FULL TITLE: **Cannabinoid drugs against chemotherapy-induced adverse effects: focus on nausea/vomiting, peripheral neuropathy and chemofog in preclinical animal models.**

SHORT TITLE: Cannabinoid drugs vs. chemotherapy.

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ABSTRACT

Although new drugs are being developed for cancer treatment, classical chemotherapeutic agents are still front-line therapies, despite their frequent association with severe side effects that can hamper their use. Cannabinoids may prevent or palliate some of these side effects. The aim of the present study is to review the basic research which has been conducted evaluating the effects of cannabinoid drugs in the treatment of three important side effects induced by classical chemotherapeutic agents: nausea and vomiting, neuropathic pain and cognitive impairment. Several published studies have demonstrated that cannabinoids are useful in preventing and reducing the nausea, vomits and neuropathy induced by different chemotherapy regimens, though other side effects can occur, such as a reduction of gastrointestinal motility, along with psychotropic effects when using centrally-acting cannabinoids. Thus, peripherally-acting cannabinoids and new pharmacological options are being investigated, such as allosteric or biased agonists. Additionally, due to the increase in the survival of cancer patients there are emerging data that demonstrate an important cognitive deterioration due to chemotherapy, and because the cannabinoid drugs have a neuroprotective effect, they could be useful in preventing chemotherapy-induced cognitive impairment (as demonstrated through studies in other neurological disorders), but this has not yet been tested. Thus, although cannabinoids seem a promising therapeutic approach in the treatment of different side effects induced by chemotherapeutic agents, future research will be necessary to find pharmacological options with a safer profile. Moreover, a new line of research awaits to be opened to elucidate their possible usefulness in preventing cognitive impairment.

KEYWORDS: Animal models; cannabinoid; chemotherapy; chemotherapy-induced cognitive impairment; chemotherapy-induced neuropathic pain; chemotherapy-induced nausea and vomiting; neuroinflammation; oxidative stress; pica.

ABBREVIATIONS

2-AG: 2-arachidonoylglycerol

5-HT: serotonin

AC: adenylyl cyclase

AD: Alzheimer's disease

AEA: anandamide (N-arachidonoyl-ethanolamine)

BBB: blood-brain barrier

BDNF: brain-derived neurotrophic factor

CBD: cannabidiol

CBDA: cannabidiolic acid

CFA: conditioned flavor avoidance

CIAE: chemotherapy-induced adverse effects

CICI: chemotherapy-induced cognitive impairment (chemofog or chemobrain)

CINP: Chemotherapy – induced neuropathic pain

CINV: Chemotherapy-induced nausea and vomiting

CNS: central nervous system

ECS: endogenous cannabinoid system

FAAH: fatty acid amide hydrolase

MAGL: monoacylglycerol lipase

NK_1: neurokinin 1

PAG: periaqueductal gray

PAM: Allosteric ligand positive

PD: Parkinson's disease

PEA: palmitoylethanolamide

PNS: the peripheral nervous system

ROS: reactive oxygen species

RNS: reactive nitrogen species

TBI: traumatic brain injury

Δ^9-THC: tetrahydrocannabinol

TRP: transient receptor potential

TRPV-1: TRP vanilloid 1

WIN: WIN 55,212-2

1. INTRODUCTION

Cancer is a disease in which some of the cells of the body proliferate uncontrollably and form *in situ* tumours or invade distant organs (metastasis). When at the *in-situ* stage, surgery may suffice to eliminate the tumour. However, late diagnosis is common and other treatments (i.e., radio and/or antineoplastic drug therapy) may be necessary, either to reduce the tumour size, or to kill any remaining cancerous cells at the site of the tumour after surgery and/or the metastatic cells. Although targeted therapy and immunotherapy (with a different and generally milder profile of side effects), are increasingly being applied, conventional standard-of-care (cytotoxic) chemotherapy is still used in everyday practice, also in combination with these newer treatments. Thus, chemotherapy-induced adverse effects (CIAE) deserves continuous attention (Magee et al., 2020; Kichloo et al., 2021; Yip and Papa, 2021).

With the high and increasing incidence and prevalence of cancer patients (Roser and Ritchie., 2019; WHO, 2020), it is important to find new efficient and safe therapies that may prevent the development of CIAE as common as nausea and vomiting or neuropathic pain, both of which frequently occur during anticancer treatment cycles. Furthermore, there is an urgent need to address the possible sequelae that the treatments applied to fight cancer may provoke, particularly those affecting both the peripheral and the central nervous systems (PNS and CNS, respectively), that may be relatively long-lasting and affect the quality of life of cancer survivors (Nurgali et al., 2018).

One possible strategy to counteract at least some of the adverse effects associated with cancer chemotherapy involves the use of drugs capable of activating the endogenous cannabinoid or endocannabinoid system (ECS). Interestingly, although the known psychoactive effects of cannabis derivatives have traditionally limited the development of cannabinoid-based medicines, new molecules devoid of those effects are increasingly being tested. Cannabinoid-based medicines are already clinically available to treat chemotherapy-induced nausea and vomiting (CINV), but despite their positive results in multiple preclinical studies, no cannabinoid drug has been approved for the treatment of chemotherapy-induced neuropathic pain (CINP). Furthermore, although cannabinoids have been demonstrated to exert neuroprotective actions in a number of conditions which cause damage to the brain and cognitive impairment, to our knowledge, no study so far has evaluated their therapeutic potential in this kind of brain functional alterations associated with chemotherapy.

After a brief overview of the pharmacology of cannabinoids and the endocannabinoid system, the present review summarizes the available information regarding the possible beneficial effects of cannabinoids in the context of CIAE, namely nausea and/or vomiting, neuropathic pain and cognitive impairment. To evaluate new cannabinoid-based strategies able to alleviate or, even better, prevent the development of these CIAE, adequate preclinical models are essential. Thus, for each one of the mentioned adverse effects, we will describe first the available models and the parameters that need to be studied, particularly those affecting behaviour. Finally, the difficulties and opportunities for a holistic approach to the problem will be discussed.

2. PHARMACOLOGY OF CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

The pharmacology of cannabinoids and the ECS has been recently reviewed by different authors (Hourani and Alexander, 2018; Martínez et al., 2020; Potts et al., 2020). We will only summarize the most relevant information to aid in the understanding of their potential role to counteract the CIAE reviewed here.

The ECS is composed of: (1) different endogenous cannabinoid agonists or endocannabinoids, of which the two most studied are anandamide (N-arachidonoyl-ethanolamine, AEA) and 2-arachidonoylglycerol (2-AG); (2) the receptors of these endogenous cannabinoids (i.e., the CB_1 and CB_2 receptors); and (3) the enzymes that are responsible for the biosynthesis of AEA and 2-AG, on one side, and their inactivation (i.e., fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively), on the other. In addition to CB_1 and CB_2 receptors, endocannabinoids may modulate other receptors and channels, including transient receptor potential (TRP) channels.

The CB_1 receptor is mainly found in the neurons and in microglia, astrocytes and oligodendrocytes of the CNS. These receptors are also localized in the PNS, including sympathetic nerve terminals, primary sensory neurons, and the enteric nervous system (ENS). CB_1 receptor localization is mainly presynaptic, and its activation inhibits the release of different neurotransmitters including gamma-amino butyric acid and glutamate in the CNS, or acetylcholine in the ENS. In contrast, the CB_2 receptor is mainly localized on immune cells and in both the CNS and peripheral tissues, at relatively low levels, at least under non-pathological conditions (Lutz, 2020).

Activation of cannabinoid receptors may lead to relevant side effects, depending on the situation. Importantly, the activation of the CB_1 receptor located in the CNS is responsible for most of the psychoactive side effects of cannabinoids, which include relaxation, euphoria, and disinhibition but also tolerance and addiction (Luethi and Liechti, 2020). These effects may be considered desirable or not, depending on the situation. In laboratory rats and mice, centrally-acting CB_1 cannabinoid receptor agonists typically induce a set of four responses, known as the cannabinoid tetrad, which is used in the screening of these drugs: hypothermia, hypolocomotion, analgesia and catalepsy (Howlett et al., 2002). Generally, aiming for CB_2 receptor or developing peripherally acting cannabinoids that do not cross the blood-brain barrier (BBB) are interesting strategies for the development of new pharmacological drugs to address peripheral disorders. However, recent literature supports the involvement of CB_2 receptors in cannabinoid-induced catalepsy and analgesia (Liu et al., 2017), alerting about the need to check for typical psychoactive effects of any cannabinoid-type drug using the tetrad.

In an attempt to modulate the ECS, different strategies exist. For example, inhibitors of the enzymes that metabolize endocannabinoids (FAAH and MAGL) may be used in order to maintain elevated concentrations of these endocannabinoid agonists in the synaptic cleft, or cannabinoid agonists may be used to directly activate cannabinoid receptors. In this sense, synthetic cannabinoid agonists, typically full agonists, were first developed in the 1970s (Potts et al., 2020). Cannabinoid agonists have been classified as (Howlett et al., 2002):

(1) Classical cannabinoids: these are ABC-tricyclic dibenzopyran derivatives, found naturally in the *Cannabis sativa* plant (phytocannabinoids), like Δ^9-tetrahydrocannabinol (Δ^9-THC), or their synthetic analogues.

(2) Nonclassical cannabinoids: molecules which lack the dihydropyran ring of Δ^9-THC; these were synthetized by researchers at Pfizer (such as CP-55940).

(3) Aminoalkyndoles: structurally, these compounds are not similar to classical cannabinoids; they were obtained by researchers at Sterling Winthrop when synthetizing analogues of pravadoline, and WIN 55,212-2 (WIN) is the most studied compound of this group.

(4) Eicosanoids: endogenous cannabinoids are included in this group; of these, the most frequently studied are AEA and 2-AG.

Of all phytocannabinoids, Δ^9-THC and cannabidiol (CBD) are the most studied. Δ^9-THC is the major psychoactive constituent of *C. sativa*. It binds with a similar affinity to CB_1 and CB_2 receptors, and is a partial agonist for both cannabinoid receptors, although with less intrinsic activity at CB_2 when compared to CB_1 receptor (Howlett et al., 2002). On the other hand, CBD lacks addictive properties and euphoric effects. From a pharmacodynamic point of view, CBD has numerous targets. In a recent review, there have been described 76 different enzymes, ionotropic and metabotropic receptors with which CBD can interact (Mlost et al., 2020). Amongst these, CBD has a low affinity for cannabinoid receptors. At present, there is one cannabinoid-based medicine commercialized, nabiximols (Sativex®), which contains Δ^9-THC and CBD in equal amounts and has been approved in several countries for the treatment of spasticity in multiple sclerosis patients (Syed et al., 2014) .

Interestingly, in recent years, research on allosteric ligands and biased agonism is being carried out. The International Union of Basic and Clinical Pharmacology (IUPHAR) defines an allosteric site as a "binding site on a receptor macromolecule that is non overlapping and spatially distinct from, but conformationally linked to, the orthosteric binding site" (Neubig et al., 2003). The binding sites of endogenous ligands at G protein-coupled receptors, including cannabinoid receptors, have been referred to as orthosteric, whereas binding sites that modulate orthosteric ligand activity have been called allosteric. Allosteric ligands can modulate affinity and efficacy of orthosteric ligands and are classified as positive (PAM), negative or neutral. At low doses (in the nanomolar range), CBD has been shown to antagonize the effect of orthostheric cannabinoid agonists through a negative allosteric modulation of the cannabinoid receptors (for review, see Mlost et al., 2020). Additionally, it has been shown to act as a PAM for the serotonin 5-HT_{1A} receptor and to interact with the TRP vanilloid 1 (TRPV-1) and 4 (TRPV-4) or TRP ankyrin 1 (TRPA-1) channels (Martínez et al., 2020).

Although both CB_1 and CB_2 receptors bind to $G\alpha_i$-type G protein, CB_1 is a more promiscuous receptor, binding also to $G\alpha_s$ and $G\alpha_q$ proteins. After orthostheric activation, cannabinoid receptors couple to $G\alpha_i$ protein, inhibiting adenylyl cyclase and activating mitogen-activated protein kinase and extracellular signal-regulated kinases 1 and 2. In addition, the Gβγ subunit activates inward rectifying potassium channels and inhibits voltage-dependent calcium channels. Once G proteins are activated, serines and threonines from the cytoplasmic region of the receptor can be phosphorylated by GPCR kinases, leading to β-arrestin recruitment, which will be involved in GPCR desensitization and internalization (for review see Morales et al., 2018). Some agonists, known as biased

ligands, can selectively activate G protein or β-arrestins. Additionally, biased agonism includes also compounds which can selectively activate one of the signalling pathways and act as an inverse agonist or antagonist for the other.

Finally, different antagonists have been used to block the effects of cannabinoid agonists on CB_1 or CB_2 receptors, as a way to identify the mechanisms involved. These are also used to test for the possible existence of physical dependence, which may be particularly important in the case of centrally-acting CB_1 receptor agonists. If physical dependence is developed in laboratory rodents after chronic administration of a cannabinoid agonist, the acute administration of the CB1 receptor antagonist at a high dose (i.e., rimonabant 10 mg/kg, known as the rimonabant challenge) will induce a series of behaviours (paw tremors, head shakes and scratching bouts) which are counted over a 30 minute period (Cook et al., 1998).

3. CANNABINOIDS AGAINST CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

3.1. Chemotherapy-induced nausea and vomiting

Nausea and vomiting constitute a defence system of the body to eliminate ingested toxic substances, although they can also be caused by different drugs (i.e., chemotherapy, anaesthesia) or diseases (i.e., cancer) (Horn, 2014; Sanger and Andrews, 2018). Nausea and vomiting are associated with physiological changes including stomach relaxation, tachygastria and dysrhythmia, tachycardia and elevated blood pressure, sweating, cutaneous vasoconstriction, salivation and increased plasma vasopressin (Stern et al., 2011; Koch and Hasler, 2016).

