Cannabinoids to Fight Chemotherapy-Induced Adverse Effects

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Contents

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Abstract

One of the main causes of death around the world is cancer. Although the development of antitumor drugs has increased life expectancy in these patients during the past decades, chemotherapy is associated to acute and long-lasting impactful side effects.

The endocannabinoid system is formed by the cannabinoid receptors CB_1 and CB_2, the endogenous agonists of these receptors, and all the enzymes necessary for the metabolism of the endocannabinoids. The wide distribution of the endocannabinoid system and its involvement in the modulation of a wide range of biological processes highlight the great therapeutic potential of cannabis and cannabinoids in many diseases, including gastrointestinal alterations, pain, cachexia, or cancer.

To date, only a few cannabinoid agonists have been approved for different pathologies, although in relation to cancer, only oral capsules and solutions based on synthetic analogues of Δ9-tetrahydrocannabinol have been approved for the treatment of chemotherapy-induced nausea and vomiting. Despite the vast positive results obtained from animal studies regarding the usefulness of cannabinoids to reduce other symptoms related to cancer and its treatment, such as neuropathic pain or cachexia, conflicting evidence exists in the clinical setting, due, mainly, to the lack of more high-quality clinical studies. Moreover, the psychotropic effects and immune suppression mediated by CB_1 and CB_2 agonists, respectively, arise safety concerns that need to be considered.

In conclusion, although strategies aimed at modulating the endocannabinoid system can play a pivotal role in the treatment of different side effects associated to cancer chemotherapy, future studies will be needed to confirm their effectiveness and safety in the clinical setting.

Introduction

Cancer is a generic term which encompasses multiple diseases that can affect any of the parts of the organism, although all are characterized by a rapid proliferation of abnormal cells, which can invade nearby organs and colonize distant ones (metastasis). Cancer is a leading cause of death worldwide; in 2020 it accounted for almost

ten million deaths worldwide, although the early diagnosis and the improvements in cancer therapy have prolonged the life expectancy (Cancer n.d.)

All throughout history, mankind has used cannabis with different aims: mankind used it for the prevention and treatment of different diseases; because of its fiber, resin, and oil, it has been used for industrial purposes; and it has also been used in religious contexts.

The first cultivated crops which have been found are dated approximately in the year 8000 BC, but it is not known when cannabis was first used with medical purposes. In the Chinese pharmacopoeia of Shen Nung in 2600 BC, the first written references on the use of marijuana with this aim are found.

Despite its medical use, it was not until 1839 that the first article on the antispasmodic, analgesic, and muscle-relaxing properties of cannabis was published by Sir William B. O'Shaughnessy, as a result of his studies on the therapeutic effect of cannabis. O'Shaughnessy's results were the first ones of the many to come, they caught the attention of doctors all over the world, and thereafter, an important amount of research articles have been and still are being published until today (MacGillivray 2017).

As a result, in the late nineteenth and early twentieth centuries, cannabis was included in Western medicine. Queen Victoria used it for painful menses (possibly due to endometriosis) and Empress Elisabeth of Austria used it to stimulate appetite and to calm the cough. J Russell Reynolds, physician to the household of Queen Victoria, found cannabis very useful in many painful illnesses such as facial neuralgia, migraine, dysmenorrhea, and sensory alterations due to gout, as well as for the erupting teeth in children (Crocq 2020).

Because cannabis has an important psychoactive effect and due to the introduction of new sedative and analgesic drugs, such as morphine, and safer drugs, such as aspirin, the use and interest in cannabis in the medical field declined during the first decades of the twentieth century. Finally, its use was removed from the English pharmacopoeia in 1932 and a few years later from the American one (Crocq 2020).

Although cannabis was no longer used for medical purposes by doctors, research continued, and the first component of cannabis to be isolated was cannabinol. Its entire chemical elucidation was concluded by Adams and coworkers. After this, cannabidiol was also purified and characterized. However, it was not until the 1960s that the structure of the main molecule responsible for the psychoactive effects of cannabis, Δ^9-tetrahydrocannabinol (Δ9-THC), was determined. This finding led to the discovery of the endocannabinoid system (ECS). Thus, Devane et al. characterized a first endocannabinoid receptor in the brain of rats, the CB_1 cannabinoid receptor. Following the rationale which had led to the finding of endogenous opioids, i.e., evolution could not have maintained a receptor in the organism only for a plant to stimulate, Mechoulam and coworkers discovered the first endogenous cannabinoid or endocannabinoid: N-arachidonoylethanolamine, also named anandamide, after the Sanskrit word "ananda," which means pleasure, bliss, or happiness. Afterward, another endocannabinoid was identified: 2-arachidonoylglycerol (2-AG). Since then, other compounds have been isolated such as 2-arachidonyl glyceryl

ether (noladin ether), O-arachidonoyl ethanolamine (virodhamine), or N-arachidonoyl dopamine (NADA) (Crocq 2020).

The Endocannabinoid System

Today, the ECS is known to be composed of:

– Endocannabinoids, which are different endogenous cannabinoid agonists. Of all, the two most studied are anandamide (AEA) and 2-AG.
– The receptors of these endogenous cannabinoids, mainly the CB_1 and CB_2 receptors.
– The enzymes that are responsible for the synthesis and inactivation of the endocannabinoids, i.e., N-acyltransferase and N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) participate in the synthesis of anandamide and phospholipase C and a diacylglycerol lipase (DAGL) in the synthesis of 2-AG. Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) inactivate anandamide and 2-AG, respectively.

The ECS is widely distributed throughout the body, and, thus, it is able to mediate a broad range of physiological processes, such as motor functions, pain control, sleep/wake cycle, thermogenesis, synaptic plasticity, learning and memory, stress response, mood regulation, appetite, inflammatory response, cardiac function, lipid and glucose metabolism, successful gametogenesis, and reproduction, among others (Meccariello et al. 2020).

CB_1 and CB_2 cannabinoid receptors belong to the family of G protein-coupled receptors (GPCR) characterized by the presence of seven transmembrane domains, with an extracellular glycosylated amino terminal and an intracellular carboxy-terminal. Although both receptors are found in the central and peripheral nervous system, CB_1 receptors are the most abundant and widely distributed GPCR in the mammalian brain. In both the central and peripheral nervous system, CB_1 receptors play a key neuromodulatory role (Kuipers et al. 2016). They are highly expressed in the amygdala, hippocampus, cerebral cortex, cerebellum, spinal cord, and the enteric nervous system. CB_1 receptors have also been found, with a lower density, in the liver, lung, bone, skin, spleen, heart, prostate, uterus, ovaries, and at the presynaptic level in sympathetic nerve endings (Martínez et al. 2020).

Conversely, CB_2 receptors are mainly found in cells of the immune system, especially in B lymphocytes but also in monocytes, T lymphocytes, and natural killer (NK) cells. Their function in the immune system is to modulate the release of cytokines, which are responsible for inflammation and regulation of the immune system (Cabral and Griffin-Thomas 2009). In addition, CB_2 receptors are present in the spleen, thymus, tonsils, and various peripheral tissues, including the gastrointestinal tract, adipose tissue, liver, cardiovascular system, bone, lungs, and testes (Martínez et al. 2020).

The psychoactive and behavioral effects of cannabis are mediated by the high affinity of the CB_1 receptor for some phytocannabinoids, such as Δ9-THC. Its wide distribution could explain a large part of the effects of cannabinoids in our body: the presence of CB_1 receptors in the cortical area and the hippocampus is linked to learning processes and memory; similarly, their wide presence in the basal ganglia and cerebellum is related to the regulation of motor coordination and balance; and, finally, their presence in the spinal cord and the periaqueductal gray matter corresponds to pain modulation. Interestingly, the relatively low presence of these receptors in the brain stem also explains the safety of cannabis and cannabinoids in relation to the risk of death after an acute intoxication (Bachs and Mørland 2001; Niaz et al. 2017; Zou and Kumar 2018).

In the synaptic clefts, endocannabinoids act as retrograde neuromodulators (Fig. 1). That is, endocannabinoids bind to the presynaptic CB_1 receptor, after they are released into the synaptic cleft from the postsynaptic one, and its activation inhibits the release of different neurotransmitters. Depending on the inhibited neurotransmitter, different effects can occur: when GABA release is inhibited, depolarization-induced suppression of inhibition happens, but when glutamate release is inhibited, a depolarization-induced suppression of excitation is induced (Zou and Kumar 2018). Thus, through retrograde signaling cannabinoids can exert modulatory functions on neuronal activity and neurotransmitter release. The activation of cannabinoid receptors can additionally inhibit the release of other neurotransmitters such as acetylcholine, dopamine, serotonin, aspartate, and noradrenaline. Additionally, CB_1 receptor is expressed in astrocytes regulating the release of neurotransmitters and inflammatory mediators (Boczek and Zylinska 2021).

Most of these processes are caused by the coupling of cannabinoid receptors to an effector through $G_{i/o}$ proteins (Fig. 1), although the coupling to $G_{s\alpha}$ and $G_{q\alpha}$ proteins has also been described (Walsh et al. 2021).

When the CB receptors are activated, the $G_{i\alpha}$ subunit induces the inhibition of adenylyl cyclase. This will abolish the conversion of ATP into cAMP, and consequently it reduces the concentration of intracellular cAMP. However, sometimes, the opposite effect occurs when the CB receptor interacts with the $G_{s\alpha}$ domain, increasing intracellular cAMP levels by stimulating adenylyl cyclase activity (Walsh et al. 2021).

Moreover, the CB receptor interacts with Ca^{2+} and K^+ channels through the $G_{i\ \beta\gamma}$ domain. Through this domain, N- and P/Q-type calcium channels present in the presynaptic neuron are inhibited (Schlicker and Kathmann 2001). In this way, cannabinoids can modulate the release of neurotransmitters in neurons. In addition, through interaction with K^+ channels, they control the basal K^+ concentration in the cell. This allows them to regulate neuronal excitability (Lin 2021). Importantly, cannabinoids can also activate the cascade of reactions caused by mitogen-activated protein kinase (MAPK), influencing the activation of transcription factors that mediate cell cycle control, cell growth and proliferation, and apoptosis (Zou and Kumar 2018) (Fig. 1).

