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Investigation of molecular mechanisms of cannabinoids with neuromodulator activity using *in silico* tools

Investigação de mecanismos moleculares de canabinóides com atividade neuromoduladora usando ferramentas in silico

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Abstract

This work aims to complement the investigations of the molecular mechanisms of cannabinoids and their receptors, elucidating molecular targets that explain the effect of chemical compounds present in Cannabis sativa on central neuromodulation through in silico methods. Cannabis sativa metabolites were collected bibliographically, and the coding of molecules to perform the predictions were obtained from the PubChem website. Bioactivity screening was then performed with SwissADME, ProToxII, PASS, and Molinspiration programs and target search with SuperPred Webserver servers. After target identification, the selected structure was obtained from the Protein Data Bank (PDB) site for molecular docking with the GOLD program. Cannabis sativa metabolites had their physicochemical and biological properties analyzed. The targets for molecular docking were identified and verified for each compound, with their respective structures crystallized in the Protein Data Bank (PDB). The tetrahydrocannabivarin (THCV) molecule was selected because it predicted interaction with the N-arachidonylglycine receptor (PDB ID: 4UUQ). Docking reveals a potential interaction of THCV with the N-arachidonylglycine receptor. Furthermore, the binding structure of this study showed pharmacophoric alignment with the five most potent molecules capable of antagonizing the monoglycerate lipase receptor. TCHV docking showed anchoring of this molecule in the active site of the N-arachidonylglycine receptor due to the activities of this species. Thus, this marker could act as an antagonist of this receptor, behaving as an active metabolite with neuromodulatory activity through a possible alteration of microglial activity in the central nervous system, which may act as a therapeutic agent in neurodegenerative pathologies.

Keywords: *Cannabis sativa; central nervous system; Tetrahydrocannabivarin.*

Resumo

Este trabalho visa complementar as investigações dos mecanismos moleculares dos canabinóides e seus receptores, elucidando alvos moleculares que explicam o efeito dos compostos químicos presentes na Cannabis sativa na neuromodulação central através de métodos in silico. Os metabólitos da Cannabis sativa foram coletados bibliograficamente, e a codificação das moléculas para realizar as predições foi obtida no site PubChem. A triagem de bioatividade foi então realizada com os programas SwissADME, ProToxII, PASS e Molinspiration e a busca de alvos com servidores SuperPred Webserver. Após a identificação do alvo, a estrutura selecionada foi obtida do site Protein Data Bank (PDB) para docking molecular com o programa GOLD. Os metabólitos da Cannabis sativa tiveram suas propriedades físico-químicas e biológicas analisadas. Os alvos de docking molecular foram identificados e verificados para cada composto, com suas respectivas estruturas cristalizadas no Protein Data Bank (PDB). A molécula de tetrahidrocanabivarina (THCV) foi selecionada porque previu interação com o receptor de N-araquidonilglicina (PDB ID: 4UUQ). O docking revela potencial interação do THCV com o receptor N-araquidonilglicina. Além disso, a estrutura de ligação deste estudo mostrou alinhamento farmacofórico com as cinco moléculas mais potentes capazes de antagonizar o receptor de monoglicerato lipase. O docking do TCHV mostrou ancoragem desta molécula no sítio ativo do receptor

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N-araquidonilglicina devido às atividades desta espécie. Assim, esse marcador poderia atuar como um antagonista desse receptor, comportando-se como um metabólito ativo com atividade neuromodulatória por meio de uma possível alteração da atividade microglial no sistema nervoso central, que pode atuar como agente terapêutico em patologias neurodegenerativas.
Palavras-chave: *Cannabis sativa; sistema nervosos central; Tetrahidrocabivarina.*

Introduction

The species known as "marijuana", "ganja" or "hemp", is among the oldest plants that have been cultivated and exploited by mankind for its numerous properties and uses such as obtaining fiber, food, and medicine, also thanks to its adaptability in a wide range of habitats[1].

Medicines based on cannabis extracts are produced for different therapeutic indications such as Alzheimer[2], neuropathic pain in multiple sclerosis[3] and in rheumatoid arthritis[4], schizophrenia[5], Parkinson[6], and epilepsy[7], sometimes constituting the only therapeutic alternative in the control of severe and incurable diseases.

Regarding botanical aspects, the species *C. sativa* is a dioecious annual plant, rarely monoecious, rich in trichomes, epidermal glandular protrusions that cover the leaves, bracts, and stems of the plant[8]. These glandular trichomes involve metabolites such as phytocannabinoids, which are responsible for the defense and interaction with herbivores and pests, together with terpenoids, which generate the typical aroma of *C. sativa*[9]. It is worth noting that dioecy facilitates genetic variability and consequently the plant's adaptability to different habitats since it requires that reproduction be made in other plants.

