Exploration of Medicine

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Treatment of malignant diseases with phytocannabinoids: promising observations in animal models and patients

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Academic Editor: Paul Zarogoulidis, "General Clinic Euromedica" Private Hospital, Greece
Received: July 10, 2023 **Accepted:** August 3, 2023 **Published:** December 6, 2023

Cite this article: Nahler G. Treatment of malignant diseases with phytocannabinoids: promising observations in animal models and patients. Explor Med. 2023;4:847–77. https://doi.org/10.37349/emed.2023.00182

Abstract

Amazingly, almost 50 years after the first demonstration of anticancer effects of cannabinoids *in vitro* and *in vivo*, well-designed clinical trials that definitively prove tumour-inhibiting effects in man are still missing. Whereas a large number of preclinical studies exist that describe tumour-inhibiting effects of cannabinoids, alone or in combination, but also in the form of medical cannabis or natural extracts *in vitro*, the number of *in vivo* studies is still limited. Even more limited are well-documented experiences in man. Most animal studies and experience with cannabinoids in man concern brain tumours. This review summarises the effects of phytocannabinoids in brain, breast, colorectal, head and neck, haematological, liver, lung, pancreatic, ovarian, prostate, and skin cancers in animal models and, if available, in patients. The large majority of animal studies demonstrate tumour-inhibiting effects of cannabinoids, thus confirming *in vitro* data. Experiences in cancer patients are almost exclusively limited to individual case reports and case series without a control group. Many questions are currently unanswered such as the role of pure cannabinoids compared to combinations, cannabinoids as the eventual sole cancer therapy, optimal dosages, or duration of treatment. Pure cannabidiol (CBD) seems to be superior to pure delta-9-tetrahydrocannabinol (THC) in experimental settings. The role of medical cannabis or extracts is less clear as they vary in their phytochemical composition. In conclusion, cannabis/cannabinoids may slow the progression of tumours. However, the hope that cannabinoids could eventually cure cancer as often spread in social media, is, at present, wishful thinking. Above all, well-designed clinical trials paired with long-term follow-up of cancer patients are needed.

Keywords

Cannabis, cannabinoids, cannabidiol, delta-9-tetrahydrocannabinol, cancer, case series

Introduction

Cannabis (cannabinoids) have potential pharmacotherapeutic effects in a number of tumour entities. The interest in the therapeutic use of cannabis and cannabinoids is booming for many years. According to the

National Organization for the Reform of Marijuana Laws (NORML), more than 4,300 scientific papers on cannabis or cannabinoids respectively have been published just in 2022, whereby it is often neglected that the plant, *Cannabis sativa*, has not a uniform phytochemical composition. More than 1,000 varieties (chemotypes) are known that differ in their qualitative, quantitative, and pharmacologic profile of substances which can be broadly categorised into about 140 cannabinoids, a similar number of terpenes, about two dozen flavonoids, and spirans, many of which are known to have cytotoxic effects on cancer cells [1–4]. A common and shared characteristic is that phytocannabinoids are significantly more cytotoxic against cancer cell lines than normal cells.

Cannabis and cannabis extracts are ill-defined and complex mixtures of phytosubstances

The complexity of phytocomponents of cannabis and chemical diversity respectively is further increased by external factors, notably growth conditions, parts of the plant used, harvest, time of harvesting, the extraction process (notably the solvent used, temperature, and pressure), and other procedures during preparation and manufacturing. The extraction process enriches cannabinoids and other components whereby the original qualitative and quantitative composition in the plant is changed. As an example, volatile terpenes are lost, and cannabinoid acids are decarboxylated by heating; extraction with hexane results in about two times higher amounts of terpenes than ethanolic extraction; cannabidiol (CBD) is enriched almost five-fold whereas the concentration of delta-9-tetrahydrocannabinol (THC) or cannabigerolic acid (CBGA) increases only by a factor of three with ethyl acetate as solvent, and so on [5]. As has been mentioned, cannabis, and even more extracts, are poorly defined cocktails of phytosubstances; they vary largely in their phytochemical and pharmacological profile, depending on the chemotype (variety) and extraction procedures [6]. Extracts ("cannabis oils", "CBD oils") differ therefore considerably among manufacturers. They are not produced with the same consistency and quality as pure phytocompounds; this limits generalisation of observations. In extracts of Bediol®, a commercialised cannabis variety, concentrations of CBD varied between 0.660 mg/mL and 8.297 mg/mL, and those of THC between 1.358 mg/mL and 6.596 mg/mL (54 samples tested) [7]. Consequently, effects observed with another variety, extraction process, or even with a different batch of the same variety and origin may not be identical, and even worse, may have opposite effects as different compounds activate different pathways [8–10]. Objectively, "whole plant" or "full spectrum" composition is, a misleading term, and not necessarily an advantage; extracts or flowers do not necessarily provide better treatment results compared to results with isolated cannabinoids in each case. On the contrary, opposing effects and interactions between phytosubstances can antagonise otherwise beneficial effects; e.g., CBD is an antagonist on G-protein coupled receptor 55 (GPR55) whereas THC is an agonist; the anti-nausea, anti-emetic effects of CBD are reversed by pretreatment with cannabigerol (CBG) [11, 12]. Extracts with an almost identical content of THC can vary in their cytotoxic effects by a factor of 10 [13]. Moreover, many terpenes can potentially synergise with THC [14]. This clearly demonstrates that focussing on only one or two primary cannabinoids is insufficient for predicting the properties of a cannabis chemotype or extract. Collectively, a standardised composition and quality are crucial for any medication, whereas there are many "caveats" for the therapeutic use of raw cannabis or extracts.

Cytotoxic effects of cannabinoids are well documented and are known for a long time

Cytotoxic effects of cannabinoids have been known since the very first series of *in vitro* and animal experiments by Munson et al. [15] in 1975, almost 50 years ago, performed at the request of the National Institute on Drug Abuse (US). Since then, an overwhelming number of preclinical experiments have demonstrated the potential benefit of cannabinoids for treating malignant diseases. In addition, collections of patient experiences such as that of Kander [16], originally published already 10 years ago, and reported on social media made cannabinoids/cannabis very popular also among patients affected by cancer. More than 20% up to almost 50% of patients suffering from cancer use cannabis for their symptoms and/or to

combat their disease [17–21]. A large collection of 119 cases of various cancers treated with CBD has demonstrated tumour response in a high percentage of subjects [22]. Articles like that suggest that cannabinoids may have potential for the treatment of cancer, including the symptoms and signs associated with it, namely cancer-associated pain, anxiety and depression, sleep problems, nausea and vomiting, and oral mucositis. Past research has concentrated on CBD and THC whereas studies with other cannabinoids such as cannabinol (CBN), cannabidivarin (CBDV), cannabichromene (CBC), or CBG are still at the beginning. Studies that compared cannabinoids head-to-head suggest however that in general, CBD has a higher cytotoxic activity against cancer cell lines than THC, their acid forms, or other cannabinoids, although notable exceptions may exist [3, 23–26]. Cytotoxic effects generally increase with increasing concentrations (*in vitro*) or increasing doses (*in vivo*) with very few exceptions reported so far [15, 27]. This includes also extracts rich in CBD or CBG [13].

In short, based on current overall experiences, CBD seems to be the most effective single cannabinoid for use against cancer. Moreover, combinations with other cannabinoids, chemotherapeutic agents, and radiation therapy may increase the therapeutic effect further. Surprisingly, most experience still comes from individual case reports, case series, and animal models, whereas well-designed clinical studies are almost nonexistent.

The aim of this narrative review is to summarise studies on animal tumour models and experiences in men with phytocannabinoids in order to encourage more research and targeted therapy. The focus is on products that are readily available for physicians and patients, on results with pure phytocannabinoids or defined extracts in animal models, and on cases published in peer-reviewed medical journals. Cannabinoids other than phytosubstances such as nabilone are excluded.

For the literature search, the following keywords and their combinations were used: “cancer”, “cannabis”, “cannabinoids”, “CBD”, “cannabidiol”, “THC”, “tetrahydrocannabinol”, “cannabis extract”, and similar terms (“botanical drug substance”, “cannabis drug preparation”, “CBD oil”). To maximise the search for articles, “citation chasing” was performed to identify *in viv*o studies, clinical trials, and case reports that evaluated CBD or THC and that have been included in the reference list of relevant publications. In order to identify eventual cases in “grey literature” such as presentations at national medical conferences, there were no language restrictions. For relevant studies, databases searched were PubMed, Google Scholar, ResearchGate, and medRxiv databases from 1975 through April 2023.

The role of the endocannabinoid system in cancer

Each cell suffers tens of thousands of molecular lesions per day, resulting in DNA damage that threatens genome integrity. Some mutations affect cell proliferation due to defects of certain genes, e.g., oncogenes, tumour suppressor genes, genes that control repair mechanisms, or the cell cycle. Eventually, this may lead to abnormal cell proliferation and cancer when DNA damage exceeds the repair capacity of the cell. Basically, the role of the endocannabinoid system (ECS) is to maintain tissue homeostasis. Many observations point to a dysregulation of the ECS in cancer; this can include variation in the signalling pathway, expression of receptors, enzymes, and/or concentration of endocannabinoids. Most studied are the cannabinoid receptors 1 and 2 (CB1, CB2) and their natural ligands, the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Despite that our knowledge has considerably increased, the role of the ECS in cancer as well as the anticancer activities of cannabinoids, are far from being completely understood. In a number of tumour entities, canonical receptors such as the above mentioned CB1, CB2, and particularly GPR55 were found to be upregulated, although with sometimes conflicting results. Other receptors that have been reported to be expressed differently in cancer cells compared to normal cells are e.g., transient receptor potential cation channel subfamily members, melastatin type (TRPM8), vanilloid type (TRPV1, TRPV2), or ankrin type (TRPA1). Loss/reduced expression or increased expression of CB1 and possibly CB2 may accelerate tumour growth whereas increased levels of endocannabinoids AEA and/or 2-AG may increase apoptosis as they can activate not only CB1 and CB2 but many other receptors. Conversely, enzymes such as the fatty acid amid hydrolase (FAAH) or monoacylglycerol lipase (MAGL)

decrease endocannabinoid levels and potentially promote cancers such as melanoma. Consequently, such imbalances compared to normal tissues may have prognostic value.

The role of cannabinoids in cancer

A large range of effects of cannabinoids on the tumour and tumour microenvironment respectively have been described in the past, notably inhibition of angiogenesis, metastasis, tumour proliferation, and tumour cell apoptosis. Although the exact mechanism of anticancer activities of cannabinoids is still a matter of intensive research, it is believed that substances such as CBD and THC modulate the ECS and oxidative stress conditions within cells. This seems to be a major mechanism as it induces instability of cell membranes, autophagy, mitochondrial fragmentation, and ultimately apoptosis of cancer cells. Cannabinoids and endocannabinoids target selectively and differently a wide range of receptors such as CB1, CB2, GPR55, TRPV1, TRPV2, TRPA1, TRPM8 known to play a role in cancer, and which are also differentially expressed amongst specific cancer cell lines. Effects are further modified, as cannabinoids modulate *in vivo* the level of endocannabinoids that have *per se* also anticancer properties [28, 29]. CBD as an example, increases levels of AEA by interfering with FAAH. As targets including FAAH are differently expressed in tumours, the effects of cannabinoids vary and may be cancer cell-specific. This explains why cannabinoids, but also extracts differing in their composition of cannabinoids, vary in their effects on cancer cell lines.

