Supporting Information

Evidence of potential drug interactions between Cannabidiol and other drugs: a scoping review to guide pharmaceutical care

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Supplementary Material 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title		Identify the report as a scoping review.	1
ABSTRACT			
Structured summary		Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale		Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4–6
Objectives		Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration		Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria		Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status) and provide a rationale.	6–7
Information sources*		Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search		Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7

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SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Selection of sources of evidence†		State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	7
Data charting process‡	0	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7–8
Data items	1	List and define all variables for which data were sought and any assumptions and simplifications made.	7–8
Critical appraisal of individual sources of evidence§	2	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	3	Describe the methods of handling and summarizing the data that were charted.	8
RESULTS			
Selection of sources of evidence	4	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	8–9
Characteristics of sources of evidence	5	For each source of evidence, present characteristics for which data were charted and provide the citations.	9
Critical appraisal within sources of evidence	6	If done, present data on critical appraisal of included sources of evidence (see item 12).	9–10
Results of individual sources of evidence	7	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9–10
Synthesis of results	8	Summarize and/or present the charting results as they relate to the review questions and objectives.	9–10
DISCUSSION			
Summary of evidence	9	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions	10–13

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SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		and objectives, and consider the relevance to key groups.	
Limitations	0	Discuss the limitations of the scoping review process.	13–14
Conclusions	1	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14
FUNDING			
Funding	2	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	2

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplementary Material 2. Reason for excluding studies after full-text selection (n=113).

Reason: Does not describe/analyze pharmacokinetic and/or pharmacodynamic interactions between cannabidiol and other drugs (n=112)		
Author	Year	Title
Aggarwal	2013	A Concise Clinical Primer and Survey of Randomized-controlled Trial Results
Agurell et al.	1981	Interactions Of A 1-Tetrahydroeannabinol With Cannabinol And Cannabidiol Following Oral Administration In Man. Assay Of Cannabinol And Cannabidiol By Mass Fragmentography 1
Anderson et al.	2022	In Vitro Screening of Three Commercial Cannabis-Based Products on ATP-Binding Cassette and Solute-Carrier Transporter Function
Antanaskovi ć &. Janković	2023	Guidance for interactions between antiseizure medications
Babalonis & Walsh	2020	Therapeutic potential of opioid/cannabinoid combinations in humans: Review of the evidence
Bansal et al.	2022	Comprehensive Predictions of Cytochrome P450 (P450)-Mediated In Vivo Cannabinoid-Drug Interactions Based on Reversible and Time-Dependent P450 Inhibition in Human Liver Microsomes
Ben-Ami Shor et al.	2022	The Cytotoxic Effect of Isolated Cannabinoid Extracts on Polypoid Colorectal Tissue
Benowitz & Jones	1981	Cardiovascular and Metabolic Considerations in Prolonged Cannabinoid Administration in Man
Ben-Zeev	2022	Epilepsy and cannabis: facing reality
Bergeria et al.	2022	Pharmacokinetic Profile of Δ9-Tetrahydrocannabinol, Cannabidiol and Metabolites in Blood following Vaporization and Oral Ingestion of Cannabidiol Products
Bialer & Perucca	2020	Response: Cannabidiol antiseizure activity and its interactions with clobazam: “It’s déjà vu all over again” Yogi Berra
Bindler et al.	2022	Drug-Drug Interaction Between Orally Administered Hydrocodone-Acetaminophen and Inhalation of Cannabis Smoke: A Case Report
Bornheim et al.	1981	Effect Of Cannabidiol On Cytochrome P-450 And Hexobarbital Sleep Time

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Bornheim et al.	1993	Characterization Of Cannabidiol-Mediated Cytochrome P450 Inactivation
Bornheim & Grillo	1998	Characterization of Cytochrome P450 3A Inactivation by Cannabidiol: Possible Involvement of Cannabidiol-Hydroxyquinone as a P450 Inactivator
Bouquié et al.	2018	Cannabis And Anticancer Drugs: Societal Usage And Expected Pharmacological Interactions – A Review
Brents et al.	2013	Differential Drug–Drug Interactions of the Synthetic Cannabinoids JWH-018 and JWH-073: Implications for Drug Abuse Liability and Pain Therapy
Brzozowska et al.	2017	The Differential Binding of Antipsychotic Drugs to the ABC Transporter P-Glycoprotein Predicts Cannabinoid- Antipsychotic Drug Interactions
Buchtova et al.	2023	Cannabis-derived products antagonize platinum drugs by altered cellular transport
Cabral-Pereira et al.	2021	Behavioral and Molecular Effects Induced by Cannabidiol and Valproate Administration in the GASH/Sal Model of Acute Audiogenic Seizures
Chang	2017	Cannabidiol and Serum Antiepileptic Drug Levels: The abcs of CBD With aeds
Cherniakov et al.	2017	The Effect of Pro nanolipospheres (PNL) Formulation Containing Natural Absorption Enhancers on the Oral Bioavailability of delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) in a Rat Model
Cherniakov et al.	2017	Piperine-pro-nanolipospheres as a novel oral delivery system of cannabinoids: Pharmacokinetic evaluation in healthy volunteers in comparison to buccal spray administration
Chrétien et al.	2022	Association between road traffic accidents and drugs belonging to the antiseizure medications class: A pharmacovigilance analysis in VigiBase
Cokley et al.	2022	Paxlovid™ Information From FDA and Guidance for AES Members
Dalton et al.	1975	Effects Of Marihuana Combined With Secobarbital
Dalton et al.	1976	Influence Of Cannabidiol On Secobarbital Effects And Plasma Kinetics
Debus et al.	2022	Associated factors of potential drug-drug interactions and drug–food interactions in patients with multiple sclerosis
Dewey et al.	1976	Interactions Of Active Constituents Of Marihuana With Other Drugs In The Neuron

Doran et al.	2021	Drug-Drug Interaction Between Cannabidiol And Phenobarbital In Healthy Dogs
DTB	2012	What place for cannabis extract in MS?
Engels et al.	2007	Medicinal Cannabis Does Not Influence the Clinical Pharmacokinetics of Irinotecan and Docetaxel
Finn et al.	2004	Effects Of Coadministration Of Cannabinoids And Morphine On Nociceptive Behaviour, Brain Monoamines And HPA Axis Activity In A Rat Model Of Persistent Pain
Fitzcharles et al.	2023	Cautious Hope for Cannabidiol (CBD) in Rheumatology Care
Gingrich et al.	2023	Review of the oral toxicity of cannabidiol (CBD)
Grotenherm en	2003	Pharmacokinetics and Pharmacodynamics of Cannabinoids
Hollister	1975	Interactions In Man Of Delta-9-Tetrahydrocannabinol
Hsu et al.	2019	Probable Interaction Between Warfarin and Inhaled and Oral Administration of Cannabis
Huff et al.	2021	Differential Interactions of Selected Phytocannabinoids with Human CYP2D6 Polymorphisms
Jacobsson et al.	2000	Serum-Dependent Effects of Tamoxifen and Cannabinoids upon C6 Glioma Cell Viability
Jain et al.	2022	Cannabinoids in rheumatology: Friend, foe or a bystander?
Jang et al.	2022	Machine learning-based quantitative prediction of drug exposure in drug-drug interactions using drug label information
Johnson et al.	2022	Label accuracy of unregulated cannabidiol (CBD) products: measured concentration vs. label claim
Karschner et al.	2011	Plasma Cannabinoid Pharmacokinetics following Controlled Oral 9-Tetrahydrocannabinol and Oromucosal Cannabis Extract Administration
Kim et al.	2020	In Vitro Interaction of AB-FUBINACA with Human Cytochrome P450, UDP-Glucuronosyltransferase Enzymes and Drug Transporters

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Klein et al.	2022	Ask Your Provider About Cannabis: Increasing Nurse Practitioner Knowledge and Confidence
Kocis et al.	2023	CANNabinoid Drug Interaction Review (CANN-DIR™)
Kosel et al.	2002	The Effects Of Cannabinoids On The Pharmacokinetics Of Indinavir And Nelfinavir
Kutanzi et al.	2020	Safety and Molecular-Toxicological Implications of Cannabidiol-Rich Cannabis Extract and Methylsulfonylmethane Co-Administration
Lacroix et al.	2022	What Do We Know About Medical Cannabis in Neurological Disorders and What Are the Next Steps?
Lattanzi et al.	2020	Cannabidiol Efficacy And Clobazam Coadministration: Where Do We Stand Now?
Lavender et al.	2022	Cannabinoids, Insomnia, and Other Sleep Disorders
Lord et al.	2022	Does Cannabidiol Have a Benefit as a Supportive Care Drug in Cancer?
Lyu et al.	2022	Medical Cannabis Received by Patients According to Qualifying Condition in a US State Cannabis Program: Product Choice, Dosing, and Age-Related Trends
MacCallum & Russo	2018	Practical Considerations In Medical Cannabis Administration And Dosing
MacDonald & Adams	2019	The Use Of Medical Cannabis With Other Medications: A Review Of Safety And Guidelines - An Update
MacDonald & Farrah	2019	Medical Cannabis Use In Palliative Care: Review Of Clinical Effectiveness And Guidelines – An Update
Malor et al.	1975	The Effect Of ~9-Tetrahydrocannabinol, Cannabidiol And Cannabinol On Ether Anaesthesia In Mice
Mandelbaum	2020	Cannabidiol Antiseizure Activity And Its Interactions With Clobazam: “It’s Déjà Vu All Over Again” Yogi Berra
Manini et al.	2015	Safety And Pharmacokinetics Of Oral Cannabidiol When Administered Concomitantly With Intravenous Fentanyl In Humans
Marchese et al.	2022	Description and Disposition of Patients With Cancer Accessing a Novel, Pharmacist-Led Cannabis Consultation Service
Markowitz et al.	2022	The Influence of Cannabidiol on the Pharmacokinetics of Methylphenidate in Healthy Subjects

Martin & Patel	2022	Complementary and alternative therapies in the palliative setting
McNamara et al.	2020	Thrombocytopenia In Pediatric Patients On Concurrent Cannabidiol And Valproic Acid
Minervini & France	2020	Effects Of Opioid/Cannabinoid Mixtures On Impulsivity And Memory In Rhesus Monkeys
Miziak et al.	2019	Drug-Drug Interactions Between Antiepileptics And Cannabinoids
Nabissi et al.	2016	Cannabinoids Synergize With Carfilzomib, Reducing Multiple Myeloma Cells Viability And Migration
Naderi et al.	2008	Evaluation Of Interactions Between Cannabinoid Compounds And Diazepam In Electroshock-Induced Seizure Model In Mice
Naderi et al.	2008	Interaction Between Cannabinoid Compounds And Diazepam On Anxiety-Like Behaviour Of Mice
Nadulski et al.	2005	Randomized, Double-Blind, Placebo-Controlled Study About the Effects of Cannabidiol (CBD) on the Pharmacokinetics of D9-Tetrahydrocannabinol (THC) After Oral Application of THC Verses Standardized Cannabis Extract
Nanan et al.	2022	Hyponatremic Cognitive Dysfunction Resulting from Drug-Drug-Gene Interaction between Sertraline and Cannabidiol in an Intermediate CYP2C19 Metabolizer Patient
Nayak et al.	2023	Clinical studies with Cannabis in India – A need for guidelines for the investigators and ethics committees
Neumann-Raizel et al.	2019	2-APB and CBD-mediated targeting of charged cytotoxic compounds into tumor-like cells suggests the involvement of TRPV2 channels
Nkune et al.	2022	Photodynamic Therapy Efficacy of Novel Zinc Phthalocyanine Tetra Sodium 2-Mercaptoacetate Combined with Cannabidiol on Metastatic Melanoma
Oshiro & Castro	2022	Cannabidiol and epilepsy in Brazil: a current review
Paduch & Thomason	2022	Potential Drug Interactions Between Cannabinoids and Its Derivatives and Oral Anticoagulants
Pastino & Shuster	2022	Chronic Cannabis Users: A New Special Population To Consider For Drug Development
Pautex et al.	2022	Cannabinoids for behavioral symptoms in severe dementia: Safety and feasibility in a long-term pilot observational study in nineteen patients
Qian et al.	2022	Involvement of esterases in the pulmonary metabolism of beclomethasone dipropionate and the potential influence of cannabis use
Rahimi et al.	2015	Interaction Between The Protective Effects Of Cannabidiol And Palmitoylethanolamid In Experimental Model Of Multiple Sclerosis In C57BL/6 Mice

