Medical cannabis: Preliminary results clinical study on the influence on various health conditions

Updated on December 3, 2019

This clinical study is developed to investigate the effects of cannabis products on various health condition. The main goal is that it could contribute to a better understanding of these effects and help to improve cannabinoid derived products.

The results were obtained from 135 patients from 8 different European countries that have filled an evaluation form about their use and experiences of cannabis derived products.

The results can always be improved with more data we obtain, thus If you wish to take part, then please fill in our form, it only takes a couple of minutes to it fill in:
🇬🇧https://forms.gle/mQgGRUy4rvvFf4WU6

German form 🇩🇪
French form 🇫🇷
Italian form 🇮🇹
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Polish form 🇵🇱
Croatian form 🇭🇷

If you have any questions, feedback or suggestions, then please do not hesitate to contact us.

Health Conditions researched

Patients who involved in this research had a wide range of health conditions. Related health conditions were combined as one group to allow a better fitting result. As such, all cancer types were combined into one group, this applied also for patients that indicated to use cannabis to ease pain due to cancer. Other patients indicated to use cannabis for various types of pain relief or chronic pain, therefore, all causes of pain (with the exception of cancer) were combined into another group. Patients that indicated to have suffer from depression, stress and/or anxiety were also placed as one health condition group.

Cancer was found to be present for the largest part of the patients (23,4% or 32 patients), followed by patient who were using it as pain relief (20,4% or 28 patients) and depression, stress and/or anxiety (13,1% or 18 patients) as seen in Figure 1.

Furthermore, 5,8% of the patients used cannabis for multiple sclerosis, 5,8% used it for sleeping problems like insomnia, 4,4% used it for fibromyalgia. Other users indicated to have used cannabis products for arthritis, epilepsy, diabetes, neuropathy, spinal disorders, migraine, COPD, PTSD, Lyme, crohn's disease, brochities, recreational use, sexual stimulation and more.

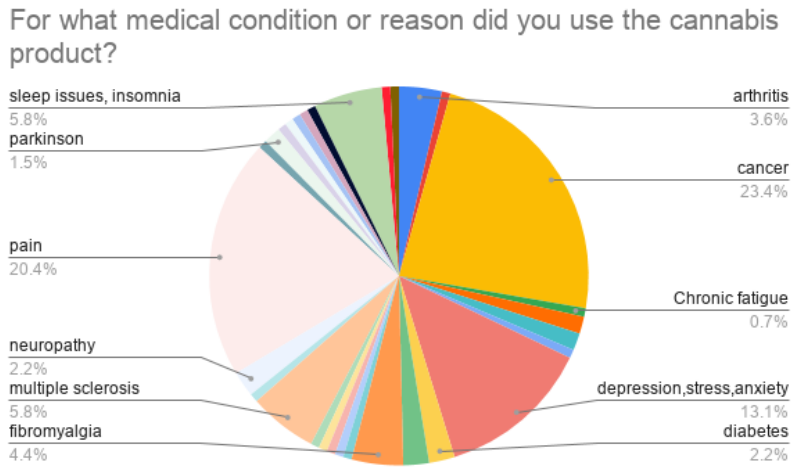

Figure 1. Use of cannabis products for health conditions or reasons.

Effects of cannabis?

Patients were asked to indicate whether the cannabis products that they used for their health conditions did satisfy their expectation.

A staggering amount of 84,7% of the patients indicated that cannabis products indeed did satisfy their expectations to use it for their health condition. 12,4% was not sure and 2,9% indicated that it did not met their expectations (see figure 2).

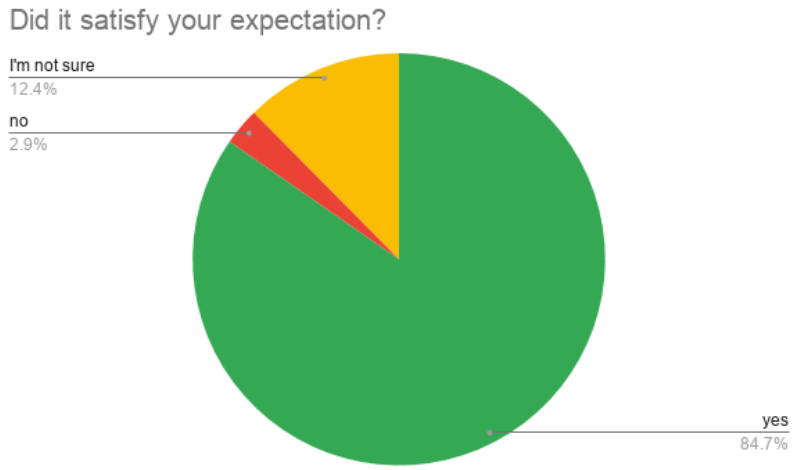

Figure 2. Expectations of cannabis products from all patients.

78,6% of the 29 cancer patients that participated in this research indicated that the cannabis products satisfied their expectations, while 21,4% did not know if it has done anything (see figure 3).

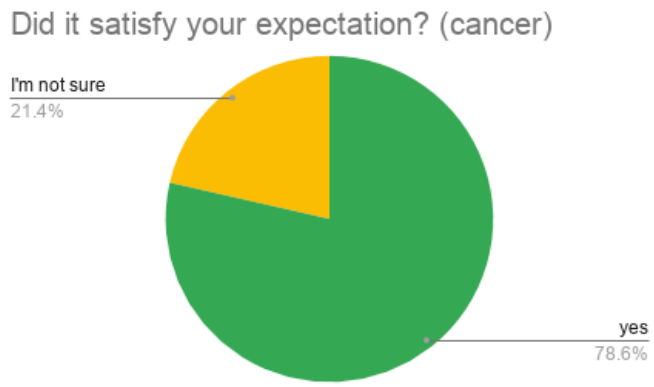

Figure 3. Expectations of cannabis products from cancer patients.

95,7% of the 21 patients with pain, indicated that the cannabis products satisfied their expectations, while 4,3% did not know if it has done anything to them (see figure 4).

Figure 4. Expectations of cannabis products from patients with pain.

