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Review Article

Pharmacological Properties of Δ (9) - Tetrahydrocannabinol: A Review

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Abstract: ***Background / Objective:*** Δ(9) - Tetrahydrocannabinol (THC) is identified as the major active component of marijuana, it can interact with several pharmacological targets by involving cannabinoid receptors. Up to this point, many studies have proven that THC has many benefits with different mechanisms of action. This review aims to examine pharmacological effects contained in the Δ(9) - Tetrahydrocannabinol compound that can be used by medical field for treatment. ***Methods:*** We summarized the studies on the pharmacological properties of THC compound published from 2010 to 2020 from database such as PubMed, ScienceDirect, and Google Scholar. The search terms that were used are as follows: "Δ(9) -Tetrahydrocannabinol OR Tetrahydrocannabinol" AND "Potential OR Properties OR Pharmacological OR Effects". ***Results:*** The results of 15 studies were included in this review based on our eligibility criteria with 6 animal studies, 4 human studies, and 5 in vitro studies that showed THC compound has many pharmacological effects, where the benefits of those effects are useful in the treatment. ***Conclusions:*** THC has potential in its use as analgesics, anti-inflammatory, anticancer, anti-nausea and vomiting, anti-tumor, hepatoprotective, and an indication of immunosuppression. More research is needed to evaluate the pharmaceutical potential of THC and the better comprehension of its pharmacological mechanisms.

Keywords: Marijuana, Cannabinoid, Δ(9) - Tetrahydrocannabinol (THC), Pharmacology.

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INTRODUCTION

Δ(9) - Tetrahydrocannabinol (THC) is known as the major active component of marijuana, and it can interact with multiple pharmacological targets [1] involving certain cell cannabinoid receptors surface [2]. Marijuana consists of three different bioactive molecules, namely terpenoids, flavonoids, and cannabinoids, whereas from various types of cannabinoids, THC is the most studied cannabinoid [3].

Cannabinoids are known to have pharmacological potential and are widely used in medical applications, such as for the medication of spasticity and chronic pain. In addition, cannabinoids have also been related with improvements in nausea and vomiting caused by chemotherapy, sleep disorders, weight gain in HIV, and Tourette's syndrome [4]. Cannabinoids may have anticancer activity in preclinical in vivo and in vitro studies [5]. At present, THC capsules and their synthetic analog nabilone are approved for this purpose. THC capsules are used for the treatment of AIDS/ HIV-induced anorexia, and nausea and vomiting that are induced by chemotherapy [6], while nabilone is used in severe nausea and vomiting therapy associated with chemotherapy in many countries (Canada, Mexico, United States, and United Kingdom) [7]. Nabilone is also indicated in the medication of various types of pain such as pain in cancer people, including even neuropathic pain, chronic non-cancer pain, fibromyalgia, and seizures related with multiple sclerosis [8].

The therapeutic potential of cannabinoids in medication is of course not limited to the palliative effects noted above. Until now, many studies have provided evidence that THC has many benefits in treatment with different mechanisms of action and research on this compound much has been done in the past, therefore this review aims to examine what pharmacological effects are contained in the Δ(9) - Tetrahydrocannabinol compound that can be used by the medical field in the treatment based on the results of recent research (in the last 10 years).

DATA COLLECTION

Comprehensive searches were undertaken to find evidence in the literature on pharmacological properties in either animal studies, human studies, or in vitro studies of Δ(9) - Tetrahydrocannabinol compound in three different online bibliographic databases: PubMed, ScienceDirect, and Google Scholar. The search terms used were "Δ(9) - Tetrahydrocannabinol

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OR Tetrahydrocannabinol" AND "Potential OR Properties OR Pharmacological OR Effects". All abstracts and full-text articles were collected, reviewed, and summarized. The most relevant articles were selected for screening and inclusion in this review.

