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Review

Phytocannabinoids as Chemotherapy Adjuncts—A Review for Users

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Simple Summary: There is increasing evidence that cannabinoids may play an important and dual role in tumour therapy. On the one hand, they are cytotoxic to cancer cells and have low toxicity towards normal, healthy tissue; on the other hand, they can reduce the typical side effects of chemotherapy. Publications on the main motives for cannabis (cannabinoids) consumption in cancer patients show that patients' expectations exceed scientific facts. This article is aimed primarily at treating physicians. It briefly describes the results of combinations of approved cannabinoids with standard antineoplastics on tumours and the side effects of tumour therapy. The observations are largely limited to animal experiments, with only a few experiences with patients. Preliminary data suggest that adjuvant cannabinoids may improve survival in patients with glioblastoma and possibly other tumours. Some indications are established (THC for loss of appetite and chemotherapy-induced nausea/vomiting), and others still require intensive research (e.g., chemotherapy-induced peripheral neuropathic pain, and anxiety).

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 the development of resistance limit the use of antineoplastic drugs and reduce the quality of life. With easier access, a growing number of patients are using cannabis (cannabinoids) for alleviation of their symptoms, and in the hope of improving survival. This article summarizes results observed with combinations of phytocannabinoids and standard chemotherapeutic agents in animal tumour models and in patients. It is limited to approved phytocannabinoids. Preliminary preclinical data suggest that conventional antineoplastic agents combined with cannabinoids exert enhanced anti-cancer effects, reduce resistance development and improve survival. Corresponding experiences with patients are still very limited and only concern a few patients with glioblastoma and pancreatic cancer. Benefits of combinations containing cannabinoids have also been reported for chemotherapy-induced nausea and vomiting, loss of appetite (dronabinol), and chemotherapy-induced peripheral neuropathic pain and anxiety (cannabidiol). In addition, phytocannabinoids, particularly cannabidiol, may play a role in protecting organs such as the heart, lungs or kidneys from chemotherapy-related toxicity. Although the results are promising, more research is needed to ensure whether the benefits of adjuvant cannabinoids outweigh the potential risks.

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

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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 all the progress, 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 reduce side effects.

Recent years have seen a progressive legalisation in parallel to increased interest and use of cannabis or cannabinoids among cancer patients, whereby up to 80% use the internet as a 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" on the internet about the 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 the treatment of cancer, often without telling their physicians [4–7].

Cannabis can be applied in many forms. Edibles, including liquids, e.g., "CBD oil", which is basically a hemp extract, were most 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 risk 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 over recent years, namely delta-8-THC or hexahydrocannabinol (HHC); both substances are psychoactive. In contrast to natural extracts, such CBD-derived products contain dozens of unidentified synthetic reaction by-products that can put consumers at risk. Although people often use the terms "cannabis" and "marijuana" interchangeably and indiscriminately, they do not mean exactly the same thing. The word "cannabis" commonly refers to all products derived from the plant *Cannabis sativa*, whereas "marijuana" ("recreational" cannabis, "weed", "drug type", type I cannabis) refers to parts of, or products from, the plant *Cannabis sativa* that contain substantial amounts of the psychotomimetic THC. Thus, herbal cannabis, marijuana, medicinal cannabis, extracts, CBD oils and similar cannabis-based products are distinctly different to isolated, well-defined substances such as THC (dronabinol) and CBD, and effects perceived by users may not be the same. However, there is no uniform understanding of these terms. "Medicinal cannabis" are plants of a defined, standardised variety and their derivatives, rich in THC or CBD or with a more balanced content of both cannabinoids. Examples are Bedrocan™, Bediol™, Bedrolite™ (Bedrocan International; 9641 KV Veendam; Netherlands; https://bedrocan.com/, accessed on 19 September 2024), or the chemotypes FM1 and FM2 (Stabilimento Chimico Farmaceutico Militare, Firenze; https://www.agenziaindustriedifesa.it/unita-produttive/stabilimento-chimico-farmaceutico-militare-firenze/, accessed on 19 September 2024) of the Italian Military Pharmaceutical Institute of Florence or Avidekel™ (Tikun Olam, Tel Aviv, Israel; https://tikun-olam.org.il/en/home-en/, accessed on 19 September 2024). In this article, the term "medicinal cannabis" is used for herbal substances and derivatives with a defined origin and "cannabis" when the origin is unclear. Caution is 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 derivatives in place of individual cannabinoids such as CBD to alleviate symptoms of antineoplastic treatments as mentioned before.

Whereas cytotoxic effects of individual phytocannabinoids, notably CBD and THC, on tumour cell lines have been extensively studied in vitro, much less research has been carried out 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 then, it has been repeatedly argued that phytocannabinoids, when combined with standard chemotherapy drugs, may act synergistically on cancer cells, beyond their other pharmacological effects [10–13]. While some palliative effects (e.g., on nausea/vomiting, cachexia, pain, anxiety/depression, and sleep) have long been known and are more or less well documented, knowledge of antitumour effects is based predominantly on results from in vitro studies. The concentration dependence of the antitumour effects of cannabinoids in vitro has been repeatedly pointed out, with effects in the micromolar range (1–10 µM/L), sometimes with biphasic effects. Griffiths [10] raised the question of the extent to which tumour-inhibiting effects at micromolar concentrations are therapeutically relevant since CBD blood levels are in the ng/mL range, i.e., around 500–1000 times lower. This should be countered by the fact that CBD is known to bind in comparable inhibitory concentrations to targets that are responsible for the metabolism of other substances (IC50 of CBD between 0.8 µM for CYP2C19, 5.6 µM for CYP2C9 and 2.42 µM for CYP2D6) [14]). Although blood levels of CBD are only in the range of ng/mL, the metabolization of substances by the above-mentioned CYP 450 oxidases has been proven to be influenced by CBD (for example, tamoxifen, as explained later in this article).

The question therefore arises to what extent it actually makes sense to compare the in vitro inhibitory concentration on cell lines directly with the achievable in vivo blood levels in highly complex, living systems such as humans. Animal tumour models are limited in their information as well, as only immunologically modified animals can be used for studies with human cancer cell xenografts. One should therefore be aware of the limitations of the available methods. In vitro and animal models are essential because we do not have better tools, and—on another level—open human studies are better than no data at all. The present article differs from the above-mentioned reviews in this respect, as it also includes results from a number of case series and open studies in cancer patients.

While THC remains a controlled drug due to its psychotropic effects that limit wider use, 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 [15]. 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 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, and 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. A very recent ASCO guideline of May this year provides recommendations on the use of cannabis and/or cannabinoids (cannabis, herbal cannabis derivatives, and synthetic cannabinoids; single cannabinoids, as well as combinations of cannabis ingredients) and points out the insufficient data in connection with combined therapy, especially for anti-tumour therapy and reduction in side effects [16].

Since CBD, THC and their combination, and in some countries also medicinal cannabis, are currently the only approved and therefore therapeutically available phytocannabinoids, this article is limited to results with the products mentioned above.

Given the increasing popularity of cannabinoids among cancer patients, this narrative review aims to summarize the known benefits as well as the limitations of adjunctive cancer therapy with phytocannabinoids in order to provide treating physicians with decision-making aids in tumour therapy. Results with other phytocannabinoids such as cannabigerol (CBG) were largely excluded because they are not approved for treatment and therefore are not available on the pharmaceutical market.

The article is separated into two parts. The first describes the antitumour effects of cannabinoid–antineoplastic drug combinations with a focus on animal models and experiences in humans; the second part summarises the reported benefits of cannabinoids on chemotherapeutic side effects relaying 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 substances is to target the tumour concurrently at various levels of its growth and dissemination, by improving efficacy, using fewer toxic individual doses, and limiting the development of chemoresistance.

When multiple drugs are used, the sequence of administration may influence how effectively cancer cells are killed. So far, very few examples of the influence of the order of application have been described. The combination of CBD + THC added after chemotherapy (exposure to cytarabine, vincristine) resulted in greater induction of apoptosis in leukaemia cells in vitro than the use in the opposite order [17]. A similar observation was already made earlier with CBD alone; chemotherapy first, followed by CBD, significantly improved overall results against leukaemia cells [18]. 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 significantly lower tumour volume (orthotopic murine glioma) than the combination CBD + THC or radiation alone [19]. 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. In comparison to over 120 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 [20,21].

For example, in an experiment examining the inhibitory effect of a combination of tamoxifen with the cannabinoids CBD, THC and anandamide (AEA), it was found that the viability of C6 rat glioma cells increased inversely to the concentrations of fetal bovine serum in the culture medium. No effect was observed in a medium containing 10% fetal bovine serum, as is often used for cultivation [22]. Since cannabinoids show a high protein binding there is less free, unbound substance available in the cell culture medium. This could be the reason for the lack of inhibition. Other in vitro studies demonstrate antagonistic to the 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 [23]. As a further example, CBD has been repeatedly described to antagonise platinum drugs (cisplatin, oxaliplatin) [24–26]. However, CBD may also act synergistically or as an additive. Moreover, priming with CBD (sequential exposure) enhances cisplatin and paclitaxel killing of cancer cells in vitro [27]. 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 [28] (Table 1a). The reasons for these differences between in vitro and in vivo results are unclear but could be related to the fact that the conditions in living organisms are significantly more complex than in cell cultures. In any case, this discrepancy demonstrates that in vitro results cannot be transferred 1:1 to animal models and humans.

