

Review

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Review

Phytocannabinoids as Chemotherapy Adjuncts—A User Guide

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Simple Summary: There is increasing evidence, that cannabinoids may play an important and dual role in tumour therapy. On one hand, they are cytotoxic against cancer cells with a low toxicity against normal, healthy tissues, and on the other, they may reduce typical side effects of chemotherapy. Publications on the main motive for use of cannabis (cannabinoids) by cancer patients show that patients' expectations exceed scientific facts. This article briefly describes results of combinations of cannabinoids with standard antineoplastic drugs on tumours and on side effects of tumour therapy. Although observations are still limited to animal studies with very few experiences in patients, preliminary data suggest that adjuvant cannabinoids may improve the survival of glioblastoma and perhaps of patients with other tumours. Benefits have also been reported about chemotherapy-induced nausea and vomiting, chemotherapy-induced peripheral neuropathic pain, loss of appetite and anxiety. Although results are promising, much more research is necessary.

Abstract: Cancer, one of the leading causes of death worldwide, is on the rise. The high toxicity of conventional chemotherapy, often applied as drug cocktails, and resistance development limits the use of anti-neoplastic drugs and reduces the quality of life. With an easier access, a growing number of patients are using cannabis (cannabinoids) for alleviation of their symptoms, and in the hope of improving survival. This narrative article summarizes results observed with combinations of phytocannabinoids and standard chemotherapeutic agents in animal tumour models and in patients. Preliminary data suggest that standard antineoplastic agents combined with cannabinoids exert increased anti-cancer actions, reduce resistance development and improve survival. Respective experiences in patients are still scarce and concern small numbers with glioblastoma, and pancreatic carcinoma. Further benefits of combinations with cannabinoids have also been reported for chemotherapy-induced nausea and vomiting, loss of appetite (dronabinol), chemotherapy-induced peripheral neuropathic pain and anxiety (cannabidiol). In addition, phytocannabinoids, in particular cannabidiol, may play a role in the protection of organs such as heart, lung or kidney against chemotherapy-induced toxicity. Although results are promising, much more research is needed to determine whether positive experiences of adjuvant cannabinoids outweigh eventual risks.

Keywords: adjuvant therapy; benefits; cancer; cannabinoids; cannabis; cannabidiol; chemotherapy; dronabinol; resistance; delta-9 tetrahydrocannabinol

1. Introduction

Cancer, one of the leading causes of death worldwide, is on the rise. A recently published trend analysis reported that the global incidence of early-onset cancer increased tremendously, by 79.1%, during the last three decades, between 1990 and 2019; during the same period, the number of early-onset cancer deaths increased by 27.7% with a shift to younger ages [1]. More so, the number of new

cases of prostate cancer annually will even duplicate within only two decades, from 1.4 million in 2020 to 2.9 million by 2040 [2]. Despite of all efforts, the treatment of cancer remains unsatisfactory. The high toxicity of conventional chemotherapy, often applied as drug cocktails, and resistance development during treatment limits the benefit of anti-neoplastic drugs and reduces the quality of life. It is therefore mandatory to develop new therapeutic strategies for the management of cancer in order to improve survival rates and to reduce side effects.

The recent years have seen a progressive legalisation, in parallel to an increased interest and use of cannabis or cannabinoids among cancer patients, whereby up to 80% use the internet as source of information. The two main reasons that led patients to take cannabinoids seem to be symptoms of their disease and/or side effects of chemotherapy, as well as the hope to eventually improve survival. Numerous “testimonials” in the internet about a successful use of “Rick Simpson oil”, as well as popular publications suggest this possibility [3]. Recent surveys found that 75% of cancer patients use cannabis for treating physical symptoms such as pain, and 26% to 46% for treatment of cancer as such, often without telling their physicians [4–7].

Cannabis can be applied in many forms. Edibles, including liquids e.g., “CBD-oil” that is basically a hemp extract, were used second to inhalation [8]. In general, these ill-defined products are purchased online or at dispensaries. Such products commonly include, in addition to variable amounts of the primary phytocannabinoids cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), hundreds of other phytosubstances, sometimes also pesticides and other impurities, with the possibility of unexpected interactions. Patients should be warned particularly against the use of “CBD-derived” products that are increasingly popping up in gummies and vapes on the market since a few years, namely delta-8-THC or hexahydrocannabinol (HHC). In contrast to extracts, these products contain dozens’ of unidentified synthetic reaction by-products that can put consumers at risks. Although people often use the terms “cannabis” and “marijuana” interchangeably and indiscriminately, they don’t mean exactly the same thing. The word “cannabis” refers to all products derived from the plant *Cannabis sativa*, whereas “marijuana” (“recreational” cannabis, “weed”, “drug type” cannabis) refers to parts of, or products from the plant *Cannabis sativa* that contain substantial amounts of THC. Thus, herbal cannabis, marijuana, medicinal cannabis, extracts, CBD-oils and similar cannabis-based products are distinctly different to isolate, well defined substances such as THC (dronabinol) and CBD, and effects perceived by users may not be the same. “Medicinal cannabis” are plants of a defined, standardised variety, rich in THC or CBD or with a more balanced content of both cannabinoids (e.g., Bedrocan, Bediol, Bedrolite™, or the chemotypes FM1 and FM2 (Farmaceutico Militare) of the Italian Military Pharmaceutical Institute of Florence), but there is no uniform understanding for this term. Caution is therefore advised when transferring results made with isolate cannabinoids to (medicinal) cannabis and vice versa. The erroneous assumption that they may be interchangeable means neglecting the pharmacologic potential and interaction of hundreds of phytosubstances, including other, “minor” phytocannabinoids, terpenes and polyphenols. Although herbal cannabis, extracts and pure cannabinoids are clearly different, a high percentage of cancer patients use cannabis or extracts (“edibles”) in place of individual cannabinoids such as CBD to alleviate symptoms of antineoplastic treatments as mentioned before.

Whereas cytotoxic effects of individual phytocannabinoids notably of CBD and THC on tumour cell lines have been extensively studied in vitro, much less research has been done on animal models, particularly in combination with conventional antineoplastic drugs. The first study demonstrating that phytocannabinoids are cytotoxic against cancer cells in vitro as well as in vivo was published almost 50 years ago, in 1975 [9]. Since that, it has been argued repeatedly that phytocannabinoids may act synergistically on cancer cells when combined with standard chemotherapeutics. Notwithstanding, THC remains a scheduled drug because of its psychotropic effects, limiting considerably a more widely use. Conversely, CBD is one of the most promising cannabinoids due to its lack of psychotomimetic properties, a larger therapeutic window, and a high anticancer activity that has been repeatedly demonstrated in vitro and in vivo, including in a limited number of clinical trials and case series [10]. Both cannabinoids, synthetic THC (dronabinol) and cannabidiol (CBD), as well as a 1:1 standardised blend of extracts (nabiximols) have received marketing authorisation;

phyto-CBD is commercialised as Epidiolex™, semi-synthetic THC as dronabinol/Marinol™/Syndros™ and nabiximols as Sativex™. In addition to their licensed indications, they are gaining enormous scientific interest in cancer for a possible dual use. On one hand, phytocannabinoids may act as antitumour drugs per se, regulating cancer cell proliferation, invasion, metastasis, angiogenesis, differentiation and combating chemoresistance. On the other hand, cannabinoids alleviate symptoms of anti-neoplastic treatments, notably nausea/vomiting, loss of weight, and possibly also peripheral neuropathy, organ toxicity or mucositis induced by a number of standard chemotherapeutics.

Given the increasing popularity of cannabinoids in cancer patients, this narrative review aims to synthesize the known benefits but also limits of an accompanying anti-cancer therapy with phytocannabinoids. The article is separated in two parts. The first describes the antitumour effects of cannabinoid-antineoplastic drug combinations with a focus on animal models and experiences in man; the second part summarises the reported benefits of cannabinoids on chemotherapeutic side effects relating mostly on reviews.

2. Cannabinoids May Increase the Efficacy of Standard Tumour Therapy and Limit Resistance Development

When treating tumours, it is a common strategy to combine drugs with different mechanisms of action. The main principle behind the use of such cocktails of cytotoxic and/or cytostatic chemicals is to target the tumour concurrently at various levels of its growth and dissemination, by improving efficacy, using fewer toxic individual doses, and by limiting the development of chemoresistance.

When multiple drugs are used, the sequence of administration may influence how effectively cancer cells are killed. As an example, *in vitro*, the combination of CBD+THC added after chemotherapy (exposure to cytarabine, vincristine) resulted in greater induction of apoptosis in leukaemia cells than the use in the opposite order [11]. A similar observation was made already earlier with CBD alone; chemotherapy first, followed by CBD, significantly improved overall results against leukaemia cells [12]. Conversely, the exposure of mice to a CBD+THC combination (each ~2 mg *i.p.*/kg) a few hours before exposure to irradiation resulted in a significant lower tumour volume (orthotopic murine glioma) than the combination CBD+THC or radiation alone [13]. Such observations suggest that treatment strategies may be refined further by studies on concomitant versus sequential therapy.

Investigations on the effects of combinations of anticancer drugs with cannabinoids on tumours emerged relatively late, many years after studies on the alleviation of side effects of tumour therapy such as nausea/vomiting and weight loss. Compared to the large number of antineoplastic agents available for treatment, research on combinations with cannabinoids is relatively limited. The majority of publications have described interactions between phytocannabinoids and standard chemotherapeutics *in vitro*, with a few more studies on animals. Although *in vitro* studies are an essential and valuable tool in basic research, they remain artificial settings. They are influenced by many factors such as the model, test conditions, the culture medium, drug concentrations or cell lines [14,15].

As an example, an experiment assessing the inhibitory effect of a combination of tamoxifen with the cannabinoids CBD, THC and anandamide (AEA) found that the viability of C6 rat glioma cells increased inversely to the concentrations of foetal bovine serum in culture medium; no effects were seen in medium containing 10% foetal bovine serum, often used for culturing [16]. The high protein-binding of cannabinoids may be the reason for these results. Other *in vitro* studies demonstrate antagonistic to additive to synergistic effects of combinations with CBD and gemcitabine or cisplatin in highly invasive human bladder transitional cell carcinoma cells (T24), depending on the concentrations used [17]. As a further example, CBD has been repeatedly described to antagonise platinum drugs (cisplatin, oxaliplatin) [18–20]. However, CBD may act also synergistically or additive. Moreover, priming with CBD (sequential exposure) enhances cisplatin and paclitaxel killing of cancer cells [21]. In contrast to expectations from *in vitro* data, the combination of CBD with cisplatin significantly decreased tumour growth in a murine model of human head and neck

squamous cell cancer [22]. This underlines that in vitro results are influenced by a number of factors, and may not be translatable to animals and man in each case. In the following part, effects of cannabinoids on antitumour activities of standard chemotherapeutics are summarised. Main results are presented in Table 1 (appendix).