RESULTS AND DISCUSSION

The pharmacological activity of the Δ(9) - Tetrahydrocannabinol (THC) compound that has potential in treatment has been demonstrated in the animal studies, human studies, and in vitro studies. A total of 15 studies were included in this study based on our eligibility criteria. The study of the therapeutic potential of THC is summarized as follows:

1. Analgesic activity

THC has been known to produce analgesic effects on chronic pain in humans [9]. Besides, THC has also been shown to be synergistic in several research results when combined with Cannabidiol (CBD), including inhibition of glioblastoma cell proliferation in vitro [10]. CBD could also potentiate the psychoactive and physiological effects of THC in mice, most possibly by defering metabolism and relieving THC via the CYP450 enzyme action that metabolizes both drugs [11]. This suggests that there is analgesic potential of THC to be discussed in serious discussion about therapy options and the development of its preparation in the treatment of pain. The following are the results of several studies regarding the analgesic effect of THC compound:

Tabel-1: Analgesic properties of Δ (9)- Tetrahydrocannabinol

Pharmacological Effects	Methods used /Study design	Subject/Animal or Cell/specimen	Reported activity	Region	References
Analgesic	Parallel-group study	Patients with pain associated with cancer	Twice as many patients taking THC: CBD showed a reduction of more than 30% from baseline pain Numerical Rating Scale (NRS) score when compared with placebo.	UK	[12]
Analgesic	Randomized, double-blind, placebo-controlled	Cannabis-naive men aged 24 to 34 years volunteered for the study	The data reveal a significant positive correlation between the effect of THC on the BOLD response of the right amygdala and the analgesic effect of THC. Where THC can reduce the discomfort of capsaicin-induced hyperalgesia.	UK	[13]
Analgesic	A randomized, single-dose, double-blinded, placebo-controlled	Diagnosed patient with CP (chronic pancreatitis)	Δ (9) Tetrahydrocannabinol (THC) in single dose was reported to be ineffective in reducing chronic pain caused by chronic pancreatitis (CP) but was well tolerated with only mild or moderate AE.	Nijmegen	[14]
Analgesic	Experimental/ In-vivo	Adult female Sprague-Dawley rats bred	THC can reduce migraine-like pain when given in the right dose (0.32 mg / kg) and immediately after AITC. The antimigraine effect of THC is mediated by the CB1 receptor. An effective method used to assess migraine treatment is running wheel.	USA	[15]

Human studies

The study conducted by Johnson *et al*., [12] by using a parallel-group study method, in which patients enrolled in the study were randomly selected through screening from 192 patients for 25 months with progression stage cancer and uncontrolled cancer pain despite long-term use of opioids. This study consisted of three groups, namely the THC: CBD extract group, the THC extract group, and the placebo group. The results of this study reported that THC: CBD group was superior in pain relief, with twice as many patients experiencing a 30% reduction in pain from baseline pain NRS score when compared to placebo, while THC performance was similar to the placebo group. So it can

be concluded that in humans the CBD-THC 1: 1 combination can produce better pain relief than THC alone [12].

In addition, Lee *et al*., [13] also revealed that THC has an analgesic effect. This study was performed to examine the effect of capsaicin-induced THC on its role in providing analgesic effects. Capsaicin sensitization can increase blood-oxygen-level-dependent (BOLD) activity during pain provocation in the thalamus. The study found a significant positive correlation in the THC effect on the BOLD response of the right amygdala and the analgesic effect of THC, this finding was interpreted as a reduction in the discomfort of capsaicin-induced hyperalgesia. The study also found that THC has different analgesic effects depending on the intensity and discomfort of ongoing pain [13].

The results of research conducted by Vries *et al*., [14] with two groups of patients receiving treatment doses, where the first group received a single dose of Δ(9) - Tetrahydrocannabinol and the other group received a single dose of diazepam. The analysis results showed no effect of Δ (9) - Tetrahydrocannabinol treatment compared with diazepam on VAS (visual analog scale) delta pain at rest. That means a single dose of Δ(9) - Tetrahydrocannabinol is not effective in decreasing chronic pain due to CP (chronic pancreatitis) but was well tolerated with only mild or moderate AEs (Adverse events) [14].

