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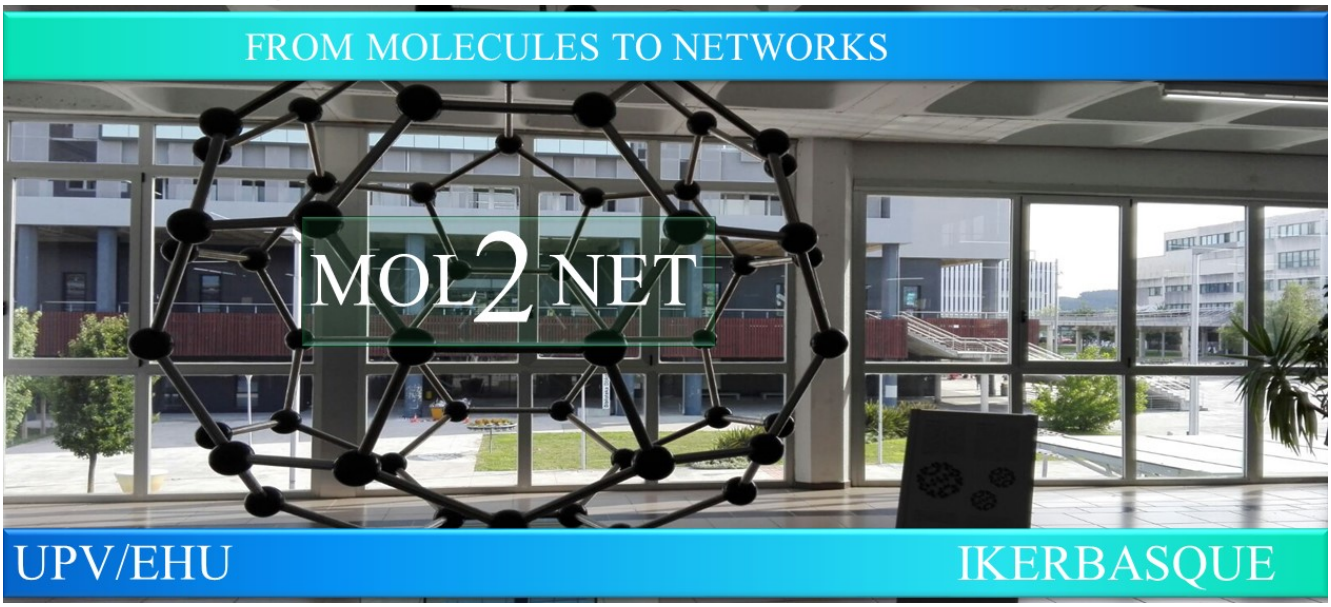

Terpenes activity towards the central nervous system: Perspectives for health

Hélida M. D. S. Almeida[a], Thayanne V. Souza[a], Aleph M. S. Souza[a], Renata C. Feitosa[a], Wellydo K. M. Escarião[a], Alianda M. Cornélio[b], Arnóbio A. da Silva-Júnior[b]**

[a] *Program in Pharmaceutical Sciences, Health Sciences Center, Federal University of Rio Grande do Norte (UFRN), Natal 59012-570, Brazil;*

[b] *Department of Morphology, Federal University of Rio Grande do Norte (UFRN), Natal 59012-570, Brazil;*

* *Correspondence: arnobiosilva@gmail.com; aliandamaira@gmail.com.*

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Graphical Abstract	**Abstract.** *Terpenes are hydrocarbons from secondary metabolism of plants, which have known biological activities (e.g., antimicrobial, antioxidants, chemotherapy, and*

