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Review Article
Therapeutic Uses of Medical Cannabis: An Overview of its Functions in Disease Management

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Abstract

Cannabis belongs to the genus *Cannabis sativa*. It is popular globally and used widely for several purposes. Its use was illegal in many countries due to prohibitive regulations but now some laws have approved it, providing permission to some industries to produce cannabis just for medicinal use and it is not available as an over-the-counter drug. It is available in different modern medicine forms like capsules and tablets and can be administered as a tea formulation. In some countries, it is used as an effective analgesic for chronic and intense pain management. In ancient times, the use of cannabis was common as medicine, but the complete mechanism of action was not known. Advancement in medicine began again in India, China and Africa, but they still needed modern techniques for the development of medicine that were not available at that time. It resulted in slowing the speed of progress. But in recent times, many compounds have been isolated from cannabis and their pharmacological actions have been evaluated and explained. Some of the constituents include nabiximols, nabilone, tetrahydrocannabinol and cannabidiols. However, these all are given in low or medium dosage forms otherwise they cause undesired side effects including but not limited to panic attacks, dizziness, drowsiness and vertigo. But these are not so severe to cause discontinuation of therapy. This review brings to fore the important roles of cannabis in the management of some disorders in modern medicines.

Key words: Cannabinoids, pharmacological activities, anxiety disorder, analgesic, antiemetic, antispastic

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The generic name cannabis is used for the drugs produced from the genus cannabis[1]. It is popular worldwide and used at least once by up to 178 million people between the age of 15-65 in 2012[2]. Its use is illegal in most countries but in 1961 in a convention held in the UN named "Single Convention on Narcotic Drugs," it was approved for use as a controlled drug.

Chemical constituents extracted from cannabis are called cannabinoids used in medical therapy for the treatment of diseases and symptoms[3]. Cannabinoids can be used in different ways of administration like orally, sublingually, topically, as an inhaler or in diet (mixed in tea). These can be used as a natural extract from a plant in crude or synthetic form. Some examples are capsules forms of dronabinol, nabilone and mucosal sprays of nabiximols[4]. In some countries like Canada and Netherlands, the use of cannabis as a medicine for chronic diseases is legal as the government approved the production and supply of medicinal quality-controlled cannabis for some companies[5]. In the US in May 2005, 23 states and Washington, introduced some laws related to the use of cannabis as a medicine in some illnesses however their benefits and adverse effects must be under observation.

The use of cannabis in the twentieth century was a very common practice however its complete mechanism of action was unknown leading to its use being banned. But in recent times, the mechanism of action and constituents of cannabis have been explained. Their actions have been studied by comparing cannabinoids with synthetic drugs to observe the efficacy and unwanted side effects[6].

Cannabis was used as a medicine for a very long time. It has a very old and long history. In 3rd century B.C., in India, the earliest surgeon Sushruta came to know that it can act as an anti phlegmatic drug by drying mucus membrane. In addition to it religious and cultural uses, physicians in India also used it as antispasmodic and analgesic.

In the same century, Hippocrates tried, for the first time in history, the logical processes to prove the medicinal effects of cannabis. He did observational experiments on his patients and recorded the changes in diet, mood, emotions and improvements in disease. In his Era, there was no concept of using the medicine for treatment. He first identified the cause and set a proper way of cure. He recommended exercise, diet and medicine. Then another physician, Dioscorides, a physician of the emperor gave the name *Cannabis sativa* to plant hemp which is still in use today. When the Roman Empire collapsed, science and herbal medicine also faced neglect. There was no concept of hygiene and medicines and people again started believing in myths and magics[7].

In other countries of the world, there were continuous advancement in health and medicine. China developed medicinal and acupuncture methods for treatment and in India surgery was taught and performed. Then they all started filtering the old knowledge about medicines and came to know the use of cannabis as a treatment of motion sickness and nausea in sailing ships. In the 16th century, a Chinese manuscript was published named "Pen T'sao Kang Mu" by Li Shish-chen which included and explained all the earliest uses and writings about cannabis as an anti-ageing, stimulant and lactation booster[7].

Cannabis as medicine: Europeans returning from South Africa reported the use of cannabis as an anti-malarial drug and its used in the treatment of dysentery, so the people from Europe started travelling to India and Africa to learn medicine and surgery. Hence, advancements and research in the field of medicine began but there was still a lack of experimental proof. Nowadays, many researchers are performing experiments and are also able to isolate the different chemical constituents from cannabis and check their actions separately for use in drug synthesis.

The molecular study of cannabis and its active constituents became easy after CB_1 receptor discovery in the brain and CB_2 in peripheral tissues of mammals. CB_1 receptor substrate, anandamide, was isolated from the porcine brain and its metabolism was observed by hydrolase enzyme. Further study showed that the inhibition of anandamide results in an analgesic effect with vasodilation. So, the 4 receptor systems were discovered to have effects on pain, immune system, appetite and motor disorders. These system proteins are CB_1, CB_2, anandamide transporter and amide hydrolase.

