

Cannabidiol (CBD) — what we know



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Cannabidiol (CBD) has been recently covered in the media, and you may have even seen it as an add-in booster to your post-workout smoothie or morning coffee. What exactly is CBD? Why is it suddenly so popular?

How is cannabidiol different from marijuana?

CBD stands for cannabidiol. It is the second most prevalent of the active ingredients of cannabis (marijuana). While CBD is an essential component of medical marijuana, it is derived directly from the hemp plant, which is a cousin of the marijuana plant. While CBD is a component of marijuana (one of hundreds), by itself it does not cause a “high.” According to a report from the [World Health Organization](#), “In humans, CBD exhibits no effects indicative of any abuse or dependence potential.... To date, there is no evidence of public health related problems associated with the use of pure CBD.”

Is cannabidiol legal?

CBD is readily obtainable in most parts of the United States, though its exact legal status is in flux. All 50 states have laws legalizing CBD with varying degrees of restriction, and while the federal government still considers CBD in the same class as marijuana, it doesn’t habitually enforce against it. In December 2015, the FDA eased the regulatory requirements to allow researchers to conduct CBD trials. Currently, many people obtain CBD online without a medical cannabis license. The [government’s position](#) on CBD is confusing, and depends in part on whether the CBD comes from hemp or marijuana. The legality of CBD is expected to

change, as there is currently bipartisan consensus in Congress to make the hemp crop legal which would, for all intents and purposes, make CBD difficult to prohibit.

The evidence for cannabidiol health benefits

CBD has been touted for a wide variety of health issues, but the strongest scientific evidence is for its effectiveness in treating some of the cruelest childhood epilepsy syndromes, such as Dravet syndrome and Lennox-Gastaut syndrome (LGS), which typically don't respond to antiseizure medications. In numerous studies, CBD was able to reduce the number of seizures, and in some cases it was able to stop them altogether. Videos of the effects of CBD on these children and their seizures are readily available on the Internet for viewing, and they are quite striking. Recently the FDA approved the [first ever cannabis-derived medicine](#) for these conditions, Epidiolex, which contains CBD.

CBD is commonly used to address anxiety, and for patients who suffer through the misery of insomnia, studies suggest that CBD may help with both falling asleep and staying asleep.

CBD may offer an option for treating different types of chronic pain. A study from the *European Journal of Pain* showed, using an animal model, CBD applied on the skin could help lower pain and inflammation due to arthritis. Another study demonstrated the mechanism by which CBD inhibits inflammatory and neuropathic pain, two of the most difficult types of chronic pain to treat. More study in humans is needed in this area to substantiate the claims of CBD proponents about pain control.

Is cannabidiol safe?

Side effects of CBD include nausea, fatigue and irritability. CBD can increase the level in your blood of the blood thinner coumadin, and it can raise levels of certain other medications in your blood by the exact same mechanism that grapefruit juice does. A significant safety concern with CBD is that it is primarily marketed and sold as a supplement, not a medication. Currently, the FDA does not regulate the safety and purity of dietary supplements. So you cannot know for sure that the product you buy has active ingredients at the dose listed on the label. In addition, the product may contain other (unknown) elements. We also don't know the most effective therapeutic dose of CBD for any particular medical condition.

The bottom line on cannabidiol

Some CBD manufacturers have come under government scrutiny for wild, indefensible claims, such that CBD is a cure-all for cancer, which it is not. We need more research but CBD may be prove to be an option for managing anxiety, insomnia, and [chronic pain](#). Without sufficient high-quality evidence in human studies we can't pinpoint effective doses, and because CBD is currently is mostly available as an unregulated supplement, it's difficult to know exactly what you are getting. If you decide to try CBD, talk with your doctor — if for no other reason than to make sure it won't affect other medications you are taking.

Cannabinoid Receptors

Cannabinoid receptors are part of the endocannabinoid system, which is now known to be a ubiquitous neuromodulatory system with wide-ranging actions.