Moreover, cannabinoids (among other substances) affect tumour growth also by epigenetic modulation. Hypomethylation, as an example, is often found in tumours [30]. Hypo- and hypermethylation are complex mechanisms and can occur in parallel. On one hand, DNA methylation activates the formation of repair enzymes, but on the other, aberrant methylation can activate proto-oncogenes and inactivate tumour suppressor genes. As epigenetic changes are potentially reversible there is much hope that drugs ("epigenetic drugs") can restore a normal epigenetic pattern and, perhaps, reduce the malignancy and/or growth of tumour cells. Noteworthy, CBD reduces the expression of inhibitor of DNA-binding-1 (ID-1), a transcriptional regulatory protein and key regulator of tumour cell invasiveness that is epigenetically activated in many tumours such as breast cancer and glioma [26].

In the native plant, cannabinoids are almost exclusively found in their acid forms such as CBD acid (CBDA) or THC acid (THCA); the respective decarboxylated, "neutral" cannabinoids such as CBD, THC, or CBN are, in fact, artifacts formed naturally by aging or artificially by heating. Overall, it seems that most cannabinoids have cytotoxic properties although they vary to a high degree. In head-to-head tests, CBD was generally the most effective phytocannabinoid, acid forms the least [25, 31, 32]. An *in vitro* study that assessed 12 different extracts on 12 cancer cell lines demonstrated that cytotoxicity differs considerably, whereby extracts with a high percentage of decarboxylated (neutral) cannabinoids (≥ 50% weight/weight) were generally more cytotoxic [13]. Pure THC, however, was less effective than the extracts. Only the LNCaP prostate carcinoma cell line was exceptionally sensitive to extracts containing natural phytocannabinoids in their "native", acid form (e.g., THCA, CBDA, and others). As mentioned before, phytocannabinoids work through different pathways and receptors, the expression of which varies among cancer cell populations.

Overall, there is abundant literature demonstrating *in vitro* anticancer activities of cannabinoids and cannabis extracts. As such results have lower therapeutic evidence than animal models and observations in patients, these articles are excluded from the present overview. Moreover, effects *in vitro* do not always match results observed *in vivo* [24]. In the following, articles describing the effects of cannabinoids in animal models and/or patients with the brain, breast, colorectal, head and neck, haematological, hepatocellular, lung, pancreatic, ovarian, prostate, and skin cancers are summarised.

Antitumour effect of cannabinoids in selected cancers

Brain tumours, glioma, and glioblastoma

There are over 150 different types of brain tumours. The most malignant (and most common in adults) is glioblastoma multiforme (also called glioblastoma or grade IV astrocytoma). Its incidence is around 2 to 4

per 100,000 and accounts for roughly 50% of the primary brain tumours. Within the various types of gliomata, glioblastoma ranks among the deadliest cancers with a mean overall survival of around 15 months; this is one of the shortest among cancers. Glioblastoma has a high degree of genetic heterogeneity which influences also prognosis. As an example, glioblastoma with an (epigenetic) O^6-methylguanine-DNA methyltransferase (MGMT) promotor methylation does not produce the DNA-repair enzyme MGMT and shows a better response to standard chemotherapy with temozolomide (TMZ). The situation in glioblastoma is further complicated by the fact that molecular heterogeneity of cells seems to occur even within the same tumour. This contributes to tumour recurrence and treatment resistance [33].

There is a general consensus that high-grade glioma, including glioblastoma, express high levels of CB2 receptors whereby their expression positively correlates with tumour malignancy [34]. Levels of 2-AG can be elevated in surrounding tissues but the role of endocannabinoids is not entirely clear [35]. Patients with low MAGL expression (therefore higher 2-AG levels) had a slightly shorter overall survival than those with high MAGL expression [36].

A further receptor expressed in glioblastoma and also correlating with malignancy is GPR55. Conversely, levels of AEA seem to be decreased whereas CB1 and CB2 were elevated [35], or demonstrated no big differences between healthy and malignant cells, except isocitrate dehydrogenase (IDH)-wild type glioma compared to IDH-mutant. IDH-wild type glioma expressing CB1 may eventually better respond to agonists such as THC. TRPV1, another potential target of CBD, is under-expressed in glioma.

In contrast to many other substances including cannabinoid acids, decarboxylated cannabinoids penetrate the blood-brain barrier very easily [37]. Numerous publications described the effects of CBD and THC against glioma cells *in vitro*. Intriguingly, THC at submicromolar concentrations of 100 nmol/L increased the proliferation of glioblastoma U373-MG cells *in vitro* whereas much higher micromolar concentrations of 4 μmol/L or above induced apoptosis, indicating that the effect depends on concentration [38]. Similarly, increased viability of glioma stem cells occurred *in vitro* with moderate concentrations for CBD (below 10 μmol/L) and for CBG (below 5 μmol/L) but not with higher concentrations (10–15 μmol/L) [39]. The reason for this is not entirely clear but the lack of the influence of the natural antitumour immune system in such *in vitro* models may play a role. Studies in glioma cell lines have demonstrated that CBD triggered TRPV2-dependent Ca^{2+} influx, increasing the uptake of chemotherapeutic drugs such as TMZ, carmustine, and doxorubicin, and synergising with the drugs to induce apoptosis of glioma cells. The pro-apoptotic effect was greater than with the drugs alone, with no such effect in normal human astrocytes [40]. CBD most likely induces cell death (apoptosis) by upregulating reactive oxygen species (ROS), whereby apoptosis is dependent on the activation of TRPV2 [40].

The largest number of animal studies investigating cannabinoids in cancer has been on brain tumours. *In vivo*, locally delivered microparticles loaded with CBD (15 mg/kg) reduced the weight of U87MG cell-derived tumour xenografts in mice slightly more than THC (15 mg/kg) or their combination (7.5 mg/kg each) [41]. Other *in vivo* studies on brain tumour cell lines and cannabinoids are summarised below (Table 1).

In no other disease entity, so many animal experiments have been performed with cannabinoids as in brain tumours. Altogether, with the exception of only one study [42], results demonstrated a reduction of tumour growth in animals by cannabinoids administered mostly in the order of 15–25 mg/kg, more by CBD than THC. Combinations of CBD + THC or TMZ or triple combinations increased effects further. In one experiment complete eradication of tumour cells was observed in 1/5 animals after treatment with CBD (15 mg/kg i.p., 5 days per week for 28 days) [52]. Importantly, in another experiment that tested various combinations of CBD + THC in subcutaneous xenografts, no notable differences were observed in tumour growth inhibition with ratios of THC:CBD varying between 1:1 and 1:6 [47].

Although therapeutic experience with cannabinoids in patients with brain tumours is still very limited, all eight articles summarised below describe positive effects (Table 2).

Table 1. Brain tumours, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
2 human medulloblastoma (D283, D425), intracranial xenografts, mice	Synthetic CBD 50 mg/kg i.p. or p.o.; 5 times a week, over 5 weeks	D283: THC 15 mg/kg; Combination: 50 mg CBD + 15 mg THC; D425: CBD 22.5 mg/kg; THC 45 mg/kg, or CBD + THC = 22.5 mg/kg + 22.5 mg/kg	CBD ≈ THC ≈ vehicle; No signif. change in survival compared to vehicle was observed with CBD, THC or THC + CBD combination in both xenografts; (D283 xenograft: THC 23 days, CBD 25 days, combination 21 days, vehicle 30 days); D425: neither THC nor CBD + THC improved survival; results were similar for i.p. and p.o.	[42]
2 glioma (C6.9 or C6.4), s.c. xenografts; mouse, immuno-deficient	THC peri-tumoral, 0.5 mg/day for 8 days (~20 mg/kg)	Vehicle	THC decreases tumour volume and down-regulates MMP-2 expression of C6.9 by about 50% but not of C6.4 cells	[43]
Neuro-blastoma cells (SK-N-SH), s.c. xenograft; Nonobese diabetic immuno-deficient NOD/SCID mice	Synthetic CBD 20 mg/kg per day i.p. for 14 days	THC 20 mg/kg per day i.p., or ethanol vehicle or untreated	CBD > THC; Response to treatment was better in the group with CBD; median xenograft volume at the end of treatment was 2.31 cm^3 in the CBD-treated group compared with 3.46 cm^3, (THC), 4.28 cm^3 (untreated) and 4.31 cm^3 in the vehicle-treated group	[44]
Glioma model (C6 cells), intracerebral implanted; rats (250—300 g b.w.)	THC intra-tumoral, total dose 2.5 mg/rat over 7 days (~1.5–2 mg/kg THC per day)	WIN-55,212-2 0.25 mg/kg (synthetic cannabinoid similar to THC)	THC was ineffective in 3/15 rats, but tumour was completely eradicated in 3/15 rats, survival prolonged in 9 rats (up to 19–35 days *vs.* controls 12–18 days); WIN-55,212-2 was roughly similarly effective in the prolongation of survival (ineffective in 6, complete eradication of tumours in 5 rats)	[45]
Human glioblastoma (U87MG cells), orthotopic xenograft, nude mice	CBD 15 mg/kg i.p. per day for 21 days	TMZ 25 mg/kg per day; CBD + TMZ, for 21 days	50% survival: CBD + TMZ ~60 days, TMZ ~52 days, CBD ~50 days, *vs.* control ~42 days; 0% survival: CBD + TMZ 84 days, TMZ 60 days, CBD 55 days, *vs.* control 50 days	[46]
Human glioma (U87MG), heterotopic s.c. xenografts, nude mice	Synthetic CBD 15 mg/kg p.o. per day for 15 days	TMZ 5 mg/kg i.p. twice weekly; CBD + TMZ, or vehicle	Tumour volume TMZ < CBD + TMZ < CBD (~30% lower with CBD, ~70% lower with TMZ and ~50% lower with CBD + TMZ compared to controls); no enhancement of anticancer activity by combination CBD + TMZ	[47]
Glioma (U87MG), s.c. xenografts, nude mice	CBD, THC (extracts) p.o. daily for 15 days	Ratio THC:CBD = 1:1 or 1:4 (5 mg/kg p.o. each or THC 6.5 mg/kg + CBD 24.5 mg/kg, TMZ 5 mg/kg i.p.	THC + CBD at a 1:4 ratio resulted in a marginally lower tumour size than the 1:1 combination (but still higher than TMZ, as determined by MRI; combination with TMZ increased survival, a higher ratio of CBD had no effect	[47]
Glioma (U87MG), s.c. xenografts, nude mice	CBD, THC (extracts) p.o. daily for 15 days	CBD + THC + TMZ (ratio THC:CBD = 1:1, 1:4, 1:6); 3.5 mg/kg p.o. each or THC 4.5 mg/kg + CBD 16.5 mg/kg or THC 5.2 mg/kg + CBD 29.5 mg/kg); TMZ 5 mg/kg i.p.	All CBD + THC combinations inhibit tumour growth to a very similar extent but less than TMZ alone; effect was enhanced by the combination with TMZ with no relevant difference between 1:1, 1:4 and 1:6 ratio of THC:CBD	[47]
Orthotopic intracranial glioma xenografts U87MG, nude mice	CBD, THC (extracts) p.o. daily for 15 days	CBD + THC + TMZ; THC + CBD (1:4); THC 6.5 mg/kg + CBD 24.5 mg/kg; TMZ 5 mg/kg i.p.	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 significantly from ~30 (control) to > 50 days	[47]
Orthotopic intracranial xenografts, 12O12 GICs, nude mice	Synthetic CBD, synthetic THC p.o.	THC + CBD (1:1 or 1:5) 5 mg/kg each or THC 5 mg/kg p.o. + CBD 25 mg/kg daily for 14 days, then 3 times a week for further 2 weeks; TMZ (5 mg/kg i.p. twice a week); CBD + THC + TMZ	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; Pure single CBD or THC was not included	[47]