Table 1. Effects of cannabinoid-chemotherapy combinations in animal models and in man.

Anti-neoplastic Drug	Cannabinoid Adjunct	Comments	Ref.
Cisplatin (2.5 mg CIS i.p./kg/w)	CBD 5 mg p.o./kg, 4x/w, 4 w (sequence not stated)	human head and neck squamous cells (FaDu) s.c. xenografts, BALB/c nude mice; estimated tumour volume: CBD+cisplatin ~300mm ³ < CBD ~600mm ³ < cisplatin ~800mm ³ < vehicle ~1.500mm ³ ; tumour weight after CBD+cisplatin was about 75% lower than in the vehicle-treated group. When FaDu cells were injected into tongues, CBD alone (5 mg i.p./kg, 3x/w) also reduced tumour growth by more than 60%.	[22]
Cisplatin (3mg CIS i.p./kg, 3x weekly)	THC 45mg p.o. /kg, or THCe (with 45mg THC/kg) 3-times weekly	Breast cancer, s.c. xenografts (triple negative human MDA-MB-231 cells, female nude mice); tumour volume after 30 days: CIS+THCe < CIS < THCe < THC < vehicle;	[23]
Doxorubicin (2 mg DOX i.v./kg, 2x/w, 2 w)	CBD-EV (5 mg i.p./ kg, 2x/w, 2w) or free CBD (5 and 10 mg i.p./kg, 2x/w, 2w)	Breast cancer s.c. xenografts, (triple negative, MDA-MB-231cells, female athymic Envigo nude mice); CBD, one day before DOX, sensitized tumour cells, enhanced effect of combination. The tumour volume after 2 weeks, extracellular vesicles (EV): CBD-EV+DOX < CBD (5mg/kg)+DOX < DOX < CBD (10mg/kg) ≈ CBD-EV (5mg/kg) < EVs/controls); tumour volume with the CBD-EV+DOX combination was at least 50% lower than the average tumour volume in control animals	[28]
Irinotecan (IRI) single MTD dose (100 mg i.p. /kg) on day 1	THC (7 mg p.o./kg/d); (sequence not stated)	healthy male Wistar rats; haematological and biochemical tests on day 1, 3, 7; the combination demonstrated a decrease of neutrophils and a tendency to decrease leucocyte counts, but alleviated the IRI induced elevation of aspartate amino-transferase (AST); diarrhea was not observed; serum level of bilirubin and triglycerides were lower after combined treatment then after individual THC or IRI; no signif. effect on erythrocytes and platelets	[36]

Irinotecan (IRI) (60 mg i.p./kg on day 1, 5)	THC (7 mg p.o./kg /d, 7d) (sequence not stated)	colon cancer, s.c. xenografts, (syngeneic CT26.WT cells, male BALB/c mice); tumour volume on D7: irinotecan < IRI+THC < control < THC; tumour volume decreased with IRI by -27 %, with IRI+THC by -14%; THC reduced the efficacy of IRI;	[39]
Irinotecan (IRI) (mostly 600 mg, 90-minute i.v. infusion)	Medicinal cannabis 200 ml of herbal tea (1 g/l), daily	10 days after the 1 st infusion of IRI, patients with metastatic cancer started with cannabis tea (Bedrocan) for 15 consecutive days; 21 days after the 1 st infusion, patients received a second treatment with IRI, this time as concomitant treatment to Bedrocan; 12 patients were evaluated; Bedrocan administration did not significantly influence exposure to and clearance of IRI	[40]
Gemcitabine (GEM) (100mg i.p./kg, every 3 days)	CBD (100mg i.p./kg/d until death)	Pancreatic ductal adenocarcinoma, KPC mice; mice receiving CBD+GEM survived 2.8 times longer than mice not given any treatment (1.3 times longer with CBD and 1.4 times longer with GEM alone); mean survival: no treatment 18.6 days < CBD 25.4 days (+37%) < GEM 27.8 (+49%) < CBD+GEM 52.7 days (+183%)	[42]
Gemcitabine + paclitaxel	CBD (mainly 400 mg/day)	6 of 9 patients with pancreatic cancer received CBD in addition to standard chemotherapy (mostly gemcitabine + paclitaxel), one patient received one cycle of paclitaxel, followed by one cycle of irinotecan-calcium folinate, 5-fluoruracil; two patients received only cannabinoids; overall survival was about 11 months	[44]
Tamoxifen (2.5 mg TAM i.p./kg, 3x weekly); lapatinib (100 mg LAPA/kg) daily, oral gavage	THC 45mg p.o. /kg, or THCe (with 45mg THC/kg) 3-times weekly	human breast cancer, s.c. xenografts (female nude mice) T47D-cells (ER+/PR+/ HER2-), tumour volume: TAM+THCe < THCe ≈ TAM < syn.THc < vehicle; triple positive BT474- cells, (ER+/PR+/HER2+), tumour volume: THCe < LAPA+THCe < LAPA < THC < control;	[23]
Tamoxifen	CBD (below 50 mg/day)	Concomitant oral CBD decreases the AUC of the active metabolite endoxifen; it seems to be unlikely that this affects the clinical efficacy of tamoxifen. Conversely, endocrine complaints and adverse effects improved significantly in patients	[51,52]
Aromatase inhibitors; 71.8% of patients	CBD (titrated up to 2x 100 mg p.o./d	An observational study did not report a negative impact of a combined treatment; conversely, CBD alleviated the symptoms of arthralgia pain. Of 28 patients completing the 15-weeks study, 17 (60.7%) reported a ≥2-point	[58]

	received over 4 weeks, then 20.5% at the maximum dose)	improvement in the Brief Pain Inventory (BPI) between baseline and week 15. In addition, there was a significant improvement in PROMIS T score at week 15 in both physical function and ability to participate in social roles and activities	
Bicalu-tamide (BIC) 25–50 mg p.o./kg, 3x per week	CBD-BDS, 1-10-100 mg i.p./kg/d;	Prostate cancer, s.c. xenografts, (LNCaP, androgen-receptor positive/AR+, athymic nude mice); CBD–BDS (~65% CBD) enhanced efficacy of BIC on LNCaP (no significant difference between 25 and 50 mg BIC)	[14]
Trametinib (MEKi)	1:1 (7.5 mg/kg/d, 21 days	Melanoma (A2058 cells, s.c. injection, NSG mice); CBD:THC = CBD+THC (7.5mg/kg/d, 21d) reduced melanoma growth by about 50%, MEKi alone by about 75% compared to vehicle; the addition of CBD+THC to MEKi did not increase the effect of MEKi further; tumour volume D22: vehicle > CBD+THC > CBD+THC+MEKi ≈ MEKi.	[64]
anti-PD-1 antibodies, Pembrolizumab	THC, medical cannabis, assumed to be THC-rich	tumour-bearing mice (CT26 non-small cell lung cancer cells) survived significantly longer with a combined anti-PD-1 antibody + THC therapy (control 21 days, < THC 24 days, < anti-PD-1 antibody 31 days < THC+anti-PD-1 antibody 54 days); patients with metastatic NSCLC were treated with Pembrolizumab as a first-line monotherapy; no negative impact of cannabis on the activity of Pembrolizumab as treatment for advanced NSCLC was observed	[60]
Docetaxel (DOC) 5 mg i.v./kg once weekly	CBD-BDS (~65% CBD), 100 mg i.p./kg/day;	Prostate cancer, s.c. xenografts, (DU-145, androgen-receptor negative/AR-, athymic nude mice); CBD–BDS enhanced the efficacy of DOC on DU-145 xenografts; CBD–BDS at the highest concentration tested (100 mg i.p./kg) reduced the tumour growth of LNCaP (androgen-receptor positive/AR+) xenografts similar to that of DOC (5 mg.i.v./kg), although it reduced the inhibitory effect of DOC	[14]
Paclitaxel	CBD micro-particles	In an animal model of ovarian cancer or MDA-MB-231-derived breast cancer, combined treatment of paclitaxel with CBD (administered as solution daily over 10 days or as a single administration of a topical microparticle formulation) showed a 2-fold higher tumour growth inhibition compared to a 1.5-fold decrease with paclitaxel alone	[65,66]

Temozolomid (20 mg TMZ/kg) for 21 days	CBD (15 mg i.p./kg) for 21 consecutive days	orthotopic model of human glioma (U87) in nude mice. Animals were treated with CBD or TMZ or both. Mice receiving the combination lived significantly longer than consecutive with TMZ or CBD alone (0% survival: CBD+TMZ 84 days > TMZ 60 days > CBD 55 days > control 50 days)	[71]
	TMZ -like extracts, p.o.	nabiximols-like extract, combined with TMZ produced a strong antitumoral effect in both xenografts (s.c. THC+ CBD xenograft and intracranial glioma cell-derived tumour (nabiximols xenograft, U87MG) tumour volume: TMZ+THC+CBD < TMZ < THC+CBD < control). A higher portion of CBD (THC:CBD = 1:5) seems to increase the effect; a combination of nabiximols-like extracts (THC:CBD ≈ 1:1) with BCNU (carmustine) did not show a stronger effect than individual treatments	[72,73].
standard radio-chemo- therapy (mostly TMZ)	CBD (mainly 400 mg/day).	case series of 15 patients; mean overall survival was 30.9 months which is twice as long as has been commonly reported; three patients (20%) were still alive after more than 5 years [80].	[63]
TMZ 5 mg/kg/d, peritumoral injections, for 14 days	THC 15 mg/kg/d, peritumoral , for 14 days	Human glioma U87MG s.c. xenograft, nude mice; tumour volume on day 15: THC+TMZ < TMZ < THC; compared to vehicle, tumour growth was signif. reduced with both, TMZ and THC; a tumour-decrease was only observed with the combined treatment with THC+TMZ; a combination CBD+TMZ was not tested.	[74]
TMZ up to one year	nabiximols oro- mucosal spray (mean 7.5 sprays/day)	Survival at 1 year was 83% for nabiximols- (10/12) versus 44% (4/9 subjects) for placebo-treated patients, and 50% for patients treated with nabiximols versus 22% for those treated with placebo at 2 years. Median survival was > 550 days with CBD:THC treatment (not significant) and 369 days in the placebo group;	[75]

Hu – human; BDS – botanical drug substance (extract); b.w. – body weight; CBC – cannabichromene; CBDc – cannabidiol extract/botanical drug substance (BDS); d – day; GIC - Glioma Initiating Cells exchangeable with GSC – glioma stem cells; h -human; i.p.- intraperitoneal; MTD – maximal tolerated dose; nu – nude; s.c. – subcutaneous; signif. – significantly; syn. – synthetic; THCe – d9-deltahydrocannabidiol extract/botanical drug substance (BDS); TMZ - temozolomide; w – week;.

