

## Plant-based pharmacological alternatives in the seizure treatment: A patent review

Alternativas farmacológicas baseadas em plantas para o tratamento de convulsões: Uma revisão de patentes

Alternativas farmacológicas a base de hierbas para el tratamiento de las convulsiones: Revisión de patente

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### Abstract

Epilepsy, a neurologic condition associated with recurring seizures, affects around 70 million people worldwide and it is responsible for health costs. The current drug therapies used for treating epilepsy have low efficacy and many adverse side effects. In addition, drug resistance can also be found. The association of these factors considerably compromises the patient's pharmacotherapy care. Therefore, natural plant-derived products are promising therapeutic alternatives in the search for new curative options to treat epileptic seizures. Thus, the search was carried out at the patents database in the world, Espacenet, in January 2021 and compiled plant species (extracts, essential oils and isolated plant compounds) with a potential effect on the seizure, published between 2015 and 2020. In recent years, researchers and pharmaceutical companies have developed several methods for obtaining extracts, essential oils and purification of natural compounds, which have proven to be effective for the treatment of epileptic seizures in pre-clinical animal models. These findings hold potential promising for the treatment of epilepsy, especially for the management of drug-resistant, however, these reports are in their early stages and further studies need to be done for these compounds to be marketed.

**Keywords:** Medicinal plants; Seizure; Epilepsy; Anticonvulsant.

### Resumo

A epilepsia, uma condição neurológica associada a crises recorrentes, afeta cerca de 70 milhões de pessoas em todo o mundo e é responsável por custos de saúde. As terapias medicamentosas atuais utilizadas para o tratamento da epilepsia têm baixa eficácia e muitos efeitos colaterais adversos. Além disso, a resistência aos medicamentos também pode ser encontrada. A associação desses fatores compromete consideravelmente os cuidados farmacoterapêuticos do paciente. Portanto, produtos naturais derivados de plantas são alternativas terapêuticas promissoras na busca de novas

opções terapêuticas para o tratamento de crises epilêpticas. Assim, a busca foi realizada na maior base de patentes do mundo, Espacenet, em janeiro de 2021 e compilou espécies vegetais (extratos, óleos essenciais e compostos vegetais isolados) com potencial efeito na convulsão, publicadas entre 2015 e 2020. Nos últimos anos, pesquisadores e empresas farmacêuticas desenvolveram diversos métodos para obtenção de extratos, óleos essenciais e purificação de compostos naturais, que se mostraram eficazes para o tratamento de crises epilêpticas em modelos animais pré-clínicos. Esses achados apresentam potencial promissor para o tratamento da epilepsia, principalmente para o manejo de fármacos resistentes, porém, esses relatos estão em seus estágios iniciais e mais estudos precisam ser feitos para que esses compostos sejam comercializados.

**Palavras-chave:** Plantas medicinais; Convulsão; Epilepsia; Anticonvulsivante.

### Resumen

La epilepsia, una afección neurológica asociada con convulsiones recurrentes, afecta a alrededor de 70 millones de personas en todo el mundo y es responsable de los costos de salud. Las terapias farmacológicas actuales utilizadas para tratar la epilepsia tienen una eficacia baja y muchos efectos secundarios adversos. Además, también se puede encontrar resistencia a los medicamentos. La asociación de estos factores compromete considerablemente la atención farmacoterapéutica del paciente. Por lo tanto, los productos naturales derivados de plantas son alternativas terapéuticas prometedoras en la búsqueda de nuevas opciones terapéutica para tratar las crisis epilêpticas. Así, la búsqueda se realizó en la base de datos de patentes más grande del mundo, Espacenet, en enero de 2021 y recopiló especies vegetales (extractos, aceites esenciales y compuestos vegetales aislados) con potencial efecto en las convulsiones, publicadas entre 2015 y 2020. En los últimos años, investigadores y compañías farmacéuticas han desarrollado varios métodos para la obtención de extractos, aceites esenciales y purificación de compuestos naturales, que han demostrado ser efectivos para el tratamiento de ataques epilêpticos en modelos animales preclínicos. Estos hallazgos tienen un potencial prometedor para el tratamiento de la epilepsia, especialmente para el manejo de la resistencia a los medicamentos; sin embargo, estos informes se encuentran en sus primeras etapas y es necesario realizar más estudios para comercializar estos compuestos.

