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Review

Medicinal Cannabis - Potential Drug Interactions

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Abstract: Endocannbinoids system (ECS) engrossed a considerable interest as potential therapeutic targets in various carcinomas and cancer related conditions alongside with neurodegenerative diseases. Cannabinoids are implemented in several physiological processes such as appetite stimulation, energy balance, pain modulation and the control of chemotherapy induced nausea and vomiting (CINV). However, pharmacokinetics and pharmacodynamics interactions could be perceived in drug combinations, so in this short review we tried to shed the light over the potential drug interactions of medicinal cannabis. Hitherto, few data have been provided to the healthcare practitioners about the drug-drug interactions of cannabinoids with other prescription medications. In general, cannabinoids are usually well tolerated, but the bidirectional effects may be expected with concomitant administered agents *via* affected membrane transporters (glycoprotein p, breast cancer resistance proteins) and metabolizing enzymes (Cytochrome P450 and UDP-glucuronosyltransferases). The caveats should be undertaken to closely monitor the responses of cannabis users with certain drugs to guard their safety, especially for the elderly and people with chronic diseases or kidney and liver conditions.

Keywords: cannabis; cannabinoids; THC; CBD, drug-drug interactions; pharmacokinetic; cytochrome P450; UDP- glucuronosyltransferases; glucoprotein-P

1. Introduction

The *Cannabis sativa* L. (cannabis) has long been used in traditional medicines around the world for treating various conditions [1]. The cannabis is used for either medicinal or recreational purposes are utterly based on the content of a group of compounds in the plant, designated as cannabinoids. Recently, there have been significantly increasing interest in cannabis, as shown in the inclined publications, reviews, and clinical trials throughout the years (Fig 1), largely due to a change of attitudes towards the use of cannabis in many countries. For example, the FDA recently approved the first cannabis derived drug (Epidiolex®) for the treatment of severe seizure disorders, and the projected sales of cannabidiol (CBD) products are as high as $1.9 billion by 2020 [2].

It was widely accepted that delta 9-tetrahydrocannabinol (Δ^9-THC) alongside with less abundant Δ^8-THC are the most potent psychoactive cannabinoids in cannabis, in contrast to the cannabinol (CBN) and the CBD are lacking the psychoactive properties. The CBD interacts with other receptor such as peroxisome proliferator-activated receptors (PPARs), orphan G-protein coupled receptor (GPR55), and transient receptor potential channel subfamily V member 1 (TRPV1) [3,4]. These non-cannabinoid receptors have been postulated as endocannabinoid receptors with debatable contribution in endocannabinoid signalling [5]. The phytocannabinoids have been shown with a range of biological effects by mimicking the endocannabinoids namely; the anandamide and 2-arachidonoylglycerol which are the endogenous ligand of cannabinoid receptors CB_1 and CB_2 [5-7]. The endocannabinoid system (ECS) as a potential therapeutic target for various pathological conditions has attracted a substantial interest, particularly in cancer treatment and neurological disorders [8]. In fact, inclined endocannabinoid level by either externally administered cannabinoid or by curtailing the degradation pathways might represent a useful strategy in neurodegenerative diseases, nausea and vomiting, chronic pain and several carcinomas. A recent review scrutinised the

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preclinical and clinical studies for medical use of cannabis [8]. Several reviews outlined the potentiality of cannabinoid as anticancer agents, alleviators of chemotherapy induced nausea and vomiting CINV, and cancer related pain [9-14]. Studies of oral or oromucosal cannabinoid spray or even pulmonary administration of cannabis smoke in oncology patients showed its tolerability with dose dependent adverse effects (Table 1). Generally, cannabinoids containing products are used socially in cancer patients for its orexigenic, analgesic, antitumour, anxiolytic and antiemetic effects [15]. The resiliency and complexity of cancer cell could rationalise the intervention with synergistic combinations, where smaller doses and curtailed side effect could be achieved. Notably, the opportunities to oppose the defensive hallmarks of cancer could be executed by the polypharmacological effects of natural products [16-19].. With this in mind, a cocktail of medications is usually given to cancer patients to overcome resilient cancer complexity which requires in most cases combinatorial chemotherapeutic agents alongside with a list of adverse effects alleviating medications such as antiemetics, appetite stimulant, and pain killers. Thus, any additional use of cannabinoid necessitates the study of its potential drug interactions, particularly there is no preponderance of sufficient data out of clinical studies investigated the possible interactions between cannabis and other prescription medications such as chemotherapeutic agents.