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Rajaraman et al.	2018	Successful Use Of Pure Cannabidiol For The Treatment Of Super-Refractory Status Epilepticus
Roberti et al.	2020	Pharmacokinetic Considerations About Antiseizure Medications In The Elderly
Sanders et al.	1979	Interactions Among the Cannabinoids in the Antagonism of the Abdominal Constriction Response in the Mouse
Schubert et al.	2022	Medicinal cannabis for patients with chronic non-cancer pain: analysis of safety and concomitant medications
Shafaroodi et al.	2004	The Interaction Of Cannabinoids And Opioids On Pentylenetetrazole-Induced Seizure Threshold In Mice
Shafaroodi et al.	2008	Elevation Of Pentylenetetrazole-Induced Seizure Threshold In Cholestatic Mice: Interaction Between Opioid And Cannabinoid Systems
Sholler et al.	2020	Therapeutic Efficacy of Cannabidiol (CBD): a Review of the Evidence From Clinical Trials and Human Laboratory Studies
Siemens et al.	1974	Effect Of Cannabis On Pentobarbital-Induced Sleeping Time And Pentobarbital Metabolism In The Rat*
Silva et al.	2020	Cannabidiol in the Treatment of Epilepsy: A Focused Review of Evidence and Gaps
Souza et al.	2022	Case Report: Cannabidiol-Induced Skin Rash: A Case Series and Key Recommendations
Souza et al.	2022	Adverse Effects of Oral Cannabidiol: An Updated Systematic Review of Randomized Controlled Trials (2020–2022)
Suzuki et al.	2022	Cannabidiol Effect on Cue-Induced Craving for Individuals with Opioid Use Disorder Treated with Buprenorphine: A Small Proof-of-Concept Open-Label Study
Suzuki et al.	2023	Impact of cannabidiol on reward and stress-related neurocognitive processes among individuals with opioid use disorder: A pilot, double-blind, placebo-controlled, randomized cross-over trial
Thomas et al.	2022	Case Report: Medical Cannabis—Warfarin Drug-Drug Interaction
Torres et al.	2011	A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma
Tomko et al.	2022	Anti-cancer properties of cannflavin A and potential synergistic effects with gemcitabine, cisplatin, and cannabinoids in bladder cancer

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Treyer et al.	2023	Phytochemical Comparison of Medicinal Cannabis Extracts and Study of Their CYP-Mediated Interactions with Coumarinic Oral Anticoagulants
Vidaurre & Herbst	2019	Nuevos Fármacos Antiepilépticos
Vierke et al.	2021	Buprenorphine–Cannabis Interaction In Patients Undergoing Opioid Maintenance Therapy
Watanabe et al.	2017	Cannabinoids as Potent Inhibitors of Human CYP1 Enzymes
Whynot et al.	2023	Anticancer properties of cannabidiol and Δ9-tetrahydrocannabinol and synergistic effects with gemcitabine and cisplatin in bladder cancer cell lines
Woerdenbag et al.	2019	Potential, Limitations and Risks of Cannabis-Derived Products in Cancer Treatment
Yamamoto et al.	1995	Recent Advances in the Metabolism of Cannabinoids
Yamaori et al.	2011	Cannabidiol, a Major Phytocannabinoid, As a Potent Atypical Inhibitor for CYP2D6
Yamreudeewong et al.	2009	Probable Interaction Between Warfarin and Marijuana Smoking
Yeung et al.	2022	Verifying in vitro-determined enzyme contributions to cannabidiol clearance for exposure predictions in human through physiologically-based pharmacokinetic modeling
Zhang et al.	2008	Mechanism-Based Inhibition of Human Cytochromes P450: In Vitro Kinetics and In Vitro–In Vivo Correlations
Zhu et al.	2006	Characterization of P-glycoprotein Inhibition by Major Cannabinoids from Marijuana
Reason: The article is not in English, Spanish, Portuguese, or French (n=1)		
Author	Year	Title
Watanabe & Yamamoto	1992	Interactions of Marihuana Constituents with Centrally-Acting Drugs

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Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepileptics (N03A)	Valproic Acid (N03AG01)	**Mechanism:** CBD is UGT2B7, UGT1A9 and CYP2C9 inhibitor; Valproic acid induces CYP3A4. **Outcomes:** ↑ Valproic acid level; ↓ Clearance of Valproic Acid; ↑ CBD levels; ↑ [active CBD metabolite]; ↑ ALT and AST	Abu-Sawwa et al., 2020; Amaral Silva et al., 2020; Ben-Menachem et al., 2020; Brown & Winterstein, 2019; Cogan, 2019; Dos Santos et al., 2020; Foster et al., 2019; Gaston & Szaflarski., 2018; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Kocis & Vrana, 2020; Landmark & Brandl, 2020; Lopera et al., 2022; Lord et al., 2022; Narouze et al., 2020; Patsalos et al., 2020; Vázquez et al., 2021; Vázquez et al., 2020; Gaston et. al, 2023; Li et. al, 2023; Lopera et. al, 2022; Talwar et. al, 2023; Smith & Gruber, 2023; Sankar et. al, 2023
Antiarrhythmics (C01B)	Amiodarone (C01BD01)	**Mechanism:** CBD is a CYP3A4 inhibitor and CYP2C19 and substrate. **Outcomes:** ↑ Levels of amiodarone and CBD.	Brown & Winterstein, 2019; Lattanzi et al., 2020; Narouze et al., 2020
Antiemetics and antinauseants (A04A)	Aprepitant (A04Ad12)	**Mechanism:** Aprepitant is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD levels	Brown & Winterstein, 2019
Psychostimulants - Agents used for ADHD and nootropics (N06B)	Armodafinil (N06BA13)	**Mechanism**: Armodafinil is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD levels.	Lattanzi et al., 2020
Direct acting antivirals (J05A)	Atazanavir (J05AE08)	**Mechanism:** Atazanavir is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD levels.	Lattanzi et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Lipid Modifying Agents (C10A)	Atorvastatin (C10AA05)	**Mechanism:** CBD is CYP3A4 and inhibitor. **Outcomes:** ↑ Atorvastatin level; ↑ CBD levels.	Balachandran et al., 2021; Vázquez et al., 2021
Immunosuppressants (L04A)	Baricitinib (L04AA37)	**Mechanism:** CBD interacts with CYP3A4, CYP1A2, CYP2C9, CYP2C8, CYP2C19 and CYP2B6. **Outcomes:** ↑ Levels of CBD and Baricitinib.	Land et al., 2020
Antiepileptics (N03A)	Carbamazepine (N03AF01)	**Mechanism:** CBD inhibits UGT2B7; Carbamazepine induces CYP3A4 and CYP2C19. **Outcomes:** ↑ Carbamazepine levels; ↓ CBD levels	Balachandran et al., 2021; Brown & Winterstein, 2019; Darweesh et al., 2020; Franco et al., 2021; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Landmark & Brandl, 2020; Narouze et al., 2020; Perucca, 2017; Schaiquevich et al., 2020; Vázquez et al., 2021; Vázquez et al., 2020; Bardhi et al., 2022; Duda & Reinert, 2022; Stöllberger & Finsterer, 2023

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antimycotics for systemic use (J02A)	Ketoconazole (J02AB02)	**Mechanism:** Ketoconazole is a CYP3A4 and CYP2C19 inhibitor; CBD's inactive metabolite inhibits BSEP. **Outcomes:** ↑ CBD levels	Amaral Silva et al., 2020; Antoniou et al., 2020; Brown & Winterstein, 2019; Franco et al., 2021; Horn & Hansten, 2014; Karaźniewicz-Łada et al., 2021; Lattanzi et al., 2020; Lopera et al., 2022; Lucas et al., 2018; Nagao et al, 2020; Narouze et al., 2020; Perucca, 2017; Schaiquevich et al., 2020; Stott et al., 2013; Stout & Cimino, 2014; Ujváry & Hanuš, 2016; Vázquez et al., 2021; Lopera et. al, 2022
Immunosuppressants (L04A)	Cyclosporine (L04AD01)	**Mechanism:** CBD inhibits hepatic microsomal metabolism of cyclosporine; Ciclosporin inhibits CYP3A4. **Outcomes:** ↑ CBD levels; ↑ ciclosporin levels;	Balachandran et al., 2021; Jaeger et al., 1996; Lattanzi et al., 2020
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Cimetidine (A02BA01)	**Mechanism:** CBD inhibits CYP2C19 and CYP3A4; CBD inhibits BCRP. **Outcomes**: ↑ or ↓ CBD levels	Balachandran et al., 2021; Brown & Winterstein, 2019; Karaźniewicz-Łada et al., 2021; Narouze et al., 2020
Antibacterials -Macrolides, Lincosamide and Streptogramins (J01F)	Clarithromycin (J01FA09)	**Mechanism:** Clarithromycin inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Balachandran et al., 2021; Lattanzi et al., 2020; Narouze et al., 2020; Vázquez et al., 2021

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Anxiolytics (N05B)	Clobazam (N05BA09)	**Mechanism:** CBD inhibits CYP2C19 and CYP3A4. **Outcomes:** ↑ CBD levels	Abu-Sawwa et al., 2020; Amaral Silva et al., 2020; Anderson et al., 2022; Antoniou et al., 2020; Balachandran et al., 2021; Bialer & Perucca, 2020; Brown & Winterstein, 2019; Chong & Lerman, 2016; Cogan, 2019; Czuczwar, 2020; Dos Santos et al., 2020; Franco et al., 2021; Gaston et al., 2017; Gaston & Szaflarski., 2018; Geffrey et al., 2015; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Klein et al., 2019; Kocis & Vrana, 2020; Kolla et al., 2022; Landmark & Brandl, 2020; Lattanzi et al., 2020; Lopera et al., 2022; Lord et al., 2022; Lucas et al., 2018; Morrison et al., 2019; Narouze et al., 2020; Perucca, 2017; Qian et al., 2019; Rong et al., 2018; Schaiquevich et al., 2020; Schmitz & Richert, 2020; Ujváry & Hanuš, 2016; Vázquez et al., 2020; Zendulka et al., 2016; Bardhi et. al, 2022; Duda & Reinert, 2022; Gaston et. al, 2023; Georgieva et. al, 2023; Johannessen Landmark et. al, 2023; Klein & Clark, 2022; Kolla et. al, 2022; Lopera et. al, 2022; Reddy, 2023; Samanta, 2022; Talwar et. al, 2023; Strzelczyk & Schubert-Bast,

