

# The Role of Cannabinoids in the Treatment of Children with Cancer

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Cannabinoids are a heterogeneous group of compounds that exhibit activity by binding to specific receptors called cannabinoid receptors. Cannabinoids are classified into three groups:

- phytocannabinoids, which are natural compounds present in the *Cannabis sativa* plant [1]
- endogenous cannabinoids, also known as endocannabinoids
- the synthetic analogs of both groups, called synthetic cannabinoids [2].

The well-studied cannabinoid is  $\Delta$ 9-tetrahydrocannabinol (THC), which is also the most active constituent of the plant. In addition to THC, cannabis has high concentrations of cannabidiol (CBD), a non-psychoactive constituent of the plant [3]. The two most studied compounds of the endocannabinoid system are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Commercially available synthetic cannabinoids and THC analogs include Sativex® (GW Pharmaceuticals, UK), Dronabinol® (AbbVie Inc., USA) and Nabilone® (Meda Pharmaceuticals Inc, Sweden), which are approved for the treatment of cancer-related side effects [4].

Cannabinoid activity is regulated by the endocannabinoid system (ECS), which comprises cannabinoid receptors, transporters, and enzymes involved in cannabinoid synthesis and breakdown. So far, two major cannabinoid-specific receptors – CB1 and CB2 – have been cloned and characterized from mammalian tissues [2]. These receptors are present throughout the body and regulate a variety of physiological functions, including neuronal development and energy metabolism. The distribution of CB1 and CB2 accounts for many of the observed effects associated with cannabis use. CB1 receptors appear to be ubiquitously located throughout the body, with the highest

concentration of receptors found in the central nervous system [5]. CB2 receptor expression occurs mainly in the immune system, the highest expression in B lymphocytes which are involved in immune suppression and cell migration induction [2]. Both CB1 and CB2 belong to the large family of G protein-coupled receptors. Other receptors have been proposed to act as endocannabinoid receptors, including the transient receptor potential cation channel subfamily V member 1 (TRPV1) and certain orphan G protein-coupled receptors – GPR55, GPR119 and GPR18 [6].

Cannabis has been used in folk medicine to alleviate pain, depression, amenorrhea, inflammation and numerous other medical conditions. In cancer patients specifically, cannabinoids are well known to exert palliative effects; their best-established use is the inhibition of chemotherapy-induced nausea and vomiting, but they are applied also to alleviate pain, stimulate appetite, and attenuate wasting [7]. More recently, cannabinoids have gained special attention for their role in cancer cell proliferation and death. A huge number of cannabinoids has been elucidated, and significant research has been undertaken to evaluate the therapeutic utility of these compounds in the treatment of cancer.

## CURRENT LEGAL STATUS AND BARRIERS FOR CANNABIS USE IN CHILDREN

The current state of cannabis use for both medical and recreational purposes is highly debated. While the legality of its use varies from country to country, possession of cannabis is illegal in most countries. In the United States, it is a controlled substance and is classified as a drug with a high potential for abuse and no currently accepted medical use. Despite this classification, many states in the United States have moved to decriminalize or legalize marijuana for medical or recreational use [8]. In addition, Canada, New Zealand and several countries in Europe approved a few synthetic cannabinoid analogs for spasticity associated with multiple sclerosis, as an adjunct analgesic for patients with advanced cancer, and for prevention of chemotherapy-induced nausea and vomiting. In Israel, cannabis for recreational purposes is illegal but it is approved for cancer patients and for patients with pain-related illnesses such

as Parkinson's, multiple sclerosis, Crohn's disease, other chronic pain and post-traumatic stress disorder.

Physicians have mixed attitudes regarding the legalization of medical cannabinoid use since there is no information on the dose, frequency of use, potency, potential side effects, risks and benefits of use, interaction with other prescribed medications, and lack of regulation and quality control. Indeed, according to a new position statement the American Academy of Neurology does not advocate for the legalization of medical marijuana to treat neurological conditions because of the lack of evidence [9].