CINV are very prevalent among cancer patients under this kind of treatment, with rates reaching 60-80% (Adel, 2017; Natale, 2018). CINV affect the quality of life of the patients and their treatment outcomes (Darmani and Ray, 2009; Adel, 2017; Natale, 2018; Eliasen et al., 2020), for this reason it is necessary to prevent and treat these symptoms. There are five types of CINV, acute, delayed, breakthrough, refractory and anticipatory (Adel, 2017), but the most frequent and impactful for the patients probably are anticipatory, acute (when CINV occur in the first 24 hours after chemotherapy) and delayed (when CINV occur after those first 24 hours). Increased risk of CINV depends on the antitumoral drug and patient-related risk factors, such as age, gender and history of alcohol intake (Adel, 2017; Eliasen et al., 2020). Chemotherapy agents vary with respect to their ability to stimulate emesis, i.e., their emetogenic risk, which is influenced by the drug, dose, administration route, schedule, and the combination with other chemotherapy agents. Therefore, according to their potential to elicit CINV, chemotherapeutic drugs are classified as high (> 90 % of patients), moderate (30 - 90 % of patients) or low (< 30% of patients) risk (Adel, 2017).

To prevent CINV, it is necessary to use antiemetic drugs (Sugino and Janicki, 2015; Sanger and Andrews, 2018). Serotonin (5-HT) and 5-HT_3 receptors, on one hand, and substance P (SP) and neurokinin 1 (NK_1) receptors, on the other, are the main systems involved in acute and delayed CINV, respectively (Wickham, 2019). Indeed, since the introduction of antiemetics based on 5-HT_3 and NK_1 antagonists, CINV has been better controlled, but these drugs are more effective in treating vomiting than nausea (Uranga et al., 2018). Furthermore, all antiemetic drugs have their own adverse effects (i.e., 5-HT_3 antagonists, produce headache and gastrointestinal effects such as constipation,

and NK_1 antagonists, produce diarrhoea, nausea, fatigue, and hiccups, among others (Adel, 2017). Thus, new drugs with improved antiemetic/antinauseant efficacy and safety need to be developed.

Before being evaluated in clinical trials, drugs need to be studied in preclinical models, which are not always easy to develop. Nausea and vomiting involve multiple organs and systems, and the lack of a specific target organ makes it difficult to apply molecular techniques to develop new anti-emetics (Sanger and Andrews, 2018). Moreover, preclinical animal models of nausea are necessary to specifically evaluate antinausea compounds (Rock and Parker, 2016). However, developing effective pre-clinical models to study nausea has been particularly difficult because of subjectivity, and this may also explain why current drugs are not too efficacious against nausea, as compared with their effect against vomiting.

In the context of nausea and vomiting two main kinds of animal models need to be considered (Table 1): animals that vomit, such as dog, cat, *Suncus murinus*, and others, and animals that do not vomit, namely, rodents. Whereas in the first investigations, non-human primates and dogs were commonly used, in recent years these have been replaced by other animals also capable of vomiting, like ferrets. Although ferret and dog models of emesis have been shown to be truly predictive and relevant to humans (Du Sert et al., 2011, 2012), they are not available in most laboratories due to their elevated cost and more difficult management and accessibility. Thus, these models are generally restricted to the last preclinical phases of drug development or for evaluating particular pathophysiological aspects of nausea and vomiting in more detail.

Studies using small laboratory animals are more convenient for most laboratories and may be essential during the first preclinical phases of drug development. Animals with a small size offer the important advantage of a reduced maintenance cost. Musk shrew *(Suncus murinus*) and least shrew (*Cryptotis parva*) are animals capable of vomiting and are very convenient for the development of new antiemetics, since they are very sensitive to emetogenic stimuli and only need small amounts of drug because of their very small size (<100 g and 5 g, respectively) (Sanger and Andrews, 2018).

As shown in Table 1, in animals capable of vomiting, the parameters that are usually measured are retching (i.e., the number of rhythmic abdominal contractions and wide opening of the mouth with protrusion of the tongue), emesis (i.e., the number of forced expulsions of upper gastrointestinal contents, either solid or liquid), latency to first retching or vomiting, and emetic periods (sequence of contractions of the abdomen inducing an increase of abdominal pressure signals and expulsion of content). Other important behaviours measured in animal models are gaping (the rapid triangular opening of the mouth exposing the bottom teeth), conditioned flavour avoidance (CFA, the selective association between a flavour and the aversive effects of a drug), and conditioned gaping. Additionally, a visual analogue scale (VAS) can be applied to detect the presence and frequency of one or more of the following: salivation, lip licking, lethargy, restlessness or turning/circling behaviour, signalling that vomiting is imminent.

Rodents, despite being the mammals most frequently used in preclinical studies all over the world, due to their small size, easy handling and abundant knowledge of their anatomy, physiology and genetics, have an important drawback in the search for

antiemetics: they are not capable of vomiting. Hence, preclinical researchers in this area have used these animal models to develop indirect markers of nausea/vomiting (Table 1) such as: pica (the consumption of non-nutritive substances: kaolin clay, cage bedding…), lying on belly, facial expression alterations (similar to clinical evidence of nausea in humans (Yamamoto et al., 2017)), and even gastric dysmotility. Moreover, retching, CFA and conditioned gaping may also be measured in rodents, thus facilitating comparisons with animals able to vomit. Another parameter that is sometimes measured is forward locomotion (movement along the surface of the floor), but it is not specific for nausea. In contrast, the rat model of pica, although questioned by some authors (Goineau and Castagné, 2016), has been proposed as useful for the study of nausea, and it is considered truly predictive and relevant to humans (Du Sert et al., 2012).

In these regards, it is important to note that, in animal studies searching for antiemetic drugs, cisplatin is generally used as the emetogenic drug of reference, because it has a high-risk potential to elicit CINV, and it also elicits substantial acute and delayed pica in rodents (Cabezos et al., 2008, 2010). In contrast, antitumoral drugs like vincristine, which does not cause serious nausea and vomiting in the clinic, does not induce pica in the rat either (Yamamoto et al., 2007). However, both cisplatin and vincristine produce a significant delay in gastric emptying (Cabezos et al., 2008, 2010; Vera et al., 2017; López-Gómez et al., 2018), suggesting that, in contrast to pica, gastric dysmotility may not be a reliable indirect marker of nausea/vomiting in rodent studies, despite the demonstration of a temporal relationship between both parameters after both acute and repeated cisplatin administration (Cabezos et al., 2008, 2010). Instead, gastric

dysmotility might be more related with anorexia, another important side effect caused by chemotherapy and more universally-induced than nausea/vomiting/pica (Yamamoto et al., 2007).

3.2. Cannabinoids against chemotherapy-induced nausea and vomiting

Cannabinoids have been proposed as an alternative to prevent CINV (for review see Abalo et al., 2012; Uranga et al., 2018; Rock et al., 2021). Antiemetic guidelines are published by several major cancer organizations, but one notable difference among them is that only the National Comprehensive Cancer Network (NCCN) lists cannabinoids as an option for breakthrough/refractory CINV (for review see Adel, 2017).

The major psychoactive component of marijuana, Δ^9-THC, is an effective antiemetic and binds to CB_1 and CB_2 cannabinoid receptors (Natale, 2018; Richards, 2018). The activation of CB_1 receptors in the medulla inhibits gastrointestinal motor function and decreases the incidence of nausea and vomiting (Natale, 2018; Richards, 2018). Cannabinoids were investigated as antiemetics against CINV between 1970 and 1980: although superior to placebo, they were not used at that time because of secondary effects (mainly psychotropic) and the discovery of the more efficacious and better tolerated 5-HT_3 receptor antagonists (Sanger and Andrews, 2018). Currently, prescribed cannabinoids include nabilone capsules (Cesamet®), dronabinol capsules (Marinol®) and the oromucosal spray nabiximols (Sativex®) (Whiting et al., 2015; Adel, 2017; Taylor et al., 2021). Dronabinol and nabilone act as partial agonists of CB_1 and CB_2 receptors (Rock and Parker, 2016), and are generally accepted for the treatment of CINV (Wickham, 2019), particularly breakthrough or refractory types (Adel, 2017). Two early systematic

reviews comparing Δ^9-THC-derived drugs with older anti-emetics as first-line therapy demonstrated greater effectiveness of cannabinoids, especially in medium emetogenic chemotherapy regimens (Tramèr et al., 2001; Ben Amar, 2006). Further systematic reviews suggested that cannabinoids were associated with decreases of nausea and vomiting (Smith et al., 2015; Whiting et al., 2015), and these improvements were greater with dronabinol and nabiximols, although evidence was considered low in these analyses. One study (Meiri et al., 2007) compared oral doses of dronabinol with a modern treatment of dexamethasone and ondansetron, reporting superior efficacy of oral cannabinoid relative to the combined dexamethasone and ondansetron treatment, but comparisons with other antiemetics are lacking (Whiting et al., 2015; Chow et al., 2020).

Adverse effects have been demonstrated to occur after cannabinoid use in human studies. For example, dronabinol inhibited gastric emptying in females in a clinically relevant manner (Camilleri, 2018). In contrast, adverse effects had minor clinical significance in children receiving nabilone as part of their antiemetic regimen (Polito et al., 2018). Different authors suggest that gastroparesis (which has also been demonstrated for the synthetic cannabinoid WIN in experimental animals: see Abalo et al., 2009, 2010, 2011, 2012), reduces the antinauseant efficacy of cannabinoids. Thus, dronabinol is considered unlikely to be efficacious to treat nausea (Camilleri, 2018), and nabilone control of acute CINV is considered poor (Polito et al., 2018). Furthermore, the recently described cannabinoid hyperemesis syndrome is characterized by cyclic vomiting associated with heavy use of cannabis derivatives (see Richards, 2018 for review), suggesting an extremely complex interaction of cannabinoids with the

mechanisms underlying gastric motor function and nausea/vomiting, which warrants further investigation.

However, in everyday practice, the main drawback for the clinical use of cannabinoids is their psychoactive effects, and, therefore, the non-psychoactive phytocannabinoids offer a safer alternative (Martínez et al., 2020; Rock et al., 2021). Cannabidiol suppresses nausea and vomiting in different animal models (Parker et al., 2011; Turgeman and Bar-Sela, 2019), probably via the indirect activation of somatodendritic 5-HT_{1A} receptors in the dorsal raphe nucleus, which reduces the release of 5-HT in terminal forebrain regions (Martínez et al., 2020). The combination of CBD with Δ^9-THC (i.e., nabiximols, Sativex®) decreases nausea and vomiting, although further clinical investigation is necessary (Grimison et al., 2020; Martínez et al., 2020). Moreover, clinical experience has shown that there are significant inter-individual gene-based differences in the occurrence of CINV among cancer patients and the response to antiemetics, including cannabinoids (Eliasen et al., 2020). For example, in individuals carrying genetic variants associated with diminished CYP2C9 gene function, dronabinol may accumulate due to reduced metabolism, potentially increasing exposure (and the risk for adverse effects) by 2 to 3 fold (Dean and Kane, 2020). More studies focused on genetic polymorphisms will certainly provide new and important information about CINV that will be helpful in order to implement a better targeted therapy. Furthermore, the comparison of cannabinoids with newer antiemetics is an important but underdeveloped area of investigation, as is the study of the potential advantage of smoked marijuana in treating CINV (Turgeman and Bar-Sela, 2019).

As mentioned above, cannabinoids are an attractive alternative to prevent CINV, despite the adverse effects shown in some recent studies and meta-analyses (Camilleri, 2018; Polito et al., 2018; Uranga et al., 2018). However, studies of cannabinoid effects in preclinical models are relatively scarce. Table 2 summarizes the studies that have focused on the activity of cannabinoids to counteract the effects of chemotherapy agents against nausea and vomiting in animals capable of vomiting, whereas table 3 shows the studies performed using cannabinoids in rodents treated with antitumoral drugs and analysing indirect markers of nausea/vomiting.

Thus, in animals capable of vomiting, Δ^9-THC, WIN and CP-55940 were effective in reducing CINV (table 2). Curiously, nabilone was effective in cats (London et al., 1979), but not in dogs (Gylys et al., 1979), suggesting that it is necessary to investigate the effect of cannabinoids in different animal species. In ferrets, agonists of CB_1, CB_2 and TRPV-1 receptors showed antiemetic effects, whereas the non-psychoactive drugs, CBD, and its precursor, cannabidiolic acid, reduced emesis in musk shrews. Similarly, the endocannabinoids AEA and 2-AG reduced emesis, and the inhibitors of FAAH (URB597) and MAGL (JZL184) were able to reduce nausea and emesis without causing the typical CB_1-mediated central side effects (Hasenoehrl et al., 2016; Uranga et al., 2018).

The possible beneficial effects of cannabinoids against CINV have also been studied in animals that do not vomit, through the evaluation of indirect markers of nausea and vomiting after administration of antitumoral drugs. In these relatively scarce studies, some cannabinoids, such as Δ^9-THC or nabilone were shown to be able to reduce cyclophosphamide-induced CFA in rodents (Landauer et al., 1985; Limebeer and Parker,

1999), whereas other cannabinoid agonists, namely WIN, did not reduce pica or delayed gastric emptying in rats treated with cisplatin (Vera et al., 2007; Abalo et al., 2013). Interestingly, the CB_1 antagonist, AM251 partially prevented the effects of vincristine on gastric emptying (Vera et al., 2017; Uranga et al., 2018), suggesting a partial involvement of the ECS in the gastric dysmotility induced by this specific chemotherapeutic agent.

