PharmacologyOnLine

Archives • 2021 • vol.3 • 80-98

PLANTS WITH ANTICONVULSANT POTENTIAL

López-Rosas, C. A.[1]; Olguín-Guerrero, M. C.[2]; *Ramos-Morales, F. R.[3]; Saavedra-Velez, M. V.[1]

[1]Universidad Veracruzana, Instituto de Neuroetología, Luis Castelazo Ayala s/n, Col. Industrial Ánimas, 91190, Xalapa, Veracruz, México.

[2]Universidad Veracruzana, Instituto de Investigaciones Cerebrales, Luis Castelazo Ayala s/n, Col. Industrial Ánimas, 91190, Xalapa, Veracruz, México.

[3]Universidad Veracruzana, Instituto de Química Aplicada, Luis Castelazo Ayala s/n, Col. Industrial Ánimas, 91190, Xalapa, Veracruz, México.

* framos@uv.mx

Abstract

Epilepsy is a brain disease that affects the central nervous system, which has become a serious public health problem. This disorder is characterized by involuntary movements, called seizures, but it must be taken to find that not all seizures are related to epilepsy. Antiepileptic drugs are used for its treatment, which, despite having proven clinical effects, only 2 thirds of the population with epilepsy manage to control the seizures, but with the advances that have recently been made, new treatments are being developed that improve the quality of life of patients. Medicinal plants have been gaining relevance in recent years, mainly because they continue to be a primary treatment for mild to moderate discomfort, in addition to its easy application and being a treatment used ancestrally. Medicinal plants remain an essential source of chemical structures and active principles; therefore, they have an important place in the search and development of new treatments for epilepsy (as well as other disorders). Some of the families of secondary metabolites with anticonvulsant activity are flavonoids, alkaloids, some saponins and essential oils, however, there are few studies that mention which is the metabolite responsible for the anticonvulsant activity, this becomes important, since anticonvulsant drugs have a hormesis effect, which could occur in secondary metabolites with anticonvulsant activity. The investigation on medicinal plants become important, this in order to find safer, effective and affordable treatments, this mainly because according to World Health Organization About 80% of the population with epilepsy is in low- to middle-income countries.

Keywords: *medicinal plants, anticonvulsants, epilepsy, secondary metabolites, hormesis.*

Introduction

Epilepsy is a chronic brain disease that affects 50 million people in the world, being one of the most common neurological disorders. Epilepsy is characterized by excessive or hypersynchronous brain activity, called seizures, which are treated or controlled with antiepileptic drugs, in turn, these are divided into first generation drugs (carbamazepine, phenobarbital and phenytoin), second generation (lamotrigine and gabapentin), third generation (retigabine and perampanel) and orphan drugs (rufinamide and stiripentol) [1-3] Pharmacological treatment must be individualized, as well as an assessment of time, dose, and combination with other drugs, which gives infinite treatment results, so you must act taking some background, such as genetic predisposition, comorbidities, adulthood, lack of drug adherence, patient sex, and minimization of adverse effects, followed by optimization of the administration regimen [4]. Although antiepileptic drugs have proven clinical efficacy, they are not exempt from having side effects such as hepatotoxicity, drowsiness, gastrointestinal effects, impaired concentration, depressed mood, irritability, behavioral effects, psychiatric effects, among others that are related to a low quality of life, in addition to the aforementioned, a third of patients are resistant to these drugs [5-8]. Therefore, it is important to look for alternatives that are more effective, safe, and economical, an example can be found in medicinal plants, which have an important place in the discovery of new chemical structures with anticonvulsant potential [9]. We will explore this alternative, in the present review work.

Methods

Internet resources, advanced search using SciFinder, PubMed, google academic, Springer, Science Direct and Scopus.

Results and discussion

Epilepsy

Epilepsy is a common neurological condition that affects around 5 to 8 people per 1000 in developed countries, while in Mexico about 3 million Mexicans have been reported with this pathology; In relation to this, treatments can have very high costs, because they are for life and in some cases, surgery is required to control seizures, having a great economic impact on families. In addition, epilepsy is associated with symptoms of anxiety, depression, and increased mortality [10-12]. Epilepsy is a chronic neurological disorder distinguished by involuntary and spontaneous movements, called epileptic seizures, which are divided in those that affect a one hemisphere of the brain (focal seizures) or both hemispheres (generalized seizures) and the classification of unknown origin will also be added, on some occasions, the seizure is accompanied by loss of consciousness and sphincter control; sometimes a focal seizure may become bilateral, as in generalized seizures. Seizures are caused by a sudden imbalance of signals between the excitatory and inhibitory systems in the brain. Epilepsy is diagnosed when the following conditions occur: 1) two seizures or reflexes with a range of less than 24 hours, 2) one unprovoked (or reflex) seizure and a probability of new seizures similar to the risk of general recurrence (at minus 60%) after two unprovoked seizures, occurring over the next 10 years, 3) Diagnosis of epilepsy syndrome. Epilepsy is considered to result when a person with epilepsy syndrome has not had seizures in the last 10 years and has not needed anticonvulsant drugs in the last 5 years. [3,13-15]. In this sense, it is necessary to mention "The International League Against Epilepsy (ILAE)", which is aimed at the study, classification, and terminology of seizures practically since its creation in 1909. Additionally, in 2017 was ban important change in the classification of seizures (Figure 1). There are several reasons for the need to improve the 1981 classification, among which are: 1) some types of seizures may have a focal or generalized origin, 2) previously used terms lack community acceptance or are confusing for staff non-clinical, 3) some types of seizures excluded in the 1981 version are added, 4) lack of knowledge about seizure onset makes classification difficult in the 1981 system, and 5) improve seizure-related communication between the medical and non-medical community and researchers [3,16].

Treatment of epilepsy

The main objective of antiepileptic drugs is the control of seizures; these have improved in the last 3 decades. Among these, carbamazepine, ethosuccimide, phenobarbital, phenytoin and valproic acid can be highlighted [17,18]. Antiepileptic drugs (AEDs) have a wide variety of mechanisms of action, some examples are blockade of Na^+ channels, blockade of Na^+ and Ca^{2+} channels, allosteric modulation of the GABAA receptor, increased levels of GABA by inhibiting GABA transaminase or the transporters GABA, glutamate receptor agonist α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and modulation of synaptic vesicle protein 2A. [19-21]. However, only in 75-80% of patients are these treatments effective in controlling seizures, the rest of the people with epilepsy (20-25%) remain without an adequate therapeutic regimen. In addition to this, antiepileptic drugs do not affect epileptogenesis and are associated with side effects such as: teratogenicity, chronic toxicity, effects on cognition, hepatotoxicity, gastrointestinal and behavioral problems, they are also related to drug interactions, making it difficult to control seizures convulsive [18,22,23]. At the economic level, innovative antiepileptic drugs become more expensive in relation to their generic counterpart, placing them in most cases out of reach of the majority of the population with epilepsy, even if the prices are negotiated. Prices for national health systems, becomes a growing burden for developed countries [24]. Therefore, it is necessary to search for alternative or complementary treatments, more effective and with fewer side effects, which can support their effectiveness supported by animal models.

Plants with anticonvulsant activity

Natural products have been a primary treatment for a wide variety of diseases; therefore, medicinal plants have an important role in the search and development of new drugs [9,25]. Some of the metabolites that exert anticonvulsant actions are found in polar extracts. For example, the ethanolic extract of *Aegle marmelos, Alternanthera basiliana* (L.), *Berberis integerrima, Crassula arborecens* (Mill) and the methanolic extract of *Melissa parviflora* [26,27,28,29,69], currently the validation of anticonvulsant plants is continuing, as an example we have the *Euphorbia nivulia* plant and *Cocculus laurifolius* [30,31], other examples of plants with anticonvulsant activity can be observed in Table 1.