In the last years, the activation of cannabinoid receptors has also been associated to β-arrestin2, which has been related to the sensitization and internalization of the receptor. Historically, it was thought that all agonists would activate GPCR.
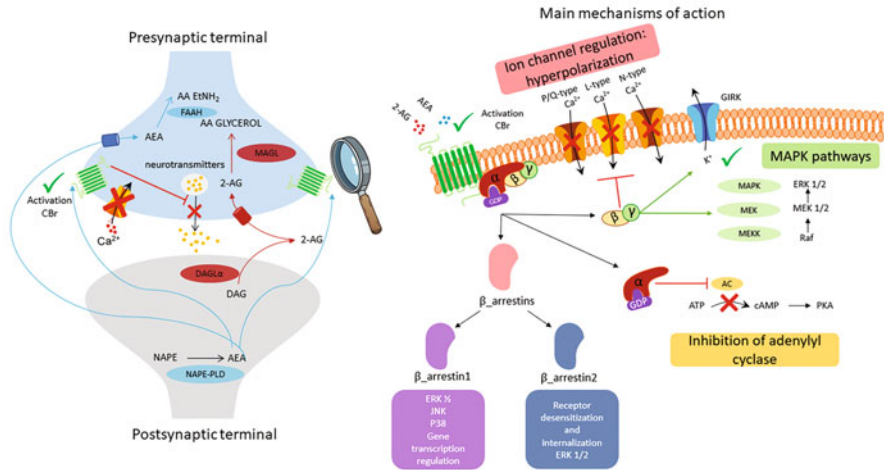
Fig. 1 A schematic representation of the synthesis of AEA and 2-AG and their release to the synaptic cleft from the postsynaptic neuron, activation of the presynaptic cannabinoid receptor and posterior internalization through transporters, and degradation of these two endocannabinoids in the presynaptic neuron by the FAAH and MAGL enzymes is depicted on the left side of the image. On the right-hand side of the image, the activation of CB receptors, which in turn can signal through G proteins and β-arrestins, and these have different downstream effectors, is depicted. Signaling through G protein-coupled receptors inhibits calcium channels and activates potassium-rectifying channels, thus leading to neuronal hyperpolarization and inhibition of neurotransmitter release through different pathways. Additionally, cannabinoid receptor activation can induce β-arrestin recruitment and consequently receptor desensitization and internalization among others. Abbreviations: *2-AG* 2-arachidonoylglycerol, *AA EtNH2* arachidonate and ethanolamine, *AA Glycerol* arachidonic acid and glycerol, *AC* adenylyl cyclase, *AEA* anandamide, *AMP* adenosine monophosphate, *ATP* adenosine triphosphate, *cAMP* cyclic AMP, *CBr* cannabinoid receptors, *DAG* diacylglycerol, *DAGLα* diacylglycerol lipase-alpha, *ERK* extracellular signal-regulated kinases, *FAAH* fatty acid amide hydrolase, *GIRK* G protein-gated inwardly rectifying potassium channels, *JNK* c-Jun N-terminal kinase, *MAGL* monoacylglycerol lipase, *MAPK* mitogen-activated protein kinase, *MEK* mitogen-activated protein kinase kinase, *MEKK* mitogen-activated protein kinase kinase kinase, *NAPE* N-arachidonoyl phosphatidylethanolamine, *NAPE-PLD* N-acylphosphatidy-lethanolamide-hydrolyzing phospholipase D, *p38* p38 mitogen-activated protein kinase, *PKA* protein kinase A. (Modified from Wouters et al. 2019)

However, different agonists have the capacity of modifying the conformation of the receptor in a different manner once they bind to this receptor. Consequently, these ligands could preferentially transduce certain downstream signaling pathways over others, this is named "biased signaling," and it has grown into an increasingly active area of research (Wouters et al. 2019) (Fig. 1).

Endocannabinoids have similar properties to phytocannabinoids but have a different structure. This is because they are derived from membrane phospholipids, mostly long-chain polyunsaturated acids such as arachidonic acid.

Anandamide has similar pharmacological effects to Δ9-THC, although they have different structures. Anandamide is notable for its association with the reward mechanisms in the brain. However, it is also involved in many other physiological

processes, such as its modulatory effects on sensory nerve signaling, mood, appetite, apoptosis, control of energy balance, and control of inflammation (Ritter et al. 2016; Scherma et al. 2018).

Endocannabinoids are usually synthesized "on demand" at the postsynaptic membrane in response to specific signals, and they are not stored in the cell, as opposed to classical neurotransmitters (deRoon-Cassini et al. 2020). The synthesis of anandamide occurs from the hydrolysis of N-arachidonoyl phosphatidylethanolamine (NAPE) by a phospholipase D (NAPE-PLD) (di Marzo et al. 1994). On the other hand, 2-AG has a higher concentration than anandamide in the brain, and it is synthesized from the hydrolysis of inositol phospholipids, through different processes which involve first phosphoinositol phospholipase C and then DAGL (diacylglycerol) α and β (Kuipers et al. 2016). In contrast, the degradation of AEA and 2-AG is primarily due to fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (di Marzo and Piscitelli 2015). Therefore, the activity of these two enzymes can directly influence the activity of the endocannabinoid system (Fig. 1).

Endocannabinoid ligands can also interact with receptors and channels other than CB_1 and CB_2. This affinity could explain many of the side effects of cannabinoids. These additional targets include transient receptor potential (TRP) channels and G protein-coupled receptor (GPR) 55, GPR18, GPR119, peroxisome proliferator-activated receptors (PPARs), and glycine receptors (Martínez et al. 2020; Walsh et al. 2021). TRP channels belong to the family of ionotropic channels. By regulating ion flux, TRP channels mediate a wide range of sensory processes, including those involved in the sensation of temperature, pressure, and pH, as well as the perception of smell, taste, and vision. The TRP channel families include vanilloid (TRPV), ankyrin (TRPA), and melastatin (TRPM) channels. Both AEA and 2-AG couple to TRPV1 channels and activate them, inducing Ca^{2+} influx and depolarization of the cell membrane potential (Muller et al. 2019). Besides, activation of GPR18 and GPR55 receptors by cannabinoids can activate cell signaling pathways that modulate acute and chronic pain pathways (Walsh et al. 2021).

Additionally, heterodimers between CB_1 receptors and several other GPCR, including adenosine A2A, dopamine D2, and orexin 1 receptors, have been observed; this might also explain the variety of endocannabinoid targets and their multiple effects (de Petrocellis and di Marzo 2009).

Cannabinoid Drugs

Depending on their origin, cannabinoids can be classified as:

- Molecules which can be found in the plant (phytocannabinoids). It is known that the *Cannabis sativa* plant has many compounds belonging to different chemical families; one of them is the family of phytocannabinoids, which share a characteristic basic chemical structure (see below).

- Endogenous substances found in the animal organisms which form part of the endocannabinoid system (endocannabinoids), which derive or are chemically related with arachidonic acid, as mentioned above.
- Molecules which are synthesized in the laboratory (synthetic cannabinoids), with chemical structures analogue or not to either phytocannabinoids or endocannabinoids.

Until recently, phytocannabinoids were thought to be synthesized exclusively in the *Cannabis sativa* plant, but in recent years cannabinoids have also been found in *Rhododendron* species, the liverwort genus *Radula,* some legumes, and some fungi (Gülck and Møller 2020). Although three different varieties may be recognized, namely, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*, *Cannabis sativa* is the plant where the biosynthesis of cannabinoids has been best described (Martínez et al. 2020). The cannabis plant contains around 500 different chemical compounds, including a wide variety of terpenes, fatty acids, flavonoids, and more than 120 phytocannabinoids. The concentration of these cannabinoids in the plant varies depending on its variety, age, and environmental conditions, among many other factors (Martínez et al. 2020).

Phytocannabinoids are terpenophenolic compounds, with a carbocyclic structure of 21 carbon atoms with an alkyl side chain, and are synthesized and stored in the glandular trichomes of the plant (Walsh et al. 2021). Initially, the plant synthesizes cannabinoids in their acidic precursor form (Δ9-THCA, CBDA, CBCA, and CBGA). However, due to its poor oxidative stability, each of these molecules loses its carboxyl group in the form of carbon dioxide on exposure to light or heat, giving rise to the neutral forms of the popularly known cannabinoids, which are more pharmacologically active (Gülck and Møller 2020).

To date, 11 different classes of phytocannabinoids have been identified. Δ9-Tetra-hydrocannabinol (Δ9-THC) and cannabidiol (CBD) are two of the most abundant phytocannabinoids synthesized by the cannabis plant. In addition to these two phytocannabinoids, other cannabinoids are synthesized such as cannabinol (CBN), cannabichromene (CBC), cannabigerol (CBG), cannabidivarin (CBDV), Δ9-tetra-hydrocannabivarin (Δ9-THCV), cannabicyclol (CBL), cannabigerol monomethylether (CBGM), cannabielsoin (CBE), cannabinodiol (CBND), and cannabitriol (CBT) (Walsh et al. 2021). Of all these phytocannabinoids, only CBD as monotherapy and CBD and Δ9-THC in combination have been approved as drugs to be used in the clinic for the treatment of different pathologies. More precisely, the US Food and Drug Administration (FDA) approved the use of Epidiolex[®] in 2018 and the European Medicines Agency (EMA) in 2019, as an add-on treatment for Dravet and Lennox-Gastaut syndromes (two rare forms of epilepsy) in those patients older than 1 year of age. Two years later the FDA in 2020 and the EMA in 2021 approved the use of Epidiolex[®] oral solution for tuberous sclerosis complex (Peng et al. 2022). Other synthetic Δ9-THC analogues in monotherapy or in combination with CBD have also been approved with different indications: Marinol[®] (dronabinol; a synthetic Δ9-THC analogue), as an antiemetic and appetite stimulant; Cesamet[®] (nabilone; another synthetic Δ9-THC analogue) as an antiemetic; and Sativex[®] (combination of Δ9-

THC and CBD in a precisely formulated ratio of 1:1) for the treatment of muscle spasticity in multiple sclerosis (Wouters et al. 2019).

Additionally, medical cannabis or cannabinoids are now legally available in Argentina, Australia, Barbados, Bermuda, Brazil, Canada, Chile, Colombia, Croatia, Czech Republic, Denmark, Ecuador, Estonia (with a permit), Finland, Germany, Ghana (only for products with <0.3% Δ9-THC), Israel, Italy, Jamaica, Lebanon, Lesotho, Malta, Mexico, the Netherlands, New Zealand, Peru, the Philippines, Saint Vincent and the Grenadines, San Marino, South Africa, South Korea, Sri Lanka, Switzerland, Thailand, the United Kingdom, the United States (not at the federal level, but in 36 states and the District of Columbia), Uruguay, Vanuatu, Zambia, and Zimbabwe. Under the commercial name of Sativex®, the cannabis extract consisting of Δ9-THC and CBD (which is also known as nabiximols) has been available in all European Union member states since 2018, except for Bulgaria, Cyprus, Greece, Hungary, Latvia, Romania, and Slovakia (Busse et al. 2021). However, the legal status of cannabis, cannabis extracts, and phytocannabinoids is subject of continuous update and may change in the near future in many countries. Furthermore, phytocannabinoids that are non-psychoactive including CBD are being investigated by food researchers and may be soon included in new food formulations and dietary supplements (Martínez et al. 2020).

Δ9-THC is a partial agonist of both CB_1 and CB_2 receptors, but it is also being investigated for its pharmacological effects outside the cannabinoid system, such as an antagonist of the serotoninergic receptors, allosteric mechanisms potentiating the glycine-activated currents, or PPARγ which could imply important effects on the cardiovascular system, causing vasorelaxation, and potentially in cancer treatment. Other potential receptors which Δ9-THC may target are the G protein-coupled receptors GPR55 and GPR18, now considered to be novel cannabinoid receptors, or it can act as an allosteric modulator of the μ and δ opioid receptors. It has also been shown to act as an agonist of different TRP receptors and as an antagonist of the TRPM8 receptor (Martínez et al. 2020).

On the other hand, the mechanism of CBD is much more complex, to date it has not been completely elucidated, and this molecule has been demonstrated to bind to multiple different GPCR and channels. Differently as Δ9-THC, CBD binds with a very weak affinity to the orthosteric site of the cannabinoid receptors and acts as a negative allosteric modulator of the cannabinoid receptors. Additionally, it has been shown to interact with other G_i-coupled receptors, such as the serotoninergic $5HT_1$, as a receptor agonist. More possibly, CBD acts as a positive allosteric modulator of the μ and δ opioid receptors or the dopamine D_2 receptors. Cannabidiol has also been shown to activate TRPA1, TRPV1, TRPV4, and TRPV2 cation channels and is an antagonist of TRPM8 receptor. It is a negative allosteric modulator of serotonin receptor $5HT_{3a}$ and α7 nicotinic acetylcholine receptor and acts as a positive allosteric modulator of the $GABA_A$ receptors among others (for a more extensive review on the mechanisms of action of CBD, see Mlost et al. 2020).