The following section should be preceded by the fact that there is very little data on patients and all of it is only of a pilot nature. Unless otherwise stated, these are results of open, uncontrolled observational studies or case series. Results from high-quality controlled clinical trials on a sufficient number of patients are lacking.

Table 1. (**a**) Effects of cannabinoid-chemotherapy combinations in animals (overview). (**b**) Effects of cannabinoid-chemotherapy combinations in man (overview).

(a)

Anti-Neoplastic Drug	Cannabinoid Adjunct	Comments	Ref. (Selected)
Cisplatin (2.5 mg CIS i.p./kg/w)	CBD 5 mg p.o./kg, 4x/w, 4 weeks; (sequence not stated)	human head and neck squamous cells (FaDu) s.c. xenografts, BALB/c nude mice; estimated tumour volume: CBD + cisplatin ~300 mm^3 < CBD ~600 mm^3 < cisplatin ~800 mm^3 < vehicle ~1500 mm^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%.	[28]
Cisplatin (3 mg CIS i.p./kg, 3x weekly)	THC 45 mg p.o./kg, or THCe (with 45 mg THC/kg, 3x/w)	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 (animals were sacrificed after one month of treatment)	[29]
Doxorubicin (2 mg DOX i.v./kg, 2x/w, 2 w)	CBD-EV (5 mg i.p./kg, 2x/w, 2 w) or free CBD (5 and 10 mg i.p./kg, 2x/w, 2 w)	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. Tumour volume after 2 weeks, extracellular vesicles (EV): CBD-EV + DOX < CBD (5 mg/kg) + DOX < DOX < CBD (10 mg/kg) ≈ CBD-EV (5 mg/kg) < EVs/controls); tumour volume with the CBD-EV + DOX combination was at least 50% lower than the average tumour volume in control animals	[30]
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 in 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	[31]
Irinotecan (IRI) (60 mg i.p./kg on day 1, 5)	THC (7 mg p.o./kg/d, 7 d) (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% (day 7), with IRI + THC by −14%; THC reduced the efficacy of IRI by about half.	[32]
Gemcitabine (GEM) (100 mg i.p./kg, every 3 days)	CBD (100 mg 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: CBD + GEM 52.7 days (+183%) > GEM 27.8 (+49%) > CBD 25.4 days (+37%) > no treatment 18.6 days	[33]
Tamoxifen (2.5 mg TAM i.p./kg, 3x weekly); Lapatinib (100 mg LAPA/kg) daily, oral gavage	THC 45 mg p.o./kg, or THCe (with 45 mg 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 (animals were sacrificed after one month of treatment)	[29]
Bicalutamide (BIC) 25–50 mg p.o./kg, 3x per week	CBD-BDS (CBDe), 1–10–100 mg i.p./kg/d,	Prostate cancer, s.c. xenografts, (LNCaP, androgen-receptor positive/AR+, athymic nude mice); dosing was initiated on day 15 and was terminated on day 38; CBDe (~65% CBD) enhanced efficacy of BIC on LNCaP (no significant difference between 25 and 50 mg BIC); tumour volume LNCaP, Day 35: CBDe(100 mg i.p./kg/d) + BIC(25 mg p.o./kg, 3x/w) < CBDe(100 mg i.p./kg/d) < BIC(25 mg p.o./kg, 3x/w) ≈ vehicle, and% survival (D47): BIC(25 mg p.o./kg, 3x/w) + CBDe(100 mg i.p./kg/d) > BIC(50 mg p.o./kg, 3x/w) > CBDe(100 mg i.p./kg/d) > BIC(25 mg p.o./kg, 3x/w) > vehicle	[20]

Table 1. *Cont.*

(a)			
Anti-Neoplastic Drug	**Cannabinoid Adjunct**	**Comments**	**Ref. (Selected)**
ICI, 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).	[34]
Trametinib (MEKi) (0.75 mg s.c./kg/d)	CBD/THC = 1:1	Melanoma (A2058 cells, s.c. injection, NSG mice); CBD + THC (each 10 mg s.c./kg/d, 21 d) 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 Day 22: MEKi ≈ CBD + THC + MEKi < CBD + THC < vehicle	[35]
Docetaxel (DOC) (5 mg i.v./kg once weekly)	CBD-BDS (CBDe) (~65% CBD), 100 mg i.p./kg/d;	Prostate cancer, s.c. xenografts, (DU-145, androgen-receptor-negative/AR-, athymic nude mice); CBDe enhanced the efficacy of DOC on tumours; CBDe 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); Tumour volume, LNCaP, Day38: DOC(5 mg/kg) ≈ CBDe(100 mg/kg) < CBDe(10 mg/kg) < CBDe(100 mg/kg) + DOC ≈ CBDe(1 mg/kg) < vehicle; Tumour volume, DU-145, D90: CBDe + DOC < DOC (5 mg/kg) < CBDe(10 mg/kg) < vehicle ≈ CBDe(1 mg/kg) < CBDe(100 mg/kg);	[20]
Temozolomid (25 mg TMZ/kg/d) for 21 days	CBD (15 mg i.p./kg/d) for 21 days	orthotopic model of human glioma (U87) in nude mice; animals were treated with CBD or TMZ or both. Mice receiving the combination lived signif. longer than with TMZ or CBD alone (0% survival: CBD + TMZ 84 days > TMZ 60 days > CBD 55 days > control 50 days)	[36]
TMZ 5 mg i.p./kg twice a week,	Syn. CBD 15 mg p.o./kg/d for 15 days	heterotopic s.c. glioma U87MG xenografts, nude mice; Tumour volume TMZ < CBD + TMZ < CBD < vehicle; CBD + TMZ reduced tumour volume less than TMZ alone, although more than CBD alone; Tumour volume TMZ < CBD + TMZ < CBD < vehicle;	[37]
TMZ 5 mg i.p./kg twice a week,	CBD + THC (extracts)	heterotopic s.c. glioma U87MG xenografts, nude mice; ratio THC/CBD = 1:1 or 1:4 (5 mg p.o./kg each or THC 6.5 mg/kg + CBD 24.5 mg/kg, as extracts); oral administration of THC + CBD (1:4 ratio) resulted in a similar tumour size as the 1:1 combination (but still higher than TMZ, as determined by MRI); combination with TMZ increased survival, a higher ratio of CBD did not increase the effect on tumour growth; tumour volume: TMZ + THC + CBD (1:4) ≈ TMZ + THC + CBD (1:1) < TMZ < THC + CBD (1:4) ≈ THC + CBD (1:1) < vehicle; In a similar murine study, a combination with BCNU (carmustine, instead of TMZ) did not show a stronger effect than individual treatments; tumour volume TMZ + CBD + THC (1:1) < CBD + THC (1:1) ≈ CBD + THC + BCNU < vehicle;	[37,38]
TMZ 5 mg i.p./kg twice a week,	CBD + THC (extracts),	heterotopic s.c. glioma U87MG xenografts, nude mice; combinations with a higher proportion of CBD (THC/CBD = 1:4, 1:6) (3.5 mg p.o./kg each or THC 4.5 mg/kg + CBD 16.5 mg/kg or THC 5.2 mg/kg + CBD 29.5 mg/kg) are similar synergistic as a 1:1 combination; effect increases with a combination with TMZ; CBD + THC reduced tumour volume less than TMZ alone, although more than vehicle alone; tumour volume: TMZ + CBD/THC (6:1) ≈ TMZ + CBD/THC (4:1) ≈ TMZ + CBD/THC (1:1) < TMZ < CBD/THC (4:1) ≈ CBD/THC (1:1) ≈ CBD/THC (6:1) < vehicle;	[37]