On the other hand, regarding the panorama of the investigation of plants with anticonvulsant potential in Latin America, a study was carried out by Auditeau *et al.,* in 2018 [32], the article compares the reports of plants with anticonvulsant activity between Asia, Africa and Latin America, it mentions that in the latter only 66 species are mentioned in comparison with the other continents that together have 431 reported species, this may be due to the fact that in these continents, traditional medicine is included in the health system. In this sense, the study of plants with anticonvulsant activity is important, especially in Latin America, for in the future, with sufficient rigorously applied scientific evidence; it can be inserted into the public health system. In Mexico for the regulation of medicinal plants, we have the herbal pharmacopoeia of the United Mexican States of 2013, which contains the monograph of 213 species recognized for their pharmacological utility [33], however, there are still many medicinal plants, to which, their pharmacological activity has not been validated. It should also be considered that medicinal plants can be adjuvants in the treatment of epilepsy, as an example, there is the report made by HIjikata *et al*., in 2006 [34] of three cases, in which the seizures could not be controlled. Due to this, it was decided to resort to traditional Chinese medicine along with conventional treatments to achieve any improvement They concluded that the application of traditional medicine alongside conventional treatments reduced the frequency and severity of seizures in all three cases. This type of success case shows us the importance of traditional medicine; therefore, we must also focus on its possible use as an adjuvant in the treatment of seizures, as well as determined if there are any adverse effects during seizures, or it co-administration, to obtain a more effective and safe therapy.

Secondary metabolites with anticonvulsant activity

Chemistry is important in the study of medicinal plants, it allows us to identify and group plants by their components (flavonoids, alkaloids, tannins, etc.), giving us a guide in the search for new drugs to treat various diseases. In the past decade, a large amount of evidence has emerged that supports the potential of natural products; in this review we will highlight the reports of various plants that contain secondary metabolites with anticonvulsant activity [35,36]. Some examples are the alkaloid (+)-erythravine, (+)-11-α-hydroxy-erythravine, piperine and sparteine, which delayed the time of onset of seizures, protected against the death of research animals and in some tested doses, they avoided the appearance of seizures in different animal models [35,37,38]. In some cases, mechanisms of action have been proposed, for example, there is nantenine that acts as a modulator of NMDA receptors and montanin with a possible interaction with the GABAergic system [39,40].

Flavonoids are a family of metabolites with anticonvulsant activity, within these; quercetin, isoquercitrin, hispidulin, ororylin A and rutin have been observed. As a mechanism of action, flavonoids bind alosterically to the benzodiazepine site, modulating the GABAA receptor, favoring the flow of Cl^- ions, therefore, the cell is hyperpolarized, reducing the propagation of electrical signals [41-44]. Other examples of secondary metabolites with anticonvulsant activity are: Saikosaponins A, the essential oil of *Ducrosia anethifolia* with its major constituent α-pinene, diterpene phytol, monoterpenes, finally the coumarin schoolletin [45-48,108]. As can be seen, efforts are being added around the world to discover new molecules with anticonvulsant activity, however, it is necessary to continue with more in-depth investigations, which allow us to identify the families and structures of the secondary metabolites responsible for their pharmacological activity, as well as its mechanisms of action, with the aim of being able to synthesize them in the future and obtain the maximum benefits, with the least possible risk. In Figure 2, some chemical structures of secondary metabolites with anticonvulsant activity are observed.

Animal models in the study of epilepsy

In the last 80 years, research animals have been an important tool for evaluating new molecules with anticonvulsant potential; this led to the advancement of first, second and third generation antiepileptic drugs. In general, the experimental models of epilepsy in rats or mice can be divided into pro-epileptic agents of the chemical type (tetanus toxin, kainic acid, pentylenetetrazole, etc.), physical (electric shocks, hyperthermia, etc.) and genetic (modified animals prone to seizures). Two of the most used models in the search for new treatments for epilepsy are maximal electroshock seizure (MES, physical type) and pentylenetetrazole (PTZ, chemical type), in these models use rats or mice as a standard procedure [49-51]. In 1975, the Anticonvulsant Screening Project (ASP) was established in the United States, whose main goal is the development of new anticonvulsant drugs. With this tool, the pharmaceutical industry was able to evaluate many new antiepileptic compounds in rodents. The ASP allowed the development of many drugs endorsed by FDA (Food and Drug Administration), these include felbamate, topiromate and retigabine [51,52]. As can be seen, animal models allow us the development and validation of new antiepileptic drugs, with fewer and more effective side effects, therefore improving the quality of life of patients with epilepsy. However, it must be recognized that no animal model fully represents the condition, mainly due to the different etiologies of epilepsy [53].

Hormesis

To understand this concept, we must relate that biological stress such as intellectual (critical thinking, etc.), physical (light, radiation, physical exercise, etc.) or chemical (food, medications, etc.), produce adaptive responses. At low doses, these responses produce a protective effect by stimulating mechanisms such as macrophage production, ion channel openings, autophagy, protein-related heat shock response pathways, etc. On the other hand, when applying this concept in research, we relate it to a relatively large number of different doses to be tested, which results in a biphasic dose-response relationship; In general, we

can say that hormesis is characterized by a beneficial effect at low doses and that high doses generate a negative effect, this phenomenon can be associated with a quantitative measure of biological plasticity (adaptive response) under stress conditions. This effect has gained relevance in the last 20 years [54-57]. This phenomenon has been observed in pharmaceutical products such as anticonvulsants, anxiolytics, newly created molecules for the therapy of Parkinson's and Huntington's, in drugs to treat diabetes, infections and cancer [57-61]. Hormesis is also described in plants and is caused by stress (abiotic and biotic), which triggers an adaptation process under adverse conditions, to maintain homeostasis [62]. Health benefits have been reported in small amounts As an example of the aforementioned, we have nicotine, cocaine, morphine and strychnine, which lose efficacy with increasing doses; sulforaphane protects mesenchymal stem cells from oxidative stress and apoptosis in low doses (1 µM), while at doses High doses (20 µM) produce damage to the genetic material (DNA) and cytotoxic effects; resveratrol reduces stomach ulcers and inflammation in mice at doses of 2 mg/Kg while high doses (5 and 10 mg/Kg) produce the opposite effect [63-67]. For all the effort mentioned, it is important to continue studying in depth the properties of medicinal plants.

Conclusions

The use ancestral of medicinal plants had served as a primary treatment for multiple diseases, especially in developing countries. In recent years the use of medicinal plants has increased, in the same way the number of investigations is increasing, giving the opportunity to explore new families of chemical structures with anticonvulsant capacity, to develop a drug or adjuvant in treating epilepsy (like other conditions), this search becomes important, since it is necessary to develop new anticonvulsant drugs that are safer, more effective, affordable and with fewer side effects. There is still a long way to walk, especially the chemical characterization of the metabolites of medicinal plants and the mechanisms of action; however, progress is still being made to increase the quality of life of people with epilepsy.

Conflict of Interest

All authors confirm that they have no conflict of interest.

References

1. Jacob, S., & Nair, A. B. (2016). An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. *Drugs in R&D*, 16 (4), 303-316. doi:10.1007/s40268-016-0148-6
2. OMS, 2021. https://www.who.int/topics /epilepsy/es/. 23/04/2021. 10:54 am.
3. Fisher, R. S., Cross, J. H., D'Souza, C., French, J. A., Haut, S. R., Higurashi, N., Hirsch, E., Jansen, F. E., Lagae, L., Moshé, S. L., Peltola, J., Roulet Perez, E., Scheffer, I. E., Schulze-Bonhage, A., Somerville, E., Sperling, M., Yacubian, E. M., & Zuberi, S. M. (2017). Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*, 58(4), 531–542. https://doi.org/10.1111/epi.13671
4. Cheng, J. Y., French, J. A. (2018). Intelligent use of antiepileptic drugs is beneficial to patients. *Current Opinion in Neurology*, 31(2),169-175. doi:10.1097/WCO.0000000000000532
5. Chen, B., Choi, H., Hirsch, L. J., Katz, A., Legge, A., Buchsbaum, R., & Detyniecki, K. (2017). Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. *Epilepsy & behavior*: E&B, 76, 24–31. https://doi.org/10.1016/j.yebeh.2017.08.039
6. Vidaurre, J., Gedela, S., & Yarosz, S. (2017). Antiepileptic drugs and liver disease. *Pediatric Neurology*, 77, 23-36. doi:10.1016/j.pediatrneurol.2017.09.013
7. Wagner, J. L., Mueller, M., Kellermann, T., Griffin, M., Smith, G., Soliven, M., Guilfoyle, S. M., Junger, K. F., Mucci, G., Huszti, H., Barrett, L., Zupanc, M., & Modi, A. C. (2019). Vulnerabilities to antiepileptic drug (AED) side effects in youth with epilepsy. *Epilepsy Behavior*, 97, 22-28. doi:10.1016/j.yebeh.2019.05.012

