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In Silico Examination of Drug-Drug Interactions of Medical Cannabis and Antidepressant Drug Groups

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This study was conducted to investigate the drug-drug interaction of medical cannabis with antidepressant drug groups by using the in silico method. In our study, drug-drug interactions of medical cannabis and antidepressant drug groups were analyzed on the Way2Drug and PubChem web platforms by using their isomeric structures. It was found that selective serotonin reuptake inhibitors (SSRIs) usually posed a minimal risk or showed no interaction; they caused adverse effects when used together with cannabidiol (CBD) and tetrahydrocannabinol (THC), minimum bet occurred when monoamine oxidase (MAO) inhibitors were used with CBD, adverse effects were observed when they were used with THC, and that the use of trazodone, milnacipran, agomelatine, vilazodone, and desvenlafaxine, which are among other antidepressants, with both molecules resulted in adverse effects.

Keywords: Medical Marijuana, Cannabidiol, Antidepressant, Drug Interactions, In Silico

INTRODUCTION

The therapeutic use of plant parts and bioactive products that plants naturally produce to survive and adapt to the environment dates back centuries (Odieka et al. 2022). Bioactive products found in a plant are called photochemical (Choudhary et al. 2014), and plants that contain therapeutic photochemical and are used for drug synthesis are called medical plants (Sofowora et al. 2013). One medical plant used for centuries is *Cannabis sativa*, also known as cannabis.

Cannabis sativa, which belongs to the Cannabaceae family, is a plant that has been used since ancient times in many fields, especially in health, with its rich phytochemical content. It contains hundreds of compounds, including phytocannabinoids, terpenes, and flavonoids, called unique secondary metabolites (Arnold, 2021). This plant is named medical cannabis due to the medical use of its parts or herbal products containing these metabolites (Bridgeman and Abazia, 2017). The most investigated compounds of the plant in terms of its therapeutic effects are delta-9-tetrahydrocannabinol (Δ^9-THC/THC) and cannabidiol (CBD) (Figure 1). These compounds exert their therapeutic effects through the endocannabinoid system, which plays a role in many physiological events (Abu-Amna et al. 2021).

The endocannabinoid system (ECS) consists of endogenous ligands, cannabinoid receptors to which ligands bind, and enzymes responsible for the biosynthesis and degradation of ligands (Büyüker et al. 2021). Since ECS is a neuromodulatory system, it is based on using one or more chemicals by a particular neuron to regulate different neuron populations (Klumpers and Thacker, 2019). This system is associated with the body's homeostasis, affecting many physiological events such as energy balance, blood pressure, appetite stimulation, pain, nausea and vomiting, and memory (Katona and Freund, 2012). It is found in almost every tissue of the body. Although ECS is associated with the pathology of many disorders, such as addiction and schizophrenia, it has shown positive effects on treating diseases, such as Alzheimer's, epilepsy, and cancer (Kaur et al. 2016).

The treatment of some diseases may require co-medication, and this leads to drug-drug interactions (DDI). Drug-drug interactions are divided into three groups: pharmaceutical, pharmacodynamic, and pharmacokinetic. These interactions usually occur in four steps through cytochrome P450 (CYP450) metabolism via pharmacokinetic interactions. Pharmacokinetic interaction occurs when a drug causes a change in the pharmacological effect of another drug by affecting its absorption, distribution, metabolism, and excretion (ADME). Studies have shown that pharmacokinetic drug-drug interactions occur through CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isoenzymes (Klumpers and Thacker, 2019; Dmitriev et al. 2021).

The Operational Classification (ORCA) system has

been created to calculate the risks that may occur due to the combined administration of the two drugs. This system is used to classify drug-drug interactions and is divided into five classes: Class 1 (contraindicated), Class 2 (temporarily contraindicated), Class 3 (conditional), Class 4 (minimum risk), and Class 5 (no interaction) (Dmitriev et. al.,2019)

In vivo and clinical studies on drug-drug interactions are costly and time-consuming. Compared to other methods, the in silico process, a kind of biological experiment performed on a computer, has high efficiency, is conducted in a short time, is cost-efficient, and requires less use of experimental animals (Gangrade et al. 2016). In addition, in silico methods allows the estimation of many significant parameters of chemicals, such as interaction with a biological system, the molecular mechanism of action, physicochemical properties, three-dimensional structure-activity relationship, pharmacokinetics, toxicity, unintended effects, and environmental effects (Raunio, 2021).

Although drugs containing cannabis are viewed with suspicion due to their abuse and their psychoactive component, they have undeniable therapeutic effects in treating many diseases today. Cannabis is essential for new drug discoveries due to the inadequacy of the drugs used to treat some diseases. Investigation of the drug-drug interactions that may occur when used with other medications is also necessary.