As a whole, the ECS seems to play a role in the mechanisms leading to nausea/vomiting, through a complex interaction. Further research is needed to understand and determine the molecular mechanisms involved, and to evaluate the possible usefulness of other drugs, like allosteric ligands and biased agonists.

4. CANNABINOIDS AND CHEMOTHERAPY-INDUCED NEUROPATHIC PAIN

4.1. Chemotherapy-induced neuropathic pain

CINP is a major side effect induced by different antitumoral drugs, which can be dose-limiting or even cause the cessation of chemotherapy (Quintão et al., 2019). This makes the prevention and treatment of neuropathic pain necessary. Neuropathic pain is due to the deafferentation of the nerve fibres causing pathological discharge of the nociceptors. Neuropathic symptoms are mainly characterized by pain, tingling, numbness and cold and heat sensitivity. Indeed, two features are important in neuropathic pain: allodynia and hyperalgesia, which are due to the decrease of the sensitivity threshold for non-noxious and noxious stimuli, respectively. Despite the importance of controlling CINP, the pharmacological options to treat it are scarce. The currently available pharmacological alternatives include anticonvulsant and

antidepressant drugs, but their efficacy and safety are not completely satisfactory (Kremer et al., 2016; Cavalli et al., 2019).

With the aim of finding new pharmacological targets and testing new drugs, preclinical models of chemotherapy have been developed in which the chemotherapy agent is administered to the experimental animals, mainly rats or mice. In this manner, the physiopathology of the induced neuropathy is replicated in the studied animals and a more translational approach can be used. As shown in table 4, depending on the antitumoral drug, different doses and administrating regimes have been used across the literature (for review, see Kumar et al., 2018).

In these models, the presence of CINP is classically evaluated using different approaches in which the behaviour of an animal is observed after the application of a determined mechanical, thermal, chemical or electrical stimulus. Perhaps, the most widely used tests are the von Frey test for mechanical stimuli, the Hargreaves' test and hot plate test for heat stimuli and the acetone evaporation test and cold plate test for cold stimuli. All these tests may be used to evaluate the presence of CINP, which would cause an increased responsiveness to the different stimuli, and also to test how drugs may modify CINP signs (drugs may alleviate these signs once established or may prevent their development). Importantly, in all tests that require the animal to move, it is imperative to bear in mind that motor activity may be supressed by the compound tested if it is psychoactive (as mentioned above for cannabinoids, which display hypolocomotion in the cannabinoid tetrad), i.e., a lack of movement should not be directly interpreted as a

lack of pain (specific tests for evaluating motor activity supression must be also performed).

In addition to using these classical tests, the analgesic effects of drugs may be analysed in the conditioned place preference paradigm. This is based on the assumption that pain relief (analgesia) is rewarding and that pairing pain relief with a distinctive environment (even if this is aversive) will increase the time spent in that environment (for review see Tappe-Theodor et al., 2019). However, when testing psychoactive agents, carefulness must be taken when analysing the results of this test: since the pairing procedure implies repetitive dosing, addiction development might contribute to the animal response to the psychoactive drug.

Finally, one of the characteristics of neuropathic pain is the presence of spontaneous pain (Vos et al., 1994; Colloca et al., 2017), which can be denoted by weight loss, reduced movement or sleep disturbances. This type of pain cannot be studied with the classical stimulus-response tests and needs of different behavioural assays as the grimace scales, weight bearing, sleep behaviour, measuring both audible and non-audible vocalizations or automated behavioural analysis (for review see: Deuis et al., 2017; Kumar et al., 2018).

4.2. Cannabinoids against chemotherapy-induced neuropathic pain

Many preclinical studies have demonstrated the potential of cannabinoid-based strategies to alleviate or even prevent CINP (Table 4). As explained below in more detail, these are based on two main facts: that cannabinoid receptors are expressed in anatomical structures and cells involved in pain transmission and modulation; that the

expression of cannabinoid receptors and the levels of endocannabinoids are modified during the development of neuropathic pain (of varied aetiology, Maldonado et al., 2016; Donvito et al., 2018; Hossain et al., 2020).

The CB_1 receptor is located in key areas for pain transmission and modulation. In the PNS, there is expression of CB_1 receptors in the peripheral sensory neurons and in the ganglia, while in the CNS it can be observed in the spinal cord, cortex, thalamus, amygdala and periaqueductal grey (PAG), among others. As mentioned above, activation of central CB_1 receptors is well recognized for inducing analgesia in control animals, when different stimuli (chemical, mechanical, thermal, electrical) are applied. Unfortunately, the activation of these central CB_1 receptors generally leads also to the typical cannabinoid psychoactive effects (tested in rodents as the cannabinoid tetrad, see above).

The CB_2 receptor is also expressed in the CNS in brain areas such as the cerebral cortex, amygdala, thalamus, PAG, dorsal horn, among others, and in the peripheral ganglia of the PNS. Although CB_2 receptor expression in the CNS is normally much lower than that of the CB_1 receptor, multiple pathological conditions can upregulate the expression of CB_2 receptors (Bie et al., 2018). This upregulation together with its high expression in cells of the immune system have made this receptor an important target for the treatment of neuropathic pain conditions with a neuroinflammatory/neuroimmune component. Additionally, it is generally considered that CB_2 receptor activation is not associated with the generation of psychoactive effects.

In contrast with other neuropathic conditions, only a few studies have assessed the levels of endocannabinoids in models of CINP, all involving cisplatin administration in male rodents (Khasabova et al., 2012, 2014; Guindon et al., 2013; Uhelski et al., 2015). In general, the main changes associated with cisplatin-induced neuropathic pain seem to be an increased expression of both AEA and 2-AG in the spinal cord, but reduced expression of these molecules in the dorsal root ganglia and the paw skin, suggesting that strategies aimed at increasing the peripheral levels of these endocannabinoids may be therapeutically useful, with relatively low risk of psychoactive effects (Masocha, 2018).

Thus, the most reasonable strategies to address CINP should involve an increase in the endocannabinoid signal. Indeed, the pharmacological approach most often evaluated in the treatment of peripheral neuropathy is the use of cannabinoid agonists, either natural or synthetic. Alternatively, the levels of endocannabinoids may be maintained elevated by the use of inhibitors of their metabolism or their transport from the synaptic cleft back into the cells. Finally, molecules aimed at modulating cannabinoid receptor activity through allosterism or biased agonism have also recently been tested in models of CINP. Research using all these strategies will be discussed below.

Regarding the phytocannabinoids, Δ^9-THC has been shown to be effective in reversing the mechanical and cold allodynia induced by paclitaxel and mechanical allodynia in animals treated with cisplatin (Harris et al., 2016) and vincristine, but curiously not with oxaliplatin (King et al., 2017). CBD, the other main (non-psychotropic) phytocannabinoid, was shown to have preventive effects in the mechanical and cold

allodynia induced by paclitaxel in female mice, and reversed the mechanical allodynia, which was sensitive to the serotoninergic 1A antagonist, but not the cannabinoid antagonists (Ward et al., 2011, 2014). Importantly, CBD did not induce conditioned place preference in C57Bl/6 mice using parameters that readily detect the conditioned rewarding properties of the same doses of morphine (Ward et al., 2014).

Numerous synthetic CB_1 and CB_2 agonists have been shown to have an antinociceptive effect in different CINP models. Possibly, the most studied compound in these models is WIN. It has high affinity for both cannabinoid receptors, with a moderate selectivity in favour of the CB_2 receptor (Howlett et al., 2002). WIN has shown to have an antinociceptive effect in cisplatin (Vera et al., 2013), paclitaxel (Pascual et al., 2005) and vincristine (Rahn et al., 2007) neuropathic pain models. Additionally, when administering the cannabinoid agonist at the same time as paclitaxel or cisplatin, WIN has been able to prevent the development of allodynia and hyperalgesia induced by these antitumoral agents (Vera et al., 2007; Burgos et al., 2012; Abalo et al., 2013; Rahn et al., 2014).

The antinociceptive effect of systemically administered WIN was reversed by CB_1 and CB_2 antagonists, in those studies in which antagonism was tested. Additionally, in the study performed by Rahn et al., 2014, mechanical and cold allodynia were prevented by WIN in the paclitaxel model; the preventive effect on mechanical allodynia was mediated through the CB_1 receptor, but not CB_2 receptor, and curiously, the preventive effect on cold allodynia was not mediated by either receptor. Although the authors could not administer both antagonists due to methodological issues, they state in their

discussion that the blockade of both receptors may be required to fully prevent the antiallodynic effect of WIN. This would be in accordance with the results obtained by Vera et al., 2013, who found that antagonism was more robust when both antagonists were jointly administered.

Those authors who additionally have performed the cannabinoid tetrad or at least some of its assays, have found other centrally mediated effects of acutely administered WIN at the studied doses, such as a decrease in the spontaneous locomotor activity, but not hypothermia or catalepsy (Pascual et al., 2005; Rahn et al., 2007; Vera et al., 2013), whilst Vera et al., 2007 did find a slight catalepsy, but only with the highest dose of WIN (2 mg/kg).

To avoid central effects, one of the possible approaches is to administer the cannabinoid agonist locally. Different results have been obtained. Thus, whilst intraplantar (i.pl.) administration of WIN did not induce analgesia in the paclitaxel (Pascual et al., 2005), or vincristine (Rahn et al., 2007) model, it did induce an antiallodynic effect in the neuropathy induced by cisplatin (Vera et al., 2013), only reversed through the CB_1 receptor, although selective CB_1 and CB_2 agonists did have an antiallodynic effect when i.pl. injected.

Another frequently used synthetic cannabinoid agonist is CP-55940, which binds to CB_1 and CB_2 receptors with similar affinity and behaves as a full agonist for both, being more potent than Δ^9-THC in the cannabinoid mouse tetrad (Howlett et al., 2002). This compound has been studied in the neuropathy induced by paclitaxel (Deng et al., 2015b) and cisplatin (Nealon et al., 2019), both studies performed in mice. CP-55940 reversed

the mechanical allodynia in both models and cold allodynia in the paclitaxel pain model (in cisplatin-treated animals, the effect of CP-55940 on cold allodynia was not tested). Though when chronically administrating CP-55940 at low doses (0.3 mg/kg), which do not induce effects in the cannabinoid tetrad, animals developed tolerance and dependence to the antinociceptive effect in a CB_1 dependent manner (Deng et al., 2015b). The mechanisms by which CP-55940 induces this tolerance to mechanical allodynia differ from those of WIN, because when tolerance to these two compounds were studied in mice, in which the serine residues at two putative phosphorylation sites necessary for desensitization were replaced for non-phosphorylatable alanines, tolerance to the effect of WIN was retarded when compared to CP-55940.

To avoid the central side effects observed in the cannabinoid tetrad and the appearance of tolerance and addiction, which are CB_1 dependent, several CB_2 selective agonists have been developed. Possibly the most studied compound is AM1710, a cannabilactone agonist displaying a ~54 – fold greater affinity for the CB_2 receptor (Khanolkar et al., 2007), which has been shown to be effective in reversing the neuropathic signs caused by cisplatin (Deng et al., 2012) and paclitaxel (Deng et al., 2012; Rahn et al., 2014; Deng et al., 2015a).

Because CB_1 receptor is much more abundant in the CNS, some studies have speculated that the therapeutic efficacy of CB_2 agonists is mediated via CB_1 receptor activation and that these ligands could also induce classical cannabinoid side effects. However, Deng et al., 2015 demonstrated that rats treated with high doses of AM1710 did not develop physical dependence (through the rimonabant challenge) (Deng et al., 2015a).

Other CB_2 receptor agonists have also been shown to be effective in reversing the mechanical allodynia induced by paclitaxel, such as AM1241 and AM1714 (Rahn et al., 2008), and MDA7, which can both suppress and prevent mechanical allodynia (Naguib et al., 2008, 2012; Xu et al., 2014). Additionally, AM1241 also was shown to suppress mechanical allodynia induced by vincristine (Rahn et al., 2007).

Several studies have evaluated the effect of FAAH (URB597 and URB937) and MAGL (JZL184 and MJN110) inhibitors in behavioural CINP responses. Thus, FAAH inhibitors reversed the mechanical and thermal hypersensitivity induced by cisplatin in both rats (Guindon et al., 2013) and mice (Khasabova et al., 2012). Similarly, MAGL inhibitors suppressed the mechanical and thermal hypersensitivity induced by cisplatin in rats (Guindon et al., 2013). The effects were sensitive to CB_1 and CB_2 receptor antagonists in rats (Guindon et al., 2013), but mediated only through the CB_1 receptors in the case of URB597-treated mice (Khasabova et al., 2012) who had received cisplatin. Interestingly, these inhibitors were also able to prevent the development of mechanical allodynia induced by cisplatin (Khasabova et al., 2012).

Additionally, vincristine and paclitaxel induced mechanical and cold allodynia and also mechanical hyperalgesia, which were reversed by the FAAH inhibitors (Caprioli et al., 2012; Slivicki et al., 2018). In the paclitaxel neuropathic pain model, MAGL inhibitors also induced an antiallodynic effect, mediated through both the CB_1 and CB_2 receptors (Curry et al., 2018). Curiously, the antiallodynic effect of the MAGL inhibitor JZL184 in paclitaxel-treated animals was dependent on both dose and pattern of administration, with the low doses being effective only when chronically administered, and higher doses

being also effective after acute administration. However, tolerance developed after chronic administration of these higher doses. Additionally, place preference in the paclitaxel-treated mice was found with the MAGL inhibitor MJN110, but not in the control mice; the authors suggested that this effect could be related to the relief of affective or sensory aspects related to paclitaxel-induced nociception (Curry et al., 2018).