C. sativa is characterized by a chemical complex, including terpenes, carbohydrates, fatty acids, and their esters, amides, amines, phytosterols, phenolic compounds, and the specific compounds of this plant, namely, cannabinoids[9]. Cannabinoids are meroterpenoids, obtained from the alkylation of an alkylresorcinol with a monoterpene[10]. They are mainly synthesized in glandular trichomes, which are more abundant in female inflorescences[9].

More than 100 cannabinoids have been isolated, characterized, and divided into 11 chemical classes. Typically, the most abundant cannabinoids present in drug-type plants are Δ-tetrahydrocannabinolic acid (Δ9-THCA) and Δ9-tetrahydrocannibinol (Δ9-THC). In contrast, fiber-type plants are known to contain mainly cannabinoid acids, such as cannabidiolic acid (CBDA) and cannabigerolic acid (CBGA), followed by cannabidiol (CBD) and cannabigerol (CBG)[11,12]. Other minor cannabinoids include cannabichromenic acid (CBCA), cannabichromene (CBC), cannabinolic acid (CBNA), and cannabinol (CBN), with the latter two being the oxidative degradation products of Δ9-THCA and Δ9-THC, respectively, present in Aged cannabis.

The pharmacological effects are attributed to the interaction of cannabinoids with their receptors distributed in the central nervous system (CB1) and peripheral (CB2)[13]. Δ9 -THC binds to CB1 and CB2 receptors, acting as a partial agonist, exerting a mixed neural activity, excitatory and inhibitory, in different areas of the brain, showing that it does not affect only on specific cannabinoid receptors[14].

In this sense, endocannabinoids (ECS) appear like a complex and widespread brain signaling in the nervous system that plays a role in affective and cognitive functions and in psychotic disorders and may be the target for the act of various therapeutic compounds. The elucidation of ECS also sheds light on the human fascination with cannabis, which appears to be the only plant that produces a potent cannabinoid activator of CB119.

The current development of drugs that alter endocannabinoid signaling and how this complex system could be pharmacologically manipulated in the future should be the focus of further studies. In this sense, the discovery of new chemical entities (NEQ), candidates for new drugs in *Cannabis sativa*, comprises a complex chain that needs to be well articulated to be effective.

Thus, a new drug candidate can emerge by selecting bioactive molecules, employing molecular targets, and defining biochemical pathways that these compounds can interfere9. Therefore, using this planning, it is possible to predict and verify biological activities of interest to the pharmacology of molecules present in a potential drug[15].

Phytocannabinoids are highly unique compounds; they are promiscuous in action, modulating a range of pharmacological targets and exhibiting high antioxidant capacity due to their phenolic structures and the presence of hydroxyl groups[16-18]. Together with their lipophilicity and ability to act as anti-inflammatory agents, these characteristics make them desirable therapeutic candidates for the treatment of CNS disorders, as they can effectively cross the blood-brain barrier

(BBB), modulate the immune response, and address the many aspects of neurodegeneration[19].

These characteristics have been well established for Δ9-THC and CBD, but some secondary plant constituents are less known. Thus, to understand the full therapeutic potential of Cannabis sativa, the pharmacology of the lesser-known components of the plant must be elucidated[17].

Thus, within the current scenario of recent authorizations, this work aims to complement the investigations of the molecular mechanisms of cannabinoids and their receptors, elucidating molecular targets that explain the effect of cannabinoid metabolites present in this species regarding central neuromodulation through *in silico* methods.

Therefore, this study of the cannabinoids present in Cannabis sativa may provide new information about its high efficacy and safety margins and may continue to inspire a rich source of refined compounds pharmacologically associated with new therapies. Therefore, such results can facilitate the regulatory and bureaucratic path for physicians and scientists to conduct well-designed studies seeking to mitigate the symptoms of neurological and psychiatric diseases.

Methods

The active compounds present in the *Cannabis sativa* species were identified by searching scientific articles in the Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Scielo (https://www.scielo.org/) databases), ScienceDirect (https://www.sciencedirect.com/) and Capes Periodicals (https://www-periodicos-capes-gov-br.ezl.periodicos.capes.gov.br/index.php?). After identifying these compounds, the coding of the molecules (through the canonical smiles) was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/)[20] for further analysis. Furthermore, to screen for pharmacokinetic, biological, and toxicological properties, the SwissADME[21] programs (http://www.swissadme.ch/) were used. PASS PREDICTION[22,23] (http://way2drug.com/PassOnline/), Molinspiration[24] (http://way2drug.com/PassOnline/) and ProToxII [25,26] (https://tox-new.charite.de/protox_II/).