After the elucidation of the endocannabinoid system and the purification of several phytocannabinoids, synthetic cannabinoids started to be synthetized, in order to modulate this endocannabinoid system. These synthetic drugs can be full/

partial agonists, which directly activate the cannabinoid receptors, but there are also antagonists or molecules that can inhibit the enzymes which degrade endo-cannabinoids. With regard to synthetic agonists, they were first developed in the 1970s, and since then many have been developed by academic and pharmaceutical companies, although very few have entered clinical trials to date, for example, the CB_2-selective cannabinoid receptor agonist ajulemic acid (JBT-101) is currently in a phase II/III trial for the treatment of systemic sclerosis, cystic fibrosis, dermatomy-ositis, and systemic lupus erythematosus (Burstein 2018).

With regard to their pharmacokinetics, the main administration ways in the clinical setting are inhaled (through vapors and smoked), oral (edibles and tinctures), oromucosal or sublingual (lollipops, pills), and topical or rectal (herbal cannabis, resins, and concentrates). Δ9-THC has a poor and erratic absorption through the oral route; additionally it suffers a high first-pass metabolism that reduces its oral bioavailability (which is around 13%). When inhaled, Δ9-THC reaches maximum plasma concentration in minutes, and psychotropic effects start just after seconds to a few minutes after it is inhaled, while through ingestion it appears in blood after 30–90 minutes. Δ9-THC penetrates highly vascularized tissues very fast, resulting in a rapid decrease of plasma concentrations; afterward there is an intensive accumulation in less vascularized tissues and finally in body fat, which acts as a reservoir. Metab-olism occurs mainly in the liver by enzymes of the cytochrome P450 CYP2C subfamily through microsomal hydroxylation and oxidation. Major metabolites are mono-hydroxylated compounds, mainly 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-Δ9-THC) and further oxidation into 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (Δ9-THC-COOH). Penetration into the brain of 11-OH-Δ9-THC seems to be faster and higher than that of Δ9-THC, and the brain tissue constitutes an important and substan-tial proportion of the deposit in fat. Due to the slow rediffusion of Δ9-THC from body fat and other tissues into the blood, Δ9-THC is eliminated slowly from plasma. Indeed, the elimination half-life of Δ9-THC is very variable and difficult to calculate; after high doses it has been estimated as 12.6 days with 4 weeks of observation. Δ9-THC is excreted primarily as acid metabolites through different routes: 20–35% in urine and 65–80% in feces, less than 5% of an oral dose as unchanged drug in the feces within days to weeks (Grotenhermen 2003).

Cannabinoids and Chemotherapy

The wide distribution of the endocannabinoid system and its involvement in the modulation of a wide range of biological processes highlight the great therapeutic potential of cannabinoids in many diseases, including neurodegenerative, inflamma-tory, cardiovascular, liver, gastrointestinal, and skin diseases, obesity, diabetes, pain, psychiatric disorders, cachexia, or cancer (Fraguas-Sánchez and Torres-Suárez 2018). The main beneficial effects of cannabinoids for medicinal use are anti-inflammatory, antinociceptive, analgesic, antiemetic, antispasmodic, anxiolytic, anti-oxidant, antitumor, anticonvulsant, appetite stimulation, muscle relaxation, and sleep induction (Bagues et al. 2022; Fraguas-Sánchez and Torres-Suárez 2018; Zou and

Kumar 2018). Thus, these properties theoretically make these compounds of great interest for the management of chemotherapy side effects.

Chemotherapy is one of the main treatments for cancer, alone or in combination with radiotherapy or surgery. Classical chemotherapy aims to inhibit cell proliferation through different mechanisms depending on the drug, thus having an important effect on fast dividing cells, for example, cells of the bone marrow and gastrointestinal epithelium. Additionally, it has important toxic effects on the nervous system inducing peripheral, autonomic, and central neurotoxicity, which translate into numerous symptoms, including nausea and vomit and peripheral neuropathy. Although these effects are shared by many antineoplastic drugs, some of these drugs are known to produce specific side effects in particular organs. A schematic drawing of these specific side effects of chemotherapy can be observed in Fig. 2.

Cannabinoids have been proposed as potential drugs for the treatment and prevention of these side effects, although the most studied are nausea and vomit and peripheral neuropathy (Bagues et al. 2022; Was et al. 2022).

Cannabinoids for the Management of Chemotherapy-Induced Nausea and Vomit

Chemotherapy-induced nausea and vomit (CINV) is very prevalent among patients receiving chemotherapy, with rates that reach 60–80%. It is one of the side effects which mostly affects the quality of life of patients and can interfere with the treatment even causing the reduction or interruption of the antitumoral administration. On top of this, CINV can be accompanied by additional side effects caused by nausea and vomiting, which can be psychological (demeaning, anticipatory nausea), physical (rib fracture, esophageal tears, and dental erosion), and metabolic (dehydration, loss of appetite); these symptoms will further deteriorate the quality of life of the patient (Mortimer et al. 2019).

There are numerous drugs used for cancer treatment. Depending on the emetic risk, they have been divided into four categories: (1) highly emetogenic therapy, which causes CINV among $\geq$90% of patients, wherein in this group high-dose cisplatin, carmustine, and cyclophosphamide at doses greater than 1500 g/m^2, dacarbazine, mechlorethamine, streptozocin, and combinations of anthracyclines and cyclophosphamide are included; (2) moderate emetogenic chemotherapy, which causes CINV among 30–60% of patients, in which in this group numerous chemotherapy agents can be included, such as carboplatin, doxorubicin, irinotecan, oxaliplatin, and cyclophosphamide; (3) low emetic risk therapies that induce CINV in 10–30% of patients; and (4) minimal emetic risk chemotherapies causing emesis in $\leq$10% of patients (Razvi et al. 2019).

The mechanism by which antitumoral drugs induce CINV is due to a complex interaction between the central nervous system and the gastrointestinal system. The area postrema of the medulla receives afferents of the small intestine. Chemotherapy induces the release of serotonin from the enterochromaffin cells of the gastrointestinal epithelium. This can be the initial trigger for nausea and vomit, through
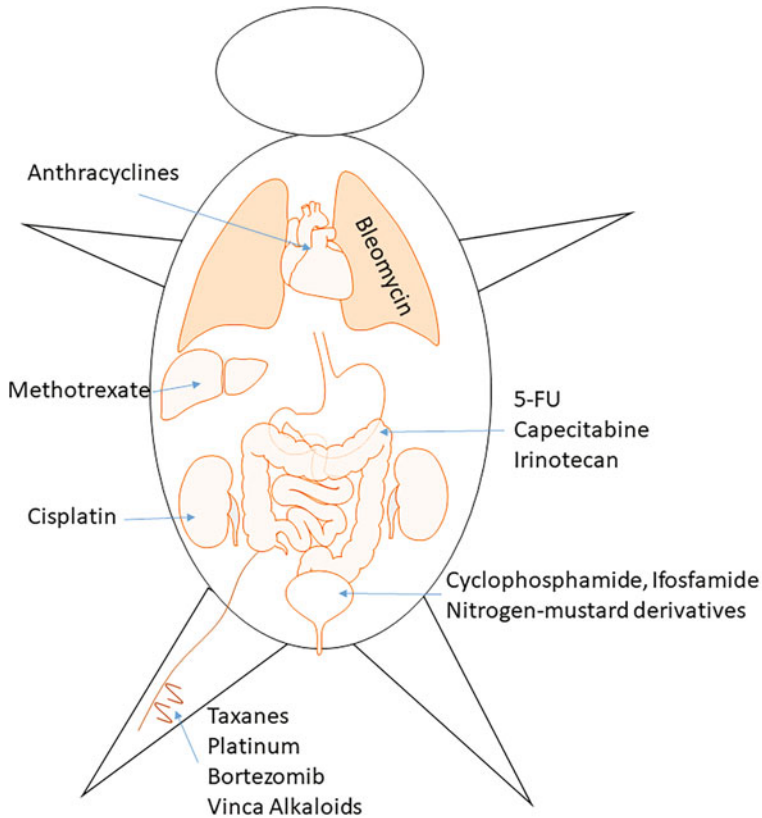
Fig. 2 Schematic representation of the specific side effects of different antitumor drugs, classified by organs involved in those effects. Anthracyclines are associated with cardiotoxicity, leading to arrhythmias or cardiac failure. In the lungs, the toxic effects of bleomycin can lead to primary pulmonary fibrosis. Methotrexate can cause liver damage, leading to increased liver enzymes, fibrosis, and, sometimes, cirrhosis. Cisplatin can cause nephrotoxicity and ototoxicity. 5-FU, capecitabine, and irinotecan have toxic effects on the gastrointestinal tract, causing acute diarrhea. Cyclophosphamide, ifosfamide, and nitrogen mustard derivatives, in certain doses, are metabolized to acrolein and cause hemorrhagic cystitis. Taxanes, platinum, bortezomib, and vinca alkaloids cause peripheral neuropathy, among many other effects (Bagues et al. 2022; Parlar et al. 2021; Was et al. 2022). Abbreviations: *5-FU* 5-fluorouracil

activation of its vagal afferents, which stimulate the 5-HT$_3$ and 5-HT$_4$ receptors of the area postrema. These signals are processed in the vomiting center (also in the medulla), which in turn sends efferent signals to the abdominal muscles, the stomach, and the diaphragm (Fig. 3).

Depending on the time onset of the CINV, it can be classified into different types, and they are mediated through different neurotransmitters; thus acute (within the 24 hours of treatment) is thought to be mediated through the serotonin pathway, while in delayed CINV (after those first 24 hours after treatment), substance P is the
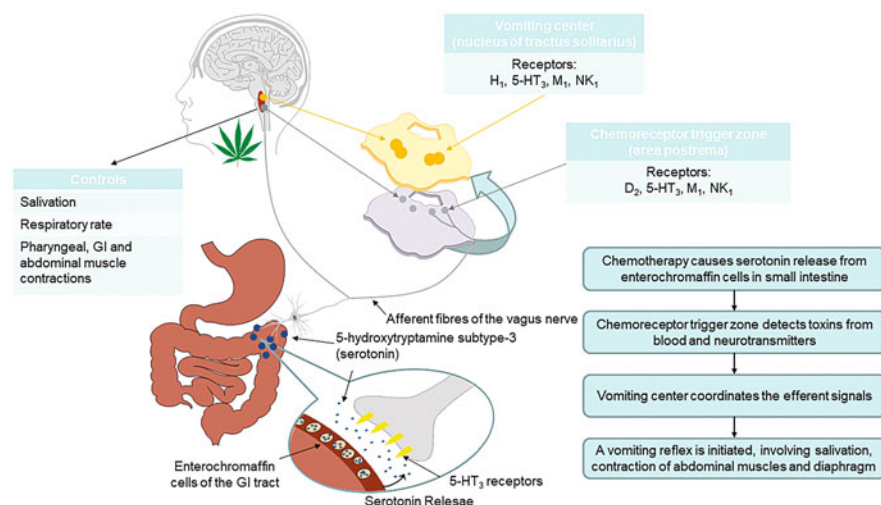
Fig. 3 Schematic representation of the mechanisms involved in chemotherapy-induced nausea and vomit and their alleviation through cannabinoid agonists. Chemotherapy induces the release of serotonin from the enterochromaffin cells of the gastrointestinal epithelium; this signal travels through the vagal afferents to the chemoreceptor trigger zone, which additionally is activated through the detection of chemotherapy in the blood. The vomiting center coordinates these signals and initiates the vomiting reflex increasing salivation and contraction of abdominal muscles and the diaphragm. Cannabinoids bind to presynaptic cannabinoid receptors in the area postrema and possibly bind to 5-HT$_3$ receptors as allosteric inhibitors and therefore inhibit serotonin release. Abbreviations: *5-HT$_3$* subtype 3 serotoninergic (hydroxytryptamine) receptor, *D$_2$* subtype 2 dopaminergic receptor, *GI* gastrointestinal, *H$_1$* histamine subtype 1 receptor, *M$_1$* subtype 1 muscarinic receptor, *NK$_1$* neurokinin subtype 1 receptor

main neurotransmitter involved. The mechanisms of the antiemetics that are used for CINV are based on 5-HT$_3$ and NK$_1$ antagonists, although these drugs have a higher effectiveness in the treatment of vomiting than nausea and cause several side effects such as headache, diarrhea, and fatigue. Additionally, they are not effective in the treatment of anticipatory CINV (which is a learned response and occurs prior to readministration in response to a previous negative experience), and several studies have demonstrated that a high percentage of patients do not achieve a complete protection with classical antiemetics and require breakthrough antiemetics (Razvi et al. 2019; Bagues et al. 2022).

