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# *In Silico* Assessment of Drug-Like Properties of Phytocannabinoids in *Cannabis Sativa*( 14pt/ Bold/ Align Centre)

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## Abstract(12pt/ Bold/ Align Centre)

This study investigated drug-like properties of phytocannabinoids in *Cannabis sativa* using an *in silico* study. We report sixteen phytocannabinoids: cannabidiol (CBD), cannabidiolic acid (CBDA), cannabinol (CBN), cannabichromene (CBC), cannabigerol (CBG), cannabicyclol (CBL), cannabivarin (CBV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), cannabinodiol (CBDL), cannabielsoin (CBE), cannabitriol (CBT), Δ9-tetrahydrocannabinol (Δ9-THC), Δ9-tetrahydrocannabivarin (Δ9-THCV), and Δ8-tetrahydrocannabinol (Δ8-THC). All chemical structures and properties were obtained from *PubChem Compound*, National Center for Biotechnology Information, U.S. National Library of Medicine. *Molinspiration* was used for the calculation of molecular properties and bioactivity score. The parameters were molecular weight (MW), number of hydrogen acceptor (HBA), number of hydrogen donor (HBD), partition coefficient (cLogP), polar surface area (PSA) and number of rotatable bonds (NROTB). We predicted bioactivity scores for G Protein-Coupled Receptors (GPCR) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor. Lipinski's rule was used as reference to determine the drug-like properties of the phytocannabinoids. All compounds have MW<500, HBA<10, HBD<5, TPSA<140Å$^2$ and NRTOB<10. Bioactivity score showed an active or moderately active in all compounds. Fifteen compounds were detected to have one violation. CBT did not violate any of the Lipinski's Ro5 and demonstrated as a good drug-like property and for oral absorption. This suggests that CBT can be further tested for potential orally active drugs. ( Text 10pt/ Align Left/ Justify/ Single Spacing)

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**Keywords** phytocannabinoids, in silico, drug-like properties, *Cannabis sativa* (Text 10pt/ Align Left/ Justify/ Single Spacing)

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## INTRODUCTION(Uppercase/ 12pt/ Bold/ Align Left)

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*Cannabis sativa* is an annual flowering plant from Cannabaceae family. It is also known in many names, such as cannabis, marijuana, ganja and hemp. This plant has been used for industrial, medicinal and recreational. Generally, marijuana has high amount of Δ9-tetrahydrocannabinol (Δ9-THC) and low amount of cannabidiol (CBD). Hemp or industrial hemp, contains high amount of CBD and very low in Δ9-THC. *C. sativa* contains chemical compounds that can be classified into 11 types: cannabidiol (CBD), cannabinol (CBN), cannabinodiol (CBDN), cannabichromene (CBC), cannabigerol (CBG), cannabicyclol (CBL), cannabielsoin (CBE), cannabitriol (CBT), Δ9-tetrahydrocannabinol (Δ9-THC), and

Δ8-tetrahydrocannabinol (Δ8-THC) and miscellaneous types [1]. Pharmacological investigations on phytocannabinoids has been reviewed, mainly on CBD and THC [2, 3, 4]. Various compounds in cannabis were described as anti-cancer [5], anti-nausea [2], anti-arthritic [2], anti-inflammatory [6, 8], anti-microbial [7] and anti-oxidant [8]. The pharmacological properties show beyond recreational uses; however, cannabis is not yet approved by the US Food, Drugs and Administration for medical use. ( Text 11pt/ Align left/ Justify/ Single Spacing)

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Natural products (NPs) inspire new drug development. Our nature provides an enormous source of new molecules. In 2015, more than 540 compounds were described [9] which provides information on the bioactive metabolites to scientists. Concern are raised in understanding the mechanism that regulate the secondary metabolites in cannabis, identifying novel biosynthetic pathways to produce specialized metabolites and to discover new drugs to meet the world health challenges [3]. An ideal drug should have good pharmacological effects and bioavailability profile [10]. A good bioavailability profile includes permeability, solubility, lipophilicity, stability and solubility. In a drug-likeness prediction, pharmacokinetics (absorption, distribution, metabolism and excretion (ADME)), toxicology, potency and selectivity of an identified compound has to be optimized. Optimization is a crucial step for drug development. Therefore, *in silico* approaches is to predict ADME. ( Text 11pt/ Align left/ Justify/ Single Spacing)

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## MATERIALS AND METHODS (Uppercase/ 12pt/ Bold/ Align Left)

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### Data for *in silico* assessment ( Text 11pt/ Bold/ Align left/ Lowercase)