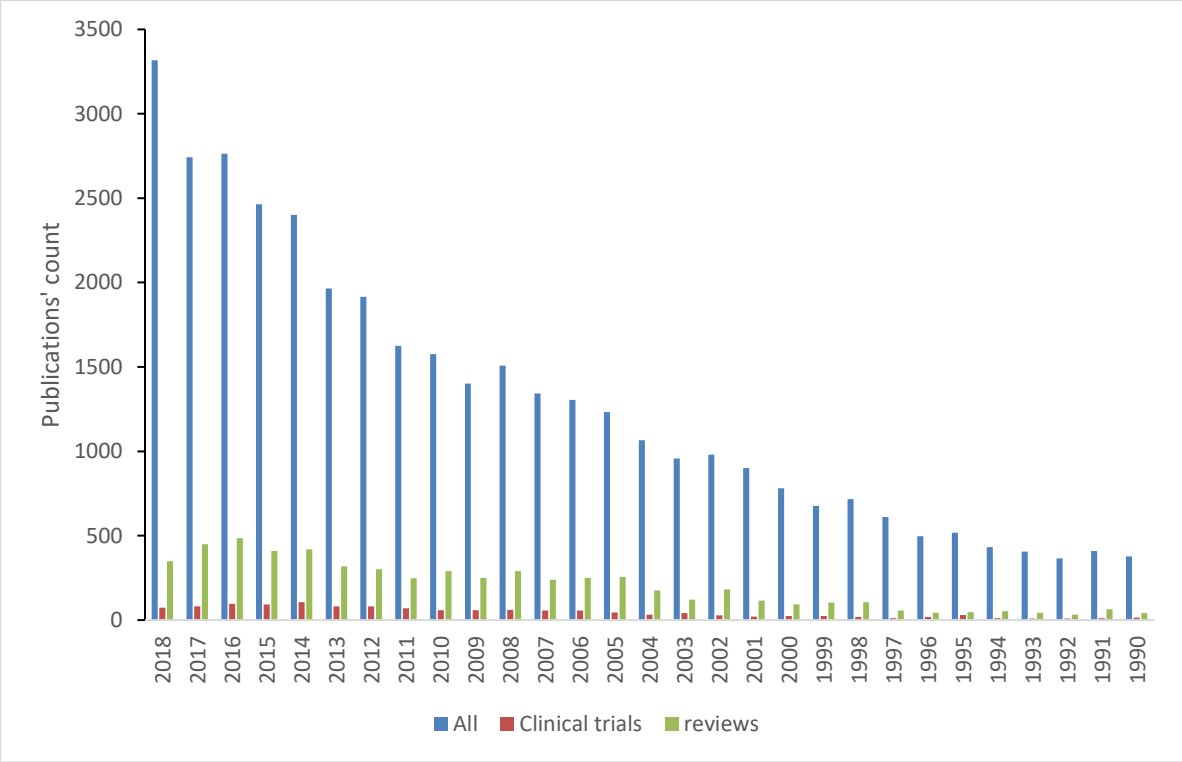

Figure 1 The retrieved publications (1990-2018) from PubMed database for medicinal cannabis or marijuana or cannabinoids or tetrahydrocannabinol (THC) or cannabidiol (CBD)

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Table 1 Recent clinical studies of cannabinoids in oncology patients

Cannabis based treatment	Study type/Location/*n*	Dosage form/dose	Efficacy, tolerability and notes	References
Chemotherapy induced Nausea and Vomiting (CINV)				
-Dronabinol (Marinol®; (-) trans Δ^9-THC) alone or in combination with ondansetron (8-15 mg IV)	-Interventional (Placebo controlled -*n*=64 -USA	-Capsule (2.5-20 mg). -Oral route.	-Both are effective in CINV and well tolerated while higher nausea absence was indicated for dronabinol. -Combination isn't more effective.	[20]
-Dronabinol (Marinol®; (-) trans Δ^9-THC)	-Interventional (retrospective) -Children with malignancy	-Solution administered orally (2.5-5 mg/m^2 body surface every 6h as needed)	-Positive response were reported for 60% of patients. -Prospective trial would be needed to define properly the dronabinol effect in CINV therapy.	[21]
-Nabilone with 5HT3 antagonist	-Interventional (retrospective) -*n*=110 with median age 14 years with malignancy	-Oral route	Adverse effect reported with minor clinical significance. Poor nausea control in nabilone treated group	[22]
Cancer Pain				
- Sativex® (Δ^9-THC: CBD at a ratio of 27:25 mg/ml) -THC (27mg/ml)	-Interventional (Double Blind, Randomized, Parallel Group, Placebo Controlled), *n*=177 -Phase 3 -UK	-Oromucodal spray with maximum Δ^9-THC: CBD (130:120 mg/day) or 130mg/day Δ^9-THC alone Each actuation is 100ul.	-Compared with the placebo, the Sativex treated group showed significant pain relief unlike the Δ^9-THC which was non-significant. -Reported adverse effects (Dizziness, gastrointestinal disorders and confusion)	[23]
-Nabiximols (Sativex®, Δ^9-THC: CBD at a ratio of 27:25 mg/ml)	-Interventional (Double Blind, Randomized, Parallel Group, Placebo Controlled). -Phase 3 -Multicentres	-Oromucodal spray to of 100 ul per actuation twice daily in the morning and evening with a maximum of 10 sprays for 5 weeks.	-No significant difference was reported in advanced cancer patient with chronic pain (unalleviated with opioids) -No evidence of abuse or misuse were reported. -*n*=399.	[24]