**Palabras clave:** Plantas medicinales; Convulsiones; Epilepsia; Anticonvulsivo.

## 1. Introduction

Epilepsy is a chronic neurological condition among the most prevalent central nervous system disorders, that affects approximately 70 million people worldwide (Beghi, 2020; Thijs et al., 2019; Thurman et al., 2011). It is characterized by the recurrence of unprovoked seizures caused by abnormal and excessive activity of brain neurons in an unpredictable manner (Fisher et al., 2005, 2017; Stafstrom & Carmant, 2015). Epilepsy has no cure, but it can be treated using surgical procedures or medications (Byun et al., 2020; Catchpool et al., 2019). The first-line treatment involves the use of antiepileptic medications, such as carbamazepine and gabapentin, which must be customized and based on medical and psychiatric considerations (Johnson, 2019). Inappropriate treatment of epilepsy leads to several problems for patients, including low quality of life, higher risk of sudden death, and greater chances of developing physical, psychological, and social comorbidity conditions (Siarava et al., 2019; Tomson et al., 2008). When treated correctly, patients suffering from seizures manage to lead a normal life (Guerreiro, 2016).

Over the past decades, most of the development of anti-epileptic drugs has been based on the use of pre-clinical epilepsy models induced by pentylenetetrazole (PTZ) (Shimada & Yamagata, 2018), maximum electroshock (MES) (Socala et al., 2019) and on the use of pilocarpine (Kim & Cho, 2018). Although the number of antiepileptic medications available on the market has grown exponentially, the percentage of people with intractable seizures remains high (Z. Chen et al., 2018; Johnson, 2019) and issues associated with conventional treatments, specially drug resistance, are still frequent (more than 30% of individuals) (Chen et al., 2018; Mesraoua et al., 2019; Ryvlin, 2005). Although, several criteria have been adopted to classify drug resistance, a precise criterion has not been agreed on. A hierarchical level framework to characterize therapeutic interventions to trials has been suggested by Kwan *et al* (2010), where failure to at least two antiepileptic drug interventions, used alone or in combination, validates drug resistance (Kwan et al., 2010).

Lately, considerable attention has been given to the use of vegetal species as a new therapeutic approach for the treatment and control of recurrent seizures (Bulaj et al., 2016; Pina et al., 2020), including the use of plant extracts (Quintans

Júnior et al., 2008), essential oils (da Fonsêca et al., 2019) and isolated compounds, such as cannabidiol (Samanta, 2019). Since ancient times, and yet aiming at establishing a balance between the physiological systems and providing healing, traditional Chinese medicine has used natural products to improve human health and well-being (Ma et al., 2016). Indeed, the application of these vegetal species has been remarkably investigated and largely used to combat drug-resistant bacteria and viruses, infectious diseases, cancer, and as central nervous system disorders, including alzheimer, parkinson e recurrent seizures (Huyan et al., 2016; Makaremi et al., 2021; Marshall, 2020; Veeresham, 2012; Vilasboas-Campos et al., 2020; Vyas et al., 2019; Y. Wang et al., 2017). In contrast to conventional therapies, these products have lesser side effects and higher tolerability, making these products a promising therapeutic alternative in the search for new antiepileptic drug options (Deivasigamani et al., 2021; Popovych et al., 2020; Verma et al., 2021).

As these new natural therapeutic alternatives become more readily available (Pina et al., 2020), so does the need for further scientific discoveries and drug development as existing conventional drugs have only symptomatic effects. Pre-clinical animal model studies are essential for establishing efficacy and adjusting the safety profile of these novel substances prior their translation into clinical settings (Löscher, 2011, 2017). Thus, the objective of this review is to conduct a survey on the recent patent fillings of new therapeutic plant-based alternatives used for treating epilepsy and/or seizures, published between 2015 and 2020.

## 2. Methodology

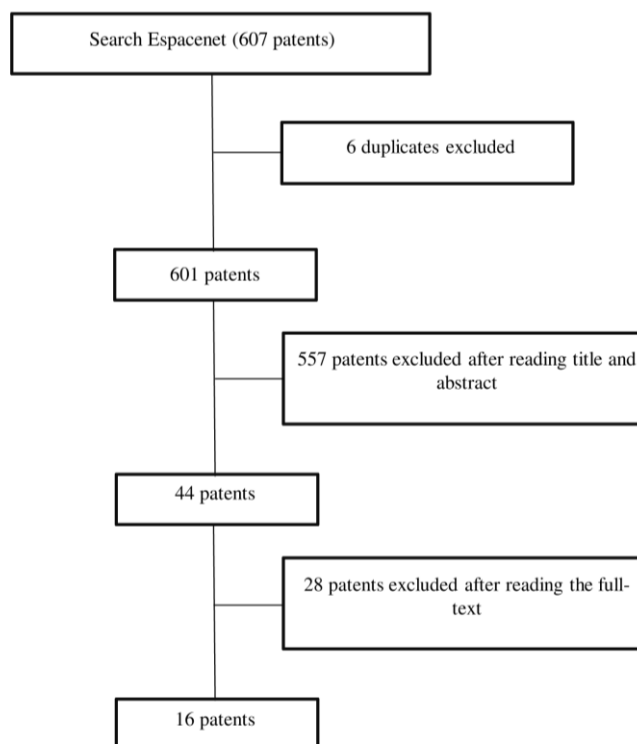
The patent search for this review was carried out using one of the largest patents data base in the world (ESPACENET) in January 2021. The criteria search included patents published between 2015 and 2020 related to the use of anticonvulsant natural/plant-based products with clinically relevant activity in humans; and the International Patent Classification (IPC) A61P25/08 (antiepileptics, anticonvulsants) and A61K36 (medicinal preparations containing algae, lichens, fungi or plants or their derivatives) categories.