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antibacterials for systemic use - Amphenicols (J01B)	Chloramphenicol (J01BA01)	**Mechanism:** Chloramphenicol inhibits CYP3A4 and CYP2C19. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020; Narouze et al., 2020
Direct acting antivirals (J05A)	Darunavir (J05AE10)	**Mechanism:** Duranavir is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020
Direct acting antivirals (J05A)	Darunavir/Cobicistat (J05AR14)	**Mechanism:** CBD interacts with CYP3A4, P-Gp, plasma proteins and BCRP. **Outcomes:** ↑ CBD and Duranavir/Cobicistat levels.	Land et al., 2020
Antidepressants (N06A)	Desipramine (N06AA01)	**Mechanism:** Desipramine interacts with CYP3A4. **Outcomes:** ↑ CBD levels.	Balachandran et al., 2021
Corticosteroids for systemic use (H02A)	Dexamethasone (H02AB02)	**Mechanism:** CBD interacts with CYP3A4, P-Gp, plasma proteins and BCRP. **Outcomes:** ↑ CBD and dexamethasone levels.	Land et al., 2020
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Dexlansoprazole (A02BC06)	**Mechanism:** Dexlanzoprazole interacts with CYP2C19. **Outcomes:** ↑ CBD and dexlansoprazole levels.	Lattanzi et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Selective calcium channel blockers with direct cardiac effects (C08D)	Diltiazem (C08DB01)	**Mechanism:** Diltiazem inhibits CYP3A4. **Outcomes:** ↑ CBD levels.	Kong et al., 2018; Lattanzi et al., 2020; Narouze et al., 2020; Qian et al., 2019
Drugs used in addictive disorders (N07B)	Disulfiram (N07BB01)	**Mechanism:** CBD interacts with CYP3A4 and CYP2C9. **Outcomes:** ↑ CBD levels and disulfiram.	Land et al., 2020
Antibacterials - Tetracyclines (J01A)	Doxycycline (J01AA02)	**Mechanism:** Doxycycline inhibits CYP3A4. **Outcomes:** ↑ CBD levels.	Lattanzi et al., 2020
Direct acting antivirals (J05A)	Efavirenz (J05AG03)	**Mechanism:** Efavirenz is a CYP2B6 substrate, which can be inhibited or induced by CBD. Efavirenz induces CYP3A4 and inhibits CYP2C19. **Outcomes:** ↑ or ↓ CBD levels	Brown & Winterstein, 2019; Karaźniewicz-Łada et al., 2021; Kocis & Vrana, 2020; Lattanzi et al., 2020
Antineoplastic agents - Hormonal antagonists and related agents (L02B)	Enzalutamide (L02BB04)	**Mechanism**: Enzalutamide induces CYP3A4. **Outcomes:** ↓ CBD levels	Brown & Winterstein, 2019
Antibacterials - Macrolides, Lincosamide, and Streptogramins (J01F)	Erythromycin (J01FA01)	**Mechanism**: Erythromycin inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020; Narouze et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepiletics (N03A)	Eslicarbazepine (n03AF04)	**Mechanism:** Induction of CYP3A4, an enzyme responsible for both tetrahydrocannabinol and cannabidiol metabolism. Induction of CYP2C9 and CYP2C19 are likely to also contribute. **Outcomes**: ↑ [eslicarbazepine] dose-dependent; ↑ Clearance of the active CBD metabolite; ↓ CBD conversion to active metabolite	Abu-Sawwa et al., 2020; Cogan, 2019; Foster et al., 2019; Gaston et al., 2017; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Landmark & Brandl, 2020; Lopera et al., 2022; Qian et al., 2019; Schmitz & Richert, 2020; Lopera et. al, 2022; Reddy, 2023; Talwar et. al, 2023; Smith & Gruber, 2023; Stöllberger & Finsterer, 2023
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Esomeprazole (A02BC05)	**Mechanism:** Esomeprazole is a CYP2C19 substrate, which is inhibited by CBD. **Outcomes:** ↑ Esomeprazole levels; ↑ CBD levels	Amaral Silva et al., 2020; Lattanzi et al., 2020
Antiepiletics (N03A)	Stiripentol (N03AX17)	**Mechanism:** CBD inhibits CYP2C19 and some UGT isoforms. **Outcomes**: ↑ Stiripentol levels; ↓ Stiripentol clearance; ↓ CBD active metabolite formation; ↑ or ↓ in the formation of the inactive metabolite of the CBD; ↑ or ↓ Stiripentol exposure	Abu-Sawwa et al., 2020; Balachandran et al., 2021; Ben-Menachem et al., 2020;, Franco et al., 2021; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Landmark & Brandl, 2020; Lopera et al., 2022; Patsalos et al., 2020; Qian et al., 2019; Bardhi et al., 2022; Lopera et. al, 2022; Stöllberger & Finsterer, 2023

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Direct acting antivirals (J05A)	Etravirine (J05AG04)	**Mechanism:** Etravirine is CYP2C9 and CYP2C19 substrate; inhibits CYP2C19 and induces CYP3A4. **Outcomes:** ↑ or ↓ CBD levels; ↑ Etravirine levels	Lattanzi et al., 2020
Antiepiletics (N03A)	Felbamate (N03AX10)	**Mechanism:** Felbamate inhibits CYP2C19. **Outcomes:** ↑ Felbamate and CBD levels; ↑ Clearance of the active CBD metabolite; ↓ CBD conversion to active metabolite	Abu-Sawwa et al., 2020; Landmark & Brandl, 2020; Narouze et al., 2020; Gaston et. al, 2023
Antiepiletics (N03A)	Phenytoin (N03AB02)	**Mechanism:** Phenytoin is a CYP2C9 substrate, CYP2C8 and CYP2C19 and induces CYP3A4 and CYP2C19; CBD inhibits CYP2C19. **Outcomes**: ↑ CBD metabolism; ↓ CBD bioavailability; ↑ [phenytoin]; ↓ phenytoin clearance;	Abu-Sawwa et al., 2020; Amaral Silva et al., 2020; Balachandran et al., 2021; Brown & Winterstein, 2019; Franco et al., 2021; Jiang et al., 2013; Kocis & Vrana, 2020; Landmark & Brandl, 2020; Narouze et al., 2020; Perucca, 2017; Savage et al., 2020; Schaiquevich et al., 2020; Vázquez et al., 2020; Duda & Reinert, 2022

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepiletics (N03A)	Phenobarbital (N03AA02)	**Mechanism:** Phenobarbital is CYP2C9 and CYP2C8 substrate and induces CYP3A4 and CYP2C19; CBD inhibits CYP2C9. **Outcomes:** ↓ CBD bioavailability; ↑ CBD conversion to active metabolite; ↑ conversion of active metabolite into inactive; ↑ [phenobarbital]; ↓ phenobarbital clearance;	Abu-Sawwa et al., 2020; Balachandran et al., 2021; Brown & Winterstein, 2019; Deutsch et al., 1991; Frías-Soria et al., 2021; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Narouze et al., 2020; Schaiquevich et al., 2020; Vázquez et al., 2021; Duda & Reinert, 2022; Stöllberger & Finsterer, 2023
Antimycotics for systemic use (J02A)	Fluconazole (J02AC01)	**Mechanism:** Fluconazole inhibits CYP2C19 and CYP3A4. **Outcomes:** ↑ CBD bioavailability;	Brown & Winterstein, 2019; Lattanzi et al., 2020
Antidepressants (N06A)	Fluoxetine (N06AB03)	**Mechanism:** Fluoxetine inhibits CYP2C19; CBD inhibits CYP2C9 and CYP2D6. **Outcomes:** ↑ CBD bioavailability; ↑ fluoxetine level;	Amaral Silva et al., 2020; Anderson et al., 2021; Anderson et al., 2019; Brown & Winterstein, 2019; Karaźniewicz-Łada et al., 2021; Lattanzi et al., 2020; Narouze et al., 2020; Wilson-Mokeh et al., 2019
Antidepressants (N06A)	Fluvoxamine (N06AB08)	**Mechanism:** Fluvoxamine inhibits CYP2C19 and is a CYP1A2 substrate. **Outcomes:** ↑ or ↓ Fluvoxamine levels; ↑ CBD bioavailability;	Brown & Winterstein, 2019; Karaźniewicz-Łada et al., 2021; Lattanzi et al., 2020; Narouze et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Direct acting antivirals (J05A)	Fosamprenavir (J05AE07)	**Mechanism:** They were fosamprenavir is a CYP3A4 inhibitor. **Outcomes**: ↑ CBD levels	Lattanzi et al., 2020
Lipid modifying agents (C10A)	Gemfibrozil (C10AB04)	**Mechanism:** Gemfibrozil inhibits CYP2C19 and is a UGT2B7 substrate; CBD inhibits UGT2B7. **Outcomes:** ↑ Gemfibrozil levels; ↑ CBD levels	Kocis & Vrana, 2020; Lattanzi et al., 2020
Antipsychotics (N05A)	Haloperidol (N05AD01)	**Mechanism:** Haloperidol interacts with CYP3A4; CBD interacts with UGT1A9. **Outcomes:** ↑ Haloperidol levels; ↑ CBD levels	Balachandran et al., 2021; Brown & Winterstein, 2019; Lattanzi et al., 2020; Narouze et al., 2020
Antineoplastic agents - Protein kinase inhibitors (L01E)	Imatinib (L01EA01)	**Mechanism:** CBD interacts with BCRP, inhibits CYP3A4 and CYP2D6 and is a CYP2C9 substrate. **Outcomes:** ↑ CBD bioavailability;	Brown & Winterstein, 2019; Lattanzi et al., 2020; Opitz et al., 2019