Table 1. Brain tumours, effect of cannabinoids in animal models (*continued*)

Disease model	Treatment	Comparator	Results	Ref.
Human glioblastoma (U87 cells), s.c. xenograft, athymic nude mice	CBD 0.5 mg/ mouse (i.e., ~25 mg/kg per day, 5 days/week, 23 days	(*vs.* control)	Tumours of animals treated with CBD were significantly smaller; day 18, 572 mm^3 (control 1,765 mm^3); day 23, 1,210 mm^3 (control 2,212 mm^3)	[48]
Patient-derived DIPGXIIIP cells orthotopically implanted into the brainstem of immunodeficient mice	CBD 15 mg/kg 5 days per week until morbidity of all control mice	Vehicle	Significantly longer survival with CBD 15 mg/kg (median 58 days *vs.* 49 days); CBD inhibited ID-1 expression	[49]
Mouse glioma (GL261 cells), orthotopically implanted, mice	CBD-E, THC-E	CBD-E + THC-E (each ~2 mg/kg on day 9, 13, and 16 after tumour implantation; followed by X-ray irradiation (4 Gy) on day 9	> 85% decrease of tumour volume and of vascularisation on day 21 (animals sacrificed); combination of CBD-E + THC-E reduced progression, further enhanced by irradiation 4 h after drug administration (stagnant tumour sizes throughout the experiment); X-rays alone had no dramatic effects; pure CBD or THC were not included	[50]
2 intracranial glioma stem cell xenografts (3832 and 387 GSC cell lines); female athymic nu/nu mice	CBD 15 mg/kg i.p., 5 times a week for ~25 days after tumour induction	(*vs.* control)	CBD inhibited tumour growth and improved significantly the survival of mice bearing intracranial glioma initially but tumour resistance was observed later on; median survival with CBD in 3832 was 33 days and in 387 GSC cell lines 26 days; compared to 27 and 21 resp. (controls)	[51]
Glioblastoma (U251 cells), orthotopic intracranial xenograft, mice	CBD 15 mg/kg i.p., 5 days per week for 28 days	(*vs.* control)	Signif. (~95%) decrease of tumour area; in 1/5 mice treated no tumour cells were observed in any of the brain regions analysed	[52]
Glioblastoma (U251 cells), s.c. xenograft, mice	CBD 20 mg/kg i.p., 5 days per week for 48 days	(*vs.* control)	A similar dose-dependent effect was observed in a s.c. model and with peritumoral injection of CBD; the tumour volume was ~30% lower with 15 mg/kg and ~50% lower with 20 mg/kg; CBD eradicated the tumour in 1 of 5 animals	[52]
2 human glioma cell lines (U87MG or T98G), s.c. xenograft, nude mice	CBD 7.5 mg/kg per day; Peri-tumoral injection, 14 days; (15 mg/kg not tested)	THC 7.5 mg/kg per day or THC 15 mg/kg or CBD + THC each 7.5 mg/kg per day or a nabiximols-like preparation (15 mg/kg per day)	CBD ≃ THC (7.5 mg/kg per day); Effect of a submaximal dose of 7.5 mg/kg THC increased when combined with CBD 7.5 mg/kg per day; THC + CBD (each 7.5 mg/kg) ≃ 15 mg/kg THC; a nabiximols-like combination of extracts reduced the growth of U87MG tumour xenografts to the same extent as an identical dose of pure THC	[53]

CBD-E: CBD-extract (synonym: CBD-BDS, CBD botanical drug substance); THC-E: THC-rich extract; GICs: glioma-initiating cells (supposed to be responsible for treatment relapse); i.p.: intraperitoneal injection; MRI: magnetic resonance imaging; signif.: significant; p.o.: per os; b.w.: body weight; resp.: respectively; s.c.: subcutaneous injection; ≃: almost equal; ~: about

As can be seen, treatments and patient population in these articles is extremely heterogenous. Cautiously, results suggest that cannabinoids, CBD, THC, and combinations including extracts achieved a treatment response in patients with brain tumours; in most cases, the concomitant chemotherapy was maintained. Three independent case series showed a benefit or an extension of overall survival with daily doses of CBD around 400 mg, and two with a THC:CBD combination. The publications on CBD include also observations with CBD of unknown purity in diffuse midline gliomas. Diffuse midline gliomas are aggressive paediatric brain tumours originating in the midline brain structures. Normally, they have a very short median survival of 10–11 months which seems, however, to double with concomitant CBD [49].

Pure THC has been used only once, as local administration in an experimental clinical trial in patients who were terminally ill; it was not aimed to study a therapeutic response. Other publications reported either results with cannabis of undefined composition or with a 1:1 combination of CBD with THC. Intriguingly, the study of Schloss et al. [58] favoured a 1:1 combination over an increased ratio of THC:CBD. To note, the experiments of Lopez-Valero et al. [47] favoured a higher ratio of CBD at the expense of THC.

Table 2. Brain tumours treated with cannabinoids

Disease	Treatment	Patient(s)	Results	Ref.
Case 1: glioblastoma grade IV; Case 2: oligodendroglioma WHO grade III	Pure CBD with < 0.3% THC, following resection and radio-chemotherapy; Case 1, 300–450 mg per day; Case 2, 100–200 mg per day	2 patients, 38 years old; both relapsing after TMZ	Treatment reduced oedema and inflammation and induced remission (MRI)	[54]
Pilocytic astrocytoma, WHO grade I	Consumption of inhaled cannabis of unknown composition, on average 3 times weekly during the last 3 years of follow-up	2 girls; case 1 aged 11, case 2, 13 years at diagnose	Tumour volume was 1.28 cm^3 at 9 months and 0.27 cm^3 at 6 years post-surgery in the first case, and 3.3 cm^3 at 18 months and 0.28 cm^3 at 6 years post-operatively in the second case; the regular use of cannabis coincided with the time course of radiological tumour regression	[55]
Glioblastoma WHO grade IV	THC (100 mg/mL in ethanol) in 30 mL of physiological saline supplemented with human serum albumin, infused into the resection cavity on days 3 to 6 after surgery; dose increased from 20 mg on day 1 up to 180 mg on day 5	9 patients progressive after standard radio-chemotherapy; (median duration of a THC-cycle was 10 days)	In 3 of 5 patients who received more than one THC-cycle, a temporary reduction of tumour proliferation was observed; median survival of the cohort from the beginning of THC administration was 24 weeks	[56]
Glioblastoma WHO grade IV	Concomitant treatment with pure CBD, 200–600 mg/day, mainly CBD 400 mg/day (add-on to standard radio-chemotherapy)	15 patients	CBD contributed to the long-term survival of glioblastoma patients (median 28 months, mean 30.9 months) effect depends on the dose	[57]
Diffuse midline gliomas	Average CBD dose ~5.4 mg/kg p.o. per day until patient passed away; CBD of unknown origin	14 patients (mean 9.79 years, range 4–16 years)	Longer overall survival with CBD (mean 22.7 months); CBD seems to suppress ID-1	[49]
High grade glioma	Cannabis extract with THC:CBD ratio of 1:1 or 4:1, single night daily dose over 12 weeks; 1:1 means THC 13.9 mg per day, CBD 9.8 mg per day; 4:1 means THC 22.2 mg per day, CBD 8.5 mg per day	61 patients	Results favoured the 1:1 ratio of THC:CBD over 4:1 with 72% of patients demonstrating a reduction of the tumour mass or stable disease compared to 53.6% after 12 weeks; participants who had a reduction in disease received the 1:1 ratio; pure THC or pure CBD was not included; sleep, functional wellbeing, and quality of life improved	[58]
Glioblastoma grade IV	Nabiximols (CBD:THC ≃ 1:1), max. 32.4 mg THC + 30.0 mg CBD following standard radio-chemotherapy with dose-intense TMZ (after Stupp protocol)	12 patients with nabiximols, 9 with placebo	Median survival was > 550 days with CBD:THC treatment (not signif.) and 369 days in the placebo group; 1 year survival was 83% and 44% in the CBD:THC and placebo groups, resp. (P = 0.042)	[59]
Anaplastic ependymoma WHO grade III, (diagnosed at the age of 1.5 years)	CBD 5 mg/day for 3 days on and then 3 days off in parallel with a ketogenic diet (start after two years of radio-chemotherapy and tumour recurrence); after relapse and further surgery/chemotherapy changed to daily dosing with a 5.6% CBD extract, 30 mg per day	5-year-old boy, (twice surgery, radio-chemotherapy)	Reduction of the tumour by ~60% with CBD; stable disease ~7 years after diagnosis (latest update January 2021)	[22]

MRI: magnetic resonance imaging; signif.: significant; p.o.: per os; resp.: respectively; ≃: almost equal; ~: about

Breast cancer

Breast cancer is the most common cancer in women (incidence 119 per 100,000), with varying molecular biologic characteristics. The most aggressive subtype, the so called triple-negative breast cancer (TNBC), is deficient in oestrogen receptor (ER), progesterone receptor (PR), and human growth factor receptor (HER2) expression. It accounts for 10–15% of breast cancers [60]. For this subtype chemotherapy and/or immunotherapy is in general the only therapeutic choice. Preclinical experiments suggest that cannabinoids, particularly CBD, may be effective against breast cancer. Repeatedly, a dose-dependent response to CBD has been reported on various breast cancer cell lines including TNBC cells. CBD is able to inhibit *ID-1* gene expression in aggressive breast cancer cells, leading to the attenuation of tumour aggressiveness [26]. ID-1 is a regulator of differentiation/DNA binding and regulator of metastasis. Other

effects of CBD include the inhibition of GPR55, known to be elevated in many malignant tumours including aggressive TNBC. Overexpression of GPR55 correlates generally with poor prognosis. In contrast, the role of the canonical receptors CB1 and CB2 is less clear. CB2 has been found to be overexpressed in HER2+ breast cancers as well as in gliomas and other cancer cell lines [61]. Opposite to previous reports, however, high expression seems to correlate with lower malignancy and better survival respectively [62]. CB2 is a receptor mainly found on immunocompetent cells such as leucocytes, monocytes, and macrophage-derived cells that are involved in tumour cell apoptosis [63].

