α-Glucosidase inhibitory activity of cannabidiol, tetrahydrocannabinol and standardized cannabinoid extracts from Cannabis sativa

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Handling Editor: Alejandro G. Marangoni

Keywords:
α-Glucosidase
Cannabidiol
Cannabinoid
Cannabis
Diabetes mellitus
Tetrahydrocannabinol

A B S T R A C T

Two major cannabinoids of cannabis, namely cannabidiol (CBD) and tetrahydrocannabinol (THC) have been reportedly used as alternative medicine for diabetes treatment in both pre-clinical and clinical research. However, their mechanisms of action still remain unclear. Therefore, this study aimed to evaluate the α-glucosidase inhibitory activity of THC, CBD and the standardized cannabinoid extracts. Based on in silico studies, THC generated hydrogen bonding and Van der Waals interactions, while CBD exhibited only Van der Waals interactions with functional residues of target α-glucosidase protein, with good binding energies of −7.5 and −6.9 kcal/mol, respectively. In addition, both of them showed excellent pharmacokinetic profiles with minor toxicity in terms of tumorigenic and reproductive effects. In addition, the enzyme based in vitro assay on α-glucosidase revealed that THC and CBD exhibited good inhibitory activity, with the IC50 values of 3.0 ± 0.37 and 5.5 ± 0.28 μg/ml, respectively. These were better than the standard drug, acarbose (IC50 of 488.6 ± 10.23 μg/ml). Furthermore, two standardized cannabinoid extracts, SCE-I (C. sativa leaf extract) and SCE-II (C. sativa inflorescence extract) exhibited stronger inhibitory activity than THC and CBD, with the IC50 values of 1.2 ± 0.62 and 0.16 ± 0.01 μg/ml, respectively. The present study provides the first evidence that the standardized cannabinoid extracts containing THC and CBD have greater potential than CBD and THC in application as an α-glucosidase inhibitor.

1. Introduction

Diabetes mellitus (DM) is a group of chronic disease characterized by abnormality of metabolic system, which leads to a high level of blood sugar. Hyperglycemia, a condition of excessive amounts glucose in the blood, is a common effect of DM. Extended period of uncontrolled hyperglycemia usually cause severe damage to many organs and tissue including nerves, and blood vessels (Galicia-Garcia et al., 2020). Over the last decade, prevalence of DM has been rapidly increasing and is now regarded as one of the most important global health issues. Approximately 460 million people or 6% of world population were affected by DM (Khan et al., 2020). Furthermore, DM was a top ten globally leading causes of death in 2019, and predicted to reach more than 500 million death in the next twenty-five years (Wu et al., 2021). DM can be managed by lifestyle/behavioral change and/or pharmacotherapeutic interventions. Presently, many classes of antidiabetic drugs are available including α-glucosidase inhibitors (Quattrocchi et al., 2020). The U.S. food and drug administration approves α-glucosidase inhibitors for treating type 2 DM patients as monotherapy or combined with other antidiabetic drugs in treatment regimen, especially in patients who have excessive postprandial glucose levels after consuming high-carbohydrate diets (Hosain et al., 2020).

α-Glucosidase is an important enzyme in the digestive system that is responsible for the digestion of carbohydrates into monosaccharides, such as glucose and fructose, allowing them to be absorbed into the bloodstream. Accordingly, the inhibition of α-glucosidase can reduce
carbohydrate digestion rate, lower glucose uptake, which result in lessened blood sugar level (DiNicolantonio et al., 2015; Alqahtani et al., 2020). However, many α-glucosidase inhibitor agents potentiate some disadvantages including gastrointestinal disturbances, causing of liver problem, and also contraindicate in patients who are at risk of diabetic ketoacidosis, inflammatory bowel disease, and colonic ulceration (Derosa and Maffioli, 2012).

Following the legalization of Cannabis sativa L., an annual herbaceous plant from the Cannabaceae family, for medical purposes in many countries, research interest in the biological and pharmacological properties of cannabis continue to rise. Furthermore, cannabinoids, a major and unique group of secondary metabolites found in cannabis, may play an important role in diabetes management (Suttithumsatid and Panichayupakaranant, 2020). Cannabidiol (CBD) and tetrahydrocannabinol (THC), the major cannabinoids commonly found in cannabis, may be the active compounds responsible for anti-diabetic effect due to their effect on the endocannabinoid system, which shares a numerous signaling pathway that maintains physiological stability and balancing many processes in the human body. However, detailed evaluation of their mechanisms of anti-diabetic effect is yet to be addressed (Horváth et al., 2012; Jadoon et al., 2016; Suttithumsatid and Panichayupakaranant, 2020). Cannabis leaves and inflorescences have been reported as the main sources of cannabinoids in cannabis plants due to abundant presence of glandular trichomes (Jin et al., 2020). In addition, leaves and inflorescences of cannabis are traditionally used as the main ingredients in the medical recipes (Crocq, 2020).