80,0% of the 16 patients, with depression, stress or anxiety, indicated that the cannabis products satisfied their expectations, while 13,3% did not know if it has done anything to them and 6,7% said it has not met their satisfaction (see figure 5).

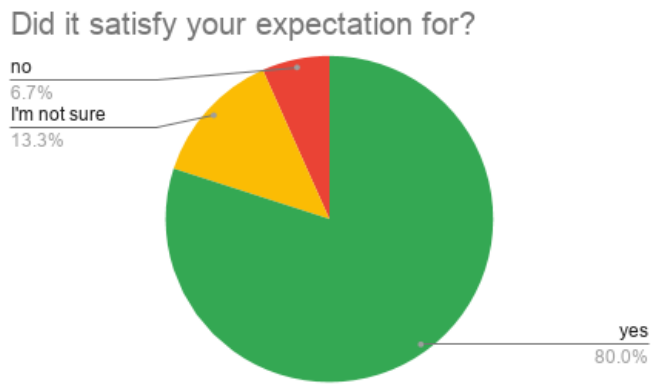

Figure 5. Expectations of cannabis products from patients with depression, stress or anxiety.

Cannabinoids used

Cannabis comes from the cannabis plant and has active ingredients called cannabinoids that can help regulate a number of biological functions in many organisms. Delta-9-tetrahydrocannabinol (THC) is a cannabinoid that produces a “high” feeling that many users attribute to cannabis/marijuana, but it can also be beneficial for many side effects of cancer and its treatments. Cannabidiol (CBD) is another cannabinoid that has many potential applications in cancer and other serious medical conditions.

38,7% of the patients used a cannabis product that contained both THC and CBD, 32,3% of the patients used mainly products with THC and 26,6% used a product with mainly CBD. 2,4% was not sure what cannabis product they had used (see figure 6).

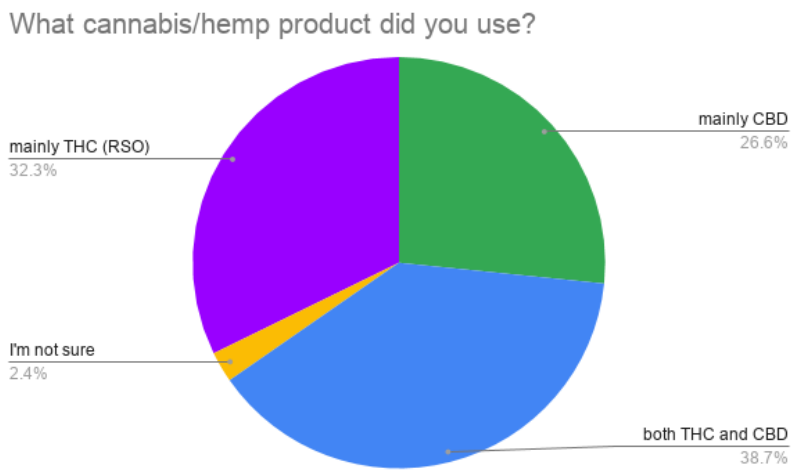

Figure 6. Cannabinoids used by all patients.

46,4% of the cancer patients used a cannabis product that contained both THC and CBD. 35,7% of these patients used mainly products with THC and 14,3% used a product with mainly CBD. 3,6% was not sure what cannabis product they had used (see figure 7).

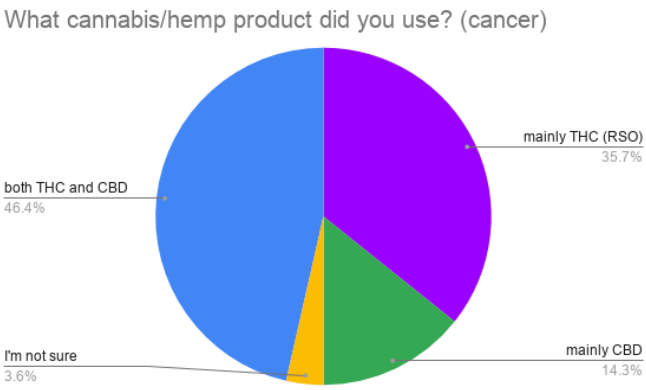

Figure 7. Cannabinoids used by cancer patients.

43,5% of the patients, that mentioned to use it for pain relief, used a cannabis product that contained both THC and CBD. 34,8% of these patients used mainly products with THC and 21,7% used a product with mainly CBD (see figure 8).

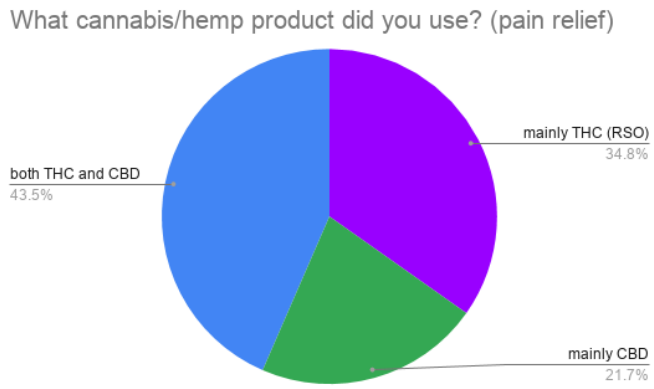

Figure 8. Cannabinoids used by patients with pain.

40,0% of the 16 patients, that mentioned to use it for either depression, stress relief or anxiety, used a cannabis product that contained both THC and CBD. 33,3% of these patients used mainly products with CBD and 26,7% used a product with mainly THC (see figure 9).

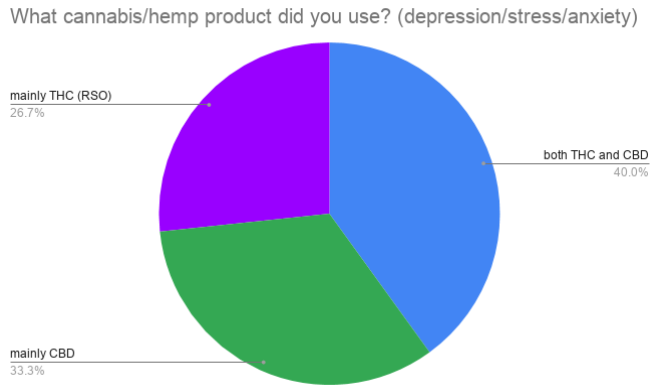

Figure 9. Cannabinoids used by patients with depression, stress or anxiety.