In contrast, physicians caring for cancer patients in the U.S. recommend medicinal cannabis for symptom management. A survey conducted in 2013 among 1446 physicians on their attitudes regarding the legalization of medical marijuana use found that 76% approved using it for a medical purpose. Most physicians in this study cited their "responsibility as caregivers to alleviate suffering" as their reason for support [8].

Regarding the use of cannabis in children and adolescents the dilemma and concern are even greater since there are no published studies on the use of medicinal marijuana or pharmaceutical cannabinoids in pediatric populations. Growing evidence suggests a differential effect of cannabis exposure on the human brain based on the age of exposure. In a recently published statement [10], the American Academy of Pediatrics (AAP) did not approve cannabis and cannabinoid use in children due to concerns about brain development and long-term cognitive effects. In the statement, the AAP warns that marijuana can affect memory and concentration and interfere with learning, motor control, coordination, judgment, reaction

time, tracking ability, and enhanced vulnerability to addiction and psychiatric disorders in later life. Despite this, the AAP's position does allow exceptions. It acknowledges that "marijuana may currently be an option for cannabinoid administration for children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate."

In conclusion, few scientific studies have systematically investigated the long-term impact of cannabis use. It is clear that more studies are needed to fully understand the long-term impact of exposure to these compounds as well as the effectiveness of these compounds specifically in children and adolescents.

#### ANTI-CANCER EFFICACY OF CANNABINOIDS: PRECLINICAL EVIDENCE

The ability of cannabinoids to reduce tumor growth was reported for the first time by Munson et al. in 1975 [11]. They showed by in vitro and in vivo experiments that several phytocannabinoids, including THC, decreased Lewis lung adenocarcinoma proliferation in a dose-dependent manner. Nevertheless, it was not until the 2000s that the interest in these compounds as anti-cancer agents was renewed, predominantly due to the work of Guzman [12] in gliomas, and the demonstration of cannabinoids' anti-cancer effects on various types of tumors [6]. The anti-tumorigenic effect of the endo- and phytocannabinoids was demonstrated in several in vitro and in vivo models of a wide variety of adult tumors including glioma, prostate, breast, leukemia, lymphoma, pancreas, melanoma, thyroid, colorectal and hepatocellular carcinoma tumors [13] [Table 1]. Significant levels of the cannabinoid receptors – CB1 and CB2 – were found to be highly expressed in these tumors especially in comparison

**Table 1.** Anticancer mechanisms of endocannabinoids and phytocannabinoids

Cannabinoids	Compound	Cancer type	Anti-cancer effect	Receptor involved	Mechanism of action	Reference
Endocannabinoids	AEA	Breast	Reduction of cancer cell viability Inhibition of cell proliferation	CB1 CB1	Cell cycle blocking at the G1-S phase Regulates Raf-1/ERK/MAP pathway, Wnt/ $\beta$ catenin signaling	Melck 2000
	AEA	Prostate	Inhibition of cell proliferation Inhibition of EGF-induced proliferation	CB1	Blocking of cell cycle at G1 phase and down-regulation of EGF receptors	Mimeault 2003
Phytocannabinoids	$\Delta^9$ -THC	Breast	Inhibition of tumor invasion	CB2	Decreasing MMP2 activity	Caffarel 2010
	$\Delta^9$ -THC	Prostate	Cancer cell death and induction of apoptosis	Receptor-independent mechanism	PI3K/Akt and Raf-1/ERK1/2 pathway	Ruiz 1999
	$\Delta^9$ -THC	Lung	Reduced lung metastases	CB1	EGFR/ERK1/2, c-Jun-NH2-kinase1/2, and Akt pathway	Preet 2008
	$\Delta^9$ -THC	Glioma	Apoptosis ER stress-mediated autophagy	CB1, CB2	MMP-2 pathway	Blazquez 2008 Salazar 2009
	$\Delta^9$ -THC	Cervical	Reduced invasiveness	Receptor-independent mechanism	Decreased MMP-2 expression	Ramer 2008
	CBD	Breast	Induction of apoptosis	CB2, TRPV1	Enhancement of reactive oxygen species	Ligresti 2006 Shrivastava 2011
	CBD	Prostate	Anti-proliferative and pro-apoptotic effects	TRPM8	TRPM8 antagonism, down-regulation of androgen receptor, p53 activation and elevation of reactive oxygen species	De Petrocellis 2013
CBD	Lung	Anti-invasive action	CB2, TRPV1	Decrease of plasminogen activator inhibitor-1 Cox-2 and PPAR- $\gamma$ regulation	Ramer 2010	