Surprisingly, despite its medical importance and the number of encouraging *in vitro* experiments with various breast cancer cell lines demonstrating the cytotoxicity of cannabinoids, the number of animal experiments is rather limited, and studies in women are completely absent. The large majority of experiments have been done with triple-negative cancer cell lines, underlining the tumour-inhibiting effects of cannabinoids. It seems that effects increase with increasing doses. Animal studies are summarised in Table 3 below.

As can be seen, most of the 7 animal experiments were performed with CBD, with a remarkably wide range of dosages (1–10 mg/kg) administered daily or 2 to 3 times a week. Only two studies included THC whereby extracts were superior to pure THC [64]. CBD, administered before chemotherapy or in parallel, has been found to sensitize breast cancer and prostate cancer cells *in vitro* to cisplatin and paclitaxel and significantly increased chemotherapy-mediated apoptosis, suggesting a potential adjuvant role [70–72]. CBD administered before doxorubicin sensitized human triple-negative MDA-MB-231 cancer cells also *in vivo*.

Surprisingly and unexpectedly, one experiment demonstrated, in contrast to a similar, later experiment, a dose-dependent increase of the tumour mass (number and size of 4T1 tumour metastases in the lungs) after THC 25 mg/kg and even more so (almost twice as high) in BALB/c mice treated with THC 50 mg/kg (every other day for 18–21 days) [67]. BALB/c mice demonstrate Th2-biased immune responses and are relatively susceptible to infection and neoplastic diseases. With MCF-7 breast cancer cells, a widely used human breast cancer cell line positive for oestrogen, progesterone, and glucocorticoid receptors, it was demonstrated that THC-induced cancer cell growth most likely by interaction with cyclooxygenase-2 (COX-2), 17β oestradiol and aromatase [73]. No similar growth enhancing effect is known for CBD. Other factors that could favour tumour cell proliferation are hypoxic conditions [74]. Moreover, THC not only suppresses antitumour immunity, but animal models use genetically manipulated mice to induce breast cancers; this differs from the situation in humans.

In contrast to TNBC-cell lines, only few studies exist about the effects of cannabinoids on hormone receptor-positive (HR+) breast cancer cell lines as they are in general amenable to hormone therapy. Approximately 70% to 80% of breast cancers express ER and are therefore HR+. Furthermore, 65% of these cancers are also PR+.

In vivo, a combined treatment with tamoxifen (2.5 mg/kg) plus a cannabis drug preparation (extract, with 45 mg/kg THC) administered three times a week for 4 weeks, reduced the tumour volume (HR+ T47D cells) more effectively (to about 180 mm^3) compared to the cannabis drug preparation alone or tamoxifen alone (each about 250 mm^3) and 45 mg/kg THC (about 400 mm^3) *vs.* vehicle alone (about 500 mm^3) [64]. Pure THC was the least effective treatment.

Tamoxifen and several other selective ER modulators (SERM) can act as inverse agonists on CB1 and CB2. Interestingly, AEA, the level of which is increased by CBD, and which is an agonist of CB1 and CB2, can inhibit the proliferation of ER+ MCF-7 and T-47D breast cancer cell lines [75].

As mentioned before, there is actually no clinical evidence evaluating cannabinoids in breast cancer patients. Kenyon et al. [22] claimed that four cases of breast cancer have been successfully treated with low dose CBD. However, the limited amount of data given in the article does not allow a more detailed description and conclusions.

Table 3. Breast cancer, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
4 human breast adenocarcinoma cell lines (ER–: HCC1954; TNBC: MDA-MB-231; ER+/PR+ tumour: BT474 and T47D); s.c. xenografts, nude mice, immune-deficient	THC 45 mg/kg, p.o., 3 times a week, for 30 days; Supra-therapeutic doses	THC-E, adjusted to THC 45 mg/kg, p.o., 3 times a week, (extract with 55% THC, 0.3% THCA, 0.4% CBG, CBD (not done); Supra-therapeutic doses	THC < THC-E; In all 4 animal tests pure THC inhibited tumour growth less than THC-E; T47D, THC < THC-E; HCC1954, THC < THC-E; BT474, THC < THC-E; MDA-MB-231, THC < THC-E (triple-negative cancer)	[64]
2 TNBC (murine 4T1.2, and human MVT-1), ortho-topically injected, Balb/C and FVB mice	CBD 10 mg/kg peri-tumoral injection on alternate days for 3 weeks	(*vs.* control)	CBD slowed down the growth of highly aggressive, TNBC cells (4T1.2) by approximately 25% to 30% (tumour volume and weight). A similar dose-dependent inhibition of cancer growth was also seen after injection of TNBC cells (MVT-1)	[65]
Murine TNBC breast cancer 4T1; Female BALB/c mice	Lioposomes loaded with CBD (5, 15, or 45 mg/kg) and 15 mg/kg PPD, every 2nd day for 14 days	20(S)-PPD-liposomes (15 mg/kg of PPD) or CBD-PPD co-loaded liposomes (CP)-liposomes or paclitaxel injection (8 mg/kg), i.v.	Tumour growth inhibition was 46.8% with 15 mg /kg liposomal CBD alone, 50.8% with liposomal PPD alone, 67.4% with CBD-PPD co-loaded liposome (each component 15 mg/kg), 64.4% with paclitaxel (8 mg/kg i.v.); an increase of the CBD component to 45 mg/kg (co-loaded with 15 mg PPD) achieved the highest inhibition (82.2%), a reduction to CBD 5 mg/kg with 15 mg PPD the lowest (46.0%)	[66]
Human breast cancer TNBC (MBA-MD-231), s.c. xenografts, athymic mice	CBD 5 mg/kg, twice per week, intra-tumoral injection, 16 days	CBD-rich extract 6.5 mg/kg twice per week, intra-tumoral injection	CBD ≃ CBD-E; Extracts were injected in the tumour in the inoculation region; signif. reduction of the tumour volume after both treatments, with no difference between CBD and CBD-E (~40% lower tumour volume)	[25]
Murine TNBC (4T1 cells), s.c. xenograft; BALB/c mice	THC 12.5, 25, or 50 mg/kg, i.p., every other day for 18–21 days	(*vs.* control)	25 mg/kg and 50 mg/kg THC led to a signif., dose-dependent increase in tumour mass and metastases, even more pronounced with 50 mg/kg	[67]
Two TNBC models: 1st, i.v. model: mouse breast cancer (4T1) or human breast cancer cells (MDA-MB231) injected i.v., mouse	CBD 1 mg/kg i.p. daily for approximately 1 month	(*vs.* control)	CBD increased significantly survival and reduced metastasis up to 75% (EC50: 0.3 mg/kg). Effects on metastasis were dose-dependent (CBD 0.5, 1, or 10 mg/kg i.p, daily	[68]
2nd, orthotopic model: mouse breast cancer cells (4T1) were injected into mammary glands	CBD 1 mg/kg i.p. per day, for approximately 1 month	(*vs.* control)	CBD reduced metastasis even when administered only three times per week. CBD did, however, not inhibit primary tumour growth	[68]
Xeno-transplanted TNBC (MDA-MB-231 cells s.c.), female nude mice	CBD 10 mg/kg, i.p., twice weekly, for 2 weeks	*vs.* control; *vs.* CBD-EV (EV loaded with CBD 5 mg/kg) *vs.* DOX 2 mg/kg, *vs.* CBD 5 mg/kg one day before DOX, *vs.* CBD-EV 5 mg/kg one day before DOX	After 2 weeks the tumour volumes were (estimated): Control 8,200 mm^3; EVs 7,500 mm^3; CBD 10 mg/kg 6,800 mm^3; CBD-EV 5 mg/kg 7,000 mm^3; DOX 2 mg/kg 4,200 mm^3; CBD 5 mg/kg with DOX 1 day later 4,000 mm^3; CBD-EV with DOX 1 day later 3,500 mm^3; CBD before doxorubicin sensitized tumour cells	[69]

CBD-E: CBD-extract (synonym: CBD-BDS, CBD botanical drug substance); PPD: protopanaxadiol; DOX: doxorubicin; EVs: extracellular vesicles; p.o.: per os; i.v.: intravenous injection; signif.: significant; ≃: almost equal; ~: about

Colorectal cancer

Colorectal cancer (CRC) ranks among the most common cancers. About 4 in 100 subjects will be diagnosed with CRC in their lifetime. CRC varies in its molecular, biological, and clinical features, and in its association with risk factors such as age and physical inactivity. Usually, cancer begins as a polyp, which is a non-

cancerous growth that develops in the mucosal layer (inner lining) of the colon or rectum; polyps are common. Despite this high incidence, and numerous *in vitro* studies, the number of animal studies is still limited. No peer-reviewed publication on the use of cannabinoids in patients with CRC could be found.

CBD, but also CBG, THC, and CBDV exert cytotoxic effects on CRC cells, mostly by apoptosis, reducing the viability of colon cancer cells [3, 76, 77]. CBD induced the inhibition of DNA synthesis and apoptosis of human CRC cells by increasing the expression of B-cell lymphoma 2 (Bcl-2) homology 3 domain-only protein (Noxa) [77].

As in many other cancer cell lines and tissues, AEA as well as the expression of CB1 was found elevated in CRC [78]. AEA demonstrates an apoptosis-promoting effect *per se*; this may be interpreted as a self-defense mechanism. Promotor hypomethylation of the CB1 receptor gene (*CNR1*, inhibition of DNA methyltransferase) elevates transcription of the *CNR1* gene and expression of CB1. Overexpression of GPR55 and also both CB1 and CB2 was correlated with poor prognosis in stage IV colorectal carcinoma whereby activation of CB2 has been reported to induce cancer cell proliferation [79–81]. As CBD and CBG are TRPM8 antagonists, their inhibiting effect in animal models sheds some additional light on other possible targets in CRCs [31].

The few animal studies with cannabinoids are summarised below (Table 4).

Table 4. CRC, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
Colon cancer induced by AOM in ICR mice	CBD 1 mg/kg or 5 mg/kg, i.p., 3 times per week, over 4 weeks	*vs.* control	CBD, starting 1 week before the first administration of AOM, reduced significantly ACF, polyps and tumour formation (40% of mice with tumours after 1 mg/kg compared to 70% after 5 mg/kg)	[82]
Colon cancer induced by AOM in mice	CBG 1 or 5 mg/kg i.p. 3 times per week, 4 weeks	AOM only (10 mg/kg i.p.) once weekly	CBG (1 mg/kg) treatment reduced the number of ACF; at the 5 mg/kg dose, CBG completely suppressed the formation of ACF, and reduced by one half the number of tumours	[31]
Colorectal carcinoma HCT 116 cells, xenograft, nude mice	CBG 1, 3, or 10 mg/kg i.p. every day for 5 days	Vehicle without CBG	After 5 days, the average tumour volume in the control group was 2,500 mm^3, in the CBG 3 mg/kg group 1,367 mm^3 (45.3% inhibition of tumour growth); CBG 10 mg/kg did not increase the effect; dose dependency: 1 < 3 ~10 mg/kg per day	[31]
Colon cancer induced by AOM in mice	CBD-E 5 mg/kg, i.p., 3 times per week up to 3 months after 1st injection of AOM	*vs.* controls	CBD-E reduced AOM-induced pre-neoplastic lesions and polyps (inhibition AOM-induced ACF by 86%, polyps by 79%) and tumour growth (by 40%)	[83]
Human epithelial colon adenocarcinoma cells (HCT 116), s.c. xenograft, ICR mice	CBD-E 5 mg/kg per day, i.p., for 7 days	*vs.* control	CBD-E ≈ control; Tumour growth between control and CBD-E was signif. different on day 4, but no difference on day 7	[83]

AOM: azoxymethane; ACF: aberrant crypt foci; signif.: significant; CBD-E: CBD-extract (synonym: CBD-BDS, CBD botanical drug substance); ≈: almost equal; ~: about

CBD and CBG are so far the only pure cannabinoids investigated in animal models, either to inhibit the formation of ACF, polyps, or tumours, or to inhibit the tumour growth of xenografts. With CBD (1 mg/kg or 5 mg/kg i.p., 3 times per week, over 4 weeks) an inverse dose-effect relationship was observed concerning the prevention of colon ACF by AOM [82], in contrast to a similar experiment using CBG (1 mg/kg or 5 mg/kg i.p., 3 times per week over 4 weeks) [31].