Table 1 below shows the average responses of patients that used cannabis products for other health conditions.

Table 1. Average responses in % for various health conditions.

Average Responses		Did it satisfy your expectation?"			What cannabis/hemp product did you use?			
Medical condition	**patients**	**yes**	**no**	**I'm not sure**	**THC + CBD**	**mainly CBD**	**mainly THC (RSO)**	**I'm not sure**
arthritis	6	67%	17%	17%	50%	33%	0%	17%
brochities	1	100%	0%	0%	100%	0%	0%	0%
cancer	32	78%	0%	22%	47%	13%	38%	3%
Chronic fatigue syndrome (CFS)	1	100%	0%	0%	0%	0%	100%	0%
COPD	2	100%	0%	0%	0%	50%	50%	0%
crohn's disease	2	100%	0%	0%	50%	0%	50%	0%
degenerative disc	1	0%	100%	0%	100%	0%	0%	0%
depression,stress,anxiety	18	78%	6%	17%	44%	33%	22%	0%
diabetes	3	33%	33%	33%	33%	33%	33%	0%
epilepsy	3	100%	0%	0%	0%	0%	100%	0%
fibromyalgia	6	100%	0%	0%	17%	33%	33%	17%
herniated disc	1	100%	0%	0%	0%	0%	100%	0%
inflammation	1	100%	0%	0%	0%	100%	0%	0%
mastocytosis	1	100%	0%	0%	0%	100%	0%	0%
multiple sclerosis	8	75%	0%	25%	38%	50%	13%	0%
neuropathy	3	67%	0%	33%	33%	67%	0%	0%
pain	28	96%	0%	4%	46%	21%	32%	0%
paresthesia	1	100%	0%	0%	0%	100%	0%	0%
parkinson	2	100%	0%	0%	0%	0%	100%	0%
prevention	1	100%	0%	0%	0%	0%	100%	0%
prostatitis	1	100%	0%	0%	100%	0%	0%	0%
PTSD	1	100%	0%	0%	100%	0%	0%	0%
recreational	1	100%	0%	0%	100%	0%	0%	0%
sleep issues, insomnia	8	100%	0%	0%	50%	25%	25%	0%
sexual stimulation	1	100%	0%	0%	100%	0%	0%	0%
spinal stenosis	1	0%	0%	100%	0%	100%	0%	0%
tremors	1	100%	0%	0%	100%	0%	0%	0%

Average Responses		Did it satisfy your expectation?"			What alternative derived product did you use?			
Medical condition	patients	yes	no	I'm not sure	Type1 +Type2	Type1	Type2	I'm not sure
arthritis	6	67%	17%	17%	50%	33%	0%	17%
brochities	1	100%	0%	0%	100%	0%	0%	0%
cancer	32	78%	0%	22%	47%	13%	38%	3%
Chronic fatigue syndrome (CFS)	1	100%	0%	0%	0%	0%	100%	0%
COPD	2	100%	0%	0%	0%	50%	50%	0%
crohn's disease	2	100%	0%	0%	50%	0%	50%	0%
degenerative disc	1	0%	100%	0%	100%	0%	0%	0%
depression,stress,anxiety	18	78%	6%	17%	44%	33%	22%	0%
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fibromyalgia	6	100%	0%	0%	17%	33%	33%	17%
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inflammation	1	100%	0%	0%	0%	100%	0%	0%
mastocytosis	1	100%	0%	0%	0%	100%	0%	0%
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neuropathy	3	67%	0%	33%	33%	67%	0%	0%
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parkinson	2	100%	0%	0%	0%	0%	100%	0%
prevention	1	100%	0%	0%	0%	0%	100%	0%
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PTSD	1	100%	0%	0%	100%	0%	0%	0%
recreational	1	100%	0%	0%	100%	0%	0%	0%
sleep issues, insomnia	8	100%	0%	0%	50%	25%	25%	0%
sexual stimulation	1	100%	0%	0%	100%	0%	0%	0%
spinal stenosis	1	0%	0%	100%	0%	100%	0%	0%
tremors	1	100%	0%	0%	100%	0%	0%	0%

Cancer and Marijuana
Do cannabinoids cure cancer?

by Dr Manuel Guzmán

Cannabinoids, the active components of cannabis and their derivatives, exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating appetite. In addition, these compounds inhibit the growth of tumour cells in laboratory animals -mice and rats. However, at the moment there is not solid evidence to prove that cannabinoids –whether natural or synthetic- can effectively treat cancer in patients, although research is ongoing around the world.

Comprehensive FAQ sections -including scientific references- on cannabinoids and cancer can

be found at the **Cancer Research UK website** and the **National Cancer Institute of the US website**. Here that information is summarized and discussed.

What is cancer?
Cancer is a broad term used for diseases in which abnormal cells divide without control and are usually able to invade other tissues, causing metastases and high rates of mortality and morbidity. Cancer is not just one disease but many diseases: more than 100 different cancers are well-typified from a histopatological point of view by the WHO and, most likely, there are hundreds if not thousands types of cancers according to molecular and genetic profiling.
Most cancers are named for the organ or type of cell in which they start. In addition, cancer types are usually grouped into the following broader categories:
- Carcinoma: cancer that begins in the skin or in tissues that line or cover internal organs.
- Sarcoma: cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- Leukaemia: cancer that starts in blood-forming tissues such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.
- Lymphoma and myeloma: cancers that begin in the cells of the immune system.
- Central nervous system cancers: cancers that begin in the tissues of the brain and spinal cord.

Conclusion: Cancer is a very serious and heterogeneous disease, so fighting it therapeutically remains an extremely difficult challenge. Cannabinoids might therefore exert beneficial effects in some cancers but not in others.