The following inclusion criteria were applied for the selection of patents: vegetal species (extracts, essential oil and compounds isolated from plants) with *in vivo* anticonvulsant effect studies applied to patients suffering from epilepsy and/or seizures. Patents in which mixtures of plants or extracts, combinations with other drugs and duplicates were excluded.

## 3. Results

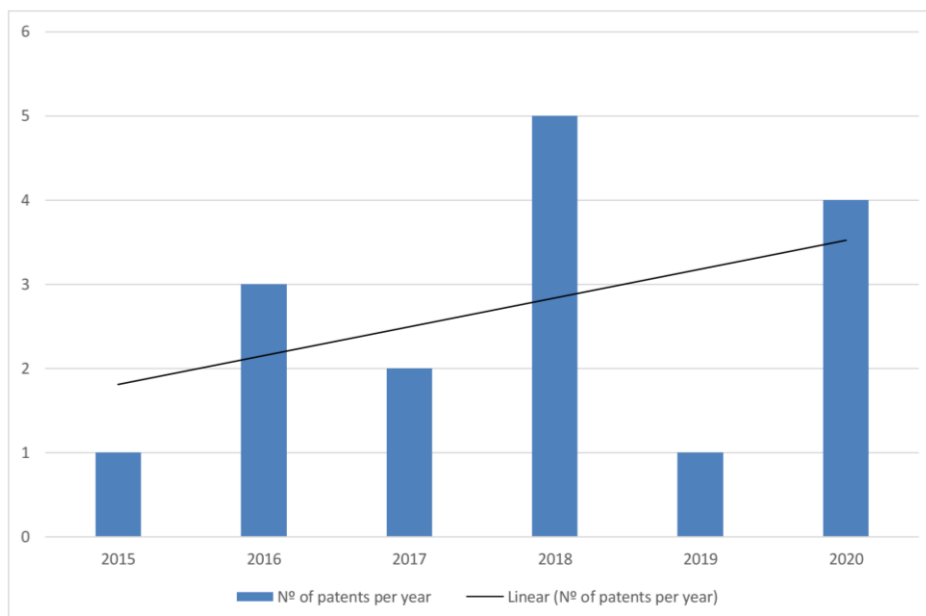
Initially, 607 patents were found comprising the use of natural products and anticonvulsants. However, not all patents provided scientific evidence of an anticonvulsant effect. Thus, 16 patents were selected by read in full (Figure 1). The selection showed that 2018 was responsible for the largest number of patent inventions filings, accounting for 31.25% (n = 5). Despite the year 2019 there was a decrease in the number of patent filings, 2020 appears with an increase, being the second year with the highest numbers of filings growth (n = 4; 25%), presenting a growth tendency as can be seen in Figure 2.

**Figure 1.** Flowchart of included patents.



Source: Prepared by the authors.

**Figure 2.** Distribution of number of patents per year.

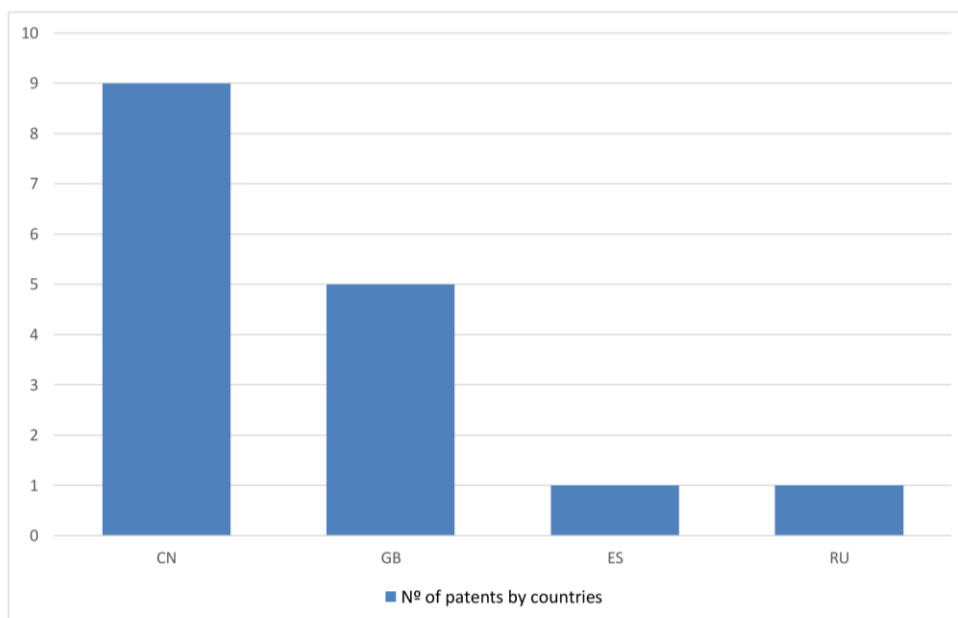


Source: Prepared by the authors.