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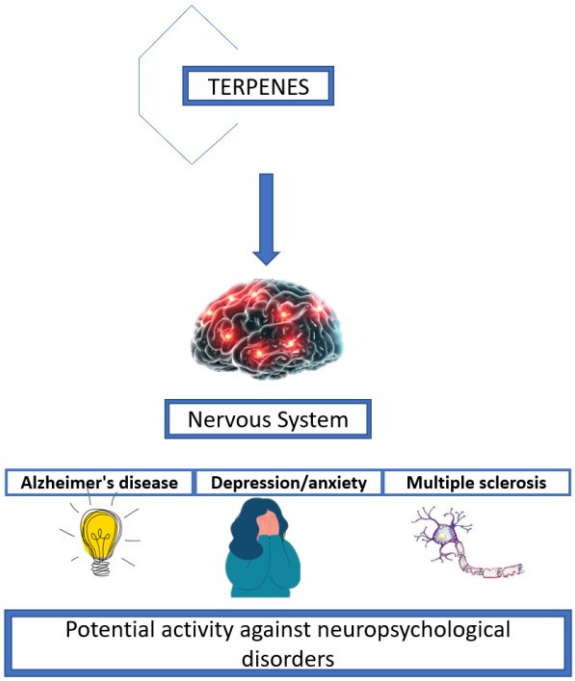

immunomodulatory agents). However, it is necessary to better explore its effects on neuropsychological disorders. This study presents a brief overview of the neuropsychotropic action of terpenes, based on a narrative review using a qualitative descriptive approach. Among the articles found, the most studied applications were for ischemia, seizures, Alzheimer's disease, multiple sclerosis, depression, and anxiety. The action of these terpenes against diseases such as Amyotrophic Lateral Sclerosis, Parkinson's and Huntington's Disease is still a little explored field that needs further studies.

Introduction

The pathological processes related to neuropsychology are gaining space and attention from researchers worldwide due to the increase in dementias and psychological disorders. This reality was intensified due to the pandemic caused by the SARS-CoV-2 virus [1].

Neurological damage and depression are frequently reported among the sequelae of this infection; moreover, social isolation was a factor associated with the emergence and worsening of anxiety disorders. Despite the existence of pharmacological therapies to intervene in these clinical conditions, fear of starting treatment is common. In addition, many of the neurodegenerative disorders are characterized as chronic and progressive, which have no known cure, acting as a disabling factor to the affected individual [1,2].

This whole panorama emphasizes the need for innovative treatments that aim to be more effective and that enable good treatment compliance. The search for natural alternatives as interventions for health problems is nothing new; however, with the advancement of science, new possibilities have been glimpsed. From the isolation of plant metabolites, the potential of molecules could be explored under different perspectives [3,4].

Terpenes are hydrocarbons derived from plant metabolism, which could also be identified as essential oils. Responsible for characteristic aromas and flavors, terpenes are protagonists of biological activity investigations, identified with a broad bioactive spectrum. Their antimicrobial, immunomodulatory, anti-nociceptive potential are described in the scientific literature [4].

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However, it is necessary to explore the effects against neuropsychological disorders, highlighting the need for pharmacological strategies to intervene against diseases of the Central Nervous System. The purpose of this research is to expose a brief panorama on the neuropsychotropic action of terpenes, from a narrative review of the scientific literature [5].

Materials and Methods

- Characterization of the Research

The methodological strategy adopted for this study was a narrative review using a qualitative descriptive approach. This type of study is considered a way of condensing information about a given subject, providing an overview.

Following the protocol, a broad examination of the scientific literature was conducted to collect the main information, focusing on the data published as relevant by the authors. Although not a rigorous method of analysis, steps proposed in the study by Almeida *et al.* [6] were followed to grant greater quality to the methodology. Then, the PICo (Population/Interest/Context) acrogram was used to construct the research guiding question.

- Investigation

Therefore, the question elected for the study was: "what does the scientific literature (P) present about the effect on the central nervous system (I) resulting from the application of terpenes (Co)?" From this point, were elected as search descriptors "neuroprotection"; "antidepressant"; "anticonvulsant"; "neurodegeneration"; "amyotrophic lateral sclerosis" crossed individually with the terms "bisabolol"; "caryophyllene"; "myrcene"; "phytol" that correspond to the nomenclature of terpenes widely present in nature.