In the xenograft model, CBG inhibited tumour growth dose dependently with 1 mg/kg and 3 mg/kg daily, but an increase to 10 mg/kg did not increase the effect further [31]. In the second xenograft model, a CBD-rich extract (5 mg/kg i.p. per day, 65.9% CBD, 2.4% THC, CBG 1.0%, CBDV 0.9%, 0.3% CBDA) reduced tumour growth significantly on day 4 but no longer on day 7 [83].

Taken together, the evidence for a tumour reducing effect of cannabinoids in CRC is still very limited; experiences in men are completely missing.

Haematological cancers

Haematological cancers are a very heterogenous group of malignancies that begin in cells of the immune system or in blood-forming tissues such as the bone marrow. Among these cancers, diffuse large B-cell lymphoma is the most common haematological malignancy with an annual incidence of 7.9 per 100,000; chronic lymphocytic leukaemia (CLL), which like diffuse large B-cell lymphoma, is also a mature B-cell neoplasm, is next most common [84]. Leukaemia is a cancer of the blood cells and bone marrow, whereas lymphoma starts in the lymph system. Their incidences generally increase with age.

Human leukocytes such as neutrophils, monocytes, and T lymphocytes express CB1 and CB2 receptors; CB2 receptors are most abundant in eosinophils and B-lymphocytes, and unsurprisingly, also in lymphoma and leukaemia cells [85, 86]. They increase inflammation and can be targeted by cannabinoids. Agonists to CB1 and CB2 demonstrate antiproliferative as well as proapoptotic effects inducing cell death of CB1 or CB2 expressing leukaemia cells [87, 88].

Up to now, preclinical research has focussed mainly on solid neoplasms. Animal studies in mice that received murine EL-4 lymphoma cells are summarised below (Table 5).

Table 5. Haematological cancer, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
C57BL/6 mice, i.p. injection of EL-4 cells, a murine lymphoma cell line	CBD (0, 12.5, or 25 mg/kg i.p.) single dose	Phosphate-buffered saline	Maximal apoptosis after 25 mg/kg; 12.5 mg/kg increased apoptosis but did not reach level of significance. CBD-induced apoptosis was mediated through CB2	[89]
C57BL/6 mice, i.p. injection of EL-4 cells, a murine lymphoma cell line	THC (0, 1, 3, or 5 mg/kg i.p.) single dose	Phosphate-buffered saline	THC caused a dose-dependent decrease in the viable tumour-cell number in the peritoneal cavity. With 5 mg/kg, a signif. proportion (77.3%) of the tumor cells showed apoptosis	[90]

signif.: significant

Experiences in man are anecdotal only. They are summarised below (Table 6).

Table 6. Haematological cancer treatment with cannabinoids

Disease	Treatment	Patient	Results	Ref.
Hodgkin lymphoma, stage IIB, with incomplete remission after radio-chemotherapy	At 26 weeks of pregnancy, the patient began on her own a treatment with “cannabis oil”, supposed to be THC-predominant (1 mL to 5 mL, 3 times per day, concomitant to opioids)	5 years after the first intervention, the patient became pregnant at the age of 21 years	Before starting with cannabis, an MRI scan revealed the progression of the disease; with cannabis, pain, and general status improved, tumour tissue decreased. The patient delivered a boy by C-section at week 34 who presented in the first 24 h postpartum with withdrawal syndrome and intestinal invagination, requiring care in neonatal intensive care unit (NICU) and surgery with bowel resection	[91]
Native leukaemia blasts (acute undifferentiated leukaemia) cultured *ex vivo*	THC 2.5 % oily solution, (2 times ~1.6 mg per day increased to 6 drops (twice ~5 mg daily); not aimed as antitumour therapy	Elderly patient, palliative supportive care for tumour cachexia	THC showed a considerable plasma inhibitory/pro-apoptotic effect in an apoptosis assay *ex vivo*; expression of the cannabinoid receptors is a prerequisite to achieve a pro-apoptotic effect in native leukaemia blasts	[87]
CLL	Nabiximols single dose, stepwise increased from one actuation (2.7 mg THC + 2.5 mg CBD) to a maximum of 7 actuations (18.9 mg THC + 17.5 mg CBD), 15 patients received the maximal dose	23 patients (18–80 years) with leukemic indolent B-cell lymphoma, without treatment indication	On the treatment day, there was a signif. decrease in lymphocyte counts; however, cell proliferation and apoptosis did not change; CBD + THC had no effect on the natural course of the disease (median follow-up was 2.8 years, range: 1.4–4.2 years)	[88]
Acute lymphoblastic leukaemia, positive for Philadelphia chromosome mutation	Five different THC-Es (“Rick Simpson oil”) over a period of 78 days, after unsuccessful bone marrow transplantation and chemotherapy	14-year-old girl	Extracts reduced blast cells but varied in their effects and side effects; with each new extract, the dose had to be adjusted again, starting with a lower dose; in parallel blast cells increased. The appropriate dose was identified by observation of side effects (euphoria, panic, appetite, nausea, fatigue) as guidance; the patient passed away due to a bowel perforation as a late effect of chemotherapy	[10]

MRI: magnetic resonance imaging; signif.: significant; ~: about

Neither pure CBD nor pure THC has been studied for treating patients with haematological cancers. Benefits have been reported in only two patients who used THC-Es. The other two articles reporting the use of THC or a combination with CBD had an experimental character. Data are inconclusive at present.

Head and neck squamous cell cancer

In Europe, the incidence of head and neck cancer (HNC), including lip/oral cavity, oesophagus, larynx, oropharynx, hypopharynx, salivary glands, and nasopharynx, is approximately 21.8 per 100,000; prevalence is higher in men. Quite half of the newly diagnosed patients are older than 65 years of age. About 90% of all HNCs are squamous cell carcinoma. Whenever possible, resection and treatment with cytotoxic drugs and radiotherapy is the strategy of choice. Recurrence is however common.

AEA effectively inhibited the proliferation of head and neck squamous cell cancer (HNSCC) cells, most likely via the production of receptor-independent ROS, whereas 2-AG did not [92]. Moreover, it was found that the genes *CNR1* and *CNR2* are upregulated in HPV+ HNSCC cancers compared with HPV– cancers. High expression of CB2 was significantly associated with reduced disease-specific survival [93]. Activation, (by agonists of CB1 and CB2), promotes *in vitro* the proliferation of HPV+ HNSCC cells whereas antagonists (e.g., rimonabant) inhibit proliferation [94]. As extracts or cannabis chemotypes differ in their composition, there are likely influences on responses; this may explain conflicting observations about cancers in cannabis users [95–97]. Results in animal models are summarised below (Table 7).

Table 7. HNC, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
Human head and neck squamous cell (FaDu), two tumour models; (1) subcutaneous xenograft; (2) tongue xenograft; BALB/c nude mice	CBD 5 mg/kg p.o., 4 times per week, 4 weeks (s.c. xenograft) or CBD 5 mg/kg i.p., 3 times per week, for 4 weeks (tongue xenograft)	(1) Cisplatin 2.5 mg/kg i.p. once a week; (2) CBD + cisplatin, (*vs.* control)	CBD slowed down the tumour increase of tongue xenografts; tumour volume after 3 weeks treatment with CBD was about 65% lower than of the controls, (cisplatin ~50%); the combination with cisplatin (5 mg CBD p.o. + 2.5 mg/kg cisplatin i.p.) decreased the tumour volume further (tumour volume ~15% of controls); tumour size was measured after three weeks	[98]
UD-SCC-2 cells (HPV+), subcutaneous xenograft; nude mice	THC 3 mg/kg i.p., daily, 2 weeks	Control: rimonabant (1 mg/kg) every other day	THC 3 mg/kg per day, i.p., enhanced tumour growth by a factor of about 2, whereas cannabinoid receptor blockade (rimonabant) inhibits tumour growth	[94]

p.o.: per os; ~: about

CBD has demonstrated time (48–72 h) and dose (0–15 µmol/L) dependent cytotoxicity against head and neck squamous cancer cells, and reduced significantly tumour volume in two xenograft models. Importantly, the combination treatment of cisplatin with CBD demonstrated a significant synergism [98]. This observation contrasts with THC in a study on HPV+ human head and neck squamous cell carcinoma UD-SCC-2, UPCI:SCC090, and UM-SCC-47 cells where very low concentrations of THC (1 nmol/L to 1 µmol/L) enhanced *in vitro* the proliferation, with the exception of 93VU147T cells (also HPV+) where 1 µmol/L THC suppressed tumour growth [94]. Enhancement of tumour growth was also seen *in vivo* in a xenograft model with UD-SCC-2 cells where nude mice received THC (3 mg/kg i.p., daily for 2 weeks). No similar effects are known for CBD.

Treatment experiences in man suffering from HNC are very limited (Table 8).

Kenyon et al. [22] described a further case of oropharyngeal cancer that has been successfully treated with low dose CBD. However, the limited amount of data given in the article does not allow a more detailed description and conclusions.

A recent study investigated the potential relationship between marijuana use and survival outcomes of HPV-related patients with proven p16-positive oropharynx squamous cell carcinoma [96]. Marijuana users were identified from a prospectively collected database of HNC patients. They were then case-matched on a 1-to-1 basis to patients who were non-marijuana users based on age, gender, and cTNM staging. No statistically significant difference between marijuana and non-marijuana users was found in terms of

Table 8. HNC treatment with cannabinoids

Disease	Treatment	Patient(s)	Results	Ref.
Squamous cell cancer of the right buccal cavity; resection and radio-chemotherapy in the years before	0.5–1.0 g dried cannabis per day (8.21% CBD, 7.25% THC), vaporised every 2 to 4 h and 15 min before his daily wound dressing change; when trismus and oral cutaneous fistula developed, the use of vaporized cannabis became technically difficult and was replaced by topical treatment (8.02% CBD, 5.24% THC)	44-year-old man	The size of his malignant wound decreased by about 5% over the first four-week interval; pain relief was so signif. that the patient was able to discontinue pregabalin and dexamethasone while reducing hydro-morphone to approximately 25% of his pre-medical cannabis dosage	[99]

signif.: significant

overall survival, disease-specific, disease-free, and metastasis-free survival after five years in contrast to much earlier reports [96, 100].

