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NATURAL PRODUCTS IN THE TREATMENT OF NEUROLOGICAL DISEASES (PART 1): CANNABINOIDS AND GINGER EXTRACTS

Maria Clara Ferrazani Santos[1], Leonardo Baptista[2*]

[1]*Programa de Pós-Graduação em Química, Instituto de Química, Universidade do Estado do Rio de Janeiro – Brazil;* mariaclaraferrazani@outlook.com

[2]*Departamento de Químcia e Ambiental, Faculdade de Tecnologia, Universidade do Estado do Rio de Janeiro - Brazil*; leobap@gmail.com

Abstract: This short review shows the potential applications of *Cannabis* and *Ginger* extracts as potential drugs for brain disease. We focus mainly on the treatment of Alzheimer's, Parkinson's, and epilepsy diseases. All studied extracts are inhibitors of acetylcholinesterase and pose as promising candidates for treating these diseases.

Keywords: Brain disease; Cannabis; Ginger; Drug development

1. Introduction

Extracts obtained from natural products have been recognized as well-suited for preventing or treating neurological diseases. Molecules extracted from ginger and cannabis sativa represent potential drugs against Parkinson's, Alzheimer's, and epilepsy diseases. The formulation and posology of these drug candidates should be studied in order to use these molecules as medication. One alternative is the formation of inclusion complexes between macrocycles and these molecules, changing their physical, chemical, and pharmacological properties [1,2].

2. Current treatments

The medications currently used to treat Alzheimer's disease are tacrine, donepezil, rivastigmine, galantamine, and memantine [3–6]. Alzheimer's patients have reduced levels of the neurotransmitter acetylcholine [3,5]. The enzyme acetylcholinesterase is responsible

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for hydrolyzing this neurotransmitter, therefore, the inhibition of this enzyme is a promising strategy for the treatment of Alzheimer's.

Most treatments for Parkinson's disease are based on replenishing dopamine levels through dopamine precursors (L-DOPA). Dopaminergic agonist medications can also be used, such as amantadine, apomorphine, bromocriptine, lisuride, cabergoline, pergolide, pramipexole, ropinirole, and rotigotine. However, treatments with these medications only promise symptom relief. The combination of current medicines with natural products is an interesting strategy for reducing clinical complications and premature neurodegeneration, also improving dopaminergic neurotransmission [7, 8]. New pharmacological treatments for epilepsy are welcome because 30% of epileptic seizures do not respond to available treatments.

3. Cannabinoids as an alternative treatment for neurological diseases

The main components of *Cannabis Sativa* are delta-9-tetrahydrocannabinol, responsible for the plant's psychoactive effects, and cannabidiol (CBD) (Figure 1), the main non-psychotropic compound in Cannabis [9–12].

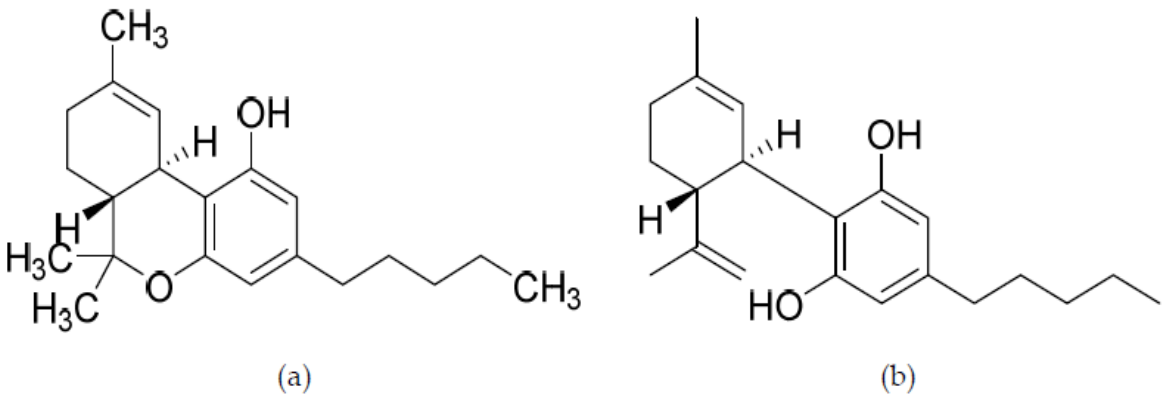

Figure 1. Chemical structures of (a) Δ9-tetrahydrocannabinol and (b) cannabidiol [11,13].