AEA = anandamide, THC =  $\Delta^9$ -tetrahydrocannabinol, CBD = cannabidiol, ER = endoplasmic reticulum

with normal tissues [14,15], and were highly correlated to tumor progression, tumor aggressiveness and disease outcome [14].

The exact mechanism of action of cannabis remains unclear. Cannabinoids have been shown to cause anti-tumor effects by various mechanisms, including induction of cell death (apoptosis), inhibition of cell growth, and inhibition of tumor angiogenesis invasion and metastasis [6,16-19]. Processes such as ceramide production, endoplasmic reticulum (ER) stress, autophagy, angiogenesis and matrix remodeling also appear to regulate the anti-tumor activity of cannabinoids [20]. At the molecular level, CB1 and CB2 receptor activation leads to various events affecting Ca<sup>2+</sup> and K<sup>+</sup> channels, modulation of adenylyl cyclase and cyclic AMP (c-AMP) levels, and changes in various signaling pathways, including AKT/mTOR complex 1, MAPKs, ERK1/2, JNK, up-regulation of stress-associated transcription factor p8, down-regulation of MMP2, and VEGF signaling [6].

Our group studied the effects of administration of THC to glioblastoma multiforme (GBM) cell lines and showed that administration of THC results in a significant decrease in cell viability [Figure 1A] via a mechanism that appears to elicit G1 arrest [Figure 1B]. Western blot analyses revealed the THC-

altered cellular content of proteins that regulate cell progression through the cell cycle. The cell content of E2F1 and cyclin A, two proteins that promote cell cycle progression, were suppressed whereas the level of p16<sup>INK4A</sup>, a cell cycle inhibitor, was up-regulated [Figure 1C]. The decrease in E2F1 levels resulted from proteasome-mediated degradation and was prevented by proteasome inhibitors [Figure 1D+E] [21].