From: [Comprehensive Natural Products II, 2010](#)

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Constitutive Activity in Receptors and Other Proteins, Part B

Tung M. Fong, in [Methods in Enzymology](#), 2010

Abstract

The cannabinoid receptors are G protein-coupled receptors that are activated by endocannabinoids or exogenous agonists such as tetrahydrocannabinol. Upon agonist binding, cannabinoid receptors will activate G_i which in turn inhibits adenylyl cyclase. Recently, inverse agonists for the cannabinoid receptors have been identified, demonstrating constitutive activity of the cannabinoid receptors. Several methods have been used to measure inverse agonist activity of ligands for the cannabinoid receptors, including G_i -cAMP second messenger assay, $GTP\gamma S$ binding assay, and electrophysiological assays. Each assay has its advantages and limitations, and the G_i -cAMP second messenger assay appears to provide the best overall measurement of inverse agonism in a cellular environment.

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Obesity management

Robert F. Kushner, in [Sleep Apnea and Snoring](#), 2009

4.5 THE ENDOCANNABINOID SYSTEM

Cannabinoid receptors and their endogenous ligands have been implicated in a variety of physiological functions, including feeding, modulation of pain, emotional behavior, and peripheral lipid metabolism.²⁷ The cannabinoid receptors, the endocannabinoids and the

enzymes catalyzing their biosynthesis and degradation constitute the endocannabinoid system or ECS. Cannabis and its main ingredient, Δ^9 -tetrahydrocannabinol (THC), is an exogenous cannabinoid compound. Two endocannabinoids have been identified: anandamide and 2-arachidonyl glyceride (2-AG). Two cannabinoid receptors have been cloned termed CB₁ (abundant in the brain) and CB₂ (present in immune cells). The brain ECS is thought to control food intake through reinforcing motivation to find and consume foods with high incentive value and regulate actions of other mediators of appetite. The first selective cannabinoid CB₁ receptor antagonist, called rimonabant, was discovered in 1994. The medication is effective in antagonizing the appetite-stimulating effect of THC and suppressing appetite when given alone in animal models.

Thus far, several large prospective, randomized controlled trials have demonstrated the effectiveness of rimo-nabant as a weight loss agent.²⁸ Taken as a 20 mg dose, subjects lost an average of approximately 6.5 kg compared to approximately 1.5 kg for placebo at 1 year. Concomitant improvements were seen in waist circumference and cardiovascular risk factors. The most common reported side effects include depression, anxiety and nausea. Rimonabant is approved for use in Europe and other countries outside the US.

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Platelet Receptors

Kenneth J. Clemetson, Jeannine M. Clemetson, in [Platelets \(Third Edition\)](#), 2013
7 Cannabinoid Receptors

Cannabinoid receptors (CB) receptors are G-protein coupled receptors and belong to the rhodopsin-like subfamily. Earlier controversial, CB1 and CB2 have now been shown to be expressed in human platelets, by Western blotting and ELISA, confocal microscopy, and binding assays. CB1, and to a lesser extent CB2, are expressed in highly purified human platelets. Both receptor subtypes were predominantly intracellular, explaining why they might remain undetected in preparations of plasma membranes.¹¹⁶ These findings may explain the procoagulatory effects of delta-9-tetrahydrocannabinol in human platelets.¹¹⁷

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Constitutive Activity in Receptors and Other Proteins, Part B

Alan C. Spivey, Chih-Chung Tseng, in [Methods in Enzymology](#), 2010
1.1 Cannabinoid receptors

Cannabinoid receptors obtained their name as a result of their response to cannabinoids, for example, Δ^9 -tetrahydrocannabinol (Δ^9 -THC) from *Cannabis sativa* (marijuana) and synthetic analogs. Cannabinoid receptors are members of the endocannabinoid system and are key mediators of many psychological processes (Wotjak, 2005). These receptors belong to the rhodopsin family of G protein-coupled receptors (GPCRs). Two subtypes of receptors have

been identified: type 1 (CB₁) and type 2 (CB₂). The CB₁ receptor abounds in the brain and central nervous system (CNS), whereas the CB₂ is found mainly in the immune system (Howlett *et al.*, 2002).

