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Combinación de cannabidiol y Medicamentos actuales
Combination of Cannabidiol and Current Medicinal Drugs

Jesús Vélez-Huerta [1], Adolfo Soto-Domínguez [2], Myrna L. Yeverino-Gutierrez[3], Ma. del Rosario González-González[4], Omar González-Santiago[5*], Mónica A. Ramírez-Cabrera [1*]

[1]Molecular Pharmacology Laboratory, Faculty of Chemical Sciences, Universidad Autónoma de Nuevo León (UANL), Monterrey, Nuevo León, México.
[2]Histology Department. Faculty of Medicine. Universidad Autónoma de Nuevo León (UANL), Monterrey, Nuevo León, México.
[3]Pharmacology Laboratory, Faculty of Chemical Sciences, Universidad Autonoma de Nuevo Leòn (UANL), Monterrey, Nuevo León, México.
[4]Microbiology Laboratory, Faculty of Chemical Sciences, Universidad Autonoma de Nuevo Leòn (UANL), Monterrey, Nuevo León, México.
[5]Posgraduate División, Faculty of Chemical Sciences, Universidad Autónoma de Nuevo León (UANL), Monterrey, Nuevo León, México.

*Autor de correspondencia: Omar González de Santiago, Mónica A. Ramírez Cabrera
Correo: **omar.gonzalezst@uanl.edu.mx; monica.ramirezcbr@uanl.edu.mx**

RESUMEN

El objetivo de este trabajo fue revisar la literatura científica sobre el cannabidiol, solo y en combinación con fármacos que se usen en la actualidad. Se realizo una búsqueda en pub med y gogle scholar, utilizando las siguientes palabras claves combinadas en inglés: Cannabidiol más analgésicos, anticonvulsivantes, antibióticos, antipsicóticos, antidepresivos, antineoplásicos, antieméticos y anestésicos. Se seleccionaron artículos con ensayos in vitro, in vivo y ensayos clínicos. Los resultados muestran que la literatura actual es sobre estudios *in vitro* e *in vivo*. Se han realizado estudios de cannabidiol combinado con antiepilépticos, analgésicos, antidepresivos, antiinfecciosos y antipsicóticos con resultados prometedores. Aunque los estudios de combinación de cannabidiol con otros fármacos son escasos, estos sugieren que el cannabidiol podría actuar sinérgicamente, aunque se necesitan mas estudios para confirmarlo. El cannabidiol es un potente inhibidor del CYP3A4 y del CYP2C9 por lo que se debe considerar esta posible interacción.

Palabras clave: cannabidiol; interacciones farmacocinéticas; combinación; efecto sinérgico.

ABSTRACT

This work aimed to review the literature on the combination de Cannabidiol and current medicinal drugs. A search in PubMed and Google Scholar was performed. We use the following keywords combination: CBD plus, analgesic, anticonvulsants, antibiotics, antipsychotics, antidepressants, antineoplastics, antiemetics, and anesthetics. Original articles with *in vitro*, *in vivo* assays, and clinical trials were selected. Current literature reports mainly *in vitro* and *in vivo* studies where CBD is evaluated in combination with other medicinal drugs for epilepsy, pain, depression, infections, and psychosis with promising results. There are few studies on the combination of CBD plus medicinal drugs, however, they suggest that CBD seems to act synergically with the studied drugs, and more confirmatory studies are needed. CBD is a potent CYP3A4 and CYP2C19 Inhibitor; therefore, potential interactions should be considered.

Keywords: Cannabidiol; pharmacokinetic interactions; combination; synergistic effect.

INTRODUCTION

Cannabidiol (CBD) or 2-[(6R)-6-isopropenyl-3-methyl-2-cyclohexen-1-yl]-5-pentyl-1,3-benzene-diol, is the main component isolated from *Cannabis sativa (C. sativa)*, and, in contrast with the other most important cannabinoid isolated from this plant, delta-9 tetrahydrocannabinol (THC), it lacks euphoric and psychoactive effects. Two pharmaceutical products containing CBD approved by the FDA are available. SATIVEX® (GW Pharmaceuticals) is a combination of THC plus CBD indicated for spasticity and neuropathic pain in multiple sclerosis and as adjunctive analgesia for moderate to severe cancer pain. The other product, EPIDIOLEX, which contains only CBD, is indicated for seizures associated with Lennox–Gastaut or Dravet syndromes. In addition to these pharmaceutical products, there are several products on the market used as drugs or supplementary food containing CBD that have not been approved by the FDA. These products are prepared from the hemp plant, a variety of *C. sativa*, and contain less than 0.3% THC.