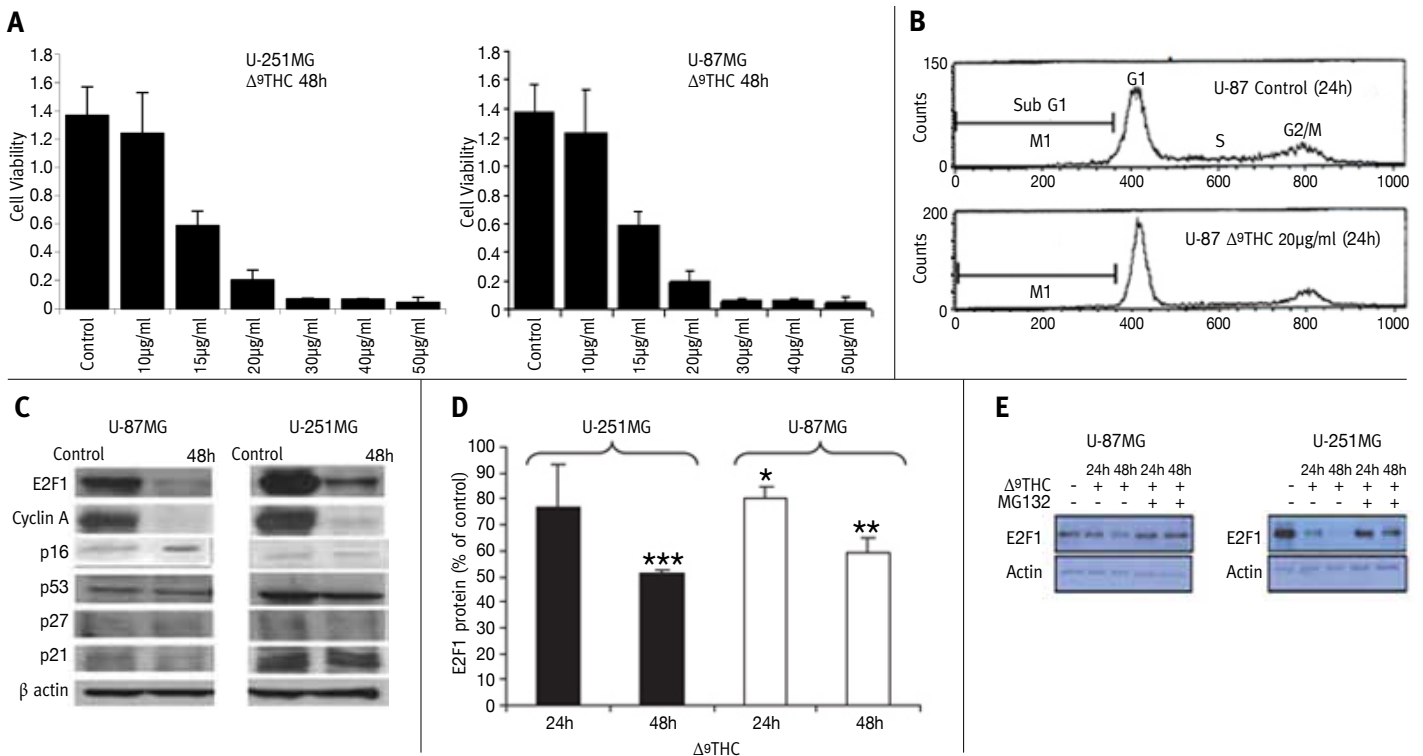
Finally, although most of the studies propose the anti-tumor efficacy of cannabinoid agonists, a few studies suggest a potential increased cancer risk following cannabinoid exposure in breast, hepatoma, and lung cell lines. In addition, a few studies have shown that, under certain conditions, cannabinoid treatment can stimulate cancer cell proliferation in vitro due to reduced immune function [22].

**ANTI-CANCER EFFICACY OF CANNABINOIDS: CLINICAL EVIDENCE**

Clinical trials conducted on medicinal cannabis are limited. However, the emergence of preclinical studies demonstrating the anti-tumor effects of cannabinoids are growing in number and have formed the basis of limited clinical studies that are beginning to shed light on the translational value of

**Figure 1. THC induces cell death in human glioblastoma multiforme cell lines through G0-G1 transition (G1 arrest) [21]**

**[A]** Dose-dependent effect of THC on cell viability is shown by the MTT assay. U87-MG and U251-MG cells were treated with increasing concentration of THC for 48 hours. **[B]** Effect of THC on induction of G0/1 arrest. The fractions of cells in G1 phase increased with the reduction of cells in S phase and G2 phase after treatment with 20 µg/ml THC for 48 hours in U87-MG. **[C]** Western blot analyses revealed a THC-altered cellular content of proteins that regulate cell progression through the cell cycle. **[D]** THC decreases E2F1 protein levels in both human GBM cell lines. **[E]** The decrease in E2F1 levels resulted from proteasome-mediated degradation and was prevented by the proteasome inhibitor MG132.



the preclinical work. There has been only one clinical trial examining the effects of THC on cancer [12]. In this first phase I human study Guzmán et al. [23] studied intracranial administration of THC to nine patients with recurrent GBM. Treatment with THC decreased tumor growth and tumor progression, as assessed by magnetic resonance imaging and biomarker expression, in at least two of the nine patients studied (Clinical trial ID# NCT01812603). Importantly, intracranial administration of THC was found to be a safe and tolerable approach with no apparent psychoactive effects. However, the study is limited by the small sample size, lack of a control group, and the study design's inability to comment on the effects of THC on survival time [23].