In the last centuries, many molecules have been designed for protein sites acting as a probe. They provide all the information about receptors including activities in systems of the body.

Analgesic in advanced stages of cancer: Patients having severe pain at the advanced stage of cancer poorly responded to opioids during investigation. They were given nabiximols, a cannabinoid. There were three groups of patients based on the severity of pain. The first group was of average pain, the second with severe pain and the third group with sleep disturbance. They were give low dose (4 sprays a day), medium dose (10 sprays a day) and high dose (16 sprays a day), respectively. Treatment continued for 5 weeks. Then a questionnaire was used to check changes in mood and pain. The analysis showed

that the response rate was higher compared to opioids in low dose and medium-dose groups but there were some adverse effects when given in high doses. It was concluded that low doses of nabiximols were safe and efficacious in chronic disease-related pain[8].

Antispastic in multiple sclerosis: Another study was done on the antispastic nature of nabiximols in patients suffering from multiple sclerosis. Spasticity is a complication of multiple sclerosis making patients immobile. In the study, patients suffering from spasticity with failure of antispasticity therapy were considered. The study was completed after 19 weeks of experimental therapy. After 4 weeks, the evaluation showed about 20% improvements in spasticity of patients when given nabiximols in a single-blind manner. The evaluation was made by responder analysis, spasm frequency and sleep level. All were in favour of nabiximols[9].

Analgesic in fibromyalgia: The second beneficial constituent is nabilone. It was under trial for its analgesic effects in patients with fibromyalgia. The study involved 40 patients. First, the baseline assessments were done then patients were given a 0.5 mg oral dose at bedtime. The dosage frequency and dosage amount were increased to 1 mg two times a day for 4 weeks. The analogue scale, pain threshold point and 'fibromyalgia questionnaire' were used to evaluate the progress. A noticeable decrease in anxiety, visual analogue scale and fibromyalgia were observed. It was therefore confirmed to be a useful and tolerable treatment for fibromyalgia pain[10].

Antiemetics in gastrointestinal toxicity: Nabilone is also considered to be an important treatment for many gastrointestinal disorders especially toxicity related to chemotherapy in cancer patients. It acts directly on the control centre, medulla oblongata and prevents emesis. It also has mild anxiolytic activity. Nabilone if started before chemotherapy and continued alongside chemotherapy with a dosage of 2 mg daily had a significant decrease in nausea and vomiting in 70% of patients with severe emesis. In a conventional system, the drug that is used as an antiemetic is prochlorperazine with a dosage of 10 mg and (four times daily), has high evidence of side effects. Nabilone appears to be an effective drug as an antiemetic when used in low dosage[11].

Chemotherapeutic agents such as cisplatin results in nausea and vomiting that cannot be cured by conventional anti-emetics. Its anti-emetic effect was first studied in 1972[12]. Tetrahydrocannabinol (THC) was first given to 20 patients having chemotherapy on clinical trial bases. The 15 mg was given to some patients while others were given 20 mg as a single dose. The THC was given in form of gelatinized capsules. Evaluation showed anti-emetic effect on 14 patients[13]. However, it had some psychological effects.

To overcome these psychological effects produced by THC, another idea was to make a synthetic form of THC, so nabilone was synthesized. Nabilone was then tested in comparison with prochlorperazine and the results were the same as THC, but mental side effects were more common. Two synthetic THC drugs (levonantradol and BRL 4664) had the same anti-emetic effects[12,14].

Post-traumatic stress disorder: In patients with Post-Traumatic Stress Disorder (PTSD), anti-depressant was used as a treatment but only a few patients recovered and most patients suffered from remitting disorder. High dosage usage, leads to addiction, raising another problem. As an alternative, THC was used and evaluated for its efficacy. Ten patients suffering from post-traumatic stress disorder were given 5 mg THC, tetrahydrocannabinol, as add-on treatment. Its efficacy and tolerance were observed. The THC proved to be useful with great efficacy and mild side effects[15].

Tourette syndrome: THC efficacy was also examined for use for tics in tourette syndrome. Twenty-four patients (18-68 years) were involved in the study. They were treated with 10 mg per day for 6 weeks[16]. The evaluation was performed in 3 stages, at the start of treatment, during treatment and when treatment ended. Four scales were used to evaluate efficacy, TS-CGI, STSSS, YGTSS and TSSL. Only one patient was excluded due to side effects, however, no severe adverse effects have been reported in THC beneficial in tics of TS[17].