Do cannabinoids inhibit cancer growth? (Laboratory research)
Virtually all the **research into cannabinoids and cancer cells** has been conducted so far using cancer cells grown in the lab or in animal models. Many scientific studies have reported that various cannabinoids (both natural and synthetic) exert a wide range of growth-inhibiting effects on cancer cells, including:
- Triggering cell death, through a mechanism called apoptosis.
- Stopping cells from dividing.
- Preventing new blood vessels from growing into tumours –a process termed angiogenesis.
- Reducing the chances of cancer cells to metastasize through the body, by stopping cells from moving or invading neighbouring tissue.
- Speeding up the cell's internal 'waste disposal machine' –a process known as autophagy – which can lead to cell death.

Conclusion: Cannabinoids are efficacious drugs to treat at least some types of cancers in laboratory animals –mice and rats.

Do cannabinoids inhibit cancer growth? (Anecdotal evidence in humans)
As mentioned above, basically all the research investigating whether cannabinoids can treat cancer has been done in the lab. It is therefore important to be very cautious when extrapolating these results up to real live patients, who are a lot more complex than a Petri dish or a mouse. Anecdotal reports on cannabis use have been historically helpful to provide hints on the biological processes controlled by the endocannabinoid system and on the potential therapeutic benefits of cannabinoids. In the precise case of cancer there is a notable presence of videos and reports on the internet arguing that cannabis can cure cancer. These anecdotal claims may be completely or partially true in some cases, but overall remain –at least to date- weak and obscure. For example:
- We do not know whether the (supposed) effect of cannabis was due to a placebo effect.
- We do not know whether the tumour has (supposedly) stopped growing by natural/endogenous reasons -some tumours regress spontaneously/owing to the body's anti-tumour defences.
- We do not know how many patients have taken cannabis and have not obtained any therapeutic benefit, that is, what is the (supposed) efficacy of the cannabis-based therapy.
- As most likely patients have gone through standard therapy prior to or concomitantly with cannabis use, we do not know whether the (supposed) effect of cannabis was in fact due -at least in part- to the standard therapy -perhaps enhanced by cannabis, but we have no proof.
- We do not know what are the parameters of tumour progression that have been monitored and

for how long the patient has been monitored -many potentially beneficial effects of antineoplastic drugs (or of cannabis in this case) are just short-term actions, but what about long-term progression-free survival and overall survival?
- Cancer is a very heterogeneous disease, and so far none has put together a sufficient number of patients for a particular type of cancer to support that cannabinoids are efficacious drugs in that precise cancer.

Conclusion: Although it is possible –and of course desirable- that cannabis preparations have exerted some antineoplastic activity in some particular cancer patients, the current anecdotal evidence reported on this issue is pretty poor, and, unfortunately, remains far from supporting that cannabinoids are efficacious anticancer drugs for large patient populations.

Do cannabinoids inhibit cancer growth? (Clinical research)
Results have been published from only one Phase I clinical trial testing whether cannabinoids can treat cancer in patients. Nine people with advanced, recurrent glioblastoma multiforme –an aggressive brain tumour– that had previously failed standard therapy were given highly purified THC through a catheter directly into their brain. Under these conditions cannabinoid delivery was safe and could be achieved without significant unwanted effects. In addition, although no statistically-significant conclusions can be extracted from such a small cohort of patients and without a control group, the results obtained suggested that some patients responded -at least partially- to THC treatment in terms of decreased tumour growth rate, as evaluated by imaging and biomarker analyses. These findings were encouraging and substantially reinforced the interest on the potential use of cannabinoids in cancer therapies. However, they also highlighted the need for further research aimed at optimizing the use of cannabinoids in terms of patient selection, combination with other anticancer agents and use of other routes of administration.

Conclusion: There are still many unanswered questions around the potential for using cannabinoids as anticancer drugs, and it is necessary and desirable that exhaustive clinical studies are conducted to determine how cannabinoids can be used, other than for their palliative effects, to treat cancer patients.

History

A long history of medical use is seen of the *Cannabis sativa* L. plant. One of the earliest evidences is found in China during the Han Dynasty (206 BC–220 AD), where cannabis was used for rheumatic pain, constipation, disorders and malaria. Although Cannabis was cultivated even earlier in Central Asia since the pre-Neolithic period for its fibres and as a food source and possibly as a psychoactive material. An archeological site in the Oki Islands near Japan contained cannabis achenes from about 8000 BC. In Western medicine, the use of cannabis was notably introduced by the work of William B. O'Shaughnessy (an Irish physician) and Jacques-Joseph Moreau (a French psychiatrist) in the mid-19th century, who described positive effects of cannabis preparations, including hashish (the compressed stalked resin glands), on pain, vomiting, convulsions, rheumatism, tetanus and mental abilities. Cannabis was recognized as a medicine in the United States (US) Pharmacopoeia from 1851, in the form of tinctures, extracts and resins. However, in the beginning of the 20th century, cannabis use decreased in Western medicine due to several reasons: increased use as a recreational drug, abuse potential, variability in the quality of herbal material, individual (active) compounds were not identified and alternative medications, with known efficacy, were introduced to treat the same symptoms [2,3]. In 1941, as the result of many legal restrictions, cannabis was removed from the American Pharmacopoeia and considered to be in the same group as other illicit drugs [3]. Consequently, the exploration of medical uses of cannabis has been significantly slowed down for more than a half of century. In 2013, a step forward was made with the inclusion of a monograph of *Cannabisspp*. in the American Herbal Pharmacopoeia [4]. Moreover, the current legislative changes in the European Union (EU), US and Canada that allow cannabis for medical and/or

recreational use, the progress in scientific research and public awareness on the benefits of medical cannabis all contributed to the rising interest in the therapeutic potential of cannabinoids [5,6].

In recent years, cannabinoids have been extensively studied for their potential anticancer effects and symptom management in cancer patients [7-9]. One of the first studies describing antineoplastic activity of cannabinoids was published in 1975 [10]. Potential antitumour activity of plant-derived or phytocannabinoids, e.g., (−)-trans-Δ9-tetrahydrocannabinol (THC), cannabinol (CBN), Δ8-THC, cannabidiol (CBD) and cannabicyclol (CBL), as well as of synthetic cannabinoids, such as WIN-55,212-2, is the focus of current research [7,8,11].

