MOLECULAR DOCKING STUDY OF CANNABINOL AGAINST HUMAN TRANSIENT RECEPTOR POTENTIAL VANILLOID TYPE 1: ITS ROLE IN THE MANAGEMENT OF FIBROMYALGIA

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ABSTRACT

Aim: To analyze the interactions of cannabinol (CBN) with human TRPV1 and compare them with cannabidiol (CBD) using molecular docking. **Methods:** This study employed an in silico molecular docking approach. The compounds used were CBN (CID 2543) and cannabidiol (CBD, CID 644019), obtained from PubChem. The human TRPV1 structure was retrieved from the Protein Data Bank (PDB ID: 8GFA). Docking simulations were performed using DockThor-VS, and binding conformations were ranked according to binding affinity. Generated poses were clustered using DTStatistics. Structural analyses were conducted using UCSF Chimera 1.14 and PyMOL. **Results:** CBN demonstrated a predicted binding affinity of −8.9 kcal/mol, whereas CBD presented −6.7 kcal/mol toward hTRPV1. Both compounds showed binding energies lower than −5 kcal/mol, suggesting favorable predicted interactions. Spatial analysis demonstrated that CBN was positioned within transmembrane alpha-helices near the channel pore region, interacting with residues Ile446, Ala443, Ile439, Met383, Cys412, Leu390, Ile387, Tyr386, Ile438, Tyr409, Phe391, and Phe416. In contrast, CBD occupied a distinct binding site. **Conclusion:** The present in silico findings suggest that cannabinol exhibits favorable predicted binding to human TRPV1, with stronger predicted affinity than cannabidiol. The localization of CBN near the pore region suggests a possible modulatory role in ion conductance and pain signaling pathways associated with fibromyalgia. Further in vitro and in vivo studies are required to validate these molecular interactions and confirm their pharmacological relevance.

Keywords: Phytocannabinoids; Cannabinol; TRPV1; Pain; Fibromyalgia.

RESUMO

Objetivo: Analisar as interações do canabinol (CBN) com o TRPV1 humano e compará-las com o canabidiol (CBD) utilizando docking molecular. **Métodos:** Este estudo empregou uma abordagem in silico de docking molecular. Os compostos utilizados foram CBN (CID 2543) e canabidiol (CBD, CID 644019), obtidos do PubChem. A estrutura do TRPV1 humano foi recuperada do Protein Data Bank (PDB ID: 8GFA). As simulações de docking foram realizadas utilizando o DockThor-VS, e as conformações de ligação foram classificadas de acordo com a afinidade de ligação. As poses geradas foram agrupadas utilizando o DTStatistics. As análises estruturais foram conduzidas utilizando UCSF Chimera 1.14 e PyMOL. **Resultados:** O CBN demonstrou uma afinidade de ligação prevista de −8,9 kcal/mol, enquanto o CBD apresentou −6,7 kcal/mol em relação ao hTRPV1. Ambos os compostos apresentaram energias de ligação inferiores a −5 kcal/mol, sugerindo interações previstas favoráveis. A análise espacial demonstrou que o CBN estava posicionado dentro das alfa-hélices transmembrana próximas à região do poro do canal, interagindo com os resíduos Ile446, Ala443, Ile439, Met383, Cys412, Leu390, Ile387, Tyr386, Ile438, Tyr409, Phe391 e Phe416. Em contraste, o CBD ocupou um sítio de ligação distinto. **Conclusão:** Os presentes achados in silico sugerem que o canabinol apresenta ligação prevista favorável ao TRPV1 humano, com afinidade prevista mais forte do que o canabidiol. A localização do CBN próxima à região do poro sugere um possível papel modulador na condução iônica e nas vias de sinalização da dor associadas à fibromialgia. Estudos adicionais in vitro e in vivo são necessários para validar essas interações moleculares e confirmar sua relevância farmacológica.

Palavras-chave: Fitocanabinoides; Canabinol; TRPV1; Dor; Fibromialgia.

1 INTRODUCTION

Transient receptor potential (TRP) channels comprise a superfamily of transmembrane ion channels involved in signal transduction in response to diverse physical and chemical stimuli. These channels participate in several physiological and pathological processes, including itch, thermosensation, inflammation, cancer, genetic disorders, and pain. Among them, TRPV1 is widely recognized as the capsaicin receptor and constitutes an important pharmacological target for analgesic therapies.

