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New insights into cannabis consumption; abuses and possible therapeutic effects

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Abstract

Cannabis is one of the oldest psychotropic drugs known to humanity. The paper assesses the current knowledge on the cannabis, including the mechanisms of action and the therapeutic potential of cannabinoids.

Three varieties of Cannabis plant are recognised: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. The variety *indica* is used predominantly to obtain the drugs. Cannabis herb is usually named marijuana, while the cannabis oleoresin secreted by the glandular hairs found mainly on the flowering or fruiting tops of the plant is known as hashish. More than 400 known chemicals are present in cannabis, at least 70 of which are called cannabinoids. The major psychoactive constituent in cannabis is delta-9-tetrahydrocannabinol (Δ^9 -THC). It is now recognized that there are three types of cannabinoids: natural (phytocannabinoids), endogenous cannabinoids, and synthetic cannabinoids.

Cannabinoids exert their actions by binding to specific membrane protein, the cannabinoid receptor. To date, two subtypes of cannabinoid receptors, named cannabinoid-1 (CB1), most abundantly expressed in the central nervous system and cannabinoid-2 (CB2) receptors, found

predominantly in peripheral tissues with immune functions have been cloned. Therefore, the concept of endogenous cannabinoid system (endocannabinoid system, SEC) has been developed. Based on the current scientific evidence, there are several effects of cannabinoids with potential therapeutic use: antiemetic, analgesic in cancerous pains, and chronic neuropathic pain, in multiple sclerosis or spinal cord injuries.

Cannabis consume can result in a state of drug dependency and cannabis withdrawal has been included in DSM-V. Cannabis plant remains controversial in the twenty-first century and the potential therapeutic of specific cannabinoid compounds and medical marijuana remains under active medical research.

Introduction

Drugs from Cannabis are currently used extensively and illicit and have a long history of use from ancient times. Originating from Central Asia, Cannabis one of is the oldest cultivated textile plant, as well as a psychotropic drugs known to humanity. It has been known by the peoples of south-east Asia for over 4,000 years, as evidenced by vessels found in China, which are painted with strains of Cannabis (1).

The first therapeutic use of cannabis as a sedative in rheumatic pain and gout has been described in the compendium of Chinese medicinal herbs elaborated by the Emperor of China, Shen Nung (2737 BC). Medical uses of cannabis were mentioned in the nineteenth century in a paper published in 1842 by the Irish physician William O'Shaughnessy, who validated folk uses of cannabis in India, and discovered new applications, recommending cannabis for a great variety of therapeutic purposes, such as analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant (2).

In 1854, cannabis was listed in the United States Dispensatory. In 1942, cannabis was removed from the United States Pharmacopoeia. Cannabis was also available in the British Pharmacopoeia in extract and tincture form for over 100 years. In 1964 (-)-trans-delta-9-tetrahydrocannabinol (delta-9-THC, dronabinol), the principal active ingredient of cannabis, was stereochemically defined.

Cannabis was banned in 1961 by adopting the Single Convention on Narcotic Drugs instituted by the United Nations. Cannabis and cannabis resin, extracts and tinctures of cannabis were placed under the heaviest control regime in the Convention, Schedule I (3).

Worldwide, cannabis is the most commonly used illicit substance. According to the current statistics (World Drug Report, 2014, elaborated by the United Nations Office on Drugs and Crime), in 2012, between 125 million and 227 million people (corresponding to between 2.7 and 4.9 per cent of the population aged 15-64 years) were estimated to have used cannabis (4). In Europe, in contrast to elsewhere, the overall use of cannabis appears to be stable or even declining, with 73.6 million (21.7% of population aged 15-64 years) using cannabis in their lifetime (European Monitoring Centre for Drug and Drug Addiction, European Drug Report, 2014) (5).

Discussion

Cannabis drugs

The plant Cannabis is the source of a number of abuse drugs, such as marijuana or hashish. The unique properties of the plant Cannabis have generated much debate on the taxonomic classification. Cannabis was reclassified several times before assigning its own family (Cannabaceae), which includes only hops plant. However, the widespread opinion is that the Cannabis plant is presented as three varieties: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*, originating in Central Asia, Southeast Asia and surrounding regions. *Cannabis sativa* variety, with spreading in the temperate continental areas, is commonly used for textile fibers and seeds; *Cannabis indica* variety, cultivated in tropical areas, is valued predominantly for the oleoresins containing psychoactive substances and is used to obtain the drugs (1).