The therapeutic uses of CBD include chronic pain, cancer, chemotherapy-induced nausea/vomiting, appetite and weight loss, irritable bowel syndrome, epilepsy, spasticity of multiple sclerosis, Tourette syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, Alzheimer's disease/dementia, glaucoma, traumatic brain injury/spinal cord injury, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia (National Academies of Sciences, Engineering, and Medicine,2017).

Despite the potential benefits, CBD is not exempt from adverse effects. These effects include developmental toxicity, embryo-fetal mortality, central nervous system inhibition and neurotoxicity, hepatocellular injuries, spermatogenesis reduction, organ weight alterations, male reproductive system alterations, and hypotension, although at higher than recommended doses for human pharmacotherapy. Human CBD studies of epilepsy and psychiatric disorders reported CBD-induced drug-drug interactions, liver abnormalities, diarrhea, fatigue, vomiting, and somnolence(Huestis, MA et al., 2019).

In addition to their potential use as monotherapy, CBD could be combined with other compounds, including medicinal drugs. This combination could have beneficial and adverse effects which merit more research. This narrative review aims to summarize current information regarding studies where the combination of CBD and other medicinal drugs has been tested *in vitro*, *in vivo*, and clinical settings.

CBD has been evaluated in combination with anticonvulsants, opioids, antineoplastics, antidepressants, antibiotics, and antipsychotic drugs with promising results making their use as an adjuvant in the treatment of epilepsy, pain, depression, infectious disease, and psychosis possible. Most of these studies have been performed in cell and murine models. Clinical trials are scarce.

CBD PLUS OPIODS

Opioids such as morphine are widely used for treating moderate to severe pain; however, their adverse effects, such as sedation, constipation, and respiratory depression, are of concern. A combination that reduces the amount of opioids could avoid these undesired adverse effects. In this sense, crude extracts of cannabis, 6-THC, and 9-THC have been shown to enhance the effect of morphine (Ghosh P et al.,1979; Cichewicz et al., 2004).

The combination of morphine/CBD has been assessed in the following assays: acetic acid-stimulated stretching; acetic acid-decreased operant response for palatable food, and hot plate thermal nociception in rats. This combination produced synergistic effects in reversing acetic acid-stimulated stretching behavior but subadditive effects in the hot plate thermal nociceptive and acetic acid-decreased operant response for palatable food assays (Neelakantan H et al., 2015).

CBD/morphine has been studied as a morphine addiction treatment in rats. The results showed that this combination attenuates the development of morphine reward in the conditioned place preference paradigm test (Markos JR et al., 2018). The administration of CBD + naltrexone has also been studied in the context of alcohol addiction in rats. This combination significantly reduced motivation and ethanol intake in the oral self-administration procedure in a greater proportion than the drugs given alone (Viudez-Martínez A et al., 2018).

CBD PLUS ANTIDEPRESSANTS

Antidepressants are used for the treatment of several conditions, in addition to major depression. These conditions include panic disorder, OCD, PTSD, attention deficit–hyperactivity disorder, bulimia, physical pain, and premenstrual dysphoric disorder (Sabella D, 2018). Although their efficacy has been proven, their adverse effects are considerable.

It has been suggested that the endocannabinoid system may be involved in the physiopathology of depression (Zhou D et al., 2017) and that CBD may have agonist activity in the 5-HT1A receptor; thus, CBD could have therapeutic potential in depression (Russo EB et al., 2005).

Co-administration of ineffective doses of CBD (7 mg/kg) and fluoxetine (5 mg/kg) or desipramine (2.5 mg/kg) resulted in antidepressant-like effects in mice submitted to the forced swimming test (FST), implicating synergistic and/or additive mechanisms. The antidepressant-like effect induced by CBD depends on serotonin levels in the central nervous system (Sales AJ et al., 2018).

The administration of CBD (10 mg/kg) and S-ketamine (10 mg/kg and 30 mg/kg), alone or combined in mice, induced antidepressant-like effects in the FST. This effect is due to the activation of the AMPA receptor, suggesting that CBD and S-ketamine share the same mechanism of action. This

combination prevents the psychostimulant effects of ketamine (Sartim AG et al., 2021).

CBD PLUS ANTICONVULSANTS

CBD has proved its efficacy in the treatment of severe epileptic syndromes. Its adverse effects are usually mild, and discontinuation is low (Silva GD et al., 2020). Its activity in combination has been studied *in vivo*.