To our knowledge, the first study to test the effect of allosteric modulators on neuropathic pain induced by chemotherapy was published in 2018 by Slivicki et al. In this study, GAT211 (a CB_1 PAM) reversed the mechanical and cold allodynia induced by paclitaxel in a dose-dependent manner, without inducing motor incoordination, catalepsy or hypothermia nor physical dependence or tolerance after chronic administration. When co-administered with WIN (non-selective agonist), JZL184 (MAGL inhibitor) or URB597 (FAAH inhibitor), it had a synergic or additive effect in reversing both the mechanical and cold allodynia (Slivicki et al., 2018). One year later, Gado et al., 2019 synthetized a CB_2 receptor PAM (C2), which was shown to have antiallodynic efficacy in the cold allodynia induced by oxaliplatin in mice; additionally it presented a synergic effect with a MAGL inhibitor (Gado et al., 2019).

Finally, very few studies have been conducted with biased agonists in CINP. In 2018, Lin et al. studied the signalling activation of LY2828360 *in vitro* and its antinociceptive efficacy and capacity in attenuating morphine tolerance in a paclitaxel-induced pain model. They found that this compound was strongly biased toward $G_{i/o}$ protein signalling, with little effect on β-arrestin signalling. It suppressed paclitaxel-induced

mechanical and cold allodynia and, when administered chronically, it did not induce tolerance. Additionally, it prevented morphine tolerance, when it was administered consecutively for 12 days prior to morphine administration or concomitantly administered with morphine, and this effect was shown to be mediated through CB_2 receptors (Lin et al., 2018). Similarly, and in the same laboratory, the CB_2 agonist AM1710 delayed the development of tolerance to morphine alleviation of mechanical and cold allodynia in the paclitaxel-induced neuropathic pain model and attenuated the physical dependence to morphine (Li et al., 2019a).

5. CANNABINOIDS AND CHEMOTHERAPY-INDUCED COGNITIVE IMPAIRMENT

5.1. Chemotherapy-induced cognitive impairment

In recent years, and particularly associated with the increase of cancer patients' life expectancy, the occurrence of cancer treatment sequelae, including cognitive impairments, has received considerable attention. These impairments may occur not only during the pharmacological treatment with chemotherapy drugs, but also long after treatment has ceased, a phenomenon known as chemotherapy-induced cognitive impairment (CICI) or, in an abbreviate form, as chemofog or chemobrain (El-Agamy et al., 2019; Mounier et al., 2020; Torrente et al., 2020).

The extent to which these cognitive deficits are related to the antineoplastic treatment itself remains unclear. Several reports have found cognitive deficits prior to the start of the pharmacological treatment, associating these cognitive deficits mostly with cancer itself or even with anxiety and stress (Wefel et al., 2004; Hermelink et al., 2007, 2017).

Nevertheless, preclinical research has shown that chemotherapeutic agents such as oxaliplatin, paclitaxel, cyclophosphamide, methotrexate, 5-fluorouracil and doxorubicin can induce short- and long-term deleterious effects in working memory and fear and spatial learning in a great variety of rodent animal models, as summarized in Table 5.

The most popular behavioural test to analyse recognition memory is the Novel Object Recognition test. Although there are several versions and modified protocols, it consists of a training in which an animal explores two identical novel objects for a certain amount of time. Subsequently, and after a period in which the object memory is consolidated, animals are re-exposed to the same environment with two objects, one of them is a replica of the familiar object (the one explored during the training session) and the other is a novel object. Since rodents exhibit predilection to explore novel, non-threatening objects, they will explore the novel object during significantly more time than the familiar one (Cohen and Stackman, 2015).

Regarding spatial memory, the most used test is the Morris water maze (Morris, 1984). This apparatus consists of a circular pool filled with opaque water in which there is a hidden escape platform (Morris, 1984). During the training or acquisition session, an animal is free to swim until it learns how to escape by finding the hidden platform. Spatial learning occurs thanks to external cues placed in areas that the animal can see while swimming. After several acquisition trials, the platform is removed, and the animal is allowed to swim freely for a certain amount of time. Spatial memory is assessed by the time that the animal spends swimming in the quadrant of the pool where the platform was hidden (Morris, 1984; Brandeis et al., 1989; D'Hooge and De Deyn, 2001).

In addition, Morris water maze allows to analyse reversal learning, by placing the platform in a different quadrant; or even working memory when the platform is hidden in a different quadrant each day (Brandeis et al., 1989; D'Hooge and De Deyn, 2001).

Another test normally used to analyse spatial memory due to its simplicity is the T-maze (Patil et al., 2009). The T-maze is an alternation task comprised of a sample phase, in which the animal runs to one goal arm and a memory trace of this event is formed, and a choice phase, in which the animal has a choice between the sampled and unsampled arms. Rodents tend to choose the arm not visited before, reflecting this way memory of the first choice, phenomenon known as spontaneous behaviour (Lalonde, 2002; Deacon and Rawlins, 2006).

Finally, fear learning and memory behavioural tests are based on classical Pavlovian conditioning. One of the most common behavioural fear learning and memory tests used is the fear conditioning test paradigm, in which the exposure to an unconditioned stimulus (typically aversive) is associated with a conditioned neutral stimulus. By associative learning, rodents learn to predict adverse events and express a certain behaviour accordingly (Arakawa and Iguchi, 2018). Thus, re-exposure to the neutral stimulus will provoke in the animals a fear-related behaviour (freezing or darting) whose duration and frequency can be measured and used as an index of fear associative learning/memory.

In addition to these preclinical behavioural studies, over the years, neuroimaging reports have collected evidence of chemotherapy-related alterations of brain structure (Wefel and Schagen, 2012; Conroy et al., 2013; McDonald et al., 2013; Sleurs et al.,

2016). Thus, independently of the level of implication of the tumour in the cognitive deficits observed, it is clear that chronic treatments with chemotherapy drugs impair cognitive function.

Currently, there is a great number of chemotherapy drugs in the market, yet preclinical and clinical research on CICI has been conducted with only a few of them. Regarding the type of cancer, most studies have focused their attention on non-CNS cancers, mainly breast cancer patients (Wefel and Schagen, 2012). However, recent research has also studied CICI in patients with other malignancies, such as colorectal, testicular and lung cancers (Du et al., 2013; Aotani et al., 2016; Dwek et al., 2017; Zandbergen et al., 2019).

Although cognitive deficiencies have been observed in patients even 10 years after chemotherapy treatment cessation (de Ruiter et al., 2011), there is a negative correlation between the number of patients reporting CICI and time after treatment cessation, which suggests certain degree of recovery (Ahles et al., 2002; Wefel et al., 2010; Conroy et al., 2013; Nguyen and Ehrlich, 2020). Among the cognitive deficiencies, the most commonly reported are short-term, working and visuospatial memories, as well as, verbal ability, executive functions and attention span (Hodgson et al., 2013; Nelson and Suls, 2013; Lindner et al., 2014; Horowitz et al., 2018). However, these deficiencies are difficult to detect since many studies find that cognitive levels in these patients are at the lower end of the normal range of the population and there are no approved tests for CICI diagnosis (Horowitz et al., 2018; Nguyen and Ehrlich, 2020). Preclinical research has been successful in replicating short- and long-term deleterious

effects of several chemotherapy agents in working memory and fear and spatial memory in a great variety of rodent animal models (Table 5).

There are a great number of biological mechanisms that seem to be implicated in the cognitive deficits induced by chemotherapy agents, including: direct neurotoxic effects, impaired neurogenesis or increased death of nervous cells, white matter abnormalities, inflammatory responses, oxidative stress and even alterations in the levels of sex and stress hormones. All these mechanisms are common side effects of chemotherapy drugs and are able to alter memory and cognition (Sleurs et al., 2016; El-Agamy et al., 2019; Mounier et al., 2020; Nguyen and Ehrlich, 2020). Moreover, it is expected that each chemotherapy drug produces also its own set of effects (Nguyen and Ehrlich, 2020).

The current treatment for cognitive deficiencies in cancer patients involves physical activity, cognitive rehabilitation and cognitive-behavioural therapy (Kesler et al., 2013; Ferguson et al., 2014; El-Agamy et al., 2019; Fernandes, 2019). These therapies although effective, take a long time and, meanwhile, patient's quality of life remains affected. Among the possible pharmacological alternatives, cannabinoids have interesting properties that might be useful to treat or even prevent CICI, as discussed next.

5.2. Cannabinoids against chemotherapy-induced cognitive impairment

Cannabinoid agonists of CB_1 receptors, including phytocannabinoids such as THC, are known to impair memory by altering hippocampal plasticity (Schreiner and Dunn, 2012; Kutlu and Gould, 2016; Cohen and Weinstein, 2018). In fact, the memory impairments found in marijuana users are recognized from the 70s (Tart, 1970). Preclinical studies have shown that, in healthy individuals, cannabinoid drugs can have an impact in

different stages of memory formation by improving or impairing it (see Zanettini et al., 2011; Kruk-Slomka et al., 2016 for review). In fact, cannabinoid drugs can modulate working, spatial and emotional memory (Puighermanal et al., 2009; Llorente-Berzal et al., 2013, 2015; Galanopoulos et al., 2014; Morena and Campolongo, 2014; Morena et al., 2015).

Interestingly, in recent years, an increasing number of animal studies in Alzheimer's disease, a neuropathology with underlying biological mechanisms similar to those observed in CICI, have shown the ability of cannabinoid drugs to ameliorate or partially revert cognitive deficits related to this pathology (Scuderi et al., 2018; Crunfli et al., 2019; Li et al., 2019b). In particular, it has rendered especial attention the role of the ECS in modulating immune system homeostasis and the activity and expression of key enzymes involved in the synthesis of oxygen reactive species in the CNS (Tanasescu et al., 2013; Lipina and Hundal, 2016; Donvito et al., 2018; Gallelli et al., 2018; Almogi-Hazan and Or, 2020). Since, as stated above, two of the biological mechanisms involved in CICI are neuroinflammation and oxidative stress in the CNS (Sleurs et al., 2016; El-Agamy et al., 2019; Mounier et al., 2020; Nguyen and Ehrlich, 2020), we have focused our discussion on the potential neuroprotective effects of cannabinoid drugs against these processes involved in the cognitive deficits induced by chemotherapy drugs.

Cancer and chemotherapy treatment induce an immune dysregulation in the body through the release of pro-inflammatory mediators responsible for an inflammatory response (Mounier et al., 2020). The most common pro-inflammatory cytokines released during chemotherapy treatment are tumour necrosis factor alpha (TNFα) and

interleukins 1 (IL-1) and 6 (IL-6) (Sleurs et al., 2016; Mounier et al., 2020). These substances can be produced directly in the CNS or indirectly by activation of peripheral immune cells such as B cells, T cells, macrophages, mast cells, neutrophils, basophils, and eosinophils. These cells produce cytokines that, in a limited way, can cross the BBB. Yet, this flux of cytokines through the BBB alters its integrity leading to an increase in the levels of cytokines and chemotherapy drugs that can reach the CNS. This provokes a secondary, indirect inflammatory response, through the activation of astrocytes and microglia that secrete further cytokines (Nguyen and Ehrlich, 2020). There is a common consensus that chronic neuroinflammation is responsible for cognitive impairments in neuroinflammatory disorders and aging (Fourrier et al., 2019). Neuroinflammation usually leads to an impairment of neurogenesis and changes in the myelination processes (Mounier et al., 2020), which can be responsible for the changes of brain structure observed after chemotherapy (Wefel and Schagen, 2012; Conroy et al., 2013; McDonald et al., 2013; Sleurs et al., 2016). Pro-inflammatory cytokines can also induce epigenetic alterations, such as impaired DNA methylation and hydroxymethylation, histone modification, and non-coding RNA regulation (Wang et al., 2015). These epigenetic modifications lead to memory deficits and cognitive impairments. Finally, neuroinflammation can also induce hormonal changes driven by impairment of the hypothalamic-pituitary axis which can further affect cognitive function (Wang et al., 2015; Sleurs et al., 2016).

The ECS has been proposed as a key therapeutic target against neuroinflammation (Kleckner et al., 2019) and it can be useful in pathologic conditions in which neuroinflammation occurs alongside cognitive impairments. For instance, cannabinoid

drugs have shown efficacy in decreasing neuroinflammatory mediators and restoring cognitive functions in as different conditions as “HIV-associated neurocognitive disorder” (see Wu et al., 2019 for further information) or “cognitive disorder associated to nicotine withdrawal” (Saravia et al., 2016). This supports cannabinoid drugs as potential therapeutic tools for CICI. Indeed, several studies have analysed the neuroprotective actions of cannabinoid drugs in pathologies that occur with both, a neuroinflammatory response and cognitive impairments, but have different aetiologies, such as Parkinson’s disease (PD), Alzheimer’s disease (AD) and traumatic brain injury (TBI) (Schurman and Lichtman, 2017; Rodrigues et al., 2019; Uddin et al., 2020).