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Cannabis based treatment	Study type/Location/*n*	Dosage form/dose	Efficacy, tolerability and notes	References
			-No significant difference was reported in advanced cancer patient with chronic uncontrolled pain -Nabiximol still beneficial on secondary endpoints. -*n*=397.	[25]
-Nabiximols (Sativex®, Δ^9-THC: CBD at a ratio of 27:25 mg/ml)	-Interventional (single group assignment) -Phase 3 -UK.	Oromucodal spray with maximum 130:120 mg/day of Δ^9-THC: CBD	-The long term use is well tolerated without any evidence of loss of pain relieving effect in terminal cancer-related pain refectory to opioids	[26]
-Nabiximols (Sativex®, Δ^9-THC: CBD at a ratio of 27:25 mg/ml)	-Interventional (Double Blind, Randomized, Parallel Group, Placebo Controlled). -Phase 2 -USA (n=360).	Oromucodal spray in low (1-4 sprays/day), medium (6-10 sprays/day) and high (11-16 sprays/day) doses	-Efficacy and safety were reported at low and medium doses against advanced cancer pain. -The adverse effects reported for high doses.	[27]
-Nabiximols (Sativex®, Δ^9-THC: CBD at a ratio of 27:25 mg/ml)	-Interventional (Double-Blind, Placebo-Controlled, Crossover Pilot trial) -n=16	Sublingual spray (7.5-30 mg/day	- No significant difference was reported against chemotherapy induced neuropathy. -2 fold reduction of the pain in the responder group were reported with adverse effects.	[28]
Cannabis cigarettes (3.56% Δ^9-THC) in combination with opiates	Interventional (open label)	Pulmonary administration for chronic pain, including cancer patients	-Declined chronic pain around 27% in patients receiving oxycodone or morphine analgesics. -No serious adverse effects were reported.	[29]

2 Δ^9-THC; Delta -9 tetrahydrocannabinol, CBD; Cannabidiol , CINV; Chemotherapy induced Nausea and Vomiting, *n*; number of participant

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2. Potential Drug Interactions

Drug interactions can occur when two or more drugs/substances with similar or different actions (including herbal substances) are co-administrated, such as warfarin with aspirin, and cyclosporine A with St John's Wort. Drug interactions may result from chemical reactions between different components or modifications by certain components of certain biochemical pathways involved in the action or metabolism of related drugs [30]. Drug interactions can be affected by various factors, including disease and patient conditions, as well as the nature of compounds involved. The potential outcome of a drug interaction can be additive (1+1=2), synergistic (1+1>2), or antagonistic (1+1<2). Therefore, a drug interaction may lead to an enhanced drug response or unexpected side effect.

Generally speaking, drug-drug interactions are conciliated by pharmacodynamic and/or pharmacokinetic mechanisms. On one hand, pharmacodynamic interactions comprise synergistic or antagonistic interactions on the same drug targets, e.g. receptors, which can often be anticipated and evaded. On the other hand, pharmacokinetic interactions involve alterations of the drug's absorption, distribution, metabolism and excretion (ADME). Utmost reported drug interactions are pharmacokinetic ones, eg. through affecting drug metabolism enzymes such as cytochrome P450 (CYP450). CYP450 may be changed by interacting components through induction and inhibition. A longer period of time, for instance, several days are usually required for the induction of CYP450, which may lead to reduced drug plasma levels *via* increased metabolism, and consequently decreased drug effects. In contarary, the CYP450 inhibition is usually instantaneous and may lead to inclined drug plasma levels via enhanced metabolism, and thus exaggerate the drug effects, which may result in substantial adverse reactions or toxicities [30]. Furthermore, cannabinoids bind many members of membrane transporters e.g. ATP- binding cassette superfamily including breast cancer resistant protein (BCRP) and Glycoprotein P (P-gp). As an illustration, preclinical interaction of cannabinoid with BCRP [31,32] and P-gp [33-35] were reported. The duration of cannabinoid exposure affects the expression of P-gp [36,37] with downregulation in chronic exposure and upregulation in brief one. In fact, the concentration uses in these studies are higher than that commonly measured in cannabis smokers [38].

Cannabis has been used in various forms as crude extracts or purified ingredients (with different THC/cannabinoids ratios), therefore drug interactions caused by cannabis depend not only on the drugs involved but also the chemical components/profiles of the cannabis preparations used.