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Direct acting antivirals (J05A)	Indinavir (J05AE02)	**Mechanism:** Indinavir inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020
Antimycobacterial - Drugs used in the treatment of tuberculosis (J04A)	Isoniazid (J04AC01)	**Mechanism:** Isoniazid inhibits CYP3A4 and CYP2C19. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020; Narouze et al., 2020
Antimycotics for systemic use (J02A)	Itraconazole (J02AC02)	**Mechanism:** Itraconazole inhibits CYP3A4. **Outcomes**: ↑ CBD levels	Balachandran et al., 2021; Lattanzi et al., 2020; Narouze et al., 2020; Vázquez et al., 2021
Direct acting antivirals (J05A)	Letermovir (J05AX18)	**Mechanism:** Letermovir inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Balachandran et al., 2021
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Lansoprazole (A02BC03)	**Mechanism:** Lansoprazole is a CYP2C19 substrate, which is inhibited by CBD. **Outcomes:** ↑ Lansoprazole levels; ↑ CBD levels	Lattanzi et al., 2020
Antipropulsives (A07D)	Loperamide (A07DA03)	**Mechanism:** Loperamide inhibits CYP3A4. CBD is P-Gp Substrate and inhibitor. **Outcomes:** ↑ CBD bioavailability;	Brown & Winterstein, 2019; Narouze et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Direct acting antivirals (J05A)	Lopinavir/Ritonavir (J05AR10)	**Mechanism**: CBD interacts with CYP3A4, plasma proteins, P-Gp and BCRP. **Outcomes**: ↑ levels of CBD and Lopinavir/Ritonavir	Karaźniewicz-Łada et al., 2021; Land et al., 2020
Antihistamines for systemic use (R06A)	Loratadine (R06AX13)	**Mechanism:** Loratadine inhibits CYP2C19. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020
Other Respiratory System Products (R07A)	Lumacaftor/Ivacaftor (R07AX30)	**Mechanism:** Lumacaflor/Ivacaflor induces CYP3A4. **Outcomes:** ↓ CBD levels	Lattanzi et al., 2020
Other antibacterials (J01X)	Metronidazole (J01XD01)	**Mechanism**: Metronidazole inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020
Psychostimulants - Agents used for ADHD and nootropics (N06B)	Modafinil (N06BA07)	**Mechanism:** Modafinil is a CYP2C19 substrate and inhibitor. **Outcomes:** ↑ CBD and Modafinil levels	Lattanzi et al., 2020
Antibacterials - Lactamic Beta (J01C)	Nafcillin (J01CF06)	**Mechanism**: Nafcillin induces CYP3A4. **Outcomes**: ↓ CBD levels	Lattanzi et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antidepressants (N06A)	Nefazodone (N06AX06)	**Mechanism:** Nefazodone is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD bioavailability;	Brown & Winterstein, 2019
Direct acting antivirals (J05A)	Nelfinavir (J05AE04)	**Mechanism:** Modafinil is CYP2C19 substrate, CYP3A4 inhibitor. CBD binds to plasma proteins and interacts with BCRP. **Outcomes**: ↑ levels of CBD and Nelfinavir	Land et al., 2020; Lattanzi et al., 2020
Agents against amoebiasis and other protozoal diseases (P01A)	Nitazoxanide (P01AX11)	**Mechanism:** CBD interacts with plasma proteins. **Outcomes:** ↑ CBD and Nitazoxanide levels.	Kong et al., 2018
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Omeprazole (A02BC01)	**Mechanism:** CBD interacts with CYP2D6. Omeprazole inhibits CYP2C19. **Outcomes:** ↑ CBD and omeprazole levels	Balachandran et al., 2021; Bansal et al., 2020; Lattanzi et al., 2020; Stott et al., 2013; Ujváry & Hanuš, 2016

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepiletics (N03A)	Oxcarbazepine (N03AF02)	**Mechanism:** CBD Inhibits UGT. **Outcomes:** ↑ [oxcarbazepine] serum and cerebral; ↓ Oxcarbazepine clearance; ↑ Clearance of the active CBD metabolite; ↓ CBD conversion to active metabolite; ↓ CBD levels; ↑ CBD brain capture	Abu-Sawwa et al., 2020; Balachandran et al., 2021; Gilmartin et al., 2021; Singh et al., 2020
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Pantoprazole (A02BC02)	**Mechanism:** Pantoprazole is substrate and inhibits CYP2C19. **Outcomes:** ↑ CBD (substrate) and Pantoprazole levels	Lattanzi et al., 2020
Hypnotics and sedatives (N05C)	Pentobarbital (N05CA01)	**Mechanism:** CYP3A4 Inducers (Strong) **Outcomes:** ↓ CBD levels	Coldwell et al., 1974
Antiepiletics (N03A)	Perampanel (N03AX22)	**Mechanism:** CBD Inhibits CYP3A4, CYP1A2 and CYP2B6. **Outcomes:** Perampanel clearance; ↑ [Perampanel];↓ or ↑ conversion of active CBD metabolite to inactive	Abu-Sawwa et al., 2020; Landmark & Brandl, 2020; Duda & Reinert, 2022; Gaston et. al, 2023

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Blood glucose lowering drugs, excl. insulins (A10B)	Pioglitazone (A10BG03)	**Mechanism:** Pionoglitazone is an inducer of CYP3A4. **Outcomes:** ↓ CBD (substrate) bioavailability	Brown & Winterstein, 2019; Narouze et al., 2020
Antimycotics for systemic use (J02A)	Posaconazole (J02AC04)	**Mechanism:** Posaconazole inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020
Analgesics - Other analgesics and antipyretics (N02B)	Pregabalin (N02BF02)	**Mechanism:** CBD inhibits CYP2D6, CYP2C19, CYP3A4, CYP1A2 and CYP2C9. **Outcomes:** ↑ [CBD] cerebral;	Balachandran et al., 2021; Gilmartin et al., 2021; Singh et al., 2020; Wilson-Mokeh et al., 2019
Antiepiletics (N03A)	Primidone (N03AA03)	**Mechanism:** CYP3A4 Inducers (Primidone) may decrease the serum concentration of Cannabis. **Outcomes:** ↓ Clearance of Primidone; ↑ [active metabolite] (phenobarbital); ↑ CBD conversion to active metabolite and inactive metabolite formation; ↓ bioavailability and [active metabolite] of the CBD	Abu-Sawwa et al., 2020;

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antibacterials - Macrolides, Lincosamide, and Streptogramins (J01F)	Quinupristin/Dalfopristin (J01FG02)	**Mechanism:** Quinupristin/Dalfopristin inhibits CYP3A4. **Outcomes:** ↑ CBD levels	Lattanzi et al., 2020
Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	Rabeprazole (A02BC04)	**Mechanism:** rabeprazole is substrate and inhibits CYP2C19. **Outcomes:** ↑ CBD and rabeprazole levels	Lattanzi et al., 2020
Antimycobacterial - Drugs used in the treatment of tuberculosis (J04A)	Rifampicin (J04AB02)	**Mechanism:** Rifampicin is a CYP2B6 substrate and induces CYP3A4 and CYP2C19. **Outcomes**: ↓ CMAX and CBD (substrate) bioavailability; ↑ CBD Clearance	Amaral Silva et al., 2020; Balachandran et al., 2021; Brown & Winterstein, 2019; Franco et al., 2021; Horn & Hansten, 2014; Lattanzi et al., 2020; Lopera et al., 2022; Lucas et al., 2018; Narouze et al., 2020; Perucca, 2017; Schaiquevich et al., 2020; Ujváry & Hanuš, 2016; Vázquez et al., 2021; Lopera et. al, 2022
Antimycobacterial - Drugs used in the treatment of tuberculosis (J04A)	Rifapentin (J04AB05)	**Mechanism:** Rifapentin induces CYP3A4. **Outcomes:** ↓ CBD (substrate) levels	Lattanzi et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Direct acting antivirals (J05A)	Ritonavir (J05AE03)	**Mechanism:** Ritonavir inhibits CYP3A4. **Outcomes:** ↑ CBD levels; ↑ ritonavir levels	Balachandran et al., 2021; Karaźniewicz-Łada et al., 2021; Lattanzi et al., 2020; Vázquez et al., 2020
Direct acting antivirals (J05A)	Saquinavir (J05AE01)	**Mechanism**: Saquinavir inhibits CYP3A4. **Outcomes:** ↑ CBD (substrate) levels	Lattanzi et al., 2020
Immunosuppressants (L04A)	Sarilumab (L04AC14)	**Mechanism**: Sarilumab induces CYP450. **Outcomes:** ↓ CBD and Sarilumab levels	Land et al., 2020
Antidepressants (N06A)	Sertraline (N06AB06)	**Mechanism:** Sertraline is a CYP2C19 substrate and inhibits CYP3A4 **Outcomes**: ↑ CBD and Sertraline levels	Anderson et al., 2021; Lattanzi et al., 2020; Vaughn et al., 2021; Wilson-Mokeh et al., 2019; Stöllberger & Finsterer, 2023
Urological (G04B)	Sildenafil (G04BE03)	**Mechanism:** Sildenafil inhibits CYP3A4. **Outcomes**: ↑ CBD and sildenafil levels	Balachandran et al., 2021

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Lipid modifying agents (C10A)	Simvastatin (C10AA01)	**Mechanism:** CBD interacts with BSEP and inhibits CYP3A4 and P-Gp. **Outcomes:** ↑ simvastatin levels; ↑ CBD levels;	Balachandran et al., 2021; Brown & Winterstein, 2019; Vázquez et al., 2021
Direct acting antivirals (J05A)	Sofosbuvir (J05AP08)	**Mechanism**: Sofosbuvir interacts with P-Gp and BCRP. **Outcomes:** ↑ CBD and sofosbuvir levels	Land et al., 2020
Androgens (G03B)	Testosterone (G03BA03)	**Mechanism:** Testosterone is a CYP3A4 substrate. **Outcomes:** ↓ CBD metabolism	Doohan et al., 2021
Direct acting antivirals (J05A)	Tipranavir (J05AE09)	**Mechanism:** Tipranavir is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD (substrate) levels	Lattanzi et al., 2020
Immunosuppressants (L04A)	Tocilizumab (L04AC07)	**Mechanism**: Tocilizumab interacts with CYP3A4, CYP1A2, CYP2C9, CYP2C19, CYP2B6. **Outcomes**: ↑ levels of CBD (substrate) and Tocilizumab	Land et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepiletics (N03A)	Topiramate (N03AX11)	**Mechanism**: Topiramate induces CYP3A4, inhibits CYP2C19 and is a P-Gp substrate. CBD inhibits P-Gp. **Outcomes**: ↑ Topiramate levels; ↓ or ↑ CBD levels	Abu-Sawwa et al., 2020; Brown & Winterstein, 2019; Cogan, 2019; Foster et al., 2019; Gaston et al., 2017; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Landmark & Brandl, 2020; Narouze et al., 2020; Perucca, 2017; Qian et al., 2019; Schmitz & Richert, 2020; Singh et al., 2020; Gaston et. al, 2023; Reddy, 2023; Talwar et. al, 2023; Smith & Gruber, 2023; Stöllberger & Finsterer, 2023
Direct acting antivirals (J05A)	Umifenovir (J05AX13)	**Mechanism:** CYP3A4 internalization and plasma proteins. **Outcomes**: ↑ [CBD] (substrate)	Land et al., 2020
Selective calcium channel blockers with direct cardiac effects (C08D)	Verapamil (C08DA01)	**Mechanism**: Verapamil is a CYP3A4 inhibitor. **Outcomes:** ↑ CBD (substrate) levels	Brown & Winterstein, 2019; Lattanzi et al., 2020; Narouze et al., 2020
Antimycotics for systemic use (J02A)	Voriconazole (J02AC03)	**Mechanism:** Voriconazole inhibits CYP2C19 and CYP3A4. **Outcomes:** ↑ CBD (substrate) and voriconazole levels	Lattanzi et al., 2020

Supplementary Material 3. Associated outcomes and the underlying mechanisms of pharmacokinetic interactions that influence serum Cannabidiol (CBD) levels (concluded).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepiletics (N03A)	Zonisamide (N03AX15)	**Mechanism:** CBD inhibits CYP3A4. **Outcomes**: ↓ Tmáx and T1/2 CBD; ↓ zonisamide clearance ↑ zonisamide	Abu-Sawwa et al., 2020; Cogan, 2019; Foster et al., 2019; Gaston et al., 2017; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Landmark & Brandl, 2020;Qian et al., 2019; Schmitz & Richert, 2020;Wang et al., 2020; Reddy, 2023; Talwar et. al, 2023; Smith & Gruber, 2023