Although CBD has been recently reported to exhibit α-glucosidase inhibitory activity, in silico and in vitro (Ma et al., 2021), the effect of THC is still unknown. Therefore, the present study focused on comparison of α-glucosidase inhibitory effects of THC and CBD, both in silico and in vitro. Pharmacokinetic/ADMET profiles of THC and CBD were also determined, in silico.

Furthermore, the standardized cannabinoid extracts from the leaves and inflorescences were also investigated for their α-glucosidase inhibitory activity relative to the marker compounds, THC and CBD in order to determine the effect of their complexation of phytochemicals on α-glucosidase activity.

2. Materials and methods

2.1. Chemicals

CBD (98% purity) was purchased from Chemface, China. THC (99% purity) was prepared in-house according to our previous report submitted to Pharmaceutical and Biomedical Research Journal (in press). Dimethylsulfoxide (DMSO), ethanol and methanol (analytical grade) were obtained from RCI Labscan, Thailand. α-Glucosidase from Saccharomyces cerevisiae and p-nitrophenyl-α-D-glucopyranoside (pNPNG) and acarbose were purchased from Sigma-Aldrich, USA. DPTassium hydrogen phosphate, monopotassium phosphate, and sodium carbonate were obtained from Merck, Germany, Loba India, and Fluka, USA, respectively.

2.2. Plant materials

Inflorescences and leaves of C. sativa were obtained from Faculty of Natural Resources, Prince of Songkla University, Hat Yai Campus Thailand. The leaves and inflorescences were dried in a hot air oven at 60 °C, for 24 h. The dried plant materials were then reduced to powder using an electric blender followed by sieving through a No. 20 sieve.

2.3. In silico experiment

2.3.1. Selection of target protein and cannabinoids

Three-dimensional structure of α-glucosidase macromolecule was downloaded from Protein databank (PDB) with accession ID: 5NNS (Roig-Zamboni et al., 2017) and acquires resolution of 2.00 Å. Chemical structures of the selected cannabinoids, CBD (CID 644019) and THC, (CID 16078) were retrieved from PubChem database for further analysis (Kim et al., 2016).

2.3.2. Molecular docking method

The structures of CBD, THC and target protein (PDB ID: 5NNS) in pdb format were imported to the Autodock Vina software (Trott and Olson, 2010). Heteroatoms, 3D protonation, and water molecules along with the default ligand attached in the target molecules were removed. Number of polar hydrogens and Kollman charges were added to the selected ligand molecular structure for molecular docking analysis (Khan et al., 2022). Grid box dimensions with centers (x = −14.806, y = −29.611, z = 96.917) and sizes (x = 74, y = 70, z = 86) were generated using the selective residues. The active binding sites containing active residues of VAL193, PRO194, LEU195, GLU196, PHE490, THR491, LEU496, LEU565, LEU574, LEU577, THR578, THR581, ILE585, ARG586, ALA604, GLY605, ARG608, ARG696, LYS697, THR700, LEU701, ILE775, GLN776, VAL778, ILE780, GLU781, THR813, LUE814, and TYR609 were involved in the binding interactions with the selected ligand molecules. A reliable scoring scheme that resulted in the formation of binding energies of the best binding poses was established, and a number of molecular interactions, such as hydrogen bonding, Pi-bonding and hydrophobic interactions were retrieved by importing the docked complex to Discovery studio (D. Studio, Discovery Studio, Accelrys [2.1], 2008) visualization tool.

2.3.3. Determination of pharmacokinetic/ADMET profile

ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles of CBD and THC were determined to evaluate the drug-like attributes of the chemical compounds (Bibi and Sakata, 2017; Saleem et al., 2021a, 2021b). SwissADME (Daina et al., 2017) and Datawarrior tools (Sander et al., 2015) were used for the estimation of ADMET profiles of CBD and THC.

