Mechanisms of Action and Pharmacokinetics of Cannabis

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ABSTRACT
At least 100 cannabis species are compounds known as cannabinoids, a molecule with a 21-carbon terpenophenolic skeleton. Cannabinoids produce more than 100 naturally occurring chemicals, the most abundant of which are Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), terpenes, and flavonoids. THC and CBD bind with cannabinoid receptors (CB1 and CB2), which are present in the brain and many organs. Metabolism of cannabis is determined by the route of consumption. When inhaled, THC and its metabolites enter the bloodstream rapidly via the lungs; they achieve peak levels within 6 to 10 minutes and reach the brain and various organs. The bioavailability of inhaled THC is 10% to 35%. After THC is absorbed, it travels to the liver where most of it is eliminated or metabolized to 11-OH-THC or 11-COOH-THC. The remaining THC and its metabolites enter the circulation. The bioavailability of ingested THC is only 4% to 12%. THC is highly lipid soluble and is therefore rapidly taken up by fat tissue. The plasma half-life of THC is 1 to 3 days in occasional users and 5 to 13 days in chronic users. The bioavailability of CBD via inhalation is 11% to 45%, whereas that of oral CBD is 6%. CBD has high lipophilicity and therefore is rapidly distributed in the brain, adipose tissue, and other organs. CBD is hydroxylated to 7-OH-CBD and 7-COOH-CBD by cytochrome P450 enzymes CYP3A4 and CYP2C9 in the liver and is excreted mainly in feces and less in urine. The plasma half-life of CBD is 18 to 32 hours.

INTRODUCTION
Cannabis (Cannabis sativa L.) has been cultivated and used medicinally for more than 4000 years in China. The earliest use of cannabis as a medicine was attributed to the legendary Chinese Emperor Shen Nung, who is thought to have lived around 2700 BC. His teachings were passed down in writing in Shen Nung Pen-ts’ao Ching, a second-century Chinese book of herbal remedies.3 Cannabis was used for medical conditions ranging from menstruation to absentmindedness and eventually for more than 100 ailments.2 The Chinese mainly used the seeds of cannabis for medicinal purposes.3,4 Cannabis was also widely used in India, Persia, and Assyria. The use of cannabis then spread to the Middle East, Africa, Europe, and the United States. In the 19th century, William B. O’Shaughnessy served in India and introduced C. sativa to England. In 1839, he published the work “On the Preparations of the Indian Hemp or Gunjah,” which described various successful human experiments using cannabis preparations mainly for muscular spasms from tetanus and rabies and also for rheumatism and convulsions.5,6 In the second half of the 19th and early 20th centuries, more than 100 scientific articles on the therapeutic value of cannabis were published in Europe and the United States.4 The cannabis plant has many species, but the three main species are C. sativa, C. indica, and C. ruderalis. More than 500 compounds have been isolated from cannabis species, approximately 100 of which are compounds known as cannabinoids, a molecule with a 21-carbon terpenophenolic skeleton.7,8

Cannabinoids in the cannabis plant are called phytocannabinoids. They produce more than 100 naturally occurring chemicals. The most abundant chemicals are Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), terpenes, and flavonoids. THC is a psychotropic chemical that makes people feel “high,” whereas CBD is a non-psychotropic chemical.9 With the recent legalization of cannabis, medical use of cannabis and its compounds has increased. This article reviews the mechanisms of action and pharmacokinetics of cannabis.

MECHANISMS OF ACTION
Until the mid-12th century, the existence of human cannabinoid pathways was not understood. The discovery of THC and CBD led to identification of the signaling pathways. Evidence that THC interacts with a particular mammalian target was uncovered in murine neuroblastoma cells, which expressed upregulated adenylate cyclase in response to exposure to the compound or its synthetic analogues. This finding paved the way for the isolation and cloning of a G protein–coupled receptor that subsequently was named cannabinoid receptor type 1 (CB1).10 Cannabinoid receptor type 2 (CB2) was later isolated from human leukemia cells.11 CBD was shown to directly exert activity at the CB2 receptor. Identification of these receptors led to the hypothesis that an endogenous cannabinoid system in the mammalian body, known as endocannabinoids, might also exist. The first endogenous cannabinoid ligand was then isolated from pig brain and named N-arachidonoylthanolamine (AEA) or anandamide.12 The second endogenous ligand was also isolated from intestinal tissue and named 2-arachidonoylglycerol (2-AG).13,14 Both AEA and 2-AG are arachidonic acid derivatives produced from...
phospholipid precursors through activity-dependent activation of specific phospholipase enzymes. A number of other endogenous ligands have since been discovered, including N-arachidonoyl dopamine, N-arachidonoyl glycerol ether, and O-arachidonoyl ethanolamine.