The selected substances were searched for possible targets using the SwissTargetPrediction program (http://www.swissstargetprediction.ch/)[27]. This server allows predicting the most likely macromolecular targets of a potential ligand molecule. The targets that demonstrated a relationship with the investigated biological activity were then obtained from the Protein Data Bank[28] (PDB) database (https://www.rcsb.org/). Finally, the compounds with the highest scores for neuromodulatory activity in the servers employed were selected for molecular docking simulations (Figure 1).

After selecting the most likely targets, the GOLD Suite 5.8.0 program performed molecular docking[29]. After preparing the molecular targets, the region of interest used (binding site) for the docking was defined as all protein residues within a radius of 10A in relation to the co-crystallized ligand. Standard conditions of all other parameters were used, and the PDB ID: 4UUQ complex was submitted to genetic algorithm analysis. The CHEMPLP38 score function associated with the ASP rescoring function was used for this docking. To validate the model parameters, redocking was performed using the ligand complex co-crystallized with the crystallized protein, and these conditions were used to perform the docking with the best ligands of the *Cannabis sativa* species.

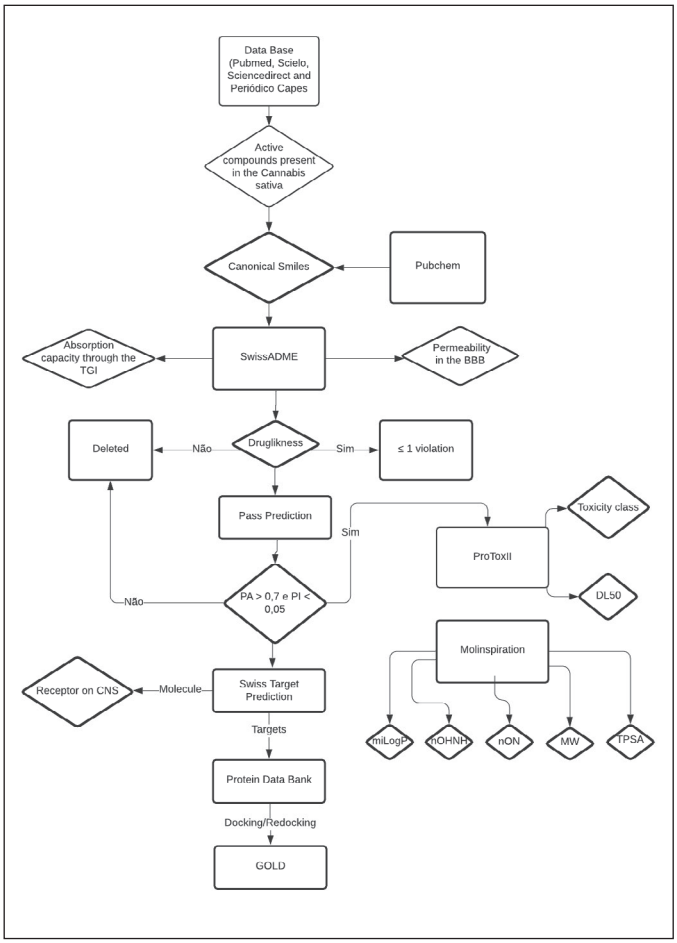

Figure 1. Schematic representation of the methodology sequence.

Results

Cannabis sativa species contains hundreds of different metabolites, divided into cannabinoid and non-cannabinoid compounds. Among these compounds, the primary cannabinoids are: cannabigerol, Δ9 -tetrahydrocannabinol, canna-

bichromene, cannabidiol, cannabielsoin, cannabicyclol, cannabinol, cannabitriol, cannabinolic acid, cannabigerolic acid, tetrahydrocannabivarine, and among the non-cannabinoids, C, 6 - cannabinoids prenilapigenin, 2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene-4-ol (Figure 2).