8. Tavakol, S., Royer, J., Lowe, A. J., Bonilha, L., Tracy, J. I., Jackson, G. D., Duncan, J. S., Bernasconi, A., Bernasconi, N., & Bernhardt, B. C. (2019). Neuroimaging and connectomics of drug-resistant epilepsy at multiple scales: From focal lesions to macroscale networks. *Epilepsia*, 60(4), 593-604. doi:10.1111/epi.14688
9. Wang, S., Dong, G., & Sheng, C. (2019). Structural Simplification of Natural Products. *Chemical Review*, 119(6), 4180-4220. doi: 10.1021/acs.chemrev.8b00504
10. Allers, K., Essue, B. M., Hackett, M. L., Muhunthan, J., Anderson, C. S., Pickles, K., Scheibe, F. & Jan, S. (2015). The economic impact of epilepsy: a systematic review. *BMC Neurology*, 15, 245. Published 2015 Nov 25. doi:10.1186/s12883-015-0494-y
11. Funck, V. R., Ribeiro, L. R., Pereira, L. M., de Oliveira, C. V., Grigoletto, J., Della-Pace, I. D., Fighera, M. R., Royes, L. F., Furian, A. F., Larrick, J. W., Oliveira, M. S. (2015). Contrasting effects of Na+, K+-ATPase activation on seizure activity in acute versus chronic models. *Neuroscience,* 298, 171-179. doi: 10.1016/j.neuroscience.2015.04.031
12. Ciencia UMAN, (2019). Epilepsia y su complejo tratamiento Tomado de: https://www.fundacionunam.org.mx/unam-al-dia/epilepsia-y-su-complejo-tratamiento/ a las 13 horas el 28 mayo del 2021.
13. Yu, Y., Xie, W., & Wang, C. (2015). Chaihushugan decoction exerts antiepileptic effects by increasing hippocampal glutamate metabolism in pentylenetetrazole-kindled rats. *Journal of Traditional Chinese Medicine*, 35(6), 659-665. doi:10.1016/s0254-6272(15)30156-4
14. Copmans, D., Orellana-Paucar, A. M., Steurs, G., Zhang, Y., Ny, A., Foubert, K., Exarchou, V., Siekierska, A., Kim, Y., De Borggraeve, W., Dehaen, W., Pieters, L., & de Witte, P. A. M. (2018). Methylated flavonoids as anti-seizure agents: Naringenin 4',7-dimethyl ether attenuates epileptic seizures in zebrafish and mouse models. *Neurochemical International*, 112, 124-133. doi:10.1016/j.neuint.2017.11.011
15. OMS,2021. https://www.who.int/topics/epilepsy/es/. A las 13 horas el 28 de mayo del 2021
16. Pack A. M. (2019). Epilepsy Overview and revised classification of seizures and epilepsies. *Continuum (Minneap Minn)*, 25(2), 306-321. doi: 10.1212/CON.0000000000000707. PMID: 30921011.
17. Golyala, A., & Kwan, P. (2017). Drug development for refractory epilepsy: The past 25 years and beyond. *Seizure*, 44, 147-156. doi:10.1016/j.seizure.2016.11.022
18. Aliyu, M. M., Musa, A. I., Kamal, M. J., & Mohammed, M. G. (2014). Phytochemical screening and anticonvulsant studies of ethyl acetate fraction of *Globimetula braunii* on laboratory animals. *Asian Pacific journal of tropical biomedicine*, 4(4), 285–289. https://doi.org/10.12980/APJTB.4.2014C925
19. Brodie, M. J., Covanis, A., Gil-Nagel, A., Lerche, H., Perucca, E., Sills, G. J., & White, H. S. (2011). Antiepileptic drug therapy: does mechanism of action matter?. *Epilepsy & Behavior*, 21(4), 331-341. doi:10.1016/j.yebeh.2011.05.025
20. Rapacz, A., Rybka, S., Obniska, J., Salat, K. (2016). Evaluation of anticonvulsant and antinociceptive properties of new N-Mannich bases derived from pyrrolidine-2,5-dione and 3-methylpyrrolidine-2,5-dione. *Naunyn Schmiedebergs Archives or Pharmacology*, 389(3), 339-348. doi:10.1007/s00210-015-1194-2
21. Farrokh, S., Tahsili-Fahadan, P., Ritzl, E. K., Lewin, J. J., 3rd, & Mirski, M. A. (2018). Antiepileptic drugs in critically ill patients. *Critical care* (London, England), 22(1), 153. https://doi.org/10.1186/s13054-018-2066-1.
22. Englot, D. J., Birk, H., & Chang, E.F. (2017). Seizure outcomes in nonresective epilepsy surgery: an update. *Neurosurgery Review*, 40(2), 181-194. doi:10.1007/s10143-016-0725-8
23. Moshé, S. L., Perucca, E., Ryvlin, P., & Tomson, T. Epilepsy: new advances. (2015). *Lancet*, 385(9971), 884-898.
24. Holtkamp, M., & Theodore, W.H. (2018). Generic antiepileptic drugs-safe or harmful

in patients with epilepsy?. *Epilepsia*, 59(7), 1273-1281. doi:10.1111/epi.14439
25. Kakeya H. (2016). Natural products-prompted chemical biology: phenotypic screening and a new platform for target identification. *Natural Product Reports*, 33(5), 648-654. doi:10.1039/c5np00120j
26. Bhat, J. U., Nizami, Q., Asiaf, A., Parray, S. A., Ahmad, S. T., Aslam, M., Khanam, R., Mujeeb, M., Umar, S., & Siddiqi, A. (2012). Anticonvulsant activity of methanolic and aqueous extracts of *Melissa parviflora* in experimentally induced Swiss albino mice. *EXCLI journal*, 11, 1–6.
27. Barua, C. C., Begum, S. A., Barua, A, G., Borah, R. S., & Lahkar, M. (2013). Anxiolytic and anticonvulsant activity of methanol extract of leaves of *Alternanthera brasiliana* (L.) Kuntze (Amaranthaceae) in laboratory animals. *Indian Journal of Experimental Biology*, 51(6), 450-457.
28. Hosseinzadeh, H., Ramezani, M., Shafaei, H., & Taghiabadi E. (2013). Anticonvulsant effect of *Berberis integerrima* L. root extracts in mice. *Journal of Acupunct and Meridian Studies*, 6(1), 12-17. doi:10.1016/j.jams.2012.07.018
29. Amabeoku, G. J., Mbamalu, O. N., Davids, T., Fakude, S., Gqwaka, A., Mbai, F., & Shaik, A. (2014). Evaluation of the anticonvulsant activity of the leaf methanol extract of *Crassula arborescens* (Mill.) Willd. (*Crassulaceae*) in mice. *Journal of Pharmacy and Pharmacology*, 2, 393-403.
30. Maqbool, S., Younus, I., Sadaf, R., & Fatima, A. (2019). Neuro-pharmacological evaluation of anticonvulsant and neuroprotective activity of *Cocculus laurifolius* leaves in wistar rats. *Metabolic Brain Disease*, 34(4), 991-999. doi:10.1007/s11011-019-00414-3
31. Rehman, A.H., Al Sharari, S. D., Ahmad, M., Akhtar, M., Khan, Y., & Ashraf, M. N. (2019). Evaluation of anticonvulsant and antiepileptogenic activity of *Euphorbia nivulia* in PTZ-induced kindling model of epilepsy in mice. *Pakistan Journal of Pharmaceutical Sciences*, 32(2), 675-681.
32. Auditeau, E., Chassagne, F., Bourdy, G., Bounlu, M., Jost, J., Luna, J., Ratsimbazafy, V., Preux, P. M., & Boumediene, F. (2019). Herbal medicine for epilepsy seizures in Asia, Africa and Latin America: A systematic review. *Journal of ethnopharmacology*, 234, 119–153. doi.org/10.1016/j.jep.2018.12.049in
33. Farmacopea Herbolaria de los Estados Unidos Mexicanos (FHEUM), 2013. Secretaria de Salud, Mexico, D.F., 2th edition. p. 371.
34. Hijikata, Y., Yasuhara, A., Yoshida, Y., & Sento, S. (2006). Traditional chinese medicine treatment of epilepsy. *Journal of alternative and complementary medicine (New York, N.Y.)*, 12(7), 673–677. https://doi.org/10.1089/acm.2006.12.673
35. Mishra, A., Punia, J. K., Bladen, C., Zamponi, G. W., & Goel, R. K. (2015). Anticonvulsant mechanisms of piperine, a piperidine alkaloid. *Channels (Austin, Tex.)*, 9(5), 317–323.https://doi.org/10.1080/19336950.2015.1092836.
36. Juvekar, M. R., Kulkarni, M. P., & Juvekar, A. R. (2008). Anti-stress, nootropic and anticonvulsant potential of fruit extracts of *Piper longum* L. *Planta Medica*, 74(09), 244.
37. Faggion, S. A., Cunha, A. O., Fachim, H. A., Gavin, A. S., dos Santos, W. F., Pereira, A. M., & Beleboni, R. O. (2011). Anticonvulsant profile of the alkaloids (+)-erythravine and (+)-11-α-hydroxy-erythravine isolated from the flowers of *Erythrina mulungu* Mart ex Benth (Leguminosae-Papilionaceae). *Epilepsy & behavior* : E&B, 20(3), 441–446. https://doi.org/10.1016/j.yebeh.2010.12.037.
38. Villalpando-Vargas, F., & Medina-Ceja, L. (2016). Sparteine as an anticonvulsant drug: Evidence and possible mechanism of action. *Seizure*, 39, 49-55. https://doi.org/10.1016/j.seizure.2016.05.010
39. Ribeiro, R. A., & Leite, J. R. (2003). Nantenine alkaloid presents anticonvulsant effect on two classical animal models. *Phytomedicine : international journal of phytotherapy and phytopharmacology*, 10(6-7), 563–568. https://doi.org/10.1078/094471103322331557
40. da Silva, A. F., de Andrade, J. P., Bevilaqua, L. R., de Souza, M. M., Izquierdo, I., Henriques, A. T., & Zuanazzi, J. A. (2006). Anxiolytic-,

