ABSTRACT

Cannabis is a plant rich in various compounds that have a variety of impacts on the physiology of humans and the effects of these metabolites have a significant role in managing a variety of clinical diseases. A substantial increase in the use of SC (synthetic cannabinoids) had seen in the last few years especially infrequent cannabis users. The SCs will generate psychoactive effects that were similar to cannabis. However, the composition and pharmacological characteristics of these drugs make them possibly hazardous.

Like all drugs, cannabis pharmacokinetics depends on the route of administration. Several studies showed that the bioavailability is less in oral administration when compared to inhalation. The main reason for this decrease in oral bioavailability is that cannabinoids undergo the first-pass metabolism before entering into the systemic circulation whereas in inhalation, it enters the circulation directly through the lungs.

Cannabis sativa is a psychoactive plant that contains more than 500 components of which 104 cannabinoids had been identified. Of these, 2 components such as Δ⁹-THC (Δ⁹-tetrahydrocannabinol) and CBD (cannabidiol) were under the scientific investigation. Δ⁹-THC is the primary cannabinoid which was responsible for the consequences of psychotrophy. The potency of cannabis is assessed based on the THC concentration of a sample that is the main psychoactive cannabinoid in cannabis. The adverse effects are in direct relation to the concentration of THC in the product after regular cannabis use. It can be assumed that several cannabinoids will find their way into the pharmacies from preclinical research within a century.

Keywords: Cannabis sativa, Synthetic cannabinoids, Δ⁹-THC, CBD, Psychoactive effects

INTRODUCTION

Cannabis sativa (also called marijuana) is a psychoactive plant that contains more than 500 components of which 104 cannabinoids had been identified [1]. Of these, 2 components such as Δ⁹-THC and CBD were under scientific investigation to their pharmacological properties [1, 2]. Δ⁹-THC is the primary cannabinoid that was responsible for consequences of psychotrophy [3]. It interacts with and activates G protein-coupled CB1 and CB2 cannabinoid receptors [4].

In the 1930s and 40s the chemical structure of the first phytocannabinoids was determined effectively [3]. Another scientific discovery in the cannabinoid research was the identification of the particular cannabinoid receptors system in mammals and their cannabinoid endogenous ligands [1, 3].

The potency of cannabis is assessed based on the concentration of a sample that is the main psychoactive cannabinoid in cannabis. The adverse effects are in direct relation to the concentration of THC in the product after regular cannabis use [2].

Several studies over the last few years had shown that CBD levels may also have an important impact [5]. When compared to THC, it has a protective action against certain negative psychological effects and are also able to antagonize some of the undesired effects [2].

Various cannabis preparations are available on the illicit drug market and proper monitoring of those agents had helped scientists to evaluate the potency of products which is currently used [3]. Changes can then be compared with the prevalence of negative health consequences in users. Certain authors hypothesize that an increase in cannabis potency and in the ratio of the psychoactive component (Δ⁹-THC) to CBD might be the reason behind the increasing harmful effects associated with cannabis use [3].

Moreover, a substantial increase in the use of SCs had seen in the last few years especially infrequent cannabis users [1]. The SCs will generate psychoactive effects that were similar to cannabis and are also readily acquired through normal screenings that are undetected. However, the composition and pharmacological characteristics of these drugs make them possibly hazardous [5].

Cannabinoid receptors

Two receptors of cannabinoids were recognized, The CB1 and the CB2 receptor had been identified as the 2 cannabinoid receptors and it exhibits 46% of the amino acid sequence [5].

In addition to their difference in amino acid sequence, they vary in signalling mechanisms, tissue distribution and sensitivity to certain agonists and antagonists showing marked selectivity for one or the other type of receptor [7]. Activation of cannabinoid receptors triggers adenylyl cyclase inhibition, thus inhibiting the conversion of ATP to cyclic AMP [8].

CB1 receptors are widely expressed in basal ganglia, cerebellum, hippocampus and dorsal primary afferent spinal cord regions, reflecting the significance of the cannabinoid system in motor control, memory processing and pain modulation with low expression in the brainstem [7]. CB1 receptors are also found in endocrine glands, urinary and gastrointestinal tracts, spleen, leukocytes, heart and parts of the reproductive system [6].

CB2 receptors are seen primarily in immune cells, mainly in leukocytes, spleen and tonsils [9]. Immune cells also express CB2 receptors, but in the immune system, there is significantly more mRNA for CB2 than CB1 receptors. Modulation of cytokine release is one of the main tasks of CB2 receptors in the immune system [6].