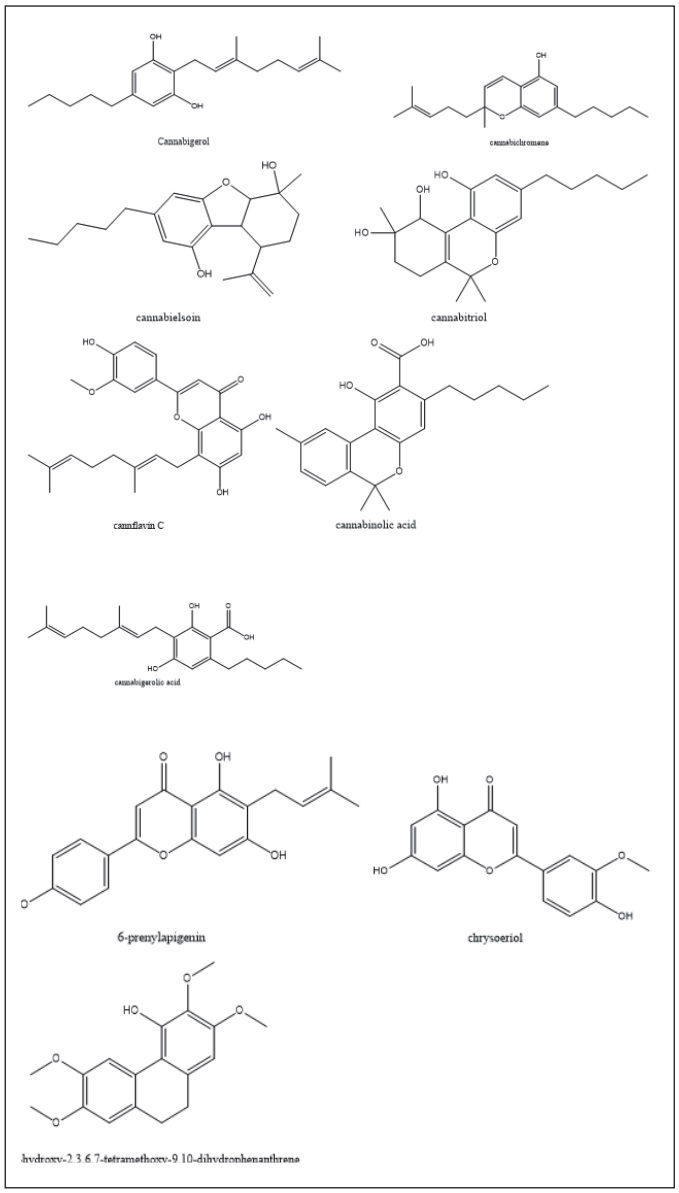

Figure 2. Structures present in the species *Cannabis sativa*

After obtaining the canonical smiles of these compounds from Pubchem[20], they were all submitted to pharmacokinetic prediction analysis and relation to biological activity using the SwissADME[21] and PassPrediction[22,23] programs, respectively. As a result, the compounds analyzed were classified as druglike, following Lipinski's criteria, which predicts the ability of their behavior to be similar to drugs used orally and the metabolic activity of these elements30. Thus, all 15 compounds studied were druglike, with a maximum of 1 violation of Lipinski's rules.

In SwissADME[21], it was also possible to predict the absorption capacity through the gastrointestinal tract (TGI) and the permeability in the blood-brain barrier (BBB) based on the structures of the compounds. Of the compounds studied, all, except cannflavin C, were shown to have high absorption by TGI. In addition, the compounds cannabigerol, cannabichromene, cannabinolic acid, cannabigerolic acid, cannflavin C, cryoeriol, and 6-prenilapigenin do not cross the BBB; the other compounds do. Furthermore, the toxicity class and the mean lethal dose (LD50) were obtained using ProToxII[25,26], which demonstrated class 4 toxicity for most compounds, with the exception of cannabinol, class 6, and those that presented class 5, cannflavin C, cryoseriol and 6-prenilapigenin. The action of these metabolic on central nervous system receptors was predicted by SwissTargetPrediction[27]. All these results are summarized in Table 1.

Table 1. Summary of the properties of metabolites present *in Cannabis* sativa species.

