



# Effect of cannabinoids on the efficacy and side effects of anticancer therapeutic strategies – Current status of preclinical and clinical research

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## ABSTRACT

Cannabinoids have attracted increasing attention in cancer research in recent decades. A major focus of current preclinical and clinical studies is on the interactions and potential risks when combined with chemotherapeutic agents, targeted therapies and other anticancer strategies. Given the extensive preclinical data on additive, synergistic and, in some cases, antagonistic tumor cell killing effects of chemotherapeutic agents and cannabinoids when co-administered, a critical analysis of these data seems essential. The available data mainly relate to combination treatments for glioblastoma, hematological malignancies and breast cancer, but also for other cancer types. Such an analysis also appears necessary because cannabinoids are used as an option to treat nausea and vomiting caused by chemotherapy, as well as tumor-related pain, and cancer patients sometimes take cannabinoids without a medical prescription. In addition, numerous recent preclinical studies also suggest cannabinoid-mediated relief of other chemotherapy-related side effects such as peripheral neuropathy, nephrotoxicity, cardiotoxicity, cystitis, bladder complications and mucositis. To summarize, the data available to date raise the prospect that cannabinoids may increase the efficacy of chemotherapeutic agents while reducing their side effects. However, preclinical studies on anticancer interactions are mostly limited to cytotoxicity analyses. An equally thorough investigation of the effects of such combinations on the immune system and on the tumorigenic

**Abbreviations:** 2-AG, 2-arachidonoylglycerol; 5-FU, 5-fluorouracil; ABC, adenosine triphosphate-binding cassette; ACEA, arachidonyl-2'-chloroethylamide; ACPA, arachidonoylcyclopropamide; AEA, N-arachidonylethanolamine; AKT, protein kinase B; AMPK, adenosine monophosphate-activated kinase; AREG, amphiregulin; ATF4, activating transcription factor 4; Atg1, protein kinase autophagy related 1; ATM kinase, ataxia-telangiectasia mutated kinase; AUC, area under the curve;  $\beta$ 5i,  $\beta$  immunoproteasome catalytic  $\beta$ 5i subunit; Bax, B-cell lymphoma 2-associated X protein; BCAS1, breast carcinoma amplified sequence 1; Bcl-2, B-cell lymphoma 2; BCRP, ABCG2, breast cancer resistant protein; bFGF, basic fibroblast growth factor; BNIP3, B-cell lymphoma 2 interacting protein 3; BRAF, v-raf murine sarcoma viral oncogene homolog B; CaMKK $\beta$ , calmodulin-activated kinase kinase  $\beta$ ; CB receptor, cannabinoid receptor; CB<sub>1</sub>, cannabinoid receptor type 1; CB<sub>2</sub>, cannabinoid receptor type 2; CBD, cannabidiol; CBDV, cannabidivarin; CBG, cannabigerol; CBGA, cannabigerolic acid; CBN, cannabinol; CCT7, chaperonin containing TCP1, subunit 7 (Eta); CD147, cluster of differentiation 147 or extracellular matrix metalloproteinase inducer (EMMPRIN); CDK, cyclin-dependent kinase; CDKN2A, cyclin-dependent kinase inhibitor 2A; CAR-T cells, chimeric antigen receptor T cells; cGAS-STING, cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes; CINV, chemotherapy-induced nausea and vomiting; CIPN, chemotherapy-induced peripheral neuropathy; COX-2, cyclooxygenase-2; COX8, cytochrome C oxidase subunit VIII; CTLA4, cytotoxic T-lymphocyte-associated protein 4; CXCR4, C-X-C chemokine receptor 4; CYP, cytochrome P450; Cyt c, cytochrome c; DDIT3, DNA damage inducible transcript 3; DHEA, N-docosahexaenylethanolamide; DNAJC11, DnaJ heat shock protein family (Hsp40) member C11; E2F1, E2F transcription factor 1; EGF, epidermal growth factor; EGR3, early growth response 3; eIF2 $\alpha$ , eukaryotic translation initiation factor 2 $\alpha$ ; EMA, European Medicines Agency; EMT, epithelial-to-mesenchymal transition; EPEA, N-eicosapentaenylethanolamine; ER, endoplasmic reticulum; ER, estrogen receptors; ERK, extracellular signal-regulated kinase; FAAH, fatty acid amide hydrolase; FABP5, fatty acid-binding protein 5; FADS2, fatty acyl desaturase 2 (FADS2); FDA, U.S. Food and Drug Administration; GBM, glioblastoma; GPR, G protein-coupled receptor; GPX4, glutathione peroxidase 4; HER2, human epidermal growth factor receptor-2; HIF, hypoxia-inducible factor; HNSCC, head and neck squamous cell carcinoma; HO-1, heme oxygenase-1; 5-HT, 5-hydroxytryptamine; IFN- $\gamma$ , interferon- $\gamma$ ; IL, interleukin; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LC3, microtubule-associated protein 1A/1B-Light Chain 3; LEA, linoleoyl ethanolamide; MAGL, monoacylglycerol lipase; MAP3K4, mitogen-activated protein kinase kinase 4; MAPK, mitogen-activated protein kinase; MDR, multidrug resistance; MEK, mitogen-activated protein kinase kinase; MGMT, methylguanine methyltransferase; MMP-13, matrix metalloproteinase-13; mPTP, mitochondrial permeability transition pore; MRP1, multidrug resistance-associated protein 1, ABCB1; mTOR, mammalian target of rapamycin; NADP, nicotinamide adenine dinucleotide phosphate; NDUFA2, NADH:ubiquinone oxidoreductase subunit A2; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NGF, nerve growth factor; NK1, neurokinin 1; NO, nitric oxide; NOS, nitric oxide synthase; NRF-2, nuclear factor erythroid 2-related factor 2; NSCLC, non-small cell lung cancer; OEA, oleoylethanolamide; p21, cyclin-dependent kinase inhibitor 1; p27<sup>Kip1</sup>, cyclin-dependent kinase inhibitor 1B; p53, tumor protein p53; PARP, poly(ADP-ribose) polymerase; PDGF, platelet-derived growth factor; PD-L1, programmed death ligand 1; PEA, N-palmitoylethanolamine; PI3K, phosphatidylinositol-3-kinase; P-gp, P-glycoprotein, ABCB1; PINK1, phosphatase and tensin homolog-induced kinase 1; PPAR, peroxisome proliferator-activated receptor; PSA, prostate specific antigen; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; RANK, receptor activator of nuclear factor- $\kappa$ B; RCC, renal cell carcinoma; ROS, reactive oxygen species; RSL3, ras-selective lethal small protein 3; SCD1, stearoyl-CoA desaturase 1; SDF-1, stromal cell-derived factor 1; SEA, stearyl ethanolamide; SLC7A11, cystine transporter solute carrier family 7 member 11; SOD2, superoxide dismutase 2; Src, Src family kinase; SQSTM1, sequestosome-1; STAT, signal transducers and activators of transcription; T-ALL, T-lineage acute lymphoblastic leukemia; TFF1, trefoil factor 1; TFRC, transferrin receptor; THC,  $\Delta^9$ -tetrahydrocannabinol; THCV, tetrahydrocannabivarin; TLR4, Toll-like receptor 4; TMZ, temozolomide; TNBC, triple-negative breast cancer; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TRB3, tribbles homolog 3; TRPV, transient receptor potential vanilloid; UBE2C, ubiquitin conjugating enzyme E2 C; VEGF, vascular endothelial growth factor.

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levels of angiogenesis, invasion and metastasis is still pending. On this basis, a comprehensive understanding for the evaluation of a targeted additional treatment of various cancers with cannabinoids could be established.

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## 1. Introduction

The anticancer effect of various phytocannabinoids, including  $\Delta^9$ -tetrahydrocannabinol (THC), was first demonstrated in animal experiments in 1975 (Munson, Harris, Friedman, Dewey, & Carchman, 1975). After the discovery of the endocannabinoid system in the early 1990s, these effects were confirmed in numerous preclinical studies in a variety of different neoplastic entities. Based on these findings and studies demonstrating the anticancer effects of cannabinoids on various hallmarks of tumorigenesis, cannabinoids have increasingly become the focus of scientific discussions as systemic tumor therapies in recent years (for an overview, see Ramer & Hinz, 2015; Hinz & Ramer, 2019). From a preclinical point of view, the systemic antitumor effects of cannabinoids thus represent the basis for combining cannabinoids with chemotherapies, which can increase the effectiveness of chemotherapeutic agents and overcome resistance.

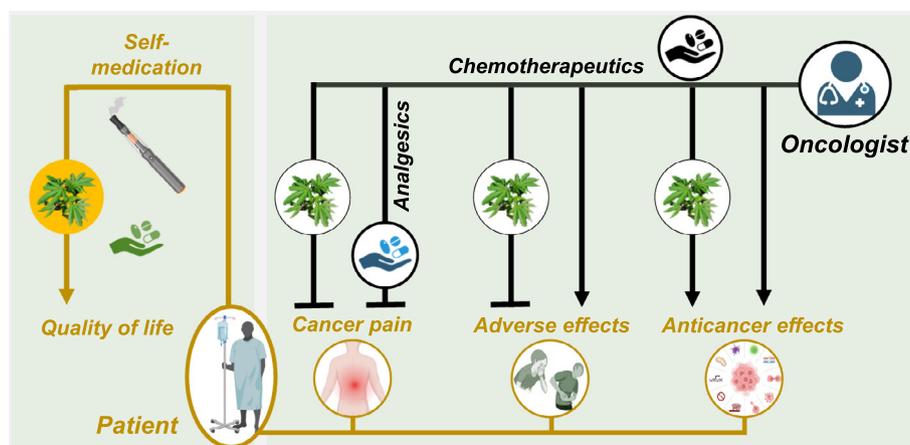
On the basis of these data, the first part of this review focuses on the interaction between cannabinoids and chemotherapeutic agents in terms of efficacy at the preclinical and clinical level. Due to the partial lack of mechanistic descriptions of the interactions of cannabinoids with chemotherapeutic agents, a brief overview of the basic anticancer effects of cannabinoids is given initially. Since these effects can be triggered by exogenous administration of cannabinoids, but also by inhibition of endocannabinoid degradation, an explanatory description of the endocannabinoid system is also provided. In the following sections, the influence of cannabinoids on the tumor cell killing effect of approaches to combat cancer is categorized by individual tumor entities and mainly includes data on viability in combination treatments of cannabinoids with chemotherapeutic agents or radiotherapy. After these preclinical data, the first successes of a randomized clinical study will be referred to. Published in 2021, a randomized, placebo-controlled phase 1b study in patients with recurrent glioblastoma multiforme (GBM) showed that patients had a longer survival time when temozolomide (TMZ) was combined with nabiximols, an oral spray consisting of a combination of THC and cannabidiol (CBD) (Twelves et al., 2021). In 2014, the US Food and Drug Administration (FDA) had already granted orphan drug designation to CBD for the treatment of GBM. The European Medicines Agency (EMA) followed in 2016 with a corresponding designation for THC and CBD from extracts of the plant *Cannabis sativa* L. for the treatment of glioma (EU/3/16/1621).

The second part of this review focuses on the interaction between chemotherapeutic agents and cannabinoids in terms of a favorable

influence of cannabinoids on chemotherapy-associated side effects. Indeed, as early as the mid-1970s, THC was shown to have an antiemetic effect in patients receiving chemotherapy for cancer, compared to placebo (Sallan, Zinberg, & Frei 3rd, 1975). Five years later, the same group was able to show in a randomized, double-blind crossover study that THC was superior to prochlorperazine in the treatment of patients with chemotherapy-induced vomiting (Sallan, Cronin, Zelen, & Zinberg, 1980), which was also confirmed in another study (Frytak et al., 1979). Dronabinol (synthetic THC) was finally approved by the FDA for chemotherapy-induced nausea and vomiting (CINV) in 1985. In addition to this well-known antiemetic effect of cannabinoids, an increasing number of preclinical studies discussed in this review have shown in recent years that cannabinoids can also have a positive effect on other side effects of chemotherapy, such as chemotherapy-induced peripheral neuropathy (CIPN), nephrotoxicity, cardiotoxicity, cystitis and mucositis. In particular, CIPN is one of the emerging critical issues in cancer treatment, so there is definitely a pharmacotherapeutic need here (Cavaletti et al., 2021). In this context, cannabinoid studies in patients with CIPN are discussed, which have already been conducted or for which patients are still being recruited.

Although this topic is only marginally addressed in this review, cannabinoids in combination with other medications are also administered in tumor therapy to alleviate tumor-related symptoms, particularly chronic cancer pain (Meng et al., 2020). Finally, due to legalization in some countries and increasing availability, cannabis is currently being used by cancer patients as a self-administered remedy (Hanganu et al., 2022), which in turn offers several individual advantages from the patient's perspective, but also harbors risks. It is to be expected that the use of cannabis by cancer patients will continue to increase (Eng, 2022). This underlines the detrimental situation that national guidelines currently lack recommendations on the therapeutic use of cannabis and that, according to a recent survey, 70 % of all doctors did not feel able to make clinical recommendations on cannabis (Worster, Hajjar, & Handley, 2022).

Taken together, the interaction of cannabinoids with currently used chemotherapeutic agents in the context of tumor therapies is of considerable clinical importance, as there are several reasons for the use of cannabinoids in tumor therapies. These can be summarized as shown in Fig. 1. The aim of this review is to provide an overview of possible systemic interactions of tumor treatment with cannabinoids and chemotherapeutics and to evaluate the individual considerations.



**Fig. 1.** Options for possible interactions between chemotherapeutic agents and cannabinoids. Cannabinoids can currently be used by oncologists to treat chronic tumor pain and to reduce chemotherapy-related side effects such as CINV. In addition, there are numerous preclinical studies and, in the case of the combination of nabiximols with TMZ, clinical evidence that form the basis for a potential combination therapy to enhance the systemic anticancer effect of chemotherapeutic agents. Finally, cannabinoids are also used by patients without medical approval as self-medication to alleviate the symptoms of a tumor disease or complications of tumor therapy in order to improve their own well-being and quality of life. Created with BioRender.com.

## 2. Mechanisms of the anticancer effect of cannabinoids

In order to understand the interactions between cannabinoids and chemotherapeutics, a detailed knowledge of the receptors and signaling pathways triggered by cannabinoids is required. The mechanisms of the anticancer effects of cannabinoids have been published in detail (Hinz & Ramer, 2022; Ramer, Wittig, & Hinz, 2021; Schwarz, Ramer, & Hinz, 2018) and are only briefly described here, with the focus on the tumor cell toxic effect.

### 2.1. Endocannabinoidome

The classical endocannabinoid system comprises the two endocannabinoids *N*-arachidonylethanolamine (AEA) and 2-arachidonylglycerol (2-AG), their anabolic and catabolic enzymes as well as the two cannabinoid receptors (CB receptors) type 1 (CB<sub>1</sub>) and type 2 (CB<sub>2</sub>). Among the plant-derived cannabinoids, THC has the properties of an agonist at the CB<sub>2</sub> receptor and a partial agonist at the CB<sub>1</sub> receptor (Pertwee, 2008). The non-psychoactive phytocannabinoid CBD, conversely, exhibits significantly weaker affinities and inverse agonistic effects at CB<sub>1</sub> and CB<sub>2</sub> receptors (Pertwee, 2008). Enzymes responsible for the degradation of endocannabinoids are the fatty acid amide hydrolase (FAAH) which degrades AEA (Deutsch & Chin, 1993), and the monoacylglycerol lipase (MAGL) that primarily mediates the hydrolysis of 2-AG (Blankman, Simon, & Cravatt, 2007). Currently, there is a concept of an “endocannabinoidome” (Di Marzo, 2018), which extends beyond the original components to include additional endocannabinoid-like lipid mediators, their synthesizing and metabolizing enzymes, as well as novel cannabinoid targets such as G protein-coupled receptors (GPRs) (GPR18, GPR55, GPR119) and several members of the transient receptor potential (TRP) family (TRPV1, TRPV2, TRPV4, TRPM8, TRPA1) (summarized in Di Marzo, 2018; Schwarz et al., 2018). CBD, for example, was further found to increase the transcriptional activity of peroxisome proliferator-activated receptor (PPAR)  $\gamma$  (O’Sullivan, Sun, Bennett, Randall, & Kendall, 2009). Moreover, the PPAR subtype  $\alpha$  was reported to be activated by various endocannabinoid-like substances such as oleoylethanolamide (OEA) (Fu et al., 2003), *N*-palmitoylethanolamine (PEA) (Lo Verme et al., 2005) as well as by other *N*-acylamines such as stearoylethanolamide (SEA), linoleoyl ethanolamide (LEA), *N*-eicosapentaenoylethanolamine (EPEA) and *N*-docosahexaenoylethanolamide (DHFA) (Artmann et al., 2008).