3. Effects of cannabis on drug metabolizing enzymes and related drug interactions

There are experimental *in vitro* and *in vivo* findings indicating that cannabinoids may act on P450 isoenzymes to affect the metabolism of various drugs. A systematic review by Stout & Cimino (2014) showed that P-450 is involved in metabolising several exogenous cannabinoids, for example tetrahydrocannabinol (THC; CYP2C9, 3A4), cannabidiol (CBD; CYPs 2C19, 3A4) and cannabinol (CBN; CYPs 2C9, 3A4), supported by clinical data on THC and CBD metabolism. The inhibition or induction of CYP by cannabis compounds, eg THC as CYP 1A2 inducer and CBD as 3A4 inhibitor, may potentially affect the metabolism of many drugs metabolised by these CYPs. However, in many cases, the relevance of research findings in cells or animals to humans has yet to be established. Specific clinical studies are often needed before a conclusion can be drawn. For example, studies showed that medicinal cannabis did not affect the clinical pharmacokinetics of irinotecan and docetaxel [39], while co-administration of cannabidiol (CBD) and clobazam (CLB) increased blood CLB level in children with epilepsy [40]. A similar recent study showed that concomitant administration of CBD significantly changed serum levels of topiramate, rufinamide, clobazam, and eslicarbazepine, and zonisamide in patients with treatment-resistant epilepsy [41]. Abnormal liver function test results were also noted in participants taking concomitant valproate, indicating the importance of monitoring serum levels of commonly used antiepileptic drugs and liver functions during treatment with CBD [41]. On the other hand, a study in healthy adults found that concomitant administration of fentanyl did not affect the plasma level of CBD, and the co-administration did not produce cardiovascular complications or respiratory depression during the test sessions and CBD

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did not potentiate fentanyl effects [42], but keloconazole (CYP3A4 inhibitor) was found to increase, and rifampin (CYP3A4 inducer) to reduce THC and CBD concentrations [43]. With referral to combination of cannabis tea, Bedrocan® with chemotherapeutic agents, a cross-over study evaluated cannabis interaction with docetaxel and irinotecan and reported no influence in chemotherapeutic agents [39]. Comprehensive overview of the pharmacokinetic medicated interactions of either synthetic and phytocannabinoids is summarised in Table 2.

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Table 2 Overview of the recent reviews of the drug-drug interactions with cannabinoids

Cannabinoid based treatment and interactions	Affected transporters and/or metabolic enzymes	Experimental results, notes and outcomes	References
Cannabis, THC, CBD, CBN with either chemotherapies, abuse drugs or medications	-Membrane transporters ABC super family (glycoprotein P; P-gp, Breast cancer resistance protein; BCRP, MRP1, 2, 3 and 4) -Cytochrome P450 (3A, 2D6, 2C9, 1A1, 1A2, 1B1, 2B6 and 2C8) -UDP-glucuronosyltransferases (UGTs)	-**P-gp, BCRB, and MRP1-4** transporters expression was dysregulated by cannabinoids, but in higher concentration than that usually measured in cannabis smokers. -**CYP3A** was competitively inhibited by THC, CBD and CBN with CBD as a most potent inhibitor in a concentration compatible with the measured upon usual cannabis inhalation. -**CYP2D6** was inhibited by THC, CBD and CBN with CBD as a most potent inhibitor in a higher concentration than that measured upon usual cannabis consumption. -**CYP2C9** was inhibited by THC, CBD and CBN with CBD where the CBD inhibitory effect was dependent on the substrate used. -**CYP1A1**, **1A2**, **1B1**, **2B6, 2C19, 3A4** and **2C8** were strongly inhibited by CBD. -**UGT1A9**, and **2B7** were inhibited by CBD. -**UGT1A7**, **1A8**, and **1A9** were inhibited by CBN. -**UGT2B7** was activated by CBN. • Cannabinoids and medications with inhibitory or stimulatory effects on the metabolic isoenzymes and/or metabolised by same pathway will interact. • Clinical studies are warranted to explore the potential interactions with chemotherapy, alcohol, abuse drugs and prescription medications.	[15,44,45]
Δ^9-THC, CBD and marijuana inhalation with psychotropic agents	-Cytochrome P450	-**CYP2C9** and **CYP3A4** were inhibited by Δ^9-THC. -**CYP2C19** and **CYP3A4** were inhibited by CBD. -**CYP1A1** and **CYP1A2** were induced by marijuana inhalation • Cannabinoids consumption via pyrolysis induced the CYP due to aromatic hydrocarbons. • The effect cannabinoids on the CYP activity influenced by the formulation, administration route and derivation (Plant based or synthetic).	[46]

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		• Clinical studies are warranted to explore the potential drug-drug interactions with cannabinoids.	