Appetizing in AIDS: A fourth important constituent of cannabis is dronabinol. Patients with AIDS suffer from anorexia resulting in weight loss. In a multi-institutional study, patients had been given 2.4 mg of dronabinol BD. In 88 patients' evaluation results, 38% increased appetite, 10% mood improvement, 22% weight gain when compared to the placebo group[18].

Anxiolytic: Last but not least pharmacologically active and broad spectral constituent of cannabis is cannabidiol. It is known for use in psychiatric disorders. To review its potential, preclinical, clinical and epidemiological studies were carried out and the results showed improvements in anxiety disorder and panic disorder etc. It is used as an acute drug dosing in clinical trials. However, its therapeutic potential for chronic disease needs to be evaluated[19]. Among all anxiety conditions, Social Anxiety Disorder (SAD) is the most common. Social anxiety disorder is unresolvable without treatment, it specifically needs a long-term treatment[20].

Although several experiments, research and guidelines are made for the treatment of SAD, it remains a problem[21] because there are still no therapeutic drugs available for the recovery of SAD and prevention of its remission[22]. Many persons with SAD use cannabis as self-medication for treatment purpose. However, its role is still not understood because of its side effect of intense anxiety and panic attacks[23].

All the constituents present in cannabis collectively influence its therapeutic activity. Cannabidiol (CBD) is the main compound having psychological effects different from others[24]. When used in healthy patients it exhibits anxiogenic effects. By using advanced techniques like neuroimaging, anxiolytic effects of CBD on limbic and paralimbic parts of the brain can be observed[25].

CBD is still under study through advanced molecular technologies like Single Proton Emission Computed Tomography (SPECT), to check its effects on cerebral blood flow to specific regions. It is assumed that CBD acts on brain areas to modulate its action and treat SAD[26].

Glaucoma: The ability of cannabis to lower intraocular pressure was an accidental discovery while studying about chronic effects of cannabis on human health. It was observed that chronic smoking of cannabis in nine of eleven persons resulted in a 45% decrease in intraocular pressure after 30 min of smoking. It did not depend on the number of cigarettes smoked, but rather on the amount of THC absorbed in the blood by smoking 19 mg of THC in a single cigarette. The effect remained for up to 5 hours after smoking. For confirmatory results, the experiment was performed in which 22 and 44 g kg^{-1} THC was given in form of IV injection which resulted in the decrease of intraocular pressure by 37% and 50%, respectively[27].

But if THC is needed for glaucoma treatment, then it would be in form of eye drops rather than smoking or IV injection. For this purpose, experiments were done on rabbits. The THC was not lipid-soluble, so it was mixed with mineral oil to use in form of eye drops. The effect of lowering the intraocular pressure was greater than conventional medicine used for this purpose, however absorption in systemic circulation was also very limited so, the mental effects were also negligible[28].

Nonpsychoactive constituents of cannabis were used alone and mixed with conventional timolol eye drops to check effects in glaucoma patients. Both drugs proved effective lowering the intraocular pressure when any other treatment failed[29]. A synthetic analogue, BW 146Y, was made for glaucoma patients and given in oral administration form, but as that was given orally, it was absorbed in the systemic circulation very quickly causing orthostatic hypotension[30].

Anticonvulsant: Earliest suggested use of cannabis was as an anticonvulsant that was done many years ago[31]. Various species were subjected to trials to confirm their action. In cats, electrographic seizures were induced by stimulation of the subcortical region and evaluated for results. This clearly showed that it reduced the seizures[32].

Then mice were induced with electric shock seizures and then given cannabidiol. Results showed that two of the cannabinoids, THC and cannabidiol, had therapeutic potential against seizures. The next goal was to check its activity in chronic seizures, rats were subjected to daily dose of electric shock to induce chronic seizures, and then given THC[33].

Clinical test performed on humans was rare. However, its activity was studied in patients with chronic smoking, but the results were not convincing. So, 15 patients were subjected to clinical trials. The 200 mg of cannabidiol gave a significant improvement when compared to the placebo[34].

Bronchial asthma: Two groups were constituted for different dose analyses. The high dose group was given 85 g kg^{-1} THC and the low dose group was given 32 g kg^{-1} of THC to check broncho dilating pharmacological activity. There was a 38% decrease in resistance and a 44% increase in air conductance in the high dose group. The low dose group showed the same changes but to a lesser extent, however, still noticeable when compared to baseline. No carbon dioxide toxicity or respiratory depression was observed[35].

Asthma was induced by methacholine in healthy patients and by exercise in asthmatic patients. Four types of drugs were given, placebo marijuana, saline, isoproterenol and the smoke of cannabis with 1 g of THC. Marijuana smoke and isoproterenol had an effect in reversing asthma attack[36]. Another study was done with 200 g THC in ethanol and 100 g THC in salbutamol, on 10 patients, both improved the ventilation for 1 hr[37].