CBD has stood out due to its wide spectrum of pharmacological properties, such as analgesic, immunosuppressive, anticonvulsant, and antipsychotic properties [14]. For these reasons, the scientific community has been testing it for the treatment of ischemia, diabetes

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[14,15], nausea, and cancer symptoms. Also, it can be used to treat anxiety, sleep and movement disorders, depression, psychosis, and epilepsy [12,16,17]. Among the benefits of its administration, the absence of toxic side effects is remarkable due to the non-development of tolerance, dependence, or abstinence crise. As CBD can prevent brain damage, it can be a promising alternative for epileptic patients who do not respond to the current treatments [18,19].

THC can be used as an oral analgesic and can stimulate appetite and maintain weight in cancer or HIV-positive patients. Furthermore, its use can alleviate nausea caused by chemotherapy treatments [13,20–22].

4. Natural compounds extracted from ginger as an alternative treatment for neurological diseases

There are compounds present in ginger extracts that have been described as potential drugs against Alzheimer's [1,2,23]. Patients treated with Ginkgo biloba extract showed similar results to patients treated with donepezil (Figure 2a), a medication currently used to treat Alzheimer's, an inhibitor of the acetylcholinesterase enzyme [5,13].

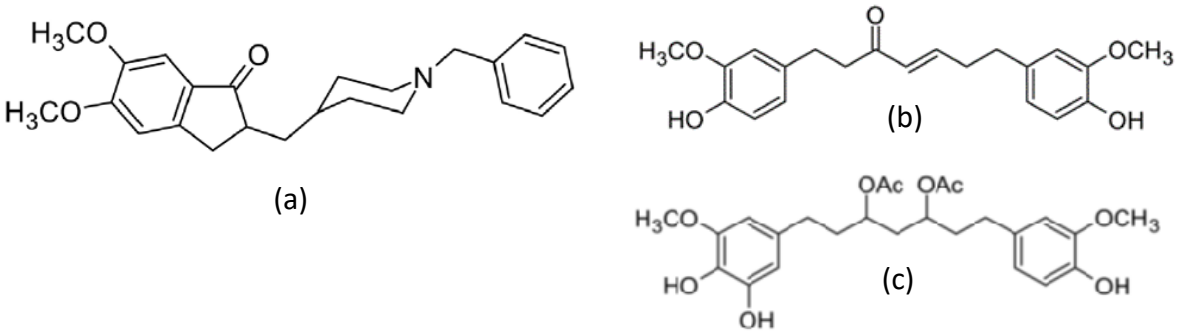

Figure 2. Chemical structure of a) donepezil**;** b) (E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hept-4-en-3-one; and c) 1-(3,4-dihydroxy-5-methoxyphenyl) diacetate -7-(4-hydroxy-3-ethoxyphenyl)heptane-3,5-diyl, respectively [1, 2].

Studies have confirmed that (E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hept-4-en-3-one (Figure 2b) and 1-(3,4-dihydroxy-5-methoxyphenyl)-7 diacetate -(4-hydroxy-3-

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ethoxyphenyl)heptane-3,5-diyl (Figure 2c), are potential acetylcholinesterase inhibitors and may be as effective as donepezil [13,24].

Other promising natural products can be extracted from Brazilian plants such as *Paullinia cupana* (guaraná) [25,26] and *Amburana cearensis* (cumaru) [27], and *Mentha piperita* [28], which also showed promising results in terms of inhibiting acetylcholinesterase

5. Final Considerations

The natural products listed in this short review are promising medicines for preventing and treating Alzheimer's, Parkinson's, and epilepsy. Notably, certain cannabinoids have already been employed in the treatment of the listed neurological diseases.. Also, more efficient drugs with lower side effects should be developed. It is suggested that the formation of inclusion complexes can be an exciting strategy to improve these natural products' physical, chemical, and pharmacological properties, which will be addressed in the next article.

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References

[1] T. Cuya, L. Baptista, T. C. C. França, and T. Celmar Costa França, "A molecular dynamics study of components of the ginger (Zingiber officinale) extract inside human acetylcholinesterase: implications for Alzheimer disease," *J. Biomol. Struct. Dyn.*, vol. 36, no. 14, pp. 3843–3855, Oct. 2018, doi: 10.1080/07391102.2017.1401004.