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Synthetic and Phyto-cannabinoids	-Cytochrome P450 -UGTs	-**CYP1A**-catalysed MROD activity was weakly inhibited by MAM-2201, JWH-019, STS-135, and UR-144. -**CYP2C8**-catalysed amodiaquine N-deethylase was strongly inhibited by AM-2201, MAM-2201, and EAM-2201. -**CYP2C9**-catalyzed diclofenac hydroxylation and **CYP3A**-catalyzed midazolam 1′-hydroxylation were inhibited by AM-2201 and MAM-2201. -**CYP2C9**-catalyzed diclofenac 4′-hydroxylation, **CYP2C19**-catalyzed [S] -mephenytoin 4′-hydroxylation, and **CYP3A**-catalyzed midazolam 1′-hydroxylation were strongly inhibited by EAM-2201 (time dependent inhibition). -**CYP2B6** and **CYP2C9** were strongly inhibited by THC, CBN, and CBD. -**CYP2A6** was inhibited by THC and CBN (Mechanism-based inhibition). -**CYP2D6** was competitively inhibited by CBD. -**CYP1A1 mRNA** expression was inclined by THC in Hepa-1 cells, but EROD activity in CYP1A1 supersomes was curtailed by the effect of THC. -**CYP1A1**, **CYP1A2**, and **CYP1B1** were strongly inhibited by CBD (Mechanism-based inhibition). -**CYP3A** was inhibited by CBD in human liver microsomes. - **CYP2C19**-catalyzed [S] -mephenytoin hydroxylation was inhibited by (CBD and THC (Mixed-type inhibition). - **UGT1A9**- and **UGT2B7**-catalyzed ethanol glucuronidation were non-competitively inhibited by CBD unlike the inclined ethanol glucouronidation in human liver microsome by CBN in a dose dependent manner. - **UGT1A3**-catalyzed chenodeoxycholic acid 24-acylglucuronidation was strongly competitively inhibited by AM-2201, MAM-2201, and EAM-2201. - **UGT2B7**-mediated naloxone 3β-D-glucuronidation was competitively inhibited by AM-2201. • Clinical studies of pharmacokinetics mediated drug interactions of synthetic and phyto-cannabinoids with the CYP and UTGs substrates are warranted.	[47,48]

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CBD with antiepileptic drugs	Cytochrome P450 or not studied	**Clinical studies of DDI**: -Non significant increment of the clobazam plasma level administered with CBD (*n*=13 children) due to potent inhibition of **CYP2C19**. -Significant inclined plasma level of N-desmethylclobazam by CBD coadminstration while no significant change in the level of valproate, stiripentol, and levetiracetam (*n*=24 open label trial) -All patients showed significant incline the plasma level of clobazam, N-desmethylclobazam, rufinamide and topiramate by increasing the CBD doses). The mean therapeutic range was exceeded for clobazam and N-desmethylclobazam only where, the level of eslicarbazepine and zonisamide were increased in adults only (*n*= 9 adults and 42 children). • The purified CBD formula is FDA approved with antiepileptic drugs as a result of the published randomized clinical trials. • CBD is well tolerated with potential DDI and adverse effects, where the drug level and liver function monitoring will be compulsory. • The outcome of this review isn't to be generalised to other cannabis products where further trials are warranted.	[49]
Cannabinoids on other drugs	Cytochrome P450	- **CYP3A4** inhibitors and stimulators affect the elimination of Δ^9-THC and CBD. • Reviewed the pharmacokinetic mediated interaction effect of cannabinoids on other drugs and vice versa. • Limited data preponderance on the drug's effects on the accumulation of cannabinoids and marijuana warrant more clinical studies.	[50]

ABC; ATP-binding cassette, AM-2201, EAM-2201, MAM-2201, JWH-019, STS-135, and UR-144; Synthetic cannabinoids, CBD; Cannabidiol, CBN; cannabinol, CYP; Cytochrome P450, MROD; 7-methoxyresorufin O-demethylation, P-gp; Glycoprotein P, THC; tetrahydrocannabinol, UGTs; UDP-glucuronosyltransferases.

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4. Other potential drug interactions

A study with 21 individuals showed that vaporized cannabis increased the analgesic effects of opioids without altering plasma opioid levels [51]. A non-controlled, prospective open-label study in 274 participants found that medicinal cannabis reduced the consumption of opioids [52]. The current research generally supports the use of medical cannabis as an adjunct or opioid substitute. On the other hand, it should be noted that a recent survey in the US indicates that cannabis may increase the risk of developing nonmedical prescription opioid use [53]. Thus, it is important to develop a program at the state or national level to monitor the use of different forms of cannabis and their associations to different medical conditions.

A study in 32 adult cannabis smokers found that low dose alcohol (approximately 0.065% peak breath alcohol concentration) increased blood levels of THC, which may explain the performance impairment observed from a cannabis-alcohol combination [54,55].

In addition, there are early studies or case reports indicating potential drug interactions with warfarin, oxymorphone, pentobarbital, cocaine, sympathomimetic amines, disulfiram, disulfiram etc, but further research is needed. Interestingly, Russo (2016) mentioned that in extensive clinical application including complex drug regimens with opioids, tricyclic antidepressants, anticonvulsants etc, no drug interactions that have been observed that would contraindicate or preclude use of nabiximols with any specific pharmaceutical, although additive sedative effects are always possible [56]. MacCallum & Russo (2018) recently pointed out that there is no drug that cannot be used with cannabis, if necessary [57].

5. Conclusion

There is still limited data on significant drug interactions caused by medicinal cannabis. Thus the evidence-based clinical guidelines on interactions of drugs with medicinal cannabis are still lacking. Nevertheless, caution should be undertaken to closely monitor the responses of cannabis users with certain drugs to guard their safety, especially for the elderly and people with chronic diseases or kidney and liver conditions.