Evidence from in vivo studies indicates that TRPV1 participates in nociceptive mechanisms associated with fibromyalgia. In this context, Cannabis-based products have emerged as promising therapeutic alternatives for symptom management in patients with fibromyalgia.

Cannabinol (CBN), a phytocannabinoid present in Cannabis sativa, has demonstrated potential pharmacological effects, including analgesic and anti-inflammatory properties. Previous studies suggest that phytocannabinoids may modulate TRPV1 activity, although the molecular mechanisms underlying these interactions remain incompletely understood.

Molecular docking is a valuable computational strategy for predicting ligand–protein interactions and identifying potential therapeutic targets. Therefore, this study aimed to analyze the molecular interaction of CBN with human TRPV1 and compare its predicted binding profile with cannabidiol (CBD).

2 METHODS

This study was designed as an in silico molecular docking analysis.

The three-dimensional structures of CBN (CID 2543) and CBD (CID 644019) were obtained from the PubChem database. The crystallographic structure of human TRPV1 (PDB ID: 8GFA) was retrieved from the Protein Data Bank.

Docking simulations were performed using DockThor-VS. Binding affinity predictions were calculated using DockTScore, which estimates free binding energy based on intermolecular interactions, torsional entropy, lipophilic interactions, and solvation terms.

The docking grid was defined using coordinates x = 103.176, y = 103.2675, and z = 84.995, with a total of 884736 grid points. Docking poses and chemical interactions were visualized using UCSF Chimera version 1.14 and PyMOL. Generated conformations were subsequently clustered using DTStatistics.

3 RESULTS AND DISCUSSION

The molecular docking into phytocannabinoids and channel hTRPV1 presented CBN with score of binding affinity of - 8.9 and CBD of - 6.7 kcal/mol in the hTRPV1 (Table 1). However, CBN showed stronger binding affinity than CBD, since CBN presented a lower binding energy. The

binding affinity of CBN was lower than - 7 kcal/mol presenting good binding activity, while CBD was lower than – 5 kcal/mol indicating a specific binding activity (Liu et al. 2023; Du et al., 2022). Another study has shown that cannabigerol (CBG) and capsaicin present similar binding affinities (Santos et al., 2025).

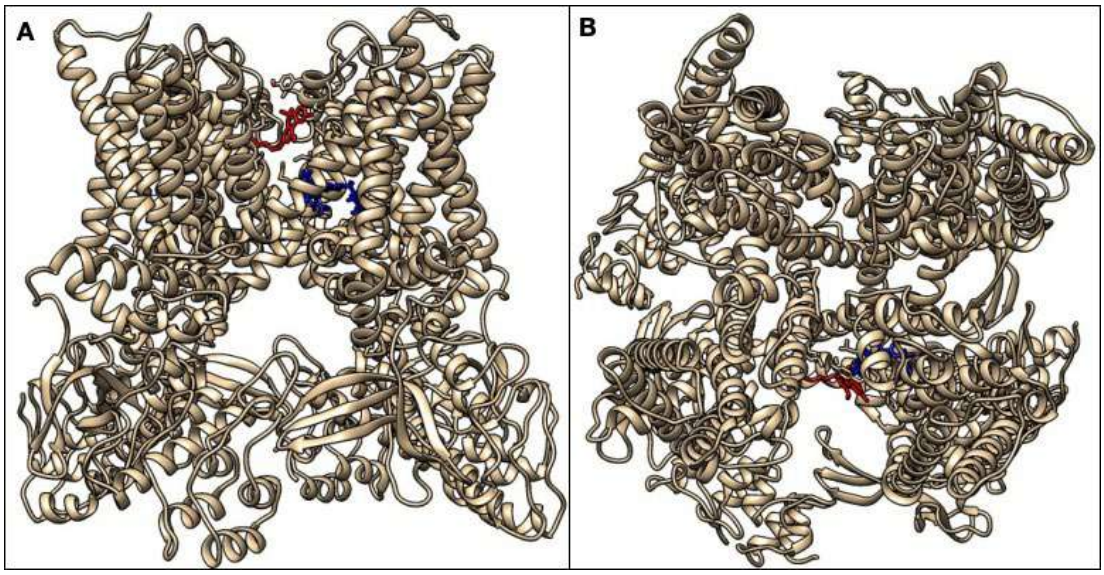
Table 1 - Scores of binding affinity of ligands with hTRPV1.