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antidepressants (N06A)	Amitriptyline (N06Aa09)	**Mechanism:** CBD is CYP2D6 inhibitor, CYP2C19, CYP3A4, CYP1A2 and CYP2C9. **Outcome:** ↑ amitriptyline level	Amaral Silva et al., 2020; Balachandran et al., 2021; Wilson-Mokeh et al., 2019
Antineoplastic agents - hormonal antagonists and related agents (L02B)	Anastrozole (L02BG03)	**Mechanism:** CBD inhibits CYP3A4 **Outcome:** ↑ Anastrozole levels	Opitz et al., 2019
Antipsychotics (N05A)	Aripiprazole (N05AX12)	**Mechanism:** CBD inhibits CYP450. **Outcome:** ↑ Aripiprazole levels	Cogan, 2019
Other antihypertensives (C02K)	Bosentan (C02KX01)	**Mechanism:** Bosentan is a CYP2C9 substrate. **Outcomes:** ↑ Bosentan levels	Lattanzi et al., 2020
Antiepileptics (N03A)	Brivaracetam (N03AX23)	**Mechanism:** CBD is CYP2C19 inhibitor. **Outcomes:** ↑ Brivaracetam level; ↓ Clearance do Brivaracetam	Abu-Sawwa et al., 2020; Franco et al., 2021; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Klotz et al., 2019; Duda & Reinert, 2022
Antidepressants (N06A)	Bupropion (N06AX12)	**Mechanism:** CBD is CYP2B6 inhibitor. **Outcome:** ↑ Bupropion levels	Doohan et al., 2021; Kocis & Vrana, 2020
Opioids (N02A)	Buprenorphine (N02AE01)	**Mechanism:** Buprenorphine is a CYP2C8 and CYP2C9 substrate. **Outcomes**: ↑ levels of buprenorphine;	Brown & Winterstein, 2019; Narouze et al., 2020

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Psychostimulants - Agents used for ADHD and nootropics. (N06B)	Caffeine (N06BC01)	**Mechanism:** CBD is CYP1A2 inhibitor. **Outcomes:** ↑ caffeine levels;	Kocis & Vrana, 2020; Thai et al., 2021
Blood glucose lowering drugs, excl. insulins. (A10B)	Canagliflozin (A10BK02)	**Mechanism:** CBD inhibits UGT1A9. **Outcomes:** ↑ Canagliflozin levels;	Brown & Winterstein, 2019; Narouze et al., 2020
Muscle relaxants (M03B)	Carisopropol (M03BA02)	**Mechanism:** Carisoprodol is a CYP2C19 substrate. CBD inhibits CYP2C19. **Outcomes:** ↑ Carisoprodol levels	Brown & Winterstein, 2019
Beta Blocking Agents (C07A)	Carvedilol (C07AG02)	**Mechanism**: Carvedilol is a CYP2C9 substrate; CBD's inactive metabolite inhibits BSEP. **Outcomes:** ↑ Carvedilol levels	Amaral Silva et al., 2020; Lattanzi et al., 2020
Antineoplastic agents - Alkylating Agents (L01A)	Cyclophosphamide (L01AA01)	**Mechanism:** Cyclophosphamide is CYP2C19 and CYP2B6 substrate; The inactive metabolite of CBD inhibits BCRP; **Outcomes:** ↑ cyclophosphamide levels; ↓ cyclophosphamide active Metabolite; ↓ decreased elimination of toxic metabolites or the drug itself	Brown & Winterstein, 2019; Lattanzi et al., 2020; Opitz et al., 2019

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Celecoxib (M01AH01)	**Mechanism:** Colecoxib is a CYP2C8 substrate, CYP2C9 and, to a lesser extent, CYP3A4; CBD inhibits CYP2D6. **Outcomes:** ↑ celecoxib levels	Amaral Silva et al., 2020; Brown & Winterstein, 2019; Narouze et al., 2020; Wilson-Mokeh et al., 2019
Antidepressants (N06A)	Citalopram (N06AB04)	**Mechanism:** CBD inhibits CYP2C19 and CYP3A4. **Outcomes:** ↑ citalopram levels	Amaral Silva et al., 2020; Anderson et al., 2021; Balachandran et al., 2021; Doohan et al., 2021; Lattanzi et al., 2020; Vaughn et al., 2021; Wilson-Mokeh et al., 2019; Smith & Gruber, 2023; Stöllberger & Finsterer, 2023
Antidepressants (N06A)	Clomipramine (N06AA04)	**Mechanism**: Clomipramine is a CYP2C19 substrate. **Outcomes:** ↑ Clomipramine levels	Lattanzi et al., 2020
Antithrombotic agents (B01A)	Clopidogrel (B01AC04)	**Mechanism:** CBD inhibits CYP2C9; Clopidogrel is CYP2C19 substrate. **Outcomes:** ↑ clopidogrel levels	Amaral Silva et al., 2020; Brown & Winterstein, 2019; Greger et al., 2019; Karaźniewicz-Łada et al., 2021; Narouze et al., 2020
Antiprotozoals - Antimalarials (P01B)	Chloroquine (P01BA01)	**Mechanism:** CBD inhibits CYP3A4 and CYP2C8. **Outcomes:** ↑ chloroquine levels	Land et al., 2020
Cough suppressants, excl. combinations with expectorants (R05D)	Codeine (R05da04)	**Mechanism:** CBD inhibits CYP2D6 and UGT2B4. **Outcomes:** ↑ codeine levels;	Amaral Silva et al., 2020; Nasrin et al., 2021; Vázquez et al., 2020; Bardhi et al., 2022

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antithrombotic agents (B01A)	Dabigatran (B01AE07)	**Mechanism:** CBD inhibits UGT1A9 and P-gp. **Outcomes:** ↑ Dabigatran levels	Brown & Winterstein, 2019; Greger et al., 2019; Narouze et al., 2020
Blood glucose lowering drugs, excl. insulins. (A10B)	Dapagliflozin (A10bk01)	**Mechanism:** CBD inhibits UGT1A9. **Outcomes:** ↑ levels of dapagliflozin	Brown & Winterstein, 2019; Narouze et al., 2020
Antimycobacterials - Drugs for treatment of lepra (J04B)	Dapsone (J04BA02)	**Mechanism**: Dapsone is a CYP2C9 substrate. **Outcomes**: ↑ Dapsone levels	Lattanzi et al., 2020
Antineoplastic agents - Protein kinase inhibitors (L01E)	Dasatinib (L01EA02)	**Mechanism:** CBD inhibits P-gp, BCRP and CYP3A4. **Outcomes:** ↑ Dasatinib levels	Opitz et al., 2019
Anxiolytics (N05B)	Diazepam (N05BA01)	**Mechanism:** CBD interacts with CYP2C19. **Outcomes:** ↑ Diazepam levels; ↑ conversion of diazepam into active metabolites; ↓ Clearance of active metabolites	Abu-Sawwa et al., 2020; Balachandran et al., 2021; Doohan et al., 2021; Kocis & Vrana, 2020; Duda & Reinert, 2022
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Diclofenac (M01AB05)	**Mechanism:** CBD inhibits CYP2C9. **Outcomes:** ↑ Diclofenac levels	Bansal et al., 2020; Doohan et al., 2021; Kong et al., 2018; Lattanzi et al., 2020; Qian et al., 2019

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Analgesics - Other analgesics and antipyretics (N02B)	Diflunisal (N02BA11)	**Mechanism:** CBD inhibits UGT1A9. **Outcomes:** ↑ Diflunisal levels	Kocis & Vrana, 2020; Narouze et al., 2020
Cardiac glycosides (C01A)	Digoxin (C01AA05)	**Mechanism:** CBD interacts with BSEP; CBD is P-Gp Substrate and inhibitor. **Outcomes**: ↑Digoxin levels	Brown & Winterstein, 2019; Narouze et al., 2020
Antithrombotic agents (B01A)	Dipyridamole (B01Ac07)	**Mechanism:** CBD interacts with BCRP. **Outcomes:** ↑ Dipyridamole levels	Brown & Winterstein, 2019
Antineoplastic agents - Cytotoxic antibiotics and related substances (L01D)	Doxorubicin (L01DB01)	**Mechanism:** CBD inhibits P-Gp. **Outcomes:** ↓ doxorubicin in studied cells	Fraguas-Sánchez et al., 2020; Opitz et al., 2019
Antidepressants (N06A)	Duloxetine (N06AX21)	**Mechanism:** CBD inhibits CYP2D6 and CYP1A2. **Outcomes:** ↑ Duloxetine levels	Amaral Silva et al., 2020; Vázquez et al., 2020; Lippert & Renner, 2022
Antidepressants (N06A)	Escitalopram (N06AB10)	**Mechanism:** CBD inhibits CYP450. **Outcomes:** ↑ Escitalopram levels	Anderson et al., 2019; Lattanzi et al., 2020; Smith & Gruber, 2023

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Etoricoxib (M01AH05)	**Mechanism:** CBD inhibits CYP2C9 and CYP3A4. **Outcomes**: ↑ Etoricoxib levels	Wilson-Mokeh et al., 2019
Antineoplastic agents - Protein kinase inhibitors (L01E)	Everolimus (L01EG02)	**Mechanism:** CBD inhibits CYP3A4. **Outcomes:** ↑ levels of Everolimus; ↑ MTOR levels	Dos Santos et al., 2020; Franco et al., 2021; Gilmartin et al., 2021; Lattanzi et al., 2020; Wiemer-Kruel et al., 2019; Samanta, 2022; Wray et. Al, 2023
Lipid-modifying agents (C10A)	Ezetimibe (C10AX09)	**Mechanism:** CBD interacts with UGT2B7. **Outcomes:** ↑ Ezetimibe levels	Brown & Winterstein, 2019
Antidepressants (N06A)	Phenelzine (N06AF03)	**Mechanism:** CBD inhibits Phenelzine metabolism. **Outcomes:** ↑ Phenelzine levels	Balachandran et al., 2021;
Antiepiletics (N03A)	Fenfluramine (N03AX26)	**Mechanism:** Not been fully investigated, but cannabidiol-mediated inhibition of CYP1A2, CYP2C19, and CYP2C9, enzymes responsible for fenfluramine metabolism, likely contributes. **Outcomes:** ↑ levels of fenfluramine	Sankar et. al, 2023

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Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Lipid-modifying agents (C10A)	Fenofibrate (C10AB05)	**Mechanism**: CBD inhibits UGT1A9. **Outcomes**: ↑ Fenofibrate levels	Kocis & Vrana, 2020; Lattanzi et al., 2020
Lipid-modifying agents (C10A)	Fluvastatin (C10AA04)	**Mechanism:** Fluvastatin is a CYP2C9 substrate. **Outcomes:** ↑ Fluvastatin levels	Lattanzi et al., 2020; Narouze et al., 2020
Antineoplastic agents - Protein kinase inhibitors (L01E)	Gefitinib (L01EB01)	**Mechanism**: CBD inhibits CYP2D6. **Outcome:** ↑ Gefitinib levels	Opitz et al., 2019
Blood glucose lowering drugs, excl. insulins (A10B)	Glibenclamide (A10BB01)	**Mechanism:** Glibenclamide is a CYP2C9 substrate; CBD interacts with BCRP and BSEP. **Outcomes:** ↑ Levels of glibenclamide;	Brown & Winterstein, 2019; Lattanzi et al., 2020
Blood glucose lowering drugs, excl. insulins (A10B)	Glimepiride (A10BB12)	**Mechanism:** CBD inhibits CYP2C9. **Outcomes:** ↑ Glimepiride levels	Lattanzi et al., 2020
Blood glucose lowering drugs, excl. insulins (A10B)	Glipizide (A10BB07)	**Mechanism**: CBD inhibits CYP2C9. **Outcomes:** ↑ Glipizide levels	Lattanzi et al., 2020