The middle-income country of China accounted for the majority of patent inventions related to innovative compounds based on vegetal species with anticonvulsant activity, accounting for 56.25% ( $n = 9$ ) of the total published applications. The United Kingdom filed 31.25% ( $n = 5$ ) of total patents found, followed by Spain and Russia with 6.25% ( $n = 1$  each) (Figure 3). These findings could be related to the fact that approximately 80% of patients suffering from epilepsy are located in developing countries, including China (66%) and India (95%) (Ding et al., 2019), and hence resulting in an increased interest

for finding effective new compounds. Determinants of pharmaceutical R&D research investments, which are based on proof of the effectiveness of traditional medicine, socioeconomic costs resulting from hospitalizations and consequences on the patient's quality of life, also would account to these results (Chatterjee et al., 2020; Ding et al., 2019; Yu et al., 2019).

**Figure 3.** Distribution of patent deposits by countries. CN: China; GB: United Kingdom; ES: Spain; RU: Russian Federation.



Source: Prepared by the authors.

The university and business sectors were responsible for the majority of published applications with 37.5% (n = 6) and 31.25% (n = 5), respectively. These sectors mainly sought to investigate the effectiveness of using traditional medicine in humans and to propose new alternative products to standard drug-resistant epilepsy treatments (Auditeau et al., 2019; Mathon et al., 2020). A small number of patents were filed by individuals (25%, n = 4) and a minor share filed by university and companies' partnership (6.25%, n = 1).

All published patents in this study reasoned their invention findings and respective anticonvulsant effects based on pre-clinical studies. The most used models to screen for antiepileptic drugs were the convulsion induced by administration of PTZ (52.63%, n = 10), MES (15.79%, n = 3) and an association of pilocarpine and lithium chloride (15.79%, n = 3), which mimic generalized and focal seizures. The remaining models represent 15.79% (n = 1, each) and include febrile seizure, administration of kainate acid and strychnine.

This review reports 10 extracts, 1 essential oil and 8 isolated compounds from plants tested in seizure models (Table 1). Luo *et al.* (2015) obtained an extract from the dry root powder of the *Salvia miltiorrhiza* plant using ultrasound and acetone as the extraction solvent. Additionally, the authors have also identified the tanshinone IIA (6,6-Trimethyl-6,7,8,9-tetrahydrofenantro [1,2-b] furan-10, 11-dione) using high-pressure liquid chromatography (HPLC). Tanshinone IIA is a multi-target drug known for its wide-ranging remedial effects, including protective properties in neurodegenerative diseases (Xu & Liu, 2013). Both the extract and the isolated compound were tested at doses of 0.1, 1.0 and 10 mg/kg, intravenous (i.v.), and demonstrated effectiveness against convulsions induced by PTZ infusion and corneal stimulation in mice. Due to their neuroprotective effects, these compounds can be used as an alternative antiepileptic drug treatment (Luo et al., 2015).