### 2.2. Tumor cell apoptosis

A pivotal mechanism underlying cannabinoid-induced apoptosis appears to involve the upregulation of the proapoptotic sphingolipid ceramide in cancer cells such as glioblastoma (GBM) cells (Del Gómez Pulgar, Velasco, Sánchez, Haro, & Guzmán, 2002; Galve-Roperh et al., 2000). In one of these studies, it was observed that the glioma cytotoxic effect of cannabinoids is reversed in vitro by the combination of antagonists against both cannabinoid receptors (Galve-Roperh et al., 2000). In other experiments, CB<sub>2</sub> receptor agonism was sufficient to achieve a tumor-regressive effect in vivo (Sánchez et al., 2001). In addition, cannabinoids have been reported to induce CB<sub>2</sub> receptor-dependent apoptosis of pancreatic tumor cells via intracellular stress responses of the endoplasmic reticulum (ER) such as upregulation of activating transcription factor 4 (ATF4) and tribbles homolog 3 (TRB3) (Carracedo et al., 2006).

In fact, cannabinoid receptors are not the sole potential mediators in such toxic responses. TRPV1 was also found to be involved in AEA-induced mitochondrial apoptosis of human neuroblastoma and lymphoma cells (Maccarrone, Lorenzon, Bari, Melino, & Finazzi-Agro, 2000). Furthermore, a continuous calcium influx via TRPV2 was demonstrated to trigger apoptosis in high-grade human urothelial carcinoma cells (Yamada et al., 2010). In addition, AEA has been shown to have a toxic effect on cholangiocarcinoma cells via activation of GPR55, with this activation leading to a c-Jun *N*-terminal kinase (JNK)-dependent increased recruitment of the death receptor Fas to the lipid rafts of the membrane (L. Huang et al., 2011). Finally, it is worth noting that receptor-independent signaling pathways have likewise been uncovered to play an important role in cannabinoid-induced toxic effects on cancer cells (Ramer et al., 2013; Ramer, Weinzierl, Schwind, Brune, & Hinz, 2003; Rupprecht, Theisen, Wendt, Frank, & Hinz, 2022; Soliman & van Dross, 2016).

### 2.3. Tumor cell autophagy, mitophagy and ferroptosis

Comprehensive research of the past years has highlighted the crucial role of autophagy signaling pathways in the cytotoxic effects of cannabinoids. The initial study conducted by Salazar et al. (Salazar et al., 2009) demonstrated that THC stimulates autophagy to induce cell death in human GBM cells. The process entails the increased formation of ceramide and the phosphorylation of eukaryotic translation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), which prompts an ER stress response, culminating in

autophagy. Similar findings were also demonstrated using hepatocellular carcinoma cell lines for THC and the CB<sub>2</sub>-preferring agonist JWH-015, in which autophagy and apoptosis induction was mediated via CB<sub>2</sub> and downstream activation of calmodulin-activated kinase kinase  $\beta$  (CaMKK $\beta$ ) leading to stimulation of the adenosine monophosphate-activated kinase (AMPK) (Vara et al., 2011). CBD has furthermore been shown to trigger autophagy in different cancer cell lines including breast cancer (Shrivastava, Kuzontkoski, Groopman, & Prasad, 2011), GBM (Ellert-Miklaszewska, Ciecchomska, & Kaminska, 2021), glioma stem-like cells (Nabissi et al., 2015) and melanoma (Armstrong et al., 2015).

Mitophagy is the selective autophagic degradation of mitochondria, involving key mitophagy-related proteins like B-cell lymphoma 2 interacting protein 3 (BNIP3), cytochrome c (Cyt c), parkin, and removal of malfunctioning mitochondria. Notably, mitophagy turns detrimental with mitochondrial dysfunction and heightened heme oxygenase-1 (HO-1) activation, with these factors synergistically promoting the process (Meyer et al., 2018). A study found that CBD-induced mitophagy in glioma cells is mediated through TRPV4 and a signaling pathway involving ATF4, DNA damage inducible transcript 3 (DDIT3), TRB3, protein kinase B (AKT) and mammalian target of rapamycin (mTOR) (T. Huang et al., 2021). Another investigation revealed that CBD inhibits cell growth and cell cycle progression in chronic myeloid leukemia cells via TRPV2, which was associated with mitochondrial dysfunction and mitophagy, as evidenced by decreased mitochondrial mass and increased expression of various mitophagy markers (Maggi et al., 2022).

Finally, recent studies have shown that cannabinoid compounds also induce ferroptosis, a type of programmed cell death that is iron-dependent and characterized by intracellular accumulation of iron and reactive oxygen species (ROS), inhibition of system Xc<sup>-</sup> (cystine/glutamate antiporter system), glutathione depletion, nicotinamide adenine dinucleotide phosphate (NADP) oxidation and lipid peroxidation (Costa et al., 2023). A ferroptosis reaction could be demonstrated for CBD in GBM cells, which was mediated by the downregulation of the ferroptosis-associated proteins glutathione peroxidase 4 (GPX4) and cystine transporter solute carrier family 7 member 11 (SLC7A11) and by upregulation of the transferrin receptor (TFRC) (Kim, Shivanne Gowda, Lee, Sethi, & Ahn, 2024). Moreover, modulation of ferroptosis has been suggested to contribute the cytotoxic effects of CBD and two CBD piperazinyl derivatives on ovarian cancer cells (Chen et al., 2024). Other studies have identified cannabinoid compounds as enhancers of the effect of ferroptosis inducers (P. Li et al., 2022; Singer et al., 2015).

### 3. Preclinical studies on the influence of cannabinoids on the tumor cell-killing effect of anticancer approaches

With regard to preclinical studies on the interaction of cannabinoids and conventional therapies in cancer treatment, data on cytotoxic and proapoptotic effects on tumor cells have been primarily published to date. These results are presented below categorized by tumor entity. To our knowledge, there are currently no findings from *in vivo* metastasis models and only a few findings at the level of tumor cell migration and invasiveness as well as epithelial-to-mesenchymal transition (EMT) that have analyzed interactions between cannabinoids and conventional tumor therapies. These are discussed in the corresponding sections on the entities.

#### 3.1. Glioma, medulloblastoma and ependymoma

Due to the high resistance of GBM to current cancer therapies, it is of crucial importance to identify new drugs that can improve the poor prognosis of affected patients. With regard to possible combination therapies for gliomas, data from an *in vivo* xenograft model in nude mice have shown that THC, together with CBD, enhances the inhibitory effect of TMZ, the main drug used to treat GBM, on tumor growth (Torres et al., 2011). In a further study by the same group, the

reinforcing action of the THC/CBD combination on the regression of gliomas by TMZ was confirmed, while the cannabinoids did not alter the effect of the DNA-alkylating agent carmustine (bischloroethylnitrosourea) (López-Valero et al., 2018). Specifically, the authors demonstrated that an orally administered THC/CBD mixture together with TMZ resulted in complete tumor regression in more than 50% of the mice with glioma xenografts treated this way, whereas none of the animals treated with the single substances administered alone exhibited complete tumor regression. In another investigation, a combination of CBD and TMZ also showed a significant synergistic effect in both controlling tumor size and improving survival in patient-derived neurosphere cultures and orthotopic mouse models (T. Huang et al., 2021). Using a GBM intracranial model with human U87 cells, an additional work found that CBD and a THC/CBD combination resulted in more effective inhibition of tumor progression and longer survival times in mice treated with TMZ, compared to TMZ alone (Soroceanu et al., 2022).

*In vitro*, synergistic toxic responses were further demonstrated when CBD was combined with either TMZ or carmustine in T98G GBM cells and with carmustine in U87MG cells, whereas CBD antagonized cisplatin-induced cell death in all GBM cell lines used as well as in murine primary GBM cells. However, experiments with primary murine GBM cells that exhibit enhanced platelet-derived growth factor (PDGF) signaling revealed also an antagonistic effect of CBD on the TMZ-induced loss of viability (Deng, Ng, Ozawa, & Stella, 2017).

While the data on the cooperative effects of chemotherapeutic agents and cannabinoids in GBM are well documented to date, the understanding of the underlying mechanisms are still limited. In one study, co-administration of submaximally toxic concentrations of THC and TMZ to GBM cells resulted in the enhancement of autophagy and apoptosis, with THC- and TMZ-induced cell death being inhibited by autophagy and apoptosis inhibitors and by silencing the expression of the protein kinase autophagy related 1 (Atg1) (Torres et al., 2011). In the same investigation, similar results were reported for the combination of TMZ with THC and CBD. In another report, CBD was shown to increase the uptake of various chemotherapeutic agents, such as TMZ, carmustine or doxorubicin, into GBM cells via a mechanism involving upregulation and increased calcium influx through TRPV2. The resulting cooperative effects were abolished by a TRPV2 blocker in each case (Nabissi, Morelli, Santoni, & Santoni, 2013).

Interesting results were also provided by studies on the influence of extracellular vesicles. Thereby, it was demonstrated that CBD in combination with TMZ enhanced the expression of the anti-oncogenic miR126 and decreased the expression of the pro-oncogenic miR21 in GBM cells and GBM-derived extracellular vesicles compared to TMZ treatment alone (Kosgodage et al., 2019). The same study revealed a reduction of prohibitin, a multifunctional protein with mitochondrial protective properties and chemoresistant functions, by CBD in GBM cells.

Yet another publication focused on the role of ROS. Here, it was demonstrated that CBD synergistically decreased the viability of GBM cells treated with TMZ and that this cooperative toxic effect was inhibited by the radical scavenger  $\alpha$ -tocopherol (Soroceanu et al., 2022). It should be noted that CBD together with TMZ showed these effects in U87 and U251 cells, whereas no such actions were observed in the TMZ-resistant GBM cell line T98 and in TMZ-resistant primary GBM cells. This is likely due to the intact unmethylated methylguanine methyltransferase (MGMT) in the resistant cells, which repairs DNA damage caused by TMZ and thus confers a lower sensitivity.

In a further work, the combined stimulation of GBM cells with CBD and TMZ strongly induced the microtubule-associated protein 1A/1B-Light Chain 3 (LC3)-II, a marker of autophagy, as well as sequestosome-1 (SQSTM1), phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), parkin, and the mitochondrial form of Keima, a mitophagy reporter referred to as mt-Keima cytochrome c oxidase subunit VIII (COX8) (T. Huang et al., 2021). In mice brain tumor

tissue, TMZ and CBD showed a clear activation of caspase-3, the main effector caspase of apoptosis, and an increased expression of parkin.

In further preclinical approaches, specific aspects of GBM development were investigated. Using animal models in which tumors developed from glioma-initiating cells, a subpopulation of glioma cells responsible for the dangerous relapses in this tumor, it was shown that a THC/CBD combination with a higher CBD content enhanced the antitumor effect of TMZ (López-Valero et al., 2018). In the experiments, mice bearing intracranial xenografts generated with glioma-initiating cells from GBM patients were also studied, with the administration of cannabinoids plus TMZ extending the survival of these mice. Another study included, in addition to GBM cell lines, brain tumor-initiating cells, so-called GBM stem cells, which are often resistant to conventional cancer therapies such as radiotherapy and chemotherapy. The study showed that the non-psychoactive phytocannabinoid cannabigerol (CBG) led to a decrease in viability of both cell types when combined with CBD (Lah et al., 2021). However, TMZ showed no additive viability-reducing effect on optimized CBD:CBG mixtures. Finally, in one report, glioma stem cell-like cells incubated in a proliferative medium containing epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) were found to be more sensitive to carmustine in the presence of CBD, with apoptotic cell death enhanced in the carmustine/CBD combination group compared to the effects of the compounds alone (Nabissi et al., 2015).

Several studies have also addressed the effect of cannabinoids on GBM in the context of concurrent radiotherapy. Accordingly, pretreatment of GBM cell lines with the combination of THC and CBD was found to enhance the efficacy of radiotherapy in vitro and in an orthotopic glioma mouse model (Scott, Dalglish, & Liu, 2014). Here, it was also demonstrated in glioma cell lines that irradiation with 5 Gy together with cannabinoids led to a reduction in the activation of extracellular signal-regulated kinase (ERK) and AKT, an upregulation of LC3-II and a slowing down of the DNA double-strand break repair process triggered by irradiation. It is noteworthy that the experiments on DNA repair were carried out with a higher radiation dose of 10 Gy. Interestingly, the combination of THC and CBD with radiation in the animal model led to a visually recognizable reduction in blood flow in situ and a recognizable reduction in CD31 staining in the tumors, suggesting a reduction in angiogenesis.

In another study, an increased sensitivity of glioma cells to  $\gamma$ -radiation was observed in the presence of CBD, without leading to increased death of neural stem/progenitor cells and astrocytes, indicating a specific sensitization of cancer cells while preserving healthy cells (Ivanov, Wu, & Hei, 2017). The latter report described a number of regulations in response to CBD and 5 Gy irradiation, such as the reduction of ERK and AKT activation and upregulation of tumor protein p53, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and HO-1 with activation of JNK and mitogen-activated protein kinase (MAPK) p38, which are involved in increased radiosensitivity (Ivanov et al., 2017). Later, the authors reported a further increase in radiosensitivity of human GBM cells when CBD was combined with the inhibitor of the ataxia-telangiectasia mutated (ATM) kinase KU60019 (Ivanov, Wu, Wang, & Hei, 2019), leading to additive apoptotic effects and an increase in the percentage of cells arrested in the G<sub>2</sub>/M phase. The latter study also found CBD to moderately downregulate radiation-induced programmed death-ligand 1 (PD-L1) levels, although the functional consequence was not examined.

There are also some studies in which cannabinoids have been combined with other experimental drugs that have not yet been approved. For example, one study showed that CBD had a synergistic effect in combination with the system Xc inhibitor erastin on the loss of viability and the reduction of cell invasion (Singer et al., 2015). Erastin is a ferroptosis inducer that inhibits the cystine glutamate antiporter, leading to glutathione depletion and lipid peroxide accumulation, which in turn results in a strong anticancer effect in gliomas (for review see Zhao, Zang, Huo,

& Zheng, 2023). In another investigation, an increase in apoptosis was described in a GBM cell line treated with CBD and the cyclooxygenase-2 (COX-2) inhibitor etoricoxib, although the loss of viability was lower with the combination of etoricoxib and CBD than in glioma cells treated with CBD alone (Kuźmińska et al., 2023).