Our study is based on the estimation of the severity classes of drug-drug interactions of CBD and THC molecules with non-selective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase A (MAO) inhibitors, and other antidepressants drug groups and the estimation of the CYP450 enzymes with which they interact by using the libraries and databases on PubChem and Way2Drug web platforms.

Medical cannabis

Medical cannabis is used in treating many diseases due to its therapeutic effects.

The difference between cannabis and medical cannabis is based on the molecular forms they contain. While biomolecules in cannabis are synthesized in the form of carboxylic acid, in medical cannabis, after the harvest of this plant, they turn into neutral states as a result of their decarboxylation due to external factors, such as heat, light, and extraction, and the seneutral forms are used for medical purposes (Flores-Sanchez and Verpoorte, 2008).

Medical cannabis has been a medicinal agent and analgesic for many years. As a medicalagent, it treatsepilepsy, muscle spasms, multiple sclerosis, neuropathic pain, neurodegenerative diseases, and cancer. Cannabis-derived pharmaceuticals such as commercially available nabilone (a compound of the same general type as Δ9-THC) or dronabinol (a synthetic Δ9-THC) are prescribed to relieve nausea and vomiting caused by chemotherapy. Nabiximol, a combination of THC and CBD, has all eviated neuropathic pain (Amin and Ali, 2019).

Antidepressant and anxiolytic effects of medical cannabis

CB1 receptors, which are densely located in the prefrontal cortex, amygdala, and hippocampus regions of the brain, affect the mechanisms that play a role in affective disorders and the elimination of psychotic effects. In addition, phytocannabinoids and other compounds that exert their antide pressant, anxiolytic, and analgesic effects via the endocannabinoid system or the 5-HT1A receptor have a therapeutic effect on depression, anxiety, post-traumatic stress disorder, pain-related insomnia, and neurodegenerative diseases (Sarris et al. 2020).

Medical cannabis can be used as a therapeutic agent for the effects of post-traumatic stress disorder, such as anxiety, insomnia, and nightmares. In vivo, studies have shown that CB1, one of the endogenous receptors, may be associated with the formation and disappearance of fear (Quirk and Mueller, 2008). Medical cannabis has limited evidence for anxiety, insomnia, and depression in studies. However, in epidemiological results, medical cannabis has an anxiety-reducing effect.

The endocannabinoid system, which plays a role in the regulation of anxiety and mood, exerts its effects through endocannabinoid receptors located in the medial prefrontal cortex, amygdaloid complex, bed nucleus of the stria terminals, and hippocampus regions of the brain (Lisboa et al. 2017). Additionally, anxiolytic and antidepressant effects occur due to the activation of 5-HT1A and cannabinoid receptor type 1 (CB1) receptors with CBD and THC (Russo et al. 2005).

It has been shown that cannabis is associated with alleles that cause schizophrenia and that some genes play a role in schizophrenia development as a result of cannabis use at an early age (Van Winkel and Kuepper, 2014). In addition, the THC-psychoactive substance in cannabis increases the psychoactive effects of schizophrenia. For this reason, the results of CBD on schizophrenia have been investigated, and CBD has been found to reduce both the impact of schizophrenia and the psychotic effects of THC (Sarris et al. 2020).

Parkinson's disease, a neurodegenerative disorder, is the second most common disease. As a result of the loss of dopaminergic neurons in the brain, this disease cause stremors at rest, slow motion, deterioration in gait and posture, and causes stiffness of the muscles. Some studies have shown that the activation of the endo cannabinoid receptor cannabinoid receptor type 2 (CB2R) increases microglial and astrocyte deactivation in some areas of the brain, ensures the survival of neuronal cells by playing a role in the reorganization of neuronal function and inhibits neuroinflammation by taking a role in regulating functional deficiencies (Hashish et al. 2021).

Attention deficit hyperactivity disorder (ADHD) and bipolar disorder are thought to be associated with endocannabinoid system disorder. However, no studies on this subject have been conducted (Sarris et al. 2020).
Studies have shown that depressive effects increase in people who use high doses of cannabis for recreational purposes (Lev-Ran et al. 2014). Therefore, when people with depressive moods are given cannabis-based drugs, it should be ensured that they do not contain high amounts of THC.

Drug-drug interactions

Sometimes more than one drug can be administered at the same time in the treatment of diseases, and this can lead to drug- drug interactions (DDI). These interactions are divided in to three groups: pharmaceutical, pharmacodynamic, and pharmacokinetic. Pharmaceutical interactions occur due to physicochemical interactions between drugs to be administered intravenously to patients due to mixing them during administration. As a result of this interaction, drugs may precipitate in infusionsor become inactive. Pharmacodynamic interactions include additive (1+1=2), synergistic (1+1>2), or antagonistic (1+1<2) interactions of drugs on the same target as a result of the administration of more than one drug. Finally, pharmacokinetic interactions occur when a drug causes a change in the pharmacological effect of another drug by affecting the absorption, distribution, metabolism, andexcretion (ADME) of the drug (Dmitriev et al. 2021).