As deduced by complementary DNA encoding (Matsuda *et al.*, 1990) and molecular cloning (Gerard *et al.*, 1991), human CB₁ receptors are encoded by an amino sequence of 472 residues. As for other proteins belonging to the rhodopsin family, the CB₁ receptor has seven transmembrane helical (TMH) domains of which the TMH-4 and -5 domains form the high-affinity ligand binding site (Shire *et al.*, 1996).

Studies of the physiological roles of the CB₁ receptor have revealed strong correlations with inhibition of adenylyl cyclase, pain control, regulation of ion channels, modulation of energy intake, and various other signal transduction pathways (Howlett, 2004; Pagotto *et al.*, 2006). Among these functions, arguably the most promising feature of this receptor's regulatory profile from a therapeutic-potential standpoint, is (or at least was, see below) its role in energy regulation and metabolism. In particular, animal models revealed that CB₁ knockout mice were leaner than wild-type species (Di Marzo *et al.*, 2001). Blocking the CB₁ receptor potentially therefore provides a therapeutic strategy for treatment of obesity and metabolic syndrome as well as drug additions and addiction to smoking (Di Marzo *et al.*, 2001).

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Analgesic Agents in Rheumatic Disease

Gregory R. Polston, Mark S. Wallace, in [Kelley and Firestein's Textbook of Rheumatology \(Tenth Edition\)](#), 2017

Cannabinoid Agonists

Cannabinoid receptors type 1 (CB₁) are located at multiple locations in the peripheral and central nervous system, whereas CB₂ receptors are located on inflammatory cells (monocytes, B/T cells, mast cells). CB₂ activation results in a reduction in inflammatory mediator release, plasma extravasation, and sensory terminal sensitization. Activation of peripheral CB₁ receptors results in a reduction in the release of pro-inflammatory terminal peptides and a reduction in terminal sensitivity. Activation of central CB₁ receptors leads to reduced dorsal horn excitability and activates descending inhibitory pathways in the brain. The net result is a reduction in both pain and hyperalgesia. Inhaled cannabis has been extensively studied in various pain syndromes with mixed results. More recent well-controlled trials in neuropathic pain have shown promise.¹¹⁸ Sativex is a sublingual spray containing a mixture of tetrahydrocannabinol and cannabidiol, which failed to reach the primary efficacy endpoint in a phase III cancer pain trial. Studies with cannabis in musculoskeletal pain are limited; however, it has been shown to reduce the pain of rheumatoid arthritis and chronic pain of various other causes.¹¹⁹

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Receptor Targets in Alzheimer's Disease Drug Discovery

J. Wallach, ... A. Adejare, in [Drug Discovery Approaches for the Treatment of Neurodegenerative Disorders](#), 2017

Cannabinoid Receptors

Cannabinoid receptors include CB₁ and CB₂. CB₁ is often stated to be the most highly expressed GPCR in the CNS and plays essential roles in numerous processes including learning, memory, sensory processing, and pain perception (Mackie, 2006). CB₁ and CB₂ cannabinoid receptor agonists show promise in neurodegenerative diseases including AD (Campbell and Gowran, 2007; Scotter et al., 2010). For example, the CB₁ agonist tetrahydrocannabinol (THC), in addition to decreasing presynaptic glutamergic signaling and AChEI activity, impairs A β aggregation (Eubanks et al., 2006). A great deal of promising preclinical research has been performed supporting the endocannabinoid system as relevant territory in the search for AD modification and symptomatic therapies (Scotter et al., 2010; Ramírez et al., 2005; Aso and Ferrer, 2014; Caoa et al., 2014). Anecdotal reports on the efficacy of cannabis, the cannabinoid-rich flowers of the *Cannabis* genus, in a large number of therapeutic areas exist and find strong support in preclinical research. Still, controlled clinical trials are drastically needed. Medicinal cannabis and cannabis products are frequently used, with reported benefits, in related NDDs including multiple sclerosis, amyotrophic lateral sclerosis (ALS) as well as epilepsy (Chong et al., 2006; Consroe et al., 1997; Maa and Figi, 2014; Carter and Rosen, 2001).