A clear limitation of the current human studies evaluating the anti-cancer effects of cannabinoid compounds is the small patient size. To date, no study findings have been replicated in multiple cohorts. Moreover, the measured outcomes and study designs are often variable across trials, making it difficult to compare their findings. There are two ongoing clinical studies aimed at evaluating the anti-tumor activity of cannabinoid use. The first is a safety study comparing nabiximol with placebo

(both with dose-intense temozolomide) in patients with recurrent GBM (Clinical trial ID# NCT01812616), and the other is a study of pure CBD as a single-agent therapy for solid tumors (Clinical trial ID# NCT02255292). Currently, there is insufficient evidence that cannabis or THC should be used for their anti-tumor properties outside of a clinical trial.

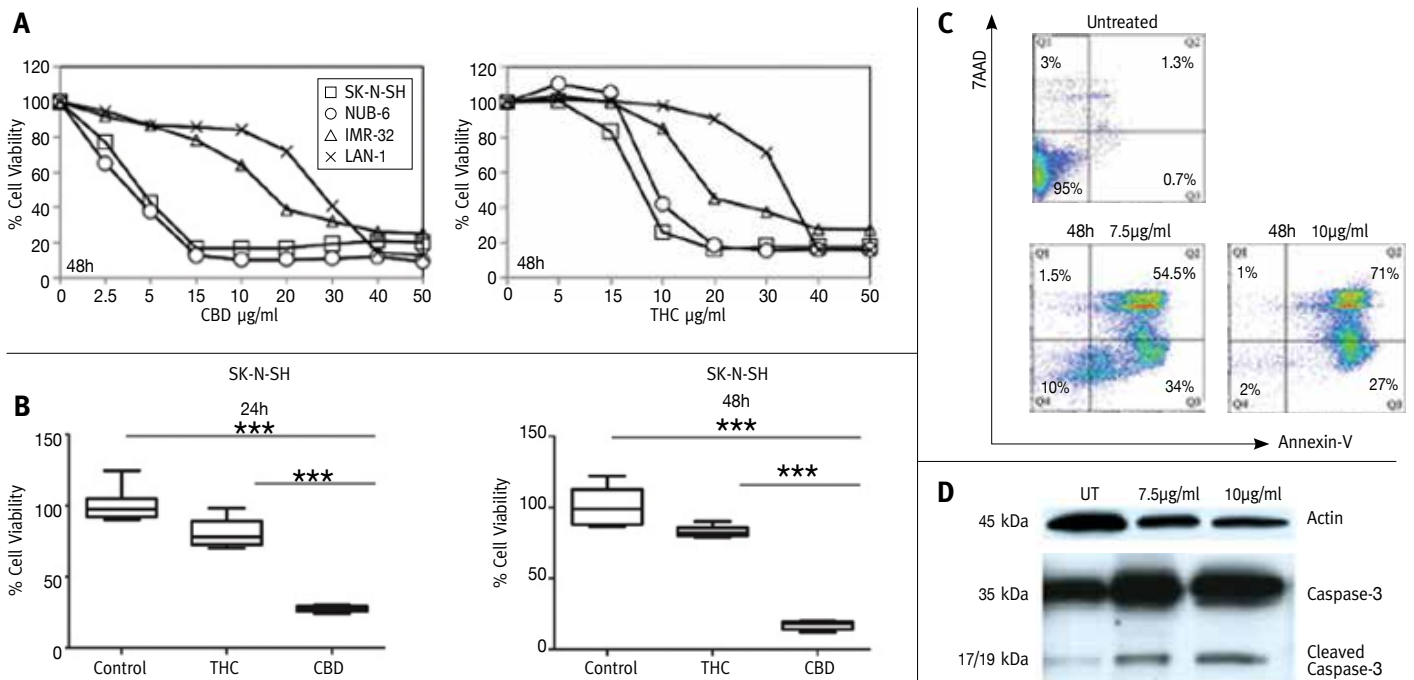
**ANTI-CANCER EFFECT OF CANNABINOIDS ON PEDIATRIC TUMORS**