Compounds	MW	nOHNH	nON	TPSA	miLogP	Druglike	Viol	TGI	BBB	DL50	CT	Target in the Nervous System
Cannabigerol	23	2	2	40.46	7.84	YES	1	HIGH	NO	500mg/kg	4	Cannabinoid receptor 1 and 2; G55 protein--coupled receptor
Δ9-rahydrocannabinol	314.47	1	2	29.46	6.69	YES	1	HIGH	YES	482mg/kg	4	Cannabinoid receptor 1 and 2; N-arachidonylglycine receptor
Cannabichrome	314.47	1	2	29.46	7.50	YES	1	HIGH	NO	750mg/kg	4	Cannabinoid receptor 1 and 2
Cannabidiol	314.47	2	2	40.46	7.14	YES	1	HIGH	YES	500mg/kg	4	Cannabinoid receptor 1 and 2; G55 protein--coupled receptor
Cannabielsoin	330.47	2	3	49.69	5.79	YES	0	HIGH	YES	500mg/kg	4	Cannabinoid receptor 1 and 2
Cannabicyclol	314.47	1	2	29.46	6.64	YES	1	HIGH	YES	860mg/kg	4	Cannabinoid receptor 1 and 2
Cannabinol	310.44	1	2	29.46	6.81	YES	1	HIGH	YES	13500mg/kg	6	Cannabinoid receptor 1 and 2
Cannabitriol	346.47	3	4	69.92	4.61	YES	0	HIGH	YES	750mg/kg	4	Cannabinoid receptor 1 and 2
Cannabinolic acid	354.45	2	4	66.76	6.31	YES	0	HIGH	NO	400mg/kg	4	Cannabinoid receptor 1 and 2
Cannabigerolic acid	360.49	3	4	77.75	7.13	YES	1	HIGH	NO	1000mg/kg	4	Cannabinoid receptor 1 and 2
Tetrahydrocannabivarin	286.42	1	2	29.46	5.62	YES	0	HIGH	YES	482mg/kg	4	Cannabinoid receptor 1 and 2; N-arachidonylglycine receptor and glycine receptor alpha-1 subunit
Cannflavin C	436.50	3	6	100.13	6.38	YES	0	LOW	NO	3919mg/kg	5	-----
Cryoserol	30.27	3	6	100.13	2.28	YES	0	HIGH	NO	4000mg/kg	5	-----
6-prenylapigenin	338.36	3	5	90.89	4.71	YES	0	HIGH	NO	3919mg/kg	5	-----
2,3,6,7-Tetra-methoxy-9,10--dihydrophenan-threne-4-ol	316.35	1	5	57.16	3.01	YES	0	HIGH	YES	1000mg/kg	4	-----

Caption: Viol: violations; TGI: gastrointestinal tract; BBB: blood brain barrier; CT: toxicity class; SN: the nervous system.

In the search for targets to perform molecular docking using the programs SuperPredWebserver[31] (https://prediction.charite.de/) and SwissTargetPrediction[27], the targets of each compound and their respective crystallographic structures in the PDB[28] (Protein Data Bank) were verified. Of the compounds shown in Table 1, the tetrahydrocannabivarin (THCV) molecule was selected for interactions with central nervous system receptors, such as cannabinoid receptor 1, cannabinoid receptor 2 and N-arachidonylgline.

Thus, THCV was chosen for its characteristics, being druglikness, according to Lipinski's criteria, without violations, presenting high absorption by the TGI, crossing the blood-brain barrier, and having a safe mean lethal dose (LD50). Thus, the structure ID: 4UUQ for the N-arachidonylglycine receptor was used to carry out the molecular anchoring study.

Initially, redocking (Figure 3) was performed to validate the model parameters, using the crystalized ligand 4-({[(4-chlorophenyl)sulfonyl]amino}methyl)piperidine-1-carboxylic acid (64D) and as the site of binding to the 4UUQ structure to demonstrate the occurrence of the binding of 4-({[(4-chlorophenyl)sulfonyl]amino}methyl)piperidine-1-carboxylic acid in the N-arachidonylglycine Receptor structure, in the same position of the form deposited in the PDB[28]. After defining the parameters of the model to be used for docking, simulations were carried out with tetrahydrocannabivarin on the active site of the 4UUQ target.

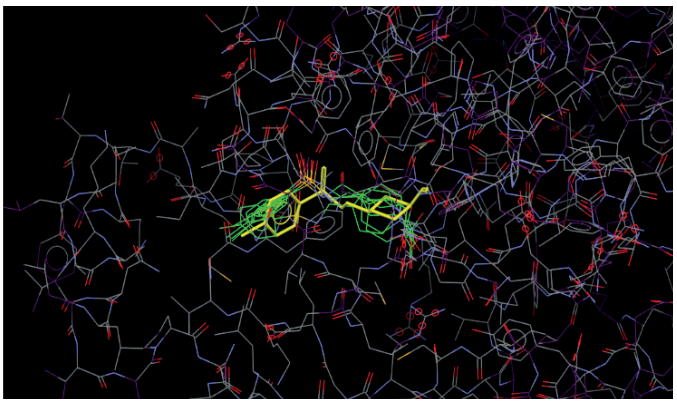

Figure 3. Redocking of 4-({[(4-chlorophenyl)sulfonyl]amino}methyl)piperidine-1-carboxylic acid on N-arachidonylglycine Receptor

Docking reveals a potential interaction of THCV with the N-arachidonylglycine Receptor receptor. Figure 3 shows the two-dimensional map of interactions that can occur between tetrahydrocannabivarin and N-arachidonylglycine receptors. The main interactions that the analysis suggests can support the structure at the active site are a hydrogen bond with SER165, π-alkyl, and alkyl-alkyl interactions with residues of ALA174, VAL217, LEU215, ALA166, LEU186, LEU224, ALA161, LEU223, LEU158, VAL227, LEU25, GLY220, LYS216, and ASN162. The three-dimensional representation of the possible interaction between tetrahydrocannabivarin and the active site of the N-arachidonylglycine receptor can be seen in Figures 4 and 5. And the pharmacophoric mapping of the tetrahydrocannabivarin substance with the five most potent antagonist ligands for the monoglycerate lipase target is shown in Figure 6.

