Cannabis: Past, present, and future

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ABSTRACT

Introduction: This work is aimed at understanding the endocannabinoid system and its derivatives, showing in a timeline where we find ourselves in relation to a controversial and marginalized subject. Methodology: The text presents a narrative review of the literature, supported by studies from the PubMed and SciELO platforms. Results and Discussion: In the face of chronic inflammatory processes, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) have been shown to be a therapeutic option in the control of nociception in some diseases, with the potential to relieve pain through activated CB1 and CB2 cannabinoid receptors, which in turn modulate responses to nociceptive stimuli, in particular, induce peripheral tissue repair. Conclusion: With more than 4,500 years of therapeutic use, today, the lack of standardization of drugs and the lack of evidence for future therapeutic solidification does not completely discredit its current role, understanding that more benefits than risks are presented.

Keywords: Cannabis, Cannabidiol, Δ9-Tetrahydrocannabinol.

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INTRODUCTION

Knowing how to bury the pains of the past, writing new stories for your life, looking ahead and having new perspectives with evolution and wisdom based on scientific evidence, is what permeates the life of the upright and up-to-date health professional. Knowing the scientific bases, unrelated to cultural and political bias, is essential to perform a clean and quality science in clinical dental practice.

After a meeting and technical discussion in 2020, the committee of the *International Association for the Study of Pain* (IASP) suggested the definition of pain as an "Unpleasant sensory and emotional experience associated with or similar to actual or potential tissue damage", excluding the need to describe the painful sensation, differing between nociception and pain.

Thus, after a series of peripheral and central tissue connections and interactions, the perception of PAIN can vary from one person to another, even varying according to the environment in which they are inserted, without forgetting their cultural characteristics and emotional/psychological history.

Historically, man's use of cannabis dates back at least 10,000 years, and botanically speaking, that's a long time of contact with humanity. If it's not the oldest plant, it's one of them. However, it is from 2,700 BC that Cannabis begins its journey for medicinal purposes in China, adding up to exactly 4,724 years of recorded use.

In India, 1,000 B.C., the medical use of cannabis was much greater and better elaborated than in China, spreading through travelers in shamanic rituals. However, at the beginning of the Christian era, 1,000 AD, renowned physicians in Arabia (Muslims) already mentioned specific treatments and protocols in their textbooks.

Until then, science was composed of observational tests and cultural methodologies passed down between generations, like trial and error, without standardization, totally different from how we know science today, having seen our norms and controls by ethics committees added to research platforms.

In 1839 the Irish physician William B. O'Shaugnessy made the first scientific publication, a book, and 21 years later, the first scientific meeting on Cannabis would take place, organized by the Medical Society of the State of Ohio.

It is estimated that Brazil was the gateway of Cannabis to all of America, coming from African slaves (Angolans) and very widespread in the rural area of the Northeast in religious rituals and as medication. And amazingly, toothache medication.

The chemical structure of cannabidiol was elucidated in 1963 and THC in 1964 in Israel by Professor Raphael Mechoulam (*in memorian*) - "Identification and isolation of active components CBD / THC" -. In the 1970s, a Brazilian named Elisado Carlini (Paulista School of Medicine) was

already researching interactions between THC and other cannabinoids, and generated the world's first evidence that cannabidiol had anticonvulsant properties – 1975.

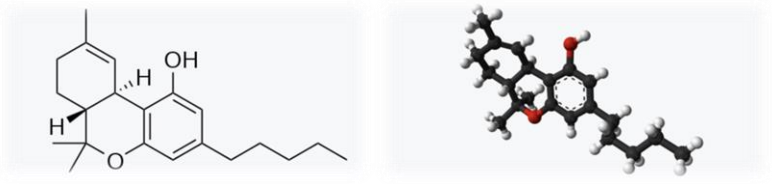
In 1988 specific receptors were discovered in the central nervous system (CNS) and in 1992 Mechoulam managed to isolate an endogenous substance (it is understood endogenous as produced by the human body) that would bind to such a receptor, called "Anandamide" (N-arachidonoyl ethanolamine), originated from the Sanskrit word that designates happiness, it is an analogue to Δ9 – tetrahydrocannabinol – THC. A few years later, another ligand was identified, "2AG" (2-Arachidonylglycerol), an analogue to cannabidiol – CBD. Voila, the endocannabinoid system (ECS) has been discovered.

In the 1980s and 1990s, another Brazilian named Antonio Waldo Zuardi published the first results indicating that CBD had anxiolytic and antipsychotic effects, and from then on, in the 2000s, research grew exponentially worldwide, with a notable contribution from Brazilian researchers, with an intensification of the resumption of valuable clinical trials from 2014 onwards.

First identified directly from the plant, the cannabinoid compounds THC (tetrahydrocannabinol) and CBD (cannabidiol) were synthesized in laboratories and later identified in the human body.

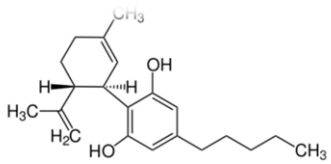
As a scientific standardization, plant-derived constituents are now called phytocannabinoids (150+ cataloged), those synthesized in the laboratory are called synthetic cannabinoids, and endogenous endocannabinoids are now called endocannabinoids.