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We analyzed sixteen compounds of phytocannabinoid using *PubChem Compound*: CBD, CBDA, CBN, CBC, CBG, CBL, CBV, CBDV, CBCV, CBGV, CBDL, CBE, CBT, Δ9-THC, Δ9-THCV, and Δ8-THC. All molecular structures were obtained in the form of Simplified Molecular-Input Line-Entry System (SMILES). The line notations for describing each of the molecular structure were imported using *PubChem Compound.* We used The American Standard Code for Information Interchange (ASCII) strings form in all software. The SMILES are listed as Table 1. Molecular structure is obtained from *ChemIDplus* software. ( Text 11pt/ Align left/ Justify/ Single Spacing)

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**Table 1** The SMILES (Text 10pt/ Justify/Align Centre/ Single Spacing)

| Compound | Canonical SMILES |
|---|---|
| CBD | CCCCCC1=CC(=C(C(=C1)O)C2C=C(CCC2C(=C)C)C)O |
| CBDA | CCCCCC1=CC(=C(C(=C1C(=O)O)O)C2C=C(CCC2C(=C)C)C)O |
| CBN | CCCCCC1=CC2=C(C(=C1)O)C3=C(C=CC(=C3)C)C(O2)(C)C |
| CBC | CCCCCC1=CC2=C(C=CC(O2)(C)CCC=C(C)C)C(=C1)O |
| CBG | CCCCCC1=CC(=C(C(=C1)O)CC=C(C)CCC=C(C)C)O |
| CBL | CCCCCC1=CC2=C(C3C4C(C3(C)C)CCC4(O2)C)C(=C1)O |
| CBV | CCCC1=CC2=C(C(=C1)O)C3=C(C=CC(=C3)C)C(O2)(C)C |
| CBDV | CCCC1=CC(=C(C(=C1)O)C2C=C(CCC2C(=C)C)C)O |
| CBGV | CCCC1=CC(=C(C(=C1)O)CC=C(C)CCC=C(C)C)O |
| CBDL | CCCCCC1=CC(=C(C(=C1)O)C2=C(C=CC(=C2)C)C(=C)C)O |
| CBE | CCCCCC1=CC2=C(C3C(CCC(C3O2)(C)O)C(=C)C)C(=C1)O |
| CBT | CCCCCC1=CC2=C(C(=C1)O)C3=C(CCC(C3O)(C)O)C(O2)(C)C |
| Δ9-THC | CCCCCC1=CC2=C(C3C=C(CCC3C(O2)(C)C)C)C(=C1)O |

| | |
|---|---|
| Δ9-THCV | CCCC1=CC2=C(C3C=C(CCC3C(O2)(C)C)C)C(=C1)O |
| Δ8-THC | CCCCCC1=CC2=C(C3CC(=CCC3C(O2)(C)C)C)C(=C1)O |

**Determination rules (Lowercase/ 12pt/ Bold/ Align Left)**

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Lipinski's rules were used to assess the drug-like properties [10]. *Molinspiration* software provided data on molecular weight, number of hydrogen bond donor (HBD), number of hydrogen bond acceptor (HBA), polar surface area (PSA) and number of rotatable bond (NROTB). Lipinski suggested the Ro5 properties that would make it likely orally an active drug in human [10]. The rules for molecular descriptors are, partition coefficient logP (cLog P)<5, molecular weight (MW)<500, number of hydrogen bond acceptors (HBA)<10, number of hydrogen bond donors (HBD)< 5, and no more than one number of violation. A drug is expected to be absorbed over 90% if the PSA value is less than 60 Å2 [13]. The molecular polar surface area (PSA) is calculated based on O- and N- centered polar fragments. The value of number of rotatable bonds (NROTB) should be less than 10 for an assessment to the absorptive ability [14]. ( Text 11pt/ Align left/ Justify/ Single Spacing)

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## RESULTS AND DISCUSSION (Uppercase/ 12pt/ Bold/ Align Left)

We evaluated drug likeness of phytocannabinoids according to Lipinski's Ro5. The bioactivity score is used as an indicator to the activeness of compounds. ( Text 11pt/ Align left/ Justify/ Single Spacing)

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## CONCLUSION (Uppercase/ 12pt/ Bold/ Align Left)

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The Ro5 filter is useful in predicting compound with good oral absorption by comparing with drugs that have reached users. CBT is the only phytocannabinoid that does not violate any of the Ro5. Therefore, CBT maybe further examine for a candidate drug. All sixteen phytocannabinoids show good oral absorption with a 100% absorptivity, except for CBDA and CBT (>90%). All phytocannabinoids obeyed Lipinski's rules which indicate good bioavailability. In addition, bioactive scores are determined as, active or moderately active. All phytocannabinoids possess active score for GCPR ligand and enzyme inhibition except CBDA is predicted as moderately active. Based on the prediction, we conclude that all phytocannabinoids are potential for further oral drug development. ( Text 11pt/ Align left/ Justify/ Single Spacing)

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## ACKNOWLEDGEMENTS (Uppercase/ 12pt/ Bold/ Align Left)

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**REFERENCES(Uppercase/ 12pt/ Bold/ Align Left)**

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