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THC: a Promising Treatment for Acute Leukemia

Despite its harmful physiological and psychological effects, THC has been proven to be a promising treatment for acute leukemia. This antitumor efficacy has been demonstrated *in vitro*, *ex vivo*, and *in vivo*.

Background Information of THC and Acute Leukemia

THC is the principal active constituent of cannabis (marijuana), which was introduced into New England in 1629 and remained a major crop in North America until after Civil War (Boyce, 1900, p. 35). However, because of the harmful physiological and psychological effects, cannabis has then been banned globally: by 2016, medical cannabis is legal in only 28 states in the U.S. and around 15 countries in the world, with most cannabis trades still taking place in black markets ("Legal Medical", 2016). While the exploration of THC's medical effects is highly limited, however, cultivation of cannabis for therapeutic use is not at all new ("History of", 2015). History of THC's medical values are documented across many cultures in many forms, such as written reports in a Chinese medical reference dating from 2737 B.C. ("History of", 2015). Additionally, it has been previously suggested by several cancer models that THC – more precisely, its main isomer (–)-*trans*-Δ^9-tetrahydrocannabinol (also known as dronabinol) – have antitumor efficacy (Rieder et al., 2010). Being interested by these discoveries, scientists and doctors have recently examined the effects of THC on acute leukemia (Kampa-Schittenhelm et al., 2016).

Leukemia is cancer of the blood cells, and different types of leukemia vary in the type of blood cell that becomes cancer. The treatment for leukemia generally depends on whether it is acute or chronic – acute leukemia undergoes malignant transformation quickly and requires immediate treatment, whereas chronic leukemia develops slowly over time. Leukemia is also classified as lymphocytic or myelogenous – lymphocytic leukemia is characterized by abnormal cell growth in the marrow cells crucial to the immune system, while meylogenous leukemia occurs on marrow cells that mature into blood cells and platelets ("Leukemia", n.d.). Therefore, the four broad classifications of leukemia are acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia, with many subtypes under each category.

Interest in medicinal use of THC against acute leukemia grows recently with the discovery of cannabinoid receptors, protein molecules that are located throughout the body and receive chemical signals that affect various physiological processes such as mood and memory (Makie, 2008). There are two known types of cannabinoid receptors, CB1 and CB2. Normally, these cannabinoid receptors bind to endocannabinoids, or cannabinoid chemicals that naturally occur in the body (McKallip et al. 2002). These endocannabinoids send chemical messages along the nervous system like neurotransmitters and influence its regular function (Volkow, 2017). It has been suggested that through acting with these cannabinoid

receptors (discussed more in depth later), THC can lead to apoptosis (cell death) in acute leukemia cells and thereby may be used to treat the cancer (Powles et al. 2005). As some laboratory and clinical evidence demonstrates positive results, this paper will attempt to investigate whether THC is a promising treatment that should be further studied and administrated more commonly on acute leukemia patients.

How THC Induces Apoptosis

THC is similar in molecular structure to the naturally occurred endocannabinoids such as anandamide [insert Fig. i]. Therefore, THC is able to bind to the cannabinoid receptors, CB1 and CB2, as a competitive inhibitor and disrupt the body's normal mental and physical functions (Yamamoto et al., 1998). Despite the side effects, such as impaired memory and reduced learning abilities, that this competitive inhibition may cause, THC is proved to induce apoptosis of acute leukemia cells through the ligation (the binding of a molecule to a site on its target protein) of cannabinoid receptors (Bifulco et al., 2006; Powles et al. 2005). As apoptosis eliminates harmful or unwanted cells from the body, it plays a crucial role in biological development and health maintaining (Rieder et al., 2010). Thus, understanding the precise receptors and pathways of THC induction of apoptosis could contribute to the development of a more promising THC treatment against acute leukemia.

In general, effects of THC can be mediated by the aforementioned cannabinoid receptors, CB1 and CB2 (Lombard et al. 2005). These two receptors appear in different locations in the body: CB1 receptors are found extensively in several influential brain regions, while CB2 receptors are present mainly in immune cells and only a few neurons (Makie, 2008). Theoretically, because of the areas affected, high toxicity may be caused by over-activating CB1 receptors, but triggering CB2 receptors can avoid the harmful psychoactive effects of THC on the body to a large extent (Jia et al., 2006). In order to determine the specific receptor responsible for the pro-apoptosis efficacy of THC, McKallip et al. (2002) examined these two types of receptors in an experiment where THC induced apoptosis in human acute leukemia lines *in vitro*. The result was that only CB2 receptors were expressed according to the screening of these cell lines (McKallip et al., 2002). Consequently, it can be concluded that THC leads to apoptosis of acute leukemia cells mainly via the ligation of CB2 receptors.