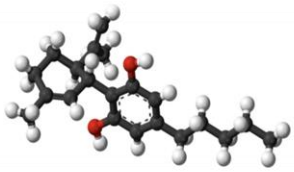
Δ9 – TETRAHYDROCANNABINOL = THC



It is the component best known by the scientific community and society in general, already present in the medical and dental class, characterized by having psychoactive/psychotropic activity.

CANABIDIOL = CBD





It is the second most abundant phytocannabinoid component in the plant, and much studied for its pharmacological safety and therapeutic properties, without psychoactive/psychotropic activity.

Main phytocannabinoids	Synthetic Cannabinoids	Endocannabinoids
Tetrahydrocannabinol - THC	Nabilone - THC Analogues	Anandamide - THC Analogue
Canabidiol – CBD	Dronabinol - THC Analogues	2AG – Análogo CBD
Canabigerol – CBG	AM630 - CBD Analogues	
Terpers	JWH133 - CBD analogue	

Thus, as with opioids, whose history, discovery, and demand were very similar to that of Cannabis (the search for an endogenous molecule in human beings through the discovery of specific receptors, derived from previous work carried out with rats), we have plant opioids, synthetic opioids and endogenous opioids. In practice, in humans we use opioids for pain control, and we can increase CNS concentrations by two routes:

1 - Exogenous = External production - synthetic tablets (injectable forms are restricted to hospital use).

2 - Endogenous = Internal production (endorphins, enkephalins and dynorphin) that increase their levels with physical activity, laughter, diet and sexual activity.

But what is cannabis? Cannabis sativa L., a technical name derived from botany, is a herbaceous plant of the Cannabis family that can be divided into some subspecies, in which, in summary, we are interested in knowing these three simple models:

1. Cannabis Sativa – higher concentration of THC
2. Cannabis Indica – higher concentration of CBD
3. Cannabis Ruderalis – very low or almost zero THC and CBD

Today, less marginalized, after long scientific processes between, in vitro models, animal models, cohort studies, clinical trials and systematic reviews, we can accurately describe the components of the endocannabinoid system. It is an independent neuronal modulation system, consisting of its own receptors, endogenous ligands, and specific metabolic enzymes that maintain its activity. In other words, ECS is an endogenous protective and regulatory system, let's say MODULATORY against noxious stimuli that would result in epileptic seizures, pain or psychological trauma, also acting directly on peripheral tissue repair processes.

It was possible to demonstrate through a synthetic cannabinoid of radiolabeled THC ([H3]CP-55940) the existence of a specific receptor for such a substance with great affinity in the membrane of the cerebral cortex of rats and subsequent perception in the induction of pharmacological effects, called CB-1 receptor.

CB-1 receptors in the CNS – Affinity for THC:

1. Cerebral cortex membrane – cognitive conditions and temporary amnesia.
2. Periqueductal gray matter – emotional changes and analgesia (hedonic effects – remaining in a relative state of happiness).
3. Hypothalamus – hypothermia and appetite.

A few years later, a second receptor was identified and cloned separately in the peripheral nervous system (PNS) and called the CB-2 receptor.

CB-2 Receptors in the SNP – Affinity for CBD:

1. Skeletal muscle – muscle inflammation/pain
2. Immune system – immune modulation
3. Dental pulp / gum – inflammatory modulation
4. Organs – tissue repairs and analgesia.

As a complete system, the endocannabinoid system calls for a beginning, middle, and end. And the finalizing mechanism of the endogenous process was missing, and this was due to the latest discovery of the enzymes responsible for the final metabolization of Anandamide and 2-AG, FAAH (Fatty Acid Starch Hydrolysis) and MAGL (Mono Acyl Glycerol Lipase) respectively.

Phytocannabinoids have high lipophilicity, which means they are more effective at absorption via the skin/mucous membrane, but they can also be prescribed orally after being correctly diagnosed and selected. Even though they can cause euphoria in predisposed patients, they are almost devoid of psychoactive influence in the concentrations used, improve sleep quality, reduce fatigue and have the potential to relieve pain and improve the immune system, given the absence of CB1 and CB2 receptors in the brainstem, an area responsible for respiratory cardio control. that is, it is not capable of leading to death due to abusive use via cardiorespiratory depression. The patient sleeps earlier, unlike other drugs, thus justifying its use with safety and benefit.

In the light of current science, the use of phytocannabinoids in dentistry is narrowed with a focus on the area of Temporomandibular Disorders and Orofacial Pain, which presents quality results and scientific support in the treatment and control of chronic pain, more specifically in therapies aimed at myofascial pain. However, some studies have shown significance in anxiety and altered sleep, however, there is a disagreement in the scientific literature, and it does not seem to be the only solution as it is propagated. It clearly does not replace conventional therapy so far.

There is a strong appeal that, because it comes from a natural source, it would be 100% safe, which is not true, and certainly the lack of standardization of these medications is the biggest problem. However, the evidence points to more benefits than risks.

Nevertheless, although we have a wealth of evidence with phytocannabinoids that support their use in chronic pain therapies in other areas (in fibromyalgia syndrome, osteoarthritis, chronic back pain, and rheumatoid arthritis pain), both in animal models and in clinical studies, especially neuropathic chronic pain, we still do not have the same number of qualified studies relating the effects of these products to the base *of cannabis in the orofacial region, and there is a lack* of further evidence for future therapeutic solidification.

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