From that, it may be supposed that HNC differ in their molecular properties, and respond therefore differently to specific cannabinoids. As extracts or cannabis chemotypes vary considerably in their composition it is likely that this influences also responses.

Hepatocellular carcinoma

The incidence of hepatocellular carcinoma (HCC) varies widely between about 18 and 94 per 100,000, depending on risk factors [99]. After glioblastoma and pancreatic cancer, liver cancer is the most lethal tumour with an estimated 5-year survival of only 18% [101, 102].

As with other cancers, the ECS is disturbed also in HCC; levels of AEA are reduced [103]. A higher expression of CB1 and CB2 correlated with improved prognosis [104].

Animal models of HCC demonstrate that cannabinoids effectively reduce tumour growth (Table 9).

Table 9. HCC, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
Female athymic nude mice; HepG2 cells s.c. xenograft	CBD suspension (40 mg/kg per day p.o.), for two weeks	Controls: castor oil	Tumour volume in controls was ~1,100 mm^3, in mice treated with CBD ~600 mm^3; CBD effectively suppresses HCC cell growth *in vivo* and *in vitro*	[105]
Male athymic nude mice; HepG2 or HuH-7 cells s.c. xenograft	THC (15 mg/kg per day s.c.), for two weeks	Controls: JWH-015 (1.5 mg/kg per day) or vehicle (saline)	Tumour volume in controls was 2 to 3 times higher than in mice treated with THC or JWH-015; THC effectively suppresses HCC cell growth	[106]
Male athymic nude mice, orthotopic HCC model. HepG2 cells inoculated in the liver	THC (15 mg/kg per day s.c.), for 10 days	Controls: JWH-015 (1.5 mg/kg per day) or vehicle (saline)	THC and JWH-015 reduced ascites and alpha-fetoprotein expression, parallel to mTORC1 inhibition, AMPK activation and autophagy stimulation	[106]

mTORC1: mechanistic (mammalian) target of rapamycin complex 1; AMPK: adenosine monophosphate-activated kinase; p.o.: per os; ~: about

Until now, no report on patients with HCC treated with cannabinoids has been found. However, the University Medical Centre Groningen (UMCG), Netherlands, is to study the effect of cannabis oil on liver cancer patients based on two separate reports that patients with advanced liver cancer had seen their tumours shrink after using cannabis oil. Now, two and five years after their diagnoses, the tumours have completely disappeared and the patients are considered cured (https://bedrocan.com/umcg-studies-cannabis-oil-for-liver-cancer-patients-with-no-further-treatment-options/).

Lung

Lung cancer is the 2nd most common cancer worldwide (after breast cancer), the most common in men, and the 2nd most common in women with an age-standardized incidence rate (ASIR) of 22.4 per 100,000 (male: 31.5; female: 14.6). Lung cancers are classified as small cell lung cancer (SCLC, 13%) and non-SCLC (NSCLC, 84%). A major problem with lung cancers is that they are usually diagnosed in advanced stages when they have already spread to other organs; moreover, cancer cells easily develop resistance to common antitumour agents.

A number of *in vitro* studies with lung cancer cell lines have demonstrated that cannabinoids inhibit cell viability, inducing apoptosis, whereby the activation of CB1, CB2, and TRPV1 receptors plays a role. Mice lacking the CB2 receptor (CB2-knockout, $CB2^{-/-}$ mice) or receiving a CB2 antagonist demonstrated a lower tumour burden than wild-type mice [107, 108]. It seems that CB2 plays a pro-oncogenic role in NSCLC; it is up-regulated in NSCLC tissues and up-regulation correlates with tumour size and pathological grading [109]. In contrast, high expression of the *CB2* receptor gene was found to correlate with improved survival in lung cancer patients [110].

CBD has been shown to decrease dose-dependently the viability of various lung cancer cells, NSCLC cell lines (A549 and H1299) as well as SCLC cells (H69) [111]. CBD is also able to potentiate the effect of THC *in vitro* [112].

In animal models using nude mice, CBD (5 mg/kg i.p.) significantly reduced tumour size and lung metastatic nodules (from an average of 6 nodules to only 1 nodule) in an A549 xenograft tumour model [113, 114]. In another experiment with A549 xenografts in nude mice, either 15 mg/kg THC s.c., or 20 mg/kg CBN, or 40 mg/kg CBN per day was administered for 20 days. Tumour volume changes were significantly lower with THC (251%) or 40 mg/kg CBN (266%) than those of control mice (716%), but not significant with 20 mg/kg CBN (345%). The effect of CBN was thus dose-dependent [115]. Intriguingly, THC (5 mg/kg four times per week) increased considerably the volume of two different tumour xenografts in two weakly immunogenic murine lung cancer models [108]. Effects of cannabinoids seem to depend on the immune status. Animal lung cancer studies are summarised below (Table 10).

Taken together, animal models demonstrate that CBD (5 mg/kg) reduces lung cancer growth (NSCLC) in mice; THC and CBN are also effective.

At present, treatment in men is limited to a few case reports summarised below (Table 11).

An 81-year-old man with biopsy-confirmed adenocarcinoma of the lung was put on a regimen with 2% "CBD oil" (extract with a dose of 1.32 mg CBD twice daily) 11 months after diagnosis. The tumour was progressive at that time. CBD oil, which was the sole therapy, was increased to twice 6 mg per day after one week. CT-imaging four months later revealed near total resolution of the left lower lobe mass and a significant reduction in size and number of mediastinal lymph nodes (stable according to a CT control two months later) [119].

Another article [120] reports the case of a subject with terminal, also biopsy-confirmed lung cancer. The patient, a 53-year-old man, had a history of intense alcohol and drug abuse and repeated injuries to his spine after multiple car accidents. He suffered from very severe pain, insomnia, post-traumatic stress disorder (PTSD), anxiety, and depression, with a loss of bladder control in parallel. In a last attempt to improve his life, the patient joined Alcoholics Anonymous where one of his fellow members advised him to inhale vaporized cannabis oil. To his surprise, he was not only able to stop substance abuse but also his lung cancer disappeared within about three months of inhaling vaporized cannabis oils (composition unknown) on a daily basis. He died from cardiac failure about a year later [120].

A third article [121] describes the case of a woman in her 80s who was diagnosed with NSCLC. At diagnosis, her tumour was 41 mm in size, with no evidence of local or further spread, so was suitable for conventional treatment of surgery, chemotherapy, and radiotherapy. As the patient refused standard cancer treatment, she was placed under "watch and wait" monitoring, which included regular CT scans every 3–6 months. She was a smoker, getting through around a pack plus of cigarettes every week (68 packs/year). She also had mild chronic obstructive pulmonary disease (COPD), osteoarthritis, and high blood pressure, for which she was taking various drugs. Surprisingly, scans showed that the tumour was progressively shrinking, reducing in size from 41 mm to 10 mm 32 months later, equal to an overall 76% reduction in maximum diameter, averaging 2.4% a month. Discussions with the physicians revealed that the patient had taken 0.5 mL of "cannabis oil" two to three times daily since her diagnosis (20% CBD, 19.5% THC, 24% THCA, according to the supplier), i.e., approximately 200–300 mg of CBD and THC per day. The woman said she had reduced appetite since taking the oil but had no other obvious "side effects". There

Table 10. Lung cancer, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
Lung cancer, human NSCLC cell line A549 s.c. xenograft, female athymic nude mice (BALB/cAJcl-nu/nu, lacking T-cell function)	THC 15 mg/kg per day, s.c., for 20 days	CBN 20 mg/kg per day or 40 mg/kg per day, s.c., for 20 days	THC was more effective than CBN; tumour volume increase was significantly lower with THC (251%) or 40 mg/kg CBN (266%) than those of the control mice (716%); not signif. with 20 mg/kg CBN (345%); effect of CBN was dose-dependent	[115]
Lewis lung adenocarcinoma, s.c. xenografts, mice	CBD 25 mg/kg or 200 mg/kg per day until death	THC (25, 50 or 100 mg/kg per day for 10 days; D8-THC (50, 100, 200, or 400 mg/kg per day until death); CBN (25, 50, or 100 mg/kg per day until death)	CBD had no effect on tumour size or survival time. However, the tumour growth rate of controls in this experiment was much lower than in previous studies. THC decreased tumour weight after 12 days, but differences approached control values after 3 weeks. Life span was increased non-linearly by 17.4, 6.2, and 36% with doses of 25, 50, and 100 mg/kg resp.; D8-THC showed maximal effects after 100 and 200 mg/kg; effects of CBN increased with the dose	[15]
Athymic mice given injections of A549 lung cancer cells	CBD 5 mg/kg i.p. every 72 h, 28 days	Vehicle	After 28 days the number of nodules in CBD-treated mice was signif. lower (84% inhibition of metastasis); CBD also downregulated PAI-1 protein	[116]
A549 xenografts in athymic nude mice	CBD 5 mg/kg every 72 h, i.p., 28 days	Vehicle	In CBD-treated animals, the tumour size was about 70% lower than in control animals (416 mm^3 ± 125 mm^3 compared to 1,405 mm^3 ± 273 mm^3 in vehicle-treated mice); CBD inhibits lung cancer cell invasion and metastasis via ICAM-1	[114]
A549 xenografts in athymic nude mice	CBD 5 mg/kg every 72 h, i.p.	Vehicle	CBD reduced the tumour volume from about 1,900 mm^3 (controls) to 750 mm^3 with CBD; apoptotic cell death by CBD was suppressed by NS-398 (COX-2 inhibitor) and GW9662 (PPAR-γ antagonist)	[117]
NCI H1437 human lung cancer xenografts in nude mice	Non-invasive inhalant CBD	Placebo	CBD significantly decreased tumour growth rate, suppressed expression of CD44, of pro-angiogenic factors VEGF and P-selectin, compromising tumour angiogenesis	[118]
Murine Lewis lung cancer (3LL) and line 1 alveolar carcinoma (L1C2) xenografts in C57BL/6 and BALB/c immunocompetent mice, resp.	THC (5 mg/kg, four times a week i.p. for 4 weeks)	Diluent (0.2% ETOH in saline)	Accelerated growth of tumour implants compared with control treatment suggesting an immunosuppressive effect of low dose THC; tumour volume was more than twice as high (3LL cell line, C57BL/6 mice), and more than four times as high (L1C2 cell line, BALB/c mice) as in the control group	[108]

PAI-1: plasminogen activator inhibitor-1; ICAM-1: intercellular adhesion molecule-1; PPAR-γ: peroxisome proliferator-activated receptor gamma; VEGF: vascular endothelial growth factor; signif.: significant; resp.: respectively

Table 11. Lung cancer treatment with cannabinoids

Disease	Treatment	Patient(s)	Results	Ref.
Lung adenocarcinoma (T1c N3 M0, biopsy-confirmed)	CBD twice 1.32 mg per day (2% CBD-oil) as the sole therapy, increased to twice 6 mg per day after 1 week	81-year-old man	11 months after diagnose, the patient started CBD; the tumour was progressive at that time. The CT 4 months later revealed near total resolution of the left lower lobe mass and a signif. reduction in size and number of mediastinal lymph nodes (stable according to a CT control 2 months later)	[119]
Lung cancer, ("aggressive", biopsy-confirmed) terminal phase	Cannabis oil of unknown composition, daily inhalation with a vaporizer	53-year-old man	After inhaling vaporized cannabis oil, his cancer disappeared within about 3 months; other symptoms improved as well; he died from a cardiac failure about a year after the diagnostic interview	[120]
Lung cancer, non-metastatic	0.5 mL cannabis oil (20% CBD, 19.5% THC, 24% THCA) p.o. 2 to 3 times daily	Woman in her 80s	Progressive shrinking of the tumour from 41 mm at diagnosis to 10 mm 32 months later; no chemotherapy or radiation, no surgical intervention	[121]

CT: computed tomography; signif.: significant; p.o.: per os

were no other changes to her prescribed medications, diet, or lifestyle, and she continued to smoke throughout [121].