Oxidative stress is caused by an increased production of reactive oxygen and nitrogen species (ROS/RNS) and a decrease in their elimination (Lipina and Hundal, 2016; Umeno et al., 2017; Gallelli et al., 2018; Atalay et al., 2020; Mounier et al., 2020). Although ROS/RNS have several functions, including immune defence and second messenger behaviour in different signalling pathways, their intracellular accumulation can damage cellular lipids, proteins and DNA because of their high redox reactivity (Umeno et al., 2017; Gallelli et al., 2018; Atalay et al., 2020). Thus, oxidative stress can damage cellular membranes and impair mitochondrial functionality inducing a progressive degradation of cell function, that will inevitably lead to cell death (Lipina and Hundal, 2016). Chemotherapy agents such as methotrexate, cisplatin, doxorubicin, among others, are used in cancer patients due to their capacity to induce oxidative stress and the cell death of cancer cells which have a higher metabolic rate than non-cancerous cells. However, the oxidative stress induced by these compounds can also damage healthy cells of the CNS (Joshi et al., 2005; Kawai et al., 2006; Rajamani et al., 2006; Tangpong et al., 2007;

Liu et al., 2009). Interestingly, the concomitant use of antioxidant agents with chemotherapy drugs is related not only to a reduction of the oxidative stress (Uzar et al., 2006; Joshi et al., 2007; Gulec et al., 2013; Turan et al., 2014), but also to an improvement of cognitive function (Caron et al., 2009; Aluise et al., 2011; Winocur et al., 2011; Hayslip et al., 2015; Lomeli et al., 2017; Ramalingayya et al., 2017; Ali et al., 2020), indicating that there is a direct relation between oxidative stress and cognition (Newton et al., 2015).

Over the last years, a dependence relation between the ECS and the oxidative reactions that synthesize ROS/RNS has been demonstrated. Several reports have shown the ability of the ECS to modulate the activity and expression of enzymes implicated in their generation, such as NOX2 and NOX4, key enzymes for the generation of reactive species in cells of the CNS under pathophysiological conditions (Lipina and Hundal, 2016; Gallelli et al., 2018). Different cannabinoids and cannabinoid-like compounds have exerted direct or indirect antioxidant effects able to protect neurons and other cells in culture (Han et al., 2009; Jia et al., 2014; Lipina and Hundal, 2016; Gallelli et al., 2018). However, the beneficial or detrimental effects of the activation of cannabinoid receptors on the generation of ROS/RNS seems to depend on the specific cell type and the aetiology and stage of the disease causing the oxidative stress (Gallelli et al., 2018).

Oxidative stress can be found in a great number of diseases, including pathologies occurring with cognitive impairments such as AD and PD. In fact, it is possible to observe the presence of a great number of oxidative stress markers in the brain of pharmacological and genetic animal models of AD and PD, among others (Niedzielska et

al., 2016). Besides, ROS pathophysiology and oxidative stress can be used as biomarkers for the study of development and stage of AD and PD patients (see Umeno et al., 2017 for review). In pathophysiological conditions, the ECS is able to modulate redox homeostasis and ameliorate the oxidative stress induced by AD or PD (van der Stelt et al., 2006; Chung et al., 2011; Crunfli et al., 2019).

In addition to the cannabinoid receptor agonists, other cannabinoid-related compounds have attracted attention for their neuroprotective and antioxidant properties, like the endogenous lipid mediator palmitoylethanolamide (PEA) (Scuderi et al., 2018; Bronzuoli et al., 2018) and CBD (García-Arencibia et al., 2006; Esposito et al., 2007; Martín-Moreno et al., 2011; Atalay et al., 2020). Thus, these non-psychoactive compounds may represent and interesting strategy to reduce the impact of chemotherapy on cognition, as demonstrated for other conditions.

6. IN PERSPECTIVE: A HOLISTIC VIEW OF THE PROBLEM

In the previous sections, it has been shown that CINV, CINP and CICI are relevant problems that many cancer patients have to face at different stages of their disease and that cannabinoids are pharmacological strategies that may help avoid or reduce their impact on the patient's quality of life.

As explained above, CINV is a common adverse effect, very annoying for the patients, and even life-threatening sometimes. Whereas acute and delayed vomiting is generally well controlled with current antiemetics (5-HT_3 and NK_1 antagonists or combinations),

other types of vomiting and, particularly nausea, are not, and new therapies are constantly being searched for. In this context, preclinical research has been relatively slow, mainly due to the fact that rodents, which are the most universally used animal species in the laboratories, do not vomit and indirect markers of nausea/vomit or the use of species which can vomit (less accessible and generally more expensive) are needed. Importantly, cannabis derivatives have been empirically used by cancer patients undergoing chemotherapy and a few drugs have even been approved for clinical use, but only low-quality evidence has been demonstrated for their therapeutic potential in this context. These drugs seem to have a better profile for anticipatory nausea and vomiting but more robust data are needed.

Another important adverse effect induced by many antitumoral drugs which affects enormously the patient's quality of life is neuropathic pain. Targeting the ECS to treat the different neuropathic signs induced by antitumoral agents has been shown to be largely effective in preclinical models, including both alleviating and preventive capabilities. However, these interesting results have not yet led to the approval of any cannabinoid-based drug for clinical use as anti-neuropathic drugs, most likely because along the analgesic effect that non-selective cannabinoid agonists have demonstrated, also (unwanted) central side effects can appear. Therefore, CB_2 selective agonists or peripherally applied cannabinoids have been tested. Interestingly, in the past few years, efforts are being directed to the modulation of the cannabinoid system through allosteric and biased agonisms, which constitute a new promising alternative awaiting further evidence of increased efficacy and safety compared with more traditional strategies.

Finally, amongst CIAE, those affecting cognition and other brain functions are particularly worrying. The occurrence of CICI (chemobrain) has been demonstrated in both preclinical models and patients and different biological mechanisms may contribute. As shown above, the ECS is implicated in at least two of the biological mechanisms in which chemotherapeutic drugs are thought to induce CICI, i.e., neuroinflammation and oxidative stress (Boullon et al., 2021). Importantly, several reports have pointed out that pharmacological modulation of the ECS is able to reverse cognitive impairments in neuropathologies in which these mechanisms are involved, such as AD, PD and TBI. These results highlight the potential of cannabinoid-based therapies as an efficient strategy against cognitive deficits induced by chemotherapy agents in cancer patients, but, to our knowledge, this has never been specifically evaluated, either preclinically or clinically. Taking into account the neuroprotective effects displayed by cannabinoids, even at relatively low doses, in models of peripheral neuropathy induced by antitumoral drugs, it would not be surprising to find that similar neuroprotective effects might also occur in the brain. Thus, future studies will have to address if the concomitant administration of chemotherapy and cannabinoid drugs, particularly those devoid of psychoactive effects, like CB_2 agonists, CBD or PEA, is able to avoid cognitive malfunction without affecting anti-cancer efficacy, or to recover cognitive function in affected cancer survivors.

Even though the three types of CIAE described here may coexist in the same individual and cannabinoids might be useful to counteract all of them, even simultaneously in certain cases, practically no report has address this in a holistic manner, either in the preclinical or the clinical context. This may be due to two main reasons. The first one is

the fact that specific animal models, methods and techniques are needed to evaluate each one of these side effects and it is uncommon that a particular research group has the tools and expertise to study them all simultaneously. This as a general limitation of the preclinical studies described here and might also affect the clinical studies. Obviously, collaborative research may easily overcome these problems.

The second reason, though, is intrinsic to the specific antineoplastic drug, dosing and animal model needed to observe the desired effect. Thus, luckily, only a few drugs characteristically cause more than one of these effects. Among them, cisplatin is probably the most "versatile" drug for preclinical studies in this context, as it is the emetogenic drug of reference in the search for antiemetics (Table 1) and is well known also for its capability to induce neuropathic pain (Table 4). However, the studies of cognitive impairment using this drug are yet scarce (Table 5) (Perše, 2021). A second candidate could be cyclophosphamide, which has been proved to cause CICI in different cognitive tests (Table 5) and is also used to induce CINV (Table 1). However, this drug does not produce relevant neuropathic tactile pain (Table 4), although it is well known for causing interstitial cystitis and bladder pain syndrome (Taidi et al., 2019). An additional difficulty is that most research carried out to evaluate CINV is performed after a single (high) dose of the antitumoral drug, and effects are generally evaluated within a short time window (1-5 days after its administration), whereas CINP and CICI generally need repeated (but relatively low) doses and longer times to develop. Furthermore, CINV is generally studied in ferrets or shrews, capable of vomiting (Table 1, 2), whereas neuropathic pain is mainly tested in rodents, which do not vomit (although these animals display pica, gastric dysmotility and other indirect markers of nausea/vomiting,

Table 1, 3). Indeed, our studies are probably the only ones that have analysed in the same animals (rats) the co-occurrence of changes in food behaviour (pica, as an indirect marker of nausea), gastrointestinal dysmotility and/or peripheral neuropathy induced by repeated cisplatin (Cabezos et al., 2010). Unfortunately, we did not evaluate then the concomitant cognitive alterations that probably occurred, considering the available literature specific to CICI (Table 5). Furthermore, when cannabinoids were evaluated in our models to see if they were able to improve pica/gastric dysmotility and neuropathic pain, no central effects were evaluated, except for the cannabinoid tetrad (Vera et al., 2007; Abalo et al., 2013). Specific cognitive studies are yet to be performed in our model. Even more translatable results would be those describing the effects of cannabinoids on this triad of CIAE in animal models of cancer. This kind of studies, to the best of our knowledge, have never been performed.

Likewise, in the clinical context, the three types of CIAE may occur simultaneously in the patients, but specific studies of the three effects are unlikely to be performed. Moreover, to the best of our knowledge, clinical trials evaluating the effects of cannabinoids on the possibly concurrent three CIAE described here are lacking.

Since strategies aimed at addressing only one CIAE may negatively affect alleviation or prevention of the others, the optimal clinical management of patients requires a holistic view of the problem, through specific integrative (and collaborative) research efforts, most desirable, but still scarce or inexistent.

7. CONCLUSIONS

Cancer treatments are aggressive and induce adverse effects both during and after therapy. This is an important problem that needs to be addressed, both therapeutically and, whenever possible, prophylactically, particularly when it comes to chemotherapy-induced neurotoxicity, which may be long-lasting, both in the peripheral and central nervous system.

Altogether, the studies reviewed here suggest that cannabinoids may have a broad potential to counteract some of the most feared chemotherapy-induced adverse effects, namely, nausea/vomiting (CINV), neuropathic pain (CINP) and cognitive impairment (CICI) (Figure 1). However, the current level of scientific and clinical evidence is different for each of them. Thus, whereas clinical uses do exist for CINV, robust evidence is available for CINP only from preclinical models, and potential beneficial effects for CICI have only been hypothesized (based on data reporting the usefulness of cannabinoids on other disorders displaying similar cognitive alterations and mechanisms to those described so far for chemofog, for whose preclinical evaluation adequate models, such as those shown in table 5, can be used). Furthermore, how cannabinoids may simultaneously interfere with the development or severity of the three types of CIAE evaluated here, especially in the presence of cancer, is largely unknown.

We hope our review will motivate preclinical and clinical researchers to collaborate, by sharing their specific tools and expertise, in order to obtain robust scientific evidence that will pave the way to a more holistic and personalized approach to the patient.

FIGURE LEGEND

Figure 1. Schematic representation of the side effects induced by chemotherapy (nausea and vomiting, sensory neuropathy, and chemobrain) on the left, and the symptomatic relief of these symptoms by the administration of drugs which interfere with the endocannabinoid system at different anatomic sites on the right side.

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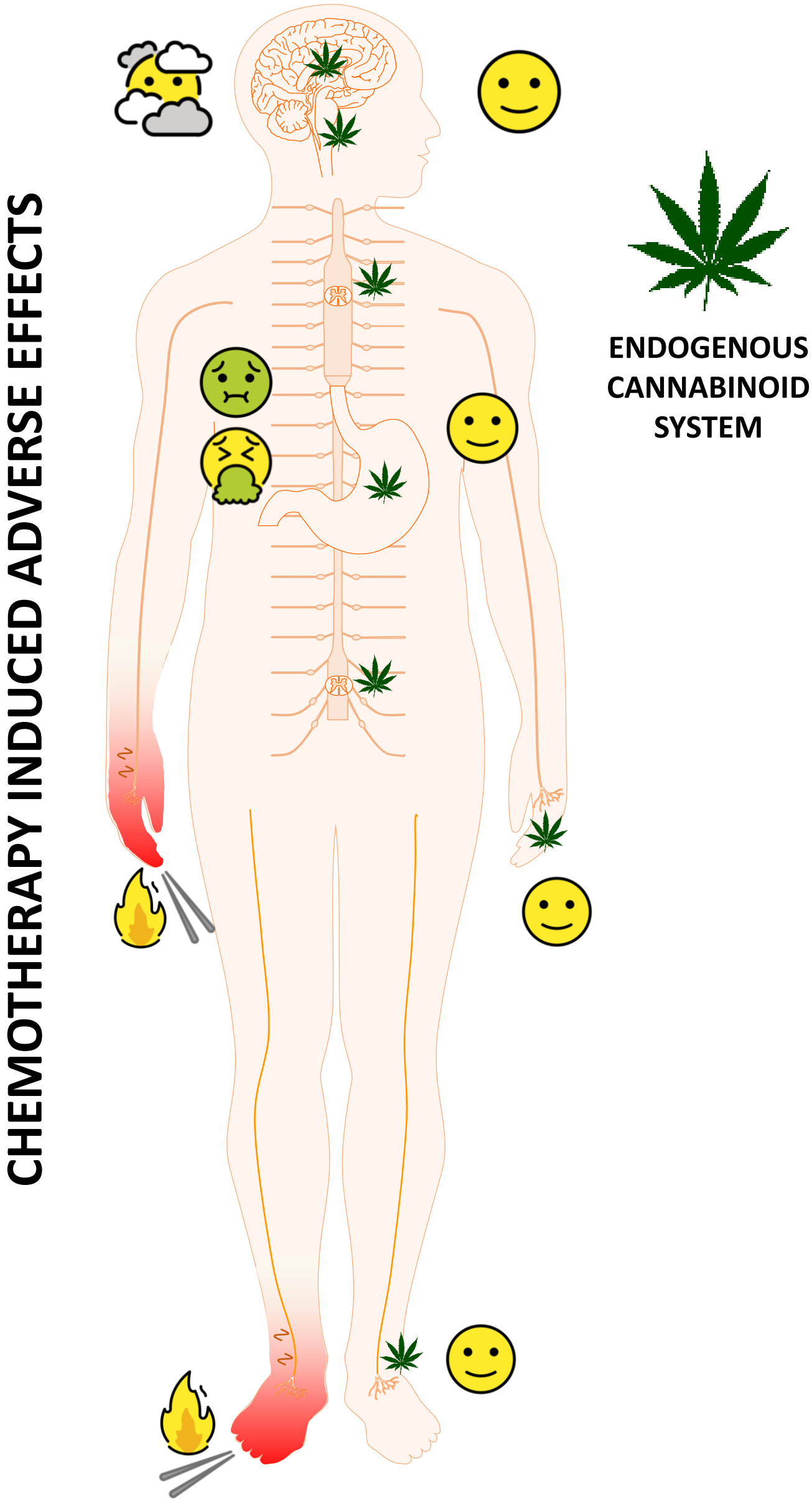
Figure