In an attempt to shed light on a potential new pharmacotherapeutic option for the treatment of pediatric brain tumors such as medulloblastoma and ependymoma, the effect of THC and CBD on medulloblastoma cell lines was investigated (Andradas et al., 2021). In vitro experiments of this investigation showed that although cannabinoids enhance cyclophosphamide-induced cleavage of poly(ADP-ribose) polymerase (PARP), they have no impact on cyclophosphamide-mediated cell cycle arrest. Both cannabinoids were therefore unable to improve the ability of cyclophosphamide to prolong the survival of mice with medulloblastoma.

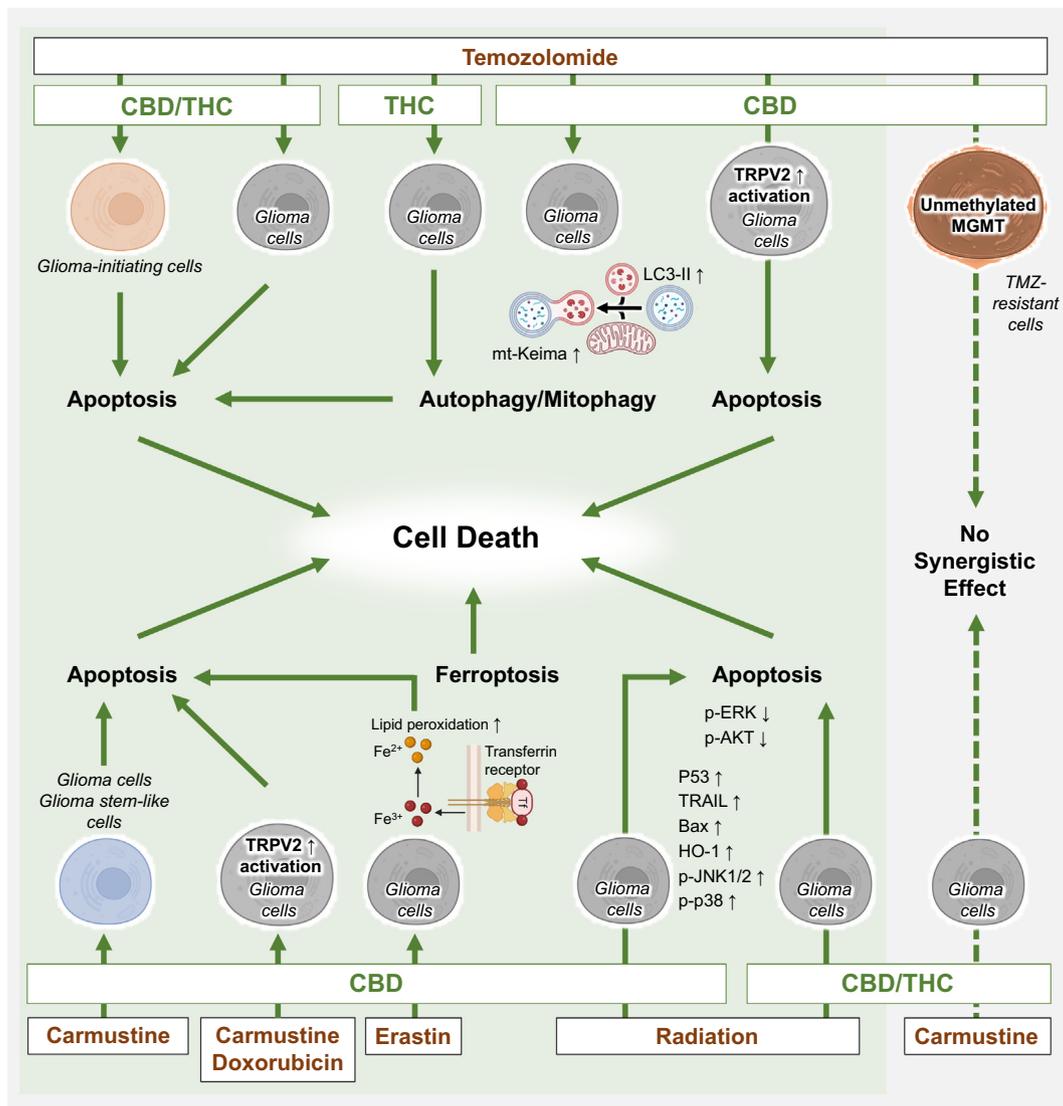
Fig. 2 provides an overview of the anti-glioma effects achieved by combining approved or experimental chemotherapeutic agents or radiotherapy with cannabinoids.

### 3.2. Hematologic malignancies

One mechanism of multidrug resistance (MDR) is the overexpression of P-glycoprotein (P-gp, ABCB1) resulting in reduced cellular accumulation of cytotoxic drugs in tumor cells. Within this context, it was found that both THC and CBD led to increased chemosensitivity to vinblastine in vinblastine-resistant leukemia cells via the downregulation of P-gp after an incubation period of 72 h (Holland et al., 2006). Interestingly, in another report of the same group, both CBD and THC led to an early transient induction of P-gp mRNA expression in P-gp-overexpressing cells and also simultaneously increased P-gp activity after 4 h incubation, as measured by reduced intracellular accumulation of the P-gp substrate rhodamine 123. Thereby, the effect of THC on P-gp expression was mediated by CB<sub>2</sub> receptors, whereas the corresponding action of CBD required the concomitant activation of CB<sub>2</sub> and TRPV1 (Arnold, Hone, Holland, & Allen, 2012).

A further study on the potentiating effect of THC on the cytostatic effects of cytarabine, doxorubicin and vincristine in leukemia cells showed that THC increases the sensitivity of leukemia cells by downregulating activated ERK. This enhancing effect could also be demonstrated at a per se non-toxic concentration of 1  $\mu$ M THC (W. M. Liu, Scott, Shamash, Joel, & Powles, 2008). The same group found that THC has a cytotoxic effect on leukemia cell lines, but does not show clear hyperadditivity/synergy in combination with cisplatin (Powles et al., 2005). The authors concluded that drugs that exert their anticancer effect by inhibiting the cell cycle, such as cytarabine and vincristine, may be better partners for THC than drugs that directly trigger a “kill” signal, such as cisplatin (Scott, Dennis, Dalglish, & Liu, 2015).

Using CD138- and TRPV2-positive cells from the blood of multiple myeloma patients and multiple myeloma cell lines overexpressing TRPV2, CBD was shown to enhance the antiproliferative and apoptosis-inducing effects of bortezomib, a standard therapy for multiple myeloma. The mechanisms postulated by the authors include activation of TRPV2 by CBD, which is associated with downregulation of activated ERK and AKT, and inhibition of signaling pathways that respond to nuclear factor- $\kappa$ B (NF- $\kappa$ B) (Morelli et al., 2014). In a separate report, the same group found that co-administration of CBD and THC synergistically interacts with carfilzomib to decrease the viability of multiple myeloma cells. In interferon- $\gamma$  (IFN- $\gamma$ )-challenged multiple myeloma cells, CBD and THC were shown to reduce the expression levels of the  $\beta$  immunoproteasome catalytic  $\beta$ 5i subunit, a component of the immunoproteasome system targeted by carfilzomib (Nabissi et al., 2016). The latter publication also showed that the combination of CBD and THC with carfilzomib significantly reduced the expression of C-X-C chemokine receptor 4 (CXCR4) and CD147, thereby explaining the reduced chemotaxis of leukemia cells treated with the combination



**Fig. 2.** Antiglioma effects due to the combination of approved or experimental chemotherapeutic agents or radiotherapy with cannabinoids. Letters written in brown indicate chemotherapeutics or radiotherapy, substances written in green are the respective cannabinoids combined with the indicated cytostatics or radiotherapy. Green arrows indicate enhancing effects, while green dashed arrows indicate no cooperative effects. The upper part of the figure shows interactions between cannabinoids and TMZ in the treatment of gliomas and the lower part lists other chemotherapeutic agents/radiotherapies for gliomas for which data on the interaction with cannabinoids are available. Abbreviations are explained in the chapters and in the list of abbreviations. The “p” placed in front of some kinases indicates the active phosphorylated form. Created with BioRender.com.

to the chemoattractants stromal cell-derived factor 1 (SDF-1) and extracellular cyclophilin A.

In another investigation, the cannabinoid agonist WIN 55,212-2 was shown to potentiate the viability-reducing effects of dexamethasone and melphalan in multiple myeloma cell lines, with the exact mechanisms of interaction not being addressed herein (Barbado et al., 2017). A possible interaction between CBD and imatinib, a standard treatment for chronic myeloid leukemia, has also been investigated. Here, CBD synergistically enhanced the toxicity of imatinib in chronic myeloid leukemia cells and also decreased the viability of imatinib-resistant cells (Maggi et al., 2022).

Synergistic cytotoxic effects have also been documented for the combination of CBD and tamoxifen in T-lineage acute lymphoblastic leukemia (T-ALL) cells. Using protein-ligand analysis, tamoxifen was shown to inhibit the mitochondrial permeability transition pore (mPTP) by binding to its obligatory component cyclophilin D, which in turn leads to calcium ion overload when CBD is administered thereafter. Thus, tamoxifen sensitizes T-ALL cells to CBD via an alteration of mitochondrial calcium ion homeostasis (Olivas-Aguirre et al., 2021).

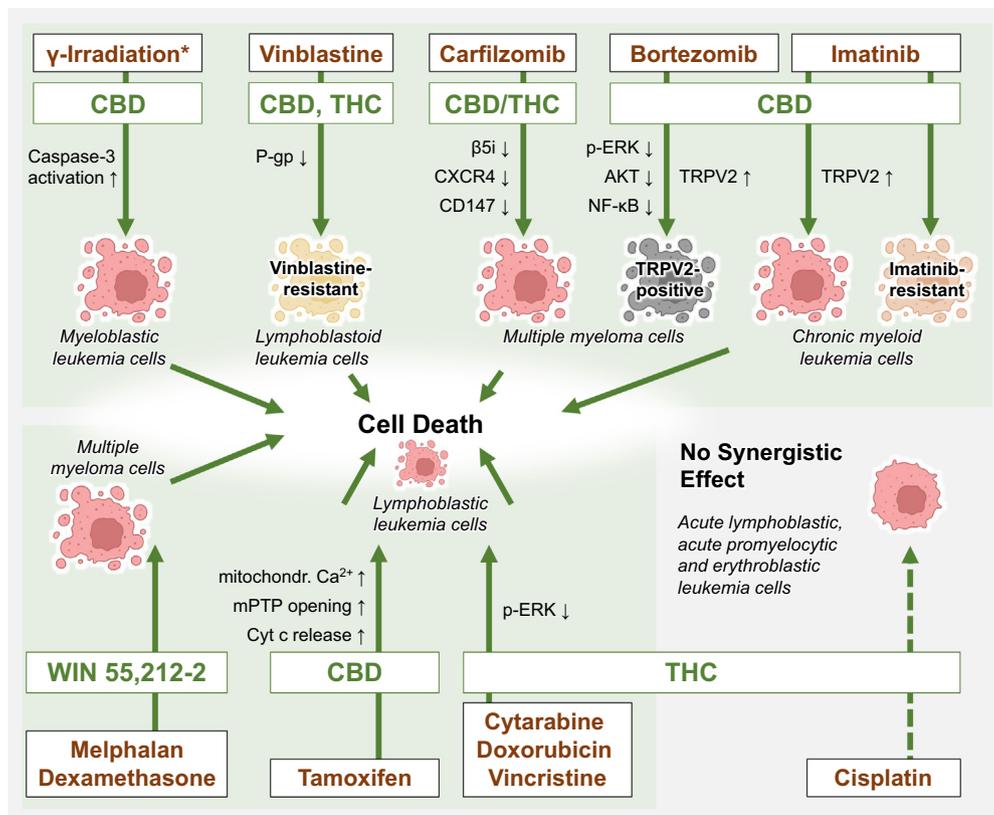
CBD has further been shown to inhibit the proliferation of chimeric antigen receptor T cells (CAR-T cells), a technology used in the treatment of relapsed and refractory hematologic B-cell tumors, while leaving their immunological properties or cytotoxic function virtually unchanged (Chantarat, Pe, Suppipat, Vimolmangkang, & Tawinwung, 2024).

Finally, in an early study with HL60 myeloblastic leukemia cells, CBD and CBD-dimethylheptyl in combination with a dose of 800 cGy  $\gamma$ -radiation were found to cooperatively induce apoptosis, whereas such effects did not occur in normal human blood monocytes (Gallily et al., 2003).

The corresponding interactions are shown in Fig. 3.

### 3.3. Breast cancer

Most breast cancer research has been conducted on triple-negative breast cancer (TNBC) models. According to histopathological criteria, these tumors lack expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor-2



**Fig. 3.** Anticancer effects induced by the combination of an approved pharmacological treatment or radiotherapy with cannabinoids on malignant blood cells. Letters written in brown indicate chemotherapeutics or radiotherapy, substances written in green are the respective cannabinoids combined with the indicated cytostatics or radiotherapy. Green arrows indicate enhancing effects, whereas green dashed arrows indicate no cooperative effects. \* The  $\gamma$ -irradiation was carried out with a dose of 800 cGy. In the experiments with  $\gamma$ -irradiation and CBD, the CBD derivative CBD dimethylheptyl was also used, which showed similar results. Abbreviations are explained in the chapters and/or in the list of abbreviations. The “p” placed in front of ERK indicates the active phosphorylated form. Created with BioRender.com.

(HER2). Regarding the sensitivity of breast tumor cells to cannabinoids, it has been shown that ER-negative cells are more susceptible than ER-positive cells (Almeida, Teixeira, Correia-da-Silva, & Amaral, 2021; Caffarel, Andradas, Pérez-Gómez, Guzmán, & Sánchez, 2012).

Using TNBC cells, a study showed that the overexpression of TRPV2 in combination with its activation by CBD leads to an increased intracellular accumulation of doxorubicin, thereby intensifying the induction of apoptosis (Elbaz et al., 2016). In the same report, a murine orthotopic tumor xenograft model using TNBC cells also revealed that the combination of CBD with doxorubicin significantly reduced both tumor volume and tumor weight compared to the individual treatment groups. Similarly, a nanomicellar formulation of WIN 55,212-2 significantly enhanced the toxic effect of doxorubicin in vitro and in a syngeneic mouse model of TNBC (Greish et al., 2018).

Synergistic effects on the reduction of tumor cell viability have also been documented for the combination of CBD with paclitaxel and doxorubicin in TNBC in vitro and with respect to paclitaxel in additional in ovo experiments (Fraguas-Sánchez, Fernández-Carballido, Simancas-Herbada, Martín-Sabroso, & Torres-Suárez, 2020). However, since this work was primarily concerned with the general effect of a new formulation of CBD in polymer microparticles, these studies did not include experimental approaches to uncover the underlying mechanisms of synergism.

An interesting aspect of the role of the endocannabinoid system could also be identified with the ferroptosis-sensitizing effect of CB<sub>1</sub> receptor antagonism in TNBC cells. Accordingly, co-administration of the CB<sub>1</sub> antagonist rimonabant (SR141716) with ferroptosis inducers such as erastin or ras-selective lethal small molecule 3 (RSL3) resulted in a significant synergistic reduction of in vitro and in vivo tumor cell

growth by increasing intracellular lipid peroxides, malondialdehyde, 4-hydroxynonenal and ROS, as well as by reducing intracellular glutathione and finally inducing a G<sub>1</sub> cell cycle arrest (P. Li et al., 2022).

On the other hand, paclitaxel and epirubicin in combination with THC or a cannabinoid extract were found to have no cooperative effects in TNBC cells, while the combination of the cannabinoid extract, but not pure THC, with cisplatin showed an enhanced antiproliferative effect (Blasco-Benito et al., 2018). Conversely, a potentiation of the antiproliferative effect could not be confirmed in the latter publication when ectopic tumors of TNBC cells were examined after combined administration of cannabinoid extract and cisplatin in corresponding nude mice. In a further study, in which the effect of CBD on TNBC cells under different cultivation conditions was primarily examined, CBD again showed an antagonistic effect against the cytotoxic effect of cisplatin (D'Aloia et al., 2022).