Animal study

Research on the analgesic effects of THC compound that has been conducted by Kandasamy *et al*., [15] using experimental methods demonstrated that administration of THC at the right time and dose can prevent pain such as migraine pain in rats as assessed by the running wheel method, and demonstrated that the anti-migraine effect of THC was mediated by CB1 receptors. Giving THC as much as 0,32 mg / kg shortly after the initial of headache induced by allyl isothiocyanate (AITC) agonists can prevent depression due to the running wheel method. The injection of AITC can produce pain such as migraine pain as assessed by the decrease rotation of running wheel in rats. There was no antimigraine effect if THC is given 90 minutes after the AITC micro-injection, or the THC dose is lowered. The results of this study proved that THC has analgesic potential [15]. As for the involvement of the CB1 receptor in providing analgesic effects in this study, it can be confirmed because a lot of CB1 receptors are found in the brain area and it modulates nociceptive processing, wherein its distribution was similar with opioid receptors [16].

Therefore THC does not have sufficient evidence to recommend first-line treatment of cancer-related pain because the THC preparation used in every research were different, however, the results showed the advantages of an adjunct drug, so more clinical studies are needed to investigate the effects of THC [3].

2. Anti-inflammatory activity

It is known that THC induction can have anti-inflammatory effects by involving the CB2 receptor [17]. These agents could be used in the treatment of cancer that tends to develop inflammation for the growth of cancer itself. The following are in vitro and in vivo studies showing the active pharmacological profile of one of the cannabinoids (THC) which includes anti-inflammatory potential:

Tabel-2: Anti-inflammatory properties of Δ(9)- Tetrahydrocannabinol

Pharmacological Effects	Methods used /Study design	Subject/Animal or Cell/specimen	Reported activity	Region	References
Anti-inflammatory	Experimental	The human colon adenocarcinoma cell line HT29	Cannabinoids (one of which was THC) inhibited the COX enzyme, but in a higher concentration range compared to anti-inflammatory drugs (ie indomethacin).	USA	[18]
Anti-inflammatory	Experimental	MG-63 cell culture	CB2 cannabinoid receptors are involved in THC-induced anti-inflammation in MG-63 cells exposed to LPS.	Cina	[19]
Anti-inflammatory	Experimental	Rat	Giving THC orally 60 minutes before carrageenan can reduce inflammation in the hind legs of rats.	Canada	[20]

In vitro studies

The results of this experimental study done by Ruhaak *et al*., [18] discussed the evaluation of the inhibitory effect of the cyclooxygenase (COX) enzyme, which is an enzyme that catalyzes prostaglandin production from arachidonic acid. Evaluation in this

study was carried out on six main cannabinoids isolated from *Cannabis sativa*, were one of the cannabinoids included in this test was Δ(9) - Tetrahydrocannabinol, and plant material used in this study can modulate COX enzyme activity with IC50 (inhibition concentration 50) values ranging from $1.7 \cdot 10^{-3}$ to $2.0 \cdot 10^{4}$ M. This in vitro study used the human colon adenocarcinoma cell line HT29. In screening, it is observed that Δ(9) - Tetrahydrocannabinol can exhibit stimulation in specific doses (between $3.18 \cdot 10^{4}$ and $3.18 \cdot 10^{5}$ M) in the COX-1 and COX-2 inhibition test. From the results of this study it can clearly be concluded that cannabinoids can inhibit the cyclooxygenase enzyme in a higher concentration range then anti-inflammatory drugs (namely indomethacin) [18].

The involvement of THC in the study conducted by Yang *et al.,* [19] using experimental methods revealed that THC has an anti-inflammatory effect, one of which is influenced by the activation of the cannabinoid CB2 receptor so that it can reduce inflammation by increasing CB2 receptor expression, inhibiting upregulation of NF-κ B (nuclear factor-kappa B) and cofilin-1 expression and decreased the release of TNF-α (tumor necrosis factor), IL-1 β (interleukin-1 β), IL-6 (interleukin-6), and IL-8 (interleukin-8) from MG-63 cells (osteoblasts) stimulated by LPS (lipopolysaccharide). THC in doses can decrease the release of IL-6 induced by LPS in MG-63 cells. IL-6 is an index indicating the level of inflammation in MG-36 cells treated using LPS. As for the dosage being discussed, co-administration of THC (0.5, 5, and 50*μM)* could relevantly reduce the release of IL-6 from cells stimulated by LPS, this is increasingly clear that THC can induce anti-inflammation [19].