Condie et al. (1996) further illustrated the mechanism of THC induction of apoptosis on many acute leukemia cell lines. For example, in T cell leukemia cell line, THC binds to CB2 receptors and influences the T cell through inhibiting the activity of adenylate cyclase, an enzyme that normally acts on adenosine triphosphate (ATP) (Condie et al., 1996). As a result, this inhibition blocks the ATP stimulation of cAMP, a second messenger used for intracellular signal transduction (Condie et al., 1996). Therefore, the activation of several proteins regulated by cAMP, such as protein kinase A and CRE, is decreased (Condie et al., 1996). This process also disrupts the function of the cAMP-regulated proteins that contribute to the growth of white blood cells, especially one of its subtypes, T cell (Condie et al., 1996). Thus, by blocking the normal function of the regulatory proteins of T cell, THC can lead to T cell apoptosis and thereby alleviates acute T cell leukemia (Condie et al., 1996). Even though

the particular proteins affected vary from different types of acute leukemia, the overall mechanisms are similar; likewise, THC may induce apoptosis in other types of acute leukemia (Condie et al., 1996).

The molecular changes on acute leukemia cells caused by THC make up two different pathways of apoptosis: the extrinsic pathway through death receptors, and the intrinsic pathway via mitochondria (Lombard et al., 2005). The intrinsic pathway is triggered by an imbalance of anti-apoptotic and pro-apoptotic proteins that controls the permeability of the mitochondrial membrane, causing leakage of certain enzymes from the electron transport chain of mitochondria into the cytosol (Kroemer and Reed, 2000). This leakage leads to reaction among enzymes that breaks down proteins and peptides and results in apoptosis (Kroemer and Reed, 2000). As for the extrinsic pathway, it is initiated by the ligation of death receptors, forming Death Inducing Signaling Complex that eventually leads to cell death (Kroemer and Reed, 2000). Both pathways play a role in THC induction of apoptosis on acute leukemia cells.

Evidence of THC's Pro-apoptotic Efficacy

Proof-of-principle data from experiments and researches confirm the pro-apoptotic efficacy of THC in a broad range of acute leukemia cell lines and blast cells cultured *ex vivo* and *in vitro*. In one study, Kampa-Schittenhelm et al. (2016) proved that THC was able to induce apoptosis in all acute leukemia cell lines, including but not limited to acute T cell leukemia, acute myeloid leukemia, and acute monocytic leukemia. In addition, the efficacy of THC was exhibited in a dose dependent manner, meaning the quantity of THC doses applied shows a direct relationship to the biological response [insert Fig. ii] (Kampa-Schittenhelm et al., 2016).

It has also been demonstrated that THC was capable of reducing viable native blast cells (a primitive blood cell often found in the blood of patients with leukemia) cultured *ex vivo*. (Kampa-Schittenhelm et al., 2016). Samples of blast cells were extracted from patients with acute lymphatic leukemia, acute myeloid leukemia, and acute lymphoblastic leukemia; and a considerable reduction of viable blast cells was observed after a 48-hour exposure to THC (Kampa et al., 2012; Kampa-Schittenhelm et al., 2016). The result also showed THC has a more significant effect on patients with acute lymphatic leukemia than those with acute myeloid leukemia [insert Fig. 3] (Kampa-Schittenhelm et al., 2016). The outcomes of these experiments and researches further prove that THC is capable of mediating antileukemic activity.

Anecdotal results of a clinical case further validated THC's antitumor efficacy *in vivo*. This case study was on a 14-year-old patient who was diagnosed with a very aggressive form of acute lymphoblastic leukemia (Singh & Bali, 2013). The attempts to treat this patient with standard bone marrow transplant, aggressive chemotherapy, and radiation therapy all failed after 34 months (Singh & Bali, 2013). Without any other solutions, the family decided to administer THC extracts orally to the patient, which proved to be an effective treatment with further indications of the aforementioned positive dose-dependent correlation (Singh & Bali, 2013). The clinical observation of this case

suggests that THC is able to effectively control the disease, as long as the dose is determined correctly depending on various factors (Singh & Bali, 2013).