Taken together, these case reports suggest tumour-reducing effects of cannabis extracts in lung cancer patients, although neither the exact composition of extracts nor the exact daily dose is entirely clear.

Ovarian cancer

Data on ovarian cancer and cannabinoids is very limited; CB1 was overexpressed and correlated with disease severity in epithelial ovarian carcinoma [122]. CBD inhibited endometrial (ECC1) and epithelial ovarian cancer (Kuramochi) cell lines, with an inhibitory concentration (IC_{50}) between 2.5 and 20 nmol/L [123].

Only one article has been found, concerning the treatment of ovarian cancer with cannabinoids in an 81-year-old woman with metastatic, low grade, ovarian carcinoma, accidentally diagnosed during surgery (Ca-125 value 77 U/mL, resected tissue oestrogen and PR+) [124]. A CT scan of the chest, abdomen, and pelvis demonstrated multiple mesenteric soft tissue masses ranging from 7 mm to 7 cm and omental carcinomatosis. A 5.8 cm solid right adnexal mass and 3.3 cm solid left adnexal mass were also identified together with lymphadenopathy along the left common iliac vessels and the left pelvic sidewall. Chemotherapy was proposed but declined. At this time, two months after surgery, the Ca-125 value had dropped to borderline 46 U/mL. Laetrile tablets (500 mg orally four times per day) and CBD oil (1 drop sublingually each evening) were started. Assuming a volume of at least 35 µL per drop and a concentration of at least 10% CBD, 1 drop contained at least 3.15 mg CBD. One month later, the Ca-125 value had dropped to 22 U/mL. This treatment was maintained. Repeated CT imaging in the following months showed a dramatic reduction in her disease burden, with near-complete resolution of all previously identified lesions seven months after surgery. Ca-125 values remained low around 12 U/mL. The authors related the dramatic decrease to the intake of CBD [124]. However, it should be noted that the Ca-125 value had already dropped from 77 at the time of the surgical intervention to 46 two months later when CBD was started; the resolution of lesions may not be due entirely to CBD.

Pancreatic cancer and pancreatic ductal adenocarcinoma

Pancreatic cancer is, like glioblastoma, an orphan disease with an incidence of around 4 to 13 per 100,000 (National Cancer Institute, US); it ranks among the most malignant forms of cancer. Unfortunately, in most cases, the cancer is diagnosed late, usually when it has already spread. Its incidence varies considerably and may be underestimated as it increases with age [125, 126]. Survival time is rather short with a mean of around 4 to 9 months after diagnosis, and correlates negatively with age [127, 128]. Younger age at diagnosis and a resectable tumour has a better prognosis. The 5-year survival rate is about 5 to 12%. Pancreatic cancer is commonly resistant to most of the available chemotherapeutic drugs.

As with other cancers, the ECS participates in the defense against cancer growth. It has been observed that 2-AG suppresses pancreatic cancer cell proliferation and tumour growth *in vitro* and *in vivo* [129]; this 2-AG-induced antiproliferative effect is CB1-receptor dependent. Another receptor that obviously plays a role is GPR55 which is increased in human pancreatic ductal adenocarcinoma (PDAC) specimens [130].

Only few animal experiments with natural cannabinoids have been published. They are summarised below (Table 12 below).

In a mouse model of PDAC pharmacological blockade of GPR55 with CBD, GEM (a standard treatment), and CBD plus GEM increased the rodent lifespan compared to vehicle (mean survival 25.4 days, 27.8 days, 52.7 days, and 18.6 days respectively), with many of the signalling pathways involved in reducing PDAC cell cycle progression and cell growth identified [130]. Most interestingly, whereas pure THC, pure CBD, and pure GEM have demonstrated a benefit in terms of reduced tumour growth or longer survival, a study using an extract containing both cannabinoids, THC and CBD in a ratio of 1:6 did not demonstrate a significant impact on the tumour volume; even worth, the highest dose of 10 mg/kg extract showed a more pronounced tumour growth than that of the negative control [27] Overall, the best effect was achieved with a combination of high CBD and GEM.

Experiences in humans with phytocannabinoids are rare. Only one small case series was found that included a total of nine consecutive patients with pancreatic cancer who received CBD, most of them as comedication to standard chemotherapy; two patients have been treated only with CBD [132]. CBD was usually administered in an oral daily dose of 400 mg. Five patients received also low dose THC for

Table 12. Pancreatic cancer, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
Pancreatic tumour cells (MiaPaCa2), s.c. xenograft; Immunodeficient nude mice	THC peri-tumoral, 15 mg/kg per day for 14 days	Vehicle or JWH (1.5 mg/kg per day, CB2-selective agonist), or vehicle	THC reduced tumour growth by ~50%, increased apoptosis	[131]
PDAC; KPC mice	CBD 100 mg/kg i.p. per day until death	GEM 100 mg/kg per day i.p.; every 3 days, or a combination of CBD + GEM	Mice receiving CBD + GEM survived 2.8 times longer than mice not given any treatment (1.3 times longer with CBD and 1.4 times longer with GEM alone); mean survival: no treatment 18.6, CBD 25.4 (+ 37%), GEM 27.8 (+ 49%), CBD + GEM 52.7 days (+ 183%)	[130]
Human PDAC cell line (Capan-2)-derived xenograft mouse model	Extract (CBD:THC = 6:1) 1 mg/kg, 5 mg/kg, or extract 10 mg/kg p.o. per day	5-FU, 5 mg/kg i.p., three times a week, compared to a negative control group (sesame oil)	Tumour volumes were marginally but not significantly lower than after 5-FU in the 1 mg and 5 mg/kg extract group, whereas the volume of the 10 mg/kg group was higher than that of the negative control (not signif.)	[27]

GEM: gemcitabine; 5-FU: 5-fluorouracil; signif.: significant; p.o.: per os; ~: about

improving appetite. The mean overall survival of these nine patients was 11.5 months (median 11 months), thus about twice as long as expected from historic data (Table 13).

Table 13. Pancreatic cancer treatment with cannabinoids

Disease	Treatment	Patient(s)	Results	Ref.
Pancreatic cancer (advanced, metastatic disease)	pure CBD, 400 mg per day, concomitant to standard chemotherapy (2 patients with CBD as the only treatment)	9 patients; mean age at diagnose 49.7 years (range 45–70 years); 5 women, 4 men	The mean overall survival was 11.5 months (median 11 months) and seems to be longer than the overall survival reported in the literature for metastatic disease (5.9 months)	[132]

Prostate cancer

Prostate cancer is the second most frequent carcinoma in males after lung cancer. The incidence increases dramatically with age and is 1% to 2% after the age of 75 years [133]. Prostate cancer presents as two subtypes, androgen-sensitive (androgen-dependent) and androgen-independent prostate cancer. Androgen deprivation therapy (ADT) is the treatment of choice for the palliation of men with androgen-sensitive disease. Androgen-independent prostate cancer is observed when cancer advances despite primary hormone therapy. Most of the patients initially responding to ADT will eventually develop castrate resistance. It seems that a protein called TRAF4 is responsible for this conversion of androgen-sensitive prostate cancer cells into castration-resistant cells; TRAF4 is frequently overexpressed in advanced prostate cancers [134]. Most intriguingly, a very recent study demonstrated *in silico* that theoretically CBD, its acid CBDA, and THC could act as androgen receptor (AR) inhibitors whereas CBDV and cannabinodiol (a natural derivative of CBN produced by photochemical conversion) could act as 5α-reductase inhibitors among other minor phytocannabinoids [135]. 5α-reductase inhibitors such as finasteride have been known for a long to reduce serum prostate-specific antigen (PSA) levels. Therefore, the observation that marijuana use was inversely associated with PSA levels deserves further investigation [136].

A study showed higher expression of CB1 receptors in androgen-sensitive as well as androgen-independent prostate cancer cell lines compared to normal prostate epithelial cells; the over-expression of CB1 and TRPV1 correlates with increased grades of prostate tumours [137]. Basically, prostate cancer cell lines used in preclinical studies can be divided into AR+ (LNCaP and 22RV1) and AR– (DU-145 and PC-3). Intriguingly, receptors are expressed differently in specific cancer cell lines: 22RV1 which is AR+, only expresses CB1 while DU-145 (AR–) only expresses CB2. Though CB1 and CB2 can be found in both LNCaP and PC-3, their levels are much more prominent in PC-3. TRPV1 is expressed in all four prostate cancer cell lines, with the highest expression found in DU-145 cells, whereas TRPM8 receptor has been found in LNCaP cells [137, 138]. *In vitro*, CBD can inhibit the expression of the AR in AR+ cell lines [139]; CBD is also a

TRPM8 antagonist. *In vivo*, results are actually restricted to only two studies that are summarised below (Table 14).

Table 14. Prostate cancer, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
2 prostate cancer cell lines (LNCaP, DU-145), s.c. xenografts, athymic nude mice; 6 groups for each cell line	CBD-E (~65% CBD) 1 or 10 or 100 mg/kg i.p. daily; Initiated D15, terminated D38	Docetaxel 5 mg/kg, i.v. once weekly; Bicalutamide 25–50 mg/kg p.o. 3 times per week; CBD-E 100 mg/kg per day i.p. plus either docetaxel 5 mg/kg i.v. once weekly, or bicalutamide 25–50 mg/kg p.o. 3 times per week	CBD-E (extract) dose-dependently inhibited the growth of xenografts from LNCaP (AR+), but not from DU-145 (AR–) cells; CBD-E potentiated docetaxel/taxotere effects in DU-145, less so in LNCaP xenografts; CBD-E enhanced efficacy of bicalutamide on LNCaP only at the highest concentration tested (100 mg/kg i.p.); A group receiving pure CBD was not included	[139]
Prostate cancer, BALB/c nude mice, s.c. PC3-xenograft (AR–)	CBD (150 mg/kg per day), injected peri-tumoral for 10 days combined with siRBBp6 gene therapy (RBBp6 antibodies)	Cisplatin (50 mg/kg per day), *Cannabis sativa* extract (200 mg/kg per day) or vehicle	Tumour sizes were reduced with CBD and cisplatin by approximately 90% and significantly more than by the cannabis extract	[140]

CBD-E: CBD-extract (synonym: CBD-BDS, CBD botanical drug substance); p.o.: per os; i.v.: intravenous injection

The effect of CBD (150 mg/kg per day), cisplatin (50 mg/kg per day), *Cannabis sativa* extract (200 mg/kg per day, "complete cannabis extract", composition unknown) or vehicle, injected peritoumorally for 10 days in combination with siRBBp6 gene therapy (RBBp6 antibodies), was studied in mice (BALB/c nude mice, s.c. PC3-xenograft). The protein RBBp6 is implicated in cell cycle regulation and is supposed to promote tumour genesis. Tumour sizes were reduced with both, CBD and cisplatin, by approximately 90% and significantly more than by the cannabis extract [140].