AEA and 2-AG do not share the same biosynthetic or metabolic pathways. Different pathways can produce AEA from the phospholipid precursor N-arachidonoyl-phosphatidylethanolamine, the most important being a direct conversion catalyzed by an N-acyl-phosphatidylethanolamine-selective phosphodiesterase. After its reuptake, AEA is hydrolyzed by the enzyme fatty acid amide hydrolase, producing arachidonic acid and ethanolamine.

2-AG is mainly synthesized through activation of phospholipase C and subsequent production of diacylglycerol, which is converted to 2-AG by diacylglycerol lipase. 2-AG is primarily metabolized by monoacylglycerol lipase, leading to the formation of arachidonic acid and glycerol. CB1 and CB2 receptors are certainly the most well-known targets for AEA and 2-AG, which activate them with different affinity. AEA has the highest affinity in both cases. Physiological or pathological stimuli induce synthesis and release of endocannabinoids, which can subsequently activate cannabinoid receptors. Therefore, endocannabinoids are synthesized and released “on demand” through the cleavage of membrane phospholipid precursors.

THC and CBD of the phytocannabinoid system can also bind to G protein–coupled cannabinoid receptors CB1 and CB2. CB1 receptors are particularly abundant in the frontal cortex, hippocampus, basal ganglia, hypothalamus, cerebellum, spinal cord, and peripheral nervous system. They are present in both inhibitory GABAergic neurons and excitatory glutamatergic neurons. CB2 is most abundantly found on cells of the immune system, hematopoietic cells, and glia cells. CB2 is mainly expressed in the periphery under normal healthy conditions; in conditions of disease or injury, this upregulation occurs within the brain and CB2 is therefore expressed in the brain in unhealthy states. CB1 and CB2 are also widely distributed in the cardiovascular system.

Apart from their binding to CB1 and CB2, endocannabinoids and phytocannabinoids also bind with other G protein–coupled receptors (GPR55, GPR18, GPR3, GPR6, GPR12), transient receptor potential channels (TRP vanilloids TRPV1 to TRPV4, TRP ankyrin TRPA1, TRP M member TRPM8), peroxisome proliferator–activated receptors (PPAR2, PPARγ), monoamine transporters (norepinephrine, dopamine, serotonin 1A receptor), fatty acid amide hydrolase, monoacylglycerol lipase, transport fatty acid–binding proteins, adenosine equilibrative nucleoside transporters, and glycine receptors α1 and α3. There is evidence that endocannabinoid function is decreased in various medical disorders such as migraine, fibromyalgia, irritable bowel syndrome, multiple sclerosis, diabetic neuropathy, Parkinson disease, and others. The endocannabinoid deficiency theory also posits that such deficiencies could arise for genetic or congenital reasons or be acquired due to intercurrent injury or disease that consequently produces characteristic pathophysiological syndromes with particular symptomatology. Phytocannabinoids that have similar actions on cannabinoid receptors may have therapeutic potential in these medical disorders.

Cannabinoids produced in the laboratory to structurally or functionally mimic endocannabinoids or phytocannabinoids are synthetic cannabinoids. Most synthetic cannabinoids are designed based on THC of the natural cannabinoids. They strongly bind to CB1, which is linked to the psychoactive effects or “high” of cannabis. At least 180 synthetic cannabinoids were reported by the European Monitoring Centre for Drugs and Drug Addiction in 2019. Synthetic cannabinoids are typically consumed through smoking or in a concentrated liquid form. The negative effects of synthetic cannabinoids include palpitations, paranoia, intense anxiety, nausea, vomiting, confusion, poor coordination, and seizures. Interestingly, some individuals reported strong compulsions with persistent cravings to reuse a week after cessation and some reported withdrawal symptoms such as headache, nausea, and vomiting.