Remarkable preclinical findings were also obtained regarding the interaction between CBD and the PD-L1 antibody atezolizumab, which has been approved by the FDA in combination with protein-bound paclitaxel for adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1. However, only about 5 to 20% of patients with TNBC and PD-L1-positive tumors respond to atezolizumab (Kwa & Adams, 2018), so even more effective combination strategies are being explored currently. In a recently published study, the combination of CBD and atezolizumab led to enhanced anticancer immune responses in in vitro and in vivo experiments (Kim et al., 2024). As the underlying mechanism, CBD was shown to stimulate PD-L1 expression in TNBC cells by activating the cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes (cGAS-STING) pathway, a major sensor of DNA damage in tumor cells

and a promoter of anticancer immunity. Interestingly, and in line with the theory, CBD alone reduced T cell activation in the presence of TNBC cells due to increased PD-L1 expression, while CBD in combination with atezolizumab enhanced the antitumor activity of the latter by increasing its targetability due to increased PD-L1 levels.

Finally, in a study with TNBC cells, it was shown that the MAGL inhibitor JJKK048, when tested at a non-toxic concentration under hypoxic conditions, not only downregulated the expression of hypoxia-inducible factor (HIF)-1 $\alpha$  and vascular endothelial growth factor (VEGF), but also counteracted the hypoxia-induced upregulation of breast cancer resistant protein (BCRP, ABCG2) (Puris et al., 2023). Consequently, JJKK048 also reversed the hypoxia-decreased cellular accumulation of the BCRP substrate regorafenib, a tyrosine kinase inhibitor currently approved by the FDA for metastatic colorectal cancer, advanced gastrointestinal stromal tumors, and advanced hepatocellular carcinoma. This ultimately led to JJKK048 partially restoring the anti-invasive effect of regorafenib, which is lost under hypoxia. However, a mechanistic involvement of the endocannabinoid 2-AG, which is elevated when MAGL is inhibited, was not investigated in this work.

With regard to ER-positive breast cancer cells, a comprehensive study on MCF-7 cells revealed that CBD synergistically enhanced the antiproliferative activity of docetaxel, doxorubicin, paclitaxel, vinorelbine and 7-ethyl-10-hydroxycamptothecin (SN-38, active metabolite of irinotecan) in different molar ratios by promoting apoptosis (Alsherbiny, Bhuyan, Low, Chang, & Li, 2021). Focusing on gene regulation in MCF-7 cells treated with CBD and SN-38, the authors performed a shotgun proteome analysis, which revealed 91 significantly dysregulated proteins, some of which are listed in Fig. 4. Similarly, another study documented a further reduction in the viability of MCF-7 cells in response to paclitaxel or doxorubicin treatment when treated in combination with CBD (Fraguas-Sánchez, Fernández-Carballido, Simancas-Herbada, et al., 2020).

In connection with the treatment of ER-positive breast cancer, it is also important how aromatase inhibitors interact with cannabinoids. In this context, however, the use of CBD in combination with

anastrozole and letrozole in an in vitro study of ER-positive and aromatase-overexpressing breast cancer cells did not result in obvious synergistic effects in terms of loss of viability or induction of apoptosis (Almeida et al., 2023). On the other hand, when CBD was combined with exemestane, there was a potentiated effect characterized by the activation of caspase-7 and -8 signaling pathways. In addition, when administered concomitantly with exemestane, CBD showed an improved ability to suppress the transcription of downstream ER $\alpha$ -regulated targets, particularly amphiregulin (AREG), early growth response 3 (EGR3) and trefoil factor 1 (TFF1), compared to exemestane monotherapy.

Additive antiproliferative effects were also observed in vitro when a cannabis extract or THC were combined with tamoxifen and lapatinib, which are targeted therapies for ER- and HER2-positive breast cancer, respectively (Blasco-Benito et al., 2018). A closer look at the mechanisms shows that in a HER2-positive cell line (HCC1954), both the effect of THC and the effect of a cannabis extract on cell viability are mediated via CB<sub>2</sub> receptors, while in an ER/PR-positive breast cancer cell line (T47D), only the effect of THC, but not that of the herbal composition, is transduced via CB<sub>2</sub>. Noteworthy, the combinations showed no interactions, either positive or negative, in vivo (Blasco-Benito et al., 2018).

Finally, a recent study suggests that CBD in combination with hypericin photosensitizer conjugated with gold nanoparticles (hypericin-AuNP) leads to a profound induction of apoptosis in MCF-7 breast cancer cells (Mokoena, George, & Abrahamse, 2024). In photodynamic therapy, photosensitizing agents are administered that are subsequently activated by light to attack and destroy tumor cells in a targeted manner.

Fig. 4 summarizes the findings discussed in this chapter.

### 3.4. Melanoma and non-melanoma skin cancer

Using a series of melanoma cell lines, it was found that CBD enhances the anticancer effect of mitoxantrone, but antagonizes the corresponding cytotoxic activity of cisplatin (Marzęda et al., 2022). The

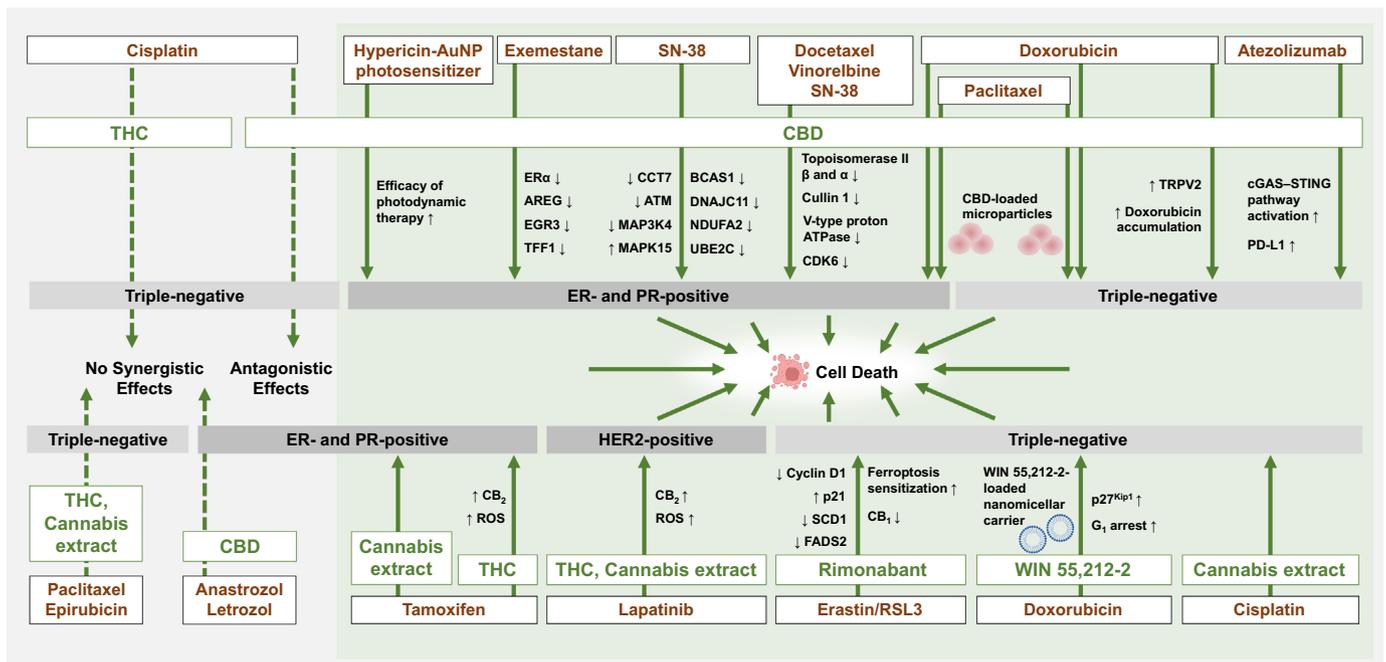


Fig. 4. Anticancer effects caused by combination of chemotherapeutics with cannabinoids in breast cancer. Letters written in brown indicate chemotherapeutics or photodynamic therapy, substances written in green are the respective cannabinoids combined with the indicated cytostatics or photodynamic therapy. Green arrows indicate enhancing effects, whereas green dashed arrows indicate no cooperative effects or antagonizing effects. The direction of the arrow after “CB” indicates whether the effect is mediated by the activation (upward direction) or antagonism (downward direction) of the respective CB receptor. The abbreviations can be found in the chapters and/or in the list of abbreviations. Created with BioRender.com.

authors therefore emphasized that a combination of CBD with platinum compounds must be carefully examined. Consistent with this, the TRPV1 and CB<sub>1</sub> receptor agonists arvanil and olvanil were also found to enhance the cytotoxic effect of mitoxantrone on melanoma cells while antagonizing the effect of cisplatin (Marzęda et al., 2022). Finally, a recent study by the same group reported that AM1172, an inhibitor of AEA uptake, additively enhances the antiproliferative effect of docetaxel, paclitaxel, mitoxantrone and cisplatin in melanoma cell lines, with the combination of AM1172 and paclitaxel showing a synergistic effect in A375 cells (Marzęda, Wróblewska-Łuczka, Florek-Łuszczki, Góralczyk, & Łuszczki, 2024).

In a further study with melanoma cells, possible interactions with specific targeted therapies were investigated. This showed that the combination of THC and CBD inhibited tumor growth in mice to a similar extent as the mitogen-activated protein kinase (MEK) inhibitor trametinib. Co-administration of THC/CBD and trametinib did not lead to any detectable interaction in tumor growth when using a xenograft model. This observation could be due to the almost complete reduction in tumor volume achieved with the two individual approaches, such that potential synergies could no longer be detected (Richtig et al., 2023). In this work, trametinib at a lower concentration of 30 nM showed a statistically significant reduction in the viability of A2058 melanoma cells when combined with THC at 6 μM or CBD at 10 μM. In the same cell line, vemurafenib, a v-raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor, at 5 μM led to a significant increase in the loss of viability induced by 6 μM CBD or 15 μM THC.

Another investigation was aimed at possible interactions between cannabinoids and radiation. Here, the results of viability tests showed a significant loss of metabolic activity of melanoma cells, leading to cell necrosis rather than apoptosis after treatment with a cannabis extract. However, no significant difference was observed between the metabolic activity of cells treated with cannabis extract alone and cells treated with cannabis extract plus 6 Gy of radiation (Naderi et al., 2020).

Finally, a recently published review summarized several studies that suggest cannabinoids as part of a multitargeted approach to reduce the resistance of melanomas to photodynamic therapy approaches (Nkune & Abrahamse, 2024).

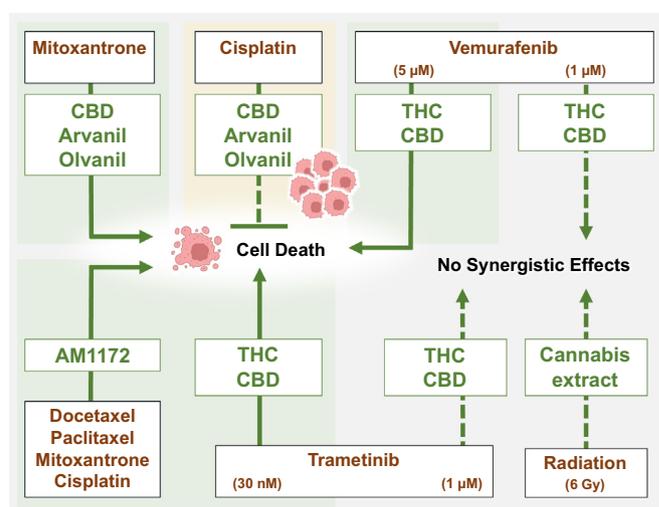
Concerning non-melanoma skin cancer, a recent study described a combinatorial lipid-based nanocarrier loaded with 5-fluorouracil (5-FU) and CBD that reduced non-melanoma skin cancer in rats (Hasan et al., 2023). However, this study did not examine the synergistic effect of the two substances compared to the individual ones.

Regarding the interaction between immunotherapeutics and cannabinoids, THC has been shown to significantly reduce the tumor-regressive effect of a PD-1 antibody in mice with melanoma xenografts (Xiong et al., 2022). The mechanism underlying this THC effect involves CB<sub>2</sub> receptor-dependent suppression of Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling.

Fig. 5 summarizes the data concerning effect of cannabinoids on chemotherapeutic or ionizing radiation toxic efficacy toward melanoma cells.

### 3.5. Lung cancer

The preclinical data on the effects of cannabinoids in combination with chemotherapeutic agents in lung cancer are inconsistent. In one report (Misri et al., 2022), cisplatin-resistant lung cancer cell lines were found to exhibit reduced viability, colony and sphere formation when treated with CBD alone. These effects were mediated by ROS induction and inhibition of the nuclear factor erythroid 2-related factor 2 (NRF-2), a master regulator of neutralizing cellular ROS and restoring redox balance. Similar results were obtained in animal studies with a reduction in tumor growth and metastasis in mice treated with CBD. A functional involvement of TRPV2 was confirmed by a reversal of the apoptotic effect of CBD when lung cancer cells were pretreated with the TRPV2 inhibitor tranilast. However, the authors did not find any



**Fig. 5.** Anticancer effects by combining chemotherapeutic agents or radiation with cannabinoids in melanoma cells. Letters written in brown indicate chemotherapeutics or radiotherapy, substances written in green are the respective cannabinoids combined with the indicated cytostatics or radiotherapy. Green arrows indicate enhancing effects, whereas green dashed arrows indicate no cooperative effects. The dashed blocking arrow indicates antagonistic effects of cannabinoids against cytostatic drugs. Explanations: Arvanil/Olvanil (TRPV1/cannabinoid receptor hybrid agonists), Trametinib (MEK inhibitor), Vemurafenib (BRAF inhibitor). Abbreviations are explained in the chapters and in the list of abbreviations. Created with BioRender.com.

synergistic effects of CBD and cisplatin on cell viability. Although this study showed that CBD could be a therapeutic option for cisplatin resistance after completed treatment with cisplatin, a combined treatment of cisplatin and CBD were not investigated in the animal experiments.

In another study, CBD was shown to confer protective effects on lung cancer cell lines against the cytotoxicity of cisplatin and carboplatin, while leaving oxaliplatin-induced toxicity unaffected (Buchtova et al., 2023).

On the other hand, CBD in combination with the tyrosine kinase inhibitor dasatinib exhibited a synergistic effect on the inhibition of lung tumor cell growth by modulating the Src/phosphatidylinositol-3-kinase (PI3K)/AKT pathway in vitro and in vivo (Ye et al., 2024). This work also showed that the migration and invasion of A549 lung tumor cells was significantly reduced in response to dasatinib plus CBD.

Finally, in an effort to test ferroptosis-inducing CBD nanoparticles, another recently published report provided evidence for antitumor immune responses which initiate T cell response and enhance the antitumor properties of these cannabinoid nanoparticles in combination with the toll-like receptor agonist Poly(I:C) (Yang et al., 2023).