Table 1. *Cont.*

(a)			
Anti-Neoplastic Drug	**Cannabinoid Adjunct**	**Comments**	**Ref. (Selected)**
TMZ 5 mg i.p./kg twice a week,	CBD, THC (extracts) p.o. daily for 15 days	orthotopic intracranial glioma U87MG xenografts nude mice; administration of THC + CBD at a 1:4 ratio did not affect tumour size significantly (as determined by MRI) and did not increase survival in contrast to TMZ; the combination with TMZ decreased tumour growth and increased survival signif. from ~30 (control) to > 50 days; Tumour volume TMZ + CBD + THC (4:1) < TMZ < CBD + THC (4:1) ≈ vehicle;	[37]
TMZ 5 mg i.p./kg twice a week,	Syn. CBD, synthetic THC, p.o.	orthotopic intracranial glioma xenografts 12O12 glioma-initiating cells (GICs), nude mice; TMZ + THC + CBD (1:5) was most effective in reducing tumour growth (MRI) and increasing survival; THC.CBD (1:1) was less effective than 1:5, and less effective than TMZ alone; a combination (THC/CBD 1:1 or 1:5) with TMZ increased these effects; Survival TMZ + CBD + THC (5:1) > TMZ + CBD + THC (1:1) > TMZ > CBD + THC (1:1) > ≈ vehicle;	[37]
TMZ 5 mg/kg/d, peritumoural injections, for 14 days	THC 15 mg/kg/d, peritumoural, 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; (the combination CBD + TMZ was not tested)	[39]
(**b**)			
Anti-Neoplastic Drug	**Cannabinoid Adjunct**	**Comments**	**Ref. (Selected)**
Irinotecan (IRI) (mostly 600 mg, 90 min i.v. infusion)	Medicinal cannabis 200 mL of herbal tea (1 g/L), daily, 15 days	Patients with metastatic cancer (observational study); 10 days after the 1st infusion of IRI, patients started with cannabis tea (Bedrocan™, THC-dominant medicinal cannabis) for 15 consecutive days; 21 days after the 1st infusion, patients received a second treatment with IRI, this time as concomitant treatment to Bedrocan-tea; 12 patients were evaluated; Bedrocan administration did not significantly influence exposure to and clearance of IRI	[40]
Gemcitabine + paclitaxel	CBD (mainly 400 mg/d) until death	Patients with pancreatic cancer (case series); 6 of 9 patients received CBD in addition to standard chemo-therapy (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 (CBD, THC); overall survival was about 11 months	[41]
Tamoxifen	CBD (below 50 mg/d)	Women receiving tamoxifen (single case and observational study); concomitant oral CBD decreased 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	[42,43]
Aromatase inhibitors; 71.8% of patients received anastrozole, 20.5% exemestane, 7.7% letrozole	CBD (titrated up to 2x 100 mg p.o./d over 4 weeks, then at the maximum dose)	Women with hormone-receptor-positive breast cancer; an observational study did not report a negative impact of a combined treatment. Conversely, CBD, known to have anti-inflammatory effects, alleviated the symptoms of arthralgia pain. Of 28 patients completing the 15-weeks study, 17 (60.7%) reported a ≥2-point 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	[44]

Table 1. *Cont.*

(**b**)			
Anti-Neoplastic Drug	**Cannabinoid Adjunct**	**Comments**	**Ref. (Selected)**
various ICIs Pembrolizumab or Nivolumab or Durvalumab or Atezolizumab or Ipilimumab plus Nivolumab	cannabis, (composition unknown)	Patients with various metastatic stage IV malignancies, prospective observational study; 34 patients received cannabis plus immunotherapy (76% as second line treatment), 68 patients received immunotherapy only (54% as second line treatment). Data suggest that concomitant cannabis use was associated with shorter time to tumour progression and shorter overall survival. Results also suggested a halving of immune-related adverse events by cannabis	[45]
ICI, anti-PD-1 antibodies, Pembrolizumab	THC, medical cannabis, assumed to be THC-rich	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	[34]
Bevacizumab + radio-chemo-therapy (lomustine)	CBD (400 mg/d)	Single patient with glioblastoma; this patient is included in a case series of 15 patients with glioblastoma; the patient survived 51 months	[46]
Docetaxel, (mostly 180 mg, 90 min i.v. infusion)	Medicinal cannabis 200 mL of herbal tea (1 g/L), daily	Patients with various metastatic, refractory carcinoma; 10 days after the 1st infusion of docetaxel, patients with metastatic cancer started with cannabis tea (Bedrocan™, THC-dominant medicinal cannabis) for 15 consecutive days; 21 days after the 1st infusion, patients received a 2nd treatment with docetaxel, this time as concomitant treatment to Bedrocan™; 12 patients were evaluated; Bedrocan administration did not significantly influence exposure to and clearance of docetaxel	[40]
standard radio-chemo-therapy mostly Temozolomid (TMZ)	CBD (mainly 400 mg/d)	Patients with glioblastoma; prospective 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	[46,47]
TMZ up to one year	nabiximols oro-mucosal spray (mean 7.5 sprays/d)	Patients with glioblastoma, randomised pilot study; 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 signif.) and 369 days in the placebo group;	[48]

Hu—human; BDS—botanical drug substance (extract); b.w.—body weight; CBC—cannabichromene; CBDe—cannabidiol extract/botanical drug substance (BDS); d—day; GIC—Glioma Initiating Cells exchangeable with GSC—glioma stem cells; h -human; ICI—immune checkpoint inhibitor; i.p.—intraperitoneal; MTD—maximal tolerated dose; nu—nude; s.c.—subcutaneous; signif.—significantly; syn.—synthetic; THCe—delta-9-tetrahydrocannabinol 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 about a 75% slower tumour growth; estimated tumour volume: CBD + cisplatin ~300 mm^3 < CBD ~600 mm^3 < cisplatin ~800 mm^3 < vehicle ~1500 mm^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/week) also reduced tumour growth by more than 60% [28] (Table 1a). The combination

with THC enhanced the effect of cisplatin as well. Synthetic THC (45 mg p.o./kg, 3x/week, or an extract (THCe) with 45 mg 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) [29] (Table 1a).

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 [49]. The 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) [50]. 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) [51]. Moreover, research data indicate that CBD is able to decrease the self-renewal of lung cancer stem cells [52]. 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 for promoting cancer growth as well as inducing chemoresistance and may serve also as biomarkers. Generated artificially, they can be used as delivery systems for anticancer drugs and others.

2.2. CBD Potentially Enhances the Anti-Tumour Effect of Doxorubicin and of Other Anthracyclines (Animal Studies)

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, such as cancers of the breast, ovary, bladder, prostate and thyroid but also bone sarcomas. 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), CBD enhanced the effect of doxorubicin (DOX). 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 DOX (2 mg DOX i.v./kg). The tumour volume after 2 weeks was lowest with 5 mg CBD-EV +DOX, followed by 5 mg free CBD + DOX, and DOX alone, and was at least 50% lower than the average volume in control animals; estimated tumour volume, D14: CBD-EV (5 mg/kg) + DOX (2 mg/kg) ~3000 mm^3 < free CBD (5 mg/kg) + DOX (2 mg/kg) ~4000 mm^3 < DOX (2 mg/kg) ~4500 mm^3 < free CBD (10 mg/kg) ~6700 mm^3 < CBD-EV (5 mg/kg) ~7000 mm^3 < EVs ~8000 mm^3 < control ~9000 mm^3. 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 DOX [30] (Table 1a).

As with other antitumour agents, the development of clinical resistance is common. Although changes in DNA-damage-triggered apoptosis are a major mechanism, changes in the transport via the already mentioned P-glycoprotein (P-gp), which is responsible for multiple drug resistance, play a role as well. It was found that CBD, and marginally less so cannabinol (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 the intracellular accumulation of these drugs concentration-dependently [53,54]. Moreover, a reduction in 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 for 2 weeks) enhanced the cytotoxicity of doxorubicin in resistant, triple-negative breast tumours, obviously inhibiting epigenetic histone modifications [55]. *Cannabis sativa* L. extracts also have a direct, selective cytotoxic effect on colon cancer cells and potentially reverse doxorubicin resistance [56].

A well-known doxorubicin analogue is mitoxantrone. It is approved for the treatment of adult acute myeloid leukaemia and for hormone-refractory prostate cancer. In addition, it appears to be active 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 an immunomodulator, enhancing on one hand T-cell suppressor function, and inhibiting on the other B-cell function and antibody production. In addition, mitoxantrone inhibits myelin degradation by macrophages, which explains its use in various forms of multiple sclerosis [57]. The most common side effects are infections, nausea, vomiting and sores in the 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 μM) in combination with mitoxantrone decreased the resistance by four to six times by inhibiting the breast cancer resistance protein (BCRP/ABCG2) [58].

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 is primarily used as chemotherapy for metastatic colorectal cancer, but also against other solid tumours such as lung, ovarian, or pancreatic cancer or malignant gliomas. IRI is a pro-drug that is activated by carboxylesterases and further metabolised via highly complex mechanisms also including liver cytochrome P450 oxidase CYP3A4 that metabolises a large number of common drugs [59]. 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 have been investigated in healthy male Wistar rats. During the 1-, 3- and 7-day assessment period, animals received either a single dose (100 mg IRI i.p./kg) or IRI together with THC (7 mg p.o./kg/day). Both single IRI and IRI + THC administration caused moderate leukopenia with a greater decrease in leukocyte counts in the IRI + 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 [31] (Table 1a); concomitant THC seems to protect the liver against IRI-induced toxicity [60]. At present, it is insufficiently known whether this effect of IRI (eventually combined with THC) may be used for treating acute lymphoblastic leukaemia [61].

In addition, the antineoplastic effects of IRI + THC combinations have been studied in a murine colon cancer model. Intriguingly, 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 by about half, as the tumour in the IRI + THC group shrank by only 10%, 15%, and 14% on respective days 3, 5, and 7 [32] (Table 1a).

