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Review

A pharmacological basis of herbal medicines for epilepsy

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ABSTRACT

Epilepsy is the most common chronic neurological disease, affecting about 1% of the world's population during their lifetime. Most people with epilepsy can attain a seizure-free life upon treatment with antiepileptic drugs (AEDs). Unfortunately, seizures in up to 30% do not respond to treatment. It is estimated that 90% of people with epilepsy live in developing countries, and most of them receive no drug treatment for the disease. This treatment gap has motivated investigations into the effects of plants that have been used by traditional healers all over the world to treat seizures. Extracts of hundreds of plants have been shown to exhibit anticonvulsant activity in phenotypic screens performed in experimental animals. Some of those extracts appear to exhibit anticonvulsant efficacy similar to that of synthetic AEDs. Dozens of plant-derived chemical compounds have similarly been shown to act as anticonvulsants in various in vivo and in vitro assays. To a significant degree, anticonvulsant effects of plant extracts can be attributed to widely distributed flavonoids, (furano)coumarins, phenylpropanoids, and terpenoids. Flavonoids and coumarins have been shown to interact with the benzodiazepine site of the $GABA_A$ receptor and various voltage-gated ion channels, which are targets of synthetic AEDs. Modulation of the activity of ligand-gated and voltage-gated ion channels provides an explanatory basis of the anticonvulsant effects of plant secondary metabolites. Many complex extracts and single plant-derived compounds exhibit anti-inflammatory, neuroprotective, and cognition-enhancing activities that may be beneficial in the treatment of epilepsy. Thus, botanicals provide a base for target-oriented antiepileptic drug discovery and development. In the future, preclinical work should focus on the characterization of the effects of plant extracts and plant-derived compounds on well-defined targets rather than on phenotypic screening using in vivo animal models of acute seizures. At the same time, available data provide ample justification for clinical studies with selected standardized botanical extracts and plant-derived compounds.

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

1. Introduction

Epilepsy is the most common chronic neurological disease worldwide with the burden of lifetime epilepsy affecting approximately 70 million people [1,2]. Almost 90% of people with epilepsy are thought to live in developing countries [1]. Epilepsy was first described in written texts around 2000 BCE [3]. The disease is still often considered a divine punishment or a consequence of witchcraft. Since antiquity, however, a possible familial propensity for the disease has been recognized [3,4]. As early as 600 BCE, Indian and Greek doctors considered epilepsy to be a disorder of the brain [3].

1.1. Definition of epilepsy

According to the most recent definition released by the International League Against Epilepsy (ILAE), epilepsy is a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring more than 24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) seizures occurring as symptoms of a known epilepsy syndrome. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [5].

The ILAE has also recently updated the terminology and concepts used for the classification of seizures and forms of epilepsy [6]. Roughly speaking, seizures are classified as either generalized or focal. Generalized epileptic seizures originate at a single point but rapidly engage bilaterally distributed networks in the central nervous system. The

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affected bilateral networks can include cortical and subcortical structures but do not necessarily involve the entire cortex. Although the points of onset of individual seizures can appear localized, the location and lateralization can change from one seizure to another. Focal epileptic seizures originate within networks of only one hemisphere and may be discretely localized or more widely distributed. Focal seizures may also originate in subcortical structures. Overall, various forms of epilepsy are classified into 1) electroclinical syndromes, 2) epilepsies associated with structural or metabolic conditions, and 3) epilepsies of unknown cause. The electroclinical syndromes can be further classified according to age of onset.

1.2. Drug treatment of epilepsy

Treatment for epilepsy has historically included punishment, incantations, amulets, special diets and living arrangements; mineral, animal and plant products; X-ray irradiation, surgery; and, only since the second decade of the 20th century, synthetic drugs [3,7]. Today, people with epilepsy are first treated with synthetic AEDs. In cases when drugs are not successful, a special diet, alternative and complementary medicine based therapy, vagus nerve stimulation, direct brain stimulation, or epilepsy surgery may be indicated [8].

The first synthetic AED was phenobarbital, which was introduced in 1912 by Hauptmann [9]. The drug was considered superior to bromide drugs (in use since 1857) and preceded the introduction of phenytoin (diphenylhydantoin) in 1939. Phenytoin is still one of the most widely used drugs globally and remains a drug of choice in the emergency treatment of seizures and in status epilepticus [10]. The 1960s saw the introduction of the "second generation" AEDs carbamazepine and valproate (first prepared in 1882, but its anticonvulsant effects were only serendipitously discovered in 1962) followed by another wave of new ("third generation") AEDs in the 1990s [11–13]. Third generation AEDs are not more effective than the older drugs, but they appear to exert fewer pharmacokinetic interactions with other drugs and exhibit fewer adverse effects [14]. Importantly, all AEDs act as anticonvulsants, i.e., they prevent or shorten the occurrence of seizures, but not as antiepileptogenics (i.e., they do not prevent the development of epilepsy in humans such as after traumatic brain injury) [15] even though levetiracetam and ethosuximide have done so in animal models of genetic epilepsy [16]. Overall, 70% to 80% of the treated patients can lead seizure-free lives with appropriate medication; seizures in the remainder are considered pharmacoresistant or "treatment resistant" [17]. Nonetheless, it is estimated that, globally, 80% of patients with epilepsy (mostly residing in developing countries) receive no drug treatment for the disease at all [18,19]. In order to overcome this treatment gap, the World Health Organization (WHO), ILAE, and International Bureau for Epilepsy (IBE) have united in a global campaign against epilepsy in Africa [20]. This partnership advocates the use of phenobarbital as a first-line drug for all patients with epilepsy. It has been estimated that phenobarbital may cost as little as $5 to $10 per patient/year in sub-Saharan Africa but up to six times more in many developing Asian countries [21].