There are no published clinical studies describing the use of cannabinoids in pediatric patients. There are, in fact, only a few anecdotal case reports that demonstrate regression of tumor during cannabinoid treatment that was given with palliative intent to terminally ill children [24,25].

Basic research exploring the putative anti-tumorigenic properties of cannabinoids in pediatric tumors is still limited, and the molecular mechanisms underlying the anti-tumorigenic effect are poorly understood. The anti-tumorigenic activity of cannabinoids was studied so far in only two pediatric tumors: alveolar rhabdomyosarcoma [26] and osteosarcoma [27]. We therefore investigated the role of cannabinoids in another aggressive pediatric tumor, neuroblastoma (NBL), which is the

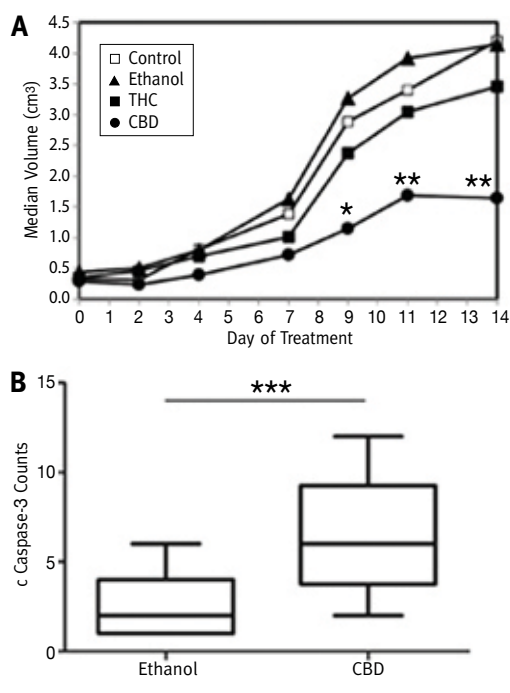
**Figure 2. CBD and THC reduce viability of NB cell lines in vitro with a better effect of CBD [29]**

**[A]** Cell lines SK-N-SH, NUB-6, IMR-32 and LAN-1 were incubated with increasing concentrations (0–50 µg/ml) of THC and CBD for 48 hours. Subsequent viability measurements are shown by means of MTT assay. **[B]** Mean ± STDEV of SK-N-SH cell viability following incubation with 10 µg/ml THC or CBD for 24 and 48 hours. \*\*\*denotes significant change relative to control ( $P = 0.0004$ ). **[C]** Apoptotic effect of CBD on SK-N-SH cells analyzed by annexin-V assay. Cells were treated with CBD in a dose-dependent manner (7.5 µg/ml, 10 µg/ml) for 48 hours and were stained with annexin and 7AAD. Q1 = percentage of death cells, Q2 = percentage of cells in late apoptosis, Q3 = percentage of cells in early apoptosis, Q4 = percentage of live cells. **[D]** Apoptotic effect of CBD on SK-N-SH cells analyzed by caspase 3 assay. Cells were treated with increasing doses of CBD (7.5 µg/ml, 10 µg/ml) for 24 hours.