Then, a bibliographic search started in November 2022 in databases intended for indexing scientific journals and articles. The keywords used were the combination of previously defined terms separated by the Boolean operator AND. The selection of studies published in the last ten years was prioritized; however, relevant information from a longer period was considered.

- Eligibility Criteria

For selection and eligibility, the works had to portray explicitly in their abstract or title that the manuscript refers to the activity of terpenes against the nervous system, with some neuro- or psych modulatory effect.

Preference for data inclusion was given to works published as scientific articles in English, Portuguese and Spanish. Duplicate articles, or those with insufficient information to answer the research question were excluded from the sample. Then, the selected manuscripts were included in their entirety.

- Data Analysis and Information Synthesis

After the individual analysis of each paper, the construction of the state of the art began, aiming to answer the scope of the review. There was no need to use judges to perform a qualitative treatment of the extracted data, due to the type of methodology chosen, and no need to submit to the research ethics committee.

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Results and Discussion

The growing concern with the pathologies in the neurological and psychiatric field is emphasized in scientific productions and worries researchers all over the world. Therefore, there is a diversity of methodological approaches used to mimic related diseases. Studies with products of natural origin are not new; the consideration of the bioactive potential of plants occurs due to the quantity of biomolecules present in different preparations, among which are the terpenes.

Four terpenes were chosen to guide the investigations, which are widely described and found as constituents of vegetable oils and extracts. **Table 1** contains the information considered pertinent to answering the research scope, describing the terpene, the evaluation objective and the response obtained during the test. In all, 15 scientific works were consulted for the construction of this review.

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Table 1. Characteristics of terpenes and investigations on the Central Nervous System described in the literature.

Terpene	Profile	Evaluation	Effect/Response	Reference
α-(-)-bisabolol	Monocyclic sesquiterpene, insoluble in water. Found in several plants, especially *Matricaria chamomilla.*	Action against ischemia-induced brain damage in mice.	Significantly reduced brain infarction, neurological and aversive memory deficits, decreased MPO and cytochrome c, NF-κB and SOD-2 immunoreactivity.	[7]
			The treatment reduced the infarct area and neurological deficits. It increased cell viability and decreased neuronal degeneration. There was an increase in locomotor activity that was reduced by cerebral ischemia and an improvement in object recognition and aversive memories. It also prevented increased myeloperoxidase activity, TNF-α in the temporal cortex and increased iNOS in both temporal cortex and corpus striatum, and prevented astrogliosis.	[8]
		Antidepressant and anxiolytic evaluation against tests: Open Field, Forced Swim Test, Tail Hanging Test and Sucrose Solution Preference Test, Perforated Plate Test, Elevated Cross Maze and Y Maze Test.	It has antidepressant, anxiolytic and short-term memory effects at doses of 25mg/kg and 50mg/kg, without altering locomotor activity. At the 50mg/kg concentration it was able to reduce malondialdehyde (MDA) levels in the hippocampus and reduce nitrate/nitrite levels in the prefrontal cortex, demonstrating its antioxidant effect.	[9]