Cannabis is a generic term for the drugs obtained from the plant Cannabis. Usually, Cannabis designates the dried vegetal material ("Cannabis herb", the name usually in slang, marijuana). Hashish or "hash" represents the cannabis resin, secreted by the glandular hairs found all over the plant but mainly around the flowers. Hashish oil is the extract from Cannabis or hashish, using a solvent (e.g.

acetone) and evaporated. The cannabis plant can be used as a source of hemp fibres, as well as hemp seeds and fatty oil (6).

According to the Single Convention on Narcotic Drugs (United Nations 1961) Cannabis represents the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted; Cannabis resin is the separated resin, whether crude or purified, obtained from the Cannabis plant. These definitions are based on traditional Indian terms ganja (cannabis) and charas (resin) (3). Ganja/ganga refers to the small upper leaves and flowering tops of the cultivated flowering plants. Another Indian term, Bhang represents the dried leaves and flowering tops of the uncultivated female cannabis plant, smoked or consumed as a beverage in the Indian subcontinent.

Routes of administration

Smoking is the most common way of cannabis use (often mixed with tobacco). Marijuana is typically smoked as a joint, but it can be prepared in food for oral consumptions, as in brownies, cookies, or spaghetti. Bhang is used as an infusion in the Indian subcontinent. Because THC has low water solubility, ingestion of cannabis leads to poor absorption.

The “typical” marijuana cigarette is obtained from a gram of *C sativa* leaves and buds and contains about 20 mg of THC. The resin (hashish) is also smoked in a smoking device (bong), while the liquid cannabis (hashish oil) is used by smoking, vaporization, or may be consumed orally.

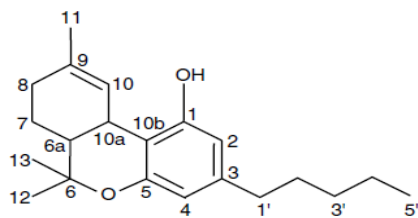
Chemical components of Cannabis

It is recognized that there are about 400 chemicals in hemp resin secreted by the flowering tops and leaves of female plants; this resin contains at least 70 chemicals, terpenophenolic derivatives, called cannabinoids. Small amounts are found in the stems; the seeds do not contain cannabinoids.

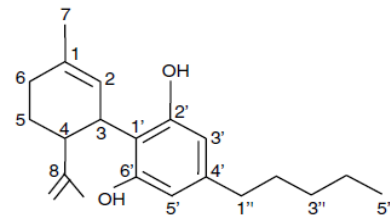
The major psychoactive constituent in cannabis is delta-9-tetrahydrocannabinol (Δ^9 -THC), which is formed in plant during biosynthesis of natural cannabinoids. To synthesize THC, the plant needs a high average temperature, during flowering, daily over 35°C.

There are three types of cannabinoids:

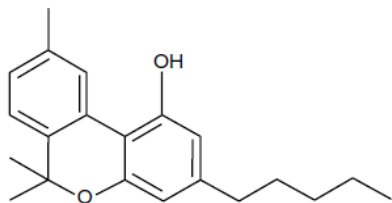
- natural cannabinoids (phytocannabinoids, Figure 1), such as Δ^9 -THC), cannabidiol (CBD), a major constituent without psychoactive properties, but with anticonvulsant, anxiolytic and anti-inflammatory activity, delta-9-tetrahydrocannabivarinine (Δ^9 -THCV, the analog of THC with propyl radical), a CB1 receptor antagonist, which attenuates the psychoactive effects of THC. Other cannabinoids present in Indian hemp include delta-8-tetrahydrocannabinol (Δ^8 -THC), cannabinol (CBN), cannabicyclol (CBL), cannabichromene.
- endogenous cannabinoids, that include arachidonic acid derivatives; the two most researched endocannabinoids are anandamide (arachidonoyl ethanolamide, AEA) and 2-AG (2-arachidonoyl glycerol).