2.1. CBD, Combined with Platinum Drugs, May Reduce Tumour Growth

Cisplatin, carboplatin, oxaliplatin are prominent and widely used members of the platinum compounds. While differing in their mutagenic properties and side effects, they share the induction of damage to DNA by forming covalent adducts. Most dose-limiting side effects of cisplatin and other platinum drugs are nausea/vomiting, nephrotoxicity, gastrointestinal- and ototoxicity. A further major limitation is the development of cisplatin resistance by tumours.

Inhibitory effects of a CBD + cisplatin combination have been studied in a murine model of human head and neck squamous cell cancer (FaDu s.c. xenografts, BALB/c nude mice). Combined

treatment (CBD 5 mg p.o./kg, 4x/week, 4 weeks, cisplatin 2.5 mg i.p./kg/week) demonstrated an about 75% slower tumour growth; estimated tumour volume: CBD+cisplatin ~300mm³ < CBD ~600mm³ < cisplatin ~800mm³ < vehicle ~1.500mm³; tumour weight after CBD+cisplatin was about 75% lower than in the vehicle-treated group. When FaDu cells were injected into tongues, CBD alone (5 mg i.p./kg, 3x/week) also reduced tumour growth by more than 60%. (Table 1, appendix) [22]. The combination with THC also enhanced the effect of cisplatin. Synthetic THC (45mg p.o. /kg, 3 times weekly or an extract (THCe) with 45mg THC significantly reduced the tumour growth of s.c. breast cancer xenografts (triple negative human MDA-MB-231 cells) (tumour volume after 30 days: CIS+THCe < CIS < THCe < THC < vehicle) [23].

Clinical resistance, particularly multiple drug resistance, is a common phenomenon in oncology and can be caused by a range of different mechanisms. Although changes in DNA-damage triggered apoptosis is a major cause for resistance against platinum drugs, the overexpression of the ATP-binding cassette (ABC), drug efflux transporters such as ABCB1, encoding P-glycoprotein (P-gp), plays also a role. A very recent in vitro study suggests that pro-drugs combining CBD with platinum drugs may not only improve therapeutic efficacy but also overcome drug resistance in colorectal cancer cells [24]. Combination of oxaliplatin and CBD decreased nitric oxide synthase 3 (NOS3) phosphorylation, inducing mitochondrial dysfunction, overproduction of ROS and finally autophagy, thus overcoming oxaliplatin resistance of human colorectal cancer cells (DLD-1 R and colo205 R) [25]. Similar in vitro results were reported for cisplatin-resistant human non-small cell lung cancer (NSCLC) cells, and have been confirmed in a murine model (10 mg CBD/kg, once a week for 4 weeks, s.c. xenografts) [26]. Moreover, research data indicate that CBD is able to decrease self-renewal of lung cancer stem cells [27]. In addition, CBD blocks the natural release of exosomes from a wide range of cancer cells including prostate cancer (PC3), hepatocellular carcinoma (HEPG2) and breast adenocarcinoma (MDA-MB-231), and sensitizes cancer cells to antineoplastic drugs. Exosomes are nanosized extracellular vesicles with a lipid bilayer membrane. They are increasingly recognised to promote cancer growth as well as to induce chemoresistance, and may serve also as biomarkers. Generated artificially, they can be used as delivery systems for anticancer drugs and others.

2.2. CBD Enhances the Anti-Tumour Effect of Doxorubicin and Other Anthracycline Drugs In Vivo

The group of anthracyclines includes many drugs such as adriamycin, doxorubicin, daunorubicin, epirubicin or mitomycin C. Anthracyclines act on cells by complex mechanisms, such as apoptosis, abrogation of the cell cycle, activation of caspases, stimulation of the production of reactive oxygen species (ROS), inhibition of topoisomerases I and II and activation of intracellular second messengers.

Doxorubicin ranks among the most effective and most widely used chemotherapies. It slows or stops the growth of cancer cells by intercalating within DNA base pairs, causing breakage of DNA strands, inhibiting both DNA and RNA synthesis, and blocking the enzyme topoisomerase II which controls supercoiling of the DNA. Doxorubicin is widely used to treat soft tissue cancers, bone sarcomas and cancers of the breast, ovary, bladder, prostate and thyroid. Common adverse reactions limiting its long-term use are alopecia, oral sores, nausea and vomiting as well as cardiac toxicity that may be progressive and irreversible.

In a murine model of triple negative breast cancer (MDA-MB-231 xenografts, female nude mice), it CBD enhanced the effect of doxorubicin. Pre-sensitization with CBD, entrapped in extracellular vesicles (EV) (5 mg CBD-EV i.p./kg) or as pharmaceutical grade free CBD (5 or 10 mg CBD i.p./kg, twice weekly for 2 weeks), significantly increased the anti-tumour effect of doxorubicin (2 mg DOX i.v./kg). The tumour volume after 2 weeks was lowest with 5 mg CBD extracellular vesicles+doxorubicin, followed by 5 mg free CBD+doxorubicin, and doxorubicin alone, and was at least 50% lower than the average tumour volume in control animals (estimated volume, D14: CBD-EV (5 mg/kg)+DOX (2 mg/kg) ~3,000mm³ < free CBD (5 mg/kg)+Dox (2 mg/kg) ~4,000mm³ < Dox (2mg/kg) ~4,500mm³ < free CBD (10 mg/kg) ~6,700mm³ < CBD-EV (5 mg/kg) ~7,000mm³ < EVs ~8,000mm³ < control ~9,000mm³. Conversely, tumour volumes after 5 mg CBD extracellular vesicles/kg alone and 10 mg free CBD/kg were only about 20% lower than the average tumour

volumes of control animals and much higher than in combination with doxorubicin (Table 1, appendix) [28].

As with other antitumour agents, development of clinical resistance is common. Although changes in DNA-damage triggered apoptosis is a major mechanism, changes of the transport via the already mentioned P-glycoprotein (P-gp) which is responsible for multiple drug resistance, play also a role. It was found that CBD, marginally less also cannabinal (CBN) and THC, significantly counteracts P-gp-mediated drug efflux of various agents including anthracyclines (doxorubicin), vinca alkaloids, taxol and podophyllotoxin derivatives in vitro, thus enhancing concentration-dependently the intracellular accumulation of these drugs [29,30]. Moreover, a reduction of the expression of P-gp may further contribute to the observed inhibition of drug efflux. This resistance-reducing effect has been confirmed recently in a murine model of MDA-MB-231 breast cancer xenografts where CBD (10 mg i.p./kg, twice weekly, 2 weeks) enhanced the cytotoxicity of doxorubicin in resistant, triple-negative breast tumours, obviously inhibiting epigenetic histone modifications [31]. Cannabis sativa L. extracts also have a direct, selective cytotoxic effect on colon cancer cells and potentially reverse doxorubicin resistance [32].

A well-known doxorubicin analogue is mitoxantrone. It is approved for the treatment of adult acute myeloid leukaemia and for hormone-refractory prostate cancer. It appears to be active also in ovarian cancer, lung cancer and hepatocellular carcinoma. Mitoxantrone is – similar to doxorubicin – a topoisomerase type II inhibitor, disrupting DNA synthesis and repair in healthy and cancer cells. It acts also as immunomodulator, enhancing on one hand T-cell suppressor function, and inhibiting on the other B-cell function and antibody production. Moreover, mitoxantrone inhibits macrophage-mediated myelin degradation, which explains its use in various forms of multiple sclerosis [33]. Most common side effects are infections, nausea, vomiting and sores in mouth and throat.

Interactions of mitoxantrone with cannabinoids including effects on resistance development have only been studied in vitro. Administration of CBD, CBN and THC (10 μ M) in combination with mitoxantrone decreased the resistance by four to six times by inhibiting the breast cancer resistance protein (BCRP/ABCG2) [34].

Irinotecan (IRI) is also a topoisomerase inhibitor (topoisomerase type I inhibitor) but different to the above-mentioned compounds as it does not directly interact with DNA. It is a member of the class of pyranoindolizinoquinolines and primarily used as chemotherapy of metastatic colorectal cancer, but also against other solid tumours such as lung-, pancreatic- or ovarian cancer or malignant gliomas. IRI is a prodrug that is activated by carboxylesterases, and further metabolised via highly complex mechanisms including also the liver cytochrome P450 oxidase CYP3A4 that metabolises a number of common drugs [35]. Side effects include diarrhoea (which may be severe), sweating, stomach cramps, increased production of saliva, and watery eyes but also neutropenia.

The effects and tolerance of a combination of IRI with THC has been investigated in healthy male Wistar rats. Animals received either a single dose (100 mg IRI i.p./kg), or IRI together with THC (7 mg p.o./kg/day), during the 1, 3 and 7-day assessment period. Both, single IRI and IRI+THC administration, caused moderate leukopenia with a greater decrease in leukocyte counts in the irinotecan+THC group, suggesting higher cytotoxicity of the combination. IRI treatment induced elevation of aspartate aminotransferase (AST) without diarrheal symptoms and without an increase in circulating pro-inflammatory mediators. Interestingly, the elevation of AST was not observed in the IRI+THC group [36]. Concomitant THC seems to protect the liver against IRI-induced toxicity [37]. At present, it is insufficiently known whether this effect of IRI (eventually combined with THC) may be used for treating acute lymphoblastic leukemia [38].

Antineoplastic effects of IRI+THC combinations have also been studied in a murine colon cancer model. In this study, a combination with THC (7 mg p.o./kg/day, 7 days), reduced the effect of IRI (60 mg i.p./kg on day 1, 5). Whereas IRI alone reduced tumour growth by 35 % on day 3, 22 % on day 5, and 27 % on day 7 compared to control, THC lowered the efficacy of IRI, as the tumour in the IRI+THC group shrank by only 10 %, 15 %, and 14 % on respective days 3, 5, and 7 (Table 1, appendix) [39].

In a small number of cancer patients treated with IRI (600 mg i.v.) the concomitant daily use of medicinal cannabis (200 ml herbal tea, 1 g/l) for 15 consecutive days, starting 12 days before the second treatment) did not significantly influence exposure to and clearance of IRI [40]. However, the true in vivo implications of a combination with cannabinoids remain unknown as cannabinoids are barely soluble in water and their uptake from daily tea was certainly negligible. Interactions of IRI with higher, therapeutic doses of CBD or THC have not been studied.

2.3. CBD can Increase the Efficacy of the Antimetabolite Gemcitabine

Antimetabolites are similar to normal body molecules but have a slightly different structure. Gemcitabine is a pyrimidine analogue, and a front-line chemotherapeutic agent for the treatment of pancreatic cancer. It is also used for a range of other cancers including transitional cell carcinoma of the bladder and cancer of the ovary. Common side effects include nausea/vomiting, loss of hair, appetite, dyspnoea, myelosuppression or flu-like symptoms.

Intriguingly, it has been reported that the cannabinoid receptors CB1 and CB2 - both are overexpressed in pancreas adenocarcinoma - are further enhanced by gemcitabine. Cannabinoid agonists acting on CB1 and/or CB2 receptors are able to inhibit the growth of human pancreatic cancer xenografts (PaCa44 cells, nude mice), particularly in combination with gemcitabine [41].