In a small, open-label, observational study, patients treated with IRI (600 mg IV) for various metastatic cancers concurrently received daily medicinal cannabis tea (Bedrocan™, 200 mL herbal tea, 1 g/L, for 15 consecutive days starting at 12 days before the second treatment). Cannabis tea had no significant effect on IRI exposure and clearance IRI [40] (Table 1b). However, cannabinoids are barely soluble in water, and their uptake from daily tea was certainly negligible. Combinations of IRI with therapeutic doses of CBD or THC have not been studied. Therefore, no conclusions can be drawn from this study and interactions of IRI with higher doses of CBD or THC remain unknown.

Taken together, a single animal study showed that combinations of doxorubicin with intraperitoneally injected CBD reduced tumour growth of breast cancer cells more than doxorubicin or CBD alone, while another animal study with the type I topoisomerase inhibitor, irinotecan, found that THC, at a relevant dose of 7 mg p.o./kg/day, reduced the effectiveness of irinotecan by about half.

There are currently no relevant studies on patients.

2.3. CBD May 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 first-in-class chemotherapy drug used to treat pancreatic cancer. It is also used in a number of other cancers, including transitional cell carcinoma of the bladder and ovarian cancer. Common side effects include nausea/vomiting, loss of hair, appetite, dyspnoea, myelosuppression or flu-like symptoms.

Intriguingly, the cannabinoid receptors CB1 and CB2—both of which are overexpressed in pancreatic adenocarcinoma—have been reported to be further enhanced by gemcitabine. Therefore, as expected, cannabinoid agonists acting on CB1 and/or CB2 receptors can inhibit the growth of human pancreatic cancer xenografts (PaCa44 cells, nude mice), especially in combination with gemcitabine [62].

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 a relatively high intraperitoneal daily dose (100 mg i.p./kg) [33] (Table 1a). Furthermore, CBD was able to counteract in vitro the mechanisms involved in gemcitabine resistance in pancreatic cancer [63].

A case series of patients with pancreatic cancer describes their first experiences with a phytocannabinoid-combination therapy [41] (Table 1b). Out of nine patients, seven 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 (4.8 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 gemcitabine therapy and is essentially consistent with the mouse study mentioned above.

Overall, only one rodent study and a small case series describe the beneficial effects of combining gemcitabine with CBD. A combination of cannabinoids (CBD) and gemcitabine may be worth further investigation.

2.4. Combinations of CBD with Hormonal Anti-Cancer Agents Seem to Be Promising

Tamoxifen is an anti-oestrogen (hormone) and selective oestrogen receptor modulator. It is commonly used as a 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 [64,65]. Whereas CBD is a negative allosteric modulator of CB1, it acts as an inverse agonist on CB2 receptors similar to tamoxifen [66]. 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) [67]. CBD could therefore be a suitable candidate for combinations with tamoxifen. Tamoxifen is metabolised to the primary active metabolite endoxifen via the cytochrome P450 enzyme CYP2D6. Endoxifen and N-desmethyl-tamoxifen are potent inhibitors of aromatase [68]. CYP2D6 metabolises up to 25% of commonly used drugs; it is subject to genetic polymorphism. About 15% of the population are intermediate, another 5–10% poor, and about 75% extensive ("normal") metabolisers (European population); in addition, about 1% to 10% are ultra-rapid metabolisers. Consequently, 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 [69]; this mechanism is targeted by CBD as has been mentioned before.

Antitumour 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, three times a week by oral gavage (a dose of the extract contained 45 mg THC/kg). Tamoxifen (2.5 mg/kg in 100 µL of sesame oil) and cisplatin (3 mg/kg in 100 µL of phosphate-buffered saline) were administered i.p. three times a week; and lapatinib (100 mg/kg/day) by oral gavage in 200 µL 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; unfortunately, combinations with pure, synthetic THC were not tested [29] (Table 1a). To date, no further animal studies have been published on combinations of tamoxifen with other cannabinoids.

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 metabolization of tamoxifen to the active metabolite endoxifen was observed. CBD was prescribed to treat persistent postsurgical pain inadequately managed by alternate analgesics [42] (Table 1b). Similarly, a slight decrease in the active metabolite by concomitant use of CBD was also observed in a small, open-label, single-arm study of 26 evaluable breast cancer patients (12 of which were excessive, 13 intermediate metabolizers) in which the pharmacokinetic profile of tamoxifen was assessed while taking pharmaceutical-grade CBD oil (dosage less than 50 mg CBD) as food supplement (10% CBD in almond oil, THC-free, exact composition not described). 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. In contrast, CBD oil had a positive impact on the side effects of tamoxifen, particularly hot flashes, arthralgia and insomnia; the endocrine subscale of the FACT-ES which assesses endocrine complaints and adverse effects, improved clinically relevantly by 6.7 points ($p < 0.001$), and health-related quality of life improved by 4.7 points with CBD [43] (Table 1b). Of note, both THC and CBD are also metabolized to some extent via CYP2D6, similar to tamoxifen, although the main metabolic pathway is via CYP3A4.

From the above, it may be concluded that a CBD + tamoxifen combination potentially 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 for an eventual reduced efficacy. Currently, human results are only available from observational studies; controlled clinical studies are lacking.

In addition, neither the effects of higher doses (the daily CBD dose in the publications mentioned was below 50 mg) nor an "optimal CBD dose" are known. In principle, it is not advisable to use CBD oil of unknown quality due to possible other, unknown components.

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 oestradiol E2, the most potent oestrogen in the body. This stops the production of oestrogen in women who are postmenopausal, reduces the oestradiol 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 [70]. CBD combined with exemestane potentiates its anti-tumour effects in vitro, whereas no beneficial effect was observed when combined with anastrozole or letrozole [71]. Intriguingly, CBD, THC and AEA reduced aromatase and oestrogen receptor ERα expression levels in receptor-positive (ER+) breast cancer cells that overexpress aromatase (MCF-7aro) [72]. Besides that, THC, CBD and AEA revert the resistance to exemestane, therefore underscoring their potential use as adjuvant treatment [73].

One of the main side effects of aromatase inhibitors is the development of arthralgia and myalgia in more than 25% of patients, which may be due to increased inflammation in the body in response to oestrogen deficiency [74]. A very recent, small 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; the majority received anastrozole (71.8%), followed by exemestane (20.5%) and letrozole (7.7%). 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, $p = 0.02$) without a negative impact on breast cancer treatment [44] (Table 1b). This article is only available as an abstract of a meeting.

Bicalutamide is a nonsteroidal antiandrogen and is 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 diarrhoea.

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 ~1000 mm^3 < CBD-BDS ~1200 mm^3 < bicalutamide ≈ vehicle 1500 mm^3). Similarly, 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 [20] (Table 1a).

Overall, results on combinations of cannabinoids with hormonal anticancer agents are still very limited. Regarding tamoxifen, one article describes experiments in mice in which a combination with a THC-rich extract reduced tumour growth of breast cancer xenografts better than the individual compounds. Two other articles describe a small reduction in tamoxifen plasma levels in patients after concurrent use of CBD. While a reduction in effectiveness seems unlikely, the combination may have a positive impact on typical tamoxifen side effects.

As far as aromatase inhibitors are concerned, there is only one small open trial in patients. In addition to a series of aromatase inhibitors (mostly anastrozole), patients

also received up to 100 mg of CBD/day. Approximately 60% of the patients reported a significant reduction in typical muscle and joint pain and an improvement in physical function over a period of 15 weeks. It remains to be seen whether this combination also affected the tumour.

2.5. Combinations of THC, CBD or Medical Cannabis with Immune Checkpoint Inhibitors Show Promising Effects in Preclinical Cancer Models: Results in Patients Are Still Inconclusive

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 over 12 months after the 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 first retrospective study in a heterogeneous population of 140 patients with various solid tumours (advanced melanoma, non-small cell lung cancer, renal cell carcinoma) examined the effect of concomitant use of cannabis with ICIs. According to the authors, concomitant use of cannabis reduced the response rate of Nivolumab immunotherapy, regardless of the composition of cannabis (37.5% response rate with Nivolumab alone vs. 15.9% with combinations) [75]. However, the relevance of this observation is unclear because an independent follow-up analysis was unable to confirm many of these results (therefore not included in Table 1b) [76].

In a later, small, prospective observational study by the same research group on patients with advanced cancer (various metastatic malignancies, stage IV), 34 patients who received immunotherapy plus cannabis were compared with 68 patients who received immunotherapy but no cannabinoids. Data suggest that concomitant cannabis use was associated with shorter time to tumour progression and shorter overall survival. In addition, the results suggested a halving of immune-related adverse events [45] (Table 1b). In this study, cannabis users were significantly more likely to receive immunotherapy as a second line of treatment (76% of patients vs. 54%) and received a wide range of different ICIs, including anti-PD-1 (Pembrolizumab or Nivolumab), anti-PD-L1 (Durvalumab or Atezolizumab) or combined anti-PD-1 and anti-CTLA4 (Ipilimumab and Nivolumab); no information was provided on the composition of cannabis.