In the 1990s, the main components of the endocannabinoid system (ECS) were identified as follows: (i) two types of cannabinoid (CB) receptors, CB_1 and CB_2 receptor; (ii) two main endogenous ligands (endocannabinoids) in mammals, anandamide or N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG); and (iii) endocannabinoid metabolic enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAG lipase). FAAH is the primary catabolic enzyme for fatty acid amides (FAAs), a class of bioactive lipids including AEA, while MAG lipase is a key enzyme in the hydrolysis of 2-AG [12-16]. Subsequent studies demonstrated the important role of the ECS and endocannabinoids in different physiological and pathological processes, such the regulation of excitatory and inhibitory synaptic transmission in the central nervous system (CNS), food intake, nociceptive signaling, analgesia, immunomodulation, inflammation, and cancer cell signaling [17-19].

In cancer patients, cannabinoids have primarily been used as a part of palliative care to alleviate pain, relieve nausea and stimulate appetite [8,20]. In addition, numerous cell culture and animal studies showed antitumour effects of cannabinoids and suggested new therapeutic opportunities for cancer patients [20]. However, recent research also emphasizes the importance of safety measures when using cannabinoids, since these compounds can potentially impair cognitive functions, especially in adolescents [21].

MOLECULAR BASIS FOR CANNABINOID TREATMENT OF CANCER

The role of the endocannabinoid system in cancer

Endocannabinoids interact with different types of receptors, including the two $G_{i/o}$-coupled CB receptors, CB_1 and CB_2 [18]. While CB_1 receptors are mainly located in the CNS and, to a lesser degree, in some peripheral tissues, CB_2 receptors are primarily expressed on the surface of immune cells [22]. Due to the low expression of CB_2 receptors in the CNS they represent a promising pharmacological target, as selective CB_2 ligands potentially would not have psychotropic effects [23]. In addition, other CB receptor types and isoforms or completely different pharmacological targets of cannabinoids have been described, for example transient receptor potential vanilloid receptor 1 (TRPV1), orphan G-protein coupled receptor (GPR)55, peroxisome proliferator-activated receptors (PPARs) [24,25], transient receptor potential melastatin 8 (TRPM8), TRP vanilloid 2 (TRPV2) and TRP ankyrin 1 (TRPA1) channel [26]. It is important to note that cannabinoids may also exert their antitumour effects independent of the CB receptors, for example as demonstrated in human pancreatic cancer cell line MIA PaCa-2 [27].

The biological role of the ECS in cancer pathophysiology is not completely clear [20] but most studies suggest that CB receptors and their endogenous ligands are upregulated in tumour tissue [28,29,31,34-39,41,48] and that the overexpression of ECS components (i.e., receptors, ligands, and enzymes) correlates with tumour aggressiveness [49-51]. However, a tumour-suppressive role of ECS was also indicated by some studies, e.g., the upregulation of endocannabinoid-degrading enzymes was observed in aggressive human cancers and cancer cell lines [51]. Moreover, experimental studies showed that the activation of CB receptors by cannabinoids is antitumourigenic in most cases, i.e., it inhibits tumour cell proliferation, induces apoptosis *in vitro*, and blocks angiogenesis and tumour invasion/metastasis *in vivo* [35,46,51,52]. The effects of CB receptor (over)expression in selected human tumour cell lines are described in more detail in Table 1.

Table1.

Cancer cell type	Regulation of CB_1/CB_2	Mechanisms and other relevant circumstances	Reference
Breast cancer	Elevated CB_2 receptor expression in HER2+breast tumors.	HER2 induces CB_2 expression activating ELK1 (ERK/MAPK cascade); activated pro-oncogenic signaling through tyrosine kinase c-Src.	[28,29]
	Presence of TRPV1 in human breast adenocarcinoma cell line (MCF-7).	TRPV1 agonists/antagonists induce significant inhibition of MCF-7 cell growth.	[30]
	Elevated CB_1 receptor expression.	Activation of Akt signaling pathway was proposed. Increased CB_1 and FAAH levels correlate with severity of the disease.	[31-34] [35,36]
Prostate cancer	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Additionally: Presence of TRPV1 and TRPA1 in all prostate cancer cells (except LNCaP cells), TRPV2 in DU-145 and PC-3 cells only, TRPM8 in AR-dependent prostate cell lines (e.g., LNCaP).	[37-39]
	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Expression of GPR55 in PC-3 and DU-145 cell lines has been reported, mediating effects of LPI.	[40]
Chemically induced hepatocellular carcinoma	Upregulation of CB_1 receptors.	Diethylnitrosamine induced liver cancer.	[41]
Hepatocellular carcinoma	Overexpression of CB_1 and CB_2 receptors.	Overexpression of CB_1 and CB_2 receptors is associated with improved prognosis.	[42]
Non-small cell lung cancer	Overexpression of CB_1 and CB_2 receptors.	Activation of Akt signaling pathway, MMP9 expression and activity.	[43]
Chronic lymphocytic leukemia	Overexpression of CB_1 and CB_2 receptors.	CB_1 receptor expression correlated with high-risk markers.	[44]
Pancreatic cancer	CB1 and CB_2 receptors expressed in normal and pancreatic cancer cells (higher expression of CB_1).	Cannabinoids induced apoptosis via CB_2 receptor (ceramide dependent pathway).	[45-47]
Melanoma	CB_2 is overexpressed in human melanoma tissues and cell lines.	Not reported.	[48]

HER2: Human epidermal growth factor receptor 2; ELK1: ETS domain-containing protein; c-Src: Tyrosine-protein kinase Src; ERK: Extracellular-signal-regulated kinase; MAPK: Mitogen-activated protein kinase; TRPV1: Transient receptor potential vanilloid receptor 1; Akt: Protein Kinase B; FAAH: Fatty acid amide hydrolase; TRPA1: Transient receptor potential ankyrin 1; GPR55: Orphan G-protein coupled receptor 55; AR: Androgen receptor; LPI: Lysophosphatidylinositol; MMP9: Matrix metallopeptidase 9

Antitumour effects of cannabinoids

By targeting the ECS, cannabinoids affect many essential cellular processes and signaling pathways which are crucial for tumour development [51,53,54]. For example, they can induce cell cycle arrest, promote apoptosis, and inhibit proliferation, migration and angiogenesis in tumour cells (Figure 1) [53,54]. In addition to CB receptor-mediated (CB_1 and CB_2 receptors) cannabinoid effects, it appears that these processes can also be CB receptor-independent (e.g., through TRPV1, 5-hydroxytryptamine $[5\text{-HT}]_3$, or nicotinic acetylcholine receptor [nAChR] among others) [53], suggesting that molecular mechanisms underlying the antitumour activity of cannabinoids are even more complex than originally thought. Moreover, it is expected that future studies will discover novel molecular targets of cannabinoids [53].