CHEMOTHERAPY INDUCED ADVERSE EFFECTS
ENDOGENOUS CANNABINOID SYSTEM

Figure

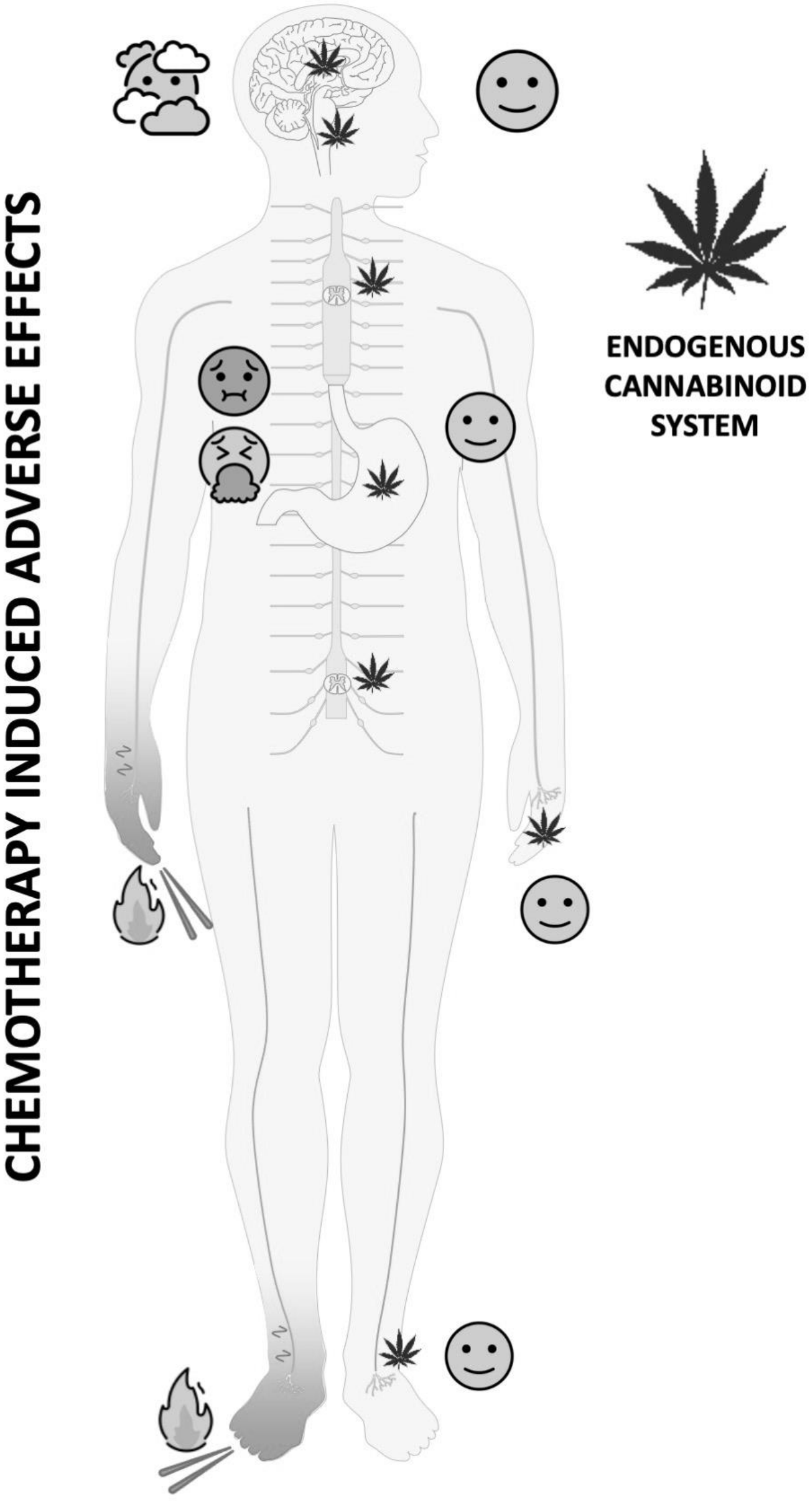

CHEMOTHERAPY INDUCED ADVERSE EFFECTS
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Table

Table 1. Animal models and parameters used to study nausea and vomiting.

	PARAMETER	ANIMAL MODEL AND ANTITUMORAL DRUG/S TESTED	COMMENTS
ANIMALS THAT VOMIT Pigeon *Cryptotis parva* (least shrew) *Suncus murinus* (musk shrew) Ferret Cat Dog Monkey	Latency to first retching or vomit	Pigeon, ferret, dog, monkey → cisplatin *Suncus murinus* → cisplatin, cyclophosphamide, 5-FU, methotrexate, mitomycin C, adriamycin, bleomycin Cat→ cyclophosphamide	**COMMON FEATURES:** - Emesis is easy to see. - Normally, animals can adapt to the place and during that time food is restricted. - In shrews, it is common to offer worms prior to drug administration. **PARTICULAR FEATURES:** **LATENCY:** Similar in humans, dogs and ferrets (Du Sert et al., 2012). **RETCHING**: In animals that do not vomit, it may resemble gaping **EMESIS:** Dog and ferrets require doses 20 times higher than humans for a comparable incidence of emesis (Du Sert et al., 2012). **EMETIC PERIODS:** Different authors use different times of observation.
	Retching	*Cryptotis parva*, *Suncus murinus*, ferret, cat, monkey → cisplatin	
	Emesis or vomit	Pigeon, *Cryptotis parva*, *Suncus murinus*, ferret, cat, dog, monkey → cisplatin	
	Emetic periods	Pigeon, ferret, cat, dog → cisplatin *Suncus murinus* → cisplatin, cyclophosphamide, 5-FU, methotrexate, mitomycin C, adriamycin, bleomycin	
	Gaping	-	- So far, only tested with LiCl in musk shrew (Parker and Kemp, 2001). - In animals which can vomit, it may resemble retching.
	CFA	Monkey → cyclophosphamide	- It is a measure of an animal's reluctance to consume flavors of foods that have been previously paired with nausea-inducing treatments. - Does not measure nausea directly, it relies upon conditioning. - Easy to see. - Easy to compare with animals that do not vomit.
	Conditioned gaping	-	- So far, only tested with LiCl in musk shrew (Parker et al., 2006)
	Pica	*Suncus murinus* → cisplatin	- Not found in this species, probably because it is capable of vomiting
	Gastric dysmotility	*Suncus murinus* → cisplatin	- Theoretically, easy to compare with animals that do not vomit. - Not seen in *Suncus murinus*. - It would be interesting to measure it with radiographic methods as in animals that do not vomit.
	VAS	Dog → cisplatin	- Standardized protocol to detect the presence and frequency of one or more of the following: salivation, lip licking, lethargy, restlessness or turning/circling behavior, signaling that vomiting is imminent. - It would be interesting to use this parameter in more animal models.
	Forward locomotion	-	- Not specific for nausea - So far, only tested with LiCl in musk shrew (Parker and Kemp, 2001)

ANIMALS THAT DO NOT VOMIT Hamster Mouse Rat	Monitoring facial expression	Rat → cisplatin	- Similar to humans. - It is necessary to perform more studies with other animal species.
	CFA	Hamster → cyclophosphamide Rat → cisplatin, cyclophosphamide	- It is a measure of an animal's reluctance to consume flavors of foods that have been previously paired with nausea-inducing treatments. - Does not measure nausea directly, it relies upon conditioning. - Easy to see. - Easy to compare with animals that do vomit.
	Conditioned gaping	Rat → cyclophosphamide	- Quite selective for conditioned nausea: only produced by emetogenic drugs and consistently prevented by anti-emetic drugs. - It represents an animal model of anticipatory nausea, because the animals are re-exposed to a context previously paired with nausea.
	Pica	Mouse → cisplatin Rat → cisplatin, cyclophosphamide	- It is the intake of non-nutritive substances in non-vomiting species; it may be induced by different emetogenic stimuli, and blocked by different anti-emetic drugs - Easy to work with. - Not reliably demonstrated in mouse. - It may be difficult to apply to a species when intake is small, and it can be produced by factors other than nausea, such as stress or pain (Sharkey et al., 2014). - The reliability of pica as a screening model for predicting nausea or vomiting in human has been questioned (Goineau and Castagné, 2016)
	Gastric dysmotility	Mouse → cisplatin Rat → cisplatin, vincristine	- X-Ray is a non-invasive method that allows for transit and morphological studies (stomach size). - Gastric emptying delay and gastric distension are both found after cisplatin (emetogenic, induces pica) and vincristine (non-emetogenic, does not induce pica), therefore, it is questionable as a screening method for predicting nausea or vomiting.
	Lying on belly	-	- So far, only tested with LiCl in rat (Bernstein et al., 1992; Tuerke et al., 2012). - Difficulty in discriminating from non-specific locomotor suppression (may not be specific for nausea).

Abbreviations: 5-FU, 5-fluorouracil; CFA, conditioned flavor avoidance; LiCl, lithium chloride; VAS, visual analogue scale.

Table

Table 2. Chemotherapy-induced nausea and vomiting (CINV): effects of cannabinoids in experimental animals capable of vomiting.

Animal	Antitumoral drug	Parameters	Cannabinoid agonist	Effects and mechanism	References
Pigeon (mixed breed), male and female	**Cisplatin** 10 mg/kg (iv)	Latency to first retching or vomiting; emesis	**HU-211** 1.5, 2, 2.5, 3 or 10 mg/kg (sc) **Δ^1-THC** 1.25, 2.50 or 5 mg/kg (sc)	HU-211: up to 90% protection against cisplatin-induced emesis. Δ^1-THC: no statistically significant activity against cisplatin, but up to 90% protection against $CuCl_2$-induced emesis.	Feigenbaum et al., 1989
	Cisplatin 7.5 mg/kg, (iv)	Latency to first retching or vomiting	**HU-210** 12.5, 25 or 50 µg/kg (sc)	HU-210 counteracted cisplatin-induced vomiting even at a low dose (12.5 µg/kg) not able to interfere with the animal normal behavioral pattern.	Ferrari et al., 1999
	Cisplatin 7 mg/kg (iv)	Latency to first retching or vomiting; emetic periods	**CS-HexFr** 5, 10 or 15 mg/kg	The n-hexane extract has been reported to contain the cannabis major active constituent, Δ^9- THC. CS-HexFr was effective to attenuate cisplatin-induced emesis.	Ullah et al., 2018
Cat (unselected as to sex)	**BCNU** 10 or 20 mg/kg (iv) **HN2** 5 mg/kg (iv) **Cisplatin** 5 or 10 mg/kg (iv)	Latency to first retching or vomiting; emetic periods	**Nabilone** 100 µg/kg (iv)	Nabilone protected against vomiting evoked by all of the anticancer drugs employed in this study.	London et al., 1979
	Cisplatin 3, 5, 7.5 or 10 mg/kg (iv)	Latency to first retching or vomiting; emetic periods	**Nabilone** 25, 50 or 100 µg/kg (iv) **N-methyl-levonantradol** 3, 7.75 or 20 µg/kg (iv)	N-methyl-levonantradol and nabilone provided dose-related protection from cisplatin emesis.	McCarthy LE, 1981
Dog	**Cisplatin** 3 mg/kg (iv)	Emesis	**Nabilone** 0.1 mg/kg (iv)	Nabilone failed to demonstrate any significant antiemetic activity.	Gylys et al., 1979
Ferret, male	**Cisplatin** 10 mg/kg (iv)	Retching	**Δ^9-THC** 0.5 to 1 mg/kg (ip)	Δ^9-THC dose-dependently reduced emesis induced by cisplatin. **SR-141716A** (CB_1 antagonist, 5 mg/kg, ip) reversed the antiemetic action of Δ^9-THC 1 mg/kg. **SR-144528** (CB_2 antagonist, 5 mg/kg, ip). SR-144528 failed to reverse the antiemetic action of Δ^9-THC 0.5 mg/kg, ip	Van Sickle et al., 2003
Least shrew, male and female	**Cisplatin** 20 mg/kg (ip)	Emesis	**Δ^9-THC** 1, 2.5, 5 or 10 mg/kg (ip)	Δ^9-THC prevented cisplatin-induced emesis in a dose-dependent manner; its antiemetic effect was maximal at 5 and 10 mg/kg. **SR141716A** (CB_1 antagonist, 1, 5 or 10 mg/kg, sc). SR-141716A reversed the antiemetic action of Δ^9-THC 5 mg/kg. **SR-144528** (CB_2 antagonist, 10 mg/kg, sc). SR-144528 failed to reverse the antiemetic action of Δ^9-THC 5 mg/kg.	Darmani, 2001a
			WIN 1, 2.5 or 5 mg/kg (ip)	WIN prevented cisplatin-induced emesis in a dose-dependent manner; its antiemetic effect was maximal at 5 mg/kg. **SR-141716A** (CB_1 antagonist, 0.25, 0.5 or 1 mg/kg, sc). Low doses of SR-141716A counteracted the antiemetic effect of WIN 5 mg/kg. **SR-144528** (CB_2 antagonist, 5 mg/kg, sc). SR-144528 failed to reverse the antiemetic action of WIN 5 mg/kg.	Darmani, 2001b