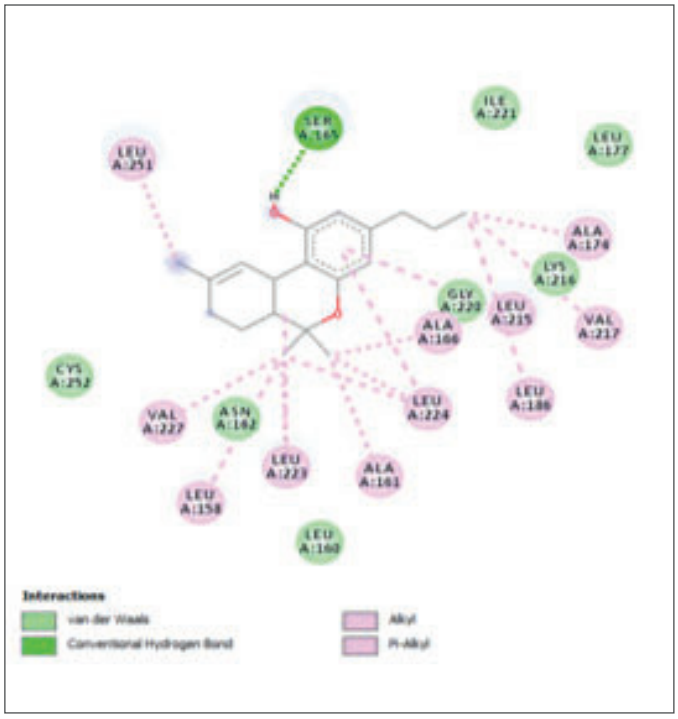

Figure 4. Pose 1 of tetrahydrocannabivarin anchorage within the N-arachidonylglycine receptor site Figure generated with the Pymol 1.1r1 software.

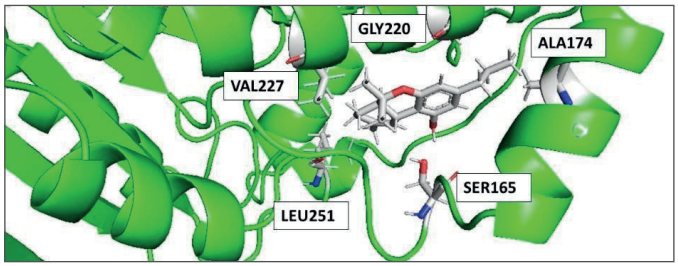

Figure 5. 2D interaction diagram of tetrahydrocannabivarin at position 1 on the N-arachidonylglycine receptor. This picture was generated with Discovery Studio 3.5 Visualizer.

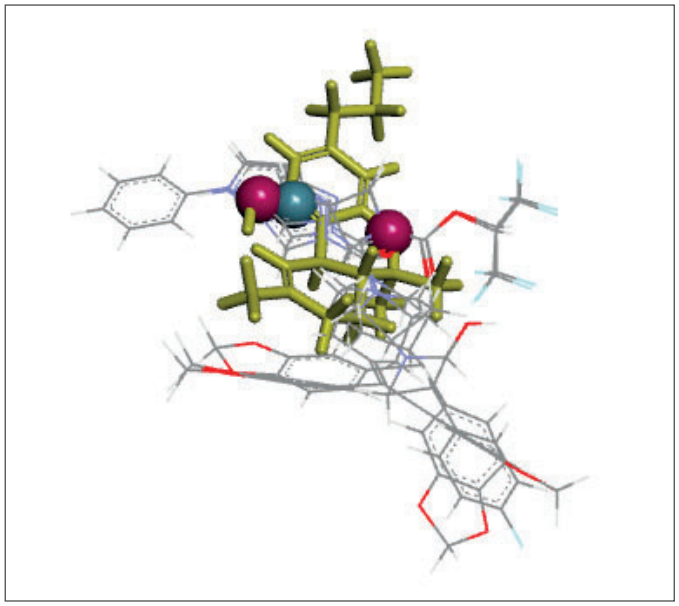

Figure 6. Pharmacophoric mapping of tetrahydrocannabivarin substance with the five most potent antagonistic ligands for the monoglycerate lipase target. Pharmacophoric characteristics are colored red for hydrogen bond acceptors and blue for aromatic rings (B).