**Figure 3. CBD suppresses tumor growth in a mouse xenograft model and increases cleaved caspase-3 in treated xenografts [29]**

**[A]** Growth rate of SK-N-SH cell-derived tumor xenografts treated during 14 days with intraperitoneal injections of ethanol vehicle (n=12), 20 mg/kg THC (n=12), 20 mg/kg CBD (n=12) and control (un-treated) (n=12). Data represent tumor volume during 14 days of treatment. \* $P < 0.05$  and \*\* $P < 0.01$  for CBD treatment vs. ethanol. **[B]** Counts of cleaved caspase-3 immunoreactive cells from 18 x10 lens fields from xenografts of CBD and ethanol-treated mice.\*\*\* $P < 0.0001$  compared with ethanol.



most frequent extracranial solid tumor of childhood and which still carries a very poor prognosis despite a multimodal and intensive therapy [28]. The results obtained in our in vitro studies showed that THC and in particular CBD reduced the viability and invasiveness of NBL cells. The effect of CBD seemed to be mediated by apoptotic cell death, as demonstrated by morphology changes, annexin V assay, and increased expression of cleaved caspase 3 [Figure 2A-D]. Based on that first set of results, we studied the effect of CBD and THC on xenograft tumors generated in NOD/SCID mice from the NBL cell line SK-N-SH that already demonstrated the greatest sensitivity to the effect of those molecules in vitro. In accordance with the findings from the in vitro experiments, THC and CBD both reduced the xenograft growth rate, with CBD showing a superior effect [29]. The results obtained in our study indicate that of the two cannabinoids tested CBD was more effective on the NBL cell line and on xenografts in comparison to THC. As a potential therapeutic agent, CBD could have many advantages compared with psychoactive THC [30] because most – if not all – of the psychoactive effects of cannabinoids are produced

by activation of the central CB1 receptors. CBD, which has been shown to act independently of CB1, is devoid of psychoactive effect [31] and can serve as a more suitable treatment, especially in children. Additionally, CBD shares the palliative properties and low toxicity profile described for other cannabinoids, has none of the strong side effects associated with chemotherapeutic agents, and might have synergistic activity with well-established anti-neoplastic substances.

Given our positive results, we suggest that non-THC cannabinoids such as CBD might provide a basis for the development of novel therapeutic strategies without the typical psychotropic effects of THC that limit its use in pediatric patients.

**SUMMARY**

Overall, the cannabinoids, and specifically the non-psychoactive CBD, may show future promise in the treatment of cancer, but there are still many significant hurdles to be overcome. Questions surrounding the effects of chronic cannabinoid use continue to increase especially with regard to its use in pediatric patients. Currently, much of the data are based on animal data and small trials and are outdated. Moreover, the results from studies lack sufficient depth of understanding and do not allow the acceptance and use of cannabinoid outside a clinical study.

Finally, while most eyes have been set on the presidential race in the U.S. during the 2016 election, additional states vote to legalize the use of marijuana. This decision reflects an increasing change and a shift in attitudes to cannabis use and reinforces the need to further conduct more robust preclinical and clinical studies that will increase our knowledge on the effectiveness and consequences of the use of these compounds in general and in children in particular.

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**“Cowardice asks the question, ‘Is it safe?’ Expediency asks the question, ‘Is it politic?’ Vanity asks the question, ‘Is it popular?’ But, conscience asks the question, ‘Is it right?’ And there comes a time when one must take a position that is neither safe, nor politic, nor popular but one must take it because one’s conscience tells one that it is right”**

Martin Luther King, Jr (1929-1968), American Baptist minister and leader in the Civil Rights Movement. He helped organize the 1963 March on Washington, where he delivered his famous “I Have a Dream” speech. In 1964 King received the Nobel Peace Prize. Following his assassination in Memphis, Tennessee in 1968, riots broke out in many U.S. cities. King was posthumously awarded the Presidential Medal of Freedom and the Congressional Gold Medal. Martin Luther King Jr. Day was established as a holiday in numerous cities and states and as a U.S. federal holiday in 1986. Hundreds of streets in the U.S. have been renamed in his honor. The Martin Luther King Jr. Memorial on the National Mall in Washington, D.C., was dedicated in 2011