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Molecular Docking Study Of Cannabigerol Aganist Human Transient Receptors Potential: Its Role In The Management Of Pain And Fibromyalgia

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Abstract:
Background*: Transient receptor potential (TRP) channels present role important in pain and it have been modulated phytocannabinoids. Cannabigerol (CBG) is a non-psychoactive cannabinoid found in the cannabis plant and have presented effects on TRPV1 and TRPA1 in vitro. However, the CBG molecular action mechanism is not clear yet.*
Materials and Methods*: In this in silic study carried out by DockThor® program. The 3D structures of CBG (CID: 5315659), capsaicin (CID: 1548943), an TRPV1activator , and 2-chloro-N-(4-(4-methoxyphenyl)thiazol-2-yl)-N-(3-methoxypropyl)-acetamide (JT010, CID: 18524489), an TRPA1 agonist , were downloaded from the PubChem. the human proteins targets, hTRPV1 (ID: 8GFA)23 and hTRPA1 (ID: 6PQO)24 were from the PDB database.*
Results*: CBG presented good binding activity in hTRPs and similar to specific ligands, capsaicin and JT010, since scores were less than - 7.0 kcal/mol. CBG formed two hydrogen bonds with TRPV1 residues and capsaicin only one bond. This biding pocket-CBG can be essential to modulate pore and desensitize/close TRPV1, suggesting ions conductance blockade and inhibiting pain stimulus. It was observed that both CBG and JT010 were docked at TRPA1 coupling domain but distinct regions and also bound to two different residues. It is suggestive that CBG be acting differently of agonist JT010, probably an desensitizer/blocker channel and may modulate pain*
Conclusion: *Cannabigerol interacts in human transient receptors potential and the potential binding sites that can modulate channels were identified.*
Key Word*: Phytocannabinoids; Cannabigerol; Transient Receptors Potential; Pain; Fibromyalgia.*

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I. Introduction

Transient receptor potential channels are a super family of trans-membrane ion channels involved in transduction in response to a several range of physical and chemical stimuli.[1] These channels have also been implicated as sensors of many physiological and pathological processes including itch, temperature sensation, cancers, genetic disorders, and pain.[2-4] *Cannabis* derivatives products might have potential effects in chronic pain patients with fibromyalgia.[5-7] TRP channels (TRPV1–4, TRPA1, and TRPM8) have been modulated by phytocannabinoids.[8-11]

CBG is a non-psychoactive cannabinoid found in the cannabis plant. CBG converts from its acid form cannabigerolic acid, which is the principal precursor to most of the other phytocannabinoids.[12] CBG has been shown to modulate pain *in vivo* and to be the most potent inhibitor at TRPV1 and TRPM8, and to active TRPA1 *in vitro*.[5,13-16]

Docking-based virtual screening is a structure based drug design approach widely used by the scientific community to assist drug discovery in searching for new lead compounds against relevant therapeutic

targets.[17,18] The putative cannabidiol (CBD) binding sites in TRP channels have been identified.[19-21] However, the CBG molecular action mechanism is not clear yet.

II. Material And Methods

This experimental study was carried out *in silico* approach. Molecular docking insights understand the function-structure relation in a pharmacological target and its ligand-protein binding.[22]

Procedure methodology

The 3D structures of CBG (CID: 5315659), capsaicin (CID: 1548943) and 2-chloro-N-(4-(4-methoxyphenyl)thiazol-2-yl)-N-(3-methoxypropyl)-acetamide (JT010, CID: 18524489) were downloaded from the PubChem database and the human proteins hTRPV1 (ID: 8GFA)[23] and hTRPA1 (ID: 6PQO)[24] were from the PDB database. The channel protein and chemicals were molecularly docked by DockThor® and classified in order of highest affinity (Aff) with the channel.[22] The simulations were processed from the grid center coordinates (x = 103,176, y = 103,2675 and z = 84,995) for TRPV1 and coordinates (x = 138,2465, y = -138,125 and z = 158,4815) for TRPA1 and both with 884736 total grid points. The docking poses selected and chemical interactions were visualized by UCSF Chimera version 1.14 (University of California, San Francisco, CA).

III. Results

Table no 1 shows CBG or capsaicin Aff with hTRPV1 and CBG or JT010 with hTRPA1. The Aff with hTRPV1 were - 9.0 and - 8.4 kcal/mol, and with hTRPA1 were - 7.4 and - 7.5 kcal/mol, respectively. The Aff values of hTRPV1 were lower than hTRPA1.

Table 1: Scores binding energy between CBG and chemicals with hTRPs.

Ligand	Affinity (kcal/mol)	
	hTRPV1	hTRPA1
CBG	- 9.0	- 7.4
capsaicin	- 8.9	N.D.
JT010	N.D.	- 7.5

N.D.: not determined

Spatial analyses present CBG position closed at B chain of TRPV1 (Fig. 1A and B). Similarly, capsaicin also was on B chain and CBG overlap (Fig. 1A and B).