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		Effects of α-bisabolol on cognitive deficits and neuronal damage in mice subjected to the model of streptozotocin-induced Alzheimer's disease	Improved deficits in working memory, aversive memory, recognition and spatial memory, with no locomotor changes. Was able to decrease the increase in MDA concentration in the prefrontal cortex. It prevented neuronal neuronal damage and the reduction of synaptophysin expression in the hippocampus, increasing synaptophysin expression.	[10]
β-Caryophyllene	Bicyclic sesquiterpene, found in several oils such as clove and rosemary	To evaluate whether there is an antidepressant-type action in rats, from a model of stress-induced depression.	In the tail suspension test and the forced swim test, chronic stress-induced despair behaviors were reduced by BCP. BCP also ameliorated stress-related changes in hippocampal expression of COX-2, BDNF, and CB2 receptor expression. It improved behavioral and biochemical changes related to chronic stress, and may be effective in treating depression and stress-related mental illness.	[11]
		Acute antidepressant and anxiolytic evaluation through the tests: elevated cross maze, open field, marble burying test, novelty suppressed feeding tests, tail suspension test, and forced swim.	The results indicated that adult mice receiving BCP showed improvement of all parameters observed in the elevated cross maze test.	[12]
		In vitro and *in vivo* immunomodulatory effects of BCP in C57BL/6 mice experimental autoimmune encephalomyelitis (EAE), for multiple sclerosis study.	EAE mice, treated orally with BCP (mainly at 50mg/kg/day), showed cytokine levels and clinical signs similar to animals without disease. Treatment significantly reduced the number of inflammatory infiltrates and attenuated neurological damage.	[13]
		Evaluate neuroprotective effect on cerebral ischemia-reperfusion injury through inhibition of	BCP alleviates ischemic brain damage potentially by inhibiting necroptotic neuronal death and the	[14]

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		necroptotic cell death and inflammation. *In vitro* tests: neuronal damage, type of neuronal death and mixed lineage kinase domain protein expression. *In vivo* tests: Neurological dysfunction, brain infarct volumes, cell death, cytokine levels, central necroptosis molecules, and HMGB1-TLR4 signaling.	inflammatory response. This study suggests a novel application for BCP as a neuroprotective agent.	
		Evaluate the effect of β-caryophyllene against pentylenetetetrazole-induced seizures. In addition, investigate the effect of β-caryophyllene on behavioral parameters and oxidative stress induced by seizures.	β-caryophyllene increased the latency for PTZ-induced myoclonic jolts.	[15]
		Systematic review of the neuropharmacological activities of β-caryophyllene	It exhibits a protective role in several nervous system related disorders, including pain, anxiety, spasm, seizure, depression, alcoholism, and Alzheimer's disease. In addition, it has local anesthetic activity and can act as an immunomodulating agent.	[16]
Myrceno	Unsubstituted acyclic, olefinic monoterpene that occurs naturally in a large number of plant species, such as lemongrass and citrus fruits	Effects of β-myrcene (MYR) on oxidative and histological damage in brain tissue caused by global cerebral ischemia/reperfusion (I/R) in mice	MYR treatment protected against the oxidative effects of I/R by inducing significant increases in GSH, GPx, and SOD and a significant decrease in TBARS formation. In addition, brain I/R increased the incidence of histopathological damage and apoptosis in brain tissue, but these neurodegenerative effects were eliminated by MYR treatment. This study demonstrated that MYR	[17]