Discussion

It is worth emphasizing a brief consideration of the current context of *Cannabis sativa* regulation policies in Brazil. Because of the clamor and pressure of social movements[32], the Federal Council of Medicine (CFM) regulated the prescription of cannabis extracts at the end of 2014. After this fact, the Resolution of the Collegiate Board (RDC) No. 156, published in the Gazette Official of the Union of May 8, 2017, included the herb in the Farmacopeia Brasileira, official pharmaceutical code of Brazil, recognizing it as a medicinal plant.

In addition, recently, the Resolution of the Collegiate Board (RDC) No. 327, published in the Official Gazette of December 9, 2019, provided for the conditions and procedures for granting the Sanitary Authorization for manufacturing and import, as well as establishes requirements for the marketing, prescription, dispensing, monitoring and inspection of industrialized products containing plant derivatives or phytopharmaceuticals of *Cannabis sativa*, called Cannabis products.

Regarding the pharmacological aspects of the species, it is essential to understand the endocannabinoid system (ECB), which, in turn, is widely expressed in the central nervous system, playing roles in the regulation of synaptic plasticity through retrograde signaling. In a strict sense, it is composed of type 1 (CB1, which is widely expressed in the nervous system) and type 2 (CB2, mainly expressed in immune cells) cannabinoid receptors, its endocannabinoid signaling molecules (e.g., anandamide (AEA); and 2-arachidonoylglycerol (2-AG), and its metabolic enzymes (NAPE-PLD, DAGL, FAAH, and MAGL)[33].

Changes to the ECB system have been observed in a variety of diseases in therapeutic areas. For example, changes in tissue concentrations of AEA and 2-AG have been observed in pain and inflammation[34], immunological disorders[35], neurological and psychiatric conditions36, obesity and metabolic syndromes[37,38], and cancer[39]. These observations have fueled significant interest in the development of drugs that manipulate ECB to treat these conditions[40,41].

Given the wide range of neuroprotective effects of Δ9-THC and CBD already established, it is necessary to suggest that other phytocannabinoids may exhibit similar or more potent neuroprotective properties[42]. In this context, from the survey of the active metabolites of Cannabis sativa, its pharmacokinetics, biological and toxicological predictive analyses, druglikeness classification, the compound tetrahydrocannabivarine (THCV) appears as a potential treatment for neurological and psychiatric conditions.

All compounds listed in the screening carried out in this study showed good solubility and permeability characteristics, according to Lipinski 1997. This classification is widely used to determine molecular properties important for the pharmacokinetic prediction of substances in vivo. According to Lipinski's rule of five on which this classification is based, a candidate molecule is more likely to have favorable properties if the molecular weight is below 500 daltons, the octanol/water partition coefficient (log P) is lower 5, if there are not more than 5 hydrogen bond donors (OH and NH groups) and if there are not 10 hydrogen bond acceptors (namely N and O)43. THCV, in turn, presented the parameters mentioned above within these good limits.

Δ9-THCV is a homolog of Δ9-THC differing only by a propyl side chain, and studies have suggested that Δ9-THCV acts as a CB1 receptor agonist, sharing properties with Δ9-THC, albeit with less potency[14,44]. They show similarities in their in vivo effects, such as inducing catalepsy in mice, and similar results to Δ9 -THC in humans.

Two studies were found where Δ9-THCV showed promise as an antiepileptic agent and protected neurons in two models of Parkinson's disease; the theory is that Δ9-THCV promotes some of its protective effects by acting on CB1 and CB2 receptors, but, in any case, the possible mechanisms of action of Δ9-THCV were largely unexplored[45]. Thus, although there is evidence to suggest Δ9-THCV mediates some of its protective effects via CB1and CB2 receptors, the data remain largely unclear, and

there is a lack of investigation into the potential of Δ9-THCV to act on other targets known cannabinoids.

N-arachidonoylglycine (NAGly) is a product of the oxidative metabolism of anandamide and shares a structural similarity with this endocannabinoid[46-48]. NAGly is believed to activate the cannabinoid receptor GPR18, but it has no affinity for the cannabinoid receptor (CB) and the potential transient vanilloid receptor 1 (TRPV1)[46-48].