An animal study using maximal electric shock and audiogenic seizure models showed that CBD potentiated the anticonvulsant effects of phenytoin twofold and modestly potentiated the effect of phenobarbital. CBD also reduced the anticonvulsant properties of chlordiazepoxide, clonazepam, and ethosuximide(Consroe P et al, 1977).

Combined administration of CBD and low doses of clonazepam in a conditional mouse model of Dravet syndrome achieved seizure control in an additive manner to reduce thermal sensitivity for seizure induction and seizure duration. This additive action may result from combining GABA-enhancing effects in both presynaptic and postsynaptic compartments of GABAergic synapses(Chuang SH et al., 2021).

Meta-analyses indicate CBD plus clobazam is effective in Lennox-Gastaut syndrome or Dravet syndrome. The most common adverse events with this combination are somnolence, rash, pneumonia, or aggression(Devinsky O et al., 2020). Furthermore, this combination enhanced inhibitory $GABA_A$ receptor activation(Anderson LL et al., 2020). CBD and clobazam have a bidirectional pharmacokinetic interaction that increases plasma levels of active metabolites of each drug.

Some potential pharmacokinetic interactions between CBD (Epidiolex) and antiepileptic drugs were identified in an open-label safety study. The results showed increases in topiramate, rufinamide, zonisamide, eslicarbazepine, and N-desmethylclobazam and a decrease in clobazam serum levels with increasing CBD doses. However, the mean level changes were within the therapeutic range. AST and ALT levels were significantly higher with concomitant valproate administration(Gaston TE et al., 2017).

CBD PLUS ANTICANCER DRUGS

Cannabinoid receptors are expressed in several tumors. Cannabinoids inhibit tumor cell growth and induce apoptosis by modulating different cell signaling pathways in gliomas and lymphomas, prostate, breast, lung, skin, and pancreatic cancer cells (Sarfaraz S et al., 2008). Several combinations of CBD and antineoplastics have been evaluated *in vitro*.

A combination of THC+CBD/temozolomide decreased viability and enhanced autophagy and apoptosis of U86MG and T98G glioma cell lines. This combination also decreased tumor volume in a U87MG cell-derived tumor xenograft model(Torres S et al., 2011). These results support the use of this combination for glioblastoma multiforme treatment. In another study, cotreatment regimens combining CBD and DNA-damaging agents temozolomide, carmustine, or cisplatin produced synergistic antiproliferation and cell-killing responses over a limited range of concentrations in all human GBM cell lines (T98G, U251, and U87MG) and mouse PDGF-GBM cells and in mouse neural progenitor cells(Deng L et al., 2016).

The combination of THC + CBD, as well as in combination with cyclophosphamide, has cytotoxic effects on medulloblastoma and ependymoma cell lines. However, the results of *in vitro* evaluations, in which synergism is reported, do not translate to orthotopic models because there was no survival advantage. The main anticancer mechanisms were ROS production and cell cycle sequestration through apoptosis and autophagy(Andradas C et al., 2021).

CBD in combination with TNF-related apoptosis-inducing ligand (TRAIL) produces a synergistic effect and induces apoptosis by increasing DR5 expression through endoplasmic reticulum stress on colorectal cancer cells and decreases tumor growth in xenograft models. However, this effect was not observed in normal colonic cells(Kim JB et al., 2019).

Combined treatment of CBD and cisplatin, 5-fluorouracil, and paclitaxel enhanced the efficacy of these chemotherapeutics on HNSCC cell lines and in a xenograft model. The main processes involved in CBD-induced cytotoxicity were apoptosis and autophagy(Go YY et al., 2020).

It was found that the CBD and THC combination can reduce cell viability by inducing autophagic-dependent necrosis and multiple myeloma (MM) cell migration. This combination can act in synergy with carfilzomib, an immune-proteosome inhibitor, to increase MM cell death and inhibit cell migration(Nabissi M et al., 2016). In another study, CBD alone or in synergy with bortezomib strongly inhibited growth, arrested cell cycle progression, and induced MM cell death by regulating the ERK, AKT, and NF-κB pathways with major effects on TRPV2+ cells(Moreli MB et al., 2013).