Since the studies performed by Darmani in which it was observed that with the blockade of CB$_1$ receptors, but not CB$_2$ receptors, emesis was induced, the involvement of the endocannabinoid system started to be defined. Furthermore, different cannabinoid agonists, both synthetic and phytocannabinoids, demonstrated to reverse this effect and also the emesis induced by cisplatin, opening a new possible antiemetic indication of cannabinoid agonists.

Different animal models can be used in the research of new therapeutics for CINV; basically they can be divided into the use of animals which can or cannot vomit. In animals which do not vomit, indirect markers, such as gaping, pica, or bedding intake,

need to be studied. In both types of animals, cannabinoid agonists such as Δ9-THC and nabilone have shown to reduce CINV or indirect markers of CINV. Furthermore, endocannabinoids such as AEA and 2-AG have shown to reduce emesis as also the inhibitors of FAAH and MAGL. On the other hand, CBD and its precursor, cannabidiolic acid (CBDA), which are non-psychoactive drugs, reduced emesis in musk shrews. For a more detailed review, see Bagues et al. (2022).

The mechanisms by which cannabinoids reduce CINV are to date not completely elucidated. Studies in animals have demonstrated that different cannabinoid agonists and anandamide act on presynaptic CB_1 receptors of the area postrema, and inhibit serotonin release, but they have also demonstrated to bind to type 5-HT_3 serotoninergic receptors as allosteric inhibitors. On the other hand, it has been demonstrated that cannabidiol has this allosteric inhibitory effect on the 5-HT_3 receptor, but its antiemetic effect seems mainly due to the activation of the 5-HT_1 receptor (a $G_{\alpha i}$ protein-coupled receptor), thus reducing the release of serotonin (Taylor et al. 2021).

To date, cannabinoids have been approved for the treatment of breakthrough CINV, i.e., nauseas or vomiting in which conventional therapy has failed. Four commercial products have been approved: Marinol[®], Syndros[®], Cesamet[®], and Canemes[®]. The first two commercial products contain the active ingredient dronabinol, which is a synthetic form of Δ9-THC, and are found as capsules and a solution to be administered through the oral route. On the other hand, Cesamet[®] and Canemes[®] contain nabilone, which is also a synthetic Δ9-THC analogue, and are both found in the dosage form of capsules.

Overall, different meta-analyses have demonstrated that cannabinoids are superior to placebo and comparative antiemetics, although the evidence is considered weak. On the other hand, cannabinoids are associated with higher frequency of adverse effects, which included dysphoria, euphoria, cognitive impairment, or sedation. Curiously, when combining cannabinoids with classical antiemetics, no additive antiemetic effect is observed (Mortimer et al. 2019).

Despite the fact that in different meta-analyses cannabinoids seem to be effective in the treatment of CINV, very little mention is made to these drugs in the different clinical guidelines. The American Society of Clinical Oncology (ASCO) recommends the use of dronabinol or nabilone in adult patients who experience nausea or vomiting that is not controlled with optimal prophylaxis and have already been treated with olanzapine, while, because the evidence is still insufficient, the use of medical marijuana instead of dronabinol or nabilone is not recommended (Hesketh et al. 2017), and MASCC (Multinational Association of Supportive Care in Cancer) and ESMO (European Society for Medical Oncology) do not mention the use of cannabis-related therapy in their guidelines (Roila et al. 2016).

Cannabinoids for the Management of Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a highly prevalent, severe toxicity that occurs in a dose-dependent manner, usually after several cycles of

neurotoxic antineoplastic therapy. It is characterized by a sensory axonal neuropathy and occasionally with motor and autonomic involvement. The typical symptoms include the presence of painful responses to normally non-painful stimuli (allodynia) and heightened response to pain (hyperalgesia), loss of sensation, or spontaneous pain. Many chemotherapy drugs, including platinum-based agents (oxaliplatin, cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), proteasome inhibitors, and thalidomide analogues, may cause CIPN. Cytotoxic drugs affect most frequently long sensory nerves. Thus, symptoms appear most frequently in the hands and feet in a glove- and stocking-like distribution, and motor, autonomic, or cranial nerve symptoms appear much less frequently (Zajączkowska et al. 2019).

One of the major side effects which antitumor drugs induce is CIPN; it can be dose-limiting or even cause the cessation of chemotherapy (Quintão et al. 2019). Additionally, CIPN may not diminish after discontinuation of the chemotherapy regimen and may even continue to progress for several months after discontinuation, a phenomenon that is known as "coasting." The pain and reduction in the quality of life that CIPN causes make the prevention and treatment of this side effect necessary. Despite the importance of controlling CIPN, the pharmacological options to treat it are sometimes not enough. The currently available pharmacological alternatives include serotonin/noradrenaline reuptake inhibitors, anticonvulsant, and tricyclic antidepressant drugs; second line of treatment includes lidocaine and capsaicin patches and weak opioids; in third line of treatment, strong opioids are included. The efficacy and safety of these treatments are to date not completely satisfactory, and new long-term effective and side effect-free therapies are needed (Blanton et al. 2019).

The possible utility of cannabinoids is based on the fact that cannabinoids are highly expressed in many of the structures involved in nociceptive transmission and also on the fact that the expression and levels of receptors and endocannabinoids are modified during neuropathic pain (Maldonado et al. 2016).

To study CIPN, animal models have been developed in which the efficacy of the different cannabinoid compounds has been studied. The most studied mechanisms are those which activate cannabinoid receptors, that is, by administrating cannabinoid agonists or increasing the levels of endocannabinoids by inhibiting the degradation of endocannabinoids. In this sense both therapeutic approaches have long been shown to reverse or prevent CIPN in numerous animal models (for review see Bagues et al. 2022; Masocha 2018; and Was et al. 2022).

Concerning cannabinoid agonists, many different drugs have been synthetized; these can be nonselective agonists or CB_1-/CB_2-selective agonists. The nonselective agonists, CP-55940 and WIN 55,212–2 (WIN), have demonstrated to have an antinociceptive effect in different CIPN animal models, such as in paclitaxel (Deng et al. 2015a; Pascual et al. 2005), cisplatin (Nealon et al. 2019; Vera et al. 2013), and vincristine (Rahn et al. 2007). Additionally, WIN prevented the development of allodynia and hyperalgesia induced by paclitaxel and cisplatin (Abalo et al. 2013; Rahn et al. 2014; Vera et al. 2007).

The effect of the FAAH (URB597 and URB937) and MAGL (JZL184 and MJN110) inhibitors has been studied previously on behavioral CIPN responses. Both inhibitors, FAAH and MAGL, reversed the mechanical and thermal hypersensitivity induced by several antitumor drugs: cisplatin (Guindon et al. 2013; Khasabova et al. 2012) and paclitaxel and vincristine (Curry et al. 2018; Slivicki et al. 2018).

Cannabinoid agonists which bind to CB_1 can induce the typical psychoactive side effects of cannabis, which include relaxation, euphoria, and disinhibition as well as tolerance and addiction; thus agonists with affinity for the CB_2 receptor or those that do not cross the blood-brain barrier (BBB) are very attractive alternatives in the development of new pharmacological drugs. Possibly the most studied CB_2-selective agonist is AM1710, which has shown to reverse the neuropathic signs caused by paclitaxel and cisplatin (Deng et al. 2012, 2015b). Other CB_2 receptor agonists, such as AM1714 and AM1241, have also shown to have the capacity to reverse the mechanical allodynia induced by vincristine and paclitaxel (Rahn et al. 2007, 2008), and MDA7 can both suppress and prevent mechanical allodynia (Naguib et al. 2008, 2012; Xu et al. 2014). Very recently, a CB_2 receptor agonist, which was safe, but failed in a phase 2 osteoarthritis treatment clinical trial, demonstrated to have antiallodynic effects in a paclitaxel model in mice. Curiously, paclitaxel increased CB_2 expression in epidermal Langerhans cells and keratinocytes; thus the authors hypothesized that these cells could be implicated in the antiallodynic effect of CB_2 agonists (Lin et al. 2021).

With the approval of medicinal cannabis, a growing percentage of patients are using it to mitigate chemotherapy-induced side effects, such as CIPN. The term medicinal cannabis generally implies the whole dried cannabis flowers; it is processed, so it can be inhaled; or it is prepared as oils, tinctures, and edible products; additionally, its labelling typically informs about the amount of Δ9-THC and/or CBD found in the product, although it also refers to commercial cannabis, such as Sativex®. To date opioids are considered the gold standard in cancer-related pain therapy, but their use is limited due to their side effects including constipation, sedation, and addiction. Because of this, in addition to the opioid epidemic, caregivers and patients are seeking for alternatives (Whitcomb et al. 2020).

Different studies have assessed the efficacy of cannabinoid-based drugs in the treatment of pain in patients, but the results are conflicting because of the use of small study populations and the wide variety of methodologies used, which includes varying periods of follow-up, a range of dosages, different types of selective cannabinoids, and inclusion of chronic pain syndromes of different etiologies. In a meta-analysis performed recently on the effects of cannabinoids on neuropathic pain, the authors found that cannabinoids were superior to placebo, but this improvement in the numerical rating scale was clinically small. However, patients of most studies presented an improved quality of life, quality of sleep, and positive results in the global impression of change (Meng et al. 2017). Similarly, a meta-analysis which aimed to study the effects of cannabinoids on cancer pain showed that the addition of cannabinoids to opioids does not improve cancer-related pain when compared to placebo (Boland et al. 2020).

In a recent systematic review, which incorporated different forms of cannabis and cannabinoids and routes of administration for the relief of different types of pains, the authors found pain ease depended on type of cannabis or cannabinoids used, administration route, and type of pain. Thus, Δ9-THC/CBD and Δ9-THC via oromucosal route were effective in neuropathic and cancer pains, Δ9-THC via oral route alleviated cancer pain, and standardized cannabis extract via inhalation route was useful for the treatment of neuropathic pain (Rabgay et al. 2020).