**Table 1.** Plant-based pharmacological alternatives anticonvulsant patented between 2015-2020.

Publication Year	Inventor/ Company (Country)	IPC	Plant/ Compound (s)	Obtainment	Experimental model/animal	Evaluation parameters	Dose (via)	Outcome	Reference
2015	Luo Guon et al./ University Leuven Kath (BE) University Tsinghua (CN)	A61K36/537 A61P25/08	<i>Salvia miltiorrhiza</i> and Tanshinone IIA	Acetone extract and isolation	PTZ (i.v. infusion 7.5 mg/mL) and 6-Hz corneal stimulation in mice	Number of seizure	10, 1 and 0.1 mg/kg, i.v.	Reduction of seizure	WO2015004093
2016	Hu Kai et al. (CN)	A61K36/46 A61P25/08	Aucubin	Isolated from <i>Eucommia ulmoides</i> ethanol extract	Pilocarpine (20 mg/kg, i.p.) and lithium chloride (125 mg/kg, i.p.) in rats	Racine scale, EEG and immunohistochemistry	5 and 10 mg/kg, p.o. for 14 days	Reduction of neuronal death and seizure intensity, reduction MLKL and RIP-1, and increased beclin LC3B-1 and II/I LC3B	CN105596357
2016	Chen Tianrui et al./ Yunnan Ruifen Biological Tech Co Ltd (CN)	A61K36/60 A61P25/08	<i>Industrial hemp</i>	Ethanol extract of <i>Cannabis</i>	PTZ (100 mg/kg, s.c.) in mice	Latency seizure and mortality	20 mg/kg, i.p.	Increased latency seizure and mortality latency	CN106074708
2016	Shan Weiguan et al./ Zhejiang Conba Pharmaceutical Co Ltd and University Zhejiang Technology (CN)	A61K36/16 A61P25/08	<i>Ginkgo biloba</i>	Ethanol extract	Pilocarpine (20 mg/kg, lumbar) and lithium chloride (3 mmol/kg, lumbar) in rats	Racine scale, EEG and immunohistochemistry	40 mg/kg, p.o. for 4 or 8 weeks	Reduction of seizure and intensity, improved EEG, increased BDNF, VEGF and GDNF protein	CN105287657
2017	Guo Liangjun et al. (CN)	A61K36/80 A61P25/08	<i>Monochasma sauatieri</i> Franch	Ethanol extract	PTZ (100 mg/kg, s.c.) and MES (100 V for 0.3s) in mice	Seizure incidence and mortality	1.25, 2.25, 3.25 mg/kg, p.o., for 7 days	Seizure and mortality reduction	CN106692436
2017	Ma Yuying et a./ University Chengdu Traditional Chinese Medicine (CN)	A61K36/8988 A61P25/08	<i>Gastrodia elata</i>	Submicron powder	PTZ (62.5 mg/kg, i.p.) in mice	Number of seizures and mortality	0.3, 0.6, 1.2 g/kg, p.o., for 5 days	Seizure and mortality reduction	CN106334100
2018	De Witte Peter A M et al. (ES)	A61K36/9066 A61P25/08	Bisabolene sesquiterpenoid	Isolated from turmeric oil	PTZ (20 mM) in zebrafish larvae	Larval movement	2.5, 5 and 10 pg/mL (not reported)	Seizure reduction	ES2661844
2018	Cao Gang et al./ University Zhejiang Chinese Medical (CN)	A61K36/87 A61P25/08	<i>Trifolium repens</i>	Ethanol extract decoction of pieces of <i>T. repens</i>	Febrile convulsion (45 °C of water baths for 5 minutes continuous) in rats	Seizure latency	20, 40 and 80 mg/kg, p.o., for 3 days	Reduced seizure latency	CN108186812
2018	Cai Decheng et al. (CN)	A61K36/28 A61P25/08	<i>Tagetespatula</i> L.	Ethanol extract	PTZ (9 mg/mL, i.p.) in mice	Racine scale	400 and 800 mg/kg, p.o.	Reduced seizure and increased mortality latency	CN107865896
2018	Stott Colin et al./	A61K36/185	Cannabidiolic acid	Purified extract	PTZ (90 mg/kg, i.p.) in	Seizure latency,	100 mg/kg (not	Increased seizure latency,	US2018228751

	Gw Pharma Ltd (GB)	A61P25/08		of <i>Cannabis</i>	rats	percentage, seizure severity and mortality	reported)	reduced seizure severity and mortality	(A1)
2018	Whalley Benjamin et al./ Gw Pharma Ltd (GB)	A61K36/185 A61P25/08	Cannabidivarin	Not reported	PTZ (80 mg/kg, i.p.) in rats	Seizure severity and mortality	100 and 200 mg/kg, i.p.	Reduced seizure severity and mortality	AU2018217303
2019	Yang Bingyou et al./ University Heilongjiang Chinese Medicine (CN)	A61K36/233 A61P25/08	<i>Bupleurum chinense</i>	Oil extracted by steam distillation and ethanol extract	PTZ (60 mg/kg, i.p.) in mice and kainate acid (0.5 µg/µL, i.c.v.) in rats	Racine scale, seizure duration and mortality	200 and 400 mg/kg, i.g. for 7 days	Reduction in seizure duration, intensity, and mortality	CN110522777
2020	Stott Colin et al./ Gw Res Ltd (GB)	A61K36/185 A61P25/08	7-hydroxy-cannabidol and/or 7-hydroxy-cannabidivarin	Pure, isolated or synthetic form	PTZ (70 or 80 mg/kg, i.p.) in rats	Latency seizure, severity and mortality	200 and 100 mg/kg, i.p.	Increased seizure latency, reduced seizure severity and mortality	EP3639814
2020	Geoffrey Guy et al./ Gw Res Ltd (GB)	A61K36/185 A61P25/08	Cannabidiol-C4	Highly purified plant extract ( <i>Cannabis</i> ) or synthetic	MES (50 mA, 0.4s, 50 Hz) in mice	Number of seizures	100 e 200 mg/kg, i.p.	Decrease in the number of seizures	GB2579179
2020	Belousov Mikhail et al./ Fed Gosudarstvennoe Byudzhethnoe Nauchnoe Uchrezhdenie Tomskij Natsionalnyj Issledovatelskij Meditsin (Ru)	A61K36/45 A61P25/08	<i>Empetrum nigrum</i> L.	Acetone fraction of the dry chloroform extract	Strychnine (1.5 mg/kg, s.c.) in mice	Life expectancy and percentage of survival	150 mg/kg, p.o., for 5 days	Increased life expectancy and survival	RU2714687
2020	Sun Hong et al./ The Second Affiliated Hospital Of College Of Medicine Of Xian Jiaotong University (CN)	A61K36/83 A61P25/08	<i>Stellera chamaejasme</i>	Extraction method of total alkaloids	Pilocarpine (30 mg/kg, i.p.) and lithium chloride (180 mg/kg, i.p.) in rats	Racine scale and immunofluorescence (CD40)	50, 100 and 200 mg/kg (not reported) for 7 days	Reduced of neuronal damage (reduced CD40)	CN110960599