antidepressant- and anticonvulsant-like effects of the alkaloid montanine isolated from *Hippeastrum vittatum*. *Pharmacology, biochemistry, and behavior*, 85(1), 148–154. https://doi.org/10.1016/j.pbb.2006.07.027

41. Kavvadias, D., Sand, P., Youdim, K. A., Qaiser, M. Z., Rice-Evans, C., Baur, R., Sigel, E., Rausch, W. D., Riederer, P., & Schreier, P. (2004). The flavone hispidulin, a benzodiazepine receptor ligand with positive allosteric properties, traverses the blood-brain barrier and exhibits anticonvulsive effects. *British journal of pharmacology*, 142(5), 811–820. https://doi.org/10.1038/sj.bjp.0705828
42. Huen, M. S., Leung, J. W., Ng, W., Lui, W. S., Chan, M. N., Wong, J. T., & Xue, H. (2003). 5,7-Dihydroxy-6-methoxyflavone, a benzodiazepine site ligand isolated from Scutellaria baicalensis Georgi, with selective antagonistic properties. *Biochemical pharmacology*, 66(1), 125–132. https://doi.org/10.1016/s0006-2952(03)00233-8
43. Wasowski C, Marder M. Flavonoids as $GABA_A$ receptor ligands: the whole story?. J Exp Pharmacol. 2012; 4:9-24. Published 2012 Feb 23. doi:10.2147/JEP.S23105
44. Cárdenas-Rodríguez, N., González-Trujano, M. E., Aguirre-Hernández, E., Ruíz-García, M., Sampieri, A., 3rd, Coballase-Urrutia, E., & Carmona-Aparicio, L. (2014). Anticonvulsant and antioxidant effects of *Tilia americana* var. mexicana and flavonoids constituents in the pentylenetetrazole-induced seizures. *Oxidative medicine and cellular longevity*, 2014, 329172. https://doi.org/10.1155/2014/329172
45. Li, X. Q., Song, Y. N., Wang, S. J., Rahman, K., Zhu, J. Y., & Zhang, H. (2018). Saikosaponins: a review of pharmacological effects. *Journal of Asian natural products research*, 20(5), 399–411. https://doi.org/10.1080/10286020.2018.1465937
46. Zamyad, M., Abbasnejad, M., Esmaeili-Mahani, S., Mostafavi, A., & Sheibani, V. (2019). The anticonvulsant effects of *Ducrosia anethifolia* (Boiss) essential oil are produced by its main component alpha-pinene in rats. *Arquivos de neuro-psiquiatria*, 77(2), 106–114. https://doi.org/10.1590/0004-282X20180147.
47. Costa, J. P., Ferreira, P. B., De Sousa, D. P., Jordan, J., & Freitas, R. M. (2012). Anticonvulsant effect of phytol in a pilocarpine model in mice. *Neuroscience letters*, 523(2), 115–118. https://doi.org/10.1016/j.neulet.2012.06.055
48. Woo, T. S., Yoon, S. Y., Pena, I. C. D., Choi, J. (2011). Anticonvulsant effect of *Artemisia capillaris* Herba in mice. *Biomolecules & Therapeutics*. 2011; 19(3), 342-347. http://DOI:10.4062/biomolther.2011.19.3.342
49. Zavala-Tecuapetla, C., & López-Meraz, M. L. (2011). Modelos experimentales de epilepsia en ratas en desarrollo.
50. Löscher, W., & Schmidt, D. (2011). Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia*, 52(4), 657–678. https://doi.org/10.1111/j.1528-1167.2011.03024.x
51. Löscher W. (2017). Animal Models of Seizures and Epilepsy: Past, Present, and Future Role for the Discovery of Antiseizure Drugs. *Neurochemical research*, 42(7), 1873–1888. https://doi.org/10.1007/s11064-017-2222-z
52. Kehne, J. H., Klein, B. D., Raeissi, S., & Sharma, S. (2017). The National Institute of Neurological Disorders and Stroke (NINDS) Epilepsy Therapy Screening Program (ETSP). *Neurochemical research*, 42(7), 1894–1903. https://doi.org/10.1007/s11064-017-2275-z
53. Grone, B. P., & Baraban, S. C. (2015). Animal models in epilepsy research: legacies and new directions. *Nature neuroscience*, 18(3), 339–343. https://doi.org/10.1038/nn.3934
54. Calabrese, E. J., & Agathokleous, E. (2019). Building Biological Shields via Hormesis. *Trends in pharmacological sciences*, 40(1), 8–10. https://doi.org/10.1016/j.tips.2018.10.010
55. Agathokleous, E., Kitao, M., & Calabrese, E. J. (2019). Hormesis: A Compelling Platform for Sophisticated Plant Science. *Trends in plant science*, 24(4), 318–327. https://doi.org/10.1016/j.tplants.2019.01.004