CBD potentially downregulates the expression of PSA, VEGF, and pro-inflammatory cytokines [138]. In the only study that analysed the effects of CBD on PSA in 18 patients with biopsy-proven adenocarcinoma of the prostate after localized therapy, who received up to 800 mg CBD once daily for 90 days, the large majority (88%) had the stable biochemical disease, i.e., an increase in baseline PSA of < 25% [141].

Kenyon et al. [22] described very briefly one case of prostate cancer that has been successfully treated with low dose CBD. However, the limited amount of data given in the article does not allow a more detailed description and conclusions.

The effect of cannabis/cannabinoids on other urogenital cancers is still a matter of debate. A recent study found that previous use of cannabis was a significant protective factor in women against renal cell carcinoma and bladder cancer. In men with a history of tobacco smoking, previous cannabis use was a significant protective factor for prostate cancer. A history of cannabis use had a null effect on rates of testicular cancer [142].

To sum it up, cannabinoids possibly have effects on prostate cancer, or may even reduce it, however, the amount of data is at present insufficient for any conclusions.

Skin cancer and melanoma

Skin cancer is a common disorder. In addition to melanoma, there are two other major types of skin cancer, basal cell carcinoma and squamous cell carcinoma; relatively rare types are Kaposi sarcoma or cutaneous T-cell lymphoma.

Melanoma is a highly heterogenous and frequent type of tumour. The incidence varies widely between about 100 per 100,000 (coloured people) and 600 per 100,000 (Caucasians). Melanoma ranks among the cancers with the highest mutational burden that implicates also a high probability of primary resistance to

any pharmacological therapy. Mutations are favoured due to exposure to mutagenic ultraviolet radiation (UV).

In vitro studies on various melanoma cell lines suggest that cannabinoids target CB1, TRPV1, and PPAR-α receptors, and induce apoptosis in a dose-dependent way. CBD and the combination of CBD + THC can reduce cell viability in different melanoma cell lines *in vitro*. The inhibitory effect of CBD plus THC was stronger than that of either drug alone [143, 144]. The reduction of the viability of melanoma cell lines seems to be mediated mainly by CB1, TRPV1, and PPAR-α receptors. Some melanoma cell lines such as A375 melanoma cells express high levels of *FAAH*, *COX-2*, *CB1*, *TRPV1*, and *GPR55* genes [145]. Unsurprisingly, AEA cytotoxicity was potentiated by FAAH inhibition.

The few animal studies that exist are summarised below (Table 15).

Table 15. Skin cancer, effect of cannabinoids in animal models

Disease model	Treatment	Comparator	Results	Ref.
Athymic nude mice, BRAF wild-type melanoma xenografts	THC (15 mg/kg per day p.o. for 20 days	Vehicle; THC-CBD (extract, ~7.5 + 7.5 mg/kg per day, p.o.); TMZ 5 mg/kg p.o. per day, 20 days	THC and CBD + THC (extract) signif. inhibited xenograft growth and were more effective than TMZ (order: CBD + THC > THC > TMZ > vehicle)	[143]
B16 melanoma; C57BL/6 wild-type mice and CB1/CB2 deficient mice	THC 5 mg /kg per day s.c., 25 days	Vehicle	THC inhibits HCmel12 melanoma growth but does not affect B16 and CB1/CB2 deficient Hcmel12	[146]
A2058 s.c. xenograft, male NOD scid gamma (NSG) mice	CBD 10 mg/kg + THC 10 mg/kg s.c. per day b.w. for 21 days	Vehicle only, MEKi (0.75 mg/kg per day) CBD + THC + MEKi	All three treatments showed a signif. reduction in tumour volume and in tumour area as compared to vehicle, without a statistically signif. difference between groups (CBD + THC *vs.* MEKi, MEKi *vs.* CBD + THC + MEKi, CBD + THC *vs.* CBD + THC + MEKi); MEKi alone reduced tumour mass more efficiently than CBD + THC	[144]
Murine B16F10 melanoma tumours, C57BL/6 mice	CBD (5 mg/kg i.p., twice weekly)	Control; cisplatin (i.p), 5 mg/kg once weekly	Increased the survival and reduced tumour size as compared to controls, although less than cisplatin; quality of life and movement of CBD-treated mice were better than with cisplatin	[147]

MEKi: mitogen-activated protein kinase inhibitor trametinib; signif.: significant; p.o.: per os; ~: about

Although the number of experiments is very limited, *in vivo* models demonstrate that pure, single cannabinoids, CBD as well as THC in a dosage between 5 mg/kg and 15 mg/kg b.w. have a strong antitumour effect that can be increased by combinations. The MEKi showed the strongest growth inhibition [144].

No publication on the treatment of melanoma in men has been found so far.

Basal cell carcinoma is the most common skin cancer in the world but has a very low mortality rate. For that, it is often not included in cancer statistics. Similar to squamous cell carcinomas, it is a descent from epidermal keratinocytes. Only two case reports have been found; they are summarised below (Table 16).

Table 16. Skin cancer treatment with cannabinoids

Disease	Treatment	Patient(s)	Results	Ref.
Basal cell carcinoma, recurrent (nose)	THC-E (exact composition unknown), topical application four times daily for two weeks	74-year-old man	After repeated surgical interventions, skin grafts and radiotherapy over the last 13 years the malignant lesion completely disappeared within two weeks of daily treatment	[148]
Squamous cell carcinoma, hand, biopsy confirmed	20% CBD-oil (exact composition unknown), topical application twice daily for 4 weeks	64-year-old woman with a history of multiple squamous cell carcinomas	The patient presented with multiple skin lesions on her hands, lichen simplex chronicus on her left and squamous cell carcinoma on her right hand; lesions disappeared within four weeks	[149]

Conclusions

Despite an uncountable number of *in vitro* experiments that clearly demonstrated the cytotoxic effects of cannabinoids on cancer cells, there is little progress in research in man. Almost 50 years after the first evidence of cancer-inhibiting effects of phytocannabinoids *in vitro* and *in vivo*, therapeutic experience in humans is still limited to a relatively small number of publications. In the overwhelming majority, they describe individual cases treated with cannabis products, often poorly defined. In a few other cases or case series respectively, pure CBD has been used. Only one phase I controlled clinical trial has been found that included glioblastoma patients treated with a THC:CBD combination (nabiximols) or placebo additional to TMZ [59].

Much more articles describe the effects of cannabinoids as well as of defined extracts in various animal models, using a wide range of cancer cell lines. Among 29 articles, 22 (76%) describe tumour-inhibiting effects. Only three studies concluded that cannabinoids (CBD, THC, extract) were not better than a control treatment (intracranial xenografts) [42], (colon adenocarcinoma xenograft) [83], and (lung adenocarcinoma) [15]. In three studies it was found that THC may eventually increase tumour growth: in breast cancer [67], HPV+ head and neck carcinoma [94], and lung cancer [108]. In a fourth study, a pancreatic cancer model, where mice received an extract (CBD:THC = 6:1), the tumour volume was only higher than that of a negative control with 10 mg/kg but not with 1 mg/kg and 5 mg/kg [27]. From preclinical studies, it can be concluded that tumours differ considerably in their characteristics and sensitivity to cannabinoids.

As most information on tumour-inhibiting *in vitro* and *in vivo* effects of cannabinoids is freely accessible on the internet, their use has become common among cancer patients. This is reflected also by numerous case reports summarised in the present article. All of them describe treatment benefits. Caution is, however, advised as individual, isolated case reports may be biased; positive effects are more likely to be reported than negative. A further limitation is that long-term results in patients treated with cannabinoids are missing. Only one article reported a follow-up of five years or longer [57]. Another case, originally described by Kenyon et al. [22] received much publicity on the internet that allowed to follow the evolution over 7 years [150]. Moreover, it still needs to be clarified whether cannabinoids can safely be used as the sole treatment, as well as how long treatments should last. At present, there is no specific cannabinoid or any specific combination ("cannabis oil") in sight that consistently works best. A "magic bullet" or a "one size fits all" ratio of cannabinoids apparently does not exist in cancer, although in many—but not all—experiments, pure CBD demonstrated outstanding effects when compared with pure THC or combinations of cannabinoids.

In conclusion, although the number of studies in various animal cancer models as well as articles on therapeutic experience with cannabinoids in cancer patients is still very limited, the large majority describes impressing tumour-inhibiting effects warranting further research.

Abbreviations

2-AG: 2-arachidonoylglycerol

ACF: aberrant crypt foci

AEA: anandamide

AOM: azoxymethane

AR: androgen receptor

b.w.: body weight

CB1: cannabinoid receptor 1

CBD: cannabidiol

CBDA: cannabidiol acid

CBDV: cannabidivarin

CBG: cannabigerol

CBN: cannabinol

CNR1: cannabinoid receptor 1 receptor gene

COX-2: cyclooxygenase-2

CRC: colorectal cancer

CT: computed tomography

ECS: endocannabinoid system

ER: oestrogen receptor

FAAH: fatty acid amid hydrolase

GEM: gemcitabine

GPR55: G-protein coupled receptor 55

HCC: hepatocellular carcinoma

HNC: head and neck cancer

HNSCC: head and neck squamous cell cancer

HR: hormone receptor

i.p.: intraperitoneal injection

ID-1: inhibitor of DNA-binding-1

IDH: isocitrate dehydrogenase

MAGL: monoacylglycerol lipase

MEKi: mitogen-activated protein kinase inhibitor trametinib

NSCLC: non-small cell lung cancer

PDAC: pancreatic ductal adenocarcinoma

PPAR-γ: peroxisome proliferator-activated receptor gamma

PR: progesterone receptor

PSA: prostate-specific antigen

s.c.: subcutaneous injection

SCLC: small cell lung cancer

THC: delta-9-tetrahydrocannabinol

THCA: delta-9-tetrahydrocannabinol acid

THC-Es: delta-9-tetrahydrocannabinol-rich extracts

TMZ: temozolomide

TNBC: triple-negative breast cancer

TRPM8: transient receptor potential cation channel subfamily M member 8

TRPV1: transient receptor potential cation channel subfamily V member 1

Declarations

Author contributions

GN: Conceptualization, Data curation, Formal analysis, Writing—original draft, Writing—review & editing.

Conflicts of interest

The author declares that he has no conflict of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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