Thus, to date it is difficult to determine the effects of cannabinoids on CIPN and future studies are needed with more standardized methodologies.

Additionally, the effectiveness of cannabis as a preventive tool for the development of neuropathic pain has recently been assessed in patients receiving oxaliplatin and 5-fluorouracil (5-FU) for gastrointestinal malignancies. This study included control patients (no cannabis consumption), patients who had started cannabis consumption before chemotherapy treatment, and another group who consumed cannabis after chemotherapy. More patients treated with cannabis did not present CIPN, and those who did revealed lower grade of CIPN than control ones, and this was more important in cannabis-first treated patients, although the group treated with cannabis first had received higher cumulative doses than the oxaliplatin first and control ones (Waissengrin et al. 2021). Thus, further studies will need to confirm the preventive efficacy of cannabinoids in the development of CIPN.

In the clinical setting, due to the inconsistent results in the different studies, the ASCO guidelines state that clinicians should not offer cannabinoids for the prevention and treatment of CIPN to patients with cancer undergoing treatment with neurotoxic agents (Loprinzi et al. 2020). On the other hand, the ESMO-EONS-EANO guidelines do not contemplate the use of cannabinoids for CIPN treatment nor prevention (Jordan et al. 2020).

Cannabinoids for Appetite Stimulation and Weight Gain in Chemotherapy-Treated Patients

Cancer-associated cachexia (CAC) syndrome is a wasting syndrome characterized by involuntary weight loss and anorexia. It affects between 50 and 80% of cancer patients; the consequences are weight loss associated with muscle wasting and lipolysis. CAC reduces quality of life of patients and tolerance to treatment and increases morbidity and mortality. Although none of the approved drugs are indicated for CAC, both Marinol® and Syndros® are approved for anorexia related to weight loss in patients.

The endocannabinoid system is crucial in the regulation of appetite. Endocannabinoids stimulate appetite through the activation of the CB_1 receptor located in the hypothalamic neurons, making it a promising target in the treatment of anorexia associated to different pathologies. Activation of these neurons with different cannabinoid agonists has shown to increase food intake. Systemic

administration of a CB_1 antagonist (rimonabant), on the contrary, reduced hunger. The mechanism by which endocannabinoids regulate hunger is quite complex; for further information excellent reviews can be consulted (Koch 2017). Additionally, patients under chemotherapy experience changes in smell and taste because of treatment, and it has been hypothesized that the CB_1 receptors can be modulated through cannabinoid agonists improving the chemosensory dysfunction.

Again, in human studies the evidence for the use of cannabinoids in CAC is poor, and to determine whether cannabinoids stimulate food intake during chemotherapy, more controlled studies are required. Overall, the scientific literature demonstrates that dronabinol and nabilone increased weight, although megestrol acetate is superior to dronabinol in improving appetite and also in the anorexia-related quality of life questionnaire (Johnson et al. 2021). On the contrary, in another systemic review and meta-analysis, cannabinoids showed to increase appetite (Wang et al. 2019). Additionally, although only a few studies have analyzed the improvement in the chemosensory dysfunction induced by cannabinoids, promising results have been obtained with dronabinol, which was shown to decrease chemosensory complaint scores and improve tastiness of food (Johnson et al. 2021).

Cannabinoids and Other Chemotherapy-Induced Side Effects

As mentioned above, in addition to CINV, CIPN, and anorexia/cachexia, cancer chemotherapy may cause many other side effects including oral mucositis and diarrhea (particularly associated with irinotecan or 5-FU), liver toxicity, nephrotoxicity and ototoxicity (especially after cisplatin), hematologic toxicity, lung toxicity (after treatment with bleomycin), cardiovascular toxicity (typically after treatment with anthracyclines), and also chemobrain (cognitive dysfunctions), as well as anxiety, depression, and insomnia. Due to their broad distribution in the body, targeting the endocannabinoid system might be helpful to alleviate or even prevent these side effects (Ostadhadi et al. 2015). However, preclinical and clinical evidence of these potential palliative or preventative effects is low, and, in some cases, the therapeutic potential of cannabis and cannabinoids in this context has only been hypothesized (Bagues et al. 2022; Boullon et al. 2021). CBD could be the most promising phytocannabinoid-based treatment for these side effects (O'Brien 2022), but other molecules with cannabinoid-like activity and also devoid of psychoactivity, like β-caryophyllene, are increasingly being studied (see below).

There is only scarce preclinical evidence on the therapeutic potential of cannabinoids against oral mucositis and diarrhea induced by chemotherapeutic drugs such as 5-FU (Abalo et al. 2017; de Cuba et al. 2020). Current treatments of these side effects induced by chemotherapy (and radiotherapy) are not completely effective, particularly in the case of oral mucositis, in which CBD might be useful, as suggested by results obtained in mice models (de Cuba et al. 2020). Due to their constipating effect, like that of the opioid agonist loperamide, the most frequently used antidiarrheal drugs, including in chemotherapy-treated patients, cannabinoid agonists may prove useful to counteract chemotherapy-induced diarrhea, even at low

non-psychoactive doses, but further research is needed to validate these findings obtained in rats (Abalo et al. 2017).

The role of cannabinoids on liver toxicity has been also scarcely studied. At a relatively low dose that neither induced diarrhea nor increased circulating pro-inflammatory mediators, but was able to reduce body weight gain, irinotecan alone elevated aspartate aminotransferase, but this did not happen when rats were co-treated with Δ9-THC (Prester et al. 2018). Furthermore, the liver is a key site for drug interactions, and CBD and other cannabis-based drugs should be used with caution in chemotherapy-treated patients (Brown and Winterstein 2019).

In rodent models, cisplatin-induced nephrotoxicity was prevented, at least partially, by different compounds, including both synthetic (Mukhopadhyay et al. 2010, 2016) and natural phytocannabinoids, such as CBD (Pan et al. 2009) and CBG (Brierley et al. 2019), as well as the sesquiterpene β-caryophyllene (Horváth et al. 2012), also contained in cannabis. The nephroprotective effect of these compounds seems to be mainly due to activation of CB_2 cannabinoid receptors, since it is abolished by antagonizing the CB_2 receptor, and nephrotoxicity induced by cisplatin is enhanced in CB_2 knockout models (Mukhopadhyay et al. 2010). The mechanism of CB_2-mediated nephroprotection involves a reduction of inflammation, oxidative/nitrosative stress, and cell death. Despite this, findings need to be interpreted with caution, because nephrotoxicity has also been described for synthetic cannabinoids used as drugs of abuse (Pendergraft et al. 2014).

Cisplatin-mediated ototoxicity is associated with upregulation of TRPV1 expression in the cochlea, and capsaicin (the spicy component of hot chili peppers that activates this receptor causing pain followed by rapid desensitization) has been shown to cause otoprotection in cisplatin-treated rats, through the activation of CB_2 receptors in the cochlea and sustained increased activation of pro-survival transcription factors (Bhatta et al. 2019). Interestingly, blockade of CB_2 receptors alone produces hearing loss, highlighting their protective role under control conditions, where it is probably tonically activated (Ghosh et al. 2018). Intratympanic administration of a CB_2 cannabinoid receptor agonist (JW-015) (Ghosh et al. 2018) and TRPV1 siRNA (Mukherjea et al. 2008) was otoprotective in rat models, and this route of administration could be useful also in patients, at least in adults.

Unfortunately, in the previously mentioned study, the combined treatment of Δ9-THC with irinotecan produced greater leukopenia than irinotecan alone (Prester et al. 2018). Indeed, immune suppression is one of the possible side effects of cannabinoids due to their interaction with CB_2 receptors (including Δ9-THC and CBD) that might not only interfere with immunotherapy, reducing the time in which the tumor progresses and, therefore, the life expectancy in these patients, but can also induce adverse events related to the immune system (Bar-Sela et al. 2020). To our knowledge, the role of cannabinoids on other hematologic effects of cancer chemotherapy (anemia, thrombocytopenia) has not been tested.

Bleomycin is an antibiotic used as a cytotoxic drug in cancer therapy. This antineoplastic drug characteristically causes fibrosis in lung, skin, and other tissues. Among these, lung toxicity is the most noxious side effect of bleomycin in cancer patients. Activation of CB_2 receptors has been shown to exert antifibrotic properties

in scleroderma in mice (Akhmetshina et al. 2009) and lung fibrosis in rats (Parlar et al. 2021) and mice (Fu et al. 2017) treated with bleomycin. The role of CB_1 receptors is not so clear with reports showing positive effects of both its inactivation and its activation. Thus, inactivation of CB_1 receptor was early found to be effective to reduce leukocyte infiltration and secondary fibroblast activation leading to skin fibrosis in bleomycin-treated mice (Marquart et al. 2010). Similarly, in other studies, the combined inhibition of CB_1 receptors and inducible nitric oxide synthase (iNOS), using a peripherally restricted hybrid agent, was an effective strategy in a mouse model of liver, lung, kidney, and skin fibrosis (scleroderma) induced by bleomycin (Zawatsky et al. 2021). However, more recently, arachidonoyl cyclopropylamide (ACPA), a selective CB_1 receptor agonist, was demonstrated to produce antifibrotic effects in both in vivo and in vitro models of pulmonary fibrosis, through fibroblast-selective inhibition of the transforming growth factor (TGF)-β-Smad2/3 signaling pathway (Chen et al. 2022). Thus, this is a still open area of research.

Interestingly, it was recently demonstrated that the CB_2 receptor agonist β-caryophyllene, considered a dietary cannabinoid, could attenuate doxorubicin-induced chronic cardiotoxicity in rats, where, through CB_2 receptor activation, it improved cardiac function and histological and ultrastructural appearance of heart tissue, with mitigation of oxidative stress, inflammation, and apoptosis (Meeran et al. 2019). This followed other preclinical studies which showed that CB_1 receptor antagonists (rimonabant, AM281 (Mukhopadhyay et al. 2007)) presented a cardioprotective role, but also anandamide (Hydock et al. 2009) and CBD (Fouad et al. 2013; Hao et al. 2015) were found to have this same effect. Furthermore, the inactivation of PPAR-α was associated with a protective effect against the cardiotoxicity induced by doxorubicin in mice, and cannabinoids (WIN) were able to potentiate this effect (Rahmatollahi et al. 2016).

The possible effects of phytocannabinoids on central neurotoxicity leading to the so-called chemobrain or chemofog (cognitive dysfunctions affecting memory and other central functions) have not been evaluated yet, but, in view of their beneficial effects mainly demonstrated in preclinical models of other conditions associated with central nervous system damage (like traumatic brain injury, Parkinson's disease, or Alzheimer's disease), it would not be surprising that cannabinoids, particularly CBD and other non-psychotropic cannabinoids, could prevent the development of these disabling alterations (Bagues et al. 2022; Boullon et al. 2021). In these regards, the CB_2 receptor agonist β-caryophyllene orally administered was recently shown to have a neuroprotective effect in rat models of neuro-inflammation and chemobrain (induced by doxorubicin), with improvements in memory, increases in acetylcholinesterase and catalase levels, and reductions in lipid peroxidation (Kanojia et al. 2021).

Finally, cancer and cancer treatment often cause psychological distress (anxiety, depression) and sleep disturbance. The psychotropic effects of cannabis (and many cannabinoids with agonistic activity on the CB_1 receptors), generally considered a drawback of cannabis-based therapy, may be beneficial and improve the quality of life of cancer patients suffering from a combination of negative organic and psychological effects derived from the disease and its treatment. Although a deep review

of the topic is out of the scope of this chapter, the reader might find helpful information in Sexton et al. (2021).