The GPR18 or N-arachidonylglycine receptor used in this study is a seven-transmembrane G protein-coupled receptor consisting of 331 amino acids. GPR18 was found in peripheral blood cells, lymphoid tissues, macrophages with different expression levels for cytotoxic and reparative cells49. It is also present in the brain[50,51], and in some glioblastoma multiforme cells[52].

N-arachidonoyl glycine (NAGly)-GPR18 signaling has been introduced as an essential pathway in microglial neuronal communication, providing a novel mechanism (receptor and ligand) for targeted migration and phenotypic changes in microglia[53]. Published data strongly support a significant role for NAGly and GPR18 in regulating microglia in the Central Nervous System and, together with subsequent work, have broader implications for our understanding of the ECB system[54].

It is worth noting that directed migration, selective phagocytosis, and free radical production are critical functions of microglia that significantly impact the overall stability of the Central Nervous System, both from a critical and long-term perspective[55,56].

In this study, THCV behaved as an antagonist ligand in the structure of the N-arachidonylglycine Receptor, allowing the inference of the possible neuromodulatory action of this molecule, similarly to what was demonstrated in redocking, in which the ligand complex co- Crystallized 4-({[(4-chlorophenyl) sulfonyl]amino}methyl)piperidine-1-carboxylic acid bound to the N-arachidonylglycine Receptor structure at the site of the crystalized protein (4UUQ).

To date, there are no Food and Drug Administration-approved drug therapies that target microglial neuronal receptor-ligand interactions. In line with this, elucidating the NAGly-GPR18 neuronal-microglial communication system can lead to new pharmacotherapies focused on augmenting (optimized GPR18 ligands) or suppression (optimized GPR18 antagonists) of microglial activation in the Central Nervous System.

The THCV molecule was selected for molecular docking because it showed a more remarkable prediction of interaction with the N-arachidonylglycine receptor anchoring in the active site of this receptor and was considered, by the computational pharmacological analyzes described in this article, as an antagonist and, therefore, a possible alteration of microglial activity in the CNS, a finding that deserves further investigation[54].

Microglial activation and neuroinflammatory factors are prominent features of Parkinson's disease and are well documented among patients[54]. Furthermore, studies have shown that microglial overactivation leads to deleterious effects and exacerbation of the immune response, especially the release of pro-inflammatory mediators. As observed with the CBG derivative VC -003.2, microglial activation was decreased at Δ9-THCV, inducing a protective effect by dampening the immune response[52].

Δ 9 -THCV also attenuated the increased microglial activation caused by 6-hydroxydopamine, as measured by OX-42 immunostaining in the substantia nigra [$F(3.18) = 31.63$, $P < 0.0001$]. This finding possibly indicates that the neuroprotective effects of Δ 9 -THCV in rats with 6-hydroxydopamine injury is due more to its antioxidant properties than its ability to activate CB 2 receptors. Given its antioxidant properties and ability to activate CB 2, but from blocking CB 1 receptors, Δ 9 -THCV has a promising pharmacological profile for slowing disease progression in PD and improving parkinsonian symptoms. This represents a significant advance in the search for potential new antiparkinsonian agents, as Δ 9 -THCV given alone or in combination with CBD can provide a much-needed improved treatment for PD[57].

Thus, using *in silico* techniques with Cannabis sativa, this article raises essential data for the future planning of a drug that uses this plant species as a basis. Therefore, it is necessary to carry out further work developed *in vitro* and *in vivo* to further the study of THCV from *Cannabis sativa* as a possible neuroprotective drug57.

Consequently, using in silico techniques with Cannabis sativa, this article raised essential data for the future planning of a drug that uses this plant species as a basis. Therefore, it is necessary to carry out further work developed in vitro and in vivo to further the study of THCV from Cannabis sativa as a possible neuroprotective drug.

Conclusion

There is growing evidence that astrocytic dysfunctions may be the primary causes of the pathogenesis of several neurodegenerative diseases, such as Parkinson's Disease (PD), Alzheimer's Disease (AD), tumor, stroke, HIV-associated neurotoxicity, and Lateral Sclerosis Amyotrophic (ALS). The generation of cell therapy approaches for the replacement of glial (and non-neuronal) cells in damaged tissues, and the development of drugs targeting glial cells could open new perspectives for the restoration of the human brain.

In this context, the in silico study of Cannabis sativa, addressed in this work, elected THCV as an active metabolite with neuromodulatory activity through a possible alteration of microglial activity in the CNS. Furthermore, TCHV docking showed anchorage of this molecule in the active site of the N-arachidonylglycine receptor due to the actions of this species. Thus, this marker could act as an receptor antagonist, acting as a therapeutic agent in such neurodegenerative pathologies.

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