### 3.6. Bladder cancer

The treatment of bladder cancer appears to be of particular interest in terms of potential treatment with cannabinoids, as a previous study has shown that the use of cannabis alone was associated with a 45 % reduction in the incidence of bladder cancer (A. A. Thomas et al., 2015). In a recent publication, THC, CBD, CBC and cannabivarin, but not CBG or the THC metabolite 11-nor-9-carboxy- $\Delta^9$ -THC, were found to reduce the viability of bladder cancer cells when administered alone (Whynot, Tomko, & Dupré, 2023). Using different urothelial carcinoma cell lines, further experiments showed that the effect of cisplatin or gemcitabine was differentially influenced depending on the concentrations of cannabinoids used, with responses ranging from antagonistic to additive and synergistic effects. Remarkably, treatment with CBD (5 μM) combined with cisplatin or with THC (5 or 12.5 μM) combined with cisplatin plus gemcitabine led to a synergistic reduction in cell

viability. The same group also reported that cannflavin A, one of over 20 flavonoids found in the cannabis plant but not chemically related to THC, in combination with gemcitabine and cisplatin, led to an additional reduction in the viability of bladder cancer cells (Tomko, Whynot, & Dupré, 2022). Finally, using canine urothelial carcinoma cells, CBD was found to have a synergistic interaction with vinblastine and mitoxantrone, but an antagonistic interaction with carboplatin (Inkol, Hocker, & Mutsaers, 2021).

### 3.7. Pancreatic cancer

A major pharmacotherapeutic challenge remains the treatment of pancreatic cancer patients, whose 5-year survival rate is about 5 % (Vincent, Herman, Schulick, Hruban, & Goggins, 2011).

When various cannabinoid compounds were tested in human pancreatic cancer cells, the CB<sub>1</sub> receptor antagonist AM-251 was shown to induce the strongest toxicity with an IC<sub>50</sub> value of 8.6 μM and a synergistic cytotoxic action with 5-FU (Fogli et al., 2006). On the other hand, AM-251 at a lower concentration of 1 μM reversed the toxic effect of the synthetic CB<sub>1</sub> agonist arachidonyl-2'-chloroethylamide (ACEA). The authors postulated that the toxic and anticarcinogenic effects of AM-251 are not mediated via cannabinoid receptors, but are due to the structural similarity of AM-251 with the selective COX-2 inhibitor celecoxib.

A comprehensive study also addressed the effects of combining the cannabinoids arachidonoylcyclopropamide (ACPA), another CB<sub>1</sub> receptor agonist, and GW405833, a CB<sub>2</sub> receptor agonist, with gemcitabine, the standard drug treatment for advanced pancreatic cancer. Thereby, gemcitabine induced ROS-dependent autophagic cell death via an NF-κB-dependent mechanism, resulting in a synergy between gemcitabine and cannabinoids in the inhibition of pancreatic cancer growth in conjunction with upregulation of LC3-II (Donadelli et al., 2011). However, similar results were also obtained for the combination of gemcitabine and the CB<sub>1</sub> receptor antagonist SR141716.

Using a genetically engineered mouse model of pancreatic cancer, one study found that CBD as a GPR55 antagonist in combination with gemcitabine significantly prolonged survival compared to animals treated with gemcitabine or CBD alone (Ferro et al., 2018). As underlying signaling pathways, CBD has been found to inhibit gemcitabine-induced ERK phosphorylation and gemcitabine-induced upregulation of the enzyme ribonucleotide reductase M1, both of which have been proposed as mechanisms of acquired gemcitabine resistance.

To improve the effectiveness of pancreatic cancer treatment, the combination of cannabinoids with radiotherapy has also been investigated (Yasmin-Karim et al., 2018). Here, CBD combined with a dose of 4 Gy led to a reduction in colony formation compared to CBD or radiation alone.

As a further physicochemical treatment option, cannabinoids were tested in pancreatic ductal adenocarcinoma cell lines in combination with oxygen-ozone therapy (O<sub>2</sub>/O<sub>3</sub>) where they resulted in improved efficacy in terms of toxicity (Luongo et al., 2020). The authors of the latter report further described a number of genes that were regulated upon combined treatment with CBD and oxygen/ozone, including upregulation of cyclin-dependent kinase (CDK) inhibitor gene 2A (CDKN2A) and downregulation of E2F transcription factor 1 (E2F1) as important features of cell cycle regulation, as well as inhibition of BRAF expression and other genes involved in carcinogenesis. It is noteworthy that CBD also enhanced the efficacy of gemcitabine and paclitaxel against pancreatic cancer cells in this study. In another investigation, it was found that combining CBD with melatonin plus oxygen/ozone and gemcitabine was more effective at reducing tumor growth than the individual treatments in a murine *in vivo* model of pancreatic cancer (Zeppa et al., 2024). *In vitro* studies on the corresponding tumor cells showed that the proapoptotic and proliferation-inhibiting combination effect of CBD plus melatonin plus oxygen/ozone and gemcitabine was enhanced by a negative modulation of the total RAS

protein and phosphorylated BRAF compared to treatment with gemcitabine alone.

What is further worth mentioning in the context of cannabinoid effects on pancreatic cancer cells is the fact that THC and CBD have been shown to lead to a downregulation of PD-L1 in this tumor entity (Yang et al., 2020). However, the functional consequence of this regulation was not investigated here.

### 3.8. Gynecological cancers

Ovarian cancer cells were among the first cells to be examined for the influence of cannabinoids on certain transport molecules. Here, cannabinoids were found to increase intracellular levels of the multidrug resistance-associated protein 1 (MRP1, ABCB1) substrate [<sup>3</sup>H]-vincristine in those cells that exhibited increased MRP1 expression, with CBD showing the highest potency over cannabidiol (CBN) and THC (Holland, Allen, & Arnold, 2008). Unfortunately, this study did not address the functional effects on viability.

Experiments on the efficacy of polymer microparticles loaded with CBD demonstrated a significant synergistic effect of CBD in combination with paclitaxel on tumor growth of ovarian cancer cells *in vitro* and on tumors formed on chorioallantoic membranes of chicken embryos (Fraguas-Sánchez et al., 2020). However, CBD did not exhibit statistically significant synergistic effects on the activity of doxorubicin or cisplatin in this investigation. On the other hand, a study on the role of TRPV2 in endometrial cancer found that daily treatment of relevant cancer cells with CBD enhanced the cytotoxic effect of doxorubicin and paclitaxel, as well as that of cisplatin, with the observed effect being more pronounced in endometrial cancer cells that overexpress TRPV2 (Marinelli et al., 2020). Finally, a recent study with human ovarian cancer cells showed that two CBD piperazinyl derivatives in combination with cisplatin exhibit a synergistic cytotoxic effect (Chen et al., 2024).

A further work examined the mechanism of the chemoresistance-overcoming effect of AEA and 2-AG in ovarian cancer cells. Here, it was shown that the latter results from the upregulation of ceramide levels, which triggers severe ER stress in chemoresistant cancer cells treated with cisplatin and paclitaxel, accompanied by increased autophagy (Y.-S. Lin, Huang, Hsu, Tang, & Chiu, 2023).

A pharmacological interaction between chemotherapy and cannabinoids in cervical cancer is currently not supported by data. However, a recently published study demonstrated an interaction between CBD and photosensitizing photodynamic therapy in a cervical cancer cell line (Razlog, Kruger, & Abrahamse, 2023).

### 3.9. Colorectal cancer

There is a body of work demonstrating combined anticancer effects of cannabinoids and chemotherapeutic agents in colorectal cancer. Thus, an increased toxicity of oxaliplatin through the treatment with CBD in intestinal cancer cell lines was reported, leading to the overcoming of the resistance to oxaliplatin (Jeong et al., 2019). This effect was related to the reversal of oxaliplatin-induced phosphorylation of nitric oxide synthase (NOS) 3 (endothelial NOS) and nitric oxide (NO) production, which reduced the concentration of the mitochondrial antioxidant superoxide dismutase 2 (SOD2) and increased the production of ROS, ultimately leading to mitochondrial dysfunction. A significant effect of the CBD/oxaliplatin combination was also demonstrated *in vivo* using a murine colon cancer xenograft model, with a significant reduction in tumor growth associated with an induction of LC3-II and a reduction in phosphorylated NOS3 and SOD2. In another study, the CB<sub>1</sub> receptor antagonist SR141716 (rimonabant) was shown to inhibit the proliferation of human colon cancer cells of the DLD-1 line in a manner similar to oxaliplatin, and that SR141716, when administered in combination, enhances the inhibitory effect of oxaliplatin (Gazzerro et al., 2010).

On the other hand, one study has described an antagonistic effect of a THC-rich cannabis extract on the effect of cisplatin in colon cancer cell lines growing in complete media (Cherkasova, Ilynskyy, Kovalchuk, & Kovalchuk, 2024). Remarkably, the same group found synergistic effects for a combination of CBD with cisplatin when a similar study design was used with intermittent serum starvation, whereas an antagonistic effect was found without intermittent serum starvation (Cherkasova, Ilynskyy, Kovalchuk, & Kovalchuk, 2023). Using a syngeneic colon cancer mouse model, a further examination revealed that combining THC with irinotecan, a topoisomerase I inhibitor, reduced the efficacy of the chemotherapeutic agent in inhibiting tumor growth (Žunec et al., 2023).

Conflicting results have been reported regarding the interaction between immunotherapeutic agents and cannabinoids in colon cancer models. While one study reported that THC significantly reduces the inhibitory effect of a PD-1 antibody on tumor growth in mice with colon carcinoma xenografts (Xiong et al., 2022), another work found that the combined administration of a cannabis extract and a PD-1 antibody in colon carcinoma xenograft mice does not antagonize the antitumor and survival-enhancing effects of PD-1 blockade (Waissengrin et al., 2023).

Finally, one study with colorectal cancer cell lines, focusing on potential cooperative effects of cannabinoids and micronutrients, showed that CBD/CBG in combination with curcumin and piperine reduced proliferation and induced apoptosis in a cooperative manner (Yüksel, Hızlı Deniz, Şahin, Sahin, & Türkel, 2023). Additionally, similar to cervical cancer cells, CBD has also been shown to further improve the efficacy of photodynamic therapy on colorectal cancer cells (Nkune, Kruger, & Abrahamse, 2022).

Special mention should also be made of interactions at the level of EMT, DNA repair and the stimulation of survival mediators, all of which increase chemotherapy resistance in colorectal cells. Here, it was recently shown that a glycosidic THC derivative (THC-9-OG) reverses the EMT induced by subtoxic doses of 5-FU in colorectal cancer cells and abolishes the DNA repair mechanism (Mir et al., 2024). On a mechanistic level, it was demonstrated, for example, that THC-9-OG significantly attenuated the 5-FU-induced expression of vimentin, the main inductor of EMT, through extensive ROS generation along with autophagy induction through LC3B I-II conversion and p62 degradation in an ATM kinase-dependent manner. In the Apc-knockout colorectal carcinoma model, the combination of 5-FU and THC-9-OG caused a remission of the crypt progenitor phenotype, which was clearly identified in the 5-FU treatment. This study also reported that 5-FU-induced migration of colon cancer cells from the nucleus of spheroids was abolished by the cannabinoid, suggesting that THC-9-OG may inhibit the potential 5-FU-induced metastatic potential of colon cancer cells.

### 3.10. Gastric cancer

In gastric cancer cells, AEA was found to enhance the proapoptotic effect of paclitaxel (Miyato et al., 2009). In addition, the latter publication described an inhibition of proliferation indicated by an increase in G<sub>1</sub> phase cells when paclitaxel was combined with AEA. In another study, the synthetic cannabinoid WIN 55,212-2 was found to induce apoptosis of 5-FU-resistant gastric cancer cells, which was associated with upregulation of cleaved caspase-3 and cleaved PARP, and downregulation of activated ERK1/2 and AKT, as well as Bcl-2 and Bax (Xian, Park, Choi, & Park, 2013).

### 3.11. Hepatocellular carcinoma

The combination of CBD with multikinase inhibitors such as cabozantinib, sorafenib and regorafenib, but not lenvatinib, showed a cooperative cytotoxic effect on hepatocellular carcinoma cell lines. Thereby, the IC<sub>50</sub> values of cell viability were lowest for the combination of CBD and cabozantinib. The underlying apoptosis

depends on the phosphorylation of p53, which in turn is regulated by ER stress and occurs independently of cannabinoid receptors (Jeon et al., 2023).

### 3.12. Head and neck squamous cell carcinoma

An enhancing effect was also confirmed in the context of tumor regression induced by the combination of CBD and cisplatin in a mouse model of head and neck squamous cell carcinoma (HNSCC) using the HNSCC cell line FaDu (Go, Kim, Kim, Chae, & Song, 2020). Applying the same HNSCC line in vitro, CBD was shown to enhance the cytotoxic effect of cisplatin, 5-FU or paclitaxel, as measured by trypan blue assay, colony formation assay and annexin V/propidium iodide staining to quantify apoptosis. These results were confirmed in two additional HNSCC cell lines. In this context, various mechanisms of cell cycle inhibition and apoptosis induction by CBD were elucidated using transcriptome analyses. However, mechanistic analyses of signaling pathways occurring in combination with cisplatin, 5-FU or paclitaxel were not covered here.

### 3.13. Osteosarcoma

In relation to osteosarcoma, a study with a corresponding cell line showed that even low CBD concentrations reduced the cytotoxicity of cisplatin and carboplatin as well as the inhibition of colony formation by cisplatin, carboplatin and oxaliplatin (Buchtova et al., 2023). The CBD effect was accompanied by reduced intracellular platinum accumulation, which could be due to changes in cellular transport, among other factors. However, it remains to be clarified why CBD did not affect the short-term toxicity of oxaliplatin, although it decreased the intracellular concentrations of this substance. In another work, the same group has previously shown in an osteosarcoma and a breast cancer cell line that CBD induces the expression of metallothioneins (Buchtova et al., 2022). The latter exhibit a protective effect on tumor cells by binding heavy metals, which plays an important role in preventing anticancer effects of disulfiram and its metabolite bis-diethyldithiocarbamate-copper complex (Buchtova et al., 2022), while this effect has not been demonstrated for platinum compounds (Buchtova et al., 2023).

In the case of the anthracycline derivative doxorubicin, synergism with CBD was found in two osteosarcoma cell lines (J. Li et al., 2023). Specifically, synergies were identified in terms of reduced viability and colony formation, induction of apoptosis and inhibition of cell progression, migration and invasion. In connection with its anti-invasive effect, the CBD/doxorubicin combination caused a strong down-regulation of matrix metalloproteinase-13 (MMP-13). Regarding the synergistic effect of the CBD/doxorubicin combination on apoptosis, a down-regulation of Bcl-2 with concomitant up-regulation of Bax was observed. With the downregulation of cyclin D1 and CDK4, typical features of a cell cycle arrest at the biochemical level were also described. Moreover, CBD and doxorubicin synergistically inhibited the growth of osteosarcoma xenografts in nude mice.

Finally, another report showed that CB<sub>2</sub> receptor activation by JWH-133 enhanced the efficacy of bortezomib in inducing apoptosis and reducing cell migration and cell cycle progression in osteosarcoma cells (Punzo et al., 2018).

## 4. Clinical studies on the outcome of cancer patients after combined administration of therapeutic anticancer approaches and cannabinoids

### 4.1. Randomized clinical studies

The currently most important findings for clinical application relate to the potentiation of the effect of TMZ by cannabinoids in the treatment of GBM, as these have also been confirmed in a clinical study.

Accordingly, in a small randomized, placebo-controlled phase 1b trial involving patients with recurrent GBM multiforme, it was shown that patients had a longer survival time when TMZ was combined with nabiximols, an oromucosal spray consisting of a combination of THC and CBD, compared with the combination of TMZ with a placebo (Twelves et al., 2021; NCT01812603, NCT01812616). This study included a total of 21 patients, of which the 12 patients treated with nabiximols had a survival rate of 83 % after one year, with 10 patients surviving, while 44 % of the 9 patients treated with placebo and thus 4 patients survived.

#### 4.2. Case reports, non-randomized open-label and observational studies

A compilation of 119 case reports showed that 92 % of patients treated with pharmaceutical-grade synthetic CBD exhibited a favorable clinical response with tumor shrinkage or a decrease in circulating tumor cells. However, the analyses of these cases, which did not include a placebo control, do not prove causality of events (Kenyon, Liu, & Dalglish, 2018).