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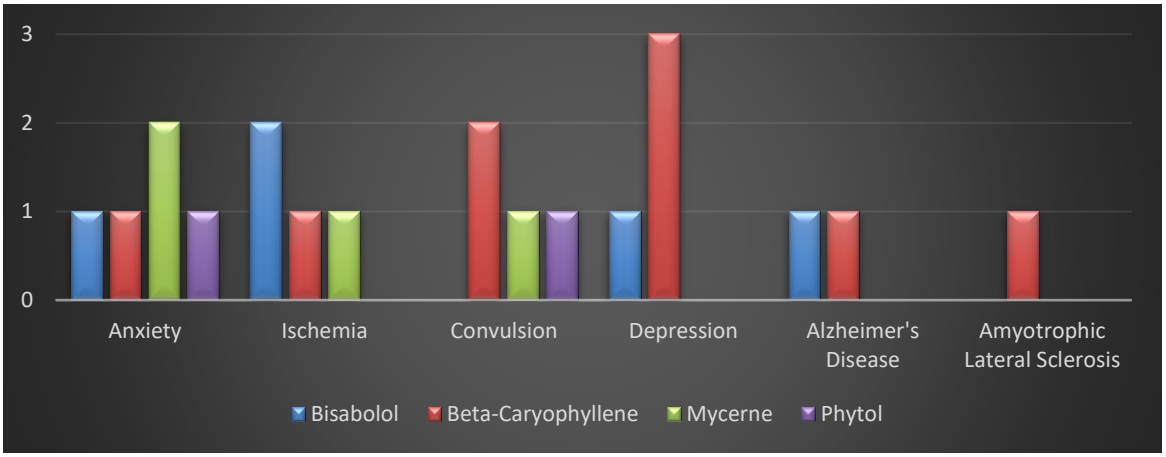
			effectively attenuates oxidative and histological damage in the brain caused by global I/R.	
		To identify the central effects of myrcene in rats, by the tests: open field. Route rod, sleep latency time, elevated cross maze.	It has sedative and relaxing effects.	[18]
		Neurobehavioral study of the effect of beta-myrcene in rodents: exploratory and emotional behavior, anxiolytic activity in a cross maze and inhibition of conditioned avoidance and seizure by PTZ.	beta-myrcene does not have anxiolytic activity similar to benzodiazepines and that a central nervous system activity (antidepressant or antipsychotic) is unlikely	[19]
Phytol	Diterpene originating from the degradation of chlorophyll-a, precursor for the synthetic manufacture of vitamin E and vitamin K1	Evaluate the anticonvulsant activity of phytol *in vivo* by pilocarpine-induced seizures.	Increased latency of the first crisis, decreased mortality rate.	[20]
		To evaluate the anxiolytic effects of phytol in animal models: open field, elevated cross maze, rota-rod, light-dark, marble burying, and pentobarbital sleep time tests	Acute doses of phytol exert anxiolytic effect in mice by interacting with the GABAergic system. Probably phytol interacts with the GABA-A receptor, in the receptor subtypes that mediate the effects of benzodiazepines, to produce sedative and anxiolytic activities.	[21]

As the evaluation of more than one condition was performed in a single article, the frequency in which each circumstance was studied was observed. We counted six distinct purposes present in the analyzed studies. Investigations about the anxiolytic effect prevailed, about 25% (n = 05) of the reports, including all the elected terpenes. Data are schematized in **Figure 1.**

Figure 1. Conditions analyzed with researches involving the chosen terpenes



The data reveal few studies involving terpenes against clinical conditions such as Alzheimer's disease and Amyotrophic Lateral Sclerosis. This data is noteworthy, as more studies were expected, as these diseases are increasingly prevalent. Furthermore, there is still no known cure, and the treatments only slow down the evolution of the disease and ease the symptoms. There is a negative repercussion on the patients quality of life, due to increased morbidity and reduced life expectancy after diagnosis. This scenario represents a high economic cost for patients and for the public system [22-23].

Moreover, degenerative disorders are commonly accompanied by psychopathologies, depression, anxiety, and delusions being the most frequent. However, psychological disorders are not restricted to this public, affecting people regardless of ethnicity, gender, social/economic status, being a reason for cognitive impairment in contemporary society, including young people. The psychic illness and the genesis of neurodegeneration have a relationship not yet fully clarified, however, mechanisms involving oxidative stress in the central nervous system are referenced as a possibility, as occurs in cases of epileptic seizures [24-25].

Thus, research envisioning new strategies for the treatment of these clinical conditions is of great relevance today. The data presented in Table I denote the promising potential of these biomolecules in the face of the exposed problems. However, the low adherence to treatment motivated by social stigma, the impossibility of cure, and undesirable effects of pharmacological therapy emphasize the need for less aggressive and more effective alternatives [26].

Conclusions

There are a range of studies involving biological investigations for clinical application of plant-derived bioactives, including terpenes. This field of research is attractive to researchers worldwide. This narrative review conducted a brief survey of the scientific literature focusing on neuropsychiatric disorders, revealing terpenes as a possible candidate for use in therapy. The achievements encorage to follow with studies exploring their potential applications in neurodegenerative diseases such as Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease.