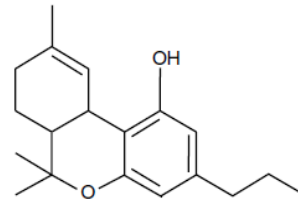
Δ^9 -THC



Cannabidiol



Cannabinol



Δ^9 -THCV

Figure 1. The chemical structures of some phytocannabinoids

- synthetic cannabinoids, functionally similar to Δ^9 -THC and initially developed over the past 40 years to be used as therapeutic agents, often for the treatment of pain. In the late of 2008, several synthetic cannabinoids were detected in herbal smoking mixtures or so-called incense/room odorisers. Spice Gold, Spice Silver and Yucatan Fire are typically sold via the Internet and in 'head

shops'. In December 2008, the synthetic cannabinoid JWH-018 was identified in spice; presumably, a solution of the cannabinoids is sprayed onto the herbal mixture. Currently, little is known about the detailed pharmacology and toxicology of the synthetic cannabinoids and few formal human studies have been published. It is possible that, apart from high potency, some cannabinoids could have particularly long half-lives potentially leading to a prolonged psychoactive effect; in addition, there is a higher potential for overdose than with cannabis.

Potential therapeutic uses of cannabinoids

Based on current scientific evidence, therapeutic effects of cannabis and/or THC (dronabinol, the levorotatory isomer of synthetic trans delta-9-THC), can be classified as follow (7):

1. proven effects: antiemetic, useful in nausea and vomiting caused by chemotherapy; appetite stimulant, useful in anorexia and weight loss in patients with devastating diseases (eg. AIDS).
2. effects relatively well documented: the spasms, pain, movement disorders, asthma, and glaucoma.
3. unproven effects: in allergies, itching, inflammation and infection, epilepsy, depression, anxiety.
4. effects under basic research: the self-resistant disease, cancer, neuroprotection, abnormal blood pressure

The problems inherent in the therapeutic use of cannabis are focused on his legal position as prohibited drug, which applies in most parts of the world, and on the smoking use, plus the uncertainty about the composition and purity of raw cannabis. In most countries, the legal classification is based on the premise that cannabis use has no demonstrable therapeutic benefit (although dronabinol and nabilone, a synthetic cannabinoid, are approved for clinical use), and rather limits opportunities for appropriate clinical evaluation.

According to Ben Amar, in the review published in 2006, there are ten pathologies and conditions with proven cannabinoids use and published controlled clinical trials (Figure 2) (2).

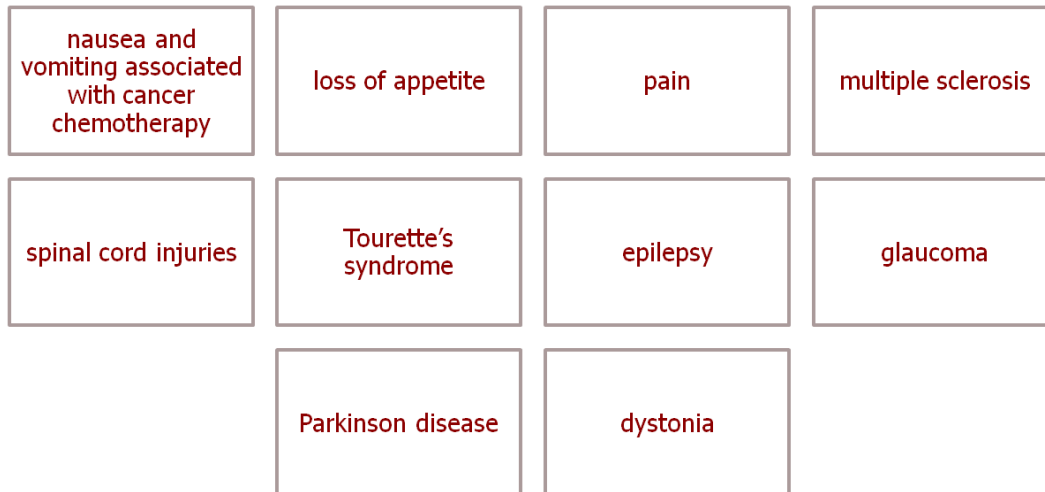


Figure 2. The therapeutic potential of cannabinoids

A number of cannabis products are being manufactured by pharmaceutical companies, including Marinol (dronabinol; THC), Cesamet (nabilone), and Sativex (THC + CBD). Dronabinol (Marinol[®]), a synthetic THC, and its analogue nabilone (Cesamet[®]) have been approved in Canada and USA for many years, for chemotherapy-associated emesis in patients who had not responded to conventional antiemetic medications. These medicines were also approved for use in anorexia associated with weight loss in patients with AIDS (8).

The drug product Sativex, oromucosal spray (manufactured by GW Pharmaceuticals), a cannabis plant extract consisting of equal amounts of dronabinol (THC) and cannabidiol (Nabiximols, THC + CBD) received approval in UK as an adjunctive treatment for multiple sclerosis patients (is used to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms); it is also developed in Phase III trials as a potential treatment to alleviate pain in cancer.