A few clinical trials evaluating Δ^9 -THC (dronabinol) and its derivative nabilone in AD patients have been undertaken. In a trial of 15 AD patients treated with dronabinol for 6 weeks, a decrease in altered behaviors was observed as well as an increase in body weight in those previously refusing food. Side effects were those common to cannabis and included euphoria, somnolence, and tiredness, but did not warrant abandonment of the therapy (Volicer et al., 1997). Similar benefits (reduction in night-time agitation and behavioral disturbances) were reported in two pilot studies involving dementia patients (Walther et al., 2006, 2011). Nabilone provided prompt and dramatic improvements in agitation and aggressiveness in advanced AD patients refractory to antipsychotic and anxiolytic treatment (Passmore, 2008). Unfortunately, these studies were small and did not evaluate cognitive or neurodegenerative disease markers. Still, the promising results reported warrant further investigations with larger controlled trials, particularly given the potential for novel selective cannabinoid receptor ligands, which may have reduced psychoactive effects (Aso and Ferrer, 2014).

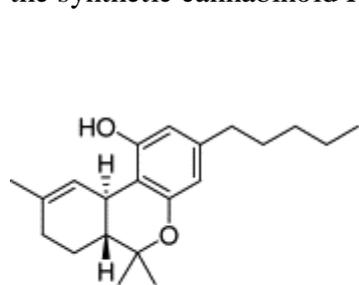
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Therapeutic Areas I: Central Nervous System, Pain, Metabolic Syndrome, Urology, Gastrointestinal and Cardiovascular

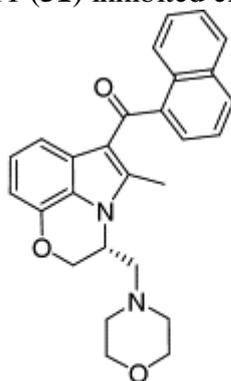
J.D. Gale, I. Mori, in *Comprehensive Medicinal Chemistry II*, 2007

6.30.5.2.6 Cannabinoid receptor agonists

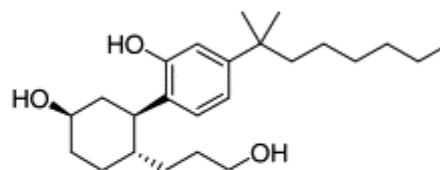
Cannabinoid receptors are involved in the control of the emetic reflex. Receptor agonists, e.g., Δ^9 -tetrahydrocannabinol (**48**, Δ^9 THC), have a marked antiemetic effect in the ferret in response to emesis evoked with either hyperosmolar saline or cisplatin.⁹⁸ The cannabinoid receptor agonist WIN-55212 (**49**) and other subtype-selective antagonists has revealed a role for CB₁ receptors in the control of vomiting in this species, which also extends to morphine-induced emesis. In a novel animal model of anticipatory emesis in the house musk shrew, a phenomenon experienced in clinical practice, Δ^9 THC and cannabidiol inhibit emesis, an effect not seen with ondansetron.⁹⁹ In the shrew, cannabinoid receptor agonists, including CP-55,940 (**50**), inhibit emesis evoked with cisplatin and lithium. In a pigeon model of emesis, the synthetic cannabinoid HU-211 (**51**) inhibited emesis evoked with cisplatin.