Two advanced glioma cases, both 38-year-old males, showed improvement after subtotal resection and pharmacologic intervention with procarbazine, lomustine, vincristine, and CBD. One patient with grade IV GBM experienced exacerbation and premature pseudoprogression, which occurs in 30 % of all patients and could be treated here by pharmacotherapeutic intervention, including CBD. The second patient was diagnosed with a grade III oligodendroglioma after brain surgery. The patient underwent a partial resection with significant reduction of the infiltrative components of the tumor and was in excellent physical condition during radiochemotherapy, which was supplemented by the administration of CBD (Dall' Stella, Docema, Maldaun, Feher, & Lancellotti, 2018).

Another publication about a series of 9 brain tumor cases, 6 of them diagnosed with grade IV GBM, found that quality of life and survival rates appear to be higher than expected when CBD at a dose of usually up to 400 mg/day was taken in addition to standard therapy (Likar, Koestenberger, Stultschnig, & Nahler, 2019). Accordingly, the authors reported an average survival time of 22.3 months, which exceeds the average survival time of 15 months for GBM patients. However, this reference to the historical control should be treated with caution due to the small number of patients.

The safety of CBD was recently confirmed in an open-label, single center, phase 1 dose escalation study in patients with recurrent prostate cancer after prostatectomy and/or salvage radiotherapy or primary definitive radiotherapy who received doses of 600 and 800 mg of this cannabinoid (Myint et al., 2023). At 12 weeks, 16 of 18 patients had stable biochemical markers, with one patient showing a decrease in prostate specific antigen (PSA). Only one patient showed an increase in PSA.

There are two further interesting reports here that, while not addressing the level of efficacy, do not rule out corresponding clinical alterations due to pharmacokinetic interactions in other cases. Accordingly, a case report of a 58-year-old Caucasian woman with ER/PR-positive, HER-2-negative breast cancer who received CBD and tamoxifen showed a decrease in serum levels of endoxifen (4-hydroxy-*N*-desmethyl-tamoxifen), the active metabolite of tamoxifen, which is formed from the latter via cytochrome P450 (CYP) enzymes CYP3A4 and CYP2D6 (Parihar et al., 2022). After discontinuation of CBD, endoxifen was increased by 18.75 %. The authors hypothesized that this interaction could lead to possible clinical complications in patients with intermediate or poor CYP2D6 metabolism. Remarkably, the measurements are consistent with those of an open, single-arm study in patients receiving tamoxifen monotherapy or tamoxifen in combination with CBD oil. Compared to tamoxifen monotherapy, treatment with CBD in addition to tamoxifen resulted in a 12.6 % reduction in the area under the curve (AUC) of endoxifen, without affecting the limits of bioequivalence. However, in patients with an intermediate metabolizer CYP2D6 phenotype, the decrease in endoxifen AUC

appeared to be more pronounced than in patients with an extensive metabolizer CYP2D6 phenotype (Buijs et al., 2023). Overall, the described interaction between tamoxifen and CBD could be related to the repeatedly described CYP2D6 inhibition by CBD (Brown & Winterstein, 2019; Graham, Martin, Lucas, Murnion, & Schneider, 2022; Yamaori, Okamoto, Yamamoto, & Watanabe, 2011).

Several observational studies have been conducted on the effects of cannabis on immune checkpoint inhibitor therapy, with some of them attributing a deleterious effect to cannabis. In a prospective observational study including 102 patients with advanced cancers who initiated immunotherapy (68 receiving PD1, PD-L1 or cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies and 34 with checkpoint inhibitor plus cannabis), the use of cannabis significantly shortened the time interval until cancer progression and the overall survival rate of cancer patients (Bar-Sela et al., 2020). One limitation of this study is that most patients changed cannabis products between months according to the recommendations of the cannabis companies and not the medical ones. In a retrospective study by the same group, 140 patients with advanced cancers received the PD-1 antibody nivolumab and 51 of whom also took cannabis. Here, a lower response rate was observed in cannabis users, without affecting overall or progression-free survival (Taha et al., 2019). According to the authors, limitations of these studies include the relatively small patient groups with a high degree of heterogeneity in the study population. A reanalysis of the data from both studies published in 2024 continued to find some significant differences between cannabinoid users and non-users that had not been reported and that may have altered the conclusions (Piper et al., 2024). In addition, the use of tobacco appears to be another potential confounding factor in some of the published data.

On the other hand, a retrospective analysis examining a homogeneous cohort of 201 patients with metastatic non-small cell lung cancer treated with the PD-1 antibody pembrolizumab and consuming cannabis revealed no significant effect of cannabis on time-to-progression or overall survival (Waissengrin et al., 2023).

Finally, a recent retrospective analysis reviewed the records of 106 patients, 28 of whom were cannabinoid users, in most cases dronabinol. Here, the median overall survival of 6.7 months among cannabinoid users was significantly lower than the 17.3 months among non-users. Likewise, median progression-free survival and disease control rate were significantly lower for cannabinoid users compared to non-cannabinoid users (Hadid et al., 2024). While the aforementioned studies used exceptionally high doses of cannabinoids ( $\geq 20$  g monthly), in the latter study, most patients received lower doses ( $\leq 0.31$  g monthly). It is noteworthy that even under these circumstances, a similar negative effect on clinical outcomes was observed.

#### 4.3. Ongoing clinical studies

The ARISTOCRAT study is a multicenter, double-blind, placebo-controlled, randomized phase 2 study comparing nabiximols to placebo in recurrent GBM patients with MGMT promoter methylation (NCT05629702). In the study, a planned target number of 234 patients will be randomized in a 2:1 ratio to receive either nabiximols or a placebo matched with nabiximols in combination with standard TMZ. Magnetic resonance imaging scans will be performed at screening, week 10, week 22, week 30 and then every 3 months after the start of study treatment according to standard practice (Bhaskaran et al., 2024).

In addition, a first-in-human, open-label, phase 1/2 study was initiated with TT-816, a novel oral cannabinoid CB<sub>2</sub> receptor antagonist. TT-816 was administered as a single agent and in combination with a PD-1 inhibitor in advanced cancers such as non-small cell lung cancer (NSCLC), ovarian cancer and renal cell carcinoma (RCC) to determine its maximum tolerated dose. However, the trial was terminated due to an operational decision of the company (NCT05525455). The rationale for the CB<sub>2</sub> antagonist therapy proposed here was that upregulated CB<sub>2</sub> receptor expression and increased levels of endocannabinoids

observed in a variety of tumor microenvironments have been associated with cancer aggressiveness.

The aim of an ongoing observational study is to determine how cannabinoid use affects the immunological microenvironment of melanoma and to what extent cannabinoids reduce tumor-infiltrating lymphocytes in melanoma (NCT05520294).

Furthermore, there is a phase 2a study of the antitumor effect of cannabis oil containing 10 % THC and 5 % CBD in patients with advanced, untreatable hepatocellular carcinoma, in which the tumor size is to be examined six months after the start of treatment (EudraCT Number: 2018–004505–34). However, there are yet no results available from this study. Another study addressed the safety and tolerability of cannabis as primary outcome in patients with GBM who received standard fractionation radiotherapy of 60 Gy in 30 treatments with TMZ. However, this study was terminated (NCT03246113). In addition, a currently recruiting study focuses on the effect of CBD on anxiety symptoms of GBM patients (NCT05753007). Finally, a phase 1b, open-label, multicenter, intrapatient dose-escalation clinical trial in patients with newly diagnosed GBM focused on the safety profile of a combination of a THC/CBD mixture with additional treatment with TMZ and radiotherapy to analyze the maximum tolerated THC/CBD dose and adverse effects (NCT03529448).

Regarding the response rate as a primary outcome, there is also a clinical trial listed in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03607643) whose status is currently unknown. This randomized, double-blind, placebo-controlled, parallel multicenter study is designed to investigate the efficacy of CBD combined with standard-of-care treatment in patients with multiple myeloma, GBM, and gastrointestinal malignancies.

## 5. Preclinical studies on the influence of cannabinoids on side effects of established chemotherapeutic agents

### 5.1. Chemotherapy-induced peripheral neuropathy

CIPN is a side effect of neurotoxic drugs such as platinum-based agents, taxanes, vinca alkaloids, proteasome inhibitors and immunomodulatory agents. It occurs in almost 30–60% of patients and is associated with an increased risk of falls, pain and insomnia (Molinares, Kurtevski, & Zhu, 2023).

Based on preclinical research, a significant number of studies suggest that cannabinoids may be a viable therapeutic option for the treatment of CIPN and neuropathic pain. Accordingly, various concentration ratios of THC and CBD reduced CIPN in mice (Sepulveda, Vrana, Graziane, & Raup-Konsavage, 2022). In a mouse model of paclitaxel-induced neuropathic pain, the combination of CBD and tetrahydrocannabinol (THCV) was also found to improve thermal and mechanical neurobehavioral symptoms. In this context, experiments with inhibitors and antagonists on spinal ganglion cells of mice revealed that the protective effect of CBD and THCV against neuropathic pain is apparently mediated via 5-hydroxytryptamin (5-HT, serotonin) 1A receptors (5-HT<sub>1A</sub>) and CB<sub>1</sub> receptors, respectively (Kumar Kalvala et al., 2022). Interestingly, in paclitaxel-treated female C57BL/6 mice mechanical sensitivity was reduced by CBD, which was likewise reversed by WAY 100635, an antagonist to 5-HT<sub>1A</sub>, but not by cannabinoid receptor antagonists (Ward et al., 2014). The anti-allodynic effect of CBD antagonized by WAY-100635 could later be substantiated using paclitaxel-treated C57BL/6j mice (Ortiz et al., 2023). Another study revealed CBD to reduce paclitaxel-induced neuropathic pain in male C57BL/6 mice by increasing AEA and 2-AG levels in the spinal cord, subsequently activating CB<sub>2</sub> receptors and reducing spinal expression of type 4 Toll-like receptors (TLR4) (Dos Santos et al., 2023). A separate study showed that CBG and CBD reduced the naloxone-induced jump behavior and, when combined, had a synergistic effect. In this context, CBG weakened the acute antinociceptive effects of morphine and CBD, while it reversed the oxaliplatin-associated mechanical sensitivity under certain dosing conditions (Hayduk, Hughes, Winter, Milton, & Ward, 2024). CBG

likewise significantly reduced mechanical hypersensitivity in cisplatin-induced neuropathy and reduced pain sensitivity up to 60–70 % of baseline (Nachnani et al., 2023).

A recent investigation was further able to prove that a cannabis extract decreased mechanical allodynia, thermal hyperalgesia, and inflammatory cytokines induced upon treatment of rats with paclitaxel (Y. Xu et al., 2024). Another study indicated that terpenes from the cannabis plant can alleviate chronic neuropathic pain, including CIPN, in various murine models (Schwarz et al., 2024). The same research group was able to identify CBN as a minor cannabinoid with analgesic effects, while in the same investigation cannabidiol (CBDV), CBG, THC and  $\Delta^8$ -THC did not show similar effects (Schwarz et al., 2024).

With regard to CBD, it was also shown that PECS-101, a fluorinated CBD analogue, reduces long-lasting mechanical and cold allodynia caused by paclitaxel (Silva et al., 2022). This effect was not mediated via cannabinoid receptors but through PPAR $\gamma$  and, accordingly, was not observed in macrophage-specific PPAR $\gamma$ -deficient mice. KLS-13019, a CBD derivative that exhibits GPR55 receptor antagonist properties, was recently demonstrated to reduce paclitaxel-induced allodynia in rats (Ippolito, Hayduk, Kinney, Brenneman, & Ward, 2024).

Substances that modulate endocannabinoid tone have also shown efficacy in preclinical models of CIPN. Accordingly, the MAGL inhibitor JZL184 reduced neuropathic pain in a murine cisplatin-induced pain model (Khasabova et al., 2014). Likewise, the novel enol carbamate FAAH inhibitor 1-biphenyl-4-ylethenylpiperidine-1-carboxylate, designated ST4070, reduced neuropathic pain in various animal models, such as vincristine-induced neuropathic pain, but also in a model of streptozotocin-induced diabetic pain and chronic constriction injury-induced neuropathic pain (Caprioli et al., 2012). Cisplatin-induced mechanical and cold allodynia was also reported to be reduced in Sprague-Dawley rats by treatment with brain permeant (URB597) and impermeant (URB937) inhibitors of FAAH and the MAGL inhibitor JZL184 via both cannabinoid receptor subtypes (Guindon, Lai, Takacs, Bradshaw, & Hohmann, 2013). Remarkably, the antiallodynic effects of endocannabinoid modulators were comparable to those of morphine and even surpassed those of morphine with respect to cisplatin-induced mechanical allodynia. These data are consistent with findings that showed that exogenously administered endocannabinoids reduce CIPN. Thus, AEA has been demonstrated to alleviate cisplatin-induced mechanical allodynia (Çengelli Ünel et al., 2021). However, the latter study showed that the administration of AEA led to a significant decrease in locomotion and an increase in catalepsy in the cannabinoid tetrad test. A further study reported URB597 and URB937 to reduce paclitaxel-induced allodynia independently of CB<sub>1</sub> receptor activation (Slivicki, Xu, Mali, & Hohmann, 2019). In yet another investigation, URB597 reduced the spontaneous activity and mechanical responses of C-fiber nociceptors from male C3H/HeJ mice treated with cisplatin via CB<sub>1</sub> receptor activation (Uhelski, Khasabova, & Simone, 2015). A recent work that likewise used the cisplatin-based murine pain and neuropathy model found the endocannabinoid system to be involved in CIPN as the inhibitor of FAAH and MAGL, JZL195, significantly reduced mechanical and cold allodynia via CB<sub>1</sub> and CB<sub>2</sub> receptors, which was associated with a reduction in TLR4 expression and thus downregulation of important neuroinflammatory factors (Kim, Nan, Kim, Cha, & Lee, 2024).

One study, moreover, has shown that during paclitaxel-induced mechanical allodynia in a murine model, there is a deficiency of 2-AG in the periphery, but not in the central nervous system. Accordingly, increasing 2-AG in the paw by local administration of 2-AG or a MAGL inhibitor alleviated mechanical allodynia in a CB<sub>1</sub> and CB<sub>2</sub> receptor-dependent manner (A. Thomas, Okine, Finn, & Masocha, 2020). The finding that 2-AG plays a pivotal role in reducing CIPN was further supported by the fact that JZL184 and MJN110, both inhibitors of MAGL, exhibited reversal of paclitaxel-induced mechanical allodynia in mice (Curry et al., 2018).

Another agent that has been shown to reduce CIPN by oxaliplatin is ART26.12 (G. Warren et al., 2024). ART26.12 represents an inhibitor of fatty acid-binding protein 5 (FABP5) (W. G. Warren et al., 2025), which is responsible for the intracellular transport of endocannabinoids (Schwarz et al., 2018).