References

1. Silva, F. S. C. A. D., Bucur, A., Rosado, S. N., Balhana, S. D. S., & Meneses-Oliveira, C. M. Disfunção neurológica associada à COVID-19. *Rev Bras Ter Intensiva* **2021**, *33*, 325-325.
2. De Falco, A., Cukierman, D. S., Hauser-Davis, R. A., & Rey, N. A. Alzheimer's disease: etiological hypotheses and treatment perspectives. *Quim. Nova* **2016**, *39*(1), 63-80.
3. Cunha, M. D. F., & Gandini, R. D. C. Adesão e não-adesão ao tratamento farmacológico para depressão. *Psicol.: Teor. Pesqui.* **2009**, *25*, 409-418.
4. Faustino, T. T., Almeida, R. B. D., & Andreatini, R. (2010). Plantas medicinais no tratamento do transtorno de ansiedade generalizada: uma revisão dos estudos clínicos controlados. *Braz J Psychiatry* **2010**, *32*, 429-436.
5. Yang, W., Chen, X., Li, Y., Guo, S., Wang, Z., & Yu, X. Advances in pharmacological activities of terpenoids. *Nat. Prod. Commun.* **2020**, *15*(3), 1934578X20903555.
6. Almeida, H. M. D. E. S., Brandão, L. B. S., de Melo, T. R., & Ferreira, S. B. Anti-Bacterial Perspective of Non-Antibiotic Drugs. In Proceedings of the 2nd International Electronic Conference on Antibiotics—Drugs for Superbugs: Antibiotic Discovery, Modes of Action and Mechanisms of Resistance, 15–30 June **2022**. Medical Sciences Forum. Online Conference, 15–30 June 2022.
7. Fernandes, M. Y. S. D., da Silva, A. T. A., Bezerra, J. R., Pires, R. C., Mendonca, R. C., & de Andrade, G. M. (−)-α-Bisabolol Promotes Neuroprotection on Neuronal Damage, Motor and Memory Deficits Induced by Focal Cerebral Ischemia in Mice. *FASEB J* **2019**, *33*(S1), 500-6.
8. Fernandes, M. Y. D., do Carmo, M. R. S., Fonteles, A. A., de Sousa Neves, J. C., da Silva, A. T. A., Pereira, J. F., ... & de Andrade, G. M. (-)-α-bisabolol prevents neuronal damage and memory deficits through reduction of proinflammatory markers induced by permanent focal cerebral ischemia in mice. Eur. J. Pharmacol. **2019**, *842*, 270-280.
9. Rebouças, M. D. O. (**2019**). Efeito antidepressivo do (-)-α-bisabolol em camundongos C57BL/6 submetidos a um modelo de estresse crônico imprevisível. Master's degree, Federal University of Ceará, Ceará–Brazil, July 19, 2019.
10. Bezerra, J. R. (**2019**). O α-bisabolol protege camundongos da perda neuronal e déficits cognitivos em modelo animal de doença de Alzheimer esporádica induzido por estreptozotocina. Master's degree, Federal University of Ceará, Ceará–Brazil, July 19, 2019.
11. Hwang, E. S., Kim, H. B., Lee, S., Kim, M. J., Kim, K. J., Han, G., ... & Park, J. H. Antidepressant-like effects of β-caryophyllene on restraint plus stress-induced depression. *Behav. Brain Res.* **2020**, *380*, 112439.
12. Bahi, A., Al Mansouri, S., Al Memari, E., Al Ameri, M., Nurulain, S. M., & Ojha, S. β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. *Physiol. Behav.* **2014**, *135*, 119-124.
13. Fontes, L. B., Dias, D. D. S., Aarestrup, B. J., Aarestrup, F. M., Da Silva Filho, A. A., & do Amaral Corrêa, J. O. β-Caryophyllene ameliorates the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. *Biomed. Pharmacother.* **2017**, *91*, 257-264.
14. Yang, M., Lv, Y., Tian, X., Lou, J., An, R., Zhang, Q., ... & Dong, Z. Neuroprotective effect of β-caryophyllene on cerebral ischemia-reperfusion injury via regulation of necroptotic neuronal death and inflammation: in vivo and in vitro. *Front. Neurol.* **2017**, *11*, 583.