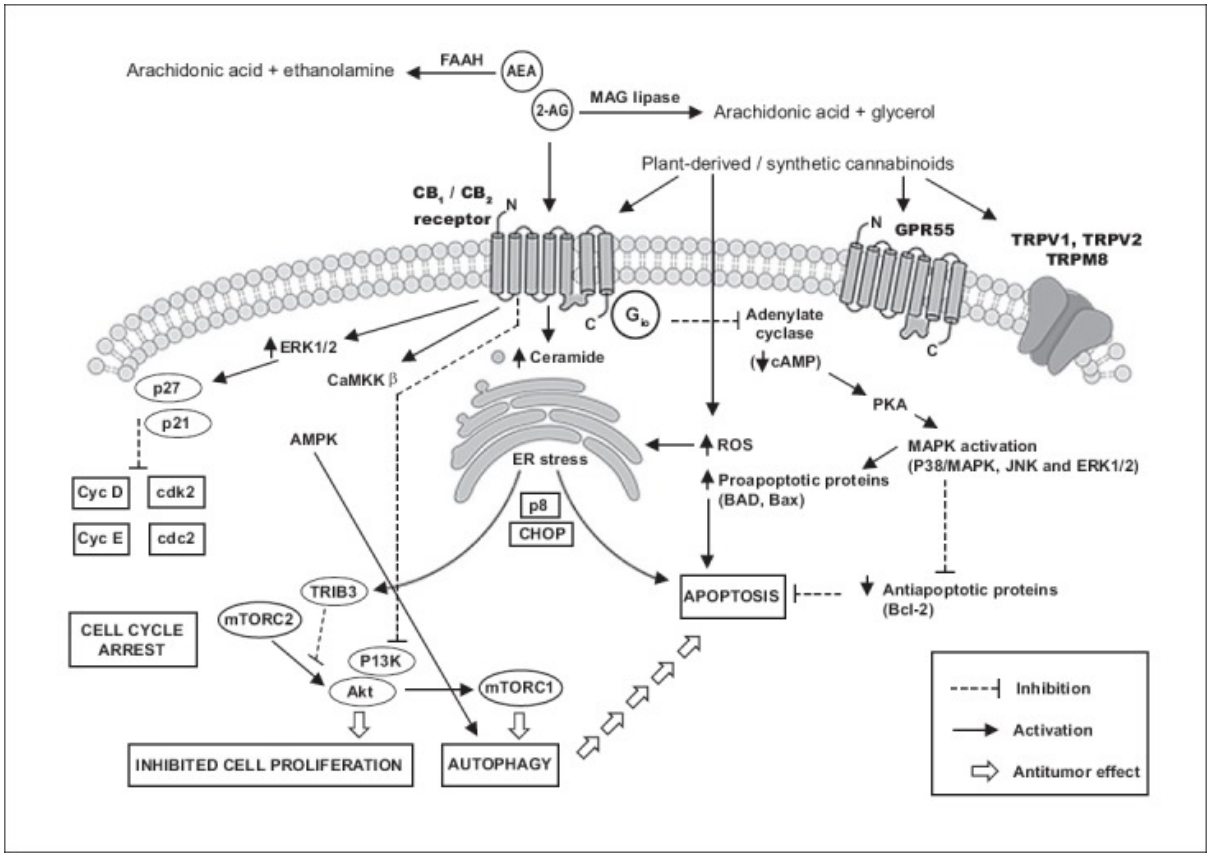

Figure 1.

The ability of plant-derived and synthetic cannabinoids to control cancer cell growth, invasion, and death has been demonstrated in numerous experimental studies using cancer cell lines and genetically engineered mouse models. Also, different types of cannabinoids may have different modes of action. For example, a phytocannabinoid THC promotes apoptosis in a CB-receptor dependent manner, while CBD exerts this effect independently of CB_1/CB_2 receptors and possibly includes the activation of TRPV2 receptor, at least in some cancer types. Also, some CB receptor agonists are less efficient in promoting cancer cell death although they demonstrate higher affinity for CB receptors than THC, such as synthetic CB receptor agonist WIN-55,212-2. Better understanding of homo- or hetero-oligomerization of CB receptors, their interactions with lipid rafts for example, and mechanisms of selective G-protein coupling may clarify these differences [54]. Finally, because molecular changes are tumour-specific in most cases (i.e., the presence of intra- and inter-tumour heterogeneity), CB-receptor mediated antitumour effects largely depend on the type of cancer that is being investigated and characteristics of derived

tumour cell line, including the donor characteristics, tumour site of origin and hormonal responsiveness [53-55].

PLANT-DERIVED CANNABINOIDS AND THEIR ANTITUMOUR ACTIVITY

Phytocannabinoids are a group of C_{21} terpenophenolic compounds predominately produced by the plants from the genus *Cannabis*. Different resources indicate that there are more than 90 different cannabinoids together with their breakdown products, although some report that > 60 compounds is a more accurate estimation. Among these, the most abundant are THC, CBD, CBN and cannabichromene (CBC) followed by ∆8-THC, cannabidiolic acid (CBDA), cannabidivarin (CBDV) and cannabigerol (CBG). The highest content of cannabinoids is located in the flowering tops of the plant and small, young leaves around the flowers [56].