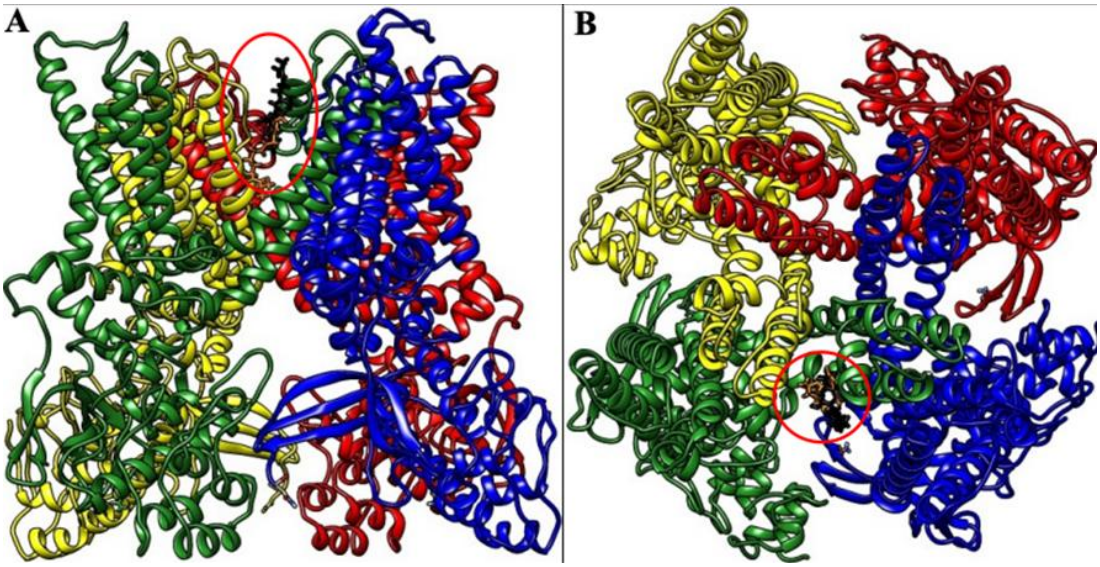

Figure 1: 3D modeling of molecular docking between CBG (black) or capsaicin (orange) and TRPV1. A (blue), B (green), C (yellow) and D (red) chain. Side (**A)** and top (**B)** views.

However, on TRPA1 the CBG was situated between the C and D channel chains and near pore channel (Fig. 2A and B). Differently, JT010 was closed at D chain (Fig. 2A and B).

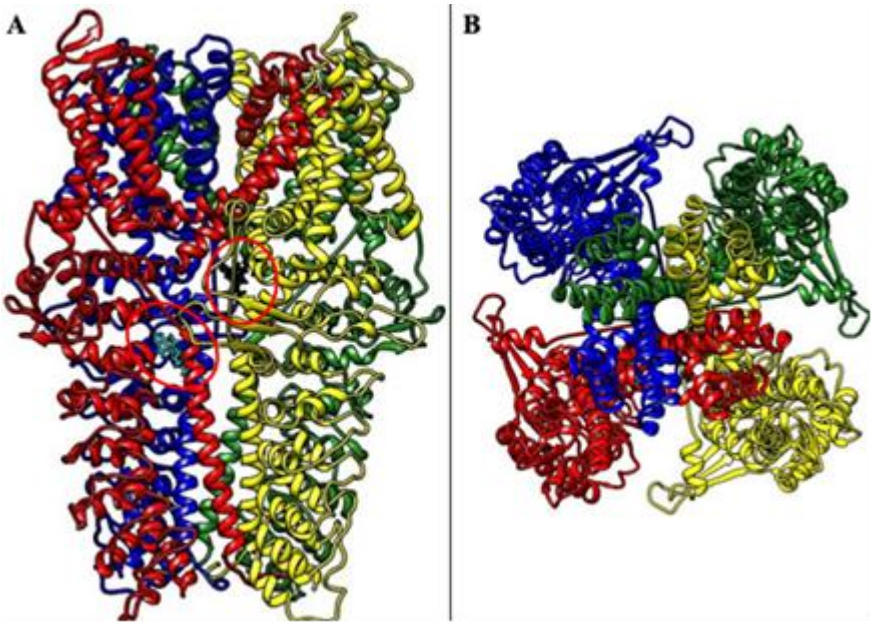

Figure 2: 3D modeling of molecular docking between CBG (black) or JT010 (cyan) and TRPA1. A (blue), B (green), C (yellow) and D (red) chain. Side (**A**) and top (**B**) views.

In the TRPV1, CBG formed hydrogen bonds with the Cys412 and Leu408 residues that presented 2.65 and 2.18 Å, respectively (Fig. 3A). While, capsaicin bonded to Tyr409 at 2.33 Å distance. Since, on the TRPA1, CBG hydrogen bonds with the Lys517 and Glu514 residues (1.99 and 1.54 Å, respectively) (Fig. 3B), while JT010 was bonded twice to Lys146 (3.04 and 1.94 Å, respectively) (data not shown).