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Conflicts of Interest:

References

1. Bonini, S.A.; Premoli, M.; Tambaro, S.; Kumar, A.; Maccarinelli, G.; Memo, M.; Mastinu, A. Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. *Journal of ethnopharmacology* **2018**.
2. Corroon, J.; Kight, R. Regulatory Status of Cannabidiol in the United States: A Perspective. *Cannabis and Cannabinoid Research* **2018**, *3*, 190-194.
3. Brown, A. Novel cannabinoid receptors. *British journal of pharmacology* **2007**, *152*, 567-575.
4. De Petrocellis, L.; Di Marzo, V. Non-CB 1, non-CB 2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: Focus on G-protein-coupled receptors and transient receptor potential channels. *Journal of Neuroimmune Pharmacology* **2010**, *5*, 103-121.
5. Pertwee, R.G.; Howlett, A.; Abood, M.E.; Alexander, S.; Di Marzo, V.; Elphick, M.; Greasley, P.; Hansen, H.S.; Kunos, G.; Mackie, K. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacological reviews* **2010**, *62*, 588-631.

6. Matsuda, L.A.; Lolait, S.J.; Brownstein, M.J.; Young, A.C.; Bonner, T.I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *346*, 561.
7. Munro, S.; Thomas, K.L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61.
8. Fraguas-Sánchez, A.I.; Torres-Suárez, A.I. Medical Use of Cannabinoids. *Drugs* **2018**, *78*, 1665-1703, doi:10.1007/s40265-018-0996-1.
9. Guzmán, M. Cannabinoids: Potential anticancer agents. *Nature Reviews Cancer* **2003**, *3*, 745-755, doi:10.1038/nrc1188.
10. Bogdanovic, V.; Mrdjanovic, J.; Borisev, I. A Review of the Therapeutic Antitumor Potential of Cannabinoids. *Journal of alternative and complementary medicine (New York, N.Y.)* **2017**, *23*, 831-836, doi:10.1089/acm.2017.0016.
11. Vuger, A.T.; Šeparović, R.; Silovski, T.; Pavlović, M.; Pavlica, V.; Knežević, S.V. Cannabis in oncology. *Libri Oncologici* **2016**, *44*, 51-57.
12. Davis, M.P. Cannabinoids for Symptom Management and Cancer Therapy: The Evidence. *Journal of the National Comprehensive Cancer Network : JNCCN* **2016**, *14*, 915-922.
13. Velasco, G.; Hernández-Tiedra, S.; Dávila, D.; Lorente, M. The use of cannabinoids as anticancer agents. *Progress in neuro-psychopharmacology and biological psychiatry* **2016**, *64*, 259-266.
14. Fraguas-Sánchez, A.I.; Torres-Suárez, A.I. Medical Use of Cannabinoids. *Drugs* **2018**, 1-39.
15. Bouquié, R.; Deslandes, G.; Mazaré, H.; Cogné, M.; Mahé, J.; Grégoire, M.; Jolliet, P. Cannabis and anticancer drugs: societal usage and expected pharmacological interactions – a review. *Fundamental & Clinical Pharmacology* **2018**, *32*, 462-484, doi:doi:10.1111/fcp.12373.
16. Xie, L.; Xie, L.; Kinnings, S.L.; Bourne, P.E. Novel computational approaches to polypharmacology as a means to define responses to individual drugs. *Annual review of pharmacology and toxicology* **2012**, *52*, 361-379.
17. Liu, H.; Wang, J.; Zhou, W.; Wang, Y.; Yang, L. Systems approaches and polypharmacology for drug discovery from herbal medicines: an example using licorice. *Journal of ethnopharmacology* **2013**, *146*, 773-793.
18. Alsherbiny, M.A.; Abd-Elsalam, W.H.; El badawy, S.A.; Taher, E.; Fares, M.; Torres, A.; Chang, D.; Guang Li, C. Ameliorative and protective effects of ginger and its main constituents against natural, chemical and radiation-induced toxicities: A comprehensive review. *Food and Chemical Toxicology* **2018**, https://doi.org/10.1016/j.fct.2018.10.048, doi:https://doi.org/10.1016/j.fct.2018.10.048.
19. Alsherbiny, M.A.; Ezzat, S.M.; Elsakhawy, F.S.; Kamel, G.M.; Abdel-Kawy, M.A. Impact of certain Solanum speciess natural products as potent cytotoxic and anti-Inflammatory agents. *Journal of Medicinal Plants Research* **2015**, *9*, 779-786.
20. Meiri, E.; Jhangiani, H.; Vredenburgh, J.J.; Barbato, L.M.; Carter, F.J.; Yang, H.-M.; Baranowski, V. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Current Medical Research and Opinion* **2007**, *23*, 533-543, doi:10.1185/030079907X167525.
21. Elder, J.J.; Knoderer, H.M. Characterization of dronabinol usage in a pediatric oncology population. *The Journal of Pediatric Pharmacology and Therapeutics* **2015**, *20*, 462-467.
22. Polito, S.; MacDonald, T.; Romanick, M.; Jupp, J.; Wiernikowski, J.; Vennettilli, A.; Khanna, M.; Patel, P.; Ning, W.; Sung, L., et al. Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: A multicenter, retrospective review. *Pediatric Blood & Cancer* **2018**, *65*, e27374, doi:10.1002/pbc.27374.