56. Calabrese, E.J., Mattson, M.P. How does hormesis impact biology, toxicology, and medicine?. npj Aging Mech Dis 3, 13 (2017). https://doi.org/10.1038/s41514-017-0013-z
57. Calabrese E. J. (2008). Hormesis and medicine. *British journal of clinical pharmacology*, 66(5), 594–617. https://doi.org/10.1111/j.1365-2125.2008.03243.x
58. (a) Calabrese, V., Santoro, A., Monti, D., Crupi, R., Di Paola, R., Latteri, S., Cuzzocrea, S., Zappia, M., Giordano, J., Calabrese, E. J., & Franceschi, C. (2018). Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. *Free radical biology & medicine*, 115, 80–91. https://doi.org/10.1016/j.freeradbiomed.2017.10.379
59. (b) Calabrese, V., Santoro, A., Trovato Salinaro, A., Modafferi, S., Scuto, M., Albouchi, F., Monti, D., Giordano, J., Zappia, M., Franceschi, C., & Calabrese, E. J. (2018). Hormetic approaches to the treatment of Parkinson's disease: Perspectives and possibilities. *Journal of neuroscience research*, 96(10), 1641–1662. https://doi.org/10.1002/jnr.2424
60. De Haes, W., Frooninckx, L., Van Assche, R., Smolders, A., Depuydt, G., Billen, J., Braeckman, B. P., Schoofs, L., & Temmerman, L. (2014). Metformin promotes lifespan through mitohormesis via the peroxiredoxin PRDX-2. *Proceedings of the National Academy of Sciences of the United States of America*, 111(24), E2501–E2509. https://doi.org/10.1073/pnas.1321776111
61. Pearce, O. M., Läubli, H., Verhagen, A., Secrest, P., Zhang, J., Varki, N. M., Crocker, P. R., Bui, J. D., & Varki, A. (2014). Inverse hormesis of cancer growth mediated by narrow ranges of tumor-directed antibodies. *Proceedings of the National Academy of Sciences of the United States of America*, 111(16), 5998–6003. https://doi.org/10.1073/pnas.1209067111 doi:10.1073/pnas.1209067111
62. Jalal, A., Oliveira Junior, J. C., Santos Ribeiro, J., Fernandes, G. C., Guerra Mariano, G., Dias Rezende Trindade, V., & Rodrigues dos Reis, A. (2021). Hormesis in plants: Physiological and biochemical responses. *Ecotoxicology Environmental Safety*. 207, 111225. doi:10.1016/j.ecoenv.2020.111225
63. Hadacek, F., Bachmann, G., Engelmeier, D., & Chobot, V. (2011). Hormesis and a chemical raison d'ĕtre for secondary plant metabolites. *Dose-response,* 9(1), dose-response. doi:10.2203/dose-response.09-028.
64. Langenheim, J. H., Lincoln, D. E., Stubblebine, W. H., & Gabrielli, A. C. (1982). Evolutionary implications of leaf resin pocket patterns in the tropical tree *Hymenaea (Caesalpinioideae: Leguminosae). American Journal of Botany*, 69(4), 595-607.
65. Zanichelli, F., Capasso, S., Di Bernardo, G., Cipollaro, M., Pagnotta, E., Cartenì, M., ... & Galderisi, U. (2012). Low concentrations of isothiocyanates protect mesenchymal stem cells from oxidative injuries, while high concentrations exacerbate DNA damage. *Apoptosis*, 17(9), 964-974. doi:10.1007/s10495-012-0740-3
66. Dey, A., Guha, P., Chattopadhyay, S., & Bandyopadhyay, S. K. (2009). Biphasic activity of resveratrol on indomethacin-induced gastric ulcers. *Biochemical and biophysical research communications,* 381(1), 90-95. doi:10.1016/j.bbrc.2009.02.027
67. Martel, J., Ojcius, D. M., Ko, Y. F., Ke, P. Y., Wu, C. Y., Peng, H. H., & Young, J. D. (2019). Hormetic effects of phytochemicals on health and longevity. *Trends in Endocrinology & Metabolism*, 30(6), 335-346. doi:10.1016/j.tem.2019.04.001
68. Chen, Q. X., Miao, J. K., Li, C., Li, X. W., Wu, X. M., & Zhang, X. P. (2012). Anticonvulsant activity of acute and chronic treatment with a-asarone from *Acorus gramineus* in seizure models. *Biological and Pharmaceutical Bulletin,* 36(1):23-30. doi:10.1248/bpb.b12-00376.
69. Sankari, M., Chitra, V., Silambujanaki, P., & Raju, D. (2010). Anticonvulsant activity of

ethanolic extract of *Aegle marmelos* (leaves) in mice. *International Journal of PharmTech Research,* 2(1), 640-643.
70. Barua, C. C., Begum, S. A., Barua, A. G., Borah, R. S., & Lahkar, M. (2013). Anxiolytic and anticonvulsant activity of methanol extract of leaves of *Alternanthera brasiliana* (L.) Kuntze (Amaranthaceae) in laboratory animals.*Indian J Exp Biol.* 2013; 51(6):450-457.
71. Anaka, O. N., Ozolua, R. I., Ikpefan, E. O., & Ogieva, D. O. (2014). Anticonvulsant activity of the aqueous extract of *Allium cepa* L.(Amaryllidaceae) in rats and mice. *Journal of Pharmacy & Bioresources,* 11(1), 1-7. http://dx.doi.org/10.4314/jpb.v11i1.1
72. Arash, A., Mohammad, M. Z., Jamal, M. S., Mohammad, T. A., & Azam, A. (2013). Effects of the Aqueous Extract of *Anethum graveolens* Leaves on Seizure Induced by Pentylenetetrazole in Mice. *The Malaysian journal of medical sciences : MJMS,* 20(5), 23–30.
73. Konate, A., Sawadogo, W. R., Dubruc, F., Caillard, O., Ouedraogo, M., & Guissou, I. P. (2012). Phytochemical and Anticonvulsant Properties of" *Annona senegalensis*" Pers.(Annonaceae), Plant Used in Burkina Folk Medicine to Treat Epilepsy and Convulsions. *British Journal of Pharmacology and Toxicology,* 3(5), 245-250.
74. Khan, I., Karim, N., Ahmad, W., Abdelhalim, A., & Chebib, M. (2016). GABA-A Receptor Modulation and Anticonvulsant, Anxiolytic, and Antidepressant Activities of Constituents from *Artemisia indica* Linn. Evidence-based complementary and alternative medicine : *eCAM,* 2016, 1215393. doi:10.1155/2016/1215393.
75. Hosseinzadeh, H., Ramezani, M., Shafaei, H., & Taghiabadi, E. (2013). Anticonvulsant effect of *Berberis integerrima* L. root extracts in mice. Journal of acupuncture and meridian studies, 6(1), 12–17. https://doi.org/10.1016/j.jams.2012.07.018
76. Ya'u, J., Yaro, A. H., Malami, S., Musa, M. A., Abubakar, A., Yahaya, S. M., Chindo, B. A., Anuka, J. A., & Hussaini, I. M. (2015). Anticonvulsant activity of aqueous fraction of *Carissa edulis* root bark. *Pharmaceutical biology*, 53(9), 1329–1338. https://doi.org/10.3109/13880209.2014.981280
77. Showraki, A., Emamghoreishi, M., & Oftadegan, S. (2016). Anticonvulsant Effect of the Aqueous Extract and Essential Oil of *Carum Carvi* L. Seeds in a Pentylenetetrazol Model of Seizure in Mice. *Iranian journal of medical sciences*, 41(3), 200–208.
78. Anaeigoudari, A., Hosseini, M., Karami, R., Vafaee, F., Mohammadpour, T., Ghorbani, A., & Sadeghnia, H. R. (2016). The effects of different fractions of *Coriandrum sativum* on pentylenetetrazole-induced seizures and brain tissues oxidative damage in rats. *Avicenna journal of phytomedicine,* 6(2), 223–235.
79. Lahon, J., Phukan, S., & Sharma, U. (2016). Study of the anticonvulsant potential of leaves of *Clitoria ternatea* linn. in pentylenetetrazole and maximum electroshock seizure induced-convulsions in experimental animals. *asian j pharm clin res,* 9(2), 258-261.
80. Amabeoku, G. J., et al. (2014). Evaluation of the anticonvulsant activity of the leaf methanol extract of *Crassula arborescens* (Mill.) Willd.(Crassulaceae) in mice. *Journal of Pharmacy and Pharmacology*, 2, 393-403.
81. Abdel-Rahman, R. F., Soliman, G. A., Yusufoglu, H. S., Tatli-Çankaya, I., Alqasoumi, S. I., Anul, S. A., & Akaydin, G. (2015). Potential anticonvulsant activity of ethanol extracts of *Cichorium intybus* and *Taraxacum serotinum* in rats. *Tropical Journal of Pharmaceutical Research*, 14(10), 1829-1835.
82. Chaulya, N. C., Haldar, P. K., & Mukherjee, A. (2011). Antidiabetic activity of methanol extract of rhizomes of *Cyperus tegetum* Roxb. (Cyperaceae). *Acta poloniae pharmaceutica,* 68(6), 989–992.
83. Chinchawade, A. B., Deshmukh, D. B., Gaikwad, D. D., & Grampurohit, N. D. (2013). Anticonvulsant Activity of Chloroform Extract of Bark and Root of *Erythrina variegata* L. *International Journal of Pharmaceutical and Clinical Research,* 5(01), 23-25.