Animal study

An experimental study researched by Rock *et al.,* [20] also revealed that giving THC through oral gavage for 60 minutes before carrageenan administration can reduce inflammation in the hind legs of mice and produce anti-hyperalgesic effects. This research was experimentally carried out on rats induced by carrageenan to produce hyperalgesia, and then the animals were given 1000 μg / kg THC through oral gavage. Post hoc LSD analysis showed that the mice took significantly longer to lift inflamed legs in the 1000 THCI group than in the VEH-I group, this suggests analgesic properties at a dose of 1000 μg / kg of THC administered orally thereby reducing inflammation [20].

3. Anti-cancer activity

Several preclinical studies have shown THC has anti-cancer performance, as revealed by [21], wherein in vitro THC has been shown to fight breast cancer, lung carcinoma, skin carcinoma, pancreatic cancer, and prostate carcinoma [21]. The anti-cancer potential of THC compounds apart from the in vitro studies mentioned above can also be proven in this review through the following studies:

Tabel-3: Anti-cancer properties of Δ(9)- Tetrahydrocannabinol

Pharmacological Effects	Methods used /Study design	Subject/Animal or Cell/specimen	Reported activity	Region	References
Anti-cancer	Experimental	Patients undergoing surgical resection for primary EC	Cannabinoid receptors are strongly expressed in EC tissues. THC could inhibit the migration of human EC cells through the regulation of EMT and MMP-9 pathways.	Cina	[22]
Anti-cancer	Experimental	Tumor samples from patients with NSCLC	Cannabinoids could reduce the in vitro migration of the lung cancer cells lines used.	Spain	[23]
Anti-cancer	Experimental	Human breast adenocarcinoma cell lines	Pure THC or CDP could decrease the viability of T47D and MCF7 cells in a concentration-dependent manner. This suggests that THC or CPD can be used to manage breast cancer.	Spain	[24]

Human study

Data in a study conducted by Zhang *et al*. [22] with experimental methods in patients undergoing surgical resection for primary EC (endometrial cancer) and on para-tumor endometrial tissue showed that CB1 and CB2 receptors are more present in EC tissue than normal endometrium. Additionally, CB1 and CB2 receptor expression correlated positively with VIM (vimentin). The results also indicated that THC in concentration could inhibit cell growth. THC results in a significant reduction in cell migration and has the ability to suppress proliferation and migration of HEC-1B (human endometrial cancer-1b) and An3ca (human endometrial carcinoma) cells. THC also plays an

important role in EMT (epithelial-mesenchymal transition) tumors as well as in inhibiting the expression of MMP-9 (matrix metalloproteinase-9) in EC cells. MMP is functionally related to the network renovation process. This study also found that THC significantly inhibited MMP-9 secretion in HEC-1B and An3ca cells. This means that THC can regulate EC metastatic cells mediated by EMT and MMP-9. The results in this study also showed that MMP-9 mediating THC reduces EMT and cell mobility in endometrial cancer cell and has the potential to reveal that the transfer of these THC signals into cells via CB1 and CB2 receptors aims to develop anti-tumor capabilities [22].

In vitro studies

The results of research conducted by Milian *et al*., [23] used 157 tumor samples from patients with NSCLC (non-small cell lung cancer) showed that THC / CBD can inhibit the proliferation and expression of endothelial growth factor receptor (EGFR) in lung cancer cells, and inhibit the EMT in lung cancer cells. Besides, the research results also stated that cannabinoids can inhibit cell motility induced by epidermal growth factor (EGF) in cancer cells. From these results, it can be concluded, THC and CBD can suppress proliferation of cells and EMT. Besides, their combination can minimize the unwanted effects of THC [23].

A research conducted by Blasco-Benito *et al.* [24] using an experimental method and human breast adenocarcinoma cell lines showed the results that breast cancer treatment using pure THC or CDP (cannabis preparation) in concentrations can reduce the viability of one of the breast cancer cells, T47D. Similar experiments were carried out on MCF7 (Michigan cancer foundation-7) cells and found similar results. In addition, the results of this research also showed that THC effect on T47D cells is generated by CB2 receptor activation and the formation of free radicals. In addition, this study also analyzes what if cannabinoid-based therapy is given with cancer drugs, specifically, the researchers combined THC or CDP with tamoxifen and then applied them together in cell culture, finding that the viability of T47D cells decreased by means of additives, and when CDP was given in the same dose as THC it resulted in a marked reduction in tumor growth. This study confirms that the THC and CPD preparations have potential for their use in cancer treatment [24].