15. de Oliveira, C. C., de Oliveira, C. V., Grigoletto, J., Ribeiro, L. R., Funck, V. R., Grauncke, A. C. B., ... & Oliveira, M. S. Anticonvulsant activity of β-caryophyllene against pentylenetetrazol-induced seizures. *Epilepsy Behav.* **2016**, *56*, 26-31.
16. Machado, K. D. C., Islam, M. T., Ali, E. S., Rouf, R., Uddin, S. J., Dev, S., ... & Melo-Cavalcante, A. A. D. C. A systematic review on the neuroprotective perspectives of beta-caryophyllene. *Phytother Res* **2018**, *32*(12), 2376-2388.
17. Ciftci, O., Oztanir, M. N., & Cetin, A. Neuroprotective effects of β-myrcene following global cerebral ischemia/reperfusion-mediated oxidative and neuronal damage in a C57BL/J6 mouse. *Neurochem. Res.* **2014**, *39*(9), 1717-1723.
18. Do Vale, T. G., Furtado, E. C., Santos Jr, J. G., & Viana, G. S. B. (2002). Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from Lippia alba (Mill.) NE Brown. *Phytomedicine* **2002**, *9*(8), 709-714.
19. Da-Silva, V. A., De-Freitas, J. C., Mattos, A. P., Paiva-Gouvea, W., Presgrave, O. A., Fingola, F. F., ... & Paumgartten, F. J. (1991). Neurobehavioral study of the effect of beta-myrcene on rodents. *Braz. J. Med. Biol.* **1991**, *24*(8), 827-831.
20. 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. *Neurosci. Lett.* **2012**, *523*(2), 115-118.
21. Costa, J. P., de Oliveira, G. A. L., de Almeida, A. A. C., Islam, M. T., de Sousa, D. P., & de Freitas, R. M. (2014). Anxiolytic-like effects of phytol: possible involvement of GABAergic transmission. *Brain Res.* **2014**, *1547*, 34-42.
22. Deuschl, G., Beghi, E., Fazekas, F., Varga, T., Christoforidi, K. A., Sipido, E., ... & Feigin, V. L. (2020). The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. *Lancet Glob. Health* **2020**, *5*(10), e551-e567.
23. Calderón-Garcidueñas, L. (2022). Common Fatal Neurodegenerative Diseases Revisited: Beyond Age, Comorbidities, and Devastating Terminal Neuropathology There Is Hope With Prevention. *Front. Neurol.* **2022**, 854.
24. Zenki, K. C., Kalinine, E., Zimmer, E. R., Dos Santos, T. G., Mussulini, B. H. M., Portela, L. V. C., & de Oliveira, D. L. Memantine decreases neuronal degeneration in young rats submitted to LiCl-pilocarpine-induced status epilepticus. *Neurotoxicology* **2018**, *66*, 45-52.
25. Lêdo, S., Leite, A., Souto, T., Dinis, M. A. P., & Sequeiros, J. Depression as the middle-and long-term impact for pre-symptomatic testing of late-onset neurodegenerative disorders. *Temas psicol.* **2016**, *24*(2), 579-594.
26. Cardoso, A., Byrne, M., & Xavier, M. Adesão ao tratamento nas perturbações psiquiátricas: o impacto das atitudes e das crenças em profissionais de serviços de psiquiatria e saúde mental em Portugal. Parte I: aspetos conceptuais e metodológicos. *Rev. Port. de Saude Publica* **2016**, *34*(3), 209-219.