CB1 receptor activation generates marijuana like impacts while CB2 receptor activation does not [10]. Selective CB2 receptor agonists have therefore become an increasingly researched target for therapeutic uses of cannabinoids [11].

Known cannabinoids and their effects on cellular and system physiology

In many tissues throughout the body, CB1 receptors are abundantly found in most of the brain areas and the peripheral nervous system.
inhibits cytochrome P450 enzyme activity, which in turn affects research revealed that the bioavailability of cannabinoids undergo comprehensive first-pass metabolism with metabolism especially after oral administration [29].

This is probably due to selective antagonism by Δ9-THC of endocannabinoids, as stated by Patel and Hillard [14] when anti-anxiety effects of Δ9-THC administration in mice were observed. However, cannabidiol does not share psychotrophic activity with Δ9-THC, but acts as an inverse agonist or even antagonist of CB1 and thus attenuates in vivo response to Δ9-THC in various model species [15]. On the other side, cannabinoid CB2 receptors are more commonly found in immune related organs and attenuate pro-inflammatory reactions such as cytokine release and immune cell response when it gets activated [16]. There is proof that CBD interacts as an inverse agonist with CB2 receptors resulting in a well-documented decrease of clinical pro-inflammatory markers such as TNFα, iNOS and COX-2 expression [17]. In relation to the impacts on CB2, CBD also interacts with receptors related to the immune system [18]. CB2-receptors are also found in reduced concentrations in both brain and peripheral neuronal tissue compared to CB1 receptors, but their function has not yet been elucidated [19].

Pharmacokinetics of cannabis based on route of administration

Like all drugs, cannabis PK (pharmacokinetics) depends on the route of administration most of the human clinical trial have assessed the cannabis PK activity following inhalation or ingestion [20]. While various trials report a broad variety of PK parameters due to variations in dosage, it remains apparent that the onset, absorption rate and bioavailability of THC and CBD after inhalation are considerably greater than after ingestion or oral administration [21].

THC can be detected in the blood almost instantly after smoking and maximum plasma levels can be measured after 5–10 min [22]. The reported peak values differ with the dose given. For example, one research revealed that cigarette inhalation comprising 1.75% THC (equal to 16 mg THC) and 3.55% THC (34 mg THC) resulted in mean plasma peak levels of 84.3 mg/ml and 162.2 mg/ml respectively [20]. However, the range of maximum plasma levels measured for the low dose cigarette was 50-129 mg/ml and the high dose cigarette was 76-267 mg/ml.

When comparing reported bioavailability values such broad ranges are also discovered. In some research, the bioavailability of inhaled THC was recorded as 30% 10-35%and 18% [23-25]. One research comparing THC’s pharmacokinetics between regular and occasional users found that bioavailability was 23-27% for regular users and 10-14% for occasional users [26]. These variations arise from the difference in smoking techniques with variables such as puff length, quantity of intake and holding time to determine medication consumption [27].

Fewer studies concentrated solely on CBD’s PK activity. One research revealed that the bioavailability of CBD after inhalation was 31%, while others commented on the resemblance between THC and CBD in PK activity. It has been noted, however, that CBD may change THC’s PK activity and may mediate some of its adverse effects, such as paranoia and anxiety [28]. The precise reason for this modulatory impact is unknown, but the present scientific opinion is that CBD inhibits cytochrome P450 enzyme activity, which in turn affects THC metabolism especially after oral administration [29].

The main reason for this decrease in oral bioavailability is that cannabinoids undergo comprehensive first-pass metabolism with CYP 450 genes before systemic circulation is achieved [20].

With an inhalation, first-pass metabolism is prevented, as cannabinoids enter the circulation through the lungs [20].

Synthetic cannabinoids

When scientists first explored the endocannabinoid system and tried to create new medicines for cancer pain, SCs appeared in the 1970s. SC emerged on the illegal drug market around the year 2000, where there prevalence was underestimated for a long time [30]. Since then their market place has risen steadily. The illicit market has recognized more than 560 synthetic psychoactive substances. In the last 5 years, there has been a steep increase with the appearance of 380 fresh synthetic drugs [31]. More than 160 SCs have been recognized in different products since 2008. Most SCs are produced by Asian based chemical companies [32].

The rise in consumption of SCs was particularly remarkable compared to other new drugs on the market [33]. In general, these products are provided as herbal blends. Tablets, capsules or powders can also be purchased [34]. They are often smoked by pipe or as a joint [35]. Newer liquid formulations have recently emerged which can be vaporized by electronic cigarette [36].