Cannabinoids and Tumor Suppression

During the last years, compelling evidence has been obtained which indicates that cannabinoids can be used in the treatment of cancer. The mechanisms which can explain this effect are explained by the great number of cancer-related pathways that are modulated by the activation of CB_1 or CB_2 receptors or through activation of TRP channels among others by cannabinoid agonists, which ultimately block the cell cycle. Additionally, the inhibition of MAGL has also proven to be effective in decreasing tumor cell invasion (Hinz and Ramer 2022).

Succinctly, the main targets for cancer inhibition have been described as (1) inhibition of the PI3K (phosphoinositide 3-kinases)-Akt pathway and the activation of the MAPK (mitogen-activated protein kinase) pathways, resulting in apoptotic death; (2) de novo synthesis of ceramide, a pro-apoptotic sphingolipid, that in turn activates an endoplasmic reticulum stress-related signaling pathway, which leads to the inhibition of the AKT/mTORC1 axis and, thus, death by autophagy; and (3) antiangiogenesis effects, mainly by blocking the activation of the vascular endothelial growth factor pathway, an inducer of angiogenesis (Pagano et al. 2022).

Despite the growing evidence which exists on the potential effect of cannabinoids for cancer treatment, only one clinical study has been performed to determine the antitumor effect of cannabinoids. A pilot study with 21 patients with glioblastoma multiforme showed that the survival rate of those patients treated with a combination of nabiximols (standardized extract of *Cannabis sativa* L. with an approximate 1:1 ratio of Δ9-THC and CBD) oromucosal spray with temozolomide was greater than those treated with placebo. Despite this promising finding, no further standardized controlled trials have been carried out (Hinz and Ramer 2022).

Specific studies aimed at determining if the coadministration of lower doses of anticancer drugs with cannabinoids might be able to increase the antiproliferative efficacy of chemotherapy and at the same time diminish its adverse effects are likewise awaited.

Conclusion

The modulation of the cannabinoid system has shown promising results in the treatment of chemotherapy-induced side effects and also in cancer treatment, but these findings have not yet been demonstrated to translate to the clinic, possibly due to the fact that more robust, controlled randomized clinical trials are needed but also to the fact that, logically, the pharmacological tools used in the clinical setting are much more limited than those used in animal research.

Future studies will be necessary to ascertain if the cannabinoid drugs which are now available for clinical use are effective in the treatment of chemotherapy side

effects and whether the development of new drugs might also have a role in these regards.

All efforts directed toward a reduction in the side effects induced by chemotherapy will translate into a better quality of life of the patient. This is especially important taking into account that they may be severe and in some cases lifelong sequelae. However, cannabinoids also produce their own set of side effects and may cause drug interactions. Thus, medicinal cannabis and cannabinoids should be used with care in cancer patients to avoid complications.

More research is needed to determine the best therapeutic approaches to use cannabinoids and cannabis-based medicines (and even food supplements) in the clinical setting.

Cross reference

► Central neurotoxicity of chemotherapy
► Chemobrain in cancer treatment: mechanisms and its prevention
► Chemotherapy-induced cardiotoxicity in cancer treatment: mechanisms and its prevention
► Cytotoxic cancer drugs
► Diagnosis and management of toxicities associated with immunotherapy in cancer
► Endocrine toxicities related to Immunotherapy
► Gastrointestinal adverse effects of chemotherapy
► Immunological effects of conventional anticancer drugs
► Mechanisms of immunological toxicity in immunotherapy
► Neurotoxicity related to cancer immunotherapy
► Plants, phytochemicals and cancer
► Pulmonary side effects of immunotherapy
► Skin toxicity due to chemotherapy, target therapy and immunotherapy
► The endocannabinoid system as a target in cancer: current status and future perspectives
► Toxicity when combining immunotherapy and radiotherapy

References

Abalo R, Cabezos PA, Vera G, López-Pérez AE, Martín MI (2013) Cannabinoids may worsen gastric dysmotility induced by chronic cisplatin in the rat. Neurogastroenterol Motil 25(5):373–e292. https://doi.org/10.1111/NMO.12073

Abalo R, Uranga JA, Pérez-García I, de Andrés R, Girón R, Vera G, López-Pérez AE, Martín-Fontelles MI (2017) May cannabinoids prevent the development of chemotherapy-induced diarrhea and intestinal mucositis? Experimental study in the rat. Neurogastroenterol Motil 29(3):e12952. https://doi.org/10.1111/NMO.12952

Akhmetshina A, Dees C, Busch N, Beer J, Sarter K, Zwerina J, Zimmer A, Distler O, Schett G, Distler JHW (2009) The cannabinoid receptor CB2 exerts antifibrotic effects in experimental dermal fibrosis. Arthritis Rheum 60(4):1129–1136. https://doi.org/10.1002/ART.24395

Bachs, L., & Mørland, H. (2001). Acute cardiovascular fatalities following cannabis use. Forensic Sci Int, 124(2–3), 200–203. https://doi.org/10.1016/S0379-0738(01)00609-0

Bagues A, López-Tofiño Y, Llorente-Berzal Á, Abalo R (2022) Cannabinoid drugs against chemotherapy-induced adverse effects: focus on nausea/vomiting, peripheral neuropathy and chemofog in animal models. Behav Pharmacol 33(2 & 3):105–129. https://doi.org/10.1097/FBP.0000000000000667

Bar-Sela G, Cohen I, Campisi-Pinto S, Lewitus GM, Oz-Ari L, Jehassi A, Peer A, Turgeman I, Vernicova O, Berman P, Wollner M, Moskovitz M, Meiri D (2020) Cannabis consumption used by cancer patients during immunotherapy correlates with poor clinical outcome. Cancers 12(9): 1–18. https://doi.org/10.3390/CANCERS12092447

Bhatta P, Dhukhwa A, Sheehan K, al Aameri, R. F. H., Borse, V., Ghosh, S., Sheth, S., Mamillapalli, C., Rybak, L., Ramkumar, V., & Mukherjea, D. (2019) Capsaicin protects against cisplatin ototoxicity by changing the STAT3/STAT1 ratio and activating Cannabinoid (CB2) receptors in the cochlea. Sci Rep 9(1):4131. https://doi.org/10.1038/S41598-019-40425-9

Blanton, H. L., Brelsfoard, J., DeTurk, N., Pruitt, K., Narasimhan, M., Morgan, D. J., & Guindon, J. (2019). Cannabinoids: current and future options to treat chronic and chemotherapy-induced neuropathic pain. In Drugs 79, 9, pp. 969–995). Springer. https://doi.org/10.1007/s40265-019-01132-x

Boczek T, Zylinska L (2021) Receptor-dependent and independent regulation of voltage-gated Ca2+ channels and Ca2+-permeable channels by endocannabinoids in the brain. Int J Mol Sci 22(15). https://doi.org/10.3390/IJMS22158168

Boland EG, Bennett MI, Allgar V, Boland JW (2020) Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. BMJ Support Palliat Care 10(1):14–24. https://doi.org/10.1136/BMJSPCARE-2019-002032

Boullon L, Abalo R, Llorente-Berzal Á (2021) Cannabinoid drugs-related neuroprotection as a potential therapeutic tool against chemotherapy-induced cognitive impairment. Front Pharmacol 12. https://doi.org/10.3389/FPHAR.2021.734613

Brierley DI, Harman JR, Giallourou N, Leishman E, Roashan AE, Mellows BAD, Bradshaw HB, Swann JR, Patel K, Whalley BJ, Williams CM (2019) Chemotherapy-induced cachexia dysregulates hypothalamic and systemic lipoamines and is attenuated by cannabigerol. J Cachexia Sarcopenia Muscle 10(4):844–859. https://doi.org/10.1002/JCSM.12426

Brown JD, Winterstein AG (2019) Potential adverse drug events and drug-drug interactions with medical and consumer Cannabidiol (CBD) use. J Clin Med 8(7). https://doi.org/10.3390/JCM8070989

Burstein SH (2018) Ajulemic acid: potential treatment for chronic inflammation. Pharmacol Res Perspect 6(2):e00394. https://doi.org/10.1002/PRP2.394

Busse JW, Vankrunkelsven P, Zeng L, Heen AF, Merglen A, Campbell F, Petter L, Aertgeerts B, Buchbinder R, Coen M, Juurlink D, Samer C, Siemieniuk RAC, Kumar N, Cooper L, Brown J, Lytvyn L, Zeraatkar D, Wang L et al (2021) Medical cannabis or cannabinoids for chronic pain: A clinical practice guideline. The BMJ 374. https://doi.org/10.1136/bmj.n2040

Cabral GA, Griffin-Thomas LT (2009) Emerging role of the CB2 cannabinoid receptor in immune regulation and therapeutic prospects. Expert Rev Mol Med 11:e3. https://doi.org/10.1017/S1462399409000957

Cancer (n.d.) Retrieved April 6, 2022, from https://www.who.int/news-room/fact-sheets/detail/cancer

Chen D, Tang H, Jiang H, Sun L, Zhao W, Qian F (2022) ACPA alleviates bleomycin-induced pulmonary fibrosis by inhibiting TGF-β-Smad2/3 signaling-mediated lung fibroblast activation. Front Pharmacol 13. https://doi.org/10.3389/FPHAR.2022.835979

Crocq MA (2020) History of cannabis and the endocannabinoid system. Dialogues Clin Neurosci 22(3):223–228. https://doi.org/10.31887/DCNS.2020.22.3/MCROCQ

Curry ZA, Wilkerson JL, Bagdas D, Kyte SL, Patel N, Donvito G, Mustafa MA, Poklis JL, Niphakis MJ, Hsu KL, Cravatt BF, Gewirtz DA, Damaj MI, Lichtman AH (2018) Mono-acylglycerol lipase inhibitors reverse paclitaxel-induced nociceptive behavior and

proinflammatory markers in a mouse model of chemotherapy-induced neuropathy. J Pharmacol Exp Ther 366(1):169–183. https://doi.org/10.1124/jpet.117.245704

de Cuba LF, Salum FG, Guimarães FS, Cherubini K, Borghetti RL, de Figueiredo MAZ (2020) Cannabidiol on 5-FU-induced oral mucositis in mice. Oral Dis 26(7):1483–1493. https://doi.org/10.1111/ODI.13413

de Petrocellis L, di Marzo V (2009) An introduction to the endocannabinoid system: from the early to the latest concepts. Best Pract Res Clin Endocrinol Metab 23(1):1–15. https://doi.org/10.1016/J.BEEM.2008.10.013

Deng L, Guindon J, Vemuri VK, Thakur GA, White FA, Makriyannis A, Hohmann AG (2012) The maintenance of cisplatin- and paclitaxel-induced mechanical and cold allodynia is suppressed by cannabinoid CB2 receptor activation and independent of CXCR4 signaling in models of chemotherapy-induced peripheral neuropathy. Mol Pain 8. https://doi.org/10.1186/1744-8069-8-71

Deng L, Cornett BL, Mackie K, Hohmann AG (2015a) CB1 knockout mice unveil sustained CB2-mediated antiallodynic effects of the mixed CB1/CB2 agonist CP55,940 in a mouse model of paclitaxel-induced neuropathic pain. Mol Pharmacol 88(1):64–74. https://doi.org/10.1124/mol.115.098483