Drug-drug interactions generally show their pharmacokinetic interactions in four steps via CYP450 metabolism.

Cannabinoids, which have an important role in the treatment of many diseases, are metabolized by CYP isozymes and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) when taken into the body, and it is known that they can accelerate drug-drug interactions. CBD is converted to active metabolite 7-hydroxy cannabidiol (7-OH-CBD) via the CYP2C19 pathway in the liver and intestine (Landmark and Brandl, 2020). Glucuronoids, which are inactive metabolites, are metabolized to carboxylic acid via UGT and CYP3A4 pathway. Inactive metabolites are excreted from the body in feces or urine. THC is converted to 11-hydroxy-∆9-THC, an active metabolite, via the CYP2C9 pathway, and then to 9-nor-carboxy-THC (Greger et al. 2020). Both metabolites are metabolized to glucuronides, inactive metabolites, via UGT and CYP3A4 pathway, and are excreted in the feces or urine. CBD has the potential to inhibit CYP2C8, CYP2C9, and CYP2C19 enzymes, as well as UGT enzymes (Greger et al. 2020). THC can be an inhibitor of the CYP2C9 enzyme and induces the CYP1A2 enzyme (Damkier et al. 2019). In addition, THC inhibits CYP1A2, CYP2B6, CYP2C9, and CYP2D6 competitively, while CBD competitively inhibits CYP3A4, CYP2B6, CYP2C9, CYP2D6, and CYP2E1. As a result, it has been observed that the effects of other drugs given to patients can also change.

MATERIALS AND METHODS

Drug selection

The Anatomical Therapeutic Chemical (ATC) Classification System of drugs found in the World Health Organization Collaboration Center for Drug Statistics Methodology (WHOCC) data base was used to detectantide pressant medicines. Antidepressant drug groups are in the N06A category.

PubChem

The simplified molecular-inputline-entry system (SMILES) formula with defined structures was used to determine drug-drug interactions of biomolecules. The SMILES formats of the substances were accessed on the PubChem (https://pubchem.ncbi.nlm.nih.gov/) web server.

Way2Drug

In our study, these verity classes resulting from drug-drug interactions of antidepressant drug groups with CBD and THC molecules and the relationships of these interactions with P450 enzymes were estimated on the Way2drug-DDI web platform by using SMILES formats (http://way2drug.com/ddi/).

RESULTS

Probabilities predicting DDIs due to interactions with various cytochrome P450 isoforms were calculated as ∆P value = Pa (probability of belonging to a particular class of DDI severity) – Pi (in the opposite case).

Drug-drug interactions of non-selective monoamine reuptake inhibitors with medical cannabis

DDI classes and their interactions with P450 enzymes were analyzed on the Way2Drug platform to determine drug-drug interchanges. The severity classes of drug-drug interactions with CBD and THC are given in Table 1 and Table 2, respectively.

Interactions of desipramine, amitriptyline, and doxepin with CBD and THC molecules yielded positive ∆P values in Class 1, Class 4, and Class 5, and these interactions showed contraindicated effect and minimal risk in different cases but no interactions in some cases. In other severity classes, these interaction results yielded negative ∆P values, and no instances belonged to these severity classes. Maprotiline had positive ∆P values in Class 4 and Class 5 in its interactions with CBD and THC molecules, and these interactions showed minimal risk in different cases but no interactions in some cases

Table 1: The severity classes of drug-drug interactions between CBD and antidepressant groups

	Drug-drug interactions with CBD				
	Class 1 Contraindicated	**Class 2** Temporarily contraindicated	**Class 3** Conditioned	**Class 4** Minimum risk	**Class 5** No interaction
	No condition where the benefit of the combination outweighs its risks has been detected.	The combination increases the risk of side effects.	Risks can increase based on clinical conditions.	The risk of negative results looks small.	Drugs do not interact with each other.
Desipramin	X			X	X
İmipramin					
Klomipramin				X	X
Opipramol				X	
Amitriptilin	X			X	X
Doksepin	X			X	X
Maprotilin				X	X
Fluoksetin	X			X	X
Sitalopram	X				
Paroksetin	X				
Sertralin	X	X		X	
Fluvoksamin				X	X
Essitalopram	X				
Moklobemid	X			X	
Mianserin				X	
Trazodon	X				
Mirtazapin					
Bupropion		X		X	X
Tianeptin				X	X
Venlafaksin	X			X	X
Milnasipran	X			X	X
Reboksetin	X			X	X
Duloksetin				X	X
Agomelatin	X	X		X	X
Desvenlafaksin	X			X	X
Vilazodon	X				
Vortioksetin					
Esketamin				X	X

Table 2: The severity classes of drug-drug interactions between THC and antidepressant groups

	Drug-drug interactions with THC				
	Class 1 Contraindicated	**Class 2** Temporarily contraindicated	**Class 3** Conditioned	**Class 4** Minimum risk	**Class 5** No interaction
	No condition where the benefit of the combination outweighs its risks has been detected.	The combination increases the risk of side effects.	Risks can increase based on clinical conditions.	The risk of negative results looks small.	Drugs do not interact with each other.
Desipramin	X			X	X
İmipramin					
Klomipramin	X			X	X
Opipramol	X			X	
Amitriptilin	X			X	X
Doksepin	X			X	X
Maprotilin				X	X
Fluoksetin	X			X	X
Sitalopram	X				
Paroksetin	X				X
Sertralin	X			X	X
Fluvoksamin	X				
Essitalopram	X				
Moklobemid	X			X	X
Mianserin				X	
Trazodon	X			X	
Mirtazapin					
Bupropion				X	X
Tianeptin				X	X
Venlafaksin	X			X	X
Milnasipran	X			X	X
Reboksetin	X			X	X
Duloksetin				X	X
Agomelatin	X			X	X
Desvenlafaksin	X			X	X
Vilazodon	X				
Vortioksetin	X				
Esketamin				X	X

While the exchange of clomipramine with the CBD molecule yielded positive ΔP values in Class 4 and Class 5, its interactions with the THC molecule yielded positive ΔP values in Class 1, Class 4, and Class 5. Its interaction with CBD showed minimal risk or no interaction in different cases.

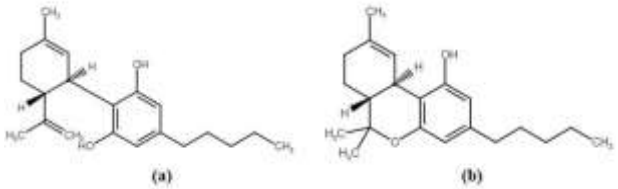

Figure 1: Chemical structures of CBD, cannabidiol (a); Δ^9 -THC, tetrahydrocannabinol (b).

In contrast, its interaction with THC was contraindicated in other instances and showed minimal risk or no interaction. Opipramol had positive ΔP values in Class 4 in its interaction with CBD, while it had positive ΔP values in Class 1 and Class 4 in its interaction with the THC molecule. While it had a minimum risk effect in different cases in its interaction with CBD, it was contraindicated in other patients. It had a minimum risk effect in its interaction with THC. Individual interactions of both molecules with imipramine had negative ΔP values in all severity classes, indicating the absence of DDI cases belonging to severity classes (Figure 2).

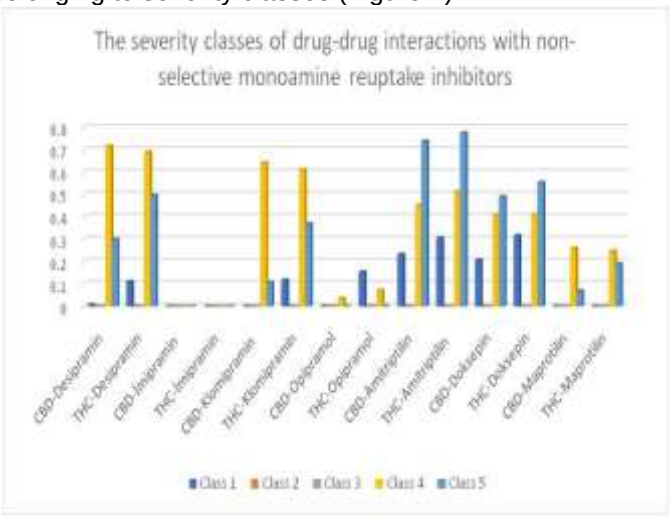

Figure 2: The severity classes of drug-drug interactions of SSRIs with CBD and THC molecules

In the predictive analysis of P450-mediated DDIs, the interactions of desipramine with CBD and THC molecules occurred at the biotransformation level accomplished by CYP2D6 and CYP2C19. While clomipramine showed its interaction with the CBD molecule through CYP2C8 and CYP2C19, its interaction with the THC molecule was through CYP2C19. The exchange of opipramol with the THC molecule occurred at the level of biotransformation accomplished by CYP2C19. Negative ΔP values for other isoforms of cytochrome P450 indicated that they were not involved in DDIs at the biotransformation level (Figure 3).

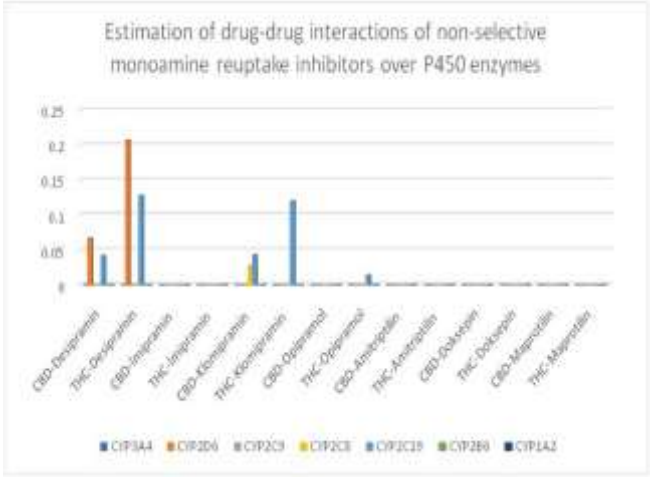

Figure 3: The relationship of P450 enzymes with drug-drug interactions of SSRIs and CBD and THC molecules

Drug-drug interactions of selective serotonin reuptake inhibitors (SSRIs) with medical cannabis

DDI classes and interactions with P450 enzymes were analyzed in silico to determine drug-drug interchanges. Fluoxetine had positive ΔP values in Class 1, Class 4, and Class 5 in its interactions with CBD and THC molecules. While these interactions were contraindicated and showed minimal risk in different cases, they indicated no interaction in some cases. Citalopram and escitalopram had positive ΔP values in Class 1 in their interactions with both molecules, and these interactions created a contraindicated effect in cases. While the exchange of paroxetine with CBD had positive ΔP values in Class 1, it had positive ΔP values in Class 1 and Class 5 when interacting with THC. While these interactions had a contraindicated effect in some cases, they showed no interactions in others. The exchange of sertraline with CBD had positive ΔP values in Class 1, Class 2, and Class 4, and these interactions showed a contraindicated effect, were temporarily contraindicated, and led to minimal risk effects in different cases. In its interaction with THC, it had positive ΔP values in Class 1, Class 4, and Class 5, and these interactions were contraindicated in different cases, showing minimal risk or no interaction at all. Fluvoxamine had positive ΔP values in Class 4 and Class 5 when interacting with CBD and Class 1 with THC. It showed minimal risk or no interaction at all in its interaction with CBD. However, it had a contraindicated effect when interacting with THC (Figure 4).

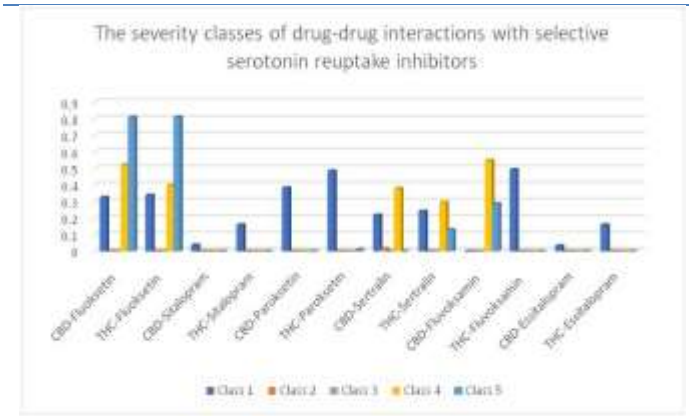

Figure 4: The severity classes of drug-drug interactions of selective serotonin reuptake inhibitors with CBD and THC molecules

In the predictive analysis of P450-mediated DDIs, the interaction of fluoxetine with CBD occurred at the biotransformation level accomplished by CYP2D6 and CYP2C19, and its interaction with THC occurred at the biotransformation level completed by CYP2D6, CYP2C8, and CYP2C19. The interactions of citalopram with both molecules occurred at the biotransformation level performed by CYP2C8 and CYP2C19, the exchange of sertraline by CYP2B6, and that of escitalopram by CYP2C8 and CYP2C19. Paroxetine showed its interaction with CBD over CYP2C19 and THC over CYP2D6. The interactions of fluvoxamine with CBD occurred at the biotransformation level accomplished by CYP2C9 and CYP2C8, and its interaction with THC occurred at the biotransformation level performed by CYP2C9, CYP2C19, and CYP1A2. Negative ΔP values for other isoforms of cytochrome P450 indicated that they were not involved in DDIs at the biotransformation level (Figure 5).

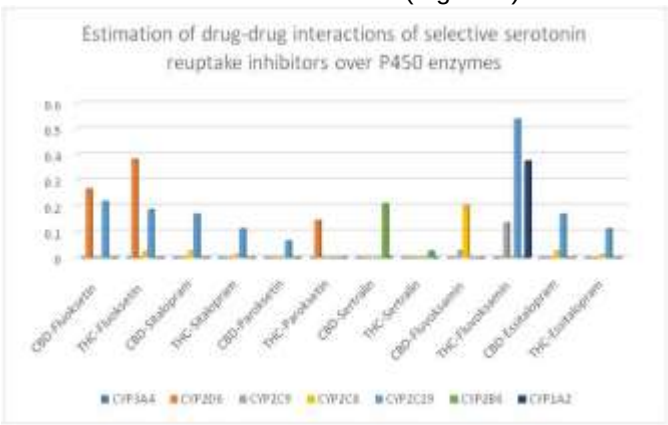

Figure 5: The relationship of P450 enzymes with drug-drug interactions of SSRIs and CBD and THC molecules

Drug-drug interactions of monoamine oxidase A (MAO) inhibitors with medical cannabis

While the interaction of moclobemide with CBD had positive ΔP values in Class 1 and Class 4, it had positive ΔP values in Class 1, Class 4, and Class 5 when interacting with THC. As a result of its interaction with CBD, it showed a contraindicated effect and minimal risk in different cases. Its interaction with THC showed a contraindicated effect and minimal risk in some cases, while it did not interact in others (Figure 6).

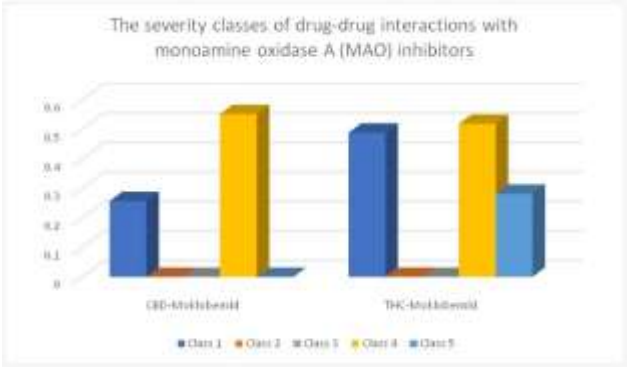

Figure 6: The severity classes of drug-drug interactions of MAO inhibitors with CBD and THC molecules

In the predictive analysis of P450-mediated DDIs, the interaction of moclobemide with CBD occurred at the biotransformation level accomplished by CYP2C8 and CYP2C19, and its interaction with THC happened at the level of biotransformation performed by CYP2C19. Negative ΔP values for other isoforms of cytochrome P450 indicated that they were not involved in DDIs at the biotransformation level (Figure 7).

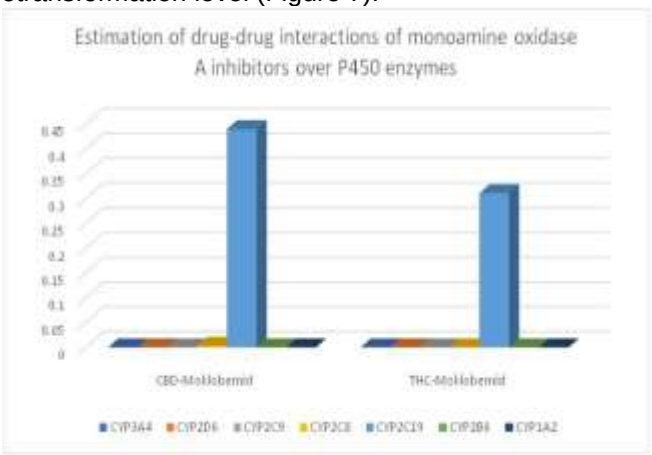

Figure 7: The relationship of P450 enzymes with drug-drug interactions of MAO inhibitors and CBD and THC molecules

Drug-drug interactions of other antidepressants with medical cannabis

The interaction of mianserin with CBD and THC molecules had positive ΔP values in Class 4, and as a result of this interaction, it showed minimum risk in cases. The interactions of tianeptine, duloxetine, and ketamine with both molecules had positive ΔP values in Class 4 and Class 5, and these interactions showed minimum risk effects in some cases and no interactions in others. The

interactions of venlafaxine, milnacipran, reboxetine, and desvenlafaxine with both molecules had positive ΔP values in Class 1, Class 4, and Class 5. These interactions showed a contraindicated effect and minimal risk in different cases, and they did not indicate any interaction in some cases. The interaction of vilazodone with both molecules had positive ΔP values in Class 1, creating a contraindicated effect. The exchange of trazodone with CBD had positive ΔP values in Class 1, and its interaction with THC had positive ΔP values in Class 1 and Class 4. In its interaction with CBD, a contraindicated effect was observed in some cases, while its interaction with THC had a contraindicated effect and minimal risk in different circumstances. The exchange of bupropion with CBD had positive ΔP values in Class 2, Class 4, and Class 5, and its interaction with THC had positive ΔP values in Class 4 and Class 5. Its interaction with CBD showed a temporary contraindicated effect or minimal risk in different cases, while in some cases, it did not yield any interaction.