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Hypnotics and sedatives (N05C)	Hexobarbital (N05CA16)	**Mechanism:** CBD inhibits CYP3A4 and CYP2C. **Outcomes**: ↑ Bioavailability and half-life time of the Hexobarbital; ↓ clearance and volume of hexobarbital distribution	Amaral Silva et al., 2020; Benowitz et al., 1980; Fernandes et al., 1973; Hollister, 1986; Lopera et al., 2022; Stout & Cimino, 2014; Ujváry & Hanuš, 2016; Zendulka et al., 2016; Lopera et. al, 2022; Zhou et. al, 2022
Corticosteroids for systemic use (H02A)	Hydrocortisone (H02AB09)	**Mechanism:** CBD inhibits CYP3A4. **Outcomes:** ↓ hydrocortisone clearance;	Wilson-Mokeh et al., 2019
Opioids (N02A)	Hydromorphone (N02AA03)	**Mechanism:** CBD interacts with UGT2B7. **Outcomes:** ↑ Hydromorphone levels	Brown & Winterstein, 2019
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Ibuprofen (M01AE01)	**Mechanism**: CBD interacts with UGT1A9 and UGT2B7. **Outcomes:** ↑ ibuprofen levels	Brown & Winterstein, 2019; Narouze et al., 2020
Antineoplastic agents - Alkylating Agents (L01A)	Ifosfamide (L01AA06)	**Mechanism:** Ifosfamide is a CYP2C19 substrate. **Outcomes:** ↑ Ifosfamide levels.	Lattanzi et al., 2020

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antidepressants (N06A)	Imipramine (N06AA02)	**Mechanism:** CBD interacts with CYP2C19. **Outcomes:** ↑ Imipramine levels	Balachandran et al., 2021; Lattanzi et al., 2020
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Indomethacin (M01AB01)	**Mechanism:** CBD inhibits CYP2C19. **Outcomes:** ↑ Indomethacin levels	Amaral Silva et al., 2020
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Irinotecan (L01CE02)	**Mechanism:** CBD interacts with UGT1A9 and inhibits P-Gp. **Outcomes:** ↑ Irinotecan levels	Brown & Winterstein, 2019; Opitz et al., 2019; Narouze et al., 2020
Antidepressants (N06A)	Isocarboxazid (N06AF01)	**Mechanism:** CBD inhibits metabolism of isocarboxazid. **Outcomes:** ↑ Levels of isocarboxazid	Balachandran et al., 2021
Antiepiletics (N03A)	Lacosamide (N03AX18)	**Mechanism:** Lacosamide inhibits CYP3A4, CYP2C19 and CYP2C9. **Outcomes**: ↑ Lacosamide levels; ↓ lacosamide clearance; ↑ penetration of BHE by lacosamide and CBD	Abu-Sawwa et al., 2020; Gilmartin et al., 2021; Singh et al., 2020; Duda & Reinert, 2022
Antiepiletics (N03A)	Lamotrigine (N03AX09)	**Mechanism:** CBD inhibits UGT2B7. **Outcomes:** ↑ Lamotrigine level; ↓ Clearance of Lamotrigine	Abu-Sawwa et al., 2020; Balachandran et al., 2021; Kocis & Vrana, 2020; Duda & Reinert, 2022

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antineoplastic agents - Protein kinase inhibitors (L01E)	Lapatinib (L01EH01)	**Mechanism:** CBD inhibits CYP2C19. **Outcomes:** ↑ Lapatinib levels	Opitz et al., 2019
Antiepiletics (N03A)	Levetiracetam (N03AX14)	**Mechanism:** Additive CNS depressant effects. **Outcomes**: ↑ Levetiracetam levels	Wang et al., 2020; Gaston et. al, 2023
Antiarrhythmics - Classes I and III (C01B)	Lidocaine (C01BB01)	**Mechanism:** CBD inhibits CYP2D6. **Outcomes:** ↑ Lidocaine levels	Amaral Silva et al., 2020
Antipsychotics (N05A)	Lithium (N05AN01)	**Mechanism:** CBD induces renal dysfunction. **Outcomes**: ↑ Creatinine levels	Singh et al., 2020
Anxiolytics (N05B)	Lorazepam (N05BA06)	**Mechanism:** CBD inhibits UGT2B7. **Outcomes:** ↑ Lorazepam levels	Balachandran et al., 2021; Kocis & Vrana, 2020
Angiotensin II receptor blockers (C09C)	Losartan (C09CA01)	**Mechanism:** Losartan is a CYP2C8 substrate, CYP2C9 and interacts with UGT2B7. **Outcomes:** ↑ Losartan levels	Abu-Sawwa et al., 2020; Brown & Winterstein, 2019; Lattanzi et al., 2020; Narouze et al., 2020
Lipid-modifying agents (C10A)	Lovastatin (C10AA02)	**Mechanism:** CBD interacts with UGT2B7. **Outcomes:** ↑ Lovastatin levels	Brown & Winterstein, 2019

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepiletics (N03A)	Mephenytoin (N03AB04)	**Mechanism:** CBD inhibits CYP2C19. **Outcomes**: ↑ Mephenytoin levels	Doohan et al., 2021; Kocis & Vrana, 2020; Qian et al., 2019
Drugs used in addictive disorders (N07B)	Methadone (N07BC02)	**Mechanism:** CBD inhibits CYP3A4, CYP2C19 and CYP2B6. **Outcomes**: ↑ methadone levels	Franco et al., 2021; Lattanzi et al., 2020; Lopera et al., 2022; Madden et al., 2020; Vázquez et al., 2020; Lacroix et. al, 2023; Lopera et. al, 2022; Micallef et. al, 2022
Immunosuppressants (L04A)	Methotrexate (L04AX03)	**Mechanism:** CBD inhibits BCRP and P-Gp. **Outcomes:** ↑ Methotrexate levels	Brown & Winterstein, 2019; Opitz et al., 2019
Immunosuppressants (L04A)	Mycophenolate (L04AA06)	**Mechanism:** CBD interacts with UGT1A9. **Outcomes:** ↑ Mycophenolate levels;	Brown & Winterstein, 2019; Narouze et al., 2020
Antimycotics for systemic use (J02A)	Miconazole (J02AB01)	**Mechanism:** Miconazole inhibits CYP2C19 and is a CYP2C9 substrate. **Outcomes:** ↑ Miconazole levels	Lattanzi et al., 2020
Hypnotics and sedatives (N05C)	Midazolam (N05CD08)	**Mechanism:** CBD inhibits CYP3A4 and CYP3A12. **Outcomes:** ↑ Midazolam levels	Bansal et al., 2020; Nasrin et al., 2021; Court et. al, 2023; Stöllberger & Finsterer, 2023

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antidepressants (N06A)	Mirtazapine (N06AX11)	**Mechanism**: CBD inhibits CYP1A2, CYP2D6 and CYP3A4. **Outcomes:** ↑ Mirtazapine levels	Anderson et al., 2021; Balachandran et al., 2021; Wilson-Mokeh et al., 2019
Antineoplastic agents - cytotoxic antibiotics and related substances (L01D)	Mitoxantrone (L01DB07)	**Mechanism:** CBD interacts with BCRP. **Outcomes:** ↑ Mitoxantrone levels	Brown & Winterstein, 2019
Other systemic drugs for obstructive airway diseases (R03D)	Montelukast (R03DC03)	**Mechanism:** Montelukast is a CYP2C8 and CYP2C9 substrate. **Outcomes:** ↑ Montelukast levels	Brown & Winterstein, 2019; Lattanzi et al., 2020
Opioids (N02A)	Morphine (N02AA01)	**Mechanism:** CBD inhibits UGT2B7. **Outcomes**: ↑ Morphine levels	Fernandes et al., 1973; Kocis & Vrana, 2020; Lattanzi et al., 2020; Vázquez et al., 2020
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Naproxen (M01AE02)	**Mechanism:** Naproxen is a CYP2C8 and CYP2C9 substrate. CBD interacts with UGT1B7. **Outcomes:** ↑ Naproxen levels	Brown & Winterstein, 2019; Wilson-Mokeh et al., 2019

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Other antibacterials (J01X)	Nitrofurantoin (J01XE01)	**Mechanism:** CBD inhibits BCRP **Outcomes:** ↑ Nitrofurantoin levels.	Balachandran et al., 2021; Brown & Winterstein, 2019
Antipsychotics (N05A)	Olanzapine (N05AH03)	**Mechanism:** Olanzapine is a CYP1A2 substrate. **Outcomes:** ↑ or ↓ Olanzapine levels	Lattanzi et al., 2020
Opioids (N02A)	Oxycodone (N02AA05)	**Mechanism:** CBD inhibits CYP2D6 and UGT2B7. **Outcomes**: ↑ Oxycodone levels	Vázquez et al., 2020
Opioids (N02A)	Oxymorphone (N02AA11)	**Mechanism:** CBD inhibits CYP2D6 and UGT2B7. **Outcomes:** ↑ Oxymorphone levels	Vázquez et al., 2020
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Paclitaxel (L01CD01)	**Mechanism:** CBD interacts with BSEP and inhibits P-Gp, BCRP and CYP3A4. **Outcomes:** ↓ Paclitaxel levels	Brown & Winterstein, 2019; Fraguas-Sánchez et al., 2020; Opitz et al., 2019
Analgesics - Other analgesics and antipyretics (N02b)	Acetaminophen (N02BE01)	**Mechanism:** Acetaminophen is a UGT1A9 substrate. **Outcomes:** ↑ Acetaminophen levels	Brown & Winterstein, 2019; Narouze et al., 2020; Bardhi et al., 2022
Antidepressants (N06A)	Paroxetine (N06AB05)	**Mechanism:** CBD inhibits CYP2D6. **Outcomes:** ↑ Paroxetine levels	Balachandran et al., 2021; Wilson-Mokeh et al., 2019

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Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antipsychotics (N05A)	Pimozide (N05AG02)	**Mechanism:** Pimozide is a CYP1A2 substrate. **Outcomes:** ↓ Levels of pimozide	Lattanzi et al., 2020
Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Piroxicam (M01AC01)	**Mechanism:** CBD Inhibits CYP2C9. **Outcomes:** ↑ Piroxicam levels	Amaral Silva et al., 2020
Antihypertensives-Antiadrenergic Agents of Peripheral Action (C02C)	Prazosin (C02CA01)	**Mechanism:** CBD interacts with BCRP. **Outcomes:** ↑ Prazosin levels	Brown & Winterstein, 2019
Corticosteroids for systemic use (H02A)	Prednisolone (H02AB06)	**Mechanism:** CBD inhibits CYP3A4. **Outcomes:** ↓ Clearance of Prednisolone	Wilson-Mokeh et al., 2019
General anesthetics (N01a)	Propofol (N01AX10)	**Mechanism:** CBD inhibits UGT1A9. **Outcomes:** ↑ Propofol levels	Brown & Winterstein, 2019; Kocis & Vrana, 2020; Narouze et al., 2020; Nasrin et al., 2021; Bardhi et al., 2022; Duda & Reinert, 2022
Beta-Blocking Agents (C07A)	Propranolol (C07AA05)	**Mechanism:** Propanolol is a CYP1A2 and CYP2C19 substrate. **Outcomes:** ↑ Propanolol levels	Amaral Silva et al., 2020; Brown & Winterstein, 2019; Lattanzi et al., 2020