BDNF: Brain-derived neurotrophic factor; EEG: Electroencephalography; GDNF: Glial cell line-Derived Neurotrophic Factor; MES: Maximal electroshock; MLKL: Mixed Lineage Kinase domain-Like; PTZ: Pentylenetetrazole; RIP-1: Receptor Interacting Protein; VEGF: Vascular Endothelial Growth Factor. Source: Prepared by the authors.

In 2016, 3 patents using compounds initially obtained from ethanolic extracts were filed in China (Chen & Hu, 2016; Hu et al., 2016; Shan et al., 2016). Ethanol is a commonly used extraction solvent due to its safety and ability to extract a variety of active compounds from plants (Sabedra et al., 2017). Hu Kai and collaborators report the purification of aucubin, an iridoid glycoside obtained from the ethanolic extract of *Eucommia ulmoides* via ultrasound. Aucubin treatment (5 and 10 mg/kg orally) administered for 14 days reduced neuronal death by reduced mixed lineage kinase domain-like (MLKL) domains and receptor-interacting protein kinase 1 (RIP-1) proteins. When induced by pilocarpine (20 mg/kg, intraperitoneal (i.p.)) and lithium chloride (125 mg/kg, i.p.), animals treated with aucubin increased the expression of beclin LC3B-1 and the levels of the structural proteins of autophagosomal membrane LC3B-II/I, suggesting a potential neuroprotective effect (Hu et al., 2016). Similarly, Yunnan Ruifen Biological Tech Co Ltd also discloses in their invention several methods for obtaining ethanol extract from Industrial hemp. Industrial hemp is a plant of the species *Cannabis sativa* L. used in the industry due to its high nutritional value and potential functional characteristics (Farinon et al., 2020). Treatment administered at 20 mg/kg, i.p., of the ethanolic extract have demonstrated an increase in seizure latency and mortality latency in mice induced by PTZ (100 mg/kg, subcutaneous (s.c.)) (Chen & Hu, 2016).

Zhejiang Conba Pharmaceutical Co Ltd and the Zhejiang University of Technology report the obtention of *Ginkgo biloba* ethanolic extract with 11% lactones, 40% flavonoids and 48% procyanidins. *Ginkgo biloba* is a medicinal plant used in the treatment of Alzheimer's disease, cognitive impairment, diabetes, hypertension and dyslipidemia (Eisvand et al., 2020; G. Yang et al., 2016). The inventors were able to show that a more pronounced antiepileptic effect is achieved when the extract formulation has a higher content of procyanidin than the total flavonoids. Studies using this extract formulation for 4 or 8 weeks at 40 mg/kg, orally, also reduced the seizure incidence and increased the expression of proteins responsible for promoting differentiation of neuronal cells, including brain-derived neurotrophic factor (BDNF), vascular endothelial factor (VEGF) and glial cell line-derived neurotrophic factor (GDNF), after administration of lithium chloride (3 mmol/kg, lumbar) and pilocarpine (20 mg/kg, lumbar) (Shan et al., 2016).