Antihypertensive: THC was used in specific cases for orthostatic hypotension[38]. Usually dimethylheptyl derivatives used for lowering blood pressure as well as in tachycardia had the same effects as THC. There are many effective antihypertensive drugs already available in the markets with proven effects and efficacy, therefore it is difficult for THC to be used as an antihypertensive drug. For this purpose, its complete composition and mechanism of action must be understood and explained[39].

Antineoplastic action: It was studied both *in vivo* and *in vitro* by transplanting lungs tumour in animals. The isomers of THC, delta 8 and 9, cannabinol have antineoplastic activity. These can halt nucleic acid synthesis. So, DNA and RNA will not form resulting in inhibition of proliferation.

Antimicrobial activity: An *in vitro* study was done to discover the antibacterial activity of cannabis. Cannabidiol and THC added in an amount of 1-5 g mL^{-1} could be lethal to *staphylococci* and *streptococci*. But in humans, high doses are required for antimicrobial activity and that appeared to be impracticable[40].

Tolerance/addiction: With continuous use, tolerance to cannabis is a common problem. In chronic users low or moderate dosages are not enough to have pharmacological effects, they need a very high dose for this[41]. The demonstration of tolerance practically was impossible because of the restriction of dosage that could be given to humans for experimental or medicinal purposes. So, a study was done by giving 20 mg orally at bedtime for 4 days. Then evaluation on the 5th day showed that there was no tolerance for psychic effects however, tolerance in tachycardia and dizziness were observed[42].

The use of cannabis cigarettes for 21 days also helped in understanding the concept of tolerance[43]. However, high doses of cannabis can be given to animals and evidence of tolerance can be collected.

Later on, the use of high dose of cannabis for humans for experimental purposes was permitted[44]. A person was given 70-120 mg per day of THC orally for 30 days. In the end, tachycardia turned into bradycardia. Another test was performed in which the subject had to smoke one cigarette of cannabis a day for 64 days and tolerance to respiratory depression was observed[37].

When cannabis is used in small frequent doses just for medicinal purposes, tolerance is not a problem[45]. It only becomes a problem when used in high doses and chronically[46]. There seems to be no study or experiment done to reverse the tolerance of cannabis[47].

Tolerance related to other drugs: In humans, the effects of THC are the same as the effects of hallucinogens and alcohol and in the case of animals are the same as morphine[48,49]. Rats are tolerant to both THC and alcohol but when the tolerance level of both were compared; THC had a lower tolerance level[50]. Due to this difference, THC had never been used for the withdrawal of alcohol. The tolerance of THC and morphine was compared by analgesic effects in rats[51].

Physical addiction: With chronic use of THC, both humans and animals can suffer from addiction and dependence. A study on monkeys was used to explain all the withdrawal effects. Monkeys were injected with a 0.4 mg kg^{-1} dose daily and showed signs when withdrawal occurred. When monkeys were allowed to be administered the drug for 8 weeks, the signs appeared after 12 hours of withdrawal and continued for 5 days. These included irritated nature, aggression, fits and penile electability[52].

In men, spontaneous withdrawal results in nausea, vomiting, abdominal cramps, restlessness, sweating and muscle cramps and these symptoms continued for 3 days[53]. The combined effects of alcohol, cannabis and tobacco on testicular function in Wistar rats were compared in a recent study. The combined treatment caused degeneration and morphological abnormalities of testicular cells[54].

Cannabis is an extraordinary medicinal drug with a drawback of tolerance. The tolerance of cannabis was not completely understood because of fewer experimental studies on its tolerance in humans and animals. But as the use of cannabis is illegal and is not available over the counter in most countries, tolerance is not a big issue.

Toxicity of cannabis: Its long term or high dose use could result in psychic and behavioural changes such as:

- Panic attacks
- Memory impairment
- Disorientation
- Paranoia
- Hallucinations
- Hypomania
- Violence
- Loss of motivation
- Psychomotor impairment
- Neurological damage

CONCLUSION

Cannabis sativa simply known as cannabis was hitherto considered to be an addictive drug without any therapeutic role hence its ban on cultivation and use. The earlier reports on its therapeutic uses were initially resisted by many. However, previous data by physicians were without any analytical value to prove the therapeutic importance, but now, a surprising advancement in analytic techniques has made it obvious. Cannabis with many constituents like nabiximol, nabilone, THC, dronabinol and cannabidiol, has many medicinal uses. It is effective as antiemetic, anxiolytic, in gastrointestinal toxicity, weight gain, anorexia and in many psychiatric disorders that have no other alternative treatment. As it is moderately tolerated and with noticeable efficacy, its side effects include drowsiness, dizziness and postural hypotension etc., should not be ignored but rather used in the low dosage form.

SIGNIFICANCE STATEMENT

This review discussed some of the therapeutic uses of medical cannabis in some disease management. This study will help researchers to get an overview of the uses of medical cannabis.

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