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Review Article

CHEMICAL APPROACH TO THE HEALTH EFFECT OF MARIJUANA DEPENDENCE:A MEDICINAL ALTERNATIVE TO OPIOID - A REVIEW

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Abstract:
Marijuana is a plant that has medicinal properties including the ability to relieve pain. Moreover, marijuana has become a rising alternative medicine for Opioid drugs. The side effect due to the usage of Opioid drugs as pain reliever has increased significantly as the number of addicts and overdose continue to escalate. The efficient use of marijuana (*Cannabis sativa L. (Limaeus))* a psychoactive plant material, has led to increased recreational dependency of drug. Hence, there is a need to examine the phytochemical properties and biological studies. *In vivo and In vitro*, biological effects on the brain (Central Nervous System) and body can be studied. There is report on the effects of marijuana. The frequent use of marijuana poses a risk of an overdose or death and infrequent use causes long-term health problems. This article reviews the reason for marijuana dependency and various drug developments enhanced by their chemical constituents. This review provides evidence that marijuana is not just used for pain relief but also contains medicinally important bioactive compounds. THC (tetrahydrocannabinol), CBD (cannabidiol), α- pinene, apigenin, quercetin, are compounds found to be present in marijuana. The use of this plant species as traditional medicine for treatment of various diseases requires scientific justification and validation.

Keywords: Marijuana, Dependency, Traditional medicine, Opioid, Bioactive compound.

Introduction

The side effects caused by opioid drugs remain problems to be resolved. Opioid are substances that act on opioid receptors to produce morphine-like effects.[1]They are primarily used for pain relief and anesthesia. Other medical uses include suppression of diarrhea, treating opioid use disorder, reversing opioid overdose, suppressing cough, and suppressing opioid induces constipation.[2] Opioid is also frequently used non-medically for their euphoric effects or to prevent withdrawal from side effect caused by other addictive drugs. Examples of these drugs are Opium, Heroin, Morphine, Methadone, Oxycodone, and Hydrocodone. They are derived from a plant known as the poppy plant. Morphine and heroin in particular exist as the two strongest natural opium derivatives, [3] while others like methadone, oxycodone, hydrocodone, etc., are synthetically produced.

In former times, opium and heroin have been commonly used in pharmaceutical preparations for pain relief until the early 1900s. This effected a significant increase in the number of addicts and overdose death [4]. Despite this, many doctors and patients insist that these opioid drugs are needed. However, study has revealed that over 50% of pain patients cannot tolerate the side effects of the opioids while some users do not find them effective, those who continue to use them get only an average of 39% pain relief.

The use of Opioid and marijuana dependence have sociological implications. People who become opioid dependents are scavengers, tannery laborers, mine workers, truck drivers, masons, construction workers, unemployed youth, children of single parents, the frustrated youths, the socially marginalized, the lonely persons, and persons in debts. The psychological conditions of opioid dependents are critical. Opioid dependents have high tendency of committing suicide, Opioid dependents develop reduced intellectual functioning (Telling lies, deceiving others). Opioid dependents experience dejection which causes lower life satisfaction. Opioid dependents engage in Criminal behaviors such as stealing money, looting, burglary, begging, raping, murdering etc. Mental illness caused by loneliness, feeling of failure, lack of confidence, lack of moral uprightness is one of the major psychological effect caused by Opioid dependence. Opioid dependents also have strained relationship with family members, co-workers, boss and employers.

Economic Implications of Opioid Dependence

The marijuana dependents lose money and become economically poor due to the following.
1. Gambling
2. Visiting bars/ clubs/ race club/ horse race/ lottery
3. Getting debts
4. Inability to pay loans
5.Mortgaging properties, jewels, utensils
6. Becoming bankrupt
7. Spending money for medical treatment
8.Deteriorization of children education and health
9. Malnutrition of mothers and infants.

The recent survey suggests that opioid is not totally effective. Therefore, it is of high relevance to recognize and understand that there are other plants with similar properties that are

considered safer and more effective than the poppy plant. Listed below are a few of the alternative plants [5].

1.Marijuana (*Cannabis*)

Marijuana is a plant that has medicinal properties, including the ability to relieve pain. References to using marijuana as an analgesic date back to 2700 BC. Marijuana grows wild everywhere in the world except in the coldest climates. In the thousands of years that marijuana has been used, there has not been a single reported case of overdose resulting to death. But, the dependency ratios along with other drugs continue to increase drastically, although a few evidences suggest side effects after its use. Marijuana contains hundreds of pharmaceutical compounds. Its primary active ingredient is THC- Tetrahydrocannabinol. The constituent compounds of marijuana are used in the body to relive body pain, reduce inflammation and restore the body to a balanced state after stress or injury. 64% success was recorded in pain relieving potential of marijuana.

2. **Kratom (*Mitragyna speciose*)**

Kratom, a species of plant like cannabis, has different strains, classified generally into red, green and white veins. Red veins are calming and work better for pain and sedation. Green veins are a little more stimulating than reds and also tend to last the longest. White veins are the most stimulating and are good for energy boost and mood elevation. The key psychoactive compounds in Kratom are mitragynine and 7-hydroxymitragynine (7-HMG).Some kratom users use different strains at different times of the day, using more stimulating strains in the morning and more calming strains at night. Kratom are also significantly good alternative for opioid drugs.