Following, in 2017 two patents employing ethanolic extracts and ultrafine powder have been disclosed (Guo et al., 2017; Ma et al., 2017). Guo Liangium and collaborators disclose the invention of a drug based on different methods of acquiring *Monochasma savatieri* Franch ethanol extract. Studies have shown that treatment with this ethanolic extract at doses of 1.25 to 3.25 g/kg, p.o. for 7 days reduced seizures and mortality in mice subjected to the administration of PTZ (100 mg/kg, s.c.) and MES (100 V for 0.3s) (Guo et al., 2017). Similarly, patent developed by Chengdu University of Traditional Chinese Medicine discloses a preparation of ultrafine powder from *Gastrodia elata*. *Gastrodia elata* is a traditional Chinese medicine known for its broad pharmacotherapeutic properties to treat central nervous system disorders, including epilepsy (Liu et al., 2018). Inventors claims include reduced seizure and mortality of animals when subjected to PTZ at 62.5 mg/kg, i.p. upon oral administration of the ultrafine powder at 0.3, 0.6, 1.2 g/kg doses, after a period of 5 days administration, (Ma et al., 2017).

Five patent applications were found in 2018 (Cai & Ran, 2018; Cao & Zhang, 2018; De Witte Petter et al., 2018; Stott et al., 2018; Whalley et al., 2018). Among the patents, the invention filed by De Witte Petter *et al.* (2018) reports the evaluation of the bisabolene bioactive compound isolated from turmeric oil through hydrodistillation in a Clevenger type apparatus. The authors state that the pharmacotherapeutic effect of bisabolene at doses of 2.5, 5 and 10 µg/mL appears to reduce induced convulsive movements after PTZ administration (20 mM) (De et al., 2018). Another patent invention disclosed, includes the obtention of the extract of *Trifolium repens* by decoction extraction method (Cao & Zhang, 2018). *Trifolium repens* is a plant with antioxidant, anti-inflammatory, analgesic and antimicrobial effects also used in traditional Chinese medicine (Ahmad & Zeb, 2020). The invention filed by the Zhejiang Chinese Medical University suggests administration of the extract for 3 days at doses of 20, 40 and 80 mg/kg, orally. The *Trifolium repens* extract formulation has proven to be effective against febrile seizures in rats (Cao & Zhang, 2018). Similarly, another patent application employing plant extracts in



antiepileptic drugs includes the use of total flavonoids from the ethanolic extract of *Tagetespatula* L.. The use of these phytochemicals at 400 and 800 mg/kg, p.o. accounted for reducing the seizure and increasing the latency of death in mice also induced by PTZ administration (9 mg/mL, i.p.) (Cai & Ran, 2018).

Over the last few years increased interest in cannabis-based products has been observed within the clinical pharmacology sector for its properties in reducing the frequency of convulsive seizures (Perucca, 2017; Russo & Marcu, 2017). Two patents filed in 2018 by Gw Pharma Ltd refer to methods of obtaining purified cannabinoid compounds from *Cannabis*. Cannabidiolic acid (100 mg/kg) demonstrated anticonvulsant effects throughout increased seizure latency, as well as reducing severity and mortality in rats subjected to administration of PTZ (90 mg/kg, i.p.) (Stott et al., 2018). Similarly, the same company also report that the use of Cannabidivarin (100 and 200 mg/kg, i.p.), an analogue of cannabidiol, which also reduced seizure severity and mortality in the PTZ models (80 mg/kg, i.p.) (Whalley et al., 2018).

In 2019, only one patent belonging to the Heilongjiang University of Chinese Medicine was found (B. Yang et al., 2019). The treatment with the *Bupleurum chinense* ethanol extract and its essential oil (obtained by steam distillation) at 200 and 400 mg/kg, i.p. reduced seizure and duration in experimental animal models after the administration of PTZ (60 mg/kg, ip) and kainate acid (0.5 µg/µL, i.c.v.). In addition, the extract and essential oil showed neuroprotective effects in hippocampal cells, suggesting that these compounds may be a promising alternative to the treatment of seizures (B. Yang et al., 2019).

Finally, in 2020, 4 patent inventions were found (Belousov et al., 2020; Geoffrey et al., 2020; Stott et al., 2020; Sun et al., 2020). The first patent invention, deposited by the company Gw Res Ltd, claims the isolation for the first time of the compounds 7-hydroxy-cannabidol and 7-hydroxy-cannabidivarin (100 and 200 mg/kg, i.p.), which have shown to act on the nervous system increasing seizure latency time, and reducing the severity and mortality of animals submitted to PTZ (70 or 80 mg/kg, i.p.) (Stott et al., 2020). This same company, also obtained another cannabinoid compound derived from *Cannabis*, Cannabidiol-C4. Treatment of mice with Cannabidiol-C4 at 100 and 200 mg/kg, i.p. was responsible for reducing the number of seizures induced to electrical stimulation (Geoffrey et al., 2020).