In a mouse model (KPC mice lacking the gene encoding GPR55) of human pancreatic ductal adenocarcinoma, CBD, gemcitabine and CBD+gemcitabine increased the rodent lifespan significantly compared to vehicle (CBD+gemcitabine 52.7 days > gemcitabine 27.8 days > CBD 25.4 days > no treatment 18.6 days). No major side/adverse effects and no weight loss were observed in mice treated with CBD despite of a relatively high intraperitoneal daily dose (100 mg/kg, Table 1, appendix) [42]. In vitro, CBD was able to counteract the mechanisms involved in gemcitabine resistance in pancreatic cancer [43].

A case series of patients with pancreatic cancer describes first experiences with a phytocannabinoid-combination therapy (Table 1; appendix) [44]. Out of 9 patients, 7 had received CBD (mainly 400 mg/day) in addition to standard chemotherapy, mostly gemcitabine + paclitaxel (Abraxane™); two subjects refused chemotherapy and were treated with CBD alone and a minimal dose of THC. Low dose dronabinol (up to 7.5 mg/day) was added in four of nine cases to improve appetite. A mean overall survival of 11.5 months has been observed, without notable side effects. This is about twice as long as after standard therapy with gemcitabine.

Overall, a combination of high CBD and gemcitabine may be worth to be studied further.

2.4. Combinations of CBD with Hormonal Anti-Cancer Agents are Promising

Tamoxifen is an anti-oestrogen (hormone) and selective oestrogen receptor modulator. It is commonly used as chemo-preventive agent as well as to treat hormone receptor-positive breast cancers. In addition to its action on oestrogen receptors, tamoxifen acts as an inverse agonist at cannabinoid receptors CB1 and CB2, a property that is shared with other oestrogen receptor modulators [45,46]. Whereas CBD is a negative allosteric modulator of CB1, it acts as inverse agonist on CB2 receptors similar to tamoxifen [47]. Furthermore, CBD inhibits the development of oestrogen receptor positive (ER+) tumours as has been demonstrated recently in murine studies (MCF-7 epithelial human breast cancer xenografts) [48]. Therefore, CBD may be a suitable candidate for combinations.

Tamoxifen is metabolised via the cytochrome P450 enzyme CYP2D6 to the primary active metabolite endoxifen. Endoxifen and N-desmethyl-tamoxifen are potent inhibitors of aromatase [49]. CYP2D6 metabolises up to 25% of the drugs commonly used; it is subject of genetic polymorphism. About 15% of the population are intermediate, another 5-10% poor, and about 75% extensive ("normal") metabolisers (European population); about 1% to 10% are ultra-rapid metabolisers. Therefore, blood levels of endoxifen (tamoxifen) may considerably vary among patients. Side effects of tamoxifen include nausea, increased risk of stroke, deep vein thrombosis, cataracts, and uterine cancer. Unfortunately, a substantial proportion of patients initially responding acquire resistance to tamoxifen. Although the precise mechanisms are still incompletely understood, an increased drug

efflux via the multi-drug resistance P-glycoprotein drug pump is one out of several possibilities responsible for resistance development also against tamoxifen [50]; this mechanism is targeted by CBD as has been mentioned before.

Anti-tumour effects of cannabinoid-combinations with antineoplastic drugs have been studied in murine models against various breast cancer cell lines (s.c. xenografts, female nude mice). Pure THC and a THC-rich extract, THCe ("Cannabis-Derived Product") were administered at a dose of 45 mg/kg, 3 times a week by oral gavage (a dose of the extract contained 45 mg THC/kg). Tamoxifen (2.5 mg TAM/kg in 100 μ L of sesame oil) and cisplatin (3 mg CIS/kg in 100 μ L of PBS) were administered i.p. 3 times a week; and lapatinib (100 mg LAPA/kg) daily by oral gavage in 200 μ L of 0.5% hydroxypropyl methylcellulose plus 0.1% Tween 80. Control animals received the corresponding vehicles with the same pattern and route of administration. Animals were sacrificed after one month of treatment. The combination of THCe with antineoplastic drugs reduced the growth of tumours in all cases; combinations with pure synthetic THC were not tested [23]. So far, no animal studies of other combinations with cannabinoids have been published. A potential interaction between tamoxifen and CBD has been described in a recent case report, arguing that low dose CBD (40 mg CBD/day) may result in a decreased response to tamoxifen. In a 58-year-old female with a history of bilateral breast carcinoma in remission, and treated with tamoxifen for breast cancer prevention for over 6 years, a diminished metabolism of tamoxifen to the active metabolite endoxifen was observed. CBD was prescribed to treat persistent postsurgical pain, inadequately managed by alternate analgesics [51]. A slight decrease of the active metabolite by concomitant CBD has also been observed in an open-label, single-arm study that investigated the pharmacokinetic profile of tamoxifen in patients using concomitant CBD-oil (dosage below 50 mg CBD). The AUC of endoxifen decreased after CBD-oil by 12.6% (through CYP2D6 inhibition) but remained within bioequivalence boundaries, questioning a therapeutic relevance for the large majority of patients. Importantly, a decreased clinical effect has not been demonstrated. Conversely, CBD-oil had a beneficial influence on tamoxifen side effects; the endocrine sub-scale of the FACT-ES which assess endocrine complaints and adverse effects, improved - clinically relevant - by 6.7 points ($p < 0.001$), and health-related quality of life improved by 4.7 points with CBD [52]. To note, both THC and CBD, are metabolised to some extent also via CYP2D6, similar to tamoxifen, despite that the main metabolism route is via CYP3A4.

From the above it may be concluded that a CBD+tamoxifen combination increases preventive and therapeutic effects, possibly diminishing tamoxifen-related side effects and the risk of resistance; this could be a solution for the high frequency of tamoxifen discontinuation and likely compensates an eventually reduced efficacy. Nonetheless, caution is advised concerning any uncontrolled use of OTC-cannabinoid preparations by patients taking tamoxifen as medicinal cannabis and CBD-oils contain hundreds of other pharmacologically active substances that may interact with anticancer drugs.

Other hormonal anti-cancer agents are the so-called aromatase inhibitors. Aromatase inhibitors are another hormone therapy for breast cancer treatment. They work by blocking the enzyme aromatase, which converts cholesterol to estradiol E2, the most potent estrogen in the body. This stops the production of estrogen in women who are post-menopausal, reduces the estradiol level in breast tissue, and furthermore the growth of hormone receptor-positive breast cancer cells. However, after prolonged treatment, endocrine resistance may develop.

Currently, the three aromatase inhibitors used to treat breast cancer are anastrozole, exemestane and letrozole. Exemestane inhibits aromatase in an irreversible manner in contrast to anastrozole and letrozole. Since CBD is also a good aromatase inhibitor, a combination should be advantageous [53]. CBD combined with exemestane potentiates its anti-tumour effects in vitro, whereas no beneficial effect was observed when combined with anastrozole or letrozole [54]. Intriguingly, CBD, THC and AEA reduced aromatase and oestrogen receptor ER α expression levels in receptor-positive (ER+) breast cancer cells that overexpress aromatase (MCF-7aro) [55]. Besides that, THC, CBD and AEA, revert the resistance to exemestane, underscoring therefore their potential use as adjuvant treatment [56].

A major side effect of aromatase inhibitors is arthralgia and myalgia developing in more than 25% of patients [57]. A very recent observational study found that concomitant CBD (titrated up to twice 100 mg p.o./day over 4 weeks, then administered at the maximum dose over 15 weeks), alleviates symptoms of arthralgia pain in patients receiving aromatase inhibitors without a negative impact on breast cancer treatment. Of the 28 patients who completed the study, 17 (60.7%) reported a ≥ 2 -point improvement in Brief Pain Inventory (BPI) worst pain between baseline and week 15. There was a significant improvement in PROMIS T score at week 15 in both physical function (2.34, $p = 0.01$) and ability to participate in social roles and activities (2.71, $p = 0.02$) (Table 1, appendix) [58].

Bicalutamide is a nonsteroidal antiandrogen and most widely used against localised nonmetastatic prostate carcinoma. It competitively inhibits the action of androgens by binding to the androgen receptor. Relatively frequent side effects are hot flushes, pain, tiredness, nausea and diarrhea.

The effect of a CBD-rich extract (CBD-BDS, “botanical drug substance”) in combination with bicalutamide was tested in athymic nude mice that received a subcutaneous xenograft of androgen-receptor positive (AR+) human prostate cancer cells (LNCaP). Tumour volume was significantly lower in mice treated with the combination (25 mg bicalutamide + 100 mg CBD-BDS) than after treatment with single substances (tumour volume combination $\sim 1000\text{mm}^3 < \text{CBD-BDS} \sim 1200\text{mm}^3 < \text{bicalutamide} \approx \text{vehicle } 1500\text{mm}^3$). Similar, CBD-BDS plus bicalutamide significantly prolonged survival compared with bicalutamide or CBD-BDS alone whereby an increase to 50 mg bicalutamide + 100 mg CBD-BDS did not increase the survival rate further (Table 1, appendix) [13].

2.5. Combinations of THC or Medical Cannabis with Immune Checkpoint Inhibitors Improve the Survival of Mice in a Non-Small Cell Lung Cancer Model

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that achieve immune activation by inhibiting key regulatory mechanisms known as checkpoints (e.g., Pembrolizumab, Nivolumab, and Cemiplimab as anti-PD-1 antibodies, Ipilimumab as an anti-CTLA-4 antibody, as well as Atezolizumab, Avelumab, and Durvalumab as anti-PD-L1 antibodies). Although immune checkpoint inhibitors are generally well-tolerated, their use is associated with several side effects including acute kidney injury, fatigue, nausea, vomiting, diarrhoea, and dermatological reactions, thought to be immune-related. They can appear with a latency period of one to more than 12 months from start of treatment. As immune-competent cells bear cannabinoid receptors, notably CB2, agonists such as cannabinoids influence the immune system and may therefore interact with ICIs.

A preclinical study found that the combination of CBD and anti-PD-L1 antibody (Atezolizumab) enhances the anti-cancer immune response, in vitro and in vivo [59]. In a similar study with THC, tumour-bearing mice (CT26 non-small cell lung cancer cells) survived significantly longer with a combined anti-PD-1 antibody + THC therapy (control 21 days, < THC 24 days, < anti-PD-1 antibody 31 days < THC+anti-PD-1 antibody 54 days). Moreover, correlation between use of medical cannabis (composition not provided, assumed to be THC-predominant) and clinical outcome was evaluated in a cohort of 201 consecutive metastatic NSCLC patients treated with Pembrolizumab alone as first-line treatment. About half of patients (102 of 201) were given licenses for medicinal cannabis. No negative impact of cannabis on the activity of Pembrolizumab as first-line monotherapy for advanced NSCLC was observed (Table 1, appendix) [60].