Several well-studied as well as novel synthetic cannabinoids have been preclinically tested for the treatment of CIPN. In a recent study in male Wistar rats, WIN 55,212–2 was described as an option for the relief of neuropathic and visceral pain caused by 5-FU, without affecting the cannabinoid tetrad (Vera et al., 2023). The same research group had previously shown that WIN 55,212–2, ACEA and JWH-133 were able to reduce mechanical allodynia in a rat model with cisplatin-induced neuropathy and that these effects were reduced by antagonists against both cannabinoid receptors (Vera, Cabezos, Martín, & Abalo, 2013). One further investigation reported the combination of tramadol with WIN 55,212–2 in cisplatin-challenged rats as an option for treatment of CIPN (Haddad et al., 2023). In other experiments with rats, WIN 55,212–2 was found to reduce the mechanical hypersensitivity caused by paclitaxel, an effect that was reversed by a CB<sub>1</sub> antagonist. On the other hand, paclitaxel-induced cold allodynia was relatively sensitive to blockade with either CB<sub>1</sub> or CB<sub>2</sub> receptor antagonists (Rahn et al., 2014). A further study demonstrated that JWH-182 that acts as full agonist with higher affinity to CB<sub>1</sub> than to CB<sub>2</sub> exhibited antinociceptive potential in animals with neuropathic pain caused by paclitaxel (Filipiuc et al., 2024). This report, however, did not address the role of cannabinoid receptors. In a rat model of cisplatin-induced peripheral neuropathy, the peripherally restricted cannabinoid receptor agonist 4-[2-[–(1E)-1[(4-propyl-naphthalen-1-yl)methylidene]-1H-inden-3-yl]ethyl]morpholine (PrNMI) was found to effectively reduce mechanical and cold allodynia via activation of the CB<sub>1</sub> receptor (Mulpuri et al., 2018). Furthermore, the CB<sub>2</sub> receptor agonists AM1710 and LY2828360, which also show limited central penetration, suppressed the mechanical and cold allodynia caused by paclitaxel (X. Lin et al., 2022).

Allosteric modulation of the CB<sub>1</sub> receptor was also addressed in corresponding experiments. Accordingly, GAT211, a novel positive allosteric modulator of the CB<sub>1</sub> receptor, has been reported to be effective in animal models in reducing paclitaxel-induced allodynia (Slivicki et al., 2018). GAT229, another positive allosteric CB<sub>1</sub> agonist, reduced and slowed the progression of thermal hyperalgesia and mechanical allodynia in a model of murine cisplatin-induced peripheral neuropathic pain via CB<sub>1</sub> receptor activation (Bagher, Binmahfouz, Shaik, & Eid, 2023).

A number of studies addressed the role of CB<sub>2</sub> receptors in more detail in the protection against CIPN. Thus, using a model of oxaliplatin-induced peripheral neuropathy, it was shown that  $\beta$ -caryophyllene, a sesquiterpene lactone present in cannabis and non-cannabis plants, reduces mechanical and cold allodynia in mice through CB<sub>2</sub> receptor activation without reducing the effect of oxaliplatin on experimental tumor growth (Agnes et al., 2023). This finding is consistent with another study showing that the CB<sub>2</sub> receptor agonist AM1710 reduces both mechanical and cold allodynia in cisplatin- and paclitaxel-induced neuropathic pain models (Deng et al., 2012). The prevention of paclitaxel-induced mechanical allodynia in rats and mice has also been reported for the selective CB<sub>2</sub> agonist MDA7 (Naguib et al., 2012). In this context, it is worth mentioning that paclitaxel can induce the expression of CB<sub>2</sub> receptors in microglia in the dorsal horn of rats, making the animals more receptive to CB<sub>2</sub>-activating drugs (Wu, Hocevar, Bie, Foss, & Naguib, 2019). Suppression of mechanical allodynia developed in paclitaxel-treated animals was also proven for two further CB<sub>2</sub> agonists, the aminoalkylindole AM1241 and the cannabylactone AM1714 (Rahn et al., 2008). Likewise, experiments with paclitaxel-treated knockout mice demonstrated the prominent role of the CB<sub>2</sub> receptor. Here, the CB<sub>2</sub> receptor agonist AM1710 reduced allodynia in wild-type and CB<sub>1</sub> knockout mice, whereas it did not produce similar effects in CB<sub>2</sub> knockout mice

(Deng et al., 2015). In a further study comparing AM1710 with WIN 55,212–2 in rats treated with paclitaxel, it was found that the mechanical and cold allodynia caused by paclitaxel was reduced by treatment with both cannabinoids (Rahn et al., 2014). With regard to cold allodynia, only higher doses of AM1710 were effective here. Another study showed that JWH-007, a non-selective CB<sub>1</sub> and CB<sub>2</sub> agonist, and the CB<sub>1</sub> agonists AM-694 and MAB-CHMINACA, as well as some extracts from the cannabis plant, had a protective effect on the viability of fibroblasts and primary cultured neurons treated with paclitaxel in vitro (Creanga-Murariu et al., 2024).

Interestingly, there are several publications that have recorded gender differences in cannabinoid effects on CIPN. Experiments using cisplatin in a CIPN model showed that both CB<sub>1</sub> and CB<sub>2</sub> receptor agonism elicit antinociceptive effects, with sex differences in the effect of cannabinoid receptor activation (Barnes et al., 2024). Accordingly, female mice developed tolerance more rapidly than males after administration of the CB<sub>1</sub> agonist ACEA, whereas the antiallodynic effect of selective CB<sub>2</sub> agonism did not lead to tolerance development. Another study that likewise considered the sex-specificity of such effects focused primarily on the regulation of neuroinflammatory markers in a paclitaxel-induced neuropathy model (H. Li & Ward, 2024). Prophylactic administration of CBG protected male and female mice to a comparable extent from increased mechanical sensitivity. Here, CBG prevented increased expression of inflammatory and pain markers in the periaqueductal gray of female C57Bl/6 mice, while neither paclitaxel alone nor combinations with CBG affected the expression of genes involved in inflammatory processes. In addition, another CB<sub>2</sub> receptor agonist, LY2828360, which reduced chemotherapy-induced neuropathic nociception in male mice, triggered a morphine-sparing and thus inhibition of the naloxone-induced morphine withdrawal effect in male mice, which did not occur in female mice (Guenther et al., 2024). Gender differences were further observed in a murine model of cisplatin-induced neuropathic pain. Accordingly, application of different ratios of THC and CBD revealed a significant decrease in mechanical hypersensitivity that was obvious in female and male mice when a dose of 4 mg/kg THC was combined with 2 mg/kg CBD, whereas a dose of 2 mg/kg THC combined with 4 mg/kg CBD did reach significant reduction of mechanical hypersensitivity only in female mice (Sepulveda et al., 2022). Finally, the CBD analogue KLS-13019 administered by oral gavage reversed paclitaxel-induced allodynia in male and female rats to a comparable extent (Ippolito et al., 2024).

There are also other new approaches to how CIPN can be treated. One study found that heteromers of CB<sub>1</sub> and delta opioid receptors are upregulated in the spinal cord of mice treated with paclitaxel and humans diagnosed with CIPN due to treatment with paclitaxel and/or platinum compounds. Accordingly, mixed cannabinoid/opioid agonists, such as SNC80, have been shown to be effective in reducing mechanical allodynia in context with CIPN in paclitaxel-treated animals, thus offering innovative concepts (Sierra et al., 2019).

## 5.2. Nephrotoxicity

Attenuation of the adverse effects caused by chemotherapy could possibly also be achieved via attenuation of their nephrotoxic effects by cannabinoids. In line with this, experiments with FAAH knockout mice demonstrated a role of the endocannabinoid system in this context. Accordingly, these mice showed a significantly higher protection against the nephrotoxic effects of cisplatin compared to control animals (Chen et al., 2023). Furthermore, a recent study described that cannabigerolic acid (CBGA), but not CBD, protects the kidney from cisplatin-induced nephrotoxicity and acute kidney disease (Suzuki, Fleig, & Penner, 2023). Similarly, the selective CB<sub>2</sub> receptor agonist 1-phenylisatin improved cisplatin-induced nephrotoxicity in mice (Chafik, Michel, & El-Demerdash, 2022). CB<sub>2</sub>-dependent inhibition of cisplatin-induced neuropathy was also confirmed for other substances such as the CB<sub>2</sub> receptor-activating compounds LEI-101

(Mukhopadhyay et al., 2016) and  $\beta$ -caryophyllene (Horváth et al., 2012). This also seems to be consistent with the finding that activation of the CB<sub>2</sub> receptor leads to an inhibition of inflammatory processes and oxidative stress in the kidney (Mukhopadhyay et al., 2010).

### 5.3. Cardiotoxicity

There is also evidence that cannabinoids can modulate the cardiotoxic effects of chemotherapeutic agents. In this regard, several studies on the inhibition of doxorubicin-induced cardiotoxicity by cannabinoid compounds exist. In the first of these investigations, doxorubicin-induced cardiotoxicity in mice was reduced by the CB<sub>1</sub> receptor antagonists rimonabant and AM-281 (Mukhopadhyay et al., 2007). Later, the same group was able to confirm the cardioprotective effect of CB<sub>1</sub> receptor antagonism using FAAH knockout mice, which were more sensitive to doxorubicin-induced cardiotoxicity (Mukhopadhyay et al., 2011). In contrast to these data, AEA has been shown to attenuate the acute depression of fractional shortening, ventricular wall thickness or developed pressure caused by doxorubicin in rats, thus exerting a cardioprotective effect (Hydock, Lien, & Hayward, 2009). Without clarifying the actual role of the CB<sub>1</sub> receptor in the cardiotoxic effect of doxorubicin, other cannabinoids were later investigated. Here it was shown that CBD can contribute to a reduction in the cardiotoxic effect of doxorubicin in rats (Fouad, Albuli, Al-Mulhim, & Jresat, 2013) and mice (Hao et al., 2015), as can the CB<sub>2</sub> receptor agonist  $\beta$ -caryophyllene in rats (Meeran et al., 2019). A recent review article highlighted the effect of CBD in the context of cardiovascular diseases, including doxorubicin-induced cardiotoxicity, which is mediated by the anti-inflammatory, vasodilatory, antifibrotic and antioxidant properties of this cannabinoid (Naya, Kelly, Hogwood, Abbate, & Toldo, 2024).

### 5.4. Cystitis and bladder complications

Another clinical problem associated with chemotherapy that could be reduced with cannabinoid-derived substances involves cystitis and bladder complications. In this context studies in FAAH-knockout mice have shown that these mice exhibit higher AEA levels compared to wild-type mice, a significantly milder course of cyclophosphamide-induced cystitis with reduced levels of COX-2, interleukin (IL)-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), nerve growth factor (NGF), and NOS2 (inducible NOS) (Wang, Wang, Hillard, & Bjorling, 2015). These data suggest that the endocannabinoid system may play an important role in bladder function and thus represents a potential target for the treatment of inflammation there. In line with this notion, a protective function of the CB<sub>1</sub> receptor was demonstrated in the cyclophosphamide-induced cystitis model in mice (Walczak & Cervero, 2011). Here, the authors were able to demonstrate *ex vivo* that local activation of CB<sub>1</sub> receptors with the non-selective cannabinoid agonist AZ12646915 reduces the sensitization of afferent bladder neurons during acute inflammation.

However, these results are in contrast to a recently published report that the peripheral CB<sub>1</sub> receptor antagonist JD5037 mitigated severity in a mouse model of cyclophosphamide-induced cystitis in association with the downregulation of proinflammatory factors (Hinden et al., 2023). Regarding the effect of the CB<sub>1</sub> antagonist, the authors postulated an alternative signaling pathway that reduces lower urinary tract symptoms by downregulating CB<sub>1</sub> receptors on urothelial cells and detrusor muscle, rather than by modulating CB<sub>1</sub> activity in sensory neurons that innervate the bladder (for review see also Christie, Brookes, & Zagorodnyuk, 2021). The contradictory results regarding the role of CB<sub>1</sub> in the modulation of cyclophosphamide-induced cystitis may be due to the use of different animal models, but also to the different read-out parameters, which on the one hand address the modulations in bladder neurons (Walczak & Cervero, 2011) and on the other hand reflect bladder function and urination patterns

by a voiding spot assay (Hinden et al., 2023). In order to properly assess the therapeutic options, there is a need for clarification here, which must be addressed in future studies.

Meanwhile, further receptors that can be activated by cannabinoids are also thought to play a protective role in cystitis. Accordingly, one study found that cyclophosphamide upregulates CB<sub>2</sub> receptor expression in the mouse bladder and that the CB<sub>2</sub> receptor agonist JWH-133 reduces cyclophosphamide-induced bladder tissue inflammation and oxidative stress damage. The regulation by JWH-133 included an increase of LC3-II/LC3-I ratio and a decreased expression of SQSTM1/p62, which indicate autophagy-mediated effects (Q. Liu et al., 2020). Studies in rat models have shown that the bladder-protective effect of the endocannabinoid-like compound PEA is abolished in the presence of a CB<sub>1</sub> receptor and a PPAR $\gamma$  antagonist (Pessina et al., 2015). Moreover, in female Wistar rats, the GPR55 agonist O-1602, a CBD analogue, was shown to reduce numerous histological and cystometric features associated with cystitis and bladder dysfunction caused by cyclophosphamide (Wróbel, Zapła, Zapła, Piecha, & Radziszewski, 2020).

### 5.5. Mucositis

In an experimental periodontitis rat model, CBD-treated animals showed less alveolar bone loss, less expression of receptor activator of nuclear factor- $\kappa$ B (RANK) and its ligand (RANKL), and reduced neutrophil migration in gingival tissue, which was associated with less production of IL-1 $\beta$  and TNF- $\alpha$  (Napimoga et al., 2009). Subsequently, and in line with these results, CBD was finally shown to accelerate the healing of oral mucositis caused by 5-FU through its anti-inflammatory and antioxidant effects (L. d. F. Cuba et al., 2020). In this study, oral mucositis was induced in mice by administering 5-FU, followed by mechanical trauma to the tongue, which was improved morphologically and in terms of hematological and oxidative stress response by CBD. However, the use of CBD for chemotherapy-induced mucositis requires more data collection to evaluate the potential benefits for patients with this condition (L. F. Cuba, Salum, Cherubini, & Figueiredo, 2017).

## 6. Clinical studies and case reports on the effect of cannabinoids on adverse side effects of chemotherapeutic drugs

### 6.1. Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is one of the few indications for which various cannabinoids have been approved by the FDA and the EMA, with approvals for dronabinol and nabilone (FDA) and nabilone (EMA), respectively. In fact, cannabinoids are considered a promising treatment option for complicated conditions, including breakthrough, anticipatory, or refractory CINV (Hoch et al., 2024). Consistent with this notion, a recently published randomized, placebo-controlled trial reported that an oral capsule formulation containing THC and CBD was an effective adjunct in adults with refractory nausea and/or vomiting during moderately or highly emetogenic intravenous chemotherapy, despite guideline-compliant antiemetic prophylaxis (Grimison et al., 2024). The administration of cannabinoids, however, was also associated with additional adverse effects here.

According to a Cochrane review published in 2015, cannabinoids are more effective than placebo and as effective as the conventional antiemetic prochlorperazine for the treatment of CINV (Smith, Azariah, Lavender, Stoner, & Bettiol, 2015). However, to date there is only one randomized clinical trial comparing the effect of dronabinol with a current guideline medication, in this case the 5-HT<sub>3</sub> antagonist ondansetron, for CINV, in which both drugs proved to be similarly effective (Meiri et al., 2007). By contrast, there are no comparative studies between cannabinoids and other 5-HT<sub>3</sub> antagonists or neurokinin 1 (NK1) antagonists. Thus, a recent meta-analysis pointed out that further randomized controlled trials are needed to investigate the efficacy and

safety of oral cannabinoids in CINV (Chow et al., 2020). Finally, another meta-analysis assessing the quality of the existing clinical studies revealed a low quality evidence suggesting that cannabinoids are associated with improvements in nausea and vomiting due to chemotherapy (Whiting et al., 2015).

### 6.2. Chemotherapy-induced peripheral neuropathy

Cannabinoid compounds have been tested in various clinical trials for the treatment of neuropathic disorders (D'Andre et al., 2021; Langford et al., 2013; Weizman et al., 2024). Nevertheless, the guidelines of the German Neurological Society do not recommend cannabinoids for the treatment of neuropathic pain of any cause, as the efficacy is low and the rate of side effects is high (Maihöfner, Diel, Tesch, Quandt, & Baron, 2021). Clinical studies on the effects of cannabinoids in chronic pain associated with cancer include studies in which the pain is caused by the tumors themselves or by side effects of chemotherapeutic agents. In this context, only the former are to be addressed here.