[2] R. Vasquez, J. Vento, T. C. Costa França, and T. Cuya, "Ginger (Zingiber officinale) components as alternative for inhibition of the human dopamine receptor D2: a computational approach," *Mol. Simul.*, vol. 48, no. 8, pp. 672–686, May 2022, doi: 10.1080/08927022.2022.2045015.

[3] P. A. Nogara *et al.*, "Virtual Screening of Acetylcholinesterase Inhibitors Using the Lipinski's Rule of Five and ZINC Databank," *Biomed Res. Int.*, vol. 2015, no. 1, p. 870389, Jan. 2015, doi: 10.1155/2015/870389.

[4] N. Singh, V. Pillay, and Y. E. Choonara, "Advances in the treatment of Parkinson's disease," *Prog. Neurobiol.*, vol. 81, no. 1, pp. 29–44, Jan. 2007, doi: 10.1016/j.pneurobio.2006.11.009.

[5] G. Marucci, M. Buccioni, D. D. Ben, C. Lambertucci, R. Volpini, and F. Amenta, "Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease," *Neuropharmacology*, vol. 190, p. 108352, Jun. 2021, doi: 10.1016/j.neuropharm.2020.108352.

[6] H. A. Fink *et al.*, "Benefits and harms of prescription drugs and supplements for treatment of clinical Alzheimer-type dementia: A systematic review and meta-analysis," *Ann. Intern. Med.*, vol. 172, no. 10, pp. 656–668, May 2020, doi: 10.7326/M19-3887/ASSET/IMAGES/M193887FF7_APPENDIX_FIGURE_7_FOREST_PLOTS_FOR_DRUG_TREATMENT_ANTIDEPRESSANT_DRUGS_VS_PLACEBO.JPG.

[7] N. Umek, B. Geršak, N. Vintar, M. Šoštarič, and J. Mavri, "Dopamine Autoxidation Is Controlled by Acidic pH," *Front. Mol. Neurosci.*, vol. 11, p. 467, Dec. 2018, doi: 10.3389/fnmol.2018.00467.

[8] N. Ammal Kaidery, S. Tarannum, and B. Thomas, "Epigenetic Landscape of Parkinson's Disease: Emerging Role in Disease Mechanisms and Therapeutic Modalities," *Neurotherapeutics*, vol. 10, no. 4, pp. 698–708, Oct. 2013, doi: 10.1007/S13311-013-0211-8.

[9] A. Hazekamp and R. Verpoorte, "Structure elucidation of the tetrahydrocannabinol complex with randomly methylated β-cyclodextrin," *Eur. J. Pharm. Sci.*, vol. 29, no. 5, pp. 340–347, Dec. 2006, doi: 10.1016/J.EJPS.2006.07.001.

[10] V. A. N. Bragança *et al.*, "Impact of conformational and solubility properties on psycho-activity of cannabidiol (CBD) and tetrahydrocannabinol (THC)," *Chem. Data Collect.*, vol. 26, p. 100345, Apr. 2020, doi: 10.1016/J.CDC.2020.100345.

[11] R. Vasquez, L. Batista, and T. Cuya, "Computational Study on the Enzyme–Ligand Relationship between Cannabis Phytochemicals and Human Acetylcholinesterase: Implications in Alzheimer's Disease," *J. Phys. Chem. B*, vol. 127, no. 41, pp. 8780–8795, Oct. 2023, doi: 10.1021/acs.jpcb.3c04315.

[12] W. M. Raup-Konsavage, "Special Issue: Therapeutic Potential for Cannabis and Cannabinoids," *Biomedicines*, vol. 11, no. 3, p. 902, Mar. 2023, doi: 10.3390/biomedicines11030902.

[13] H. Li *et al.*, "Overview of cannabidiol (CBD) and its analogues: Structures, biological activities, and neuroprotective mechanisms in epilepsy and Alzheimer's disease," *Eur. J. Med. Chem.*, vol. 192, p. 112163, Apr. 2020, doi: 10.1016/J.EJMECH.2020.112163.