48 Δ^9 -Tetrahydrocannabinol
dronabinol



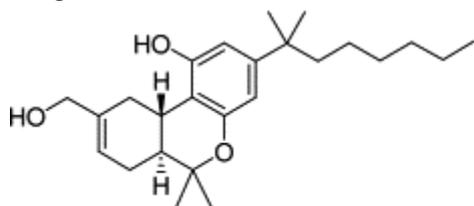
49 WIN-55212



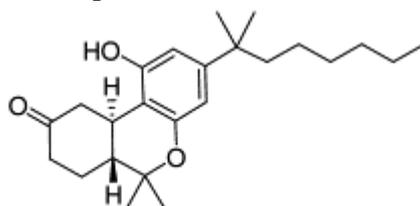
50 CP-55,940

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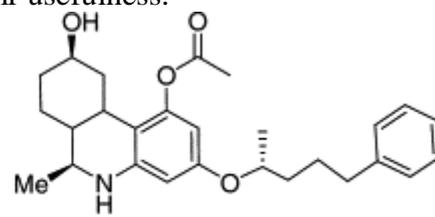
Nabilone (**52**), dronabinol (Δ^9 THC), and levonantradol (**53**) are used in clinical practice to control many forms of emesis, having inhibitory activity against nausea and vomiting evoked by cisplatin and other chemotherapeutic agents.¹⁰⁰ In addition the utility of this class of agent in the treatment of PONV has been suggested. Adverse events are common with this class of drug and include sedation, dizziness, and euphoria, and these limit their usefulness.



51 HU-211



52 Nabilone



53 Levonantradol

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Transporters and receptors in the anterior segment of the eye

Kishore Cholkar, ... Ashim K. Mitra, in [Ocular Transporters and Receptors](#), 2013

4.5.5 Cannabinoid receptors

The cannabinoid receptor belongs to G protein-coupled receptors with two subtypes referred as CB1 and CB2. This receptor is primarily located in the brain. CB2 was recognized in spleen macrophages and also in other cells of the immune system. Further, CB1 and CB2 are found in neural and non-neural tissues as well. CB1 predominates in the brain, while CB2 is abundant in peripheral tissues.

Further, the function of both the cannabinoid receptors includes the activation of the Akt/PKB survival pathway, and mitogen-activated protein kinases, extracellular signal-regulated kinase (ERK) 1/2 and p38 as well. In ocular tissue, the signaling pathways of both cannabinoids CB1 and CB2 involve differential changes in aqueous humor outflow and intraocular pressure (IOP) of the trabecular meshwork. However, no specific function of cannabinoid receptors is identified although they may be active in ocular surface epithelia. Several studies were performed on mouse and human conjunctival epithelial cells to exhibit the presence and properties of CB1 and CB2 receptors. The presence of both receptors was confirmed by mRNA and protein analyses through RT-PCR and Western blot, respectively in mouse and human conjunctival sections, a human conjunctiva-derived cell line (IOBA-NHC) and exfoliated cells. Further, it has been demonstrated that cannabinoid receptor activation decreases the levels of cAMP in IOBA-NHC cells, but specific CB1 and CB2 antagonists can overcome this effect. CB1 and CB2 are associated with several functional responses, which include decrease in cAMP levels and modulation of stress signaling pathways.

The cannabinoid receptor may have an anti-inflammatory response to the ocular surface [142]. These receptors may be involved in the inflammatory processes and also in the regulation of epithelial renewal at the ocular surface [143].

Δ^9 -THC and some other cannabinoids are associated with therapeutic potentials in reducing IOP. Colasanti [144] suggested that some compounds from this class may help in reducing IOP by either decreasing aqueous humor formation or by increasing aqueous humor outflow from the anterior chamber of the eye. Later, Pate et al. [145] found that topical administration of anandamide in rabbit eye lowers IOP. Although the CB1 and CB2 signaling pathways have been involved in the alteration of aqueous humor outflow and IOP, the exact mechanism is yet to be revealed.

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Development & Modification of Bioactivity

Arno Hazekamp, ... Renee L. Ruhaak, in [Comprehensive Natural Products II](#), 2010

3.24.3.1 The Cannabinoid Receptors: CB1 and CB2

The cannabinoid receptors are a class of receptors under the G-protein-coupled receptor superfamily. Their ligands are known as cannabinoids or endocannabinoids depending on whether they come from external or internal (endogenous) sources. Cannabinoid receptors have a protein structure defined by an array of seven transmembrane-spanning helices with intervening intracellular loops and a C-terminal domain that can associate with G proteins of the $G_{i/o}$ family.⁸⁶

Until the discovery of specific Cannabis receptors, the biochemical mode of action of cannabinoids was much debated. Because of their lipophilic character, cannabinoids can penetrate cellular membranes by simple diffusion. Therefore, possible explanations for cannabinoid activity initially included unspecific membrane binding resulting in fluidity and permeability changes of neural membranes, the inhibition of acetylcholine synthesis, an increase in the synthesis of catecholamines, and an interaction with the synaptosomal uptake of serotonin.^{87,88} However, it was established in the mid-1980s that cannabinoid activity is highly stereoselective,⁸⁹ indicating the existence of a receptor-mediated mechanism.