A recent, similar study with a more homogeneous population examined the correlation between medical cannabis consumption (composition not described, presumed to be THC-dominant) and clinical outcome in a cohort of 201 consecutive metastatic non-small cell lung cancer patients (NSCLC patients treated only with Pembrolizumab as first-line therapy). Approximately half of the patients (102 of 201) received licenses for medical cannabis. No negative impact of cannabis on the activity of Pembrolizumab was observed. Time to tumour progression was similar for cannabis-naive and cannabis-treated patients (6.1 versus 5.6 months, respectively 95% confidence interval, 0.82 to 1.38, $p = 0.386$), while overall survival was numerically higher in the cannabis-naive group (54.9 versus 23.6 months) but did not reach statistical significance (95% confidence interval 0.99 to 2.51, $p = 0.08$). In multivariate analyses, cannabis use was not an independent predictor factor for mortality [34] (Table 1b). The same article also described the results of a combined treatment of anti-PD-1 antibody with THC in a murine model. Tumour-bearing mice (CT26 non-small cell lung cancer cells) survived significantly longer with a combined anti-PD-1 antibody + THC therapy (THC + anti-PD-1 antibody, 54 days > anti-PD-1 antibody, 31 days > THC, 24 days > control 21, days) [34] (Table 1a). Similar studies with CBD are de facto non-existent. A recent conference abstract of a preclinical study briefly reports

that the combination of CBD and the anti-PD-L1 antibody (atezolizumab) enhances the immune response against cancer both in vitro and in vivo [77].

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 (400 mg/day) included one patient who received radio-chemotherapy with Bevacizumab, lomustine (CCNU) and Tumour-Treating Fields [46]. The patient survived 51 months (Table 1b).

Trametinib (MEKi, 0.75 mg s.c./kg/day), a protein kinase inhibitor, has been studied together with a nabiximols-like combination of CBD and THC (1:1, CBD + THC, each 10 mg s.c./kg/d, for 21 days) 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 to a similar extent in tumour volume and in tumour area as compared to vehicle only, which remained significant until the end of the experiment (day 21). Compared to vehicle, CBD + THC reduced melanoma growth by about 50%, MEKi alone by about 75% (difference not significant). The addition of CBD + THC to MEKi did not increase the effect further [35] (Table 1a).

In summary, heterogeneity of patient populations, unknown composition of cannabis products, different ingestion methods, variable cannabis formulations with different pharmacokinetics and pharmacodynamics, unknown doses of THC or other cannabinoids and many other factors may have resulted in mixed results; further, well-controlled clinical studies are required.

It is currently not clear to what extent the combination of cannabinoids with ICIs brings improvements or risks. There are no controlled clinical trials with pure substances, only open studies with cannabis and with a relatively small number of patients. It is also not clear whether combination treatment as initial treatment is associated with a different prognosis than second-line or subsequent treatment. Mouse models show the benefit of combined treatment of anti-PD-1 antibodies with THC or trametinib with a CBD + THC combination, but corresponding studies in patients are lacking.

2.6. Taxanes: CBD Enhances the Activity of Paclitaxel In Vitro

Paclitaxel is a frequently used first-line drug of the taxane-family of antineoplastic 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 (PTX).

Surprisingly, very little is known at present about how cannabinoids influence the effects of paclitaxel on malignant tumours. In an in vitro/in ovo model of ovarian cancer, combined treatment of PTX + CBD, administered as a solution (CBDsol), daily over 10 days, or as a single administration (SD) of a topical, extended-release microparticle formulation (CBDmps) showed a 2-fold higher tumour growth inhibition compared to a 1.5-fold decrease with PTX alone. Compared to controls, growth was reduced with PTX to about 75%, and to 50% with the PTX + CBD combination (tumour growth: PTX + CBDmps (SD) ≈ PTX + CBDsol (daily) < PTX < control). CBD enhanced the antitumour activity of PTX but not of adriamycin and cisplatin [78]. This confirms previous observations by the same authors in a similar model of breast tumours, where combined treatment with CBD (administered as a solution, daily for 10 days or as a single dose (SD) of a microparticle formulation) increased the antiproliferative activity of PTX in MDA-MB-231-derived breast tumours in ovo [79].

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 human prostate cancer cells, either androgen-receptor-negative (AR-) cells (DU-145) or androgen-receptor-positive (AR+) 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/kg CBD-BDS (tumour volume after 65 days, combination ~400 mm^3 < docetaxel ~700 mm^3). 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 DOC i.v./kg), although it reduced the tumour growth inhibitory effect of docetaxel (combination DOC+CBDe less effective than DOC or CBDe (100 mg/kg) and also less than CBDe (10 mg/kg) alone) [20] (Table 1a).

As CBD increases the levels of the endocannabinoid anandamide (AEA), it is worth mentioning 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 [80]. Therefore, CBD–paclitaxel combinations may act on cancer cells also indirectly by modulating the level of endocannabinoids.

In a small series of 24 cancer patients treated with docetaxel (180 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] (Table 1b). However, cannabinoids are barely soluble in water and their uptake was certainly negligible. Combinations of docetaxel with therapeutic doses of CBD or THC have not been studied.

In total, there were only two animal studies that examined the tumour-inhibiting effects of a combination of taxanes with cannabinoids. In one study, the combination of paclitaxel with CBD in two different formulations each showed a greater reduction in tumour growth than paclitaxel alone. The second animal study examined a CBD-rich extract in combination with docetaxel and also found that the combination caused greater inhibition of tumour growth. However, there is currently no meaningful data on patients.

2.7. Alkylating Substances: Combinations of Temozolomide with Cannabinoids Possibly 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 correctly 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 the 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 [81]. 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 tumourigenic potential but promote resistance to conventional cancer therapies such as radio- or chemotherapy [82,83].

Huang T et al. observed synergistic effects of a combination of CBD with TMZ in an orthotopic model of human glioma (U87) in male nude mice. Animals were treated with CBD (15 mg i.p./kg) or TMZ (25 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) [36] (Table 1a).

In another study on nude mice, a range of experiments with pure CBD and combinations of CBD- and THC-rich extracts in a ratio of 1:1 up to 6:1 was carried out with interesting results. Contrary to the study of Huang et al. mentioned before, the combination of pure CBD + TMZ reduced the growth of heterotopic s.c. glioma U87MG xenografts less than TMZ alone (5 mg/kg i.p. twice a week); pure, synthetic CBD (15 mg/kg p.o. daily for 15 days) was effective but less than the combination of CBD + TMZ (tumour volume TMZ < CBD + TMZ < CBD < vehicle). Differences from controls (vehicle alone) were significant [37] (Table 1a). This contradiction to the previously mentioned orthotopic study by Huang et al. (despite the same dose) could best be explained by the fact that in Huang's study, administration was intraperitoneal, whereas administration in the Lopez-Valero study was by oral route; the bioavailability of CBD would be significantly higher after i.p. injection.

When various doses of CBD and THC nabiximols-like extracts were used, with increasing proportions of CBD (THC 3.5 to 6.5 mg/kg/day and CBD 3.5 to 24.5 mg/kg/day) the tumour volume was also higher after treatment with the cannabinoids than after TMZ alone; a higher CBD/THC ratio did not increase the effect further. The combination with TMZ had, however, a strong growth-inhibiting effect, decreasing the tumour volume and improving survival. In a further experiment using an orthotopic xenograft model (intracranial injection of glioma-initiating cells, 12O12), combinations of pure, synthetic CBD and THC (1:1 or 5:1, 5 mg p.o./kg each or 25 mg CBD, respectively) were again less effective than pure TMZ (tumour volume TMZ + THC + CBD (1:5) < TMZ + THC + CBD (1:1) ≈ TMZ < THC + CBD (1:5) < THC + CBD (1.1) ≈ vehicle) [37] (Table 1a). In contrast, combined administration of nabiximols-like extracts (THC/CBD ≈ 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 in a similar murine study by the same research group [38] (Table 1a).

Another murine study also showed that the combination of THC (15 mg/kg/day, for 14 days, peritumoural injections) with temozolomide (5 mg TMZ/kg/day, for 14 days) strongly reduced the growth of glioma xenografts (U87MG), more than each compound given alone. THC (15 mg/kg/day) reduced tumour growth by approximately 50%. Tumour regression was only observed with the combined treatment with THC + TMZ (tumour volume on day 15: THC + TMZ < TMZ < THC (15 mg/kg) < vehicle). Unfortunately, the combination CBD + TMZ has not been tested.

In a second experiment comparing THC, CBD and a 1:1 combination but without TMZ, a nabiximols-like combination (7.5 mg THC + 7.5 mg CBD/kg) was not more potent than 15 mg THC/kg; the inhibition of tumour growth with 7.5 mg THC and 7.5 mg CBD/kg was comparable [39] (Table 1a).

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 [46,47] (Table 1b). 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. However, patients taking nabiximols reported more severe treatment-emergent adverse events (TEAEs) and had a higher incidence of serious TEAEs [48] (Table 1b).