23. Johnson, J.R.; Burnell-Nugent, M.; Lossignol, D.; Ganae-Motan, E.D.; Potts, R.; Fallon, M.T. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *Journal of pain and symptom management* **2010**, *39*, 167-179, doi:10.1016/j.jpainsymman.2009.06.008.
24. Fallon, M.T.; Albert Lux, E.; McQuade, R.; Rossetti, S.; Sanchez, R.; Sun, W.; Wright, S.; Lichtman, A.H.; Kornyeyeva, E. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *British journal of pain* **2017**, *11*, 119-133, doi:10.1177/2049463717710042.
25. Lichtman, A.H.; Lux, E.A.; McQuade, R.; Rossetti, S.; Sanchez, R.; Sun, W.; Wright, S.; Kornyeyeva, E.; Fallon, M.T. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *Journal of pain and symptom management* **2018**, *55*, 179-188.e171, doi:10.1016/j.jpainsymman.2017.09.001.
26. Johnson, J.R.; Lossignol, D.; Burnell-Nugent, M.; Fallon, M.T. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *Journal of pain and symptom management* **2013**, *46*, 207-218, doi:10.1016/j.jpainsymman.2012.07.014.
27. Portenoy, R.K.; Ganae-Motan, E.D.; Allende, S.; Yanagihara, R.; Shaiova, L.; Weinstein, S.; McQuade, R.; Wright, S.; Fallon, M.T. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *The journal of pain : official journal of the American Pain Society* **2012**, *13*, 438-449, doi:10.1016/j.jpain.2012.01.003.
28. Lynch, M.E.; Cesar-Rittenberg, P.; Hohmann, A.G. A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Using an Oral Mucosal Cannabinoid Extract for Treatment of Chemotherapy-Induced Neuropathic Pain. *Journal of pain and symptom management* **2014**, *47*, 166-173, doi:https://doi.org/10.1016/j.jpainsymman.2013.02.018.
29. Abrams, D.I.; Couey, P.; Shade, S.B.; Kelly, M.E.; Benowitz, N.L. Cannabinoid–Opioid Interaction in Chronic Pain. *Clinical Pharmacology & Therapeutics* **2011**, *90*, 844-851, doi:10.1038/clpt.2011.188.
30. Li, C.G.; Yang, L.; Zhou, S.-F. Interactions between Chinese herbal medicines and drugs. *Australian journal of acupuncture and Chinese medicine* **2007**, *2*, 17.
31. Holland, M.; Lau, D.; Allen, J.; Arnold, J. The multidrug transporter ABCG2 (BCRP) is inhibited by plant-derived cannabinoids. *British journal of pharmacology* **2007**, *152*, 815-824.
32. Feinshtein, V.; Erez, O.; Ben-Zvi, Z.; Eshkoli, T.; Sheizaf, B.; Sheiner, E.; Holcberg, G. Cannabidiol enhances xenobiotic permeability through the human placental barrier by direct inhibition of breast cancer resistance protein: an ex vivo study. *American journal of obstetrics and gynecology* **2013**, *209*, 573. e571-573. e515.
33. Holland, M.; Panetta, J.; Hoskins, J.; Bebawy, M.; Roufogalis, B.; Allen, J.; Arnold, J. The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells. *Biochemical pharmacology* **2006**, *71*, 1146-1154.
34. Zhu, H.-J.; Wang, J.-S.; Markowitz, J.S.; Donovan, J.L.; Gibson, B.B.; Gefroh, H.A.; DeVane, C.L. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. *Journal of Pharmacology and Experimental Therapeutics* **2006**, *317*, 850-857.
35. Tournier, N.; Chevillard, L.; Megarbane, B.; Pirnay, S.; Scherrmann, J.-M.; Decleves, X. Interaction of drugs of abuse and maintenance treatments with human P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2). *International Journal of Neuropsychopharmacology* **2010**, *13*, 905-915.