Less favourable results have been reported from a retrospective analysis with Nivolumab. According to the authors, the concomitant use of cannabis by patients with various solid tumours (advanced melanoma, non-small cell lung cancer, renal cell carcinoma) reduced the response rate of Nivolumab immunotherapy, irrespective of the composition of cannabis (37.5% response rate with Nivolumab alone vs. 15.9% with combinations) [61]. However, the relevance of this observation is unclear as a later reanalysis was unable to verify many of these results [62].

Bevacizumab is another monoclonal antibody basically directed against vascular epithelial growth factor (VEGF), which is also targeted by cannabinoids in particular by CBD. A case series of glioblastoma patients treated with adjuvant CBD included one patient who received radio-

chemotherapy with Bevacizumab, lomustine (CCNU) and Tumour Treating Fields [63]. The patient survived 51 months.

Trametinib (MEKi, 0.75 mg/kg/day), a protein kinase inhibitor, has been studied together with a nabiximols-like combination of CBD and THC (1:1, CBD+THC, 7.5mg/kg/d, 21d) in a murine melanoma model (A2058 cells, s.c. injection, NSG mice) or a combination of all. Eight days after treatment initialization, all three treatment groups showed a significant reduction and to a similar extent in tumour volume and in tumour area as compared to vehicle only. This effect remained significant until the end of the experiment (day 21). There was no statistically significant difference between the single treatment groups (CBD+THC vs. MEKi vs. CBD+THC+MEKi). MEKi alone reduced the tumour mass slightly more than CBD+THC (Table 1, appendix [64].

2.6. Taxanes: CBD Enhances the Activity of Paclitaxel

Paclitaxel is a frequently used first-line antineoplastic drug of the taxane-family of medications. Similar to the closely related substance docetaxel, it inhibits cell mitosis, inducing apoptosis. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common adverse effect of cancer therapy with paclitaxel.

Surprisingly, very little is known at present how cannabinoids influence the effects of paclitaxel on malignant tumours. In an animal model of ovarian cancer, combined treatment of paclitaxel with CBD (administered as solution daily over 10 days or as a single administration of a topical microparticle formulation) showed a 2-fold higher tumour growth inhibition compared to a 1.5-fold decrease with paclitaxel alone. CBD enhanced the antitumor activity of PTX but not of adriamycin and cisplatin [65]. This confirms earlier observations in an animal model of breast tumours, where combined treatment of CBD (administered as solution, daily over 10 days, or as a single dose of a microparticle formulation) potentiated the antiproliferative activity of paclitaxel in MDA-MB-231-derived breast tumours. CBD-microparticles allow the combination of both, pre- and co-administration strategies [66].

The effect of a CBD-rich extract (CBD-BDS, “botanical drug substance”) in combination with docetaxel was tested in athymic nude mice that received a subcutaneous xenograft of androgen-receptor negative (AR-) human prostate cancer cells (DU-145) or a xenograft with androgen-receptor positive (AR+) human prostate cancer cells (LNCaP). Tumour volume in mice with DU-145 xenografts was lowest after treatment with the combination of 5 mg/kg docetaxel + 100 mg CBD-BDS (tumour volume after 65 days, combination ~400mm³ < docetaxel ~700mm³. CBD-BDS was inactive by itself against the growth of DU-145 xenografts *in vivo*, although it potentiated the effect of docetaxel. In mice with LNCaP xenografts (AR+), the effect of CBD-BDS alone was dose-dependent. The highest CBD-BDS dose tested (100 mg i.p./kg) exerted an effect similar to that of docetaxel (5 mg i.v./kg), although it reduced the tumour growth inhibitory effect of docetaxel (Table 1, appendix) [13].

As CBD increases the levels of the endocannabinoid anandamide (AEA), it is worth to mention an *in vitro* experiment that demonstrated a biphasic effect of AEA on gastric cancer cell lines (HGC-27). AEA stimulated proliferation at concentrations below 1 µM, while strongly suppressing proliferation through the induction of apoptosis at 10 µM. Combination of AEA (10 µM) with paclitaxel synergistically enhanced cytotoxicity whereas lower concentrations showed no significant effect [67]. Therefore, CBD-paclitaxel combinations may act on cancer cells also indirectly via endocannabinoids.

In a small series of cancer patients treated with docetaxel (1800 mg i.v.) the concomitant use of medicinal cannabis (200 ml herbal tea, 1 g/l, for 15 consecutive days, starting 12 days before the second treatment) did not significantly affect exposure to and clearance of docetaxel [40]. However, cannabinoids are barely soluble in water and their uptake was certainly negligible; this limits definite conclusions. No results on the combined use of paclitaxel with therapeutic doses of CBD or THC have been reported so far in man.

2.7. Alkylating Substances: Combinations of Cannabinoids with Temozolomide Enhance Therapeutic Effects and May Reduce Resistance

Alkylating agents are a large group of compounds that work by adding an alkyl group to the guanine base of the DNA molecule, preventing the strands of the double helix from correct linking. This causes breakage of the DNA strands, affecting the ability of the cancer cell to multiply. Examples are busulfan, cyclophosphamide, chlorambucil, dacarbazine, ifosfamide, melphalan or temozolomide. Temozolomide (TMZ) makes up the backbone of glioblastoma therapy concomitantly with radiotherapy. It methylates purine residues of DNA, inducing cross-linkages and inhibiting DNA replication. Other tumours that might be treated with TMZ are malignant melanoma, lung, colon or ovarian cancer. Side effects such as bone marrow depression, nausea/vomiting, fatigue, alopecia and constipation are common. As with other chemotherapeutic agents, tumours can develop resistance. In case of TMZ, resistance development can be linked to the expression of the repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), but also to the presence of cancer stem cells. Tumours that express high levels of MGMT (in this case the promotor of the gene coding for MGMT is unmethylated) are resistant.

CBD may combat this resistance, as it favours DNA-methylation [68]. Furthermore, in vitro data suggest that phytocannabinoids, particularly CBD but also cannabigerol (CBG) or cannabinoid combinations inhibit glioma and other cancer stem cells that have not only a tumorigenic potential but promote resistance to conventional cancer therapies such as radio- or chemotherapy [69,70].

Synergistic effects of CBD and a combination with TMZ have been investigated in an orthotopic model of human glioma (U87) in nude mice. Animals were treated with CBD (15 mg/kg) or TMZ (20 mg/kg) or both daily for 21 consecutive days. Animals receiving the CBD+TMZ combination lived significantly longer than with TMZ or CBD alone (0% survival: CBD+TMZ 84 days > TMZ 60 days > CBD 55 days > control 50 days) [71].

In another murine study, the oral administration of THC+CBD (nabiximols-like extracts, each 5 mg/kg/day, 2 weeks) in combination with TMZ (5 mg i.p./kg) produced a strong antitumoral effect in both subcutaneous and intracranial glioma cell-derived tumour xenografts (U87MG) (s.c. tumour volume: TMZ+THC+CBD < TMZ < THC+CBD < control). A higher portion of CBD (THC:CBD = 1:5) seems to increase the effect of THC+CBD combinations even further. However, no enhancement of anticancer activity was found by a combination of pure, synthetic CBD+TMZ compared to individual CBD or TMZ (s.c. tumour volume TMZ < CBD+TMZ < CBD < control) [72]. In contrast, combined administration of nabiximols-like extracts (THC:CBD $\approx$ 1:1) and BCNU (carmustine, an alkylating agent which shares structural similarities with TMZ, and which is also used for the treatment of glioblastoma) did not show a stronger effect than individual treatments [73].

Torres et al. demonstrated that the combination of THC (15 mg/kg/day, for 14 days, peritumoral injections) with temozolomide (5 mg TMZ/kg/d, for 14 days) strongly reduced the growth of glioma xenografts (U87MG), more than each compound given alone. A tumour-decrease was only observed with the combined treatment with THC+TMZ. A nabiximols-like combination (7.5 mg THC + 7.5 mg CBD/kg) was not more effective than 15 mg THC/kg. The combination CBD+TMZ was not tested (Table 1, appendix) [74].

A few articles describe experiences of a temozolomide – phytocannabinoid combination therapy in patients with glioblastoma. In a case series of 15 patients, subjects received in addition to standard radio-chemotherapy (mostly temozolomide), CBD (mainly 400 mg/day). Mean overall survival was 30.9 months which is twice as long as has been commonly reported; three patients (20%) were still alive after more than 5 years [63]. Overall survival is generally considered as “hard” endpoint, relatively free from biases. Another article describes the results of a small randomised, double-blind, placebo-controlled study in which patients received nabiximols oromucosal spray (mean of 7.5 sprays/day) in addition to dose-intense temozolomide up to one year. Survival at 1 year was 83% for nabiximols- (10/12) versus 44% (4/9 subjects) for placebo-treated patients, and 50% for patients treated with nabiximols versus 22% for those treated with placebo at 2 years. Median overall survival was estimated at 21.8 months. Patients taking nabiximols reported more severe treatment-emergent adverse events (TEAEs) and had a higher incidence of serious TEAEs (Table 1, appendix) [75].

These independent observations in animals and man suggest that combinations of temozolomide with phytocannabinoids may be more effective against glioblastoma than temozolomide alone. Whereas no results have been published on combined treatments of temozolomide with individual THC, encouraging data are available for combinations with individual CBD and nabiximols. At present it is unknown whether a modified ratio of THC:CBD with less THC in exchange to a higher dose of CBD improves the efficacy further; however, it very likely reduces typical side effects caused by THC.

3. Alleviation of Side Effects of Cancer and Anti-Tumour Therapy

3.1. Anxiety: CBD Reduces Anxiety; THC has a Biphasic Effect

Cancer is threatening; uncertainty about the future, worrying about being a burden or leaving family behind after death, money worries, and many other problems cause anxiety and/or depression. Anxiety is thus a common problem in cancer patient populations, and possibly co-varies with toxicity of chemotherapy [76].

Both phytocannabinoids, THC and CBD have been reported to alleviate anxiety, whereby THC shows a pronounced biphasic effect. Oral doses of 10 mg THC or above increased anxiety while lower doses produced either no changes or anxiety reduction [77]. Conversely, CBD has demonstrated repeatedly anxiolytic effects in a number of studies [78,79]. This extends also to CBD-dominant forms of cannabis [80]. A recent review concludes that CBD had greater anxiolytic effects than THC, but no or less prominent effects on sleep [81].

Observations on the anxiolytic effect of medicinal cannabis or nabiximols-like combinations of THC+CBD are inconclusive. A study on patients with multiple sclerosis found no effect of nabiximols on anxiety and depression (Table 2, appendix) [82], whereas a nabiximols-like combination counteracted THC-induced anxiety in healthy recreational cannabis users only when baseline anxiety was low [83].

Table 2. Influence of cannabinoids on main side effects of anti-tumour therapy (overview).