			CP-55940 0.025, 0.1 or 0.3 mg/kg (ip)	CP-55940 at 0.1–0.3 mg/kg reduced the vomiting frequency by 92–99%. **SR-141716A** (CB_1 antagonist, 1, 5 or 10 mg/kg, sc). SR-141716A dose-dependently counteracted the antiemetic action of CP-55940 0.3 mg/kg. **SR-144528** (CB_2 antagonist, 10 mg/kg, sc; then CP-55940 (0.3 mg/kg, ip) and cisplatin (20 mg/kg, ip)). SR-144528 failed to counter this antiemetic effect.	Darmani et al., 2003
		Emetic periods	**AA-5-HT** (selective FAAH inhibitor, 2.5 or 5 mg/kg, ip). **URB597** (Selective FAAH inhibitor, 5 or 10 mg/kg, ip). **OMDM1** (endocannabinoid uptake blocker, 5 mg/kg, ip). **VDM11** (endocannabinoid uptake blocker, 2.5, 5 or 10 mg/kg, ip).	All drugs failed to inhibit the emesis caused by cisplatin.	Darmani et al., 2005
		Emesis	**Δ^9-THC** 0.1, 0.25, 0.5, 1, 2.5, 5 or 10 mg/kg (ip)	Δ^9-THC attenuated both the vomiting frequency and the percentage of shrews vomiting, in a dose-dependent manner. Low doses of Δ^9-THC (0.25 and 0.5 mg/kg) combined with low doses of tropisetron (0.025 and 0.1 mg/kg) demonstrated greater antiemetic efficacy than either antagonist individually administered.	Wang et al., 2009
Least shrew, female	**Cisplatin** 10 mg/kg (ip)	Emesis	**Δ^9-THC** 2.5 mg/kg (ip)	Δ^9-THC prevented acute and delayed cisplatin-induced emesis. **SR-141716A** (CB_1 antagonist, 2 mg/kg) reversed the antiemetic effect of Δ^9-THC.	Ray et al., 2009
House musk shrew, male and female	**Cisplatin** 20 mg/kg (ip)	Latency to first retching or vomiting; retching; emesis	**Δ^9-THC** 1.25, 2.5, 5 or 10 mg/kg (ip) **CBD** 5 or 40 mg/kg (ip)	Δ^9-THC dose-dependently suppressed cisplatin-induced vomiting. Ondansetron (0.02 mg/kg) and Δ^9-THC (1.25 mg/kg) produced complete suppression of vomiting and retching when they were combined. CBD produced a biphasic effect with a low dose (5 mg/kg) suppressing, and a high dose (40 mg/kg) potentiating cisplatin-induced vomiting. Since CBD has a low affinity for the cannabinoid receptors, this anti-emetic effect does not appear to be mediated by CB_1 or CB_2 activity.	Kwiatkowska et al., 2004
		Emetic periods	**AEA** 5 mg/kg (ip) **URB597** (selective FAAH inhibitor, 0.9 mg/kg, ip).	URB597 and URB597 + AEA attenuated cisplatin-induced vomiting. AEA significantly reduce vomiting but only after pretreatment with the FAAH inhibitor.	Parker et al., 2009
		Emetic periods	**CBDA** 0.5 mg/kg (ip)	CBDA reduced cisplatin-induced emesis. CBDA can suppress signs of nausea and vomiting in a CB_1 receptor-independent manner	Bolognini et al., 2013
	Cisplatin 20 or 40 mg/kg (ip)	Emetic periods	**CBD** 5 or 10 mg/kg (sc)	CBD suppressed vomiting produced by 20 mg/kg of cisplatin, but not 40 mg/kg of cisplatin. The anti-nausea-like action of CBD is produced by its action on 5-HT_{1A} receptors (**WAY100135** 1 ml/kg, ip) in the dorsal raphe nucleus.	Rock et al., 2012

Abbreviations: AA-5-HT, N-arachidonoyl-serotonin; AEA, anandamide; BCNU, carmustine; CBD, cannabidiol; CBDA, cannabidiolic acid; CS-HexFr, *Cannabis sativa* n-hexane fraction; FAAH, fatty acid amide hydrolase; HN2, mechlorethamine; ip, intraperitoneal; iv, intravenous; sc, subcutaneous; Δ^9-THC, tetrahydrocannabinol; WIN, WIN 55,212-2.

Table

Table 3. Chemotherapy-induced nausea and vomiting (CINV): effects of cannabinoids in experimental animals not capable of vomiting.

Animal	Antitumoral Drug	Parameters	Cannabinoid agonist	Effects and mechanism	References
Mice (CD-1), male	**Cyclophosphamide** 30 or 60 mg/kg (ip)	**CFA**	**Δ^9-THC** 0.3 or 1 mg/kg (ip) **Nabilone** 0.01 or 0.03 mg/kg (ip) **Levonantradol** 0.03 or 0.06 mg/kg (ip)	Δ^9-THC and nabilone attenuated the taste aversion produced by the low dose of cyclophosphamide. Only THC attenuated the effect of the high dose of cyclophosphamide. Levonantradol did not attenuate the effects of either dose of cyclophosphamide.	Landauer et al., 1985
Rat (Sprague Dawley), male	**Cyclophosphamide** 40 mg/kg (ip)		**Δ^9-THC** 0.5 mg/kg (ip)	Δ^9-THC reduced nausea and conditioned nausea.	Limebeer and Parker, 1999
Rat (Wistar), male	**Cisplatin** 1 or 2 mg/kg (ip, once a week for 5 weeks)	**Pica**	**WIN** 1 or 2 mg/kg (ip, once per week for 5 weeks)	WIN did not prevent the reduction of food ingestion or the increase in kaolin intake (pica) associated with cisplatin administration.	Vera et al., 2007
	Cisplatin 2 mg/kg (ip, once a week for 4 weeks)	**Gastric dysmotility**	**WIN** 0.5 or 1 mg/kg (ip, once a week for 4 weeks)	WIN aggravated gastric dysmotility induced by cisplatin.	Abalo et al., 2013
	Vincristine 0.1 or 0.5 mg/kg (ip)			**AM251 1 mg/kg** (CB_1 antagonist, ip) reduced the effect of vincristine on gastric emptying and intestinal transit. **AM630 1 mg/kg** (CB_2 antagonist, ip) did not modify the effect of vincristine on gut motility. The antagonists were administered once (20 min before vincristine), twice (before and 24 h after vincristine), or thrice (before, 12 and 24 h after vincristine). The triple administration of AM251 was the most effective to counteract vincristine effect.	Vera et al., 2017

Abbreviations: CFA, conditioned flavor avoidance; ip, intraperitoneal; Δ9-THC, tetrahydrocannabinol; WIN, WIN 55,212-2.

Table

Table 4. Chemotherapy-induced neuropathic pain (CINP): effects of cannabinoids in rodent models.

Rodent model	Chemotherapeutic agent	Behavioral test	Cannabinoid drugs	Effects and mechanisms	References
Male Wistar rats	**Paclitaxel** 1 mg/kg (cumulative dose 4 mg/kg)	Hargreaves test Von Frey test *Cannabinoid tetrad*	**WIN** (ip. 1-2.5 mg/kg; i.pl. 50-250 µg) Antagonists: **SR 141617 A**	Paclitaxel induced heat and mechanical allodynia The ip. (but not i.pl.) administration of WIN induced an antiallodynic effect The systemic effect of WIN was reversed by the CB_1 antagonist	Pascual et al., 2005
Male Sprague–Dawley rats	**Vincristine** 0.1 mg/kg (cumulative dose 0.5 mg/kg)	Von Frey test Hargreaves test *Bar test*	**WIN** (0.75-2.5 mg/kg) **AM 1241** (10 mg/kg) Antagonists: **SR-141716 A** **SR-144528**	Vincristine induced mechanical allodynia (but not heat hyperalgesia) WIN and AM1241 induced an antiallodynic effect, though AM1241 had less efficacy. The effect of WIN was mediated through both receptors, whilst that of AM1241 was CB_2 mediated. Intrathecal administration of WIN increased mechanical withdrawal thresholds when compared to the vincristine treated group; the maximal reversion of the antinociceptive effect was achieved when both antagonists were used together. I.pl administration of WIN did not have an antinociceptive effect.	Rahn et al., 2007
Male Wistar rats	**Cisplatin** 1 and 2 mg/kg (cumulative dose 5-10 mg/kg)	Von Frey test *Cannabinoid tetrad*	**WIN** (ip. 1-2 mg/kg)	WIN prevented the allodynia induced by cisplatin. When administered at the highest doses, WIN induced catalepsy and analgesia in the plantar test when compared to vehicle treated group.	Vera et al., 2007
Male Sprague-Dawley rats	**Paclitaxel** 1mg/kg (cumulative dose 4 mg/kg)	Von Frey test	**MDA7** (10 mg/kg)	MDA7 suppressed mechanical allodynia induced by paclitaxel.	Naguib et al., 2008
Male Sprague-Dawley rats	**Paclitaxel** 2mg/kg (cumulative dose 8 mg/kg)	Von Frey test	**AM1241** (1-10 mg/kg) **AM1714** (1-10 mg/kg)	Both, AM1241 and AM1714 reversed the mechanical allodynia induced by paclitaxel	Rahn et al., 2008
Female C57Bl/6 mice	**Paclitaxel** 1–8 mg/kg (accumulated dose 4-32 mg/kg)	Acetone drop test Von Frey test	**Cannabidiol** (5-10 mg/kg)	Paclitaxel induced mechanical but not cold allodynia in males, whilst in females it induced both cold and mechanical allodynia Cannabidiol had a neuroprotective effect (preventive effect, days 1-14) in females both to the cold and mechanical allodynia	Ward et al., 2011
Male Sprague-Dawley rats	**Cisplatin** 3mg/kg (cumulative dose 12 mg/kg) **Paclitaxel** 2mg/kg (cumulative dose 8 mg/kg)	Von Frey test Acetone test	**AM1710** (0.1-5 mg/kg) Antagonists: **AM630** **AM251**	AM1710 suppressed the maintenance of mechanical and cold allodynia in the cisplatin and paclitaxel models. The anti-allodynic effects of AM1710 were blocked by the CB_2 antagonist AM630, but not the CB_1 antagonist AM251	Deng et al., 2012
Male Wistar rats	**Paclitaxel** 1 mg/kg (cumulative dose 4 mg/kg)	Von Frey test Hargreaves test	**WIN** (ip. 1 mg/kg)	WIN had a preventive effect on the neuropathy induced by paclitaxel. Repeated administration of minocycline (blocks microglial activation) also prevented the development of neuropathy in paclitaxel treated rats.	Burgos et al., 2012

		Locomotor activity			
Male C3H/HeN mice	**Cisplatin** 1 mg/kg (cumulative dose 7 mg/kg)	Von Frey test Hargreaves test	**AEA** **URB597** (ip. 9 µg; i.pl. 10 µg) Antagonist: **AM281**	Acute i.pl administration of AEA or URB597 reversed mechanical allodynia induced by cisplatin, mediated through the CB_1 receptor. Chronic ip. administration of URB597 reduced mechanical allodynia and heat hyperalgesia induced by cisplatin, also mediated through CB_1 receptor	Khasabova et al., 2012
Male Sprague-Dawley rats	**Vincristine** 0.15 mg/kg (cumulative dose 0.9 mg/kg)	Randall-Selitto test	**ST4070** (50 mg/kg)	ST4070 suppressed mechanical hyperalgesia induced by vincristine	Caprioli et al., 2012
Male Wistar rats	**Cisplatin** 2 mg/kg (cumulative dose 10 mg/kg)	Von Frey test Hargreaves test *Cannabinoid tetrad*	**WIN** **ACEA** **JWH133** (all agonists ip. 1 mg/kg; i.pl. 50 µg) Antagonists: **AM251** **SR144528**	The allodynic effect of cisplatin was reversed with WIN in a CB_1 and CB_2 dependent manner (antagonism was more robust when CB_2 and CB_1 antagonist were jointly administered). Each selective antagonist blocked the effect of the corresponding selective agonist when ip. administered. I.pl administration of CB_1 agonists increased the mechanical thresholds, which was a CB_1 and CB_2 mediated effect. Cannabinoid agonists at the doses administered did not induce cannabimimetic effects in the cannabinoid tetrad	Vera et al., 2013
Male Sprague-Dawley rats	**Cisplatin** 3 mg/kg (cumulative dose 9 mg/kg)	Von Frey test Acetone test Hargreaves test	**URB597** (0.1-1 mg/kg) **URB937** (0.1-1 mg/kg) **JZL184** (1-8 mg/kg) Antagonists: **AM251** **AM630**	Cisplatin did not alter paw withdrawal latencies to heat stimuli. URB597, URB937 and JZL184 suppressed cisplatin-evoked mechanical and cold allodynia in a dose dependent manner. The effects of both FAAH and MAGL inhibitors were mediated through CB_1 and CB_2 receptors	Guindon et al., 2013
Male Sprague-Dawley rats	**Paclitaxel** 2 mg/kg (cumulative dose 8 mg/kg)	Von Frey test Hargreaves test Acetone test	**WIN** (s.c. 0.1-0.5 mg/kg/day) **AM1710** (s.c. 3 mg/kg/day) (osmotic pumps) Antagonists: **AM251** **AM630**	Paclitaxel only induced thermal hyperalgesia after the first administration. WIN and AM1710 prevented mechanical and cold allodynia. AM251 antagonized the effect of WIN but not the mechanical allodynia induced by AM1710. Cold allodynia was reversed by WIN, AM251 did not antagonize this effect. AM630 did not reliably antagonize either mechanical nor cold allodynia of WIN but did antagonize the cold and mechanical allodynia of AM1719 The anti-allodynic efficacy of AM1710 outlasted the one induced by chronic WIN infusion	Rahn et al., 2014