The Future of THC Treatment for Acute Leukemia

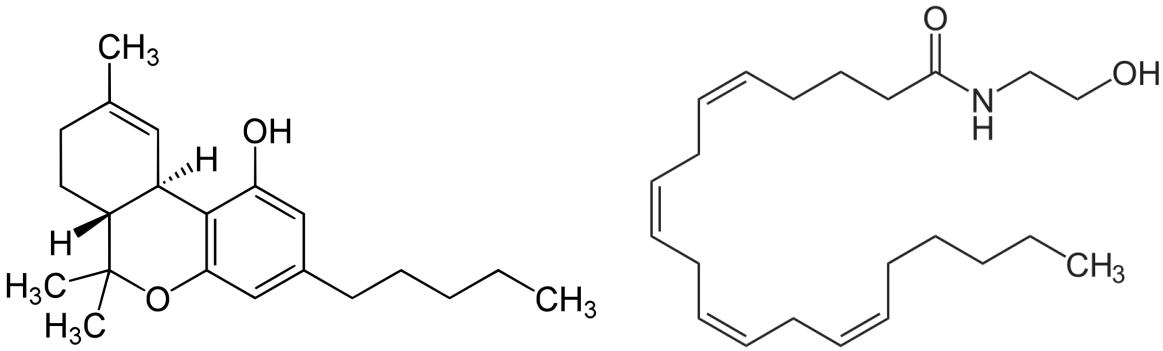
Kampa-Schittenhelm et al. (2016) demonstrated that a more systematic and widely accepted THC treatment against acute leukemia *in vivo* was achievable. With detailed drug information provided by the safety profile of THC (drug information of Marinol® - FDA), Kampa-Schittenhelm et al. (2016) extracted blood plasma from an acute leukemia patient treated with THC and showed signs of apoptosis of cancer cells. This patient was not going through any other antitumor therapies (Kampa-Schittenhelm et al., 2016). His blood plasma was immediately used to culture other acute leukemia cells *in vitro*, and apoptosis was observed (Kampa-Schittenhelm et al., 2016). Therefore, this experiment supports that a pro-apoptotic efficacy of THC is obtainable *in vivo*.

When it comes to the psychoactive side effects of THC, they may be minimized by slowly increasing the dose over time, which would build up the patient's tolerance, as shown in previous anecdotal cases (Singh & Bali, 2013). Meanwhile, the demonstrated pro-apoptotic efficacy of THC may suggest an alternative approach to treating acute leukemia: although mainly examined *ex vivo*, the fact that the ligation of CB2 receptors induces apoptosis in acute leukemia cells indicates that targeting CB2 may be another method of treating the cancer. In other words, if the concerns of legalizing medical THC widely still hinder its exploration, future studies could focus on the possibility of upregulating the patient's endocannabinoids or administrating non-psychoactive cannabis that has similar molecular structure as THC, in order to achieve the same medicinal effects through the ligation of CB2 receptors (Palazuelos et al., 2006). Therefore, treating acute leukemia while bypassing THC's psychoactive effects can be made feasible.

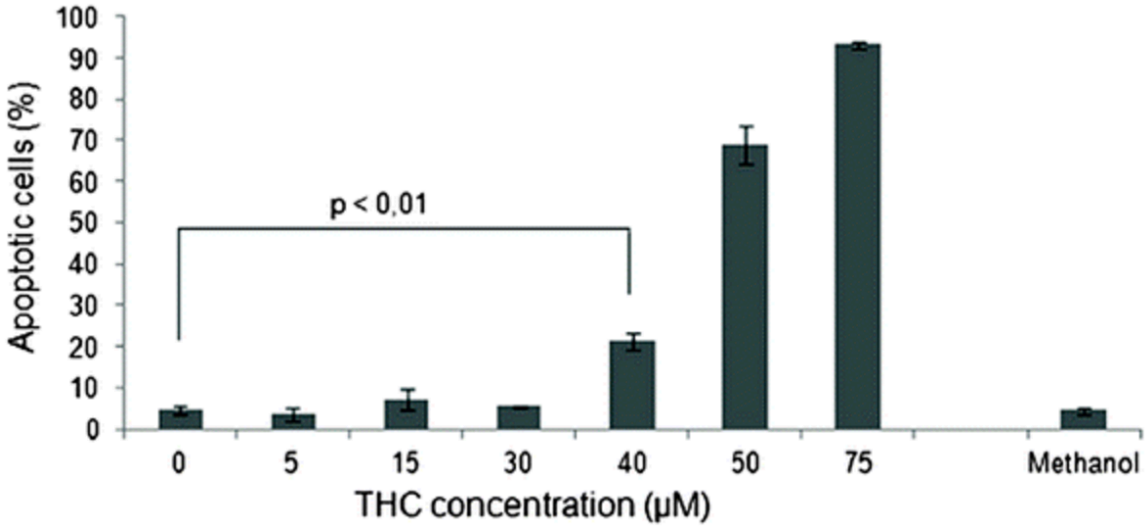
It goes without saying, however, that no matter the future therapies involves THC, endocannabinoids, or other types of cannabis; much more research and clinical trials need to be completed in order to ascertain the benefits of such treatments. Promising rationale has been provided for the medical use of THC in various entities of acute leukemia, thereby this approach should be further evaluated.

