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From ancient Asian relics to contemporaneity: A review of historical and chemical aspects of *Cannabis*

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ABSTRACT

From the Himalayan mountains to the South American coast, *Cannabis*, a general term for plants of the genus *Cannabis*, with thousands of years of contact with humankind, shows its versatility as food tools such as hemp, religious and hedonistic input, and other purposes through the millennia, according to the populations in question. In this paper, a review of the context of the use of *Cannabis* and its place in world history is presented, from ancient Mesopotamian relics, traditional Chