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Review Article

Cannabidiol's impact on drug-metabolization

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ABSTRACT

Importance: Products containing cannabidiol(CBD) are easily accessible. CBD is reported to inhibit the drug-metabolizing proteins(DMP) Cytochrome P450(CYP)3A4/5, CYP2C9, CYP2B6, CYP2D6, CYP2E1, CYP1A2, CYP2C19, carboxylesterase 1(CES1), uridine 5′diphospho-glucoronosyltransferase(UGT)1A9, UGT2B7, P-glycoprotein(P-gp) and Breast Cancer Resistance Protein(BCRP). The relevance of CBD-drug interactions is largely unknown. Aim of the study was to identify drugs, potentially interacting with orally ingested CBD, to assess whether CBD-drug interactions have been reported, and if substrates of DMP are frequently prescribed drugs.
Observations: Identified were 403 drugs as substrates of DMP. CBD-drug interactions were reported for 53/403 substrates in humans ($n = 25$), *in vivo* ($n = 13$) or *in vitro* ($n = 15$). In 31/53 substrates, CBD induced an increase, in 1/53 a decrease, in 4/53 no change in the substrate level. For 5/53 substrates, the results were controversial, and in 12/53 no substrate levels were reported. Among the 30 most frequently prescribed drugs in Germany were 67% substrates of DMP and among the 50 most frequently prescribed drugs in the USA 68%.
Relevance and conclusions: There is an urgent need for pharmacologic studies on CBD-drug interactions. Patients should be educated on the potential risk and awareness should be increased among physicians. Regulatory authorities should become aware of the problem and start an initiative on an international level to increase the safety of CBD.

1. Introduction

Cannabis and cannabis-derived substances are worldwide the most frequently consumed psychopharmaceuticals [1]. Over the past decade, attitudes toward the recreational and medicinal use of cannabis have rapidly evolved from illicit to decriminalized to legalized at the state level. By 2025, legal cannabis sales are projected to generate $23 billion in the United States [2]. Delta 9-tetrahydrocannabinol (THC) is a well described psychoactive constituent which interacts with the cannabinoid receptor type 1 (CB1) and the complex network of neurologic transmitters to induce psychopharmacological effects [3]. Cannabidiol (CBD), another cannabinoid, does not bind to the CB1 receptor and does not produce the same psychoactive responses [3]. CBD has many indications like reducing anxiety in both animals and humans and is thought to produce a positive effect on conditions such as inflammation, diabetes, cancer, neurodegenerative diseases, chronic pain and insomnia [2]. At present, clinical trials investigate CBD for different disorders [4,5].

Extraction of CBD from hemp is carried out by several procedures resulting in very different profiles of extracted cannabinoids, depending on the variety and part of the plants and extraction procedure employed. The extraction procedures may then result in a variety of chemical mixtures composed of biologically active substances. CBD can also be synthesized chemically.

The only authorized CBD product on the European Union (EU) market is Epidyolex® (or Epidiolex® outside the EU), a prescription medicine containing highly purified plant-based CBD. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved Epidiolex® as an adjunctive therapy for seizures associated with Lennox–Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex for patients two years of age and older [6,7].

The current legal status of CBD is worldwide neither clear nor harmonized, although there are many medicinal, food, or cosmetic products that contain CBD. The majority of CBD products are sold as over-the-counter products, supplements and are easily accessible to the general public [8].

CBD is a multi-target compound, acting on ionic channels, neurotransmitter receptors, and other transmembrane transporters, with

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different effects in each of them acting as activator, modulator, agonist or antagonist [9]. CBD is reported to inhibit *in vitro* the following drug-metabolizing proteins: Cytochrome P450 (CYP) 3A4/5, CYP2C9, CYP2B6, CYP2D6, CYP2E1, CYP1A2, CYP2C19, carboxylesterase 1 (CES1), uridine 5′diphospho-glucoronosyltransferase (UGT) 1A9, UGT2B7, P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) [3,10–19]. These proteins are involved in the metabolization of various drugs with the potential of CBD-drug interactions. Polymorphisms of these proteins are an additional source of variability and concern in the presence of CBD and substrates [20–22].

The clinical relevance of CBD-drug interactions is largely unknown. Aim of the study was to give an overview about drugs, potentially interacting with CBD, by identifying substrates of the drug-metabolizing proteins as mentioned above, and to assess whether CBD-drug interactions of these substrates have been reported in the literature. To assess the potential clinical relevance of CBD-drug interactions, we investigated if substrates of these drug-metabolizing proteins belong to frequently prescribed drugs.

2. Methods

Substrates of CYP3A4/5, CYP2C9, CYP2B6, CYP2D6, CYP2E1, CYP1A2, CYP2C19, CES1, UGT1A9, UGT2B7, P-gp and BCRP were identified from the literature [2,23–25]. A literature search was carried out using PubMed from 1965 to March 2023, with the search terms: “cannabidiol” and substrates of P-gp, BCRP, CYP3A4/5, CYP2C9, CYP2B6, CYP2D6, CYP2E1, CYP1A2, CYP2C19, UGT1A9, CES1, UGT2B7. The Anatomical Therapeutic Chemical (ATC) classification system was used to report the findings [26]. Additionally, it was tried to obtain information from the literature and social insurance institutions on the prescription rate of the substrates.

Included were *in vitro, in vivo* and clinical studies which investigated CBD-drug interactions with the respective substrate. Randomized clinical trials, subgroup analyses from randomized trials, longitudinal studies, cohort studies, case series and case reports were considered. For clinical studies, only articles in humans dealing with orally ingested CBD were selected. Excluded were publications investigating inhalation, smoking, topical, sublingual, transdermal routes of CBD-administration and articles on CBD-use in veterinary medicine.

3. Results

3.1. General overview

Identified were 403 drugs as substrates of CYP3A4/5, CYP2C9, CYP2B6, CYP2D6, CYP2E1, CYP1A2, CYP2C19, CES1, UGT1A9, UGT2B7, P-gp and BRCP (Supplementary eTable 1). According to the ATC classification, they comprise 42 drugs for the alimentary tract and metabolism, 10 for blood and blood forming organs, 75 for the cardiovascular system, three dermatologicals, 9 for the genito-urinary system and sex hormones, 4 systemic hormonal preparations, 32 antiinfectives for systemic use, 66 antineoplastic and immunomodulating agents, 14 for the musculo-skeletal system, 125 for the nervous system, one antiparasitic product, 20 for the respiratory system, one for sensory organs and one classified as “various”. Reports on CBD-drug interactions were found for 53 of the 403 drugs (13%), for the remaining 350 drugs (87%), no reports were found (Supplementary eTable 1). Of these reports, only 25 described CBD-drug interactions in humans, the remaining studies were *in vivo* ($n = 13$) or *in vitro* ($n = 15$) (Table 1). No reports on CBD-drug interaction were found for systemic hormonal preparations, antiparasitic products, drugs for sensory organs and drugs, classified as “various”.

3.2. Drugs for the alimentary tract and metabolism

Among the 42 drugs for the alimentary tract and metabolism,

Table 1
Effects of cannabidiol on substrates of drug-metabolizing proteins.

ATC—Class Name	ATC	Measured (or expected) effect on substrate level	Effect on clinical parameters
Omeprazole [27]	A	↑	NR
Warfarin [28,29,30, 31] CR	B	↑/±	NR
Diltiazem [10]	C	↑	NR
Verapamil [15]	C	↑	NR
Ethanol [33] CS	D	NR	↑
Testosterone [34]	G	NR	↓
Erythromycin [35]	J	↑	NR
Anthracycline [46]	L	↑	NR
Ciclosporin [42]	L	↑	NR
Docetaxel [46]	L	↑	NR
Doxorubicin [46]	L	↑	NR
Everolimus [36,37,39] CoS	L	↑	↑
Imatinib [47]	L	↑	NR
Irinotecan[46]	L	↑	NR
Methotrexate [38] CoS	L	NR	↑
Mitoxantrone [19,48]	L	↑	NR
Paclitaxel [46]	L	↑	NR
Sirolimus [39] CoS	L	↑	NR
Tacrolimus [40] CR	L	↑	NR
Tamoxifen [41] CR	L	↓	NR
Topotecan [19]	L	↑	NR
Diclofenac [27]	M	↑	NR
Acetaminophen [64]	N	NR	↑
Brivaracetam [49] CS	N	↑	NR
Caffeine [50] CoS	N	↑	NR
Carbamazepine [58]	N	Acute ↑, chronic↓	NR
Chlordiazepoxide [66]	N	NR	↓
Citalopram [51,67] CoS	N	↑	↑
Clobazam [52] CoS	N	↑	↑
Cocaine [59]	N	↑	NR
Escitalopram[51,67] CoS	N	↑	↑
Eslicarbazepine [53] CS	N	↑	NR
Fentanyl [54] CoS	N	NR	±
Fluoxetine[21] CR	N	NR	↑/±
Gabapentin [60]	N	↑	NR
Imipramine [61]	N	NR	↑
Isoflurane [62]	N	NR	↑/↓
Ketamine [55] CoS	N	NR	↑
Lamotrigine[60]	N	±	±
Methadone [56] CR	N	↑	↑
Methylphenidate [57] CoS	N	±	±
Midazolam [27]	N	↑	NR
Morphine [63]	N	NR	↑
Phenobarbital [52] Cos	N	↑/±	NR
Phenytoin [53] CS	N	±	NR
Risperidone [65]	N	NR	↓
Rufinamide [53] CS	N	↑	NR
Sertraline [22,67] CS	N	↑	↑
Stiripentol [52] CoS	N	↑/±	NR
Topiramate [52] CoS	N	↑/±	NR
Valproic acid [52] CoS	N	±	NR
Dextromethorphan [27]	R	↑	NR
Theophylline [27]	R	↑	NR

ATC = Anatomical Therapeutic Chemical, CoS = cohort study, CR = case report, CS = case series, NR = not reported, ↑ = increased, ↓ = decreased, ± = unchanged, / = controversial.
red: Interaction reported in humans; gray: interaction reported *in vivo*; violett: interaction reported *in vitro*.
ATC **-Class**: **A** ALIMENTARY TRACT AND METABOLISM, **B** BLOOD AND BLOOD FORMING ORGANS, **C** CARDIOVASCULAR SYSTEM, **D** DERMATOLOGICALS, **G** GENITO URINARY SYSTEM AND SEX HORMONES, **H** SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS, **J** ANTIINFECTIVES FOR SYSTEMIC USE, **L** ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS, **M** MUSCULO-SKELETAL SYSTEM, **N** NERVOUS

SYSTEM, **P** ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS, **R** RESPIRATORY SYSTEM, **S** SENSORY ORGANS, **V** VARIOUS [26].

potentially interacting with CBD, we found one publication on omeprazole, which was investigated *in vitro* using human liver microsomes. By using several different static models, a maximum pharmacokinetic interaction (defined as area under the plasma concentration-time curve ratio) of 7.3 was predicted between oral CBD (700 mg) and omeprazole [27].

3.3. Drugs for blood and blood forming organs

Among the 10 drugs for blood and blood forming organs, potentially interacting with CBD, we found case reports on CBD-warfarin interaction in humans with controversial results. In one patient on polypharmacy, the combination of 0.3 – 0.925 mg THC and 5.3 – 5.925 mg CBD, administered via an oromucosal route daily for up to 8 months did neither impact warfarin's metabolism nor result in any changes of the international normalized ratio (INR) [28]. Another patient required a nearly 20% warfarin dose reduction to maintain an INR within the target range after up-titrating CBD-therapy to 20 mg/kg/d [29]. In a further patient on CBD 30 mg/kg/day, the warfarin dose had to be reduced by 30% [30]. Another patient is reported who has been stable on warfarin 10 mg/d from 2010 to 2018, until INR suddenly increased to 7.2 following one month of edible cannabis ingestion and cannabis smoking. The patient was advised to hold two doses of warfarin and discontinue cannabis use. The INR dropped below 4 upon discontinuation of cannabis with dose adjustments to warfarin [31]. An *in vitro* study showed that also the formation of acenocoumarol and phenprocoumon, the hydroxylated metabolites of warfarin, was affected at different cannabinoid concentrations [32]. Extracts with a single dominant cannabinoid like CBD may have a stronger inhibitory potency than extracts containing a mixture of THC and CBD [32].

3.4. Drugs for the cardiovascular system

We identified 75 drugs for the cardiovascular system as potentially interacting with CBD. For two of these drugs, diltiazem and verapamil, *in vitro* studies indicated potential CBD-drug interactions [10,15].

3.5. Dermatologicals

We identified three dermatologicals as potentially interacting with CBD. In healthy volunteers, significant impairments of motor and psychomotor performances due to CBD-ethanol interactions, compared to placebo, were reported [33].

3.6. Drugs for the genito-urinary system and sex hormones

Among 9 drugs for the genito-urinary system and sex hormones, potentially interacting with CBD, we found one *in vivo* study in mice indicating that chronic CBD exposure was associated with changes in the male reproductive system, suggesting its reproductive toxicity [34]. It is unknown whether this finding is due to a pharmacokinetic testosterone-CBD interaction or due to other mechanisms.

3.7. Antiinfectives for systemic use

Among 32 antiinfectives for systemic use, potentially interacting with CBD, we found one *in vivo* study in rats [35]. Based on CBD-induced changes of ^{13}C-breath response, the metabolism of ^{13}C-erythromycin was shown to be inhibited by CBD at doses of 10 and 50 mg/kg, but not at 1 mg/kg [35].

3.8. Antineoplastic and immunomodulating agents

Among 66 antineoplastic and immunomodulating agents with the potential to interact with CBD due to its impact on drug-metabolizing proteins, we found studies on 14 substrates. CBD-drug interactions in humans were described in patients taking everolimus, methotrexate, sirolimus, tacrolimus and tamoxifen [36–41].

CBD-everolimus interaction was investigated in 16 healthy male volunteers [37]. A single dose of everolimus 5 mg was well tolerated when administered with multiple doses of CBD. Everolimus maximum concentration, area under the concentration-time curve (AUC) from time of dosing to the last measurable concentration, and AUC extrapolated to infinity values increased by ≈2.5-fold, and everolimus half-life remained largely unchanged in the presence of steady-state CBD relative to everolimus dosed alone. The authors of this study conclude that monitoring of everolimus serum level should be strongly advised with appropriate dose reduction when coadministered with CBD [37]. In patients with tuberous sclerosis complex, increased everolimus- and sirolimus- serum-levels, associated with clinical side effects, occurred under a comedication with CBD [36,39].

In a phase II study of 48 patients after allogeneic hematopoietic cell transplantation, the addition of CBD to standard Graft-versus-Host-Disease (GVHD) prophylaxis consisting of ciclosporin and methotrexate resulted in low incidence rates of acute GVHD by day 100. Compared with 101 historical control subjects given standard GVHD prophylaxis, the hazard ratio of developing acute GVHD among subjects treated with CBD plus standard GVHD prophylaxis was 0.3 [38]. At present, it is unclear whether this effect is due to CBD-drug interaction or due to CDB's anti-inflammatory or immunomodulatory properties [38].

In a case report, a participant in a CBD clinical trial for epilepsy is described, who was also receiving tacrolimus because of nephritis. She showed an approximately 3-fold increase in tacrolimus serum-levels while receiving 2000-2900 mg/day of CBD [40].

In vivo an interaction between ciclosporin and CBD is reported [42]. CBD-treatment in mice decreased the formation of ciclosporin metabolites by 60–86% [42].

Summarizing the data about the interaction of CBD with immunomodulating drugs, it can be expected that comedication with CBD may increase the serum levels, why diligent monitoring in is necessary, especially after organ transplantation [43–45].

An interaction of CBD with tamoxifen is reported from a female with bilateral breast carcinoma in remission, who was treated with tamoxifen for over 6 years. CBD was instituted to treat persistent postsurgical pain. The active metabolite endoxifen, which exerts the anticancer benefits, was measured while the patient chronically received CBD 40 mg/day, and after a 60-day washout period. After discontinuation of CBD, the endoxifen level increased by 18.75%. Patients receiving CBD and tamoxifen require monitoring to identify a possible subtherapeutic response to treatment [41].

CBD-drug interactions *in vitro* are reported for the following antineoplastic substances: Anthracycline, docetaxel, doxorubicin, imatinib, irinotecan, mitoxantrone, paclitaxel and topotecan [19,46–48]. In Michigan Cancer Foundation-7 (MCF7) breast adenoma cells, synergistic interactions in the apoptotic profile between CBD with docetaxel, doxorubicin, anthracycline, the irinotecan-metabolite SN-38 and paclitaxel were identified [46]. In chronic myeloid leukemia cells, a synergistic effect by combining CBD with imatinib was found regarding inhibition of cell proliferation and cell cycle [47]. In malignant melanoma cell lines, CBD reduced the cell-viability and -proliferation, and an additive interaction was observed with mitoxantrone [48]. CBD increased the intracellular accumulation of mitoxantrone and topotecan in an over-expressing cell line [19].

3.9. Drugs for the musculo-skeletal system

Among the 14 drugs for the musculo-skeletal system, potentially interacting with CBD, we found only one publication on diclofenac. Diclofenac, a substrate of CYP2C9, was investigated *in vitro* using human liver microsomes, and by using static models, a maximum pharmacokinetic interaction (defined as area under the plasma concentration-time curve ratio) of 7.3 was predicted between oral CBD (700 mg) and diclofenac [27].

3.10. Drugs for the nervous system

We identified 125 drugs for the nervous system. In humans, interactions with CBD are reported on the antiepileptics brivaracetam, eslicarbazepine, phenobarbital, phenytoin, rufinamide, stiripentol, topiramate and valproic acid; the psychoanaleptics caffeine, citalopram, escitalopram, sertraline, fluoxetine and methylphenidate; the psycholeptic clobazam, the analgesic fentanyl, the anesthetic ketamine and on methadone [21,49–57]. *In vivo* interactions with CBD are reported on the antiepileptics carbamazepine and lamotrigine, the anesthetics cocaine and isoflurane, the analgesics gabapentin, morphine and acetaminophen, the psychoanaleptic imipramine and the psycholeptics risperidone and chlordiazepoxide [58–66]. *In vitro* interactions with CBD are reported on the psycholeptic midazolam [27].

3.10.1. Interaction between CBD and antiepileptics

CBD-drug interactions in humans are reported on 8 antiepileptic drugs: Increases in brivaracetam serum levels by 95% to 280% were found in a case series of 5 patients with epilepsy who received adjunctive treatment with CBD [49].

In an open-label safety study, serum levels were monitored to identify interactions between CBD and eslicarbazepine in 4 adults with epilepsy. CBD dose was started at 5 mg/kg/day and increased every two weeks by 5 mg/kg/day up to a maximum of 50 mg/kg/day. Eslicarbazepine serum levels were elevated with a comedication of CBD [53].

An open-label safety study investigated interactions between CBD and rufinamide in 6 adults and 10 children with epilepsy. CBD dose was started at 5 mg/kg/day and increased every two weeks by 5 mg/kg/day up to a maximum of 50 mg/kg/day. Rufinamide serum levels were elevated with a comedication of CBD [53].

Conflicting results are reported on phenobarbital. Whereas in 5 patients, a comedication with CBD did not change serum phenobarbital levels, an increased level was reported on a further patient [52]. These conflicting data may be due to the fact that phenobarbital, a substrate of CYP2C9 and CYP2C19, also induces both CYP3A4 and CYP2C19 thereby reducing serum phenobarbital levels [52].

Conflicting results are reported on stiripentol. Whereas in 12 patients, a comedication with CBD increased serum stiripentol levels, no changes were found in a randomized trial [52]. The cause for these conflicting data are unknown [52].

Conflicting results are reported on topiramate. Whereas in a randomized controlled trial, a comedication with CBD did not change serum topiramate levels, an observational cohort study in 20 patients found increased levels [52]. Topiramate, a substrate of P-gp and CYP3A4, also inhibits CYP2C19 and induces CYP3A4, which may explain the controversial findings [52].

In an open-label safety study on interactions between CBD and phenytoin in two adults and one child with epilepsy, serum phenytoin levels were measured. CBD dose was started at 5 mg/kg/day and increased every two weeks by 5 mg/kg/day up to a maximum of 50 mg/kg/day. Phenytoin serum levels were not elevated with a comedication of CBD [53].

The effects of CBD-comedication with valproic acid was investigated in several randomized controlled trials, which detected no effect of CBD on valproic acid serum levels [52].

CBD-drug interactions *in vivo* are reported on two antiepileptic drugs: In rats, the co-administration of a single dose of CBD increased carbamazepine's $AUC_{\infty-0}$ by 53%. Chronic CBD, however, caused a decrease in carbamazepine's maximum serum concentration by 75% and $AUC_{\infty-0}$ by 66% [58]. These controversial findings are interpreted by the authors as follows: When CBD has been administered as a single dose, the effect is believed to be mainly caused by the inhibition of carbamazepine metabolism through CYP3A. The effect of chronic administration of CBD probably includes kinetic pathways other than the inhibition of CYP3A-dependent pathways [58]. In Mice, the co-administration of CBD to lamotrigine did neither affect the anticonvulsive effect nor the serum level [60].

3.10.2. Interaction between CBD and psycholeptics

Increased levels of clobazam's active metabolite N-desmethylclobazam with concomitant CBD were reported in observational cohort studies and in a randomized controlled trial. This rise was variable and most commonly significant. Side effects of somnolence, sedation and lethargy were observed when clobazam and CBD were co-prescribed and were associated with increased N-desmethylclobazam levels [52].

CBD-drug interactions *in vivo* are reported on two drugs: In mice, CBD reduced risperidone-induced elevated fasting blood sugar when given after the administration of risperidone. CBD also had effects on vacuous chewing movements when administered before risperidone and similarly, attenuated risperidone-induced increased muscle tone [65]. In rats, chlordiazepoxide, when given with CBD, induced a decrease in anticonvulsant potency as compared with chlordiazepoxide given alone [66].

Midazolam, a substrate of CYP3A4/5, was investigated *in vitro* using human liver microsomes. By using several different static models, a maximum pharmacokinetic interaction (defined as area under the plasma concentration-time curve ratio) of 14.8 was predicted between oral CBD (700 mg) and midazolam [27].

3.10.3. Interaction between CBD and psychoanaleptics

CBD-drug interactions in humans are reported on 6 psychoanaleptic drugs: A study in 16 healthy subjects investigated the effects of repeated doses of CBD on the pharmacokinetics of a single dose of caffeine. When caffeine was administered with steady-state CBD, caffeine exposure increased by 15% for peak concentration of drug in serum (C_{max}) and 95% for area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), the time after drug administration at which peak serum concentration occurs (t_{max}) increased from 1.5 to 3.0 h, and the terminal-phase half-life ($t_{1/2}$) increased from 5.4 to 10.9 h compared with caffeine administered with placebo [50].

CBD-citalopram interactions were examined in 6 patients with anxiety disorders on treatment with citalopram or escitalopram who received ascending daily doses of adjunctive CBD (200–800 mg) over 12 weeks in a clinical trial [51]. Concomitant CBD significantly increased citalopram serum concentrations, with variability in these changes across participants. There was a near doubling of mean citalopram concentrations after 4 and 8 weeks of adjunctive CBD treatment, but in one participant, citalopram was barely detectable at the 12-week time point [51].

Using data from the Food and Drug Administration Adverse Events Reporting System (FAERS), the relationship between CBD and sertraline and side effects were examined [67]. In pharmacokinetic models, CBD increased sertraline and es/citalopram concentrations in adolescents, and coadministration of CBD and sertraline, citalopram and escitalopram increased the risk of cough, diarrhea, dizziness, and fatigue [67]. A case is reported in whom the concomitant medication of CBD and sertraline induced a severe hyponatremia [22].

Two patients are reported in whom CBD was administered in combination with fluoxetine, but only one patient exhibited severe adverse events. In this patient with the homozygous CYP2D6×4 genotype, the authors propose a potential drug-gene-drug interaction between CBD, CYP2D6×4, and fluoxetine [21].

In 12 healthy volunteers, the potential influence of multiple doses of CBD on the pharmacokinetics of methylphenidate was investigated. The observed change in methylphenidate exposures with CBD co-administration was small and viewed as lacking clinical significance [57].

In rats, the administration of CBD and imipramine induced antidepressant behavioural and molecular effects [61].

3.10.4. Interaction between CBD and analgesics

In healthy volunteers, CBD did not exacerbate adverse effects associated with intravenous fentanyl administration [54].

CBD-drug interactions *in vivo* are reported on three drugs: In Mice, the co-administration of CBD to gabapentin produced an increase of gabapentin concentration in both serum and brain [60]. A further study in mice showed that the combination of CBD and morphine produced

Table 2
Substrates of drug-metabolizing proteins, known to be affected by cannabidiol*, among the most frequently prescribed drugs in the USA, Germany and Austria.

Name	ATC	CYP 3A4/5	CYP 2C9	CYP 2B6	CYP 2D6	CYP 2E1	CYP 1A2	CYP 2C19	UGT 1A9	UGT2B7	CES1	P-gp	Prescription range 2018 in USA[68]	Prescription range 2021 in Germany[69]	Prescription range 2022 in Austria [personal communication Felix Gruber]
Atorvastatin	C	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	3	14	NM
Simvastatin	C	+	NM	NM	NM	NM	NM	NM	NM	+	+	+	5	21 and 23	NM
Omeprazole [27]	A	+	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	6	NM	NM
Amlodipine	C	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	7	7 and 29	4
Metoprolol	C	NM	NM	NM	+	NM	NM	NM	NM	NM	NM	NM	8	8 and 25	NM
Acetaminophen [64]	N	NM	NM	NM	NM	+	+	NM	+	NM	NM	NM	9 and 16	NM	NM
Losartan	C	NM	+	NM	NM	NM	NM	NM	NM	+	NM	NM	12	NM	NM
Gabapentin [60]	N	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	13	NM	NM
Sertraline [22, 67]	N	NM	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	14	NM	NM
Furosemide	C	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	15	NM	NM
Fluoxetine [21]	N	NM	+	NM	+	NM	NM	+	NM	NM	NM	NM	20	NM	NM
Citalopram [51]	N	+	NM	NM	+	NM	NM	+	NM	NM	NM	NM	21	NM	NM
Trazodone	N	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	22	NM	2
Alprazolam	N	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	23	NM	NM
Bupropion	N	NM	NM	+	NM	NM	NM	+	NM	NM	NM	NM	25	NM	NM
Carvedilol	C	NM	NM	NM	+	NM	NM	NM	NM	NM	NM	+	26	NM	37
Tramadol	N	+	NM	+	+	NM	NM	NM	NM	NM	NM	NM	28	NM	NM
Pantoprazole	A	+	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	29	6 and 17	8
Montelukast	R	NM	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	30	NM	NM
Escitalopram [51]	N	+	NM	NM	+	NM	NM	+	NM	NM	NM	NM	31	NM	22
Prednisolone	R	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	32	NM	NM
Rosuvastatin	C	NM	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	33	NM	12 and 21
Ibuprofen	M	NM	+	NM	NM	NM	NM	NM	+	+	NM	NM	34	2 and 26	NM
Meloxicam	M	NM	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	35	NM	NM
Clopidogrel	B	+	+	NM	NM	NM	NM	+	NM	NM	+	+	40	NM	25
Glipizide	A	NM	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	41	NM	NM
Warfarin [28–32]	B	NM	+	NM	NM	NM	+	NM	NM	NM	NM	NM	42	NM	NM
Cyclobenzaprine	M	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	NM	43	NM	NM
Zolpidem	N	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	46	NM	48
Estradiol	G	+	NM	NM	NM	NM	+	NM	NM	NM	NM	NM	47	NM	NM
Duloxetine	N	NM	NM	NM	+	NM	+	NM	NM	NM	NM	NM	48	NM	NM
Ranitidine	A	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	49	NM	NM
Venlafaxine	N	+	+	NM	+	NM	NM	NM	NM	NM	NM	+	50	NM	NM
Ramipril	C	NM		NM	NM	NM	NM	NM	NM	NM	+	NM	NM	3 and 11	NM
Torasemide	C	NM	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	4	NM
Bisoprolol	C	NM	NM	NM	+	NM	NM	NM	NM	NM	NM	NM	NM	12,18,19 and 20	47
Apixaban	B	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	NM	15	15 and 28
Lercanidipin	C	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	16	39
Rivaroxaban	B	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	+	NM	30	26
Ezetimib	C	NM	NM	NM	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	12 and 21
Esomeprazole	A	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	36
Linagliptin	A	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	23
Hydromorphone	N	NM	NM	NM	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	45
Dapagliflozin	A	NM	NM	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	NM	11
Triazolam	N	+	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	24

Yellow: No report in PubMed; red: Interaction reported in humans; gray: interaction reported *in vivo*; violett: interaction reported *in vitro*.
ATC **-Class**: **A** ALIMENTARY TRACT AND METABOLISM, **B** BLOOD AND BLOOD FORMING ORGANS, **C** CARDIOVASCULAR SYSTEM, **D** DERMATOLOGICALS, **G** GENITO URINARY SYSTEM AND SEX HORMONES, **H** SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS, **J** ANTIINFECTIVES FOR SYSTEMIC USE, **L** ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS, **M** MUSCULO-SKELETAL SYSTEM, **N** NERVOUS SYSTEM, **P** ANTIPARASITIC PR ODUCTS, INSECTICIDES AND REPELLENTS, **R** RESPIRATORY SYSTEM, **S** SENSORY ORGANS, **V** VARIOUS [26].
ACT = Anatomical Therapeutic Chemical, CES1 = Carboxylesterase 1, CYP = Cytochrome P450, NM = not mentioned, P-gp = P-glycoprotein, UGT = uridine 5′diphospho-glucoronosyltransferase.
*None of the drugs are known as substrates of Breast Cancer Resistance Protein (BRCP).

synergistic effects in reversing acetic acid-stimulated stretching behavior [63]. In a further study, co-administration of CBD at the dose of 116 mg/kg (human dose of CBD is 10 mg/kg) with acetaminophen (400 mg/kg) resulted in 38% mortality associated with liver injury [64]. The co-administration of CBD led to greater activation of c-Jun N-terminal kinase (JNK). No mortality was observed in the CBD alone or acetaminophen-alone groups. It is unclear whether the increased mortality was due to pharmacokinetic interactions or due to other mechanisms [64].

3.10.5. Interaction between CBD and anesthetics

A CBD-drug interaction in humans is reported on ketamine. In healthy volunteers, CBD augmented the activating effects of ketamine, as measured by the activation subscales of the Brief Psychiatric Rating Scale [55].

CBD-drug interactions *in vivo* are reported on two drugs: cocaine and isoflurane. In mice, CBD pretreatment increased brain levels 2- to 4-fold of subsequently administered cocaine [59].

Wistar rats were pretreated with different doses of CBD one hour before isoflurane anesthesia [62]. In animals, pretreated with 20 mg/kg CBD, the induction time was shortened. Pretreatment with 100 mg/ kg CBD resulted in a prolonged induction time, while on awakening, delayed appearance of reflexes and prolonged recovery from anesthesia compared to pretreatment with 20 mg/kg CBD were observed [62].

3.10.6. Interaction between CBD and other nervous system drugs

A CBD-drug interaction in humans is reported on methadone. A 13-year-old girl with metastatic cancer and chronic pain presented with increased sleepiness and fatigue. She had been started on

7.5 mg of oral methadone twice daily 4 months earlier. Unbeknownst to her physicians, her parents had commenced her on CBD. The initial serum methadone level was 271 ng/mL, which decreased to 125 ng/mL 14 days after discontinuing CBD [56].

3.11. Drugs for the respiratory system

We identified 20 drugs for the respiratory system. *In vitro* interactions with CBD are reported for dextromethorphan and theophylline. In human liver microsomes, by using several different static models, a maximum pharmacokinetic interaction (defined as area under the plasma concentration-time curve ratio) of 4.0 was predicted between oral CBD (700 mg) and theophylline and 2.1 between oral CBD and dextromethorphan [27].

3.12. Prescription rate of substrates of drug-metabolizing proteins

Fuentes et al. compiled the 2018 most frequently prescribed drugs in the U.S.A. Among the 50 most frequently prescribed drugs were 34 substrates of drug-metabolizing proteins, affected by CBD (Table 2) [68]. In Germany, among the 30 most frequently prescribed drugs in 2021, were 20 substrates of drug-metabolizing proteins, affected by CBD [69]. In Austria among the 50 most frequently prescribed drugs in 2022 were 21 substrates of drug-metabolizing proteins, affected by CBD (Personal communication by Felix Gruber BSc MSc, Austrian Social Insurance on April 3rd 2023).

4. Discussion

In 31 of the investigated 53 substrates, CBD induced (or is expected to induce) an increase in the substrate level, for 5 substrates, the results are controversial, for further 4 substrates no change in the substrate level has been detected, in one substrate, the level decreased with concomitant CBD and in the remaining 12 substrates, no serum levels are reported (Table 1). Only for 25 of 403 (6.2%) potentially interacting drugs, an interaction with CBD in humans was investigated. Most of the available data on CBD-drug interactions derive from antiepileptic drugs [52]. The interest for these interaction can be explained by the approval of CBD as an adjunctive therapy for seizures in selected cases [6,7].

Most of the reported CBD-drug interactions in humans comprise drugs whose effects or serum-levels are easily measured. In patients on vitamin-K-antagonists like warfarin, drug-interactions can be easily observed and detected by deviations of the INR values [28–31]. Similarly, serum-levels of everolimus, sirolimus or tacrolimus are easily obtained in the clinical routine [36,39,40]. For other substrates of drug-metabolizing proteins, affected by CBD, like the non-Vitamin-K-antagonist oral anticoagulants (NOAC) dabigatran, rivaroxaban or apixaban, the detection of a CBD-drug interaction is more difficult since no routine tests with established reference levels are available for NOAC serum levels [70].

The lack of knowledge on the clinical relevance of CBD-drug interactions is worrying since substrates of drug-metabolizing proteins, affected by CBD, comprise frequently prescribed medications for hypertension, coronary artery disease, heart failure, depression and diabetes mellitus (Table 2). This finding stresses the need for pharmacological and clinical research on this topic.

5. Limitations

1. We restricted our review to CBD-drug interactions, caused by affection of drug-metabolizing proteins. Other mechanisms, however, may also lead to CBD-drug interactions like CBD's immunomodulatory properties, as observed in patients with advanced malignancies where a co-medication of CBD decreased the tumor response rate to nivolumab [71]. An overview about various CBD-chemotherapeutics interactions is given elsewhere [5]. 2.CBD-induced receptor-modulation and toxicity were not the subject of our article and are reported elsewhere [72]. 3. Most probably, we did not identify all substrates of drug-metabolizing proteins affected by CBD. 4. Interpretation of the data on CBD-drug interaction is impeded because they were conducted with different preparations, containing varying concentrations of CBD and other cannabinoids. 5. The content of other components from the extraction and enrichment process and their identity are rarely described. Consequently, there is some degree of uncertainty as to whether the effects reported in studies conducted with products with CBD content can be attributed exclusively to CBD. 6. We restricted our review on orally ingested CBD. CBD-drug interactions associated with other routes of administration like smoking are reported and should be investigated [73].

6. Conclusions

From our findings we conclude that there is an urgent need for pharmacologic studies on CBD-drug interactions, especially for frequently prescribed drugs as listed in Table 1. Since CBD is not considered a drug but a "novel food" and estimated as "purely natural", patients should be asked explicitly for concomitant intake of CBD and educated about the potential risk for drug interactions, especially in cases with polypharmacy [74]. Hopefully, a recently designed on-line platform for the detection of potentially interacting drugs will be an useful tool for physicians, pharmacists and patients [75].

Awareness of the potential for interactions with various drugs should be increased among physicians when taking the history of a patient. Special care is needed in patients after transplantation or malignancies since CBD may influence serum levels of immunomodulatory and antineoplastic drugs. In cases of unexplained adverse events, physicians should ask for concomitant CBD-intake. If potential CBD-drug interactions are observed, the co-medication should be registered and serum drug levels measured. The event should be reported to the national pharmacovigilance institution, irrespective if it occurred during a therapy with drugs known to interact with CBD or not. In view of the increase in marketing and use of CBD worldwide and in view of the potential health challenges, there is an urgent need that regulatory

authorities become aware of the problem [76]. Those working in the field should be encouraged to start an initiative on an international level to increase the safety of CBD.

Declaration of Competing Interest

No conflicts of interest, no disclosures for both authors

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.07.029.

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