84. Taiwe, G. S., Dabole, B., Tchoya, T. B., Menanga, J. R., Dzeufiet, P. D., & De Waard, M. (2016). Anticonvulsant effects of iridoid glycosides fraction purified from *Feretia apodanthera* Del. (Rubiaceae) in experimental mice models of generalized tonic-clonic seizures. BMC complementary and alternative medicine, 16(1), 285. https://doi.org/10.1186/s12906-016-1269-8
85. Bhanushali, M. M., Makhija, D. T., & Joshi, Y. M. (2014). Central nervous system activity of an aqueous acetonic extract of *Ficus carica* L. in mice. *Journal of Ayurveda and integrative medicine*, 5(2), 89–96. https://doi.org/10.4103/0975-9476.131734
86. Gahlot, K., Lal, V. K., & Jha, S. (2013). Anticonvulsant potential of ethanol extracts and their solvent partitioned fractions from *Flemingia strobilifera* root. *Pharmacognosy research*, 5(4), 265–270. https://doi.org/10.4103/0974-8490.118825
87. Aliyu, M. M., Musa, A. I., Kamal, M. J., & Mohammed, M. G. (2014). Phytochemical screening and anticonvulsant studies of ethyl acetate fraction of *Globimetula braunii* on laboratory animals. *Asian Pacific journal of tropical biomedicine*, 4(4), 285–289. https://doi.org/10.12980/APJTB.4.2014C925
88. Ebrahimzadeh, M. A., Nabavi, S. M., Nabavi, S. F., & Ahangar, N. (2013). Anticonvulsant activity of *Hypericum scabrum* L.; possible mechanism involved. *European review for medical and pharmacological sciences*, 17(16), 2141–2144.
89. Twinomujuni, S. S., Oloro, J., & Alele, P. E. (2016). Anticonvulsant and anxiolytic activity of the leaf aqueous and ethanolic extracts of *Melanthera scandens* in a rat model. *African journal of pharmacy and pharmacology*, 10(12), 216–222. https://doi.org/10.5897/AJPP2015.4488
90. Bhat, J. U., Nizami, Q., Asiaf, A., Parray, S. A., Ahmad, S. T., Aslam, M., Khanam, R., Mujeeb, M., Umar, S., & Siddiqi, A. (2012). Anticonvulsant activity of methanolic and aqueous extracts of Melissa parviflora in experimentally induced Swiss albino mice. *EXCLI journal*, 11, 1–6.
91. Adongo, D. W., Mante, P. K., Kukuia, K., Biney, R. P., Boakye-Gyasi, E., Benneh, C. K., Ameyaw, E. O., & Woode, E. (2017). Anticonvulsant activity of Pseudospondias microcarpa (A. Rich) Engl. hydroethanolic leaf extract in mice: The role of excitatory/inhibitory neurotransmission and nitric oxide pathway. *Journal of ethnopharmacology*, 206, 78–91. https://doi.org/10.1016/j.jep.2017.05.017
92. Pooja, S., Kannapan, N., Anupama, D., Parveen, K., Vishal, A., Shreya, S., & Sandeep, S. (2010). Anticonvulsant activity of flower part of *N. odorum*. *International Journal of Pharma and Bio Sciences*, 1(2).
93. Nishanthi, M., Mohanambal, E., Devdass, G., Saravanan, D., Narendiran, S., & Vijayakumar, B. (2012). Anticonvulsant Activity of *Peperomia tetraphylla* (G. Forst., Hook. & Am.). *International Journal of Novel Trends in Pharmaceutical Sciences*, 2(1), 35-38.
94. Kaushik, D., Kumar, A., Kaushik, P., & Rana, A. C. (2012). Anticonvulsant activity of alcoholic extract of bark of *Pinus roxburghii* Sarg. Zhong xi yi jie he xue bao= *Journal of Chinese integrative medicine*, 10(9), 1056-1060.
95. Okunrobo, L. O., John, U. O., Fidelis, C. P., & Enosakhare, O. (2013). Evaluation of anticonvulsant activity of aqueous extract and partitioned chloroform fraction of *Piper umbellatum* Linn (Piperaceae) leaves. West *African Journal of Pharmacy*, 24(1).
96. Abdel-Rahman, R. F., Soliman, G. A., Yusufoglu, H. S., Tatli-Çankaya, I., Alqasoumi, S. I., Anul, S. A., & Akaydin, G. (2015). Potential anticonvulsant activity of ethanol extracts of *Cichorium intybus* and *Taraxacum serotinum* in rats. *Tropical Journal of Pharmaceutical Research*, 14(10), 1829-1835.
97. Khoshnood-Mansoorkhani, M. J., Moein, M. R., & Oveisi, N. (2010). Anticonvulsant Activity of *Teucrium polium* Against Seizure Induced by PTZ and MES in Mice. *Iranian journal of pharmaceutical research : IJPR*, 9(4), 395–401.
98. Cárdenas-Rodríguez, N., González-Trujano, M. E., Aguirre-Hernández, E., Ruíz-García, M.,

Sampieri, A., 3rd, Coballase-Urrutia, E., & Carmona-Aparicio, L. (2014). Anticonvulsant and antioxidant effects of *Tilia americana* var. mexicana and flavonoids constituents in the pentylenetetrazole-induced seizures. Oxidative medicine and cellular longevity, 2014, 329172. https://doi.org/10.1155/2014/329172

99. Homayoun, M., Seghatoleslam, M., Pourzaki, M., Shafieian, R., Hosseini, M., & Ebrahimzadeh Bideskan, A. (2015). Anticonvulsant and neuroprotective effects of *Rosa damascena* hydro-alcoholic extract on rat hippocampus. *Avicenna journal of phytomedicine,* 5(3), 260–270.}
100. Anitha, K., Jyothi, Y., Veena, A. V., & Bora, D. (2015). Evaluation of antiepileptic activity of fruit pericarp of" *Sapindus mukorossi*" in rats. *Journal of Chemical and Pharmaceutical Research,* 7(5), 363-368.
101. Zolfagharian, F., Razavi, B. M., & Hosseinzadeh, H. (2016). Anticonvulsant effect of *Satureja hortensis* aerial parts extracts in mice. *Avicenna journal of phytomedicine*, 6(3), 305–312.
102. Mahendran, G., Thamotharan, G., Sengottuvelu, S., & Bai, V. N. (2014). Evaluation of anticonvulsant, sedative, anxiolytic, and phytochemical profile of the methanol extract from the aerial parts of *Swertia corymbosa* (Griseb.) wight ex C.B. Clarke. *BioMed research international,* 2014, 542385. https://doi.org/10.1155/2014/542385
103. Muhammad, N., Saeed, M., Khan, H., Raziq, N., Halimi, S. M., & Abass, M. (2013). Antipyretic and anticonvulsant activity of n-hexane fraction of *Viola betonicifolia*. *Asian Pacific journal of tropical biomedicine*, 3(4), 280–283. https://doi.org/10.1016/S2221-1691(13)60063-5
104. Baradaran Rahimi, V., Askari, V. R., Hosseini, M., Yousefsani, B. S., & Sadeghnia, H. R. (2019). Anticonvulsant Activity of *Viola tricolor* against Seizures Induced by Pentylenetetrazol and Maximal Electroshock in Mice. *Iranian journal of medical sciences,* 44(3), 220–226.
105. Olayemi, J., Bakre, A., Oshireku, E., & Olowoparijab, S. Anticonvulsant, Anxiolytic and Sedative Activities Of The Methanol Extract of *Abrus Precatorius* (Linn.) Leaves. *ACTA Pharmaceutica Sciencia*, 59(1).
106. Benneh, C. K., Biney, R. P., Tandoh, A., Ampadu, F. A., Adongo, D. W., Jato, J., & Woode, E. (2018). *Maerua angolensis* DC. (Capparaceae) Stem Bark Extract Protects against Pentylenetetrazole-Induced Oxidative Stress and Seizures in Rats. *Evidence-based complementary and alternative medicine : eCAM,* 2018, 9684138. https://doi.org/10.1155/2018/9684138
107. Ozakieoniso, K. J., & Kagbo, H. D. (2018). Anticonvulsant Potential of Dichloromethane Extract of *Aspilia africana* Leaf in Mice. *Journal of Pharmaceutical Research International,* 1-10.
108. Pina, L., Guimarães, A. G., Santos, W., Oliveira, M. A., Rabelo, T. K., & Serafini, M. R. (2021). Monoterpenes as a perspective for the treatment of seizures: A Systematic Review. *Phytomedicine : international journal of phytotherapy and phytopharmacology,* 81, 153422. https://doi.org/10.1016/j.phymed.2020.153422