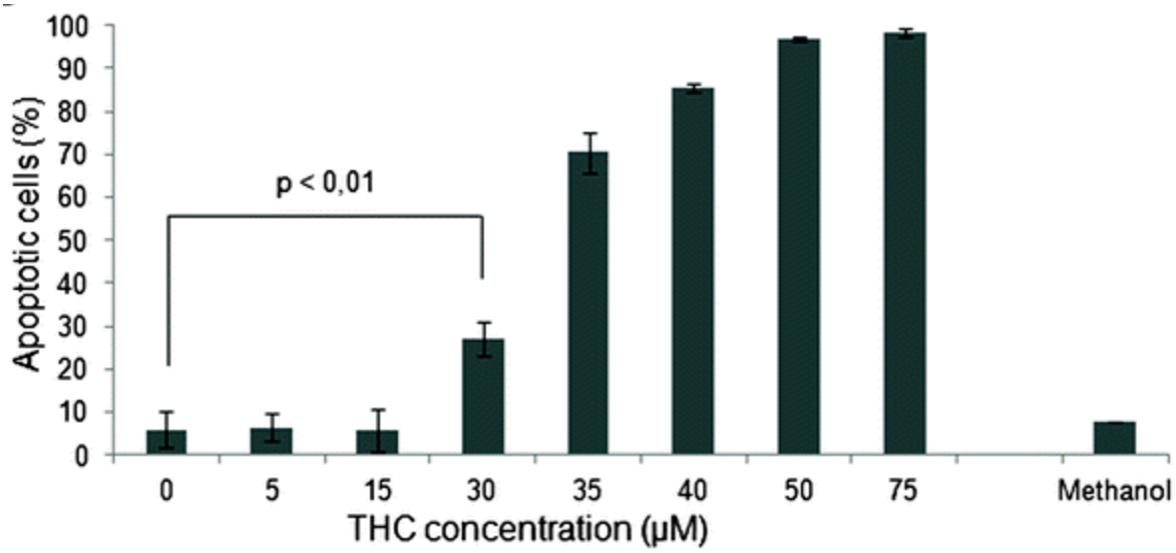
Figures

1. Skeletal formulas of THC (left) and Anandamide (right). Both molecules contain hydroxyl and methyl groups, and their three-dimensional shapes are very similar. But anandamide is more fragile than THC and breaks down quickly in the body, which explains why it doesn't produce a psychoactive effect like THC (Tetrahydrocannabinol, n.d.; Anandamide, n.d.).

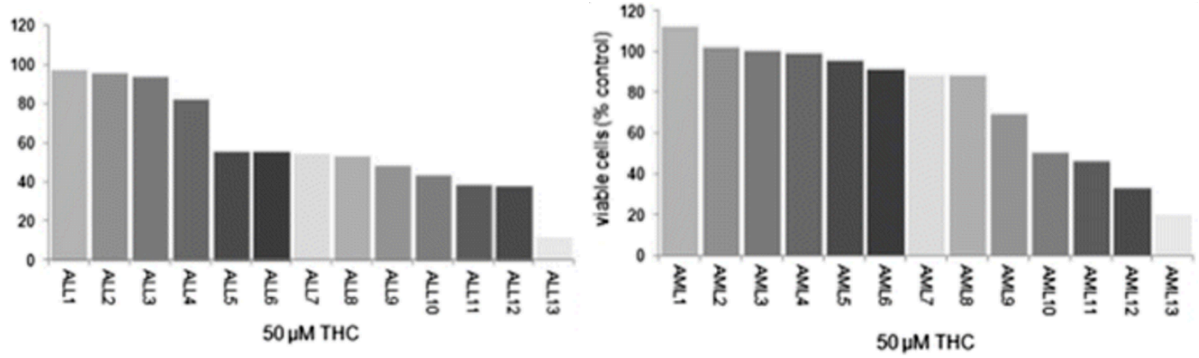


2. Dose-effect curves of dose-dependent THC treatment on Jurkat cells(top), a human T cell line used to study acute T cell leukemia, and MOLM13 cells(bottom), an acute monocytic leukemia cell line, are shown (Kampa-Schittenhelm et al., 2016).





3. Percentile waterfall plots are provided for all tested samples of patients with acute lymphatic leukemia (left) and acute myeloid leukemia (right) (Kampa-Schittenhelm et al., 2016). Patients with acute lymphatic leukemia appeared to be more sensitive to THC (Kampa-Schittenhelm et al., 2016).



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