Medicinal cannabis

Since July 2001, the Marihuana Medical Access Regulations (MMAR) allow Canadian patients suffering from a serious disease to be eligible for therapeutic marijuana consumption. The medicinal cannabis, with standard cannabinoid concentrations, has been sold in pharmacies in the Netherlands by

medical prescription. There are several side effects of the medicinal cannabis: mood-altering effects, insomnia and heart palpitations.

The genetic predisposition to psychosis (like schizophrenia) or other mental health problems are listed as precautions. In addition, smoking medicinal cannabis is not recommended due to the risk of damages to lungs); instead, inhaling cannabis using a reliable vaporiser is a more suitable method.

Mechanisms of cannabinoids action

Cannabinoids exert their actions by binding to specific membrane protein: the cannabinoid receptors (part of the G-protein coupled class; their activation results in inhibition of adenylate cyclase activity). Based on the lack of stereospecificity Δ^9 -THC activity, and its lipophilicity, the molecular mechanisms of action of cannabinoids were initially considered nonspecific, of anesthetic type. The most impressive discovery on cannabis study was the identification in 1991 of the first endogenous receptor for THC, the CB₁ receptor. The experimental observation that THC inhibits, reversible, stereoselective and dose dependent manner, adenylate cyclase in neuroblastoma cells led to the hypothesis of receptor mediated interaction for THC. The first endogenous ligand for the CB₁ receptor, arachidonyl ethanolamide (AEA, anandamide, name in Sanskrit ananda = "bringer of inner happiness") was discovered in 1992. This was followed by the identification of other types and subtypes of endogenous receptors (CB₂ receptor, with predominantly peripheral localization), as well as natural, synthetic or endogenous substances with affinity for these receptors. Therefore, the concept of endogenous cannabinoid system (endocannabinoid system, SEC) has been formulated. Consequently, the functions of this system in the body have been studied and the attempts to synthesize of substances that activate or antagonize the SEC have been made.

The other putative endocannabinoids are 2-arachidonylglycerol (2-AG), O-arachidonyl ethanolamine (virodhamine), N-arachidonyl dopamine (NADA), and 2-arachidonyl glyceryl ether (2-AGE, noladin ether). AEA and NADA are also shown to have an affinity to transient receptor potential

vanilloid 1 (TRPV1) receptors (9). In contrast to anadamide and 2-AG (which binds to both the CB₁ and CB₂ receptors), 2-AGE binds very weakly to CB₂ receptors.

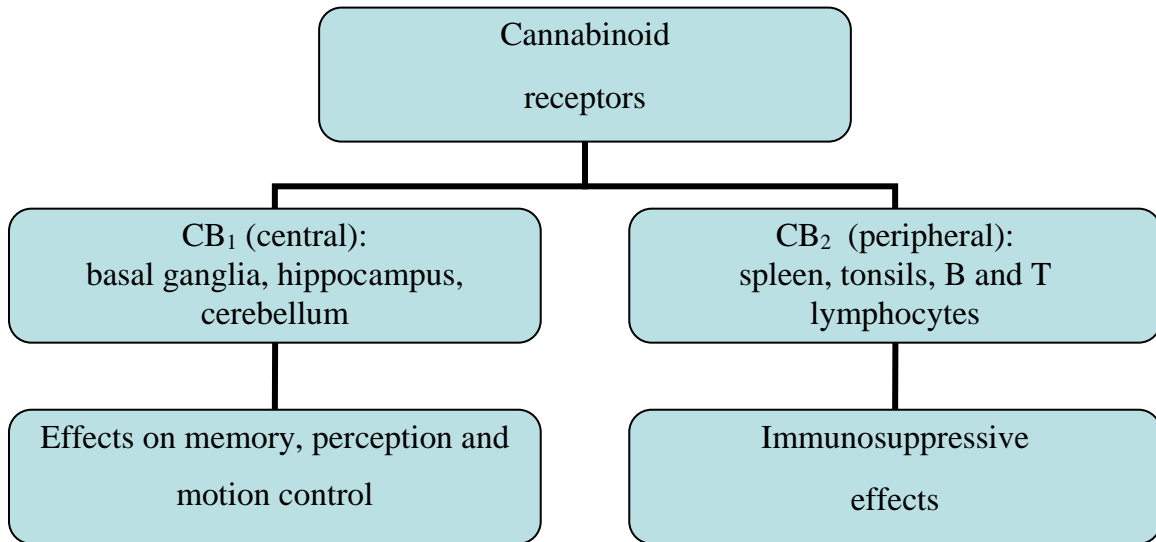


Figure 3 The cannabioids receptors

Cannabis and THC mode of action THC is absorbed rapidly across the large surface area of the lungs and takes 10 – 30 min. To reach peak plasma concentration; it is deposited in organs with high fat content (such as brain) due to its lipid solubility. THC and its metabolites can remain in the body for up to 30 days; repeated administration can lead to accumulation. When smoked, the effects can last for up to four hours, depending of the amount used.