In total, two studies in mice examined glioma-inhibiting combinations of TMZ with cannabinoids. In the first, CBD was administered as i.p. injection in an orthotopic model. The injection in combination with TMZ had the strongest growth inhibitory effect. In the

second study, a similar, this time oral dose of CBD combined with TMZ was less effective than TMZ alone. The addition of THC to CBD increased the effects of a combination with TMZ without any additional benefit when the CBD percentage was increased. In addition, there are two publications on the use of cannabinoids additive to TMZ in patients with glioblastoma. One summarizes the results of a prospective case series on 15 patients, the second publication compared 12 patients who received nabiximols in addition to TMZ with 9 others without nabiximols. Both publications found an increase in overall survival with cannabinoids, basically confirming the murine studies.

These independent observations in animals and humans suggest that combinations of temozolomide with phytocannabinoids may be more effective against glioblastoma than temozolomide alone and probably also more effective than cannabinoids alone. While therapeutic results from combined treatments of temozolomide with isolate THC are still lacking, there are encouraging data for combinations with single CBD or nabiximols. However, the dose level of nabiximols is limited by the toxicity of THC, in contrast to CBD. Whether changing the THC/CBD ratio, with less THC in favour of a higher CBD dose, improves effectiveness cannot be assessed based on the current data. However, switching to a higher percentage of CBD and a lower percentage of THC would likely reduce the typical side effects of THC. Larger, double-blind, placebo-controlled clinical trials are needed.

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; the diagnosis of a potentially deadly disease, the burden of chemotherapy, general deterioration of physical and mental health, uncertainty about the future, worrying about the family after death, money worries, and many other problems cause anxiety and/or depression. Anxiety is thus a common problem in cancer patients and possibly co-varies with the toxicity of chemotherapy [84].

Both phytocannabinoids, THC and CBD have been reported to alleviate anxiety, whereby THC shows a pronounced biphasic effect. A review concludes that oral doses of 10 mg THC or above increased anxiety while lower doses produced either no changes or anxiety reduction [85] (Table 2). THC/drug-type cannabis ("marijuana") is commonly known for its euphoric effect ("high"). Conversely, the non-psychotomimetic CBD has demonstrated repeatedly anxiolytic effects in a number of studies and attenuates or even prevents the anxiogenic action produced by higher THC doses with somewhat lower effects on depression. CBD seems to show an inverted U-shaped dose–response curve with about 300 mg/day being the most effective dose in anxiety disorders. [86,87] (Table 2). This extends also to CBD-dominant forms of cannabis [88]. Another recent review concludes that CBD had greater anxiolytic effects than THC, but no or less prominent effects on sleep [89].

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 [90] (Table 2), whereas a nabiximols-like combination of smoked THC-dominant and CBD-dominant cannabis counteracted THC-induced anxiety in healthy recreational cannabis users only when baseline anxiety was low [91]. The different intake and differences in the accompanying substances (Nabiximols is a mixture of two extracts with around 35% other cannabinoids and terpenes) could explain this supposed contradiction.

From this, it can be deduced that pure CBD in particular can have a beneficial effect on anxiety (about 300 mg/day). Systematic studies on cancer patients would be needed for confirmation. In the case of THC, daily doses should not exceed 10 mg; the potential role of nabiximols needs to be elucidated.

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

Side Effect	Cannabinoid	Comments '*'	Ref. (Selected)
Anxiety	THC	THC shows a pronounced biphasic effect; a dose of 10 mg THC or above increased anxiety whereas a low dose or combination with CBD suppresses anxiety and aversive memory expression.	[85]
	CBD	CBD reduces anxiety, stress and similar behaviours; regarding depression, the results were slightly lower. Although effective over a wide range, CBD seems to show an inverted U-shaped dose–response curve with about 300 mg/d being the most effective dose in anxiety disorders.	[86,87]
	THC + CBD	A nabiximols-like combination of THC + CBD did not reduce anxiety or depression in a small, pilot study in patients with multiple sclerosis, whereas domains involving processing speed and auditory verbal memory significantly improved after 6 months.	[90]
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; recommended dose: 2.5 mg before meals, twice daily (SmPC, current version); (confirmed later by a small, open, uncontrolled study in cancer patients); THC-dominant cannabis may also be effective.	[92,93]
	CBD	higher dosages of CBD (20 mg/kg) reduce the appetite and/or body weight or body mass index whereas low doses (2 × 100 mg/d, 13 weeks or 5 mg/kg) had no effect on appetite and body weight. CBD may positively influence taste alterations induced by chemotherapy.	[94]
Chemo-therapy-induced nausea/vomiting (CINV)	THC	CINV that failed to respond adequately to conventional antiemetic treatments is an authorised indication for THC (dronabinol); the recommended starting dosage is 5 mg/m^2, administered 1 to 3 h prior to the administration of chemotherapy, then every 2 to 4 h after chemotherapy, for a total of 4 to 6 doses per day (SmPC, current version).	[95]
	THC + CBD	THC + CBD (2.5 mg 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 signif. higher with THC + CBD (24% versus 8% with placebo; randomised, placebo-controlled trial)	[96]
	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. THC suppressed cisplatin-induced vomiting and retching, dose-dependently; the combination of per se ineffective doses of odansetron + THC was also effective.	[97,98]
Chemo-therapy-induced peripheral neuropathic pain (CIPN)	CBD, THC, THC + CBD (1:1), tetra-hydro-cannabivarin (THCV)	**Systematic studies exist only in rodents.** Pretreatment with CBD, THC and THC + CBD reduced the mechanical sensitivity induced by paclitaxel in mice with very similar dose–response curves and with two apparent peaks in efficacy (the 1st within a dose range of 1.0–2.5 mg i.p./kg, the 2nd within the 10–20 mg/kg). 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 THC+ CBD (each 0.16 mg/kg) attenuated oxaliplatin- but not vincristine-induced mechanical sensitivity. When cannabinoids were administered after the last dose of paclitaxel, 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)	[99–103]
	Nabixi-mols (up to 12 sprays/d	A randomized, placebo-controlled crossover study in 16 patients with established chemotherapy-induced neuropathic pain that received nabiximols, found a weak difference in favour of nabiximols that did not reach statistical significance.	[104]

Table 2. *Cont.*

Side Effect	Cannabinoid	Comments '*'	Ref. (Selected)
	Cannabis (unknown composition)	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.	[105]
	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 signif. by about 30% to 70% in the CBD group (10 to 15% with placebo). Two small case series also suggest a possible benefit of topical cannabinoids	[106–108]
Cue-induced opioid craving	CBD	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 consecutive days) could reduce cue-reactivity among patients with opioid-use disorder (OUD) who were not receiving medications for OUD	[109–113]
	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.	[114]
Cancer pain, opioids	THC, THC + CBD up to 48 sprays/d, up to 5 w (2.7 mg THC + 2.5 mg CBD per actuation	In the 1st study, patients were randomized to THC/CBD (~1:1) extract, THC extract, or placebo; change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically signif. in favour of THC/CBD only compared with placebo. There was no change from baseline in median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups. In the 2nd study, only the low-dose (1–4 sprays/d) and medium-dose (6–10 sprays/d) groups reported signif. analgesia for nabiximols compared to placebo. The optimal dose may vary from person to person, and it could be that patients respond differently.	[115,116]
Cancer pain, opioids	Cannabis, cannabinoids	Cannabinoids seem to reduce pain and improve quality of sleep, but the effect sizes are low. There is some evidence in favour of medicinal cannabis, THC and THC/CBD combinations, with insufficient evidence for individual CBD. Higher doses (>15 mg THC/d, nabiximols up to 10 sprays/d) correlated with increased pain relief but also with more side effects. Cannabinoids may have a role as an adjunct or even replacement for opioids but evidence remains uncertain	[117–119]
Organ toxicity Cardio-protection	CBD	In two **animal models** (mice, rats), CBD administered before doxorubicin, attenuated cardiotoxic effect (a human equivalent dose would be in the order of 1 mg/kg)	[120,121]
Protection of lung and brain	CBD	In **studies 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/d for 7 days). CBD normalised histopathological and immunohistochemical changes in all regions, in the lung and in the brain	[122,123]
Renal protection	CBD	In a **mouse model**, CBD (2.5–5–10 mg i.p./kg/d) dose-dependently attenuated the cisplatin-induced renal dysfunction (highest effect with 10 mg CBD) starting from 1.5 h before cisplatin (20 mg i.p./kg, single dose), 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).	[124,125]
Mucositis	CBD	In a **murine model**, synthetic CBD (3, 10, and 30 mg i.p./kg/d, starting on day 4), CBD reduced dose-dependently the severity of oral lesions and loss of weight induced by 5-FU.	[126,127]

* if only animal studies are available, these are highlighted in bold; AUC—area under the (plasma-time) curve; 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—delta-9-tetrahydrocannabinol extract/botanical drug substance (BDS); w—week.