Side effect	Canna- binoid	Comments	Ref.
Anxiety	THC	THC shows a pronounced biphasic effect; a dose of 10 mg THC or above increased anxiety	[77]
	CBD	CBD demonstrated anxiolytic effects	[78,79]
	THC+ CBD	nabiximols-like combinations of THC+CBD did not reduce anxiety or depression in patients	[82]
Appetite/ weight loss	THC	THC (dronabinol) has received marketing authorisation for “anorexia associated with weight loss in patients with AIDS”; it is also used in cancer patients to stimulate the appetite and reduce weight loss (SmPC, current version).	[85]
	CBD	higher dosages of CBD (20 mg/kg) reduce the appetite and/or body weight or body mass index whereas low doses (2x 100 mg/day, 13 weeks or 5 mg/kg) had no effect on appetite and anthropometric parameters. CBD may positively influence taste alterations induced by chemotherapy	[87]

Chemo-therapy-induced nausea /vomiting (CINV)	THC	CINV that failed to respond adequately to conventional antiemetic treatments is an authorised indication for THC (dronabinol); (SmPC, current version).	[88]
	CBD	There are no experiences in man; in animal models, CBD produced a biphasic effect suppressing vomiting induced by cisplatin (20 mg/kg but not by 40 mg/kg) at 5 or 10 mg/kg and potentiating it at 40 mg CBD/kg	[96,97]
	THC + CBD	THC+CBD (2.5mg each) on day -1 to day 5 reduced CINV in adults who experienced CINV during moderate and highly emetogenic i.v. chemotherapy regimens despite guideline-consistent anti-emetic prophylaxis. Complete response was significantly higher with THC+CBD (24% versus 8% with placebo)	[90]
Chemo-therapy-induced peripheral neuropathic pain (CIPN)	CBD, THC, THC + CBD (1:1), tetra-hydro-cannabivarin (THCV)	Pretreatment with CBD, THC and their combination reduced the mechanical sensitivity induced by paclitaxel (8.0 mg.i.p./kg) in mice; CBD and THC showed very similar dose–response curves with two apparent peaks in efficacy, one within a dose range of 1.0–2.5 mg/kg and the other within the 10–20 mg/kg range. A 1:1 combination of per se ineffective doses of CBD and THC (each 0.16 mg/kg) was also effective. CBD (1.25–10.0 mg/kg) attenuated oxaliplatin- but not vincristine-induced mechanical sensitivity, while THC (10 mg/kg) significantly attenuated vincristine- but not oxaliplatin-induced mechanical sensitivity. A low dose combination of CBD+THC (each 0.16 mg/kg) significantly attenuated oxaliplatin- but not vincristine-induced mechanical sensitivity. When cannabinoids were administered after the last dose of paclitaxel (8 mg/kg, i.p., every other day for four injections; C57BL/6J female mice), CBD (10 mg i.p./kg, twice a week for six weeks) and THCV (15 mg i.p./kg) reduced thermal and mechanical hyperalgesia induced by paclitaxel to a similar extent; the combination being even more effective; inhalation of THC predominant cannabis produced antinociception in both paclitaxel- and vehicle-treated animals (rat model)	[98–102]

Nabiximols		A randomized, placebo-controlled crossover study in 16 patients with established chemotherapy-induced neuropathic pain that received nabiximols, found only a weak difference in favour of nabiximols that did not reach statistical significance.	[103]
Cannabis (no further details)		a retrospective analysis of medical records of 513 patients treated with oxaliplatin and 5-fluorouracil-based combinations of which 248 patients were treated with cannabis (265 served as controls) demonstrated a remarkable effect of cannabis against CIPN. CIPN grade 2–3 was nearly half as frequent in cannabis-exposed patients compared to a group not receiving cannabis; effect was more pronounced when patients received cannabis prior chemotherapy.	
OTC creams with THC and/or CBD		A small randomised, placebo-controlled investigated the effect of a topical CBD (applied four times daily over 4 weeks) on neuropathic pain of various origin including chemotherapy. At the end of the 4-weeks blinded treatment neuropathic pain (such as intense, sharp and cold sensations) decreased significantly by about 30% to 70% in the CBD group (10 to 15% with placebo). Two case series also suggest a possible benefit of topical cannabinoids	[106–108].
Cancer pain, opioids		preclinical and observational studies demonstrate the potential opioid-sparing effects of THC in the context of general analgesia, in contrast to higher-quality RCTs that did not provide evidence of opioid-sparing effects; studies with a low risk of bias showed that for adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain	[121–123].
CBD		CBD (400 mg/d) did not reduce oxycodone use (5 mg every 6 h, with additional rescue dosing as required) and was not superior to placebo as an adjunct medication for relieving acute, non-traumatic low back pain	[118]
Cue-induced opioid craving		Over half of the patients (53%) with chronic pain and on a stable opioid dose were able to reduce or eliminate their opioids by taking soft gels of a CBD-rich hemp extract Treatment duration of this open study was 8 weeks. In a small proof-of-concept open-label study it was found that CBD (600 mg once daily for 3	[113–117].

		consecutive days) could reduce cue-reactivity among patients with opioid-use disorder (OUD) who were not receiving medications for OUD	
Cardio-protection	CBD	In two animal models, CBD administered before doxorubicin, attenuated cardiotoxic effects	[128,129]
Protection of lung and brain	CBD	In a study with rats, lesions induced by a single dose of methotrexate (20 mg i.p./kg) could be reversed with CBD (5 mg i.p./kg for 7 days). CBD normalised histopathological and immunohistochemical changes in all regions, in the lung and in the brain	[136,137]
Renal protection	CBD	In a mouse model, CBD (2.5 – 5 - 10 mg i.p./kg/day) dose-dependently attenuated the cisplatin-induced renal dysfunction (highest effect with 10 mg CBD/kg/day i.p.) starting from 1.5 h before cisplatin (single dose, 20 mg i.p./kg), and was still effective if administered 12 h after exposure; it markedly attenuated the cisplatin-induced oxidative/nitrosative stress, inflammation, and cell death in the kidney. Similar effects were observed in a study with rats; renal damage, induced by injection of doxorubicin was attenuated by a pretreatment with CBD (26 mg p.o./kg for 2 weeks) .	[138,139]
Mucositis	CBD	synthetic CBD (3, 10, and 30 mg i.p./kg/day, starting on day 4), CBD reduced dose-dependently the severity of oral lesions and loss of weight induced by 5-FU in a murine model;	[142,143]

CBDe – cannabidiol extract/botanical drug substance (BDS); d – day; 5-FU – fluorouracil; h –hour(s); i.p.- intraperitoneal; MTD – maximal tolerated dose; nu – nude; OUD - opioid-use disorder; RCTs – randomised controlled clinical trial(s); s.c. – subcutaneous; signif. – significantly; SmPC – Summary of Product Characteristics; syn. – synthetic; THCe – d9-deltahydrocannabidiol extract/botanical drug substance (BDS); w – week;.

3.2. Appetite Stimulation, Weight Loss: THC Reduces Anorexia and Cachexia

Anorexia is the common symptom of malnutrition in cancer especially in an advanced stage. The reported prevalence among patients with advanced cancer varied from 39% to 82% for weight loss and 30% to 80% for anorexia [84]. Anorexia itself may originate from several factors such as nausea, altered taste sensation, mucositis, swallowing difficulties, reduced physical activity or depression.

THC was the pioneer and door opener for palliative therapies with cannabinoids; it has received marketing approval for “anorexia associated with weight loss in patients with AIDS”, and is also commonly used in cancer patients to stimulate appetite and reduce weight loss. Appetising effects extend also to THC-predominant cannabis. A small pilot study in cancer patients with poor appetite and chemosensory alterations found that THC (twice 2.5 mg/day, 18 days) significantly improved and enhanced chemosensory perception and food 'tasted better'. Premeal appetite and proportion of calories consumed as protein increased also compared with placebo [85].

Preliminary research suggests that CBD may reduce food intake and boost metabolism, which could promote weight loss but conclusive evidence is limited and, in some cases, conflicting. According to a review that included 11 randomized controlled clinical trials, higher dosages of CBD (20 mg/kg) reduce the appetite and/or body weight or body mass index whereas low doses (2x 100 mg/day, 13 weeks or 5 mg/kg) had no effect on appetite and anthropometric parameters [86]. Although CBD has no orexigenic activity, it may affect appetite indirectly, as taste alteration is another common adverse effect particularly after paclitaxel- or oxaliplatin-based chemotherapy. In a pilot trial, where patients were treated with oxaliplatin/ capecitabine or paclitaxel/ carboplatin, the intervention group received oral CBD 300 mg/day for 8 days in every cycle, and was compared to a control group without CBD. Patients were followed for three cycles of chemotherapy. Whereas the control group lost the ability to differentiate between weak versus strong saltiness and weak versus strong sweetness, the intervention group maintained the ability to differentiate (Table 2, appendix) [87].

3.3. Chemotherapy-Induced Nausea and Vomiting (CINV): THC Suppresses Nausea/Vomiting/Retching to a Similar Extent as Newer Antiemetics

Chemotherapy-induced nausea and vomiting (CINV) develops in up to 90% of patients receiving certain emetogenic, oncolytic agents such as cisplatin. Repeatedly, it has been reported that cannabis and cannabinoids alleviate CINV. CINV is commonly divided into the categories of acute, delayed, anticipatory, and breakthrough CINV; particularly the delayed phase is common, severe and resistant to antiemetic treatment. CINV that failed to respond adequately to conventional antiemetic treatments is an authorised indication for THC (Marinol TM/Syndros TM; INN: dronabinol) in the US since 1985. The recommended starting dosage is 5 mg /m², administered 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses per day (prescribing information Marinol, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf). However, a later controlled clinical trial that compared dronabinol, ondansetron, and the combination versus placebo in patients who received moderately to highly emetogenic chemotherapy, did not find significant differences between active treatments; all were superior to placebo [88]. A more recent review did also not find a difference between cannabinoids and prochlorperazine in the proportion of participants reporting no nausea, no vomiting, or complete absence of nausea and vomiting [89]. Conversely, more participants reported adverse events with cannabinoids compared with prochlorperazine (mainly dizziness, dysphoria, euphoria or sedation).

A recent randomised, placebo-controlled, phase II/III trial investigated the efficacy of a combination of THC+CBD (2.5 mg each, on day -1 to day 5) in adults who experienced CINV during moderate and highly emetogenic intravenous chemotherapy regimens despite guideline-consistent anti-emetic prophylaxis. Complete response was significantly higher with THC+CBD (24% versus 8% with placebo, respectively) [90].