Pharmacologically, THC is a partial agonist at CB_1 and CB_2 receptor with inhibitory constant (Ki) of 40.7 nM for CB_1 and 36.4 nM for CB_2 [57]. ∆8-THC is a stable isomer of THC with similar Ki [58]. The most studied non-psychotropic phytocannabinoid is CBD which does not have psychotomimetic activity. CBD has a low affinity for CB_1 and CB_2; it was suggested that it acts as an antagonist of CB_1/CB_2 agonists but also as a CB_2 inverse agonist (an inverse agonist binds to the same receptor-binding site as an agonist and it does not only antagonize the effects of the agonist but exerts the opposite effect). Other mechanisms of action of CBD, that are independent of CB receptors, include FAAH inhibition, inhibition of AEA reuptake, it acts as an agonist at PPARγ, TRPV1, TRPA1 and an antagonist at GPR55 and TRPM8 (Table 2). CBN is a weak partial agonist at CB_1 (Ki of 308 nM) and CB_2 (Ki of 96.3 nM); CBG is a potent TRPM8 antagonist, TRPV1 and TRPA1 agonist, and CB partial agonist; while CBC is a potent TRPA1 agonist and weak inhibitor of AEA reuptake [59].

Plant-derived cannabinoids are approved only for some indications, but additionally have been used off-label. For example, a standardized alcoholic cannabis extract nabiximols, which has the THC: CBD ratio of 1:1 and is available as an oromucosal spray, was approved in Germany for the treatment of moderate to severe refractory spasticity in multiple sclerosis. Examples of off-label use of this medication are of chronic pain in several medical conditions and symptomatic treatment of selected neuropsychological disorders (e.g., anxiety and sleeping disturbances). Common side effects of cannabinoids are tiredness and dizziness (in more than 10% of patients), dry mouth, and psychoactive effects among others. Nevertheless, tolerance to these side effects develops within a short time in almost all cases. Withdrawal symptoms are rarely observed in the therapeutic setting [60].

An exciting area of research is the technological improvement of existing pharmaceutical formulations, especially the development of new cannabis-based extracts. Romano et al. [57] found that a CO_2 extracted cannabis extract, with a high content (64.8%) in Δ9-tetrahydrocannabivarin (THCV), inhibits nitrite production induced by lipopolysaccharides (LPS) in murine peritoneal macrophages, and thus may have a potential to modulate the inflammatory response in different disease conditions [57]. Another study compared *in vitro* antioxidant activity and gene expression of antioxidant enzymes between ethanol and supercritical fluid (SF) extracts of dehulled hemp seed. SF extract exhibited higher radical scavenging activities compared to ethanol extract. Both extracts upregulated the expression of the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) in human hepatoma (HepG2) cells challenged with H_2O_2, and this effect was greater for SF extracts at the concentration of 500 µg/mL [61].

Different plant-derived cannabinoids and cannabis-based pharmaceutical drugs have been the subject of intensive research for their potential antitumour activity, especially in cancer cells that overexpress $CB_1$and/or CB_2 receptors compared to normal tissues [62]. Many studies were conducted in different cell lines with cannabis extracts or individual isolated compounds and the results are sometimes confounding, because efficient anticancer effects, such as decreased proliferation of cancer cells, activation of apoptosis, inhibition of cell migration and decreased tumour vascularization are mainly recorded in breast, prostate and glioma cancer cell lines. In contrast, protumourigenic activity of natural cannabinoids, i.e., increased cell proliferation, has

been reported in lung, breast, and hepatoma cell lines [63]. It appears that the balance between protumourigenic and antitumour effects of cannabinoids critically depends on their concentration, among other factors. For example, Hart et al. [64] showed that the treatment of glioblastoma U373-MG and lung carcinoma NCI-H292 cell line with nanomolar concentrations of THC (instead of commonly used micromoral concentrations) led to increased cell proliferation. The authors also emphasized that nanomolar concentrations of THC are more likely to be detected in the serum of patients after drug treatment [64]. Therefore, in cancer therapy, it is very important to consider the risk of acceleration of tumour growth due to the concentration-dependent proliferative potential of cannabinoids [64].

In addition to THC, CBD is another plant-derived cannabinoid that has been extensively studied for its potential antitumour effects [39,65-68]. In a panel of human prostate cancer cell lines, Sharma et al. [67] showed that CBD is a potent inhibitor of cancer cell growth, while this potency was significantly lower in non-cancer cells. Moreover, CBD downregulated CB_1, CB_2, vascular endothelial growth factor (VEGF) and prostate-specific antigen (PSA) in prostate cancer cells, as well as pro-inflammatory interleukin (IL)-6 and IL-8 in LPS-stimulated dermal fibroblasts, suggesting its anti-inflammatory properties [67]. Other studies showed that CBD preferentially inhibited the survival of breast cancer cells by inducing apoptosis and autophagy [65] and inhibited proliferation and cell invasion in human glioma cell lines [66].

The expression of CB_1 and CB_2 receptors on immune cells suggests their important role in the regulation of the immune system. Recently, it was demonstrated that the administration of THC into mice induced apoptosis in T cells and dendritic cells, leading to immunosuppression. Several studies suggested that cannabinoids are able to suppress inflammatory responses by downregulating cytokine and chemokine production and upregulating T-regulatory cells. Similar results were obtained with endocannabinoids, i.e., the administration of these compounds or the use of inhibitors of enzymes that break down endocannabinoids had an immunosuppressive effect and resulted in the recovery from immune-mediated injury to organs, e.g., in the liver [69]. As indicated in previous paragraphs, cannabinoids were able to stimulate cell proliferation in *in vitro* and/or *in vivo* models of several types of cancer. For example, a treatment with THC in the mouse mammary carcinoma 4T1 expressing low levels of CB_1 and CB_2 led to enhanced growth of tumour and metastasis, due to the inhibition of the antitumour immune response, primarily via CB_2. Moreover, THC led to an increased production of IL-4 and IL-10 in these mice, indicating that it suppresses the Th1 response by enhancing Th2-associated cytokines as confirmed by their microarray data (Th2-related genes were upregulated and Th1-related genes downregulated). Lastly, the injection of anti-IL-4 and anti-IL-10 monoclonal antibodies partially reversed the THC-induced suppression of the immune response [70]. In another study, THC promoted tumourigenicity in two weakly immunogenic murine lung cancer models by inhibiting their antitumour immunity; namely, the inhibitory cytokines IL-10 and transforming growth factor beta (TGF-β) were upregulated, while interferon gamma (IFN-γ) was downregulated at the tumour site and in the spleens of the mice treated with THC [71]. These findings suggest that THC could decrease tumour immunogenicity and promote tumour growth by inhibiting antitumour immunity, probably via CB_2 receptor-mediated, cytokine-dependent pathway. Additional studies on the interactions between cannabinoids and immune cells will provide crucial data to improve the efficacy and safety of cannabinoid therapy in oncology [72].