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

Loss of appetite and malnutrition in cancer can have various triggers such as nausea, altered sense of taste, mucositis, difficulty swallowing, reduced physical activity or depression, but can also be an expression of the beginning of tumour cachexia, especially in advanced stages. The reported prevalence among patients with advanced cancer varied from 39% to 82% for weight loss and 30% to 80% for anorexia [128].

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" (current prescribing information THC, INN: dronabinol, Marinol ™/Syndros ™) and is also widely used in cancer patients to stimulate appetite and prevent weight loss. The recommended adult starting dosage is 2.5 mg orally twice daily before meals. A small, double-blind, randomised, placebo-controlled pilot study in 46 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 also increased compared with placebo [92] (Table 2). The study was too short to assess weight changes.

Appetising effects extend also to THC-dominant cannabis. In another small, open pilot study, also with cancer patients, they received cannabis capsules (9.5 mg THC + 0.5 mg CBD per capsule or capsules at half the dose twice daily). Of 17 patients who started the study, only 6 completed the 6-month study period and only 3 of them met the primary endpoint (weight gain of $\geq$10% from baseline). The majority of patients had to reduce the daily dose to 5 mg capsules twice daily or discontinue treatment due to side effects [93]. In this study, the THC dose was obviously too high and led to many dropouts.

Preliminary research suggests that CBD may have opposite effects, reducing food intake and boosting 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) reduced the appetite and/or body weight or body mass index whereas low doses (2 $\times$ 100 mg/day, 13 weeks or 5 mg/kg) had no effect on appetite and anthropometric parameters [129]. 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 [94] (Table 2).

Overall, THC and possibly THC-dominant cannabis stimulate appetite in cancer patients. The effects are rather small and are observed at low doses (5 to 10 mg THC/day). Possible benefits must be weighed against side effects. The influence of CBD and nabiximols on appetite and weight has not yet been systematically examined.

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 four categories: acute, delayed, anticipatory, and breakthrough CINV; particularly the delayed phase is common, severe and resistant to antiemetic treatment. CINV which failed to respond adequately to conventional antiemetic treatments is an authorised indication for THC (dronabinol) in the US since 1985. The recommended starting dosage is 5 mg/m^2, administered 1 to 3 h prior to the administration of chemotherapy, then every 2 to 4 h 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, ac-

cessed on 1 June 2024). 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 [95] (Table 2). A more recent systematic review of randomised controlled trials did also not find a difference between cannabinoids (dronabinol, nabilone) and prochlorperazine in the proportion of participants reporting no nausea, no vomiting, or complete absence of nausea and vomiting; cannabinoids were more effective than placebo [130]. Conversely, more participants reported adverse events with cannabinoids compared with prochlorperazine (mainly dizziness, dysphoria, euphoria/feeling high or sedation).

A recent randomised, placebo-controlled, phase II/III trial investigated the efficacy of a combination of THC + CBD (capsules with 2.5 mg each, on day −1 to day 5) in 147 adults who experienced CINV during moderate and highly emetogenic intravenous chemotherapy regimens despite guideline-consistent anti-emetic prophylaxis. Currently, only a meeting abstract of this study is available. Complete response was significantly higher with THC + CBD (24% versus 8% with placebo, respectively) [96] (Table 2).

Overall, treatment of CINV with individual THC is an approved indication, with little difference from newer antiemetics such as odansetron or prochlorperazine [131–133]. Combinations of THC + CBD also appear to be effective in CINV, but data from this study is only available as a meeting abstract.

Conversely, data on the anti-emetic effect of CBD are currently 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 odansetron and THC suppressed cisplatin-induced vomiting and retching, dose-dependently; the combination of per se ineffective doses of odansetron + 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 [97] (Table 2). In a similar study, also in shrews, animals were given CBD (5 or 10 mg i.p./kg) 30 min before 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) significantly reduced 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 [98] (Table 2).

Despite approval, some restrictions must be noted in the case of THC: it is a scheduled/controlled drug, contraindicated for the developing brain and not widely available. Moreover, high doses of THC induce psychotomimetic symptoms such as anxiety or euphoria ("high") and other side effects.

Since cannabis is widely used and highly estimated among cancer patients, it can be assumed that cannabinoids other than THC, in particular CBD and CBDA, may also contribute to the alleviating effect reported by cannabis users [134,135]. However, there are no controlled clinical trials with medicinal cannabis. Paradoxically, long-term users of drug-type cannabis (marijuana) may present with recurrent, refractory vomiting ("cannabinoid hyperemesis syndrome").

3.4. Chemotherapy-Induced Peripheral Neuropathic Pain (CIPN): CBD and THC Prevent the Development of Allodynia in Animal Models; Effects Are Substance-Specific

Chemotherapy-induced peripheral neuropathic pain (CIPN) is one of the most common adverse effects of anticancer drugs. CIPN is of toxic nature; it is substance- and dose-dependent, and includes a wide range of different drugs. It is highest with platinum-based drugs (70–100%), especially cisplatin and oxaliplatin, but occurs also with taxanes, especially paclitaxel, vinca alkaloids, and bortezomib, aromatase inhibitors (letrozole, anastrozole, exemestane) and other agents with variable incidence.

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 acutely (paclitaxel, oxaliplatin) or emerge late and last for months or years, even

after the termination of antineoplastic drugs. As chemotherapeutic neuropathy responds poorly to conventional treatments, any benefit observed with cannabinoids would be particularly 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 [99,100] (Table 2).

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 C57Bl6 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, similar to individual CBD. 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) [101] (Table 2).

In contrast to the animal experiments described before that started cannabinoids prior chemotherapy, cannabinoids were administered in the following 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 tetrahydrocannabivarin (THCV) (15 mg i.p./kg) reduced thermal and mechanical hyperalgesia induced by paclitaxel to a similar extent, the combination being even more effective [102] (Table 2). THC seems to be effective as well as has been shown in a rat model (male Sprague Dawley rats). Inhalation of THC-dominant cannabis (10.3% THC, 0.05% CBD or vehicle, four 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 [103] (Table 2).

In contrast, the number of relevant studies in man is very limited. A small, randomized, placebo-controlled crossover pilot study in 16 patients with established chemotherapy-induced neuropathic pain who received nabiximols found only a 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 [104] (Table 2).

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 CINP was more pronounced when patients received cannabis prior to treatment with oxaliplatin (75% versus 46.2%) [105] (Table 2). CBD, THC and morphine were also effective in a mouse model where neuropathic pain was induced by sciatic nerve injury [136].

A small randomised placebo-controlled study that included 29 patients investigated the effect of a topical CBD formulation on pain of various origins 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-week 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] (Table 2).

Another small 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 and 600 mg CBD per unit, tube or jar, of CBD and between 6 and 600 mg THC per unit) suggests that topical cannabinoids may be helpful, despite the fact that 4 of 26 patients did not respond, and neuropathy symptoms returned after several hours in those responding confirming a previous crossover study [107] (Table 2); some of these patients had tried other agents/acupuncture before with little or no benefit. A further case series that included eight 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).

To date, no well-controlled, high-quality patient studies have been conducted to determine whether pure CBD or THC or a combination of both can reduce peripheral chemotherapy-induced neuropathic pain (CIPN). Five animal studies and a few human studies of limited quality demonstrate 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 appear to depend on the chemotherapeutic agent. Further research and especially systematic studies are needed.

Lower Urinary Tract Dysfunction—A Special Case of CIPN?

Lower urinary tract dysfunction (lower urinary tract symptoms, LUTS) is a common and often underestimated side effect of chemotherapy. While degradation products of antineoplastic drugs can be responsible for irritation of the urinary organs such as the kidney, ureter and bladder, neurotoxic reactions are primarily responsible for dysfunction of the lower urinary tract. They most often occur with vincristine or doxorubicin [137]. Vincristine can cause neuropathy or nerve damage, and doxorubicin can cause myopathy, or muscle damage. More than 70% of patients receiving neurotoxic antineoplastic medications have reported LUTS. It is therefore not surprising that a positive association was found between CIPN symptoms and LUTS [138].

Due to the neuroprotective properties of cannabinoids, CBD and THC would be expected to have a positive effect on neurogenic dysfunction of the lower urinary tract. While observations in cancer patients are completely lacking, data from other populations (patients with multiple sclerosis) suggest that cannabinoids (nabiximols) may be an effective and safe treatment option for neurogenic lower urinary tract dysfunction [139]. However, evidence is still poor and well-designed prospective clinical trials would be needed.

3.5. Pain: Studies Suggest a Reduction in 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 worsen as cancer progresses. In a strict sense, this is not the same as chemotherapy-induced pain which is mainly of a 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 [140]. 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 reducing pain is particularly important.