Taken together, individual THC, combinations of THC+CBD and medicinal cannabis seem to be effective in CINV, with little difference to newer antiemetics such as ondansetron or prochlorperazine [91–93]. Nonetheless, dronabinol (THC), although authorised, has inherent limitations: it is a scheduled/controlled drug, contraindicated for the developing brain and not widely available. Moreover, high doses of THC induce psychotomimetic symptoms, anxiety, euphoria (“high”) and other side effects. As (medicinal) cannabis is widely used and highly estimated among cancer patients, it can be assumed that other cannabinoids than THC, notably CBD and CBDA, may contribute to the alleviating effect reported by cannabis users [94,95]. Paradoxically, long-term users of drug-type cannabis (marijuana) may present with recurrent, refractory vomiting (“cannabinoid hyperemesis syndrome”).

Conversely, data on the anti-emetic effect of CBD are actually limited to animal models. In one study, shrews were injected with CBD (5 mg/kg and 40 mg/kg) prior to an injection of cisplatin (20 mg/kg). Individual ondansetron and THC suppressed cisplatin-induced vomiting and retching, both dose-dependently; the combination of per se ineffective doses of ondansetron+THC was also effective.

Intriguingly, in contrast to the linear dose-dependent suppression by THC, CBD produced a biphasic effect, suppressing vomiting at 5 mg/kg and potentiating it at 40 mg/kg [96]. In another study, shrews were given CBD (5 or 10 mg/kg) 30 minutes before an injection of nicotine (5 mg/kg), LiCl (390 mg/kg) or cisplatin (20 or 40 mg i.p./kg). In the group treated with 20 mg cisplatin, CBD (5 and 10 mg/kg) reduced significantly the number of vomiting episodes of shrews (10 mg/kg slightly more than 5 mg/kg), but not in the group receiving 40 mg cisplatin/kg (Table 2, appendix) [97].

The low number of comparative studies limits conclusions. Further studies on the optimisation of the ratio of THC:CBD and dosages respectively, are needed. Whether CBD also reduces CINV in patients remains to be investigated.

3.4. Chemotherapy-Induced Peripheral Neuropathic Pain (CIPN): CBD and THC Prevent the Development of Allodynia In Vivo; Effects are Substance-Specific

Chemotherapy-induced peripheral neuropathic pain (CIPN) is one of the most common adverse effects of anticancer drugs, and includes a wide range of different drugs. The agents with the highest incidence are the platinum drugs, especially cisplatin and oxaliplatin, taxanes, especially paclitaxel, vinca alkaloids, and bortezomib, but occurs also with aromatase inhibitors (letrozole, anastrozole, exemestane) with variable incidence.

CIPN is substance- and dose-dependent and highest with platinum-based drugs (70–100%) as mentioned before. CIPN is a predominantly sensory neuropathy, starting with tingling, and numbness in the hands and feet, that may be accompanied by motor and autonomic changes. It can occur acute (paclitaxel, oxaliplatin) or emerge late and last for months or years, even after the termination of chemotherapeutic drugs. As chemotherapeutic neuropathy responds poorly to conventional treatments, any benefit observed with cannabinoids would be particular important.

In two animal studies (male and female C57Bl/6 mice), where peripheral neuropathy was induced by paclitaxel (8 mg i.p./kg), CBD (2.5 – 5, and 5 – 10 mg i.p./kg/day, prior injection of paclitaxel), prevented the development of cold and mechanical allodynia [98,99].

Similar results have been found in a further experiment, investigating the effect of CBD, THC and their combination on mechanical sensitivity induced by paclitaxel, oxaliplatin or vincristine. Individual CBD and THC (each 0.625–20.0 mg/kg i.p., male C57Bl/6 mice) administered on experimental days 1, 3, 5 and 7 prior paclitaxel (8.0 mg i.p./kg on days 1, 3, 5 and 7), attenuated paclitaxel-induced mechanical sensitivity. CBD and THC showed very similar dose-response curves with two apparent peaks in efficacy, one within a dose range of 1.0–2.5 mg/kg and the other within the 10–20 mg/kg range. A 1:1 combination of per se ineffective doses of CBD and THC (each 0.16 mg/kg) was also effective. When the effect of CBD and THC on mechanical sensitivity induced by oxaliplatin or vincristine was tested, individual CBD (1.25–10.0 mg/kg) attenuated oxaliplatin- but not vincristine-induced neuropathy, while THC (10 mg/kg) significantly attenuated vincristine- but not oxaliplatin-induced mechanical sensitivity. A low dose combination of CBD+THC (each 0.16 mg/kg) significantly attenuated oxaliplatin- but not vincristine-induced mechanical sensitivity. This points to differences in the mechanisms. It was concluded that CBD (1.25–10.0 mg i.p./kg/day) prevents the development of chemotherapy-induced peripheral neuropathy, and may be enhanced by co-administration of low doses of THC (0.16 mg i.p./kg/day) [100].

In contrast to the experiments described before, cannabinoids were administered in the following animal experiment after the last dose of paclitaxel (8 mg/kg, i.p., every other day for four injections; C57Bl/6J female mice). It was found that synthetic CBD (10 mg i.p./kg, twice a week for six weeks) and tetrahydrocannabinol (THC) (15 mg i.p./kg) reduced thermal and mechanical hyperalgesia induced by paclitaxel to a similar extent; the combination being even more effective [101]. THC seems to be effective as well. In a rat model (male Sprague Dawley rats), inhalation of THC-predominant cannabis (10.3% THC, 0.05% CBD or vehicle, 4 times on alternate days, i.e., days 0, 2, 4, and 6) produced antinociception in both paclitaxel- and vehicle-treated animals, and uncoupled paclitaxel-induced hyperconnectivity patterns as could be demonstrated in 3D3D magnetic resonance imaging [102].

The number of studies in man are very limited. A small, randomized, placebo-controlled crossover pilot study in 16 patients with established chemotherapy-induced neuropathic pain that received nabiximols, found only a very weak difference in favour of nabiximols (scores decreasing by 2.6 points to 3.40 during treatment with nabiximols, whereas dropping 0.6 points to 5.40 with placebo; dose individually adjusted up to 12 sprays per day); the difference did not reach statistical significance). [103].

Conversely, a retrospective analysis of medical records of 513 consecutive patients treated with oxaliplatin and 5-fluorouracil-based combinations of which 248 patients were treated with cannabis (265 served as controls; composition of cannabis not reported) demonstrated a remarkable protective effect of cannabis against CIPN. CIPN grade 2–3 was significantly less frequent in cannabis-exposed patients (15.3%) compared to the control group not receiving cannabis (27.9%). Intriguingly, the protective effect of cannabis against CIPN was more pronounced when patients received cannabis prior to treatment with oxaliplatin (75% versus 46.2%) (Table 2, appendix) [104]. CBD, THC and morphine, were also effective in a mouse-model where neuropathic pain was induced by sciatic nerve injury [105].

Up to now, no well controlled, high-quality study has been conducted in patients to assess whether pure CBD or THC can reduce peripheral chemotherapy-induced neuropathic pain (CIPN). A small randomised, placebo-controlled study that included 29 patients, investigated the effect of a topical CBD formulation on pain of various origin including chemotherapy-induced neuropathic pain (Theramu Relieve CBD compound cream, Theramu, Bakersfield, CA, containing 250 mg of CBD per 3 fl. oz container). At the end of the 4-weeks blinded treatment during which subjects were asked to apply the cream four times daily, neuropathic pain (such as intense, sharp and cold sensations) decreased significantly by about 30% to 70% in the CBD group [106].

A case series of subjects presenting with CIPN who used OTC creams containing either CBD alone (less than 0.3% THC) or variable amounts of CBD and THC (between 120–600 mg per unit, tube or jar, of CBD and 6–600 mg THC per unit) suggests that topical cannabinoids may be helpful, despite that 4 of 26 patients did not respond, and neuropathy symptoms returned after several hours in those responding confirming a previous crossover study [107]; some of these patients had tried other agents/acupuncture before with little or no benefit. Another case series that included 8 patients receiving chemotherapy, reported subjective improvement of pain with topical, 4% CBD ointments in all patients after 2 weeks, and maintenance of improvement over the next 6 months of treatment [108] (Table 2, appendix).

Taken together, animal experiments and a few observations in man suggest that CBD, THC and other cannabinoids may be effective against chemotherapy-induced peripheral neuropathy. Preliminary observations suggest that combinations of low dose CBD with THC may be synergistic, but the optimal ratio and dosages are currently unknown, and may dependent on the chemotherapeutic agent. Further studies on the optimisation of ratio and dosages are needed.

3.5. Pain: Studies Suggest a Reduction of Opioid Dosages, but the True Implications of Cannabinoids in Treatment of Tumour Pain Remain Controversial

Cancer pain can be caused by cancer itself because of a tumour pressing on nerves, bones or other organs or its treatment, and tends to get worse as cancer progresses. In a strict sense, this is not the same as chemotherapy-induced pain which is mainly of neuropathic nature and essentially caused by a toxic drug injury to the somatosensory nervous system. Pain is experienced by about 55% of patients undergoing anti-cancer treatment and by 66% of patients who have advanced, metastatic, or terminal disease [109]. It often changes throughout the day, and may vary from day to day. Cancer pain can be mild, moderate or severe, or may exacerbate suddenly for no clear reason (breakthrough pain). In most patients it can be controlled or lessened. As opioids are the mainstay of cancer pain management, the role of cannabinoids as comedication for improving treatment is particularly important.

Whereas many patients turn to cannabis for alleviating their symptoms [6,110–112], the true role of individual cannabinoids for treatment of pain and as an adjunctive non-opioid pain medication to

reduce prescription opioid use remains controversial. Preclinical and observational studies support a potential pain-alleviating and opioid-sparing effect of THC, CBD and cannabis in the context of general analgesia and a reduction of cue-induced craving (Table 2, appendix) [113–117], in contrast to higher-quality randomised controlled clinical trials [118]. Treatment with nabiximols reduced pain in two placebo-controlled studies at the expense of an increase of side effects [119,120]. Meta-analysis found – unsurprisingly – no or only modest effects on cancer pain, sleep problems and opioid consumption in patients with variable pain relief from combinations of opioids (Table 2, appendix) [121–123]. The large majority of human studies investigated the effect of cannabis on opioid consumption, less so of individual THC or fixed combinations such as nabiximols, and almost none investigated the effect of pure CBD as adjuvant to opioids. Most epidemiologic surveys concluded that medicinal cannabis, including hemp extracts reduces symptoms, curbs medication use and is relatively safe for cancer patients [124,125]. However, cannabis-based products consumed in these studies were ill-defined and contained in general an unknown mix of cannabinoids and of other phytosubstances.

A consensus guideline concluded that in patients with chronic pain taking opioids not reaching treatment goals, cannabinoids may be considered for patients experiencing or displaying opioid-related complications. This postulated benefit, however, was limited by adverse effects of cognitive impairment and dizziness imparted by an elevated dosage [126].

Taken together, opioid-sparing effects of medical cannabis for chronic pain remain uncertain due to unknown compositions and inadequate design of most studies. There is some evidence in favour of THC, but insufficient evidence for CBD.