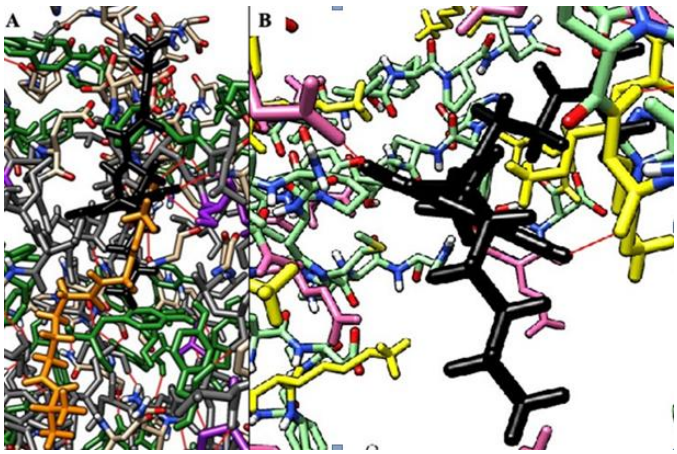

Figure 3: Hydrogen bonds (red line) between CBG (black) or capsaicin (orange) and Cys (purple), Leu (gray) or Tyr (green) residues of TRPV1 (**A**) and CBG with Lys (yelow) and Glu (pink) residues of TRPA1 (**B**).

IV. Discussion

Interactions membrane channel-ligand modulate potential and activity cellular, hence our data present docking analyses between cannabigerol and hTRPs that could be a mechanism to pain and fibromyalgia management.

TRPV1 has been related a receptor plays an important role in certain chronic pain conditions that may be involved with fibromyalgia, such as neuropathic pain, inflammatory bowel disease and migraine.[25-27] Central sensitization and upregulation of the TRPV1 signalling pathway has been observed in a murine model of fibromyalgia, indicating the direct involvement of this receptor in the pathogenesis of the disease.[28] TRPA1 is implicated in cold sensations related to painful stimuli.[29] Several studies modulating TRPA1 activity have observed that this receptor has participating in inflammatory and immune responses, and in the conversion of physical and chemical stimuli in irritative (itching) or pain sensations.[30-33] Our data showed that CBG presented good binding activity in hTRPs, being stronger for TRPV1, and similar to specific ligands, since scores were less than - 7.0 kcal/mol.[34,35] Molecular docking studies with CBD have also been shown its binding scores in hTRPs.[20,21]

Structurally, TRPV channels are arranged four subunits, each with intracellular NH2 and COOH terminal, six transmembrane helices (S1–S6), and a pore region (S5-P-S6). The pore contains a selectivity filter that, in turn, is organized by a re-entrant pore (P)-loop and small-pore helix between S5 and S6.[36] TRPV1 also contains an extracellular cap or turret that forms a dome above the pore's extracellular entrance, with four portals leading to the ion conductance pathway and is critical for channel function.[37] It was observed that both CGB and capsaicin, the canonical activator, were situated between S5 and S6 helix (Fig.1). Our data showed CBG formed two hydrogen bonds with TRPV1 residues (Cys412 and Leu408, Fig.3A), differently CBD have been bound with Asn330[21] and capsaicin only one bond (Tyr409, Fig.3A). This biding pocket-CBG can be essential to modulate pore and desensitize/close TRPV1, suggesting ions conductance block and inhibiting pain stimulus. Since,TRPV1 is primarily expressed by small-diameter neurons of sensory ganglia, such as DRG and trigeminal ganglia.[36]

TRPA1 possesses the NH2 and COOH terminal parts facing the intracellular space.[38] The overall structure of the homotetrameric TRPA1 channel may be divided into three layers. The top layer is formed of the transmembrane domain (TMD), while the middle layer contains the coupling domain (CD) and the bottom layer consists of the ankyrin repeat domain (ARD).[24] We observed that both CBG and JT010, the irreversible covalent agonist, were docked at CD but distinct regions. CBG bound to TRPA1 residues, Lys517 and Glu514, while JT010 did Lys146. It is suggestive that CBG be acting differently of agonist JT010, probably an desensitizer/blocker channel and may modulate pain. CBD have been also localized at CD, but C14-polyacetylenes at ankyrin repeat domain.[21,39] In fact, our data are related to TRPA1 that have been determined as a nociceptive channel with a plentiful presence in subpopulations of primary sensory neurons of the dorsal root, vagal and trigeminal ganglia.[40] Moreover, TRPA1 have been mainly expressed in unmyelinated C-fibers and thinly myelinated Aδ-fibers, and only occasionally large myelinated fibers that were determined pain conduction pathways.[40]

V. Conclusion

Cannabigerol interacts in human transient receptors potential and the potential binding sites that can modulate channels were identified.

These findings support the modulation of transient receptors potential by cannabigerol *in vitro* studies and reinforce the action of phytocannabinoids on pain and fibromyalgia management.

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