Whereas many patients turn to cannabis for alleviating their symptoms [6,141–143], the true role of individual cannabinoids for the 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 in cue-induced craving [109–113] (Table 2) in contrast to higher-quality randomised controlled clinical trials [114] (Table 2). Treatment with nabiximols (up to 16 sprays/day, equivalent to 43.2 mg THC + 40 mg CBD) reduced pain in two placebo-controlled studies, however at the expense of an increase in side effects [115,116] (Table 2). 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 [117–119] (Table 2). The large majority of human studies investigated the effect of cannabis on opioid consumption, less so on individual THC or fixed combinations such as nabiximols, and none investigated the effect of pure CBD as an adjuvant to opioids in cancer pain. Most epidemiologic surveys concluded that cannabis, including hemp extracts, reduces symptoms, curbs medication use and is relatively safe for cancer patients [144,145]. However, cannabis-based products consumed in these usually uncontrolled observational studies were ill-defined and contained in general an unknown mix of cannabinoids and 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 [146].

Taken together, the role of cannabis and cannabinoids in the treatment of cancer pain is still mixed. Cannabinoids seem to reduce chronic but not acute pain and improve the quality of sleep, but the effect sizes are small. There is some evidence in favour of medicinal cannabis, THC and THC/CBD combinations, with insufficient evidence for individual CBD. Higher doses (>15 mg THC/day, nabiximols up to 10 sprays/day) were correlated with increased pain relief but also with more side effects. Cannabis/cannabinoids may have a role as an adjunct or even potential replacement for opioids but evidence remains uncertain due to unknown compositions (cannabis) and inadequate design of most studies.

3.6. CBD May Protect Organs against Chemotherapy-Induced Toxicity (Only Animal Data Available)

3.6.1. CBD Demonstrated Cardioprotective Effects In Vivo

Overt cardiotoxicity of chemotherapeutic drugs is relatively rare; it may occur in >20% of patients treated with anthracyclines such as doxorubicin or daunorubicin but also with fluorouracil (5-FU) or cyclophosphamide [147]. 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 [120] (Table 2). This cardioprotective effect of CBD (10 mg i.p./kg/day, starting before doxorubicin) has been confirmed later in a mouse model [121] (Table 2).

It is currently unknown whether the above-mentioned cardioprotective effects of CBD in animals translate to patients receiving chemotherapy. However, it has been repeatedly reported that both CBD and THC showed cardioprotective effects in various animal models as well as during exhaustive exercise training [148–153]. Conversely, cannabis smoking has been added to the risk factors for myocardial infarction.

3.6.2. CBD Protected 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. Only two recently published

animal studies examined the possible protective effects of CBD against the side effects of methotrexate.

In a study on female Wistar rats, lesions induced by a single dose of 20 mg/kg methotrexate (lung hyperaemia, oedema, inflammatory cell infiltration and epithelial cell loss) could be reversed with CBD (5 mg i.p./kg CBD for 7 days) [122] (Table 2). Moreover, CBD (5 mg i.p./kg for 7 days) reversed histopathological and immunohistochemical changes induced by methotrexate in the brain, such as hyperaemia, microhaemorrhages, neuronal loss, decreased expressions of serotonin in the cortex, hippocampus, and cerebellum regions [123] (Table 2).

Observations in humans are completely missing.

3.6.3. CBD Reduces Renal Damage in Animal Models

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 [124] (Table 2).

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 [125] (Table 2).

The antibiotic gentamicin, although not an anti-neoplastic drug, 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 in BUN and creatinine as well as histological tubular damages (strongest with 10 mg CBD/kg/day, for 10 days, followed by 2.5 mg CBD/kg) [154].

Overall, these results in three different animal models suggest that CBD may protect organs from treatment-related toxicities, but observations in humans are still lacking.

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

The usual standard cytotoxic chemotherapy is not very selective and causes collateral damage to healthy tissue such as rapidly dividing epithelial or bone marrow cells. Mucositis occurs in approximately 20 to 40% of patients receiving chemotherapy for solid tumours and in varying degrees of severity, but typically within 5 to 14 days after 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 [155].

In a mouse model in which 5-FU-treated animals received different doses of synthetic CBD (3, 10, and 30 mg i.p./kg/day starting on day 4), CBD dose-dependently reduced the severity of oral lesions and weight loss compared to a positive control (5-FU + mechanical trauma + placebo) and negative control (mechanical trauma + placebo), at two experimental times (evaluation after 4 and 7 days) [126] (Table 2).

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, improved clinical scores and survival rate, and reduced ulcer sizes as well as weight loss [127] (Table 2). In addition, CBD is known for accelerating wound healing, as well as for its immunomodulatory effects, which play a role in controlling intestinal inflammation [156].

While these two independent animal studies show that CBD dose-dependently reduces mucosal lesions caused by chemotherapy as well as subsequent problems, respective data on cancer patients are lacking.

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, or 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 antineoplastic drugs 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. The 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%) [157].

The literature on the possible ototoxic effects of cannabis is controversial, and there is also a lack of systematic studies on the effects of pure cannabinoids on hearing loss. Cannabis, whether medical cannabis, CBD oils or marijuana, is, as already mentioned, not interchangeable with individual cannabinoids such as pure CBD or THC. Intriguingly, oral capsaicin, the active component of chilli peppers, prevented cisplatin-induced ototoxicity in a rat model through the activation of TRPV1 ion channels [158]. This experiment is of interest because CBD shares with capsaicin the activation of TRPV1 channels. 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 [159].

Since CBD modulates enzymes responsible for DNA methylation, it may interfere with this mechanism of ototoxicity [160,161]. In addition, cisplatin-induced ototoxicity has been linked to oxidative stress and cochlear inflammation which may be reduced by CBD [162]. Therefore, CBD would be expected to have oto-protective properties which would warrant further investigation.

4. Discussion and Conclusions

Cannabinoids are multi-target substances with a remarkably large spectrum of activities. A growing body of research indicates that cannabinoids, particularly CBD and THC as well as their combinations, represent an essential adjunct to cancer therapy, either as anticancer drugs per se or for the management of symptoms of cancer patients. Cannabinoids show relatively selective cytotoxic properties towards tumour cells, complementing or enhancing the effect of anti-neoplastic drugs.

Most of the data come from preclinical research. Apart from individual cases of cancer patients in which an antitumour effect has been reported with the use of cannabinoids and published in medical journals, some other data come from case series or small studies. There are promising preliminary results for the comedication of gemcitabine with CBD (pancreatic carcinoma) and of temozolomide with CBD and nabiximols (glioblastoma). Preclinical work also suggests benefits when combining CBD with platinum compounds (cisplatin, oxaliplatin), doxorubicin, immune checkpoint inhibitors, paclitaxel, docetaxel, tamoxifen and some aromatase inhibitors. It might be speculated that this translates eventually

to reduced dosages of anti-neoplastic drugs in patients, reducing overall costs and side effects but systematic studies are still missing. More so, preclinical results suggest that cannabinoids may 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, cannabinoids may have the potential to alleviate side effects related to the disease and cancer therapy, generally with fewer side effects than other drugs used for supportive care in cancer patients. The reduction in nausea/vomiting and the increase in appetite by THC have long been recognised; both are licensed indications for dronabinol (THC). Furthermore, studies suggest that cannabinoids have a beneficial influence on (neuropathic) pain, anxiety and oral mucositis, and potentially reduce the organ toxicity of chemotherapy (e.g., heart, kidney, lung, brain and ear) or reduce immune-related sequelae. Nonetheless, caution is advised as long as there are not more therapeutic experiences in man, notably results of well-designed controlled clinical trials.

When using cannabinoids at the same time as other active ingredients, possible interactions should not be ignored. Phase I metabolization 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 interaction, 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 antiepileptic drugs. When CBD or THC are used to relieve side effects of chemotherapy, cannabinoids are best administered before starting anti-tumour therapy, whereas one can speculate that the reverse order may have a better anti-tumour effect. CBD added to current treatment with clobazam increased the serum levels of the active metabolite for N-desmethylclobazam by a factor of three; conversely, if clobazam was added to current treatment with CBD, only a minimal increase in the active metabolites of CBD was observed [163]. This highlights the importance of drug sequence when using drugs with similar metabolization routes as adjuncts. Research on the possible benefits of concomitant treatment with cannabinoids during (radio-)chemotherapy is only beginning. Future studies should focus primarily on combinations of cannabinoids with chemotherapeutic drugs that are commonly used and have significant side effects to find out possible advantages and disadvantages of such combinations. These include, but are not limited to, platinum drugs, anthracyclines, taxanes and immune checkpoint inhibitors. With these substance classes, there is legitimate hope that cannabinoids could reduce common, including toxic side effects. However, this still needs to be proven.

The main questions are do cannabinoids improve anti-tumour therapy and, if so, what is the best dose for a dual benefit of improved effectiveness of chemotherapy and a reduction in its side effects? The next important and unresolved question is which cannabinoid(s) should be administered, when and for how long—only as an adjunct to chemotherapy or (given the side effects of chemotherapy) also for much longer?

In summary, there is increasing evidence that cannabinoids such as CBD, THC and others may be useful tools in cancer therapy. However, there is still a long way to go until the benefits of improved anti-tumour effects and fewer side effects of accompanying therapy with cannabinoids are scientifically proven and optimized.

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