Pre-administration of CBD in solution enhanced the effect of paclitaxel and doxorubicin in the breast cancer cells, MCF-7 and MDA-MB-231. The co-administration of CBD and both drugs also showed a synergistic effect. On the other hand, the combination of microparticles of CBD with paclitaxel or doxorubicin in pre- and co-administration showed a significant increase in paclitaxel and doxorubicin antiproliferative activity using MDA-MB-231-derived tumors(Fraguas- Sánchez AI et al., 2019).

Combined administration of CBD and gold nanoparticles (AuNPs) conjugated with hypericin used in photodynamic therapy as a photosensitizer in breast cancer will allow a substantial treatment advancement. Both CBD and photodynamic therapy induce cancer cell death by apoptosis, necrosis, and autophagy. This combination will reduce side effects and toxicity to normal cells and improve the patient´s quality of life(R Mokoena D et al., 2019).

CBD, in combination with other cannabinoids (cannabigerol and cannabigevarin in their neutral and acid forms), has been evaluated in leukemic cells such as the human cancer cell lines CEM and HL60. Cannabinoids have cytostatic activity and cause the arrest of the cell cycle. The treatment schedule proposed, reculturing pre-treated cells in a drug-free medium, resulted in reductions in cell viability, and combining cannabinoids was not antagonistic(Sccott KA et al., 2013).

CBD PLUS ANTIBIOTICS

The antimicrobial activity of CBD has been reported for Gram-positive and Gram-negative bacteria (Blaskovich MAT et al., 2021); however, its potential use in combination with other antibiotics has been scarcely studied. A study reported that CBD enhances the effect of bacitracin against Gram-positive bacteria (*Staphylococcus* species, *Listeria monocytogenes*, and *Enterococcus faecalis*) but was ineffective against Gram-negative bacteria (Wassmann C.S et al., 2020).

CBD plus antinausea drugs

Nausea and vomiting are frequent adverse effects of antineoplastics which alter the quality of life of cancer patients. Some do not respond to current treatments to prevent and treat these conditions; therefore, the search for alternative antinausea drugs continues.

Despite the demonstrated activity of CBD in treating nausea, there are no studies in animal models that have evaluated the effect of combining CBD with antinausea drugs. Until now, a single case report has examined the effect of adjunct CBD treatment in two male patients with gliomas who underwent chemotherapy and radiation. During their treatment period, the patients reported few symptoms of nausea(Dall`Stella PB et al., 2019).

CBD plus antipsychotic drugs

CBD has shown antipsychotic properties by an unknown mechanism of action in rodents and rhesus monkeys (Rohleder C et al., 2016); thus, their use in combination with current antipsychotic drugs has been studied in animal models and clinical trials. The literature has reported its potential as adjuvant therapy, and due to its different mechanism of action, this compound could be a new class of treatment for psychosis.

In a study in rats using the methylazoxymethanol acetate model, the combination of CBD and the atypical antipsychotic iloperidone showed a good therapeutic effect which was more notable in men than women(Thériault RK et al., 2021).

In a clinical trial, CBD plus concomitant therapy (CBD+CT) was well tolerated after six weeks of treatment. Concerning the placebo group, CBD+CT had fewer negative symptoms and was more likely to be rated with improvement. Patients also showed greater improvement in cognitive performance and overall functioning (McGuiere P et al., 2018).

In a randomized placebo-controlled open-label trial evaluating the effects of smoked CBD cigarettes as adjunctive therapy for psychotic symptoms, results revealed no significant difference in primary outcomes. After four weeks of acute treatment, the mean Positive and Negative Syndrome Scale (PANSS) and the Beck Depression Inventory (BDI) decreased in both groups, while an increase in the antipsychotic medication equivalent (expressed as mg of olanzapine) was observed in the placebo group (Köck P et al., 2021).

In another randomized, placebo-controlled, parallel-group, fixed-dose study of oral CBD (600 mg/day) or placebo augmentation in 36 stable antipsychotic-treated patients, there was a significant decrease in PANSS total scores over time. Side effects were similar in both groups, except sedation, which was more frequent in the CBD group(Boggs DL et al., 2018).

CONCLUDING REMARKS

Although most current studies are *in vitro* and animal models, CBD in combination with other drugs can potentially increase the therapeutic effects of these drugs synergistically. More *in vivo* studies are needed to corroborate these interesting findings and support the start of clinical trials. Because CBD is a potent CYP3A4 and CYP2C19 Inhibitor, the probability of adverse effects with some drugs could be more frequent when combined with CBD. Studies are needed that should focus on finding the appropriate dose.

Declaration of conflict of interest.

The authors report no potential conflicts of interest

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