The first reliable indications that cannabinoids act through receptors came when it was shown that cannabinoids can act as inhibitors of the adenylate cyclase second messenger pathway in brain tissue and neuroblastoma cell lines. This activity was dose-dependent, stereospecific, and could be modulated by pertussis toxin.^{90–94} Finally, a stereospecific G-protein-coupled cannabinoid receptor was found and cloned.⁹⁵ It was named ‘cannabinoid-binding receptor type 1’ or CB1. The CB1 receptor is most clearly localized in the central nervous system (CNS), therefore it is often called the ‘central receptor’, but it is also found in certain peripheral organs and tissues, such as lungs, liver, and kidneys.⁹⁶ CB1 receptors are thought to be the most widely expressed G-protein-coupled receptors in the brain. Activation leads to the inhibition of adenylate cyclase activity.⁹⁷ The CB1 receptor also modulates ion channels, inducing, for example, the inhibition of N- and P/Q-type voltage-sensitive Ca^{2+} channels and the activation of G-protein inwardly rectifying K^+ channels. Besides these well-established cannabinoid receptor-coupled events, cannabinoid receptors have also been shown to modulate several signaling pathways that are more directly involved in the control of cell proliferation and survival, including extracellular signal-regulated kinase (ERK), c-jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt, focal adhesion kinase (FAK), and the ceramide pathway.⁹⁸

Subsequently, a second cannabinoid receptor (CB2) was found with a possible role in immunological processes.⁹⁹ The CB2 receptor was first described as a peripheral G-protein-coupled receptor (GPCR), mainly localized in the immune system, therefore it is often called

the ‘peripheral receptor’. However, nowadays it appears that the situation is more complex, as CB2 expression was also reported to be present in neurons of the brain.¹⁰⁰ It is primarily expressed by immune tissues such as leukocytes, spleen, and tonsils, and it shows a different selectivity than the centrally acting CB1. So far, the physiological roles of CB2 receptors are proving more difficult to establish, but at least one seems to be the modulation of cytokine release.¹⁰¹ Recently, it has been recognized that CB2 may play a functionally relevant role in the CNS, mediated through microglial cells.¹⁰²

The cannabinoid signaling system is teleologically millions of years old, as it has been found in mammals, fish, and invertebrates down to very primitive organisms such as the hydra.¹⁰³ Surprisingly, the protein sequences of CB1 and CB2 show only about 45% homology. There are indications that CB receptors are evolutionary related to the vanilloid receptors.¹⁰⁴ The transient receptor potential vanilloid receptor 1 (TRVR1) can be activated by the fatty acid amide compound capsaicin. Based on the chemical similarities between capsaicin and endocannabinoids (see Section 3.24.3.2), it was hypothesized that TRVR1 and proteins of the endocannabinoid system share common ligands. This was confirmed when it was demonstrated that the endocannabinoid anandamide activates TRVR1 receptors.¹⁰⁵ Also, it was found in isolated blood vessel preparations that some endocannabinoids can activate vanilloid receptors on sensory neurons,¹⁰⁶ which raises the possibility that endocannabinoids are endogenous agonists for vanilloid receptors.¹⁰⁷ These receptors might therefore be putatively regarded as CB3 receptors.

There is mounting evidence of novel receptors expressed in endothelial cells and in the CNS that have cannabimimetic and therapeutic effects independent of the mechanisms described above.¹⁰⁸ In 2007, the binding of several cannabinoids to a GPCR (GPR55) in the brain was described.¹⁰⁹ These receptors are more likely to be functionally related than structurally, as there is currently no evidence for additional cannabinoid receptors in the human genome. However, not all of the effects of cannabinoids can be explained by receptor-mediated effects, and it is believed that at least some effects are nonspecific and caused through membrane perturbation.^{110,111}

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