In some cases, it showed minimal risk in its interaction with THC and did not lead to any interaction in other cases. The exchange of agomelatine with CBD had positive ΔP values in Class 1, Class 2, Class 4, and Class 5 and positive ΔP values in Class 1, Class 4, and Class 5 in their interaction with THC. As a result of its interaction with CBD, it was contraindicated or temporarily contraindicated, minimal risks were observed in different cases, and no interaction was observed in some cases. As a result of its interaction with THC, it showed a contraindicated effect and minimal risk in different circumstances, and it did not yield any interaction in some cases. The exchange of vortioxetine with CBD had negative ΔP values, indicating no issues of DDI that belonged to severity classes. Its interaction with THC had positive ΔP values in Class 1, and a contraindicated effect occurred due to the interaction. The exchange of mirtazapine with both molecules had negative ΔP values, indicating the absence of DDI cases that belonged to severity classes (Figure 8).

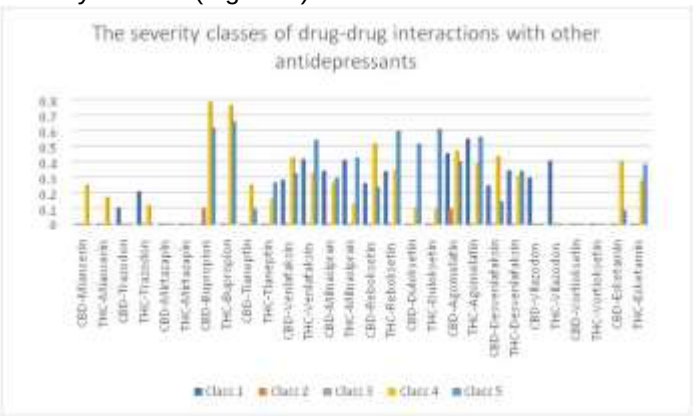

Figure 8: The severity classes of drug-drug interactions of other antidepressant groups with CBD and THC molecules

The predictive analysis of P450-mediated DDIs indicated that the interactions occurred at the level of biotransformation accomplished by P450 enzymes as follows: mianserin-CBD interaction by CYP1A2; trazodone-CBD interaction by CYP2C8; mirtazapine-CBD interaction by CYP2C8; the interaction of bupropion with both molecules by CYP2C9 and CYP2B6; the interaction of tianeptine with both molecules by CYP2C9 and CYP2C8; the interaction of venlafaxine with both molecules by CYP2D6 and CYP2C8; reboxetine-CBD interaction by CYP2C8 and CYP2C19; reboxetine-THC interaction by CYP2C8; the interaction of duloxetine with both molecules by CYP2D6 and CYP2C19; the interaction of agomelatine with both molecules by CYP2C8; desvenlafaxine-CBD interaction by CYP2D6 and CYP2C8; desvenlafaxine-THC interaction by CYP2C8; the interaction of vortioxetine with both molecules by CYP2C9, CYP2C8, and CYP2C19; the interaction of ketamine with both molecules by CYP2C9, CYP2C8, and CYP2B6 (Figure 9).

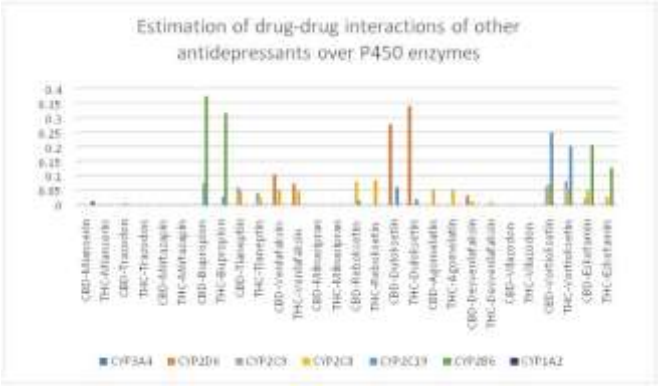

Figure 9: The relationship of P450 enzymes with drug-drug interactions of other antidepressant groups and CBD and THC molecules

DISCUSSION

Cannabis is generally defined as all the plants or bioactive compounds extracted from the parts of the plant belonging to the Cannabaceae family (Szaflarski and Sirven, 2017). It has approximately 500 bioactive compounds, and the main bioactive compounds are phytocannabinoids, terpenes, and flavonoids, which are synthesized for defense purposes (Arnold, 2021; Chandra et al. 2017). The plant is called medical cannabis when CBD and THC cannabinoids, abundantly found in it and investigated, are used for treating and healing the symptoms of diseases. The critical difference between medical cannabis and cannabis is that these bioactive compounds are synthesized as carboxylic acid in cannabis. At the same time, they are converted to neutral formats in medical cannabis. Conversion to neutral conditions results from external factors such as heat and light after the harvest of the plant (Flores-Sanchez and Verpoorte, 2008). In addition, CBD and THC biomolecules have been reported to show antidepressant and anxiolytic

effects (Sarris et al. 2020) in neurodegenerative diseases, such as depression, anxiety, post-traumatic stress disorder, pain-related insomnia, and Parkinson's.

As a result of the literature review conducted to calculate the drug interactions of CBD and THC biomolecules in cannabis in our study, drugs of antidepressant classes that could lead to drug-drug interactions were identified. The interactions of medical cannabis with drugs were estimated with the in silico examination of the activity and interaction classes of the P450 enzymes in drug metabolism.