2.4. Preparation of standardized cannabinoid extracts

The dried powders of inflorescences and leaves were separately extracted using a microwave extraction. Briefly, the dried powders (2 g) were soaked in ethanol (20 ml) and placed in a microwave oven. The extraction was performed using a microwave power of 270 W, at 60–65 °C, for 1 min. After that, the extracts were filtrated through a filter paper and subjected to solvent evaporation using a rotary evaporator, at 50 °C to produce C. sativa leaf (SCE-I) and inflorescence (SCE-II) extracts. The dried extracts were subjected to quantitative HPLC determination of CBD and THC.

2.5. Quantitative HPLC determination of CBD and THC

Quantitative HPLC determination of CBD and THC in the extracts was performed using a method previously described (Saingam and Sakunpak, 2018), with some modifications. The method was performed using a UFLC Shimadzu model equipped with a photodiode-array detector and autosampler (Shimadzu Corp. Kyoto, Japan). A Luna® C18 column 4.6 mm × 250 mm, 5 μm (Phenomenex, Thailand) was eluted with a mobile phase consisted of methanol and water (85:15, v/v) at a flow rate of 1 ml/min. Monitoring of CBD and THC was performed using a UV–Vis spectrophotometer at 220 nm. The injection volume was 20 μl. All experiments were performed in triplicate. Calibration curves of CBD and THC were established using the authentic compounds at six concentrations between 6.25 and 200 μg/ml. Based on the linear regression, the calibration curves of CBD and THC were Y = 72615X + 72146 (r² = 0.9998) and Y = 54467X + 77267 (r² = 0.9999), respectively.
2.6. α-Glucosidase inhibition assay

α-Glucosidase inhibitory activity was determined using a method previously described (Shah et al., 2017), with some modifications. Concisely, α-glucosidase enzyme (0.1 Unit/ml) was dissolved in 0.1 M potassium phosphate buffer (pH 6.8). The samples were dissolved in DMSO (the final concentration of DMSO did not exceed 7%). Subsequently, 20 μl of each sample was mixed with 20 μl of enzyme solution in a 96-well microtiter plate, then incubated at 37 °C for 10 min. After that, pNPG (40 μl) was added, and the mixture was further incubated at 37 °C for 40 min. After incubation, 0.2 mM sodium carbonate in phosphate buffer (80 μl) was added to each well to stop the reaction. The amount of final product (p-nitrophenol) was measured using a microplate reader at 405 nm. The blank control was performed by the same protocol, but the α-glucosidase enzyme solution was replaced with the boiled enzyme. The control experiment also performed with the same process, but the sample solution was replaced with the same concentration of DMSO and deionized water in the sample solution. Acarbose was used as a positive control. The experiments were carried out in triplicate. The percentage inhibition was calculated using the following equation:

\[
\text{%Inhibition} = \frac{[(\text{Ac-Ab}) - (\text{As-Ab})]}{(\text{Ac-Ab})} \times 100
\]

Where: Ac = Absorbance of control, As = Absorbance of sample, Ab = Absorbance of blank.

2.7. Statical analysis

The results are expressed as mean ± SD. Statistical significance was calculated using one-way analysis of variance (ANOVA) followed by Tukey’s multiple range test (p < 0.05).

3. Results and discussion

3.1. In silico studies

3.1.1. Molecular docking

Molecular docking is an appropriate molecular modeling application, explaining significant scoring scheme, and best binding poses generated by best docked complex. This assist in the retrieval of protein-ligand binding interaction; hence, it could be helpful in understanding the molecular mechanism of bounded ligand in the vicinity of the active site of target protein (Fathima and Murugabooopathi, 2019; Khan et al., 2021). Previous studies has proved that this is a powerful tool and very significant method in computer-aided drug design and development procedures to explain the molecular mechanism of bounded ligand with target protein/receptors, thus facilitating the identification of several bioactive compounds against many diseases (Ismail et al., 2021; Saleem et al., 2021a, 2021b). Based on a molecular docking analysis against α-glucosidase, CBD and THC exhibited best bounded conformation and interactions in the active binding site of α-glucosidase protein (Figs. 1 and 2). Therefore, they could be potentially used as therapeutic agents to manage type 2 DM. Summary of molecular docking results is presented in Table 1.