Availability and cost of drugs are, however, two obstacles hindering the treatment of epilepsy. In sub-Saharan Africa, for example, the large majority of the rural population has virtually no access to modern healthcare facilities, and patients often must travel long distances to seek medical attention. Furthermore, epilepsy is often associated with tremendous stigma. Patients, therefore, may not be able to get the psychological, logistical, and financial support needed to obtain care in far-off medical facilities [22]. In this context, traditional healers often provide the first and only source of therapy. Reportedly, most of the traditional healers in Tanzania, for example, clearly recognize the symptoms of the disease, but many believe that epilepsy is caused by witchcraft or heredity (although head injury and malaria were also recognized as potential causative factors) [23]. Even when AEDs and health care facilities are available, more than 90% of patients receive parallel treatment from traditional healers [24]. While it is viewed that most of the people with epilepsy living in developing countries who do not receive treatment could be treated with existing drugs, the problem of drug-resistant epilepsy continues to motivate the search for new AEDs. Discovery and development of synthetic antiepileptic drugs, however, has come to a crossroads, and "new avenues for anti-epileptic drug discovery and development" have been proposed [12,14].

Uncertainty creates opportunities and openings for previously underappreciated modes of discovery and treatment. One of the oldest and most widely used forms of antiepileptic treatment makes use of botanicals. For example, herbal medicine is the most common mode of treatment administered by traditional healers in sub-Saharan Africa [4,23–25]. Herbal medicines are also used for epilepsy in Asia and Central and South America and were the only available form of antiepileptic drug treatment in Europe until the mid-19th century [26]. In fact, herbal medicine is the direct progenitor of modern pharmacotherapy, and some of the most important and successful drugs are derived from natural products [27,28].

There is a large body of literature reporting research on the anticonvulsant effects of plants. To date, this knowledge has not had a major influence on mainstream antiepileptic drug development and treatment. Interestingly, however, three plant-derived compounds cannabidiol and cannabidivarin (from *Cannabis sativa*) and huperzine A (from *Huperzia serrata*) are currently under development as antiepileptic drugs [29]. In this article, the literature on anticonvulsant and antiepileptic effects of botanicals is reviewed and discussed. There is a particular focus on pharmacological effects on "established" molecular targets as well as a discussion on the activity of plant-derived compounds on emerging targets of AEDs. Concise summaries of the literature of anticonvulsant plant extracts and single plant-derived compounds underpinning this review are presented in Supplementary Tables 1 and 2, respectively.

2. Preclinical research on botanicals for epilepsy

2.1. Animal models

The anticonvulsant effects of phenobarbital were discovered serendipitously in 1912, the year of its synthesis, when the German physician Hauptmann gave the drug to patients with epilepsy as a tranquilizer and noticed a pronounced effect on their seizures [10]. The anticonvulsant activity of phenytoin was discovered when Merritt and Putnam used electroshock-induced seizures in cats to systematically screen for compounds with anticonvulsant activity almost 30 years after its synthesis by the German chemist Heinrich Blitz in 1908 [10,13,30]. Ever since, the search and discovery of AEDs has depended on the use of animal models [12]. For example, the Anticonvulsant Screening Project that was instigated by the National Institutes of Neurological Disorders and Stroke (NINDS) has used animal models to test over 25,000 investigational AEDs from academic and pharmaceutical chemists worldwide [30]. The two most widely used models are the maximal electroshock seizures (MES) and subcutaneous pentylenetetrazol (PTZ) models in rodents [12,30]. Positive results in either model suggest that the test compound likely penetrated the blood–brain barrier and exerted its effect in the central nervous system (CNS). Both models have clearly defined endpoints (e.g., time of onset and duration of seizures, death), and require only basic technical expertise [30], and appear to predict their effect in humans reasonably well [31].

Over the last decade the view of the most commonly used animal models in AED drug discovery has changed considerably [12,32]. Contrary to the long prevalent view that both the MES and PTZ models were nonselective with respect to molecular targets and mechanisms of action [32], the MES model is now considered to be particularly sensitive to drugs blocking sodium channels, while the PTZ model is thought to be especially sensitive to GABA mimetic drugs [33]. The MES model has been blamed for producing false positive data. For