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antineoplastic agents - Protein kinase inhibitors (L01E)	Regorafenib (L01EX05)	**Mechanism:** CBD interacts with UGT1A9. **Outcomes:** ↑ Levels of regorafenib;	Brown & Winterstein, 2019; Narouze et al., 2020
Antipsychotics (N05A)	Risperidone (N05AX08)	**Mechanism:** Risperidone is a substrate of CYP450 isoforms inhibited by CBD, such as CYP2D6. **Outcomes:** ↑ Risperidone levels;	Balachandran et al., 2021; Cogan, 2019; Vázquez et al., 2021
Blood glucose lowering drugs, excl. insulins (A10B)	Rosiglitazone (A10BG02)	**Mechanism:** Rosiglitazone is a CYP2C8 and CYP2C9 substrate. CBD interacts with BSEP. **Outcomes:** ↑ Rosiglitazone levels;	Brown & Winterstein, 2019; Narouze et al., 2020
Lipid-modifying agents (C10A)	Rosuvastatin (C10AA07)	**Mechanism:** Rosuvastatin is a CYP2C8 and CYP2C9 substrate. **Outcomes**: ↑ Rosuvastatin levels	Brown & Winterstein, 2019; Narouze et al., 2020
Antiepiletics (N03A)	Rufinamide (N03AF03)	**Mechanism:** CBD inhibits CYPs. **Outcomes:** ↑ Serum levels of Rufinamide (within the therapeutic range)	Cogan, 2019; Foster et al., 2019; Gaston et al., 2017; Gilmartin et al., 2021; Karaźniewicz-Łada et al., 2021; Landmark & Brandl, 2020; Qian et al., 2019; Schmitz & Richert, 2020; Reddy, 2023; Talwar et. al, 2023; Smith & Gruber, 2023; Stöllberger & Finsterer, 2023
Immunosuppressants (L04A)	Sirolimus (L04AA10)	**Mechanism:** CBD inhibits CYPs. **Outcomes:** ↑ Sirolimus levels	Ebrahimi-Fakhari et al., 2020; Franco et al., 2021; Gilmartin et al., 2021; Samanta, 2022

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antineoplastic agents - Protein kinase inhibitors (L01E)	Sorafenib (L01EX02)	**Mechanism:** CBD interacts with UGT1A9. **Outcomes:** ↑ Levels of sorafenib	Brown & Winterstein, 2019; Narouze et al., 2020
Antibacterials -Sulfonamides and Trimetoprima (J01E)	Sulfadiazine (J01EC02)	**Mechanism:** Sulfadiazine is a CYP2C9 substrate. CBD inhibits CYP2C9. **Outcomes:** ↑ Levels of sulfadiazine	Lattanzi et al., 2020
Intestinal anti-inflammatory agents (A07E)	Sulfasalazine (A07EC01)	**Mechanism:** Sulfasalazine is a BCRP substrate. CBD inhibits BCRP. **Outcomes:** ↑ levels of Sulfasalazine	Balachandran et al., 2021
Antibacterials -Sulfonamides and Trimetoprima (J01E)	Sulfisoxazole (J01eb05)	**Mechanism:** Sulfisoxazole is a CYP2C9 substrate. **Outcomes:** ↑ Sulfisoxazole levels	Lattanzi et al., 2020
Hypoglycemians - Sulfonylureas (A10B)	Sulphonylureas (A10BB)	**Mechanism**: Sulphonylureas are CYP2C8 and CYP2C9 substrates. CBD inhibits CYP2C9. **Outcomes:** ↑ Sulphonylureas levels	Brown & Winterstein, 2019

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Immunosuppressants (L04A)	Tacrolimus (L04AD02)	**Mechanism:** CBD inhibits CYP3A4. **Outcomes:** ↑ Tacrolimus levels	Cuñetti et al., 2018; Franco et al., 2021; Lopera et al., 2022; Lacroix et. al, 2023, Lopera et. al, 2022; Micallef et. al, 2022
Antineoplastic agents - hormonal antagonists and related agents (L02B)	Tamoxifen (L02BA01)	**Mechanism**: CBD inhibits CYP3A4 and CYP2D6. **Outcomes:** ↑ Tamoxifen levels	Opitz et al., 2019; Parihar et al., 2022
Angiotensin II receptor blockers (C09C)	Telmisartan (C09CA07)	**Mechanism:** CBD interacts with BSEP. **Outcomes**: ↑Telmisartan levels	Brown & Winterstein, 2019
Other systemic drugs for obstructive airway diseases (R03D)	Theophylline (R03DA04)	**Mechanism:** Theophylline is a CYP1A2 substrate. **Outcomes:** ↓ Theophylline levels	Bansal et al., 2020; Kocis & Vrana, 2020; Lattanzi et al., 2020
Antiepiletics (N03A)	Tiagabine (N03AG06)	**Mechanism:** CBD inhibits CYP3A4 and P-Gp. **Outcomes:** ↑ Tiagabine serum cerebral	Gilmartin et al., 2021; Singh et al., 2020
Antipsychotics (N05A)	Thiothixene (N05AF04)	**Mechanism:** Thiothixene is a CYP1A2 substrate. **Outcomes:** ↓ Thiothixene levels	Lattanzi et al., 2020
Immunosuppressants (L04A)	Tofacitinib (L04AA29)	**Mechanism:** CBD inhibits CYP3A4 and CYP2C19. **Outcomes:** ↑ Tofacitinib serum	Wilson-Mokeh et al., 2019

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Blood glucose lowering drugs, excl. insulins (A10B)	Tolbutamide (A10BB03)	**Mechanism:** CBD inhibits CYP2C9. **Outcomes:** ↓ Tolbutamide metabolism	Doohan et al., 2021
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Topotecan (L01CE01)	**Mechanism**: CBD inhibits BCRP. **Outcomes:** ↑ Topotecan levels	Opitz et al., 2019
Opioids (N02A)	Tramadol (N02AX02)	**Mechanism:** CBD Inhibits CYP2D6, CYP2B11 and CYP2D15. **Outcomes:** ↓ Active metabolite levels	Vázquez et al., 2020; Wilson-Mokeh et al., 2019; Court et. al, 2023
Antidepressants (N06A)	Tranylcypromine (N06AF04)	**Mechanism:** CBD inhibits metabolism of the tranylcypromine. **Outcomes:** ↑ Tranylcypromine levels	Balachandran et al., 2021
Hypnotics and sedatives (N05C)	Triazolam (N05CD05)	**Mechanism:** CBD inhibits CYP3A4 (partial inhibition of triazolam metabolism). **Outcomes:** ↑ Triazolam levels	Doohan et al., 2021
Antipsychotics (N05A)	Trifluoperazine (N05AB06)	**Mechanism**: Trifluoperazine is a CYP1A2 substrate. **Outcomes:** ↑ Trifluoperazine levels	Lattanzi et al., 2020

Supplementary Material 4. Associated outcomes and mechanisms of action underlying the pharmacokinetic interactions induced by Cannabidiol (CBD) (concluded).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antibacterials for systemic use - Sulfonamides and Trimethoprim (J01E)	Trimethoprim (J01EA01)	**Mechanism:** Trimethoprim is a CYP2C9 substrate. **Outcomes:** ↑ Trimethoprim levels	Lattanzi et al., 2020
Antidepressants (N06A)	Trimipramine (N06AA06)	**Mechanism:** CBD inhibits CYP2C19. **Outcomes:** ↑ Trimipramine levels	Balachandran et al., 2021
Angiotensin II receptor blockers - ARBs (C09C)	Valsartan (C09CA03)	**Mechanism:** Valsartan is a CYP2C8 and CYP2C9 substrate. **Outcomes**: ↑ Valsartan levels	Brown & Winterstein, 2019; Narouze et al., 2020
Antithrombotic agent (B01A)	Warfarin (B01AA03)	**Mechanism:** CBD inhibits CYP2C9 and CYP3A4. Warfarin is a CYP2C1, CYP2C8, and CYP2C9 substrate. **Outcomes:** ↑ Warfarin levels	Amaral Silva et al., 2020; Brown & Winterstein, 2019; Cortopassi, 2021; Damkier et al., 2019; Doohan et al., 2021; Grayson et al., 2018; Greger et al., 2019; Kolla et al., 2022; Lattanzi et al., 2020; Lopera et al., 2022; Narouze et al., 2020; Paduch & Thomason, 2022; Qian et al., 2019; Vázquez et al., 2021; Lopera et. al, 2022; Micallef et. al, 2022
Antineoplastic agents - other natural products (L01C)	Vincristine (L01A02)	**Mechanism**: CBD inhibits P-Gp. **Outcomes**: ↑ Vincristine levels	Opitz et al., 2019

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepileptics (N03A)	Valproic Acid (N03AG01)	**Mechanism:** Interaction in mitochondria. **Outcome:** CBD ↑ Antiepileptics activity of valproic acid; ↑ Transaminases	Franco et al., 2021; Gilmartin et al., 2021; Duda & Reinert, 2022
Immunosuppressants (L04A)	Anakinra (L04AC03)	**Mechanism:** CBD decreases Th1 and Th2, showing immunosuppressive property **Outcome:** Co-administration enhances the risk of infections	Land et al., 2020
Antibacterials - Macrolides, Lincosamides, and Streptography (J01F)	Azithromycin (J01FA10)	**Mechanism:** Not well understood **Outcome**: ↑ Diarrhea Risk	Land et al., 2020
Immunosuppressants (L04A)	Baricitinib (L04AA37)	**Mechanism:** CBD decreases Th1 and Th2, showing immunosuppressive property **Outcome:** ↑ TNF Overlapping Effect; ↑ chance of severe infections malignancy or thrombosis	Land et al., 2020
Other antineoplastic agents (L01X)	Bortezomib (L01XG01)	**Mechanism:** CBD increased the viability inhibition in Multiple Myeloma cell line **Outcome:** Synergic effect on multiple myeloma	Opitz et al., 2019
Other antineoplastic agents (L01X)	Carfilzomib (L01XG02)	**Mechanism**: Induction of apoptosis **Outcome:** Synergic effect; ↑ cytotoxicity	Olivas-Aguirre et. al., 2022

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antineoplastic - Alkylating Agents (L01A)	Carmustine (L01AD01)	**Mechanism:** CBD is agonist TRPV2. **Outcome**: Synergic effect on glioblastoma; ↑ Chemical sensitivity of glioblastoma cells to the cytotoxic effects of carmustine	Nabissi et al., 2013; Opitz et al., 2019; Olivas-Aguirre et. al., 2022
Antineoplastic - Alkylating Agents (L01A)	Cyclophosphamide (L01AA01)	**Mechanism:** ↑ Cytotoxicity, cell cycle stop and apoptosis **Outcome:** Synergic effect;	Olivas-Aguirre et. al., 2022
Other antineoplastic agents (L01X)	Cisplatin (L01XA01)	**Mechanism:** ↑ Antiproliferative effect and cytotoxic activity; there is also an antagonistic effect registration **Outcome**: Synergistic effect on glioblastoma cells	Fraguas-Sánchez et al., 2020; Opitz et al., 2019; D'Aloia et. al, 2022; Marzeda et. al, 2022; Olivas-Aguirre et. al, 2022
Antineoplastic agents - Antimetabolites (L01B)	Cytarabine (L01BC01)	**Mechanism:** CBD increased apoptosis **Outcome:** Synergic effects	Olivas-Aguirre et. al, 2022
Anxiolytics (N05B)	Clobazam (N05BA09)	**Mechanism:** ↑ Inhibitory activation of the $GABA_A$ receptor **Outcome:** ↑ Antiepileptics efficacy; ↓ seizures; Synergic effect; ↑ drowsiness and sedation; ↑ Adverse Events	Anderson et al., 2022; Cogan, 2019; Devinsky et al., 2020; Dos Santos et al., 2020; Franco et al., 2021; Gaston et al., 2019; Gilmartin et al., 2021; Gunning et al., 2021; Savage et al., 2020; Rana et. al, 2023; Strzelczyk & Schubert-Bast, 2022