3. Wild Lettuce (*Lactucavirosa*)

Wild lettuce, opium substitute, grows wild in many parts of the world such as Europe, Asia, Australia and North America. Wild lettuce contains two active compounds namely: lactucopicrin and lactucin, which bind to opioid receptors and produce pain relief. These compounds are used by drug manufacturers to produce medications to treat asthma, urinary tract disorders, painful menstruation and joint pain. The information about wild lettuce gives a clue that such properties may be present in marijuana. Therefore, experimental validation may be needed to ascertain this fact.

Marijuana is a psychoactive compound with botanical name *Cannabis sativa* L. (Linnaeus), a genus of flowering plant in the family Cannabaceae. There are numerous names and synonyms used for cannabis. They include hemp, marihuana, marijuana, pot, gandia, grass, chanvre and many more[6] There are three species of cannabis which include *Cannabis sativa*,[7]*Cannabis indica*,[8] and *Cannabis ruderalis*.[9]*C. ruderalis* may be included within *C. sativa*. All three may be treated as subspecies of a single species, *C. sativa*.[10]The genus is indigenous to central Asia and the Indian subcontinent. Cannabis has long been useful for the production of hemp-fiber and hemp oils containing cannabidiol for medicinal purposes, and in most cases, as substitute for side effects caused by opioid drugs.

Tetrahydrocannabinol (THC) is the principal psychoactive constituent of Marijuana. Industrial hemp products are made from cannabis plants selected to produce an abundance of fiber. To satisfy the UN Narcotics Convention, some cannabis strains have been bred to produce minimal levels of THC, while many other plants have been selectively bred to produce a maximum of THC (cannabinoids), which is obtained by curing the flowers. Various compounds, including hashish and hash oil (terpene), are also extracted from the plant[6].The addicts who are with initial stage of Cannabis usage are very few.

The use of cannabis for both recreational and medicinal purposes dates back to thousands of years. [11,12] Cannabis is rising as it is now being widely cultivated, trafficked and abused as illicit drug. More than half of all drug seizures worldwide are cannabis seizures. The geographical spread of those seizures is also global, covering practically every country of the world. About 147 million people, 2.5% of the world population, are marijuana users.0.2% consumes cocaine and 0.2% consumes opiates. In most recent times, cannabis usage has grown more rapidly than cocaine and opiate abuse, Asia contributes to a larger number of subscribed users annually. The marijuana plant contains over 80 unique phytochemicals (plant chemicals). Many of the bioactive compounds present in Cannabis have been identified and studied, the various medicinal properties are being recognized and justified with ongoing research. Apart from THC, some other examples are THCA (tetrahydrocannabinolic acid), THCV (tetrahydrocannabivarin), CBC (cannabichromene), CBD (cannabidiol), CBG (cannabigerol), and CBN (cannabinol) etc.

The amount of phytochemicals in marijuana differs from one topographical location to the other. Marijuana (weed) in North Asia is quite different from the one found in Africa. There is no sufficient research study to expound the variance. However, the use of marijuana introduces foreign substances into the body and produces a number of chemical changes in the user's brain and body. Given this, there is a large amount of literature focusing on the physical effects of marijuana. There is a dearth of scientific evidence for the pharmacological effect of marijuana. The health related studies available focus on the potential harm; health outcomes associated with long-term and heavy marijuana use (overdose). Smoking marijuana causes the development of respiratory ailment [13] [14], risk of cancers and deterioration of immune system. [15]

BIOLOGICAL EFFECTS OF MARIJUANA

Marijuana is used for medical and recreational reasons. The long-term effects are changes in perception and increased heart rate. Smoking marijuana may cause chronic cough and other health issues. The effects of marijuana on the body are often immediate. Long-term effects may depend on usage and consistency. Recently, the medicinal properties of marijuana are gaining public acceptance. As from 2017, over 30 states plus the District of Columbia have legalized medical use of marijuana to a certain extent. THC and another ingredient called cannabidiol (CBD) are the main compounds of therapeutic interest.

Marijuana act by involving chemical reaction with functionally important component of the living system. This mechanism of action can be explained with the help of the receptor. The receptors are macromolecular tissue constituent with which drug combine reversibly by means of ionic bonds, hydrogen bonds and Vander Waals forces. The body contains natural cannabinoid called anandamide in the endocannabinoid system of the brain which is responsible for neurotransmitter- interaction of neurons in the body. This compound is similar to the active constituent of marijuana, THC. The tolerance of marijuana use leads to stimulation of brain cells to release excess dopamine in the brain, which influence drug metabolism in the intestine, brain, kidney and lungs.