36. Arnold, J.C.; Hone, P.; Holland, M.L.; Allen, J.D. CB2 and TRPV1 receptors mediate cannabinoid actions on MDR1 expression in multidrug resistant cells. *Pharmacological Reports* **2012**, *64*, 751-757.
37. Feinshtein, V.; Erez, O.; Ben-Zvi, Z.; Erez, N.; Eshkoli, T.; Sheizaf, B.; Sheiner, E.; Huleihel, M.; Holcberg, G. Cannabidiol changes P-gp and BCRP expression in trophoblast cell lines. *PeerJ* **2013**, *1*, e153.
38. Bouquié, R.; Deslandes, G.; Mazaré, H.; Cogné, M.; Mahé, J.; Grégoire, M.; Jolliet, P. Cannabis and anticancer drugs: societal usage and expected pharmacological interactions – a review. *Fundamental and Clinical Pharmacology* **2018**, *32*, 462-484, doi:10.1111/fcp.12373.
39. Engels, F.K.; De Jong, F.A.; Sparreboom, A.; Mathot, R.A.; Loos, W.J.; Kitzen, J.J.; De Bruijn, P.; Verweij, J.; Mathijssen, R.H. Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *The oncologist* **2007**, *12*, 291-300.
40. Geffrey, A.L.; Pollack, S.F.; Bruno, P.L.; Thiele, E.A. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* **2015**, *56*, 1246-1251.
41. Gaston, T.E.; Bebin, E.M.; Cutter, G.R.; Liu, Y.; Szaflarski, J.P.; Program, U.C. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia* **2017**, *58*, 1586-1592.
42. Manini, A.F.; Yiannoulos, G.; Bergamaschi, M.M.; Hernandez, S.; Olmedo, R.; Barnes, A.J.; Winkel, G.; Sinha, R.; Jutras-Aswad, D.; Huestis, M.A. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *Journal of addiction medicine* **2015**, *9*, 204.
43. Stout, S.M.; Cimino, N.M. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug metabolism reviews* **2014**, *46*, 86-95.
44. Arellano, A.L.; Papaseit, E.; Romaguera, A.; Torrens, M.; Farre, M. Neuropsychiatric and General Interactions of Natural and Synthetic Cannabinoids with Drugs of Abuse and Medicines. *CNS & neurological disorders drug targets* **2017**, *16*, 554-566, doi:10.2174/1871527316666170413104516.
45. Zendulka, O.; Dovrtelová, G.; Nosková, K.; Turjap, M.; Sulcová, A.; Hanus, L.; Jurica, J. Cannabinoids and cytochrome P450 interactions. *Current drug metabolism* **2016**, *17*, 206-226.
46. Rong, C.; Carmona, N.E.; Lee, Y.L.; Ragguett, R.M.; Pan, Z.; Rosenblat, J.D.; Subramaniapillai, M.; Shekotikhina, M.; Almatham, F.; Alageel, A., et al. Drug-drug interactions as a result of co-administering Delta(9)-THC and CBD with other psychotropic agents. *Expert opinion on drug safety* **2018**, *17*, 51-54, doi:10.1080/14740338.2017.1397128.
47. Kong, T.Y.; Kim, J.H.; Kim, D.K.; Lee, H.S. Synthetic cannabinoids are substrates and inhibitors of multiple drug-metabolizing enzymes. *Archives of pharmacal research* **2018**, *41*, 691-710, doi:10.1007/s12272-018-1055-x.
48. Tai, S.; Fantegrossi, W.E. Pharmacological and Toxicological Effects of Synthetic Cannabinoids and Their Metabolites. In *Neuropharmacology of New Psychoactive Substances (NPS): The Science Behind the Headlines*, Baumann, M.H., Glennon, R.A., Wiley, J.L., Eds. Springer International Publishing: Cham, 2017; 10.1007/7854_2016_60pp. 249-262.
49. Gaston, T.E.; Szaflarski, J.P. Cannabis for the Treatment of Epilepsy: an Update. *Current Neurology and Neuroscience Reports* **2018**, *18*, 73, doi:10.1007/s11910-018-0882-y.
50. Anderson, G.D.; Chan, L.N. Pharmacokinetic Drug Interactions with Tobacco, Cannabinoids and Smoking Cessation Products. *Clinical pharmacokinetics* **2016**, *55*, 1353-1368, doi:10.1007/s40262-016-0400-9.
51. Abrams, D.; Couey, P.; Shade, S.; Kelly, M.; Benowitz, N. Cannabinoid–opioid interaction in chronic pain. *Clinical Pharmacology & Therapeutics* **2011**, *90*, 844-851.

 doi:10.20944/preprints201812.0032.v1

52. Haroutounian, S.; Ratz, Y.; Ginosar, Y.; Furmanov, K.; Saifi, F.; Meidan, R.; Davidson, E. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain. *The Clinical journal of pain* **2016**, *32*, 1036-1043.

53. Olfson, M.; Wall, M.M.; Liu, S.-M.; Blanco, C. Cannabis use and risk of prescription opioid use disorder in the United States. *American Journal of Psychiatry* **2017**, *175*, 47-53.

54. Ronen, A.; Chassidim, H.S.; Gershon, P.; Parmet, Y.; Rabinovich, A.; Bar-Hamburger, R.; Cassuto, Y.; Shinar, D. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. *Accident Analysis & Prevention* **2010**, *42*, 1855-1865.

55. Hartman, R.L.; Brown, T.L.; Milavetz, G.; Spurgin, A.; Gorelick, D.A.; Gaffney, G.; Huestis, M.A. Controlled cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol. *Clinical Chemistry* **2015**, *61*, 850-869.

56. Russo, E.B. Current therapeutic cannabis controversies and clinical trial design issues. *Frontiers in pharmacology* **2016**, *7*, 309.

57. MacCallum, C.A.; Russo, E.B. Practical considerations in medical cannabis administration and dosing. *European journal of internal medicine* **2018**.