Deng L, Guindon J, Cornett BL, Makriyannis A, Mackie K, Hohmann AG (2015b) Chronic cannabinoid receptor 2 activation reverses paclitaxel neuropathy without tolerance or cannabinoid receptor 1-dependent withdrawal. Biol Psychiatry 77(5):475–487. https://doi.org/10.1016/j.biopsych.2014.04.009

deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ (2020) Meet your stress management professionals: the endocannabinoids. Trends Mol Med 26(10):953–968. https://doi.org/10.1016/J.MOLMED.2020.07.002

di Marzo V, Piscitelli F (2015) The endocannabinoid system and its modulation by Phytocannabinoids. Neurotherapeutics 12(4):692–698. https://doi.org/10.1007/S13311-015-0374-6

di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz JC, Piomelli D (1994) Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 372(6507):686–691. https://doi.org/10.1038/372686a0

Fouad AA, Albuali WH, Al-Mulhim AS, Jresat I (2013) Cardioprotective effect of cannabidiol in rats exposed to doxorubicin toxicity. Environ Toxicol Pharmacol 36(2):347–357. https://doi.org/10.1016/J.ETAP.2013.04.018

Fraguas-Sánchez AI, Torres-Suárez AI (2018) Medical use of cannabinoids. Drugs 2018 78:16 78 (16):1665–1703. https://doi.org/10.1007/S40265-018-0996-1

Fu Q, Zheng Y, Dong X, Wang L, Jiang CG (2017) Activation of cannabinoid receptor type 2 by JWH133 alleviates bleomycin-induced pulmonary fibrosis in mice. Oncotarget 8(61):103486–103498. https://doi.org/10.18632/ONCOTARGET.21975

Ghosh S, Sheth S, Sheehan K, Mukherjea D, Dhukhwa A, Borse V, Rybak LP, Ramkumar V (2018) The endocannabinoid/cannabinoid receptor 2 system protects against cisplatin-induced hearing loss. Front Cell Neurosci 12. https://doi.org/10.3389/FNCEL.2018.00271

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42(4):327–360. https://doi.org/10.2165/00003088-200342040-00003

Guindon J, Lai Y, Takacs SM, Bradshaw HB, Hohmann AG (2013) Alterations in endocannabinoid tone following chemotherapy-induced peripheral neuropathy: effects of endocannabinoid deactivation inhibitors targeting fatty-acid amide hydrolase and monoacylglycerol lipase in comparison to reference analgesics following cisplatin treatment. Pharmacol Res 67(1):94–109. https://doi.org/10.1016/j.phrs.2012.10.013

Gülck T, Møller BL (2020) Phytocannabinoids: origins and biosynthesis. Trends Plant Sci 25(10):985–1004. https://doi.org/10.1016/J.TPLANTS.2020.05.005

Hao E, Mukhopadhyay P, Cao Z, Erdélyi K, Holovac E, Liaudet L, Lee WS, Haskó G, Mechoulam R, Pacher P (2015) Cannabidiol protects against doxorubicin-induced cardiomyopathy by modulating mitochondrial function and biogenesis. Mol Med (Cambridge, MA) 21 (1):38–45. https://doi.org/10.2119/MOLMED.2014.00261

Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D, Somerfield MR, Lyman GH (2017) Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35(28):3240–3261. https://doi.org/10.1200/JCO.2017.74.4789

Hinz B, Ramer R (2022) Cannabinoids as anticancer drugs: current status of preclinical research. Br J Cancer 2022:1–13. https://doi.org/10.1038/s41416-022-01727-4

Horváth B, Mukhopadhyay P, Kechrid M, Patel V, Tanchian G, Wink DA, Gertsch J, Pacher P (2012) β-Caryophyllene ameliorates cisplatin-induced nephrotoxicity in a cannabinoid 2 receptor-dependent manner. Free Radic Biol Med 52(8):1325–1333. https://doi.org/10.1016/J.FREERADBIOMED.2012.01.014

Hydock DS, Lien CY, Hayward R (2009) Anandamide preserves cardiac function and geometry in an acute doxorubicin cardiotoxicity rat model. J Cardiovasc Pharmacol Ther 14(1):59–67. https://doi.org/10.1177/1074248408329449

Johnson S, Ziegler J, August DA (2021) Cannabinoid use for appetite stimulation and weight gain in cancer care: does recent evidence support an update of the European Society for Clinical Nutrition and Metabolism clinical guidelines? Nutr Clin Pract 36(4):793–807. https://doi.org/10.1002/NCP.10639

Jordan B, Margulies A, Cardoso F, Cavaletti G, Haugnes HS, Jahn P, le Rhun E, Preusser M, Scotté F, Taphoorn MJB, Jordan K (2020) Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO–EONS–EANO clinical practice guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol 31(10):1306–1319. https://doi.org/10.1016/J.ANNONC.2020.07.003

Kanojia U, Chaturbhuj SG, Sankhe R, Das M, Surubhotla R, Krishnadas N, Gourishetti K, Nayak PG, Kishore A (2021) Beta-Caryophyllene, a CB2R selective agonist, protects against cognitive impairment caused by neuro-inflammation and not in dementia due to ageing induced by mitochondrial dysfunction. CNS Neurol Disord Drug Targets 20(10):963–974. https://doi.org/10.2174/1871527320666210202121103

Khasabova IA, Khasabov S, Paz J, Harding-Rose C, Simone DA, Seybold VS (2012) Cannabinoid type-1 receptor reduces pain and neurotoxicity produced by chemotherapy. J Neurosci 32(20):7091–7101. https://doi.org/10.1523/JNEUROSCI.0403-12.2012

Koch M (2017) Cannabinoid receptor signaling in central regulation of feeding behavior: a mini-review. Front Neurosci 11(MAY):293. https://doi.org/10.3389/FNINS.2017.00293/BIBTEX

Kuipers EJ, Yang VW, Sharkey KA, Wiley JW (2016) The role of the endocannabinoid system in the Brain–Gut Axis. Gastroenterology 151(2):252–266. https://doi.org/10.1053/J.GASTRO.2016.04.015

Lin YF (2021) Potassium channels as molecular targets of endocannabinoids. Channels (Austin) 15(1):408–423. https://doi.org/10.1080/19336950.2021.1910461

Lin X, Xu Z, Carey L, Romero J, Makriyannis A, Hillard CJ, Ruggiero E, Dockum M, Houk G, Mackie K, Albrecht PJ, Rice FL, Hohmann AG (2021) A peripheral CB2 cannabinoid receptor mechanism suppresses chemotherapy-induced peripheral neuropathy. Pain, Publish Ah(00). https://doi.org/10.1097/j.pain.0000000000002502

Loprinzi CL, Lacchetti C, Bleeker J, Cavaletti G, Chauhan C, Hertz DL, Kelley MR, Lavino A, Lustberg MB, Paice JA, Schneider BP, Lavoie Smith EM, Smith ML, Smith TJ, Wagner-Johnston N, Hershman DL (2020) Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol 38(28):3325–3348. https://doi.org/10.1200/JCO.20.01399

MacGillivray N (2017) Sir William Brooke O'Shaughnessy (1808–1889), MD, FRS, LRCS Ed: Chemical pathologist, pharmacologist and pioneer in electric telegraphy. J Med Biogr 25(3):186–196. https://doi.org/10.1177/0967772015596276

Maldonado R, Baños JE, Cabañero D (2016) The endocannabinoid system and neuropathic pain. Pain 157:S23–S32. https://doi.org/10.1097/J.PAIN.0000000000000428

Marquart S, Zerr P, Akhmetshina A, Palumbo K, Reich N, Tomcik M, Horn A, Dees C, Engel M, Zwerina J, Distler O, Schett G, Distler JHW (2010) Inactivation of the cannabinoid receptor

CB1 prevents leukocyte infiltration and experimental fibrosis. Arthritis Rheum 62(11):3467–3476. https://doi.org/10.1002/ART.27642

Martínez V, Iriondo De-Hond A, Borrelli F, Capasso R, del Castillo MD, Abalo R (2020) Cannabidiol and other non-psychoactive cannabinoids for prevention and treatment of gastro-intestinal disorders: useful nutraceuticals? Int J Mol Sci 21(9). MDPI AG. https://doi.org/10.3390/ijms21093067

Masocha W (2018) Targeting the endocannabinoid system for prevention or treatment of chemotherapy-induced neuropathic pain: studies in animal models. Pain Res Manag 2018:1. https://doi.org/10.1155/2018/5234943

Meccariello R, Santoro A, D'Angelo S, Morrone R, Fasano S, Viggiano A, Pierantoni R (2020) The epigenetics of the endocannabinoid system. Int J Mol Sci 21(3):1113. https://doi.org/10.3390/IJMS21031113

Meeran MFN, al Taee H, Azimullah S, Tariq S, Adeghate E, Ojha S (2019) β-Caryophyllene, a natural bicyclic sesquiterpene attenuates doxorubicin-induced chronic cardiotoxicity via activation of myocardial cannabinoid type-2 (CB 2) receptors in rats. Chem Biol Interact 304:158–167. https://doi.org/10.1016/J.CBI.2019.02.028

Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A (2017) Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. Anesth Analg 125(5):1638–1652. https://doi.org/10.1213/ANE.0000000000002110

Mlost J, Bryk M, Starowicz K (2020) Cannabidiol for pain treatment: focus on pharmacology and mechanism of action. Int J Mol Sci 21(22):1–22. https://doi.org/10.3390/IJMS21228870

Mortimer TL, Mabin T, Engelbrecht AM (2019) Cannabinoids: the lows and the highs of chemotherapy-induced nausea and vomiting. Future Oncol 15(9):1035–1049. https://doi.org/10.2217/FON-2018-0530

Mukherjea D, Jajoo S, Whitworth C, Bunch JR, Turner JG, Rybak LP, Ramkumar V (2008) Short interfering RNA against transient receptor potential vanilloid 1 attenuates cisplatin-induced hearing loss in the rat. J Neurosci 28(49):13056–13065. https://doi.org/10.1523/JNEUROSCI.1307-08.2008

Mukhopadhyay P, Bátkai S, Rajesh M, Czifra N, Harvey-White J, Haskó G, Zsengeller Z, Gerard NP, Liaudet L, Kunos G, Pacher P (2007) Pharmacological inhibition of CB1 cannabinoid receptor protects against doxorubicin-induced cardiotoxicity. J Am Coll Cardiol 50(6):528–536. https://doi.org/10.1016/J.JACC.2007.03.057

Mukhopadhyay P, Rajesh M, Pan H, Patel V, Mukhopadhyay B, Bátkai S, Gao B, Haskó G, Pacher P (2010) Cannabinoid-2 receptor limits inflammation, oxidative/nitrosative stress, and cell death in nephropathy. Free Radic Biol Med 48(3):457–467. https://doi.org/10.1016/J.FREERADBIOMED.2009.11.022

Mukhopadhyay P, Baggelaar M, Erdelyi K, Cao Z, Cinar R, Fezza F, Ignatowska-Janlowska B, Wilkerson J, van Gils N, Hansen T, Ruben M, Soethoudt M, Heitman L, Kunos G, Maccarrone M, Lichtman A, Pacher P, van der Stelt M (2016) The novel, orally available and peripherally restricted selective cannabinoid CB2 receptor agonist LEI-101 prevents cisplatin-induced nephrotoxicity. Br J Pharmacol 173(3):446–458. https://doi.org/10.1111/BPH.13338

Muller C, Morales P, Reggio PH (2019) Cannabinoid ligands targeting TRP channels. Front Mol Neurosci 11:487. https://doi.org/10.3389/FNMOL.2018.00487/BIBTEX