4. Anti-nausea and vomiting activity

Nausea and vomiting due to chemotherapy are important concerns for patients receiving chemotherapy. Therefore, the ability of THC compound which has the potential as anti-nausea and vomiting is useful in the development of drug preparations in the management of cancer patients in the future. The following are the results of several studies about the anti-nausea and vomiting effects of THC compound:

Animal studies

A study conducted by Limebeer *et al.*, [25] with an experimental method examined the anti-nausea effect of the CB1 agonist's receptor using a gaping nausea model conditioned on LiCl (lithium chloride)-induced cleft formation in mice. There were several experiments conducted by researchers. In the first experimental results, it was stated that systemic THC administration can weaken the conditioned gaping reaction induced by LiCl and it does not interfere with the suppression of hedonic reactions or CTA (conditioned taste avoidance). The experimental results also revealed that the mice pretreated with THC showed significantly less gaping reactions that were conditioned than the mice in the other pretreatment groups, which were not different from each other ($P < 0.025$) [25].

Research done by Rock *et al.*, [20] with experimental methods proved that THCA (tetrahydrocannabinolic acid) or it can be called the acid derivative of THC could potentially reduce conditioned cleft in rats. This is evidenced by one-way ANOVA which indicated a significant pretreatment effect. In addition, the comparison of post hoc LSD (least significant difference) showed that THCA at doses of 0.05 and 0.5 mg · kg - 1 could relatively reduce the LiCl-induced gap in the controls previously treated with VEH. Administration of THCA as much as 0.05 mg • kg - 1 can interfere with the causes of nausea by LiCl (lithium chloride) and SR (strontium) in the cortex in a way without blocking this effect. In addition, the results showed that THCA reduced the emesis caused by LiCi in shrews. This can be observed from the Bonferroni post hoc test which showed that giving both doses of THCA to shrews given LiCl after pretreatment, the vomiting experienced by these test animals is less than the control group given the previous VEH. The emesis effect appears to be suppressed by CB1 receptor mediation because mice in the THCA SR-0.05 pre-treatment group experienced more vomiting than the 0.05 THCA group. So the results of this study very clearly confirm that THCA has the potential to reduce gaping conditions in mice and vomiting in S. murinus [20]. Besides, THCA-A can also attenuate the induction of nausea in rats and vomiting in shrews through a mechanism that requires activation of CB1 reversible receptors with CB1 antagonist receptor [26].

Apart from the research mentioned above, other studies clearly proved that the cannabinoid and endocannabinoid systems can regulate nausea [27]. The endocannabinoid system itself can function to modulate the expression of nausea and vomiting [28, 29].

5. Anti-tumor activity

Cannabinoids is known as a suppressive agent for the anti-tumor immune response; hence, THC has recently been used in cancer research [21]. The mechanism of antitumor activity of THC is by causing apoptosis and depending on the cannabinoid (CB)

receptor [30]. However, the antitumor effect that is mediated by the CB receptor is highly dependent on the type of cancer present [31]. Here is study on the antitumor effect of THC compounds:

In vitro study

The results of a study by Gurley *et al.*, [32] by using experimental method and human GBM (Glioblastoma Multiforme) cell line U87MG which were analyzed for the quantification of phospho-proteins and apoptosis showed that by increasing the concentration of KM-233 (0.3 to 100 lM) in U87MG cells can reduce the value of EC50 (Effective concentration 50) significantly. KM-233 is a synthetic cannabinoid drug, a structural analogue of THC. In addition, the results also showed that administering KM-233 to U87MG cells could decrease membrane polarization, which was demonstrated by the incapacity of fluorescent staining to shape of red exciters in mitochondria for three hours, and depolarization was almost complete at six hours. In addition, there was a reduction in tumor area and 80% of tumor volume at dose of 12 mg / kg. For assess the toxicity potential, a histopathological analysis was performed on several organs, and there was no definite evidence of the toxicity of tissue injury with KM-233 administration. The results also showed that treatment using KM-233 significantly delayed tumor growth [32].