Rick Simpson oil is a cannabis extract that takes its name from the medical marijuana activist who created it. Simpson claims that applying the oil to cancer spots on his skin cleared the spots within days.

Rick Simpson oil (RSO) is unique in that it contains higher levels of tetrahydrocannabinol (THC) than other medical cannabis extracts.

Although there is some evidence to support the use of cannabis for aiding cancer treatment, the medical community needs more direct evidence of its safety and effectiveness in humans before making any firm claims.

Scientists continue to research potential uses for cannabis products in treating cancer.

RSO is a high potency cannabis extract with high levels of THC, along with other cannabinoids.

Many researchers and medical companies are now focusing on CBD oil, which contains mostly the nonpsychoactive compound cannabidiol (CBD). However, RSO contains much higher levels of THC, which is the compound responsible for the high, euphoric feeling associated with marijuana.

Although there may be a number of companies selling RSO on the market, Rick Simpson's website recommends that people make it at home.

According to the website, people should use cannabis from *Cannabis indica* strains to make the oil correctly. Some people suggest that these

strains create a more subdued, relaxed state, which the website suggests is key to assist healing

Does RSO work?

Some research has suggested that THC may be effective in treating cancer.

Although people may use the oil in any way they choose, the main claim is that RSO can treat cancer. At present, however, there is little to no evidence to support claims that it cures cancer directly.

Researchers have been studying cannabis and THC, the main component in RSO, for many years. Some evidence supports the use of the compound in cancer therapy.

For instance, a study in *Molecular Cancer Therapeutics* found that a combination of CBD and THC enhanced the effects of radiation therapy in

rodents. This appears promising, as it suggests that cannabis compounds might make standard cancer treatment better.

A case study in *Case Reports in Oncology*Trusted Source also explored the use of cannabis oil in a child with a specific cancer. She was terminally ill, having had no success with standard treatment. Her parents chose to stop standard treatment and give her a cannabis extract in the form of RSO.

Although it did appear to reduce her specific type of cancer, the girl died from other complications unrelated to its use.

This makes it hard to draw any firm conclusions about the effect that the oil would have had on the cancer cells in the long-term, or to call the treatment a success.

Some cancers may respond better to cannabinoids than others. For example, a review in the *Journal of Pancreatic Cancer*Trusted Source suggests that cannabis may be helpful as an addition to treatment for cancers that involve cannabinoids, which are the cells in the body that respond to compounds in cannabis. One such cancer is pancreatic cancer.

Their research indicated that both THC and CBD could be helpful as a supplementary treatment for pancreatic cancer, and they urged the completion of more clinical studies using cannabinoids for pancreatic cancer.

A separate review in *Frontiers in Pharmacology* studied the overall body of research into cannabinoids and their effects regarding cancer. The researchers noted that the majority of animal studies find that the active compounds in cannabis are capable of effectively decreasing tumor growth.

Also, although they are limited, the few human studies to date do show promise — particularly in the realm of preventing or slowing the growth of tumors.

These initial results look positive, but it is still too early to make any broad statements about cannabis and cancer therapy. More long-term studies using RSO or cannabis in humans would need to help back up any claims with strong evidence.

Side effects

THC is a psychoactive substance, and some people are more sensitive to it than others.

THC causes the "high" that most people associate with cannabis. As a result, it can cause temporary mental impairment, so people should not use machinery or drive while using RSO.

High doses of THC may also cause a number of side effects involving the brain, such as:

- anxiety
- paranoia
- panic attacks
- hallucinations
- irritability, especially when "coming down"
- disorientation

Physical side effects are also common when using THC, such as:

- dry, red eyes
- dizziness

- low blood pressure
- trouble sleeping
- impaired memory

These side effects are generally temporary and tend to subside as the THC starts to leave the body.

Risks and considerations

Some people worry that younger people may be at risk of adverse side effects of cannabis products.

The most important thing to remember about RSO is that there is little evidence to suggest that it directly cures cancer. A person should not stop their recommended cancer treatment to switch to RSO.

Much of the research around cannabis in humans supports using the plant as a supportive therapy, such as using it to help deal with side effects

of chemotherapy. Anyone looking for alternatives to their cancer treatment should consult a doctor to discuss their options.

Some may also worry that THC and cannabis products may pose some long-term risks, especially to younger people who use it.

One study in *Current Pharmaceutical Design*Trusted Source noted that teenagers who use cannabis more often may have a higher risk of impaired ability to think than those who do not use it often. Their brains are still developing at this stage, and cannabis may interfere with the process. However, researchers called for more evidence that takes other factors into account.

Rick Simpson's website also calls for people to make the oil themselves, which may pose a risk in areas where cannabis is still illegal.

Also, the website suggests using solvents to clean the cannabis before use. Improperly handled solvents may also pose a risk to health.

Summary

There is no solid evidence to support the claims that RSO can cure cancer directly.

Although early research shows that cannabis has some promise in the treatment of cancer, it is not conclusive.

Scientists will need to conduct more research in humans, and clinical trials will need to find strong evidence linking cannabis and cancer treatment before researchers can begin to make any firm claims.

RSO may help support cancer treatment in some cases. However, the long-term risks and effects of the oil are relatively unknown.

Anyone wanting to use THC or cannabis during cancer treatment should talk to their doctor before doing so.