The pharmacological characteristics of SCs are distinct from cannabis. This particular lipophilic [37] molecules are complete CB1 (CBD receptor 1) and CB2 (CBD receptor 2) agonists. Their potential binding affinity to these receptors is also much greater than that of THC resulting in significantly greater psychoactive effects [38].

SC effects depend on the type of product used and its dose. Similarly, the pharmacokinetics depends on the administration route. In some cases the onset of psychoactive effects and physical symptoms begins a few minutes after smoking [39]. The effects are comparable to those observed after high doses of THC.

Anxiety is frequently reported. Some users have described feeling limited in their movements, whereas no motor deficits are objectively observed. On average, the effects last for about 6 hours, steadily decreasing until the next day [40-42].

Endocannabinoids

Following the identification of cannabinoid receptors, endogenous ligands were detected for these receptors, called endocannabinoids, a family of eicosanoids [43]. There were 5 recognized endocannabinoids. These are N-arachidonylethanolamide (anandamide), 2-AG (2-arachidonoylglycerol), 2-arachidonoylglycerol ether (noladin ether), O-arachidonylethanolamine (virodhamine), and NADA (N-arachidonyl-dopamine) [44-47].

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Table 1: Pharmacokinetics of cannabis based on route of administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Inhalation</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Dose Consumed</td>
<td>~50% (loss due to pyrolysis)</td>
<td>100%</td>
</tr>
<tr>
<td>Trajectory to Circulation</td>
<td>Lungs–Bronchi–Bronchiole–Alveoli</td>
<td>Stomach–Small Intestines–Portal Vein–Liver</td>
</tr>
<tr>
<td>Other Factors Affecting Uptake</td>
<td>Intake upon inhalation (puff duration, intake volume, holding time)</td>
<td>Absorption (stomach contents, metabolic rate, genetic variants in CYP 450 enzyme activity, enzyme regulation by other drugs)</td>
</tr>
<tr>
<td>First-Pass Hepatic Metabolism</td>
<td>Bypassed</td>
<td>First-Pass Hepatic Metabolism by CYP450 enzymes</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>2-56%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Onset</td>
<td>Immediate</td>
<td>30–90 min</td>
</tr>
<tr>
<td>Time of Peak Plasma</td>
<td>5-10 min</td>
<td>1–6 h</td>
</tr>
<tr>
<td>Duration</td>
<td>2-4 h</td>
<td>4–6 h</td>
</tr>
</tbody>
</table>
Cannabinoid receptors and their endogenous ligands are the cannabinoid system found in mammals and many other species, which is teleologically millions of years old [48]. Endocannabinoids serve as neurotransmitters or neuromodulators [49]. Anandamide and NADA not only bind to cannabinoid receptors, but also activate VRI (vanilloid receptors) and selective ion channels associated with hyperalgesia [44, 50].

The endocannabinoids are produced on demand by cleavage of membrane lipid precursors and released in a stimulus dependent manner from cells [51]. They are quickly deactivated by absorption into cells and metabolized after its release [52, 53].

Therapeutic uses

Many illness have been treated with cannabis preparations. In addition to phytocannabinoids, several synthetic cannabinoid derivatives and modulation of the endocannabinoid system are under clinical investigation that are devoid of psychotropic effects [54].

Therapeutic effects can be designed as: 1) clinically, established, 2) clinically relatively well-confirmed, 3) clinically less confirmed.

Established effects

Marinol (dronabinol, Δ9-THC) is approved for medical use in HIV/AIDS patients, with refractory nausea and vomiting induced by antineoplastic medicines used for cancer therapy and loss of appetite [55]. This impacts can be considered as established effects for THC and cannabis. THC is also efficient in ipecac syrup induced cancer cachexia and nausea. Cesamet (nabilone) is approved for cancer chemotherapy related nausea and vomiting [56].

Relatively well-confirmed effects

In recent years there is also increasing evidence for therapeutic effects of THC and cannabis extracts in spasticity due to multiple sclerosis and spinal cord injury, chronic pain and Tourette's syndrome [57]. Effects in some other movement disorders (including dystonia and levodopa-induced dyskinesia), in asthma and glaucoma can also be regarded as relatively well-confirmed effects with small placebo controlled trials demonstrating benefits. However, results were sometimes conflicting [58].