[14] N. Patil, V. Chandel, A. Rana, M. Jain, and P. Kaushik, "Investigation of Cannabis sativa Phytochemicals as Anti-Alzheimer's Agents: An In Silico Study," *Plants*, vol. 12, no. 3, p. 510, Jan. 2023, doi: 10.3390/plants12030510.

[15] J. Zhang *et al.*, "The pharmacology and therapeutic role of cannabidiol in diabetes," *Exploration*, vol. 3, no. 5, p. 20230047, Oct. 2023, doi: 10.1002/EXP.20230047.

[16] K. A. Jadoon *et al.*, "Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study," *Diabetes Care*, vol. 39, no. 10, pp. 1777–1786, Oct. 2016, doi: 10.2337/DC16-0650.

[17] D. Baker, G. Pryce, G. Giovannoni, and A. J. Thompson, "The therapeutic potential of cannabis," *Lancet Neurol.*, vol. 2, no. 5, pp. 291–298, May 2003, doi: 10.1016/S1474-4422(03)00381-8.

[18] J. Wu, "Cannabis, cannabinoid receptors, and endocannabinoid system: yesterday, today, and tomorrow," *Acta Pharmacol. Sin.*, vol. 40, no. 3, pp. 297–299, Mar. 2019, doi: 10.1038/s41401-019-0210-3.

[19] M. R. Cilio, E. A. Thiele, and O. Devinsky, "The case for assessing cannabidiol in epilepsy," *Epilepsia*, vol. 55, no. 6, pp. 787–790, Jun. 2014, doi: 10.1111/EPI.12635/SUPPINFO.

[20] B. McCoy *et al.*, "A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome," *Ann. Clin. Transl. Neurol.*, vol. 5, no. 9, pp. 1077–1088, Sep. 2018, doi: 10.1002/ACN3.621.

[21] M. Haupts, C. Vila, A. Jonas, K. Witte, and L. Álvarez-Ossorio, "Influence of Previous Failed Antispasticity Therapy on the Efficacy and Tolerability of THC:CBD Oromucosal Spray for Multiple Sclerosis Spasticity," *Eur. Neurol.*, vol. 75, no. 5–6, pp. 236–243, Jul. 2016, doi: 10.1159/000445943.

[22] C. Konrad *et al.*, "Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey," *Anesthesiol. Res. Pract.*, vol. 2009, no. 1, p. 827290, Jan. 2009, doi: 10.1155/2009/827290.

[23] T. Cuya and T. C. C. França, "A molecular modeling study of components of the ginger (Zingiber officinale) extract inside human butyrylcholinesterase: implications for Alzheimer disease," *J. Biomol. Struct. Dyn.*, vol. 38, no. 9, pp. 2809–2815, Jun. 2020, doi: 10.1080/07391102.2019.1644198.

[24] S. Lovestone, N. Graham, R. Howard, and G. K. Wilcock, "Guidelines on drug treatments for Alzheimer's disease.," *Lancet (London, England)*, vol. 350, no. 9073, pp. 232–3, Jul. 1997, doi: 10.1016/S0140-6736(05)62221-0.

[25] L. P. Arantes, D. C. Zamberlan, M. L. Machado, and F. A. A. Soares, "Guarana (Paullinia cupana Kunth): Applications to Alzheimer's disease and dementias," *Treat. Nutraceuticals, Suppl. Herb. Med. Neurol. Disord.*, pp. 3–19, Jan. 2023, doi: 10.1016/B978-0-323-90052-2.00021-4.

[26] J. I. A. O. Zhilin and G. A. O. Xuemei, "Potential targets and mechanisms of Guarana in the treatment of Alzheimer's disease based on network pharmacology," *Digit. Chinese Med.*, vol. 6, no. 1, pp. 55–66, Mar. 2023, doi: 10.1016/J.DCMED.2023.02.005.

[27] L. G. de Souza, M. N. Rennã, and J. D. Figueroa-Villar, "Coumarins as cholinesterase inhibitors: A review," *Chem. Biol. Interact.*, vol. 254, pp. 11–23, Jul. 2016, doi: 10.1016/J.CBI.2016.05.001.

[28] M. Srief *et al.*, "Evaluation of In Vitro and In Silico Anti-Alzheimer Potential of Nonpolar Extracts and Essential Oil from Mentha piperita," *Foods*, vol. 12, no. 1, p. 190, Jan. 2023, doi: 10.3390/FOODS12010190/S1.

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