3.6. CBD May Protect Organs Against Chemotherapy-Induced Toxicity

3.6.1. CBD is Cardioprotective In Vivo

Overt cardiotoxicity of chemotherapeutic drugs is relatively rare, but may occur in >20% of patients treated with anthracyclines such as doxorubicin or daunorubicin but also with fluorouracil (5-FU) or cyclophosphamide [127]. Acute cardiotoxicity occurs during or soon after initiation of therapy. This is usually transient and self-limiting with a myopericarditis-like picture, non-specific repolarization changes on ECG, dysrhythmias, troponin elevation, and transient left-ventricular dysfunction, although long term effects are known as well.

In a rat model, CBD (5 mg i.p./kg/day) significantly reduced the elevations of serum creatine kinase-MB and troponin T, and cardiac malondialdehyde, tumour necrosis factor- α , nitric oxide and calcium ion levels, and attenuated the decreases in cardiac reduced glutathione, selenium and zinc ions. Histopathological examination confirmed that CBD reduced doxorubicin-induced cardiac injury [128]. This cardioprotective effect of CBD (10 mg i.p./kg/day, starting before doxorubicin) has been confirmed later in a mouse model (Table 2, appendix) [129]. At present, it is unknown whether the above cited cardioprotective effect of CBD in animals translates to patients receiving chemotherapy. However, CBD and THC have both been reported repeatedly to demonstrate cardioprotective effects in various animal models [130–134] as well as in exhaustive exercise training [135]. Conversely, cannabis smoking has been added to the risk factors for myocardial infarction.

3.6.2. CBD Protects the Lung and Brain Against Toxic Effects of Methotrexate In Vivo

The folate inhibitor methotrexate, used to treat life-threatening neoplastic diseases such as leukaemia, is associated with adverse effects on a number of organs, notably the lungs (fibrosis), liver, kidney, bone marrow and brain.

In an animal study (female Wistar rats) lesions induced by a single dose of 20 mg/kg methotrexate (lung hyperemia, oedema, inflammatory cell infiltration and epithelial cell loss) could be reversed with CBD (5 mg i.p./kg CBD for 7 days) [136]. Moreover, CBD (5 mg i.p./kg for 7 days) reversed histopathological and immunohistochemical changes induced by methotrexate in the brain, such as hyperemia, microhaemorrhages, neuronal loss, decreased expressions of serotonin in the cortex, hippocampus, and cerebellum regions) (Table 2, appendix) [137].

3.6.3. CBD Reduces Renal Damage In Vivo

Nephrotoxicity is another form of organ toxicity that may occur with antineoplastic drugs, among them cisplatin, doxorubicin, alkylating agents like cyclophosphamide, antimetabolites such as methotrexate, targeted therapeutics of epidermal growth factor receptor (EGFR) pathway inhibitors and many others in up to 60% of cancer patients. Toxicity seems to be cumulative and dose-dependent, limiting the use of high doses.

In a mouse model, CBD (2.5 – 5 – 10 mg i.p./kg/day) dose-dependently attenuated the cisplatin-induced renal dysfunction (highest effect with 10 mg CBD/kg/day i.p., starting from 1.5 h before cisplatin, single dose, 20 mg i.p./kg), and was still effective if administered 12 h after exposure; it markedly attenuated the cisplatin-induced oxidative/nitrosative stress, inflammation, and cell death in the kidney [138].

In a similar study with rats (male Sprague-Dawley rats), renal damage was induced by injection of doxorubicin. CBD (26 mg p.o./kg for 2 weeks) administered before doxorubicin (single dose of 18 mg/kg), significantly improved oxidative stress parameters (SOD and GSH), liver enzyme activity (ALT and AST), as well as serum creatinine and urea, IL-6, and MDA, confirming anti-inflammatory and protective properties (Table 2, appendix) [139].

Gentamicin, although not an anti-neoplastic drug but an antibiotic, is also known to induce renal damage in high dosages. In an animal model where rats received a high daily dose of gentamicin (100 mg/kg/day, 10 days) in parallel to CBD (2.5, 5, and 10 mg/kg/day, 10 days) CBD reduced the renal damage induced by gentamicin. It lowered the increase of BUN and creatinine as well as histological tubular damages (strongest with 10 mg CBD/kg/day, for 10 days, followed by 2.5mg CBD/kg) [140].

Taken together, these results suggest that CBD may protect organs from treatment-induced toxicities.

3.6.4. Mucositis: CBD Reduces the Severity of Therapy-Induced Oral Mucositis In Vivo

Standard cytotoxic chemotherapy is not very selective and will cause collateral damage to healthy tissues such as rapidly dividing epithelial or bone marrow cells. Mucositis occurs in about 20% to 40% of patients who receive chemotherapy for solid tumours, and with varying severity, typically within 5 to 14 days of receiving chemotherapy. It persists for days to weeks even after treatment ends, and is a catalyst for a range of secondary complications, notably weight loss, diarrhoea, stress, fever, fatigue, pain and increased risk for infections. The whole gastrointestinal tract may be affected. Mucositis is dose-dependent, but is more frequent in patients receiving drugs that affect DNA-synthesis (e.g., 5-FU, methotrexate, cytarabine). In patients with nasopharyngeal carcinoma receiving radiotherapy oral mucositis exceeds 50% and contributes to taste changes and dysphagia [141].

In a murine model where animals treated with 5-FU received different doses of synthetic CBD (3, 10, and 30 mg i.p./kg/day, starting on day 4), CBD reduced dose-dependently the severity of oral lesions and loss of weight compared to positive controls (5-FU + mechanical trauma + placebo) and a negative control (mechanical trauma + placebo), at 2 experimental times (evaluation after 4 and 7 days) [142]. These results have been confirmed by a later study, also in mice. CBD (3, 10, and 30 mg i.p./kg, administered half an hour before 5-FU) alleviated the severity of 5-FU-induced oral mucositis, including improved survival, decreased body weight loss, reduced ulcer sizes, and improved clinical scores [143]. In addition, CBD is known for accelerating wound healing and for its immunomodulatory effects that play a role in controlling intestinal inflammation [144]. Respective observations in cancer patients are still missing.

3.6.5. Ototoxic Hearing Loss: The Role of Cannabinoids Needs Further Research

Ototoxicity is an important and major side effect of some anti-neoplastic agents particularly of platinum drugs; it can be of vestibular or cochlear nature or both, which can manifest as tinnitus, ear pain, and frank hearing loss. The incidence of ototoxicity induced by cisplatin has been estimated to

be 36% of adult patients with cancer and 40%-60% of paediatric patients. Cisplatin-induced ototoxicity manifests as irreversible, bilateral, high-frequency sensorineural hearing loss. Other antineoplastics that may cause ototoxic symptoms are carboplatin, bleomycin, methotrexate, nitrogen mustard and vinblastine; less frequent reasons are common substances such as some diuretics, solvents, antibiotics or NSAIDs. Pooled prevalence of ototoxic hearing loss associated with cisplatin and/or carboplatin exposure was 43.17%; prevalence estimates were higher for regimens involving cisplatin than carboplatin (cisplatin and carboplatin: 56.05%, cisplatin only: 49.21%; carboplatin only 13.47%) [145].

The literature on ototoxic effects of cannabis is controversial, and systematic studies on effects of pure cannabinoids on hearing loss are actually missing. Cannabis, whether medical cannabis, CBD-oils or marijuana, is not exchangeable with individual cannabinoids such as CBD or THC as has already been mentioned. Intriguingly, oral capsaicin prevented cisplatin-induced ototoxicity in a rat model by activating TRPV1 channels [146]. This experiment is of interest in so far, as CBD shares with capsaicin the activation of TRPV1. Moreover, cisplatin-induced ototoxicity has been related to the activity of DNA methyltransferase. Its inhibition can markedly reduce cisplatin induced damage in murine hair cells and spiral ganglion neurons [147]; as CBD modulates enzymes responsible for DNA methylation it possibly interferes with this mechanism of ototoxicity [148,149]. In addition, cisplatin-induced ototoxicity has been linked to oxidative stress and cochlear inflammation that may be targeted by CBD [150]. Therefore, CBD should demonstrate oto-protective effects warranting further investigations.

4. Discussion and Conclusions

Cannabinoids are multi-target substances with a remarkable large spectrum of activities. A growing body of research indicates that cannabinoids, particularly CBD and THC, represent an essential adjunct to cancer therapy, either as anticancer drugs per se, or for management of symptoms of cancer patients. Cannabinoids show relatively selective cytotoxic properties towards tumour cells, complementing or enhancing the effect of anti-neoplastic drugs. There are promising results for the comedication of gemcitabine with CBD (pancreatic carcinoma) and of temozolomide with CBD and nabiximols (glioblastoma). Preclinical work also shows benefits when combining CBD with platinum compounds (cisplatin, oxaliplatin), doxorubicin, immune checkpoint inhibitors and tamoxifen. It might be speculated that this translates eventually to reduced dosages of anti-neoplastic drugs in patients reducing overall costs and side effects but this is currently unknown. More so, preclinical results suggest that cannabinoids can reduce the development of resistance during tumour therapy. Numerous studies have shown that cannabinoids particularly CBD are able to interfere with resistance mechanisms; they reduce the drug transporter P-glycoprotein (P-gp)-controlled efflux, modulate DNA-methyltransferases (glioblastoma resistance), target cancer stem cells, and inhibit the release of exosomes from a wide range of cancer cells, responsible for cancer progression and chemoresistance. As a further benefit of combination, cannabinoids alleviate side effects related to the disease and cancer therapy, generally with less side effects than other drugs used for cancer supportive care. The reduction of nausea/vomiting and the increase of appetite by THC has long been recognised; both are licensed indications for dronabinol. Furthermore, studies show that CBD has a beneficial influence on (neuropathic) pain, anxiety and oral mucositis and potentially reduces the organ toxicity of chemotherapy (e.g., heart, kidney). Nevertheless, caution is advised as long as there are not more therapeutic experiences in man. Phase I metabolism of CBD and THC is catalysed by enzymes of the cytochrome P450 (CYP) complex with CYP3A4 being the main route. In humans, CYP3A4 is responsible for the metabolism of more than 50% of medicines. This implicates that interactions, such as increased blood levels of drugs that are metabolised by the same route cannot be ruled out. The sequence of administration may have an influence as has been demonstrated with anti-epileptic drugs. When CBD or THC is used for alleviating side effects of chemotherapy, cannabinoids are best administered before starting with the anti-tumour therapy, whereas it can be speculated that the inverse sequence might have a better anti-tumour effect. CBD added to a current treatment with clobazam increased the serum levels of the active metabolite for N-

desmethyloclobazam by a factor of three; conversely, if clobazam was added to a current treatment with CBD, only a minimal increase of the active metabolites of CBD was observed [151]. This highlights the importance of drug sequence when using drugs with similar metabolism routes as adjuncts.

Taken together, there is growing evidence that cannabinoids such as CBD may be useful adjuncts in cancer therapy. However, research for most of these promising aspects is still at the beginning.

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