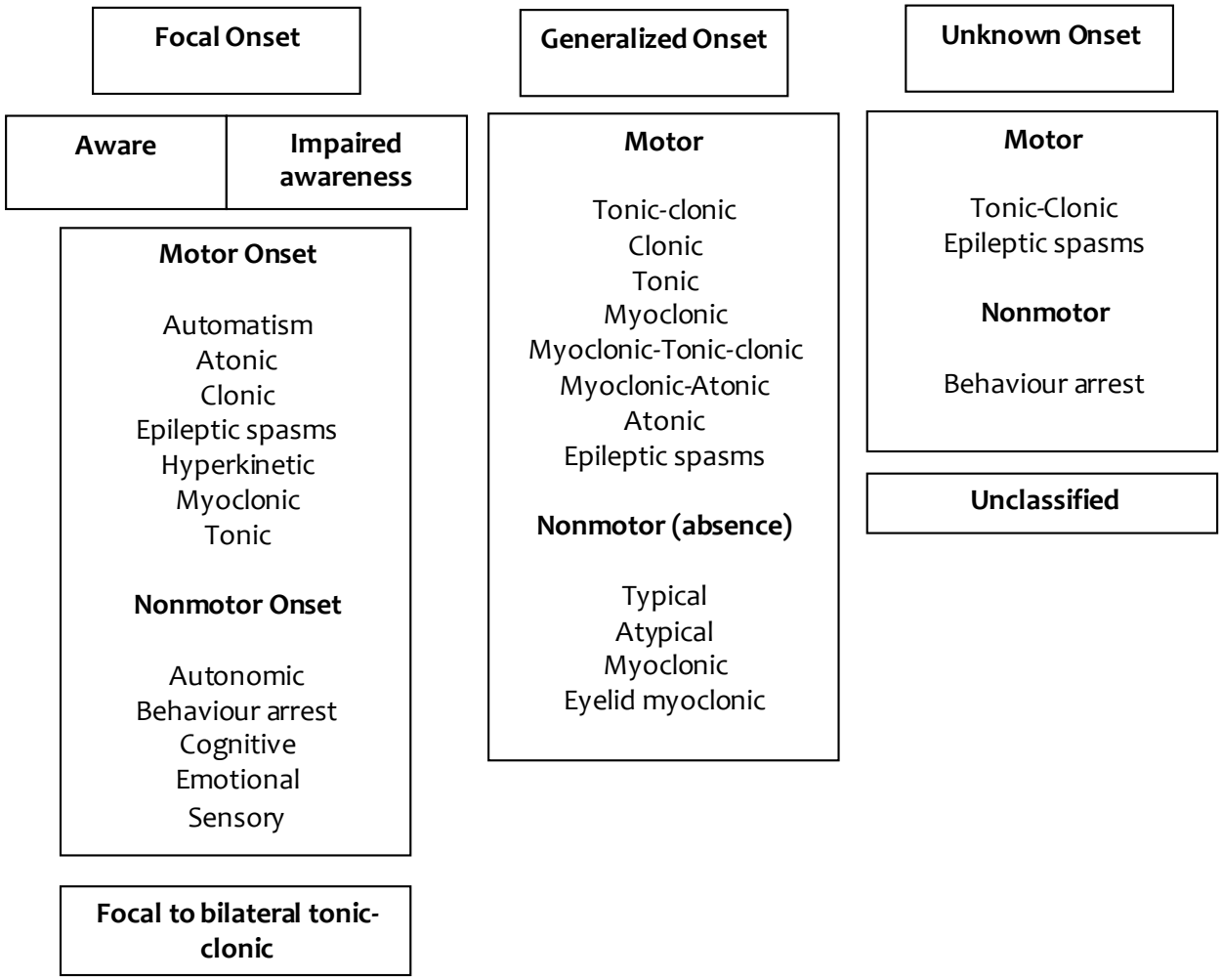

Figure 1.- New extended classification of types of seizures released in 2017 by the ILAE, triggered by the need to improve the 1981 classification. The new classification covers children and adults. Adapted from Fisher *et al.*, 2017.

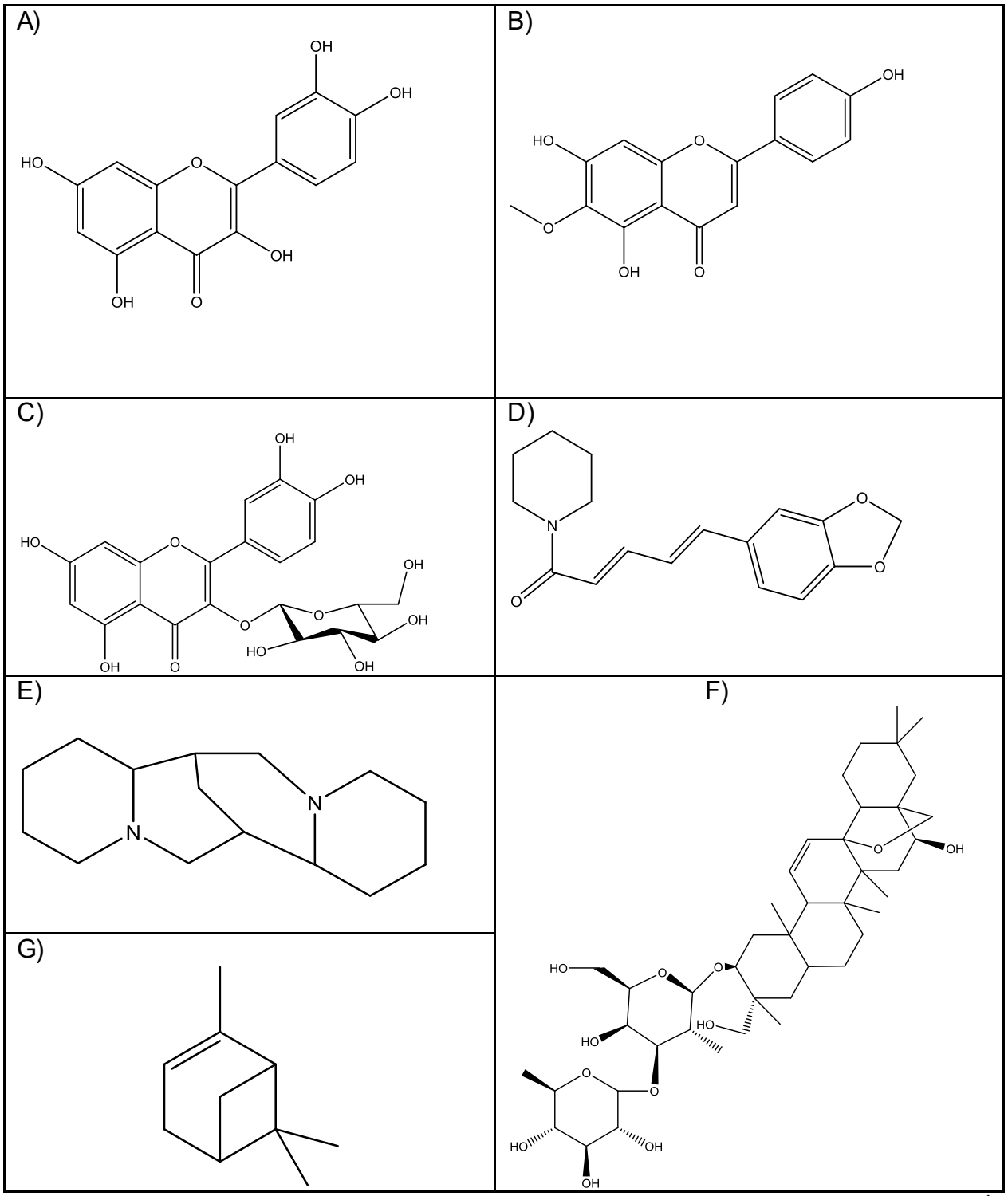

Figure 2.- The structures of secondary metabolites with anticonvulsant activity are observed. A) Quercetin, B) Hispidulin, C) Isoquercitrin, D) Piperine, E) Sparteine, F) Saikosaponin A and G) α-pinene

Table 1. Plants with anticovulsivant activity

Vegetable sources	Extract / Fraction / Isolates	Dose (mg/Kg)	Research animal / animal models	Phytochemical sieve	Proposed mechanisms	Ref.
Acarus gramineus	α-asarone	50-200	Swiss albino mouse and Rat Wistar / MES, LI-PILO (lithium–pilocarpine), PTZ			68
Aegle marmelos	Ethanolic (Leaf)	100, 200	Albino mouse / MES, PTZ	Saponins, tannins, flavonoids	GABAergic activity	69
Alternanthera basiliana (L.)	Methanolic (Leaf)	100, 300, 600	Swiss albino mouse / PTZ, MES	Triterpenes, alkaloids, steroids	GABAergic activity	70
Allium cepa L.	Aqueous (Bulb)	50, 100, 200, 400	Rat and mouse / PTZ, MES	Saponins, tannins, alkaloids, cardiac glycosides	Inhibition mediated by GABA	71
Anethum graveolens	Hydroalcoholic (Leaf)	100, 250, 400	Albino mouse BALB/c / PTZ	D-limonene, D-carvone, quercetin 3-O-beta-D-glucuronide y isoharmentin 3-O-beta-D-glucuronide		72
Annona selegalensis Pers.	Aqueous (Root bark)	200, 300, 400	Rat and mouse / Pilocarpine, picrotoxin	Triterpenes, anthocyanins, glycosides, coumarins, alkaloid flavonids.		73
Artemisia indica Linn	Methanol (Complete plant): Isolates, ursolic acid, carnasol and oleanolic acid	1, 10, 30, 100	Swiss mouse / PTZ	Essential oils, flavonoids, triterpenes, coumarins, phenolic compounds and carotenoids	GABAergic activity	74
Berberis integerrima	Methanolic, Fraction Hydroalcoholic and chloroform (Root)	20, 80, 140, 200	Mouse / PTZ, MES	Alkaloids, flavonoids, tannins and saponins	Inhibition of Ca^{+2} channels	75