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiepileptics (N03A)	Clonazepam (N03AE01)	**Mechanism**: CNS Depressants may enhance the CNS depressant effect o **Outcome:** ↑ Antiepileptics effects	Balachandran et al., 2021
Anxiolytics (N05B)	Chlordiazepoxide (N05BA02)	**Mechanism:** CNS Depressants may enhance the CNS depressant effect o **Outcome:** ↑ Antiepileptics effects	Balachandran et al., 2021
Antiprotozoals - Antimalarials (P01B)	Chlorine (P01BA01)	**Mechanism:** Not well understood **Outcome:** ↑ Diarrhea and/or Headache Risk	Land et al., 2020
Direct acting antivirals (J05A)	Darunavir/Cobicistat e (J05AR14)	**Mechanism:** Not well understood **Outcome**: ↑ Diarrhea and/or Headache Risk	Land et al., 2020
Antidepressants (N06A)	Desipramine (N06AA01)	**Mechanism:** CBD and Desipramine are 5HT1A agonists and 5HT2 antagonists **Outcome:** Synergic or additive effect (significant antidepressant effects)	Balachandran et al., 2021
Corticosteroids for systemic use (H02A)	Dexamethasone (H02AB02)	**Mechanism:** Mechanism of interaction unclear; CBD decreases Th1 and Th2, showing immunosuppressive property **Outcome:** ↑ Risk of headache; ↑ Risk of infections; antagonist effect on some models	Land et al., 2020

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Drugs used in addictive disorders (N07B)	Disulfiram (N07BB01)	**Mechanism:** Mechanism of interaction unclear **Outcome:** ↑ Risk of sedation	Land et al., 2020
Antineoplastic agents - plant alkaloids and other natural products (L01C)	Docetaxel (L01CD02)	**Mechanism:** Mechanism of interaction unclear **Outcome**: *In vitro* synergistic effect	Alsherbiny et al., 2021
Antineoplastic agents- Cytotoxic antibiotics and related substances (L01D)	Doxorubicin (L01DB01)	**Mechanism:** CBD is agonist TRPV2. **Outcome**: Synergic effect; ↑ chemical sensitivity of glioblastoma cells to the cytotoxic effects of doxorubicin	Alsherbiny et al., 2021; Nabissi et al., 2013; Olivas-Aguirre et. al, 2022
Immunosuppressants (L04A)	Eculizumab (L04AA25)	**Mechanism:** Mechanism of interaction unclear **Outcome**: ↑ Headache Risk	Land et al., 2020
Antiepileptics (N03A)	Phenytoin (N03AB02)	**Mechanism:** Mechanism of interaction unclear **Outcome:** ↓ CBD efficacy; ↑ Antiepileptics effects of phenytoin	Balachandran et al., 202; Brown & Winterstein, 2019; Chesher et al., 1974
Antiepileptics (N03A)	Phenobarbital (N03AA2)	**Mechanism**: In the CNS, the phenobarbital activates the gabaergic interneurons during seizure activity; CBD can increase subcortical glutamate levels. **Outcome:** ↓ CBD efficacy; inhibition of the CBD protective effect; ↑ phenobarbital effect;	Abu-Sawwa et al., 2020; Brown & Winterstein, 2019; Balachandran et al., 2021; Chesher et al., 1974; Frías-Soria et al., 2021

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antiprotozoals - Antimalarials (P01B)	Hydroxychloroquine (P01BA02)	**Mechanism:** Mechanism of interaction unclear **Outcome:** ↑ Diarrhea and/or Headache Risk	Land et al., 2020
Antipsychotics (N05A)	Iloperidone (N05AX14)	**Mechanism:** CNS Depressants may enhance the CNS depressant effect **Outcome:** Additive Effects	Thériault et al., 2021
Antineoplastic agents - Protein kinase inhibitors (L01E)	Imatinib (L01EA01)	**Mechanism:** CBD, through TRPV2, inhibits cell proliferation and cell cycle **Outcome:** Synergic effect; Imatinibe resistant cells were susceptible to CBD	Maggi et. al, 2022
Antiepileptics (N03A)	Lamotrigine (N03AX09)	**Mechanism:** CBD inhibits the reuptake of serotonin, dopamine, norepinephrine, and GABA, promoting anxiolytic and anti-epileptic effects. **Outcome**: ↑ drowsiness, sedation and lethargy	Duda & Reinert, 2022
Antiepileptics (N03A)	Levetiracetam (N03AX14)	**Mechanism**: CNS Depressants may enhance the CNS depressant effect **Outcome:** ↑ Antiepileptics activity of levetiracetam; ↑ drowsiness, sedation and lethargy	Balachandran et al., 2021; Gilmartin et al., 2021; Singh et al., 2020; Duda & Reinert, 2022
Direct-acting antivirals (J05A)	Lopinavir/Ritonavir (J05AR10)	**Mechanism**: Mechanism of interaction unclear **Outcome:** ↑ Risk of diarrhea, fatigue and/or headache	Land et al., 2020
Hypnotic and sedative (N05C)	Midazolam (N05CD08)	**Mechanism:** CBD modulate GABA-A receptors both directly and through the activation of CB1 and CB2 receptors **Outcome:** Synergic effects	Reddy et. al, 2023

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antineoplastic agents - Cytotoxic antibiotics and related substances (L01D)	Mitoxantrone (L01DB07)	**Mechanism:** CBD induces apoptosis by an autophagy-apoptosis crosstalk pathway and inhibits the expression of the anti-apoptotic proteins **Outcome**: Additive effect; ↑ apoptotic response	Inkol et al., 2021; Marzeda et.al, 2022
Opioids (N02A)	Morphine (N02AA01)	**Mechanism:** Distinct mechanisms of action underlie the interactions between CBD and morphine **Outcome:** Synergic and Sub-Additive Effects.	Balachandran et al., 2021
Direct-acting antivirals (J05A)	Nelfinavir (J05AE04)	**Mechanism**: Mechanism of interaction unclear **Outcome**: ↑ Diarrhea and/or Headache Risk	Land et al., 2020
Agents against amoebiasis and other protozoal diseases (P01A)	Nitazoxanide (P01AX11)	**Mechanism**: Mechanism of interaction unclear **Outcome:** ↑ Headache	Land et al., 2020
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Paclitaxel (L01CD01)	**Mechanism:** CBD interaction targets include 5-HT1A, GPR55, PPAR-γ and TRPVs receptors; CBD shows antiproliferative, pro-apoptotic and inhibitory effects on cancer metastasis, invasion, and migration. **Outcome:** Synergic effect; ↑ cytotoxicity; ↓ tumor volume; inhibition of neuropathic pain associated with paclitaxel	Alsherbiny et al., 2021; Fraguas-Sánchez et al., 2020; Olivas-Aguirre et. al, 2022; Opitz et al., 2019
Other antineoplastic agents (L01X)	Panobinostat (L01XH03)	**Mechanism:** CBD possess antitumorigenic effects on ovarian cancer. Mechanism of interaction unclear **Outcome:** Synergic effect	Griffiths et al., 2021

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Analgesics - Other analgesics and antipyretics (N02B)	Acetaminophen (N02BE01)	**Mechanism:** Activation of kinase n-terminal c-jun (jNK). **Outcome:** ↑ Mortality in animals associated with liver injury; In a higher dose of CBD, the effect was not observed (paradox)	Balachandran et al., 2021; Ewing et al., 2019; Stöllberger & Finsterer, 2023
Hypnotics and sedatives (N05C)	Pentobarbital (N05CA01)	**Mechanism**: Related to pentobarbital brain concentrations **Outcome**: ↑ Sleep prolongation	Chesher et al., 1974; Coldwell et al., 1974
Other antibacterials (J01X)	Polymyxin B (J01XB02)	**Mechanism:** CBD was described as inhibitor of membrane vesicles released from Gram-negative bacilli **Outcome:** Additive and/or synergistic effect against gram-negative diplococcus that express lipooligosaccharides	Abichabki et al.,2022
Analgesics - Other analgesics and antipyretics (N02B)	Pregabalin (N02BF02)	**Mechanism:** CBD is linked to the blockage of the T-type Ca2+ channels and agonist action on G protein-coupled receptors **Outcome:** ↑ Antiepileptics activity	Kara´zniewicz-Łada et al., 2021; Singh et al., 2020
Immunosuppressants (L04A)	Sarilumab (L04AC14)	**Mechanism:** CBD decreases Th1 and Th2, showing immunosuppressive property **Outcome:** ↑ Risk of infections; Risk of liver injury (ALT increase)	Land et al., 2020

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (continued).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antidepressants (N06A)	Sertraline (N06AB06)	**Mechanism:** 5HT1A receptor activation or allosteric modulation by CBD **Outcome:** Synergistic effect on cognitive and emotional disorders (severe anxiety and aggressive behavior)	Balachandran et al., 2021; Gasparyan et al., 2021
Direct acting antivirals (J05A)	Sofosbuvir (J05AP08)	**Mechanism:** Mechanism of action unclear **Outcome:** ↑ Diarrhea, fatigue and/or headache	Land et al., 2020
Antineoplastic agents - Hormonal antagonists and related agents (L02B)	Tamoxifen (L02BA01)	**Mechanism:** CBD increases cytotoxicity in vitro or decreases tumor size Outcome: Synergic effect	Olivas-Aguirre et. al, 2022
Antineoplastic agents - Alkylating Agents (L01A)	Temozolomide (L01AX03)	**Mechanism**: CBD is agonist TRPV2. **Outcome**: Synergistic effect on glioblastoma cells; ↑ chemical glioblastoma cells to cytotoxic effects of temozolomide; ↑ Antiproliferative effect; ↓ Volume and weight of the tumor (cell death mediated by autophagy)	Nabissi et al., 2013; Olivas-Aguirre et. al, 2022; Opitz et al., 2019
Immunosuppressants (L04A)	Tocilizumab (L04AC07)	**Mechanism**: CBD decreases Th1 and Th2, showing immunosuppressive property **Outcome:** ↑ Risk of infections	Land et al., 2020
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Vinblastine (L01CA01)	**Mechanism**: CBD has induced apoptosis, reduced cell migration, and acted as a chemotherapy sensitizer **Outcome:** ↑ Apoptotic response of vinblastine in a synergistic way	Inkol et al., 2021

Supplementary Material 5. Associated outcomes and mechanism of action of identified pharmacodynamic interactions (concluded).

Therapeutic Classification (ATC)	Drugs (ATC)	Potential interactions and/or outcomes	References
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Vincristine (L01CA02)	**Mechanism:** CBD increases citotoxicity **Outcome**: Sinétgic effects	Olivas-Aguirre et. al, 2022
Antineoplastic agents - Plant alkaloids and other natural products (L01C)	Vinorelbine (L01CA04)	**Mechanism:** CBD inhibits of topoisomerase II, cullin 1, V-type proton ATPase, and CDK-6 in MCF7 cells line **Outcome:** *In vitro* synergistic effect.	Alsherbiny et al., 2021

SUPPLEMENTARY MATERIAL 5: INCLUDED STUDIES

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