Less confirmed effects

There are several indications, in which mainly case reports suggest benefits [59]. These are allergies, inflammation, epilepsy, intractable hiccups, depression, bipolar disorders, anxiety disorders, addiction to opiates and alcohol, withdrawal symptoms, and disturbed behaviour in Alzheimer's disease [60].

Pharmacological effects of other cannabinoid

CBD is a non-psychotomimetic cannabinoid that has been shown to have sedative, anti-epileptic, anti-dystonic, anti-emetic and anti-inflammatory impacts. It decreases intraocular pressure, has been neuroprotective and has antagonised THC's psychotropic and several other effects. In psychiatry, anxiolytic and anti-psychotic characteristics may be helpful [60].

Central nervous system and neurochemistry

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators, such as acetylcholine, dopamine, GABA (γ-aminobutyric acid), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides [42].

Cannabinoids influence the activity of most neurotransmitters in a complex manner, which sometimes may result in contradictory effects with suppression or induction/intensification of seizures, emesis, pain and tremor depending on subject and condition [42].

Circulatory system

THC may be lead to tachycardia [61] and increase cardiac output with enhanced cardiac labour and demand for oxygen [62]. It can also produce peripheral vasodilation and orthostatic hypotension. Tachycardia by THC may easily be explained by vagal inhibition [63]. Regular use can lead to bradycardia [64].

Some other organ systems and effects

Bone formation

Preliminary observations show that endocannabinoids seem to stimulate bone formation [65].

Cancer

Cannabinoid agonists inhibited in vitro the proliferation of human breast cancer cells, and directly applied at the tumour site, showed antineoplastic activity against malignant gliomas [66, 67].

Digestive tract

Cannabinoid agonists inhibit gastrointestinal motility and gastric emptying in rats [68]. THC has induced a substantial delay in gastric emptying in a research with humans [69]. Furthermore, CB agonists inhibited rat's secretion of gastric acid induced by pentagastrin [70].

Eye

The proof of cannabinoid receptors at various locations (anterior eye, retina and corneal epithelium) indicates that cannabinoids regulates various physiological functions in the human eye [71]. Vasodilation in the eye is noted after expose to THC as a conjunctival reddening, THC and some other cannabinoids reduce intraocular pressure [71]. CB receptors in the eye are involved in this effect while intraocular pressure is not reduced by CB receptor agonists [72].

Toxicity

There was no substantiation of acute deadly instances in humans. However, THC can trigger myocardial infarction owing to circulation impacts [33, 34]. This is unlikely to occur in healthy individuals, but in people with heart disease who may at danger for orthostatic hypotension or elevated heart rate.

It is controversial whether heavy periodic consumption can lead to long term cognition impairment [35-37]. But irreversible impairment appears to be minimal if it occurs. Early users who begin their use before the age of 17 had poorer cognitive performance, particularly verbal IQ compared to users who begin later or non-users [58].

There is conflicting evidence that infants exposed to THC in utero suffer from development and cognitive impairment [39]. In vulnerable people, marijuana can induce schizophrenic psychosis and there is increasing evidence that there is a distinct cannabis psychosis.

Tolerance and dependence

Tolerance develops to most of the effects of THC causing changes in endocannabinoid formation and brain content [73, 59]. Cannabinoid use has been shown to replace increased heart rate to normal or slow heart rate and it also results in orthostatic hypotension [55, 60]. Tolerance can be linked primarily to modify the pharmacodynamics, probably based on receptor down regulation and desensitization of the receptor [74].

After abrupt cessation of chronic dosing with elevated doses of THC, withdrawal was noted in humans [75]. Subjects complaint of internal disturbances, irritability, insomnia and reported hot flashes, sweating, rhinorrhea, loose stools, hiccups and anorexia [76]. Symptoms of withdrawal are generally mild in humans and the risk of physical and psychological dependence is small compared to opiates, tobacco, alcohol and benzodiazepines [56-58].

CONCLUSION

Cannabis is a plant rich in various compounds that has a variety of impacts on the physiology of humans. These impacts are described mainly to cannabinoids and terpenes, large metabolite families that can interact with many of the body's cellular and physiological processes. While much studies are still remains to be done, the effects of these metabolites are a significant tool for managing a variety of clinical diseases.

Various concentrations of these compounds have distinct physiological impact and may affect the clinical utility based on how
the plant is given to patients. It can be assumed that several cannabinoids and cannabinoid system modulations will find their way into the pharmacies from preclinical research within a century.

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CONFLICTS OF INTERESTS
Declared none

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