PHARMACOKINETICS

The metabolism of cannabis depends on the route of consumption. After oral consumption, THC travels to the liver where most of it is eliminated or metabolized. THC is metabolized into other molecules by CYP2C and CYP3A in the liver. These enzymes turn THC into 11-OH-THC, which is also psychoactive, and then into 11-COOH-THC, which is not psychoactive. More than 65% of cannabis is excreted in the feces and approximately 20% is excreted within 5 days as hydroxylated and carboxylated metabolites. Among the major metabolites, THC metabolite 11-COOH-THC is the primary glucuronide conjugate in urine, whereas THC metabolite 11-OH-THC is the predominant form in feces. The remaining THC and both its metabolites reach the heart and then enter the circulation. THC and 11-OH-THC reach the brain simultaneously. The bioavailability of ingested THC is only between 4% and 12%. THC is highly lipid soluble. It is rapidly taken up by fat tissue where it accumulates. From these fat deposits, THC is slowly released back into the bloodstream.
After inhalation, THC and its metabolites enter the bloodstream quickly through the lung, with the peak achieved within 6 to 10 minutes after inhalation.\textsuperscript{30} Across all users, light and heavy, the bioavailability for inhaled THC is between 10% and 35%.\textsuperscript{30,31}

In general, inhalation produces a stronger psychoactive effect than ingestion. After inhalation, THC concentrations are higher in the brain than in the blood.\textsuperscript{32} The plasma half-life of THC is approximately 1 to 3 days in occasional users and 5 to 13 days in chronic users.\textsuperscript{33}

CBD is another chemical of cannabis. CBD enters the body similarly to THC. The pharmacokinetics of CBD is complex and the bioavailability of oral CBD is low across species.\textsuperscript{34-37} In general, the most abundant metabolites of CBD are hydroxylated 7-COOH derivatives that are excreted either intact or as glucuronide conjugates.\textsuperscript{38} CBD can either enhance or inhibit activation of its binding site targets. CBD blocks activation of the equilibrative nucleoside transporter (GPR55) and the TRP cation channel subfamily (glycine receptors, TRPM8), among others, and enhances activity of the serotonin 1A receptor, glycine receptors α1 and α3, and TRPA1.\textsuperscript{38}

The route of administration affects the pharmacokinetics of CBD. Bioavailability via inhalation is 11% to 45% (mean 31%), whereas oral bioavailability of CBD is approximately 6% in humans. CBD has high lipophilicity. It rapidly distributes in the brain, adipose tissue, and other organs.\textsuperscript{18,35} CBD has low water solubility and absorption leads to variable pharmacokinetics if CBD is given in capsules. CBD given in oil products and by oral-mucosal/sublingual delivery through sprays or lozenges has less variability. The half-life of CBD is estimated at 18 to 32 hours.\textsuperscript{18,39}

There are studies indicating that THC and CBD act on cytochrome P450 isoenzymes to affect the metabolism of various drugs. THC is a CYP1A2 inducer that may lead to reduced drug concentration via increased metabolism and consequently decreased drug effect. In contrast, CBD inhibits CYP3A4 and CYP2D6 and may lead to reduced drug concentration via enhanced metabolism, which thus exaggerates the drug’s effects and may result in substantial adverse reactions.\textsuperscript{40,41} In addition, drugs that are CYP3A4 inducers have been reported to reduce THC and CBD levels, whereas drugs that are CYP3A4 and CYP2C9 inhibitors increase THC and CBD levels.\textsuperscript{31,42}

Finally, there is growing concern about the risk of transferring inhaled cannabis into breast milk. Pharmacokinetic data indicate that THC is detected in human breast milk in low to moderate concentrations.\textsuperscript{43-46} The long-term effects of THC on the developing infant brain are not clear. Mothers should be cautious about using cannabis during pregnancy and breast feeding.\textsuperscript{46}

**CONCLUSION**

The mechanisms of action and pharmacokinetics of cannabis are related mainly to THC and CBD. Both THC and CBD bind with cannabinoid receptors CB1 and CB2 of endocannabinoids in the body. THC and CBD enter the body by inhalation or by oral ingestion. Their bioavailability is different in humans. They have high lipophilicity and rapidly distribute in the brain, adipose tissue, and other organs. THC is a psychotropic chemical that makes people feel “high,” whereas CBD is a nonpsychotropic chemical. CBD was recently shown to have therapeutic potential in a variety of medical disorders such as epilepsy. Further research should continue to look at the potential of cannabis base compounds for the treatment of different medical conditions. 

**Disclosure Statement**

The author(s) have no conflicts of interest to disclose.

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**Authors’ Contributions**

Sirichai Chayasirisobhon, MD, FAAN, wrote this article, which is a collection of the author’s 3-year experiences and those of other experts in CBD therapy listed in the references; compiled, analyzed, and oversaw materials, data, and study design; and has given final approval to the manuscript.

**How to Cite this Article**


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