Ligand	Binding affinity (kcal/mol)
CBN	- 8.9
CBD	- 6.7

Source: Authors (2026)

TRPV1 is primarily expressed by small-diameter neurons of sensory ganglia, such as Dorsal Root Ganglion (DRG) and trigeminal ganglia, and responds to noxious heat (> 43°C), small chemical agonists and animal peptide toxins, protons (produced during tissue injury, ischemia and inflammation), fatty acids, and other stimuli, generally leading to pain perception (Rosenbaum; Islas; 2023). The antidepressant amitriptyline has been shown to activate and desensitize TRPV1. This tricyclic antidepressant is currently defined as first-line therapy for neuropathic pain (Pantke et al., 2025). Structurally, TRPV channels contain four subunits, each with intracellular N and C termini, six transmembrane helices (S1–S6), and a pore region (S5-P-S6). The pore contains a selectivity filter that, in turn, is constituted by a re-entrant pore (P)-loop and small-pore helix between S5 and S6 (Rosenbaum; Islas; 2023). CBN was located within the transmembrane helices near the pore region, similarly also CBD (Fig. 1), despite occupying distinct sites. CBG may adopt the same pose during molecular docking (Santos et al., 2025).

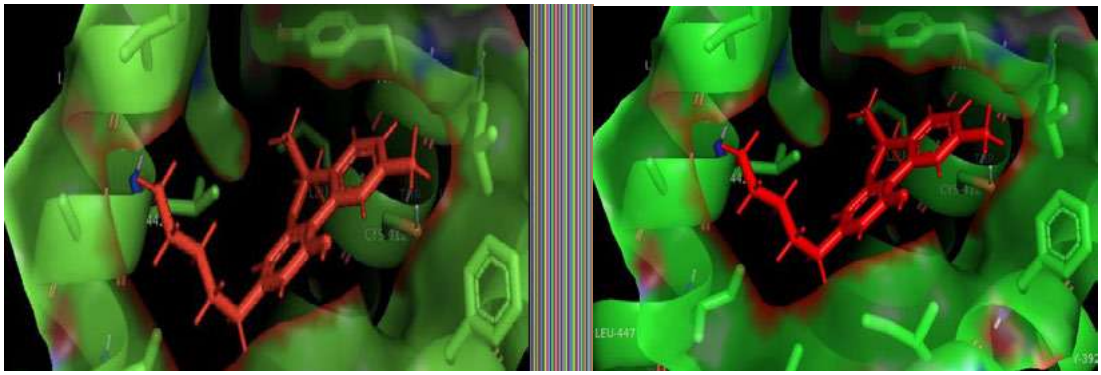
Figure 1 - 3D modeling of molecular docking between phytocannabinoids and hTRPV1. CBN (red) and CBD (blue) binding poses on the helices of hTRPV1 (gray). The side (A) and top (B) views of the channel.



Source: Authors (2026)

The binding sites were identified and confirmed different positions of CBN and CBD at channel hTRPV1 (Fig. 2). CBN formed hydrophobic bonds with Ile446, Ala443, Ile439, Met383, Cys412, Leu390, Ile387, Tyr386, Ile438, Tyr409, Phe391 and Phe416 residues (Fig. 2A). Regarding binding sites of CBG, Cys412 was the same residue involved in binding (Santos et al., 2025). In contrast, CBD formed hydrogen bonds with Asn1121 (1.9 Å) and Glu328 (2.7 Å), and hydrophobic with Asn331, Lys332, Ala1124, Gln1125 (Fig. 2B).

Figure 2 - Chemical interactions of the CBN (A) and CBD (B) with residues in the hTRPV1. The hydrogen-bond (yellow): Asn1121; Glu328.



Source: Authors (2026)

Positioning of CBN near the pore region appears to mediate channel modulation, suggesting a possible blockade of ion conductance and inhibiting pain stimulus. Since, TRPV1 is primarily expressed by small-diameter neurons of sensory ganglia, such as DRG and trigeminal ganglia (Rosenbaum; Islas; 2023).

4 CONCLUSIONS

The data corroborate the effect of cannabinol on fibromyalgia that, probably, it may act through the inhibiting hTRPV1, in a manner similar to cannabidiol.

These findings support the potential modulation of these receptors, however, further experimental studies are necessary to confirm these result.

Phytocannabinoids can interact with non-canonical molecular targets in addition to classical cannabinoid receptors.

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