Many research teams are interested in conducting tests using cannabinoids for aggressive cancer. This is due to the direct activity and sensitivity of the tumor to first-line agents resulting from treatment with cannabinoids with a low toxicity profile. However, the response that results from such testing varies due to the heterogeneity of the tumor; therefore cancer patient medication goal is to expand the tumor predictive sign of which patient's tumor will react best to cannabinoids or in combination with first-line therapy [15].

6. Hepatoprotective activity

Animal study

Research on the hepatoprotective effect of THC compound has been carried out by Hochhauser *et al*. [33] by using experimental method with experimental animals: adult female rats, in-vivo results showed that giving THC can cause hepatocyte cells to experience less apoptosis so that less liver injury was detected in mice. 2 hours before inducting the liver ischemia/reperfusion (I / R) injury, giving THC resulted in less detectable liver I / R injury in mice treated with THC and it was also found from morphological identification that hepatocyte cell apoptosis was less than untreated mice. The results of this study proved that THC also has hepatoprotection potential [33].

7. Indication of immunosuppression

Animal study

A study conducted by Yang *et al.*, [19] by using experimental method reported that there is a strong indication of cell proliferation in mice caused by Staphylococcal enterotoxin B (SEB). This experimental research was conducted using mice and female mouse cell isolation. In cells from Mice treated with THC SEB, H3K36me3 and H3K4me3 were reduced, demonstrating that the manifestation of Ifn was suppressed. IFN- is one of the most potent proinflammatory cytokines induced by SEB. The researchers validated the mRNA expression of Ifn-, IL-4, IL-5, and Tbx21 by real-time PCR. IL-2, which is involved in proliferation of T cells, was reported by the results of the study has suppressive H3K27me3 in its promoter area in THC-treated cells, which correlates with decreased mRNA expression. Researchers used the ChIP-Seq method to ascertain whether THC uses its immunosuppressive function through modification of genetics. Preliminary results showed that THC does not change the whole activity of the histone-modifying enzyme, when the genes related with this histone marker were changed by THC medication. However, when farther investigations were carried out, it was found that THC exposure during the immune response to antigens such as SEB in vivo can change histone modifications, especially H3K9me3, H3K36me3, and H3K9ac, so that it can affect global gene expression. In this study, researchers also recovered that a large quantity of the genes have H3K27me3 and H3K4me3 signals provide nearby their TSS (transcription termination site), implying that the genes may not be activated or permanently pressed but are additional finely organized [17].

Recent research (the last 10 years) regarding the potential of THC in each of the areas discussed in this review is still lacking. But it should not be ignored for the development of THC compounds in the world of medicine, especially in the field of treatment.

CONCLUSION

Δ (9) - Tetrahydrocannabinol (THC) is the main active component of cannabis. THC is found to have many pharmacological potentials, including as analgesics, anti-inflammatory, anticancer, anti-nausea and vomiting, anti-tumor, hepatoprotective, and an indication of immunosuppression. Those pharmacological potentials have been proven in human studies, animal studies, and also in-vitro studies. THC could reduce pain, such as migraine-like pain, cancer pain, and pain induced by capsaicin. THC has anti-inflammatory activity by inhibiting the cyclooxygenase enzyme, and decreasing the release of pro-inflammatory factors. THC has anti-cancer activity by preventing the migration of human EC cells, reducing the migration of the lung cancer cells lines, and decreasing the viability of T47D and MCF7 cells. THC could reduce the nausea and vomiting induced by LiCi. The tumor area was

significantly reduced using KM-233(a synthetic cannabinoid drug) at the quantities of 8 and 12 mg / kg. THC has a hepatoprotective potential because it could reduce apoptotic hepatocyte cells. In addition, THC also has an indication of immunosuppression.

We can conclude that THC is a potential pharmacological agent. However, at the same time, it still needs deeper researches to evaluate the pharmaceutical potential of THC and the better comprehension of its pharmacological mechanisms.

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