*Empetrum nigrum* L. is a plant that has been widely employed in the treatment of epilepsy, paralysis and as a sedative in folk medicine (Jurikova et al., 2016). The third patent registered by Belousov Mikhail and colleagues, refers to a method to obtain an acetonic fraction from the dry chloroform extract of the plant *Empetrum nigrum* L. The preventive treatment with 150 mg/kg, orally, for 5 days, provided increased life expectancy and survival in mice induced with strychnine (1.5 mg/kg, s.c.) (Belousov et al., 2020). The last patent was filed by The Second Affiliated Hospital Of Xi'an Jiaotong University College Of Medicine and describes ways of obtaining the flavonoid fraction of the *Stellera chamaejasme* plant. The authors attest that the flavonoids present in *S. chamaejasme* are capable of reducing neuronal damage caused by the administration of Pilocarpine (30 mg/kg, i.p.) and lithium chloride (180 mg/kg, i.p.) in rats (Sun et al., 2020). Thus, the natural products obtained from plants are effective alternatives in the treatment of partial and generalized epilepsy.

#### 4. Discussion

In this review, we assessed the published patent inventions referring to natural compounds in the form of extracts, essential oils and isolated compounds with proven anticonvulsant properties, filed between the years of 2015 and 2020. 10 patents (52.63%) reported methods of obtaining plant extracts, 1 patent (5.26%) disclosed an essential oil and 8 patents (42.11%) described purified plant compounds. These findings reinforce the idea that the use of natural products can be a promising alternative for the treatment of pathologies, including epilepsy (Elliott et al., 2020; Quintans-Júnior et al., 2008).

In view of the pharmacological potential of medicinal plants and the reduction of adverse effects, investment in the scientific production of these compounds has increased. Natural compounds derived from plants have been extensively studied

and are commercially available. Sativex<sup>®</sup>, for example, was the first medicine produced based on *Cannabis*. Despite being initially indicated for multiple sclerosis, studies have shown the effectiveness of its active principle on epilepsy (Filloux, 2015). Recently, another drug containing cannabidiol, produced in Brazil, with potential indication for the treatment of refractory epilepsy has been approved. Unlike Sativex<sup>®</sup>, the formulation containing only cannabidiol has fewer side effects due to the absence of psychoactive substances, such as  $\Delta^9$ -THC (Gaston & Friedman, 2017).

Moreover, all purified cannabinoid compounds have been patented by the pharmaceutical industry Gw Pharma Ltd, which is a pioneer in the search for new pharmaceutical compositions derived from *Cannabis*. Phytocannabinoids cannabidiolic acid, cannabidivarin, 7-hydroxy-cannabidiol, 7-hydroxy-cannabidivarin and cannabidiol-C4 act on cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) promotes reduction of neuronal excitability in the hippocampus. The biochemical interaction of these receptors results in the regulation and release of neurotransmitters, including glutamate present on the surface of brain cells (Gaston & Friedman, 2017; O'Connell et al., 2017; Rosenberg et al., 2017; Yao et al., 2019).

Although most of the patents in this review do not report the biochemical interactions of the compounds studied, a few mechanisms of action can be suggested. *Salvia miltiorrhiza*, for example, can exert its anticonvulsant effect through agonistic action on gamma-aminobutyric acid (GABA<sub>A</sub>) receptors (Lin et al., 2021). In addition, this specie can exert neuroprotective effects through the modulation of inflammatory mediators and oxidative stress (Su et al., 2015). Aucubin, studied in the patent by Hu Kai *et al.* (2016), is responsible for lessening neuronal damage by reducing Mixed Lineage Kinase domain-Like (MLKL) domains, RIP-1 receptors, Beclin-1 and LC3BII/LC3BI proteins and inflammation markers including tumor necrosis factor alfa (TNF- $\alpha$ ) and interleukin 1 beta (IL-1 $\beta$ ) (S. Chen et al., 2019; Pina et al., 2020; J. Wang et al., 2017). Similarly, *Ginkgo biloba* extract is also recognized for its neuroprotective ability to reduce neuronal damage and oxidative stress (Yan et al., 2020; D. Yu et al., 2020). Likewise, the anticonvulsant effect of *Gastrodia elata* extract studied in patent Ma et al. (2017) is known to alter the amount of GABA neurotransmitters receptors and to reduce neuronal damage induced in seizure models (Matias et al., 2016). The anticonvulsant effects of *Monochasma sauatieri* Franch extract claimed in patent Guo et al. (2017) can be related to its antioxidant ability to increase the enzymatic activities of superoxide dismutase (SOD) and glutathione (GSH), as well as to decrease the content of malondialdehyde (MDA) (Shi et al., 2013).

## 5. Conclusion

Thus, all of these compounds are promising alternatives due to their neuroprotective potential and mechanisms of action on GABA<sub>A</sub>, CB1 and CB2 receptors. In view of this, the development of new plant-based pharmaceutical compositions is a promising alternative for the treatment of epilepsy, especially for patients suffering from drug-resistant epilepsy. However, there are several limitations due to the initial state of these surveys. On the other hand, these findings are crucial for carrying out safety and efficacy studies using the tested substances.

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