of administration is inhalation, in the case of the *Moringa oleifera* Lam. root extract. From a scientific point of view, nasal administration via inhalation has the same benefits as buccal or sublingual administration, namely rapid absorption and higher bioavailability.

A clear research gap in the form of Malaysian medicinal plants without any experimental evidence on its use as a traditional epilepsy treatment; was also discovered in this review. While the solution to bridging this gap is seemingly obvious, this review has also identified Malaysian medicinal plants possessing anti-convulsive activity but with no known traditional use in epilepsy treatment. Once again, the obvious solution would be to merely screen all possible Malaysian medicinal plants to identify every possible candidate for the development of novel AEDs. However, the sheer number of Malaysian medicinal plants would make screening using the rodent model of epilepsy impractical due to time and budget constraints. Though most of the historical research regarding epilepsy has been performed using rodents, zebrafish (*Danio rerio*) are gaining popularity as a model for epilepsy, as they have a high breeding rate

and can produce large amounts of offspring for experimentation in relatively short time frames; allowing for high-throughput screening of potential anticonvulsants. Other advantages which zebrafish have over rodents are their longer lifespan and robust phenotypes, as they exhibit overt and easily quantifiable behavioural endpoints [73, 74]. The decreased screening time and increased cost-effectiveness [75] would help to more quickly and effectively bridge the research gap in terms of Malaysian medicinal plants which have not yet been experimentally proven to possess anti-convulsive properties.

## 7. CONCLUSIONS

This review has thus integrated information about the traditional use of Malaysian medicinal plants for the treatment of epilepsy together with the results of scientific investigations into the anti-convulsive properties of those Malaysian medicinal plants. By combining traditional knowledge with contemporary insight, this review identified several potential candidates for the development of novel AEDs and research gaps that could be potentially be bridged in future studies.

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