Naguib M, Diaz P, Xu JJ, Astruc-Diaz F, Craig S, Vivas-Mejia P, Brown DL (2008) MDA7: a novel selective agonist for CB 2 receptors that prevents allodynia in rat neuropathic pain models. Br J Pharmacol 155(7):1104–1116. https://doi.org/10.1038/bjp.2008.340

Naguib M, Xu JJ, Diaz P, Brown DL, Cogdell D, Bie B, Hu J, Craig S, Hittelman WN (2012) Prevention of paclitaxel-induced neuropathy through activation of the central cannabinoid type 2 receptor system. Anesth Analg 114(5):1104–1120. https://doi.org/10.1213/ANE.0b013e31824b0191

Nealon CM, Henderson-Redmond AN, Hale DE, Morgan DJ (2019) Tolerance to WIN55,212-2 is delayed in desensitization-resistant S426A/S430A mice. Neuropharmacology 148:151–159. https://doi.org/10.1016/j.neuropharm.2018.12.026

Niaz K, Khan F, Maqbool F, Momtaz S, Hassan F, Nobakht-Haghighi N, Rahimifard M, Abdollahi M (2017) Endo-cannabinoids system and the toxicity of cannabinoids with a biotechnological approach. EXCLI J 16:688. https://doi.org/10.17179/EXCLI2017-257

O'Brien K (2022) Cannabidiol (CBD) in cancer management. Cancers 14(4):885. https://doi.org/10.3390/CANCERS14040885

Ostadhadi S, Rahmatollahi M, Dehpour AR, Rahimian R (2015) Therapeutic potential of cannabinoids in counteracting chemotherapy-induced adverse effects: an exploratory review. Phytother Res 29(3):332–338. https://doi.org/10.1002/PTR.5265

Pagano C, Navarra G, Coppola L, Avilia G, Bifulco M, Laezza C (2022) Cannabinoids: therapeutic use in clinical practice. Int J Mol Sci 23(6):3344. https://doi.org/10.3390/IJMS23063344

Pan H, Mukhopadhyay P, Rajesh M, Patel V, Mukhopadhyay B, Gao B, Haskó G, Pacher P (2009) Cannabidiol attenuates cisplatin-induced nephrotoxicity by decreasing oxidative/nitrosative stress, inflammation, and cell death. J Pharmacol Exp Ther 328(3):708–714. https://doi.org/10.1124/JPET.108.147181

Parlar A, Arslan SO, Yumrutas O, Elibol E, Yalcin A, Uckardes F, Aydin H, Dogan MF, Kayhan Kustepe E, Ozer MK (2021) Effects of cannabinoid receptor 2 synthetic agonist, AM1241, on bleomycin induced pulmonary fibrosis. Biotech Histochem 96(1):48–59. https://doi.org/10.1080/10520295.2020.1758343

Pascual D, Goicoechea C, Suardíaz M, Martín MI (2005) A cannabinoid agonist, WIN 55,212-2, reduces neuropathic nociception induced by paclitaxel in rats. Pain 118(1–2):23–34. https://doi.org/10.1016/j.pain.2005.07.008

Pendergraft WF, Herlitz LC, Thornley-Brown D, Rosner M, Niles JL (2014) Nephrotoxic effects of common and emerging drugs of abuse. Clin J Am Soc Nephrol 9(11):1996–2005. https://doi.org/10.2215/CJN.00360114

Peng J, Fan M, An C, Ni F, Huang W, Luo J (2022) A narrative review of molecular mechanism and therapeutic effect of cannabidiol (CBD). Basic Clin Pharmacol Toxicol 130(4):439–456. https://doi.org/10.1111/BCPT.13710

Prester, L., Mikolić, A., Jurič, A., Fuchs, N., Neuberg, M., Lucić Vrdoljak, A., & Brčić Karačonji, I. (2018). Effects of Δ9-tetrahydrocannabinol on irinotecan-induced clinical effects in rats. Chem Biol Interact, 294, 128–134. https://doi.org/10.1016/J.CBI.2018.08.009

Quintão NLM, Santin JR, Stoeberl LC, Corrêa TP, Melato J, Costa R (2019) Pharmacological treatment of chemotherapy-induced neuropathic pain: PPARγ agonists as a promising tool. In: Frontiers in neuroscience, vol 13, Issue AUG. Frontiers Media S.A. https://doi.org/10.3389/fnins.2019.00907

Rabgay K, Waranuch N, Chaiyakunapruk N, Sawangjit R, Ingkaninan K, Dilokthornsakul P (2020) The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: a systematic review and network meta-analysis. J Am Pharm Assoc 60(1):225–234. e6. https://doi.org/10.1016/J.JAPH.2019.07.015

Rahmatollahi M, Baram SM, Rahimian R, Saeedi Saravi SS, Dehpour AR (2016) Peroxisome proliferator-activated receptor-α inhibition protects against doxorubicin-induced cardiotoxicity in mice. Cardiovasc Toxicol 16(3):244–250. https://doi.org/10.1007/S12012-015-9332-0

Rahn EJ, Makriyannis A, Hohmann AG (2007) Activation of cannabinoid CB 1 and CB 2 receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. Br J Pharmacol 152(5):765–777. https://doi.org/10.1038/sj.bjp.0707333

Rahn EJ, Zvonok AM, Thakur GA, Khanolkar AD, Makriyannis A, Hohmann AG (2008) Selective activation of cannabinoid CB2 receptors suppresses neuropathic nociception induced by treatment with the chemotherapeutic agent paclitaxel in rats. J Pharmacol Exp Ther 327(2):584–591. https://doi.org/10.1124/jpet.108.141994

Rahn EJ, Deng L, Thakur GA, Vemuri K, Zvonok AM, Lai YY, Makriyannis A, Hohmann AG (2014) Prophylactic cannabinoid administration blocks the development of paclitaxel-induced neuropathic nociception during analgesic treatment and following cessation of drug delivery. Mol Pain 10(1):1744-8069-10-27. https://doi.org/10.1186/1744-8069-10-27

Razvi Y, Chan S, McFarlane T, McKenzie E, Zaki P, DeAngelis C, Pidduck W, Bushehri A, Chow E, Jerzak KJ (2019) ASCO, NCCN, MASCC/ESMO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients. Support Care Cancer 27(1):87–95. https://doi.org/10.1007/S00520-018-4464-Y/TABLES/4

Ritter JK, Li G, Xia M, Boini K (2016) Anandamide and its metabolites: what are their roles in the kidney? Front Biosci (Schol Ed) 8(2):264. https://doi.org/10.2741/S461

Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, Clark-Snow RA, Dupuis LL, Einhorn LH, Feyer P, Hesketh PJ, Jordan K, Olver I, Rapoport BL, Roscoe J, Ruhlmann CH, Walsh D, Warr D, van der Wetering M, on behalf of the participants of the MASCC/ESMO Consensus Conference Copenhagen (2016) 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 27(suppl 5):v119–v133. https://doi.org/10.1093/ANNONC/MDW270

Scherma M, Masia P, Satta V, Fratta W, Fadda P, Tanda G (2018) Brain activity of anandamide: a rewarding bliss? Acta Pharmacologica Sinica 40(3):309–323. https://doi.org/10.1038/s41401-018-0075-x

Schlicker E, Kathmann M (2001) Modulation of transmitter release via presynaptic cannabinoid receptors. Trends Pharmacol Sci 22(11):565–572. https://doi.org/10.1016/S0165-6147(00)01805-8

Sexton M, Garcia JM, Jatoi A, Clark CS, Wallace MS (2021) The management of cancer symptoms and treatment-induced side effects with Cannabis or cannabinoids. J Natl Cancer Inst Monogr 2021(58):86–98. https://doi.org/10.1093/JNCIMONOGRAPHS/LGAB011

Slivicki RA, Xu Z, Kulkarni PM, Pertwee RG, Mackie K, Thakur GA, Hohmann AG (2018) Positive allosteric modulation of cannabinoid receptor type 1 suppresses pathological pain without producing tolerance or dependence. Biol Psychiatry 84(10):722–733. https://doi.org/10.1016/j.biopsych.2017.06.032

Taylor BN, Mueller M, Sauls RS (2021) Cannabinoid antiemetic therapy. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK535430/

Vera G, Chiarlone A, Cabezos PA, Pascual D, Martín MI, Abalo R (2007) WIN 55,212-2 prevents mechanical allodynia but not alterations in feeding behaviour induced by chronic cisplatin in the rat. Life Sci 81(6):468–479. https://doi.org/10.1016/J.LFS.2007.06.012

Vera G, Cabezos PA, Martín MI, Abalo R (2013) Characterization of cannabinoid-induced relief of neuropathic pain in a rat model of cisplatin-induced neuropathy. Pharmacol Biochem Behav 105:205–212. https://doi.org/10.1016/j.pbb.2013.02.008

Waissengrin B, Mirelman D, Pelles S, Bukstein F, Blumenthal DT, Wolf I, Geva R (2021) Effect of cannabis on oxaliplatin-induced peripheral neuropathy among oncology patients: a retrospective analysis. Ther Adv Med Oncol 13:175883592199020. https://doi.org/10.1177/1758835921990203

Walsh KB, McKinney AE, Holmes AE (2021) Minor cannabinoids: biosynthesis, molecular pharmacology and potential therapeutic uses. Front Pharmacol 12:3366. https://doi.org/10.3389/FPHAR.2021.777804/BIBTEX

Wang J, Wang Y, Tong M, Pan H, Li D (2019) Medical cannabinoids for cancer cachexia: A systematic review and meta-analysis. Biomed Res Int 2019. https://doi.org/10.1155/2019/2864384

Was H, Borkowska A, Bagues A, Tu L, Liu JYH, Lu Z, Rudd JA, Nurgali K, Abalo R (2022) Mechanisms of chemotherapy-induced neurotoxicity. Front Pharmacol 0:923. https://doi.org/10.3389/FPHAR.2022.750507

Whitcomb B, Lutman C, Pearl M, Medlin E, Prendergast E, Robison K, Burke W (2020) Use of cannabinoids in cancer patients: a Society of Gynecologic Oncology (SGO) clinical practice statement. Gynecol Oncol 157(2):307–311. https://doi.org/10.1016/J.YGYNO.2019.12.013

Wouters E, Walraed J, Banister SD, Stove CP (2019) Insights into biased signaling at cannabinoid receptors: synthetic cannabinoid receptor agonists. Biochem Pharmacol 169:113623. https://doi.org/10.1016/J.BCP.2019.08.025

Xu JJ, Diaz P, Bie B, Astruc-Diaz F, Wu J, Yang H, Brown DL, Naguib M (2014) Spinal gene expression profiling and pathways analysis of a CB2 agonist (MDA7)-targeted prevention of paclitaxel-induced neuropathy. Neuroscience 260:185–194. https://doi.org/10.1016/j.neuroscience.2013.12.028

Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J (2019) Mechanisms of chemotherapy-induced peripheral neuropathy. Int J Mol Sci 20(6). https://doi.org/10.3390/IJMS20061451

Zawatsky CN, Park JK, Abdalla J, Kunos G, Iyer MR, Cinar R (2021) Peripheral hybrid CB 1 R and iNOS antagonist MRI-1867 displays anti-fibrotic efficacy in bleomycin-induced skin fibrosis. Front Endocrinol 12. https://doi.org/10.3389/FENDO.2021.744857

Zou S, Kumar U (2018) Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci 19(3). https://doi.org/10.3390/IJMS19030833