In vivo, studies have shown that cannabis is not likely to affect noradrenaline uptake mechanisms when used together with desipramine, one of the non-selective MAO inhibitors (Chesher et al. 1974). In our research, it was found that the CBD showed a minimum risk, as well as having no interaction at all. However, it is partially consistent with the results of the in vivo study; the minimum risk effect should be addressed.

CYP2D6, CYP3A4, and CYP2C19 mainly metabolize amitriptyline. In addition, it is less metabolized by is enzymes CYP1A2 and CYP2C9. Some studies have shown that very high levels of amitriptyline and its active metabolites increase the risk of toxicity. Cannabinoids can reduce the effect of enzymes by inhibiting the activity of these is enzymes. As a result, it may cause an increase in the amount of amitriptyline (Hicks et al. 2017). In our study, it was found that amitriptyline did not show interaction through P450 enzymes. These results are limited to the data obtained from the databases of the aforementioned digital platforms.

Citalopram, an SSRI, is metabolized by CYP3A4 and CYP2C19 enzymes. Studies have shown that CBD with citalopram significantly increases citalopram plasma concentrations. However, whether this increases selective serotonin reuptake inhibitor-mediated adverse events is uncertain (Anderson et al. 2021). Our study observed that the use of citalopram with cannabis caused a high degree of adverse effects.

In vitro, studies have shown that cannabidiol has minimal effects on the metabolism of sertraline and fluoxetine, which are SSRIs, and mirtazapine, which is one of the other antidepressants. Although it was found in our study that mirtazapine did not interact with CBD and THC molecules, it was observed that these molecules interacted with fluoxetine and sertraline.

The elimination of duloxetine, one of the other antidepressants, is mainly via CYP1A2. However, it also occurs through hepatic metabolism via CYP2D6, albeit to a lesser extent. There is evidence that co-administration of duloxetine with CYP1A2 and CYP2D6 inhibitors increases duloxetine levels. THC and CBD are inhibitors of CYP2D6, and CBD is also an inhibitor of CYP1A2. Therefore, an increase in duloxetine plasma levels can be seen as a result of the simultaneous use of these two drugs (Vázquez et al. 2020).

Venlafaxine is converted to its primary active metabolite, O-desmethyl venlafaxine, via the CYP2D6 enzyme. CYP2C19 and CYP3A4 isoenzymes are also involved in the further conversion of this metabolite. In addition, this substance is metabolized at lesser rates by CYP2C19, CYP2C9, and CYP3A4 isoenzymes. Therefore, CBD and THC metabolized via CYP enzymes can cause interactions with venlafaxine (Sangkuhl et al. 2014). In our study, it was observed that venlafaxine had an interaction with these two molecules.

CONCLUSION

The interactions of medical cannabis and drugs were estimated on in silico software platforms by examining the activity and interaction classes of P450 enzymes involved in drug metabolism. SSRIs usually show minimal risk or no interaction. However, since these effects differ in cases, the adverse effects should not be ignored, even if they are minor.

Selective serotonin reuptake inhibitors with CBD and THC have adverse effects, mainly at the Class 1 level. Therefore, it is necessary to pay attention to the use of particularly citalopram, paroxetine, fluoxetine, and escitalopram, which are among these drug groups, with medical cannabis.

There is usually minimal risk associated with using MAO inhibitors with CBD. However, since these effects differ in cases, adverse effects seen at the Class 1 level should not be ignored. Special care should be taken when using them with THC. Adverse effects seen at the Class 1 level are pretty high.

Especially trazodone, milnacipran, agomelatine, vilazodone, and desvenlafaxine, which are from other antidepressants group, should be used with medical cannabis cautiously. As a result of the interaction of these drugs, contraindicated effects often occur.

In addition to these results, it was concluded that drug-drug interactions of amitriptyline, doxepin, milnacipran, and vilazodone with both molecules and DDIs of trazodone with THC did not occur via P450 enzymes. Also, the interaction results of imipramine, mirtazapine, and vortioxetine showed no cases belonging to the interaction classes.

Drugs not interacting via P450 enzymes will likely show drug-drug interactions in different pathways. Therefore, before these drugs are administered with medical cannabis, it is important to investigate possible interactions and determine their DDI classes. There are many drug groups in the treatment of diseases. However, our study is limited to certain drugs, and the data set is obtained from the databases of in silico software platforms. Therefore, determining interactions with other drug groups and conducting studies on them is essential for the use of medical cannabis.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

SMB has constructed the main idea and hypothesis of the study. SMB and TP developed the theory and arranged/edited the material and method section. SMB and TP have done the evaluation of the data in the Results section. Discussion section of the article written by SMB and TD reviewed. SMB corrected and approved. All authors read and approved the final version.

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