Cannabis intoxication. Schematically, there are four stages of Cannabis intoxication: excitation, mental instability and hallucinations, ecstatic phase, and deeply rest. Cannabis intoxication is a syndrome described in DSM-V and ICD-10, with psychological / behavioral and physical manifestations (Table 1) (10).

Psychological and behavioural effects	Physical effects
Euphoria, relaxation, wellbeing, self-confidence	Nausea and vomiting, dry mouth, hunger

Changes in perception of time, intensified visual and auditory perception	Red eyes, swollen eyelids
Enhancement of taste, touch, smell	Motor incoordination
Concentration and memory may be impaired	Tachycardia, Orthostatic hypotension
The experience may not be pleasurable (anxiety, paranoia and agitation, and occasionally panic reactions)	

Table 1 Manifestations of cannabis intoxication

Long term effects

Frequent inhalation of cannabis smoke over a period of years will contribute toward bronchitis and other respiratory disorders and possible cancer of the lung and parts of the digestive system; risks are greater if it is smoked with tobacco.

Impaired endocrine function was associated with cannabis use. Long term, high doses may result in reduced fertility in females and reduced testosterone and sperm count in males. Cannabis consumption may increase the probability of psychotic symptoms in vulnerable individuals (with a history of schizophrenia, and depending on individual predisposing factors and use of other substances) (11).

Persistent disturbance of cognitive functions and memory, risk of malformations in newborns, and immunosuppressant effects have been also cited as secondary effects of long term cannabis use. Discussion of adverse effects is often focused on the “amotivational” syndrome, resulting in lower school averages and higher dropout rates among users than non-users. This aspect is controversial, and the syndrome has not been officially diagnosed. Conflicting evidence exists of any cannabis “gateway”

effect (escalation theory suggesting that using drugs such as cannabis leads to consumption of more harmful drugs).

Cannabis dependence

Typically, few consumers fulfil DSM criteria for cannabis dependence (typically those who smoke marijuana daily and with personal or family history of addiction to psychoactive substances); most often is diagnosed cannabis abuse. However, when there is a significant level of tolerance or mental and physical problems associated with compulsive consumption context, it is necessary diagnosis of dependence, not abuse.

Tolerance, physical dependence

The development of tolerance and dependence to cannabis is a controversial issue and has not been fully established. Psychological dependence can result in chronic users of cannabis. Although regular users who stop smoking cannabis do not experience a withdrawal syndrome as opioid users, when used in high quantities, there have been reports of abstinence (withdrawal) syndrome indicating physical dependence. DSM-IV-TR describes two cannabis use disorders (cannabis dependence and abuse) and six categories of cannabis-induced disorders (cannabis dependence, cannabis abuse, cannabis-induced disorders, cannabis intoxication, cannabis intoxication delirium, cannabis-induced psychotic disorder, with delusions, cannabis-induced psychotic disorder, with hallucinations, cannabis-induced anxiety disorder, and cannabis-related disorder not otherwise specified), while DSM-V has included cannabis withdrawal (8); the syndrome developing within 48 h of cessation is reported by up to one-third of regular users in the general population and by 50%–95% of heavy users in treatment or research studies (12). The commonest signs and symptoms of cannabis withdrawal syndrome include decreased appetite, insomnia, weight loss, irritability, restlessness, anxiety, aggression. Withdrawal symptoms tend to subside in 2–12 weeks after cannabis abstinence.

Treatment No medication has been shown broadly effective in the treatment of cannabis dependence, nor is any medication approved for this condition by any regulatory. Naloxone has been shown to block the reward effects of THC, in preclinical studies. Depending on the severity of symptoms, the antidepressant medication can be useful.

Conclusions

Known for thousands of years, Cannabis plant remains disputed and controversial in the twenty-first century. In addition, the potential therapeutic of specific cannabinoid compounds remains under medical research and larger clinical trials are also needed to assess the benefits and risks of medical marijuana.

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