Fig. 1. Graphical representation of molecular docked complex of THC in the vicinity of active binding site of α-glucosidase protein (a), best bounded pose of THC presenting the potential of hydrogen bonding capacity (green presents hydrogen bond acceptor region, and purple presents the hydrogen bond donor region) with active binding site residues (b), and two-dimensional plot presenting binding interactions of the THC with target α-glucosidase protein (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
protein. In addition, Van der Waals interaction network with VAL193, GLU196, Pro194, THR195, LEU196, LEU496, LEU565, LEU574, LEU577, THR578, ILE581, ARG585, ALA604, GLY605, ARG608, TYR609, GLY605, ARG608, TYR609 residues, as well as LEU195, LEU565, LEU577, ILE581, and TYR609 residues were involved in alkyl and Pi-alkyl interactions of THC (Fig. 1c). CBD also generated the best bounded conformation at 6.9 kcal/mol (Fig. 2a). In contrast, it exhibited far less potential to generate hydrogen bond (Fig. 2b). However, the two-dimensional plot revealed that Van der Waals interaction network with ARG696, THR700, GLN776, VAL778, GLU781, and THR813 residues as well as LYS697, LEU701, ILE775, ILE780, and ILE814 residues were involved in alkyl and Pi-alkyl interactions of CBD (Fig. 2c).

### 3.1.2. Determination of Pharmacokinetic/ADMET profiles

Various studies have explained the importance of pharmacokinetic/ADMET profile estimation for the screening of databases to identify potential drug-like and a lead-like compounds that could be better suited in the design and development of new drugs (Bibi and Sakata, 2017; Khan et al., 2022). ADMET profiles are calculated by SwissADME (Daina et al., 2017) and Datawarrior tools (Sander et al., 2015). Physicochemical properties of the selected compound, namely molecular weight (MW), partition coefficient (log P), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), total polar surface area (TPSA), molar refractivity (MR), and rotatable bond (RB) are important drug-like characteristics calculated for selected compounds.

In silico ADMET profiles, including important drug-like characteristics, pharmacokinetics, drug-likeness, medicinal chemistry along with toxicity estimated for THC and CBD are summarized in Table 2.

Based on the drug-likeness theory, the physicochemical properties of THC and CBD were in the acceptable ranges without any violation (Lipinski, 2004). Their lipophilicity and water solubility classes exhibited very good outcomes, with gastrointestinal drug absorption (GI-DA) and blood brain barrier (BBB) permeability were in the range of acceptable pharmacokinetic parameters (Kimura and Higaki, 2002). Although both cannabinoids were not P-glycoprotein (P-gp) substrate, THC exhibited inhibitory potential on CYP2C19, CYP2C9 and CYP2D6, while CBD showed inhibitory potential on CYP2C19, CYP2C9, CYP2D6 and CYP3A4. THC and CBD also possessed good skin permeation, with Log Kp values of -3.27 and -3.59 cm/s, respectively. Regarding their medicinal chemistry, PAINS and Brenk alerts showed minor violations.

| Table 1 | Summary of molecular docking results of THC and CBD with α-glucosidase target protein. |
| --- | --- |
| PubChem CID | Compounds | Binding energies (Kcal/mol) | Functional residues | Binding interactions |
| --- | --- | --- | --- | --- |
| 16078 | THC | -7.5 | VAL193, PHE194, LEU195, GLU196, PHE490, THR491, LEU496, LEU565, LEU574, LEU577, THR578, ILE581, ARG585, ALA604, GLY605, ARG608, TYR609 | Van Der Waals, Hydrogen bonds, Alkyl, Pi-Alkyl |
| 644019 | CBD | -6.9 | ARG696, LYS697, THR700, LEU701, ILE775, GLN776, VAL778, ILE780, GLU781, THR813, LUE814 | Van Der Waals, Alkyl, Pi-Alkyl |