Respiratory System

Similar to tobacco smoke, marijuana smoke is made up of a variety of toxic chemicals, including ammonia and hydrogen cyanide, which causes irritation at the bronchial passages and lungs. This induces cough, wheeze, and produce phlegm [16]. There is also a high risk of bronchitis and lung infections. Marijuana may aggravate existing respiratory illnesses, such as asthma and cystic fibrosis. Researchers so far are yet to find a higher risk for lung cancer in marijuana smokers. [17]

Circulatory System

THC moves from the lungs into the bloodstream and throughout the body. One immediate response to the use of marijuana is the increase in heart rate. It is estimated that marijuana use increases the heart rate 20% to 50% immediately after consumption. [18] This response may increase the chance of heart attack. Elderly people and those with heart problems are at higher risk of heart attack.

Reproductive System

Marijuana use during pregnancy is associated to loss of weight including increased risk of both brain and behavioral problems in babies. Marijuana usage during pregnancy, affect certain developing parts of the fetus's brain. Children exposed to marijuana in the womb have higher risk of problem such as attentiveness [19], and memory usage. [20] Some research also suggests that moderate amounts of THC are excreted into the breast milk of nursing mothers. [21]

Central Nervous System [22]

The effects of marijuana extend all through the central nervous system (CNS). Marijuana is thought to ease pain, inflammation and help control spasms and seizures. Still, there are some long-term negative effects on the CNS which are yet to be probed. THC triggers the brain to release large amounts of dopamine, a naturally occurring “make-me-high” chemical. It is said to give a pleasant sensation of relaxation which heightens the sensory perception and perception over time. In the hippocampus, THC is known to impair cognition by tampering with the normal stability set-up of the brain. The hippocampus is responsible for memory. Changes also occur occasionally in the cerebellum and basal ganglia (the brain areas that play roles in movement and balance). Marijuana alters body balance, coordination, and reflex response which make overdose or addiction risky and dangerous. Large doses of marijuana or high concentrated THC causes hallucinations or delusions. According to the National Institute of Drug Abuse, there could be a link between marijuana use and some mental health disorders like depression and anxiety. More research study is necessary to understand the connection. About 30 percent of marijuana users develop a mental disorder. In young adults, whose brain are yet to be fully developed, marijuana poses long term consequence on thinking and memory processing in young brain that are yet to be fully developed. Marijuana produces their action quantitatively. Like barbiturates, it depresses the central nervous system and is used as sedative, hypnotic, anxiety reducers, pain reliever and convulsion control agent in epilepsy. Marijuana stimulates the activity of specialized cells and thus increases their activity. It stimulates the vague nerve situated at the medulla oblongata and chemoreceptor trigger zone but depresses the vomiting and coughing centers. Marijuana is used as replacement when the production of endogenous substance is reduced. These are of immense importance in the treatment of diseases of hormonal deficiencies. Marijuana also serves as antibiotics for the prevention and treatment of infection. They either stop the growth of the micro- organism or ultimately destroy it. This drug is biostatic in action and act as metabolite antagonist, inhibiting the growth of bacterial cells. The inhibition or antagonism of essential metabolite by structurally similar compounds is known as metabolite-antagonism and the inhibitor is known as metabolite-antagonist.

Digestive System

Marijuana usage while smoked is said to cause some stinging or burning in the mouth and throat when inhaled. Marijuana can cause digestive difficulties when taken orally. For example, oral THC causes nausea and vomiting because of the way it is processed in the liver which could also lead to

damage of the liver. On the other hand, marijuana is used to ease symptoms of nausea (upset stomach). Adequate increase in appetite is a significant effect while taking any form of marijuana. This is considered a benefit for people being treated with chemotherapy for cancer. For others who are looking to lose weight, this effect could be considered a disadvantage.[22]

Immune System

THC adversely affects the immune system. Studies involving animals show that THC might damage the immune system, making one extremely prone to sicknesses. They manufacture toxic antigens in the body. Further research is needed to fully understand the effects. [23]

DRUG DEVELOPMENT FROM MARIJUANA

There are two phytoconstituents which are isolated from marijuana.

Table 1: List of Phytoconstituents Isolated from Marijuana and their Uses

PHYTOCONSTITUENT	MEDICIINAL USE
Marinol (Dronabinol)	Nausea from Cancer chemotherapy
Cesamet (Nabilone)	Nausea and Neuropathic pain

Current research has focused on two compounds which are Cannabidiol (CBD) and Tetrahydrocannabinol (THC). There are some other drugs awaiting clinical testing.

Table 2: List of Phytoconstituents Isolated from Marijuana and their Uses Under Clinical Trials

PHYTOCONSTITUENT	MEDICIINAL USE
Sativex (CBD & THC)	Cancer pain & Spasticity
Epidiolex (CBD)	Childhood seizures.

Conclusion:

Marijuana as an alternative medicine for opioid drugs is gaining more recreational dependency ratio as against its medicinal properties. It contains phytochemical compounds responsible for the treatment of diseases. It also contains some biologically active constituents worthy of further investigations. An overdose of this drug has side effects which primarily disturb the body including the Central Nervous System, Digestive system, Respiratory organs and the Immune system. The use of dopamine antagonists as an antidote can reduce the effect of high dopamine level in the brain caused by marijuana. However, further analysis and research is needed to support this postulation.

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