Carissa edulis	Fraction and aqueous, ethanolic (Root bark)	150, 300, 600	Swiss albino mouse and Wistar rat / PTZ, MES, Picrotoxin, Strychnine, NMDA, INH (isoniazid), Kindling	Anthraquinones, tannins, flavonoids, carbohydrates and sterols.	Activity on sodium channels	76
Carum carvi L.	Aqueous and essential oil (Seed)	Aqueous: (200, 400, 800, 1600, 3200) essential oil (25, 50, 100, 200, 400)	Albino mouse / PTZ	Tannins, alkaloids, saponins, flavonoids, terpenoids and anthraquinones		77
Coriandrum sativum	Hydroalcoholic, ethyl acetate and n-butanol fraction (Leaf, steamy branch)	25, 100	Wistar rat / PTZ		GABAergic activity	78
Clitoria ternatea Linn.	Ethanolic extract (Leaf)	200, 400	Albino mouse / PTZ, MES			79
Crassula arborescens (Mill)	Methanolic (Leaf)	25, 50, 100, 200	Albino mouse / PTZ, bicuculine, picotroxin, NMDLA (N-methyl-DL-aspartic acid), strychnine	Steroids, saponin, tannins and flavonoids		80
Cichorium intybus	Ethanolic extract (Flower)	125, 250, 500	Rat / MES, PTZ		GABAergic activity	81
Cyperus tegetum Roxb	Methanolic (Rhizome)	250, 500, 750	Swiss albino mouse / PTZ	Alkaloids, Flavonoids, tannins, saponins.	GABAergic activity	82
Erythrina variegata (L.)	Cloroform (Bark and root)	500	Wistar rat and albino mouse/MES, PTZ	Steroids, glycosides, tannins, saponins and flavonoids		83
Feretia apodanthera Del.	Iridoid glycosides: Feretoside, gardenoside, Apodantoside, geneposodic acid, deacetylasperolosidic acid (Stem bark)	15, 30, 60, 90	Albino mouse / PTZ , bicuculine		Increased GABA concentration in the brain	84

Ficus carica L.	Aqueous - acetonic (Aerial parts)	250-500	Swiss albino mouse / PTZ, MES	Psoralen, bergapten, taraxasterol, β-sitosterol, lupeol, β-amyrin, coumarins, xanthotoxin, xanthatoxol, ficusin, tyrosine, and marmesin	Norepinephrine, 5-HT and GABA mediated activity	85
Flemingia strobilifera	Ethanolic extract and ethyl acetate, ether, chloroform and aqueous fraction	200, 400, 600	Swiss albino mouse / PTZ, MES	Steroids, flavonoids, tannins, and carbohydrates		86
Globimetula braunii	Ethyl acetate fraction (Leaf)	75, 150, 300	Swiss albino mouse / PTZ, MES, 4-aminopyrimidine	Saponins, flavonoids, tannins, anthraquinones and steroids	GABAergic interaction, blocked glutamatergic activity or inhibition of Ca^{+2} current	87
Hypericum scabrum L.	Aqueous (Aerial parts)	125, 250 and 500	Swiss albino mouse / PTZ, picrotoxin		GABA or nitric oxide mediated activity	88
Melanthera scandens	Ethanolic and aqueous (Leaf)	250, 500 1000	Wistar rat / PTZ	Phytosterols, glycosides, tannins, phenols, saponins, terpenes and flavonoids	Interaction with GABA transmission	89
Melissa parviflora	Methanolic and Aqueous Extracts (Complete plant)	250, 500	Swiss albino mouse / PTZ, MES	Alkaloids, Flavonoids, Sterols, Glycosides and saponins	GABAergic interaction, glutamatergic interaction or Inhibition of sodium channels	90
Pseudospondiasmicrocarpa	Hydroalcoholic (Leaf)	30, 100, 300	Male mouse ICR		GABAergic, Glycergic, NMDA, K^{+} Channels and GMP Nitric Oxide-Cyclic Activity	91

Nerium oderum	Petroleum ether, Methanolic and Aqueous Extracts. (Flower)	400	Swiss albino mouse and Wistar rat / MES, PTZ		GABAergic interaction	92
Peperomia tetraphylla	Methanolic and chloroformic (Complete plant)	250, 500	Wistar rat / MES	Alkaloids, glycosides, tannin, phenolic compounds, saponins and flavonoids		93
Pinus roxburghii Sarg.	Alcoholic (Stem bark)	100, 300, 500	Wistar rat / MES, PTZ	Bioflavonoids, Chlorogenic Acid, Quercitin and Rutin	Gabergic regulation or on glutamate receptors	94
Piper umbellatum Linn.	Aqueous y Chloroformic fraction (Leaf)	200, 400, 600	Swiss albino mouse / Picotroxin, strychnine	Cardiotonic glycosides, tannins, anthracenes and saponins		95
Taraxacum serotinum	Ethanolic extract (flower)	125, 250, 500	Albina rat/ MES, PTZ		GABAergic regulation or blocking of glutamatergic activity	96
Teucrium polium	Aqueous, Ethanolic and Fractions of petroleum ether, chloroform, ethyl acetate, n-butanol (Aerial parts)	Aqueous: 10, 25, 50 Fraction-es: 25, 50 and 100/ 50, 100 and 200	Mouse NMRI/PTZ, MES	Aqueous extract: Flavonoids and tannins ethanolic extract: terpenoids		97
Tilia americana var.	Methanolic, hexanic and aqueous (Flower)	100, 300, 600	Mouse / PTZ		Flavonoid-mediated activity and its antioxidant effect	98
Rosa damascena	Hydroalcoholic (Flower)	50, 100, 200	Wistar rat / PTZ		Interaction with the GABAergic system	99

Sapindus mukorossi	Aqueous and Methanolic (Fruit)	100, 200, 400	Wistar rat/MES, PTZ	Glycosides, saponins, flavonoids, tannins, phenolic compounds, sterols and steroids		100
Satureja hortensis	Aqueous and Ethanolic (Aerial parts)	200, 400, 600	Swiss albino mouse / PTZ, MES		Interaction with nitric oxide and the GABAA-BZD receptor complex.	101
Swertia corymbosa Griseb	Methanolic (Aerial parts)	125-250, 500	Swiss albino mouse and Wistar rat/PTZ, MES, isoniazid	Gentiopicrosi de and swertianine	Increased GABA levels	102
Viola betonicifolia	Hexanolic (Complete plant)	300, 400, 500	Balb c mouse / PTZ, strychnine		GABAA receptor stimulation	103
Viola tricolor	Hydroalcoholic / Ethyl acetate and n-butanol fractions (Leaf)	100, 200, 400 / 50, 100, 200	Albino mouse	flavonoids, saponins, antiocyanins, coumarins, carotenoids, tannins, salicylic acid, and phenolic acids		104
Abrus Precatorius (Linn.)	Methanolic (Leaf)	200, 400, 800	Albino Swiss mice / PTZ, Picotroxin, strychnine	Alkaloids, tannins, saponins and flavonoids	Modulation of the GABAA receptor-chloride	105
Maerua angolensis DC.	Petroleum ether and ethyl acetate mixture (Bark Extract)	100, 300, 1000	Sprague-Dawley rats / PTZ		Anti-seizure activity by affecting GABAergic and nitric oxide-cGMP pathways	106
Aspilia africana	Dichloromethane (Leaf)	25, 50, 100, 200	Mice/MES, Strychnine, PTZ		GABAergic activity	107