Male Sprague-Dawley rats CB2-KO mice	**Paclitaxel** 1 mg/kg (cumulative dose of 4 mg/kg)	Von Frey test	**MDA7** (15 mg/kg) Antagonist **AM630**	MDA7 prevented mechanical allodynia induced by paclitaxel in a CB_2 dependent manner.	Naguib et al., 2012; Xu et al., 2014
Female C57Bl/6 mice	**Paclitaxel** 8 mg/kg (cumulative dose 32 mg/kg)	Von Frey test *Conditioned place preference*	**Cannabidiol** (2.5-5 mg/kg) Antagonists: **Rimonabant** **SR-144528**	Cannabidiol reversed the mechanical hypersensitivity induced by paclitaxel, but no differences between vehicle and cannabidiol were found in the place preference test, whilst morphine induced drug conditioning The 5-HT_{1A} serotoninergic receptor was implicated in the antinociceptive effect of cannabidiol, whilst CB_1 and CB_2 antagonists did not reverse the antinociceptive effect	Ward et al., 2014
CD1 male and female mice. CB2-KO CB1-KO mice	**Paclitaxel** 4mg/kg (cumulative dose 16mg/kg)	Von Frey Acetone test *Rimonabant challenge* *Rotarod test* *Rectal temperature*	**AM1710** (1-5 mg/kg) Antagonist: **Rimonabant** **AM630**	Acute administration of AM1710 suppressed mechanical and cold allodynia induced by paclitaxel in a dose dependent manner. Chronic administration of AM1710 suppressed paclitaxel neuropathy and no tolerance was developed AM1710 did not induce tolerance to the analgesia and did not induce motor incoordination or hypothermia in acute nor chronic administration nor withdrawal effects	Deng et al., 2015a
Male and female C57BL/6J mice	**Paclitaxel** 4 mg/kg (cumulative dose 16mg/kg)	Von Frey test Acetone test *Rimonabant challenge* *Rotarod test*	**Δ^9-THC** (5-10 mg/kg) Antagonist: **Rimonabant**	Acute administration of Δ^9-THC induced analgesia but also motor incoordination and hypothermia. Chronic administration caused tolerance to analgesia, hypothermia and motor incoordination. Cannabinoid withdrawal signs were observed after chronic administration was ceased	Deng et al., 2015a
C57BL/6J male mice CB1-KO and CB2-KO mice	**Paclitaxel** 4 mg/kg (cumulative dose 16mg/kg)	Von Frey test Acetone test *Rimonabant challenge* *Temperature* *Ring test*	**CP-55940** (0.3-10 mg/kg) Antagonist: **Rimonabant**	Acute administration of CP-55940 partially reversed paclitaxel-induced allodynia, higher doses induced catalepsy and CB_1 mediated hypothermia. Chronic low dose of CP-55940 reversed mechanical and cold allodynia. Tolerance to analgesia was developed after 11 days of low dose administration and to temperature after 7 days, in a CB_1 dependent manner. CB_1 mediated dependence was developed after chronic low dose of CP-55940 administration High dose induced CB_1 mediated catalepsy and hypothermia.	Deng et al., 2015b
Male C57BL/6 mice	**Cisplatin** 2.3 mg/kg (cumulative doses 20.7 and 13.8)	Von Frey test	**Δ^9-THC** (0.5-2 mg/kg) **Cannabidiol** (0.5-2 mg/kg).	Both Δ^9-THC and cannabidiol reversed but failed to prevent cisplatin-induced allodynia	Harris et al., 2016
Male C57Bl6 mice	**Paclitaxel** 8 mg/kg (cumulative dose 32 mg/kg) **Oxaliplatin** 6 mg/kg (acute administration)	Von Frey test	**Δ^9-THC** (0.625-20 mg/kg) **Cannabidiol** (0.625-20 mg/kg).	THC and cannabidiol prevented the occurrence of allodynia in paclitaxel and oxaliplatin treated animals. THC but not cannabidiol prevented the neuropathic effect of vincristine. THC and cannabidiol had a synergic effect in the paclitaxel and oxaliplatin model	King et al., 2017

	Vincristine 0.1mg/kg (cumulative dose 0.7 mg/kg).				
Male C57BL/6J mice	**Paclitaxel** 8 mg/kg (cumulative dose 32 mg/kg)	Von Frey test *Conditioned place preference*	**JZL184** (4-40mg/kg) **MJN110** (3-5 mg/kg) Antagonists: **Rimonabant** **SR-144528**	JZL184 and MJN110 reversed paclitaxel induced allodynia, both mediated through the CB_1 and CB_2 receptors Low doses of JZL184 administered chronically reversed the allodynia induced by paclitaxel and did not develop tolerance, whilst high doses induced tolerance. MJN110 leads to development of conditioned place preference	Curry et al., 2018
Male mice S426A/S430A mutant mice	**Cisplatin** 5 mg/kg (cumulative dose 20 mg/kg)	Von Frey test	**CP-55940** (0.3 mg/kg) **WIN** (3 mg/kg)	Both CP-55940 and WIN reversed cisplatin-induced allodynia Tolerance to the anti-allodynic effects of WIN but not CP-55940 was delayed in S426A/S430A mice compared to wild-type littermates.	Nealon et al., 2019

Behavioral tests in italics (Cannabinoid tetrad, Bar test, Conditioned place preference, Rimonabant challenge, Rotarod, Rectal temperature) refer to the tests used to assess cannabinoid psychoactive side effects that would reduce the interest of their antinociceptive effect, which was tested through the other mentioned tests (Von Frey, Randal-Sellito, Acetone, Plantar/Hargreaves test). Cannabinoid antagonists tested are shown in italics.

Abbreviations: Δ9-THC, tetrahydrocannabinol; ip, intraperitoneal; i.pl, intraplantar; KO, knock-out; WIN, WIN 55,212-2.

Table

Table 5. Summary of cognitive deficits measured using cognitive behavioural tests in rodent models of chemotherapy-induced cognitive impairment (CICI)

Cognitive parameter	Cognitive behavioural test	Chemotherapeutic agent	Administration schedule	Rodent model	Effects	References
Recognition memory	Novel Object Recognition	Cyclophosphamide	Acute treatment (40 mg/kg; ip)	Adult male ICR mice	Reduction of the percentage of preference 12 hours after administration, but not 10 days later	Yang et al., 2010
		Methotrexate	Acute treatment (250 mg/kg; iv)	Adult male Wistar rats	Reduction of the discrimination index	Seigers et al., 2008
		Doxorubicin	One administration (2.5 mg/kg; ip) every 5 days for 10 cycles	Adult male Wistar rats	Reduction of the discrimination index	Verma et al., 2017
		Oxaliplatin (OXA) and/or 5-Fluorouracil (5-FU)	Acute treatment: OXA (12 mg/kg; ip) and/or 5-FU (75 mg/kg; ip)	Adult male hooded Wistar rats	Reduction of the percentage of preference by each chemotherapeutic agent individually and in combination	Fardell et al., 2012
	Social interaction test	Oxaliplatin	One administration per day (2.4 mg/kg; ip) for 5 consecutive days per week for 2 cycles	Adult male rats	No differences between the exploration of the familiar and the novel rat	Bianchi et al., 2017
Spatial learning and memory	Novel Location Recognition	Cyclophosphamide	One administration per week (50 mg/kg; ip) for 4 cycles	Adult male athymic nude rats	Reduction of the exploration ratio	Christie et al., 2012
		Methotrexate	One administration per week (75 mg/kg: iv) for 2 cycles	Adult male Sprague-Dawley rats	Reduction of the percentage of preference	Naewla et al., 2019; Sirichoat et al., 2019
		5-Fluorouracil	Acute treatment (75 mg/kg; ip)	Adult male C57BL/6J mice	Not novel location preference in the short- (23 days) and long-term (114 days after administration)	Seigers et al., 2015
		Doxorubicin	Acute treatment (10 mg/kg; iv)			
		Docetaxel	Acute treatment (33 mg/kg; ip)			
	T-maze	Cyclophosphamide (CPA)	Acute treatment (200 mg/kg; ip)	Adult male Swiss mice	Significant reduction of the percentage of alternations	Iqubal et al., 2019
		Methotrexate	Acute treatment (20 mg/kg; ip)	Adult male Sprague–Dawley rats	Significant reduction of the percentage of alternations	Shalaby et al., 2019
	Barnes maze	5-Fluorouracil	Acute treatment (75 mg/kg; ip)	Adult male C57BL/6J mice	Reduction of time in the escaping area	Seigers et al., 2015
		Doxorubicin	Acute treatment (10 mg/kg; iv)			
	Morris water maze	Methotrexate	Acute treatment (20 mg/kg; ip)	Post-weaning female C57Bl6/J mice	Impaired learning and decreased discrimination index between the placement of the old and new platform	Elens et al., 2019
		Doxorubicin	One administration per week (2 mg/kg; ip) for 4 cycles	Adult male Wistar rats	Increase of the escape latency and reduction of percentage of time in the platform quadrant	Park et al., 2018
		Paclitaxel	An administration for four consecutive days (2 mg/kg; ip; on days 1, 3, 5, and 7)	Adult male Sprague-Dawley rats	Increase of the escape latency and reduction of the number of crossings over the platform	Li et al., 2017, 2018
		Docetaxel, Adriamycin and Cyclophosphamide	Three administrations every three days: Docetaxel (10 mg/kg; ip), Adriamycin (10 mg/kg; ip) and CPA (40 mg/kg; ip)	Adult female C57/BL6J mice	Reduction of the duration and frequency of entries and marked increase of the time for the first entry into the platform quadrant	Shi et al., 2018, 2019

		Cyclophosphamide, Methotrexate (MTX) and 5-Fluorouracil	One administration per week (40 mg/kg CPA, 37.5 mg/kg MTX and 75 mg/kg 5FU; ip) for 4 cycles	Adult female Wistar rats	Reduction of the time in the platform quadrant	Briones & Woods, 2011
Fear learning and memory	Step-down latency test	Cyclophosphamide	Acute administration (200 mg/kg; ip)	Adult male Swiss mice	Decreased latency to step down	Iqubal et al., 2019
		Doxorubicin	One administration per week (2 mg/kg; ip) for 4 cycles	Adult male Wistar rats	Decreased latency to step down	Park et al., 2018
	Step-through or passive avoidance test	Cyclophosphamide	Acute administration (40 mg/kg; ip)	Adult male ICR mice	Decreased latency to step through	Yang et al., 2010
		Oxaliplatin	One administration per day (2.4 mg/kg; ip) for 5 consecutive days per week for 2 cycles	Adult male rats	Decreased latency to step through	Bianchi et al., 2017
		Methotrexate	Acute administration (20 mg/kg; ip)	Adult male Sprague–Dawley rats	Decreased latency to step through	Shalaby et al., 2019
		Doxorubicin (DOX) and Cyclophosphamide	One administration per week (2.5 mg/kg DOX and 25 mg/kg CPA; ip) for 4 cycles	Adult female Sprague–Dawley rats	Decreased latency to step through	Konat et al., 2008
	Fear conditioning (context)	Cyclophosphamide	One administration per week (50 mg/kg; ip) for 4 cycles	Adult male athymic nude rats	Reduction of freezing during context exposure	Christie et al., 2012
		Doxorubicin	One administration per week (2 mg/kg; ip) for 4 cycles			
		Methotrexate	One administration per week (250 mg/kg; iv) for 4 cycles	Adult male Wistar rats	Reduction of freezing during context exposure	Seigers et al., 2009
		Oxaliplatin and/or 5-Fluorouracil	Acute treatment: OXA (12 mg/kg; ip) and/or 5-FU (75 mg/kg; ip)	Adult male hooded Wistar rats	No effects of each chemotherapeutic agent individually, but when combined reduction of freezing during context exposure	Fardell et al., 2012
	Fear conditioning (cued)	Oxaliplatin	Acute treatment (6 mg/kg; ip)	Adult male hooded Wistar rats	Reduction of cued renewal fear	Johnston et al., 2017
		Cisplatin	One administration per day (2 mg/kg; ip) for five consecutive days	Juvenile (25 or 35 days old) male Sprague-Dawley rats	Reduction of freezing after tone re-exposure	John et al., 2017

Abbreviations: 5-FU, 5-Fluorouracil; CPA, Cyclophosphamide; DOX, Doxorubicin; ip, intraperitoneal; iv, intravenous; MTX, Methotrexate; OXA, Oxaliplatin.