Fig. 2. Graphical representation of molecular docked complex of CBD in the vicinity of active binding site of α-glucosidase protein (a), best bounded pose of CBD presenting the potential of hydrogen bonding capacity (green presents hydrogen bond acceptor region, and purple presents the hydrogen bond donor region) with active binding site residues (b), and two-dimensional plot presenting binding interactions of the CBD with target α-glucosidase protein (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
highly accessible synthesis with the scores of 4.27 and 4.05. The toxicity estimation revealed that THC and CBD exhibited low toxicity, which were also higher than in the leaves (0.01–1.24%) (Richins et al., 2018). Variation of cannabinoid content usually depends on cannabis chemovars and cultivated area (Jin et al., 2020). A ratio of THC and CBD content has been used as an important tool for characterization of C. sativa chemotypes. Generally, three chemotypes including chemotype I or “THC dominant” (CBD/THC ratio <0.5), chemotype II or “intermediate type” (CBD/THC ratio between 0.5 and 3), and chemotype III or “CBD dominant” (CBD/THC ratio >3.0) have been described (Elzinga et al., 2015). Therefore, the cannabis used in this study that have THC/THC ratios of 1.3 and 0.7 for SCE-I and SCE-II, respectively, is categorized as a chemotype II or intermediate type cannabis.

### 3.2. Preparation of SCE-I and SCE-II

Leaf and inflorescence extracts of cannabis, namely SCE-I and SCE-II were prepared using a microwave extraction and standardized using an HPLC method to contain CBD of 2.5% w/w and THC of 1.9% w/w for

| Compounds/Extracts | IC$_{50}$ (µg/ml) |
|-------------------|-----------------|
| THC               | 3.0 ± 0.37$^a$  |
| CBD               | 5.5 ± 0.28$^b$  |
| SCE-I             | 1.2 ± 0.62$^c$  |
| SCE-II            | 0.16 ± 0.01$^d$ |
| Acarbose          | 488.6 ± 10.23$^e$ |

$^a$Values with non-identical letters (a, b, c, d and e) are significantly different (p < 0.05).
of THC and CBD in animal model is still required. Interestingly, our findings also indicated that the standardized ethanol extracts of inflorescences (SCE-II) and leaves (SCE-I) of cannabis possessed significantly stronger α-glucosidase inhibitory effect than their marker compounds, THC and CBD. Therefore, the extracts have greater potential to alleviate diabetes, since very low concentrations of CBD and THC are needed. This may be due to synergistic effects between the cannabinoids or entourage effects with the other phytochemicals, such as terpenoids and flavonoids, in the crude ethanol extracts. Recently, phytochemical composition of cannabis inflorescences has been identified and reported to contain approximately 15–20% cannabinoids, 1–2% terpenoids, and 0.1% flavonoids, while cannabis leaves contained lower levels of cannabinoids (1–2%), terpenoids (0.1–0.2%), but higher level of flavonoids (0.3–0.4%) [Jin et al., 2020]. The most abundant of flavonoids in cannabis were quercetin, kaempferol, luteolin and apigenin, which have been reported to possess good α-glucosidase inhibitory activity, with the IC₅₀ values of 15, 32, 46, and 82 μM, respectively [Pronca et al., 2017]. On the other hands, terpenoids that have been identified in cannabis, including limonene, α-terpineol, α-terpinene, geraniol, and linalool exhibited weak α-glucosidase inhibitory effect (Wojnuk-Kulesza et al., 2019). Therefore, the synergistic effect might be mainly from interactions between the flavonoid compounds. However, further studies on identification of other active principles and their synergistic effect against α-glucosidase inhibitory activity are still needed.

4. Conclusion

Our findings suggest that the major active principles for α-glucosidase inhibitory effects of cannabis extracts are THC (IC₅₀ of 9.5 μM) and CBD (IC₅₀ of 17.5 μM) due to their major abundance and potent activity. However, the standardized extracts of inflorescences (SCE-II) and leaves (SCE-I) of cannabis possess higher inhibitory effect than their marker compounds suggesting the synergistic effects of phytochemicals in cannabis. In addition, SCE-II exhibited higher activity than SCE-I due to its high content of cannabinoids. Therefore, SCE-II and SCE-I are highly recommended as new α-glucosidase inhibitors for type 2 diabetes patients. However, high quality in vivo and clinical studies are still required to fully understand their efficacy and safety profiles.

CRediT authorship contribution statement

Wiwit Suttithumsatid: extraction, HPLC analysis, enzyme assay and writing the manuscript. Muhammad Ajmal Shah: molecular docking analysis and pharmacokinetic/ADMET profile, estimation and writing the manuscript. Shabana Bibi: molecular docking analysis and pharmacokinetic/ADMET profile estimation and writing the manuscript. Pharkphoom Panichayupakaranant: conceptualization of the research and methodology, project supervision and administration, writing the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments and funding

The authors wish to thank Dr. Fredrick Eze for assistance with English editing. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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