A randomized, placebo-controlled, 16-patient crossover pilot study on the benefits of using nabiximols to reduce chronic neuropathic pain associated with chemotherapies such as paclitaxel, vincristine and cisplatin showed that 5 out of 16 patients responded to the therapy with a large reduction in neuropathic pain (Lynch, Cesar-Rittenberg, & Hohmann, 2014). In line with this notion, a recent case report of a 52-year-old woman with TNBC in remission for 5 years reported a reduction in chronic CIPN in response to CBD as part of the prospective, open-label Cannabis Exercise Study (CANNEX, MUHC REB 2022–8570). CBD was used here at a maximum daily dose of 300 mg in combination with a multimodal exercise program (Vigano et al., 2024). In this case, CIPN had occurred after neoadjuvant chemo- and immunotherapy and adjuvant immune- and radiotherapy with the drugs paclitaxel, trastuzumab, and pertuzumab. On the other hand, a recently published randomized, placebo-controlled pilot study in patients with established CIPN showed that a two-week topical application of a cream containing CBD did not improve painful CIPN (D'Andre et al., 2024).

### 6.3. Cachexia

The appetite-stimulating effect of *Cannabis sativa*, which has been documented for many centuries (Kirkham, 2009), can counteract the wasting associated with cancer, which continues to be a major problem. In fact, about 30 % of all cancer-related deaths are thought to be due to cachexia (Haehling & Anker, 2010). However, in patients with cancer-related anorexia-cachexia syndrome, treatment with cannabinoids does not significantly improve appetite, oral intake or anorexia-related quality of life (S. Johnson, Ziegler, & August, 2021). The use of cannabinoids in the treatment of chemotherapy-induced cachexia is therefore currently not classified with a recommendation strength and was classified as weakly supported in the guidelines of the European Society for Clinical Nutrition and Metabolism (Arends et al., 2017).

### 6.4. Ongoing clinical studies

A number of ongoing studies are focusing on the non-psychoactive cannabinoid CBD. Accordingly, several studies are underway investigating the impact of CBD in terms of a possible reduction in the adverse effects of standard treatment in patients. One yet unpublished study is examining the effects of CBD on the body weight of patients treated with oxaliplatin or paclitaxel (NCT04585841). A further study addresses the effect of CBD for prevention of CIPN as an interventional phase 2 trial (NCT04582591). Similar monitoring of a possible reduction of chemotherapy-induced severe side effects by CBD is being investigated in the Coala-T-CBD study. Here, the impact of CBD on the severity and duration of CIPN in patients receiving neurotoxic chemotherapy for

non-metastatic breast, uterine, pancreatic, and colorectal cancer, as well as all stages of ovarian cancer, is being recorded (NCT04398446).

A phase 2 study, which is also in the recruitment phase, is investigating whether the endocannabinoid-like compound PEA can alleviate the symptoms of CIPN in cancer patients (NCT05246670). A phase 1 feasibility study (CanAroma) addressed the effect of topical cannabinoids for the treatment of aromatase inhibitor-associated musculoskeletal syndrome in adults with hormone receptor-positive breast cancer (NCT05935891). However, the results of this study have not yet been published. Moreover, the DISCOVER study examined whether dronabinol has a positive influence on quality of life and whether symptoms caused by the tumor or chemotherapy itself can be alleviated by this cannabinoid. The primary objective of this phase III clinical trial is to systematically assess both the effectiveness and safety profile of THC seeking to determine its potential as an adjunctive therapeutic agent alongside standard first-line chemotherapy in a cohort of patients diagnosed with metastatic pancreatic cancer (NCT03984214, Keil et al., 2024). The results are still pending. Finally, a completed non-randomized open-label study was designed to investigate the extent to which cannabis affects cognitive impairment in cancer patients undergoing chemotherapy (NCT01983267). However, the corresponding results have not yet been published.

## 7. Conclusions and outlook

The interactions between cannabinoids and chemotherapeutics constitute a complex subject with many yet unknown variables. There are two important therapy-relevant aspects of the interaction between cannabinoids and chemotherapeutic agents that could potentially benefit cancer patients: firstly, the systemic potentiation of chemotherapeutics by cannabinoids, primarily leading to an extension of life by overcoming therapy resistance and secondly, the reduction of chemotherapy-induced side effects.

In the second case, the most clinically relevant topic is currently the reduction of CINV through cannabinoids. Accordingly, dronabinol (FDA, EMA) and nabilone (EMA) are approved for the treatment of CINV. However, as stated and requested previously (Chow et al., 2020), this should not prevent cannabinoids from being tested in randomized clinical trials versus modern antiemetics listed in the guidelines. Similarly, well-controlled clinical trials are recommended to examine other potentially protective cannabinoid effects on chemotherapy-related side effects. For example, the clinical impact of cannabinoids on CIPN, a common side effect of platinum-based agents, taxanes, vinca alkaloids, proteasome inhibitors and immunomodulatory agents (Molinas et al., 2023), should be further investigated, especially in view of the extensive preclinical evidence obtained here in recent years.

In the first case, there is a body of preclinical evidence for additive and synergistic effects between cannabinoids and chemotherapeutic agents in killing cancer cells. Corresponding findings were listed in detail for the various tumor entities. However, there are obviously exceptions to the widely demonstrated cooperative interaction between cannabinoids and chemotherapeutic agents in inducing cancer cell death, which should be further investigated. Thus, preclinically described interactions of cannabinoids with platinum compounds must be considered particularly critically. According to some studies, cytostatic effects of platinum compounds are enhanced by cannabinoids, but others have described antagonizing effects of cannabinoids, especially CBD, on platinum-based therapies, which would also be consistent with the observations that cannabinoids can reduce platinum-induced side effects. This also raises the question of the extent to which cannabinoids inhibit platinum-induced side effects at the expense of systemic anticarcinogenic effects.

Cancer immunotherapeutics targeting PD-1 or PD-L1 are another group of important anticancer agents whose interaction with cannabinoids must be addressed in future randomized analyses with large patient cohorts to determine possible risks. To date, there are only

observational studies, most of them suggesting disadvantages for patients receiving additional cannabis (see Chapter 4.2.). However, these findings must always be considered against the background that cannabis or cannabinoids can be used by patients in advanced stages of disease already as salvage drug and that such observational studies can sometimes even lead to misleading conclusions for an actual benefit-risk assessment. An equally divergent pattern of results was reported at the preclinical level. As outlined earlier, both antagonism (Xiong et al., 2022) and lack of interference (Waissengrin et al., 2023) have been demonstrated for corresponding combinations of cannabinoids and immunotherapeutics in mouse xenograft models. Equally noteworthy is a report of increased efficacy of a PD-L1 antibody in combination with CBD, with the latter increasing PD-L1 expression in TNBC cells (Kim, Kim, et al., 2024). On the other hand, recent preclinical findings suggest that cannabinoids impair the function of tumor-specific T cells via a CB<sub>2</sub> receptor-dependent pathway involving the inhibition of JAK1/STAT signaling in T cells, which could be a plausible explanation for a cannabinoid-mediated antagonistic effect on immunotherapeutics (Xiong et al., 2022). In line with this notion, tumor-bearing CB<sub>2</sub> knockout mice responded significantly better to anti-PD-1 therapy than wild-type mice (Sarsembayeva et al., 2023). In further agreement, THC has earlier been shown to mediate a CB<sub>2</sub> receptor-dependent reduction in host immune reactivity against lung cancer (Zhu et al., 2000). On the other hand, a recently published systematic review of the immunomodulatory effects of cannabis in patients with and without cancer shows that there is no evidence of meaningful changes in immune parameters in several diseases with cannabis use (Behling-Hess, Simonson, Salz, Fleege, & Zylla, 2025). In particular, cannabis use did not appear to impact immune markers relevant to immune checkpoint inhibitor function.

There are several interactions between cannabinoids and chemotherapeutic agents that are theoretically possible but have not yet been sufficiently investigated. As recently summarized, there are a number of known drug interactions of cannabinoids as victim and perpetrator via CYP enzymes, but in which possible interactions with chemotherapeutic agents are less apparent (Herdegen & Cascorbi, 2023). In this context, further research should be conducted to determine

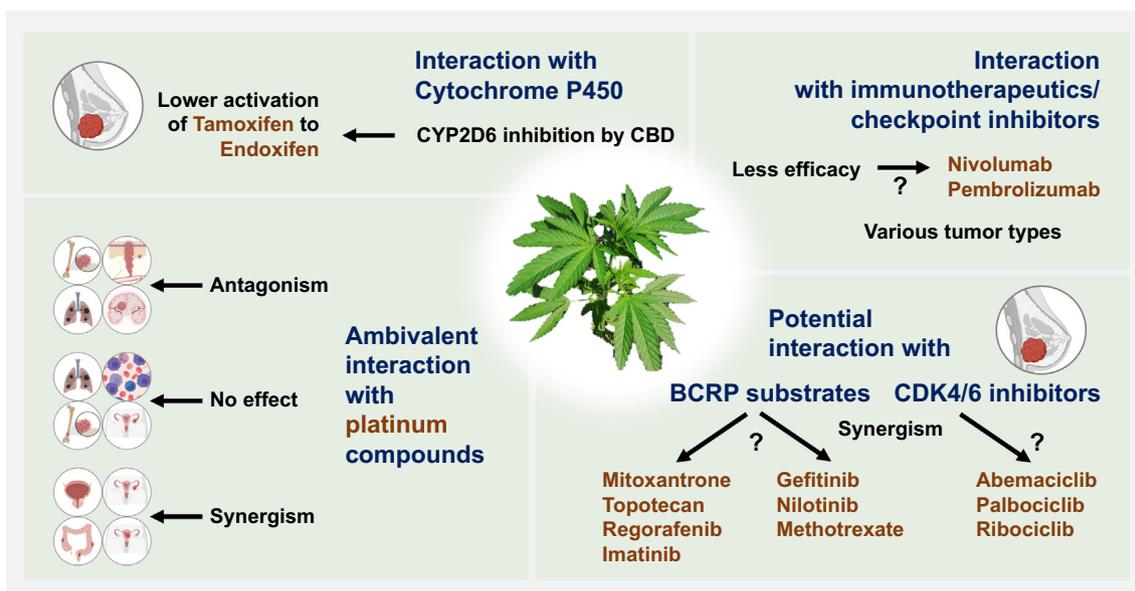
whether, for example, reduced activation of tamoxifen by CBD could have clinical disadvantages for patients. In particular, the influence of CBD on CYP enzymes such as CYP2D6 (see Chapter 4.2.) could play a role here.

However, it is also possible that cannabinoids trigger yet unknown interactions that benefit the patient. In view of data showing that CBD leads to potent inhibition of CDK6, it has also been speculated that CBD may be a potential candidate for the concomitant treatment of breast cancer patients with CDK4/6 inhibitors (Alsherbiny et al., 2021). Accordingly, the combination of CBD with abemaciclib, palbociclib and ribociclib could result in enhancements of the anticarcinogenic efficacies of these substances, although this has not yet been investigated.

In addition, there are some further findings that give rise to speculation about possible interactions between cannabinoids and chemotherapeutic agents. In fibroblasts, CBN, CBD and THC were shown to downregulate the multidrug transporter BCRP, resulting in increased sensitivity to corresponding substrates such as the cytotoxic agents mitoxantrone and topotecan (Holland, Lau, Allen, & Arnold, 2007). A similar downregulation of BCRP with a resulting higher toxicity of mitoxantrone toward trophoblasts was later confirmed for AEA (Szilagyi et al., 2019). Noteworthy, in addition to mitoxantrone, camptothecin derivatives and methotrexate, BCRP substrates also include several tyrosine kinase inhibitors such as imatinib, gefitinib and nilotinib as well as a number of photosensitizers (Mao & Unadkat, 2015). Consequently, possible interactions should also be further investigated in preclinical and clinical studies in this case as well.

Fig. 6 summarizes the as yet insufficiently investigated and critical interactions of cannabinoids with chemotherapeutic agents.

In addition to the possible positive and negative interactions between cannabinoids and chemotherapeutic agents, there are a number of other aspects that need to be considered by treating physicians and treated patients. For example, the use of cannabinoids as an adjunct to chemotherapeutic agents should be more targeted, incorporating specific biomarkers for this purpose prior to treatment. One indicator of successful application could be TRPV2, whose upregulation in tumor cells could be associated with increased efficacy of cannabinoids,



**Fig. 6.** Selected possible interactions between cannabinoids and chemotherapeutic agents, which are discussed in terms of risks and opportunities. Substances written in brown always refer to chemotherapeutic agents. Interactions with abemaciclib, palbociclib, ribociclib have so far only been the subject of hypotheses. Proven interactions with platinum compounds are inconsistent. Possible interactions between BCRP-downregulating cannabinoids and BCRP substrates used in cancer therapy should be critically evaluated. The same applies to possible interactions of CBD with the bioactivation of tamoxifen. Interactions with nivolumab and pembrolizumab have been studied in patients with a variety of cancers, but require prospective studies with pharmaceutically approved applications in larger numbers of individuals. Created with [BioRender.com](https://www.biorender.com).

according to a preclinical study (Elbaz et al., 2016). Another aspect that may need to be considered clinically is the inability of CBD to sensitize TMZ in the presence of unmethylated MGMT, which can be detected in TMZ-resistant GBM cells (Soroceanu et al., 2022). This could justify an assessment prior to treatment as part of an individualized therapeutic concept.

Finally, there is the question of the extent to which the route of administration influences the interaction with chemotherapeutic agents, particularly in the case of cannabinoids where the widespread practice of smoking is a major influencing factor. In this context, some preclinical efforts are focused on the delivery of cannabinoids such as CBD via nanoparticles in breast cancer (Fraguas-Sánchez, Fernández-Carballido, Delie F, et al., 2020; Fraguas-Sánchez, Fernández-Carballido, Simancas-Herbada, et al., 2020), as has been further explored for the combined use of 5-FU and CBD-loaded nanostructured lipid carriers to reduce non-melanoma skin cancer (Hasan et al., 2023). This also raises the question of whether these forms cause similar interactions with chemotherapeutic agents as oral, inhaled or sublingual administrations.

Overall, well-controlled clinical trials are urgently needed for various types of tumors in order to establish cannabinoids as an additional medication against cancer in existing chemotherapies. Likewise, the extensive preclinical data available on the interaction of cannabinoids and chemotherapeutic agents at the level of tumor cell death should be extended to include studies on the effects of these combinations at levels of tumor progression, such as angiogenesis, invasion, and metastasis. In this context, it is also worth noting that although cannabinoids have been used in various forms for thousands of years, it has only been possible to systematically study their pharmacological mechanisms of action since the discovery of the endocannabinoid system in the early 1990s. Accordingly, they may still hold some as yet undiscovered therapeutically relevant effects on tumor development and progression, so that preclinical research in this sector should also be consistently continued.

### CRedit authorship contribution statement

**Robert Ramer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Data curation, Conceptualization. **Burkhard Hinz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Conceptualization.

### Declaration of competing interest

Both authors declare that they have no undisclosed relationships that may pose a competing interests and no undisclosed funding sources that may pose a competing interest that could have appeared to influence the work reported in the publication entitled “Effects of cannabinoids on the efficacy and side effects of anti-cancer chemotherapeutic agents - current status of preclinical and clinical research” submitted on 31st of January 2025.

### Data availability

The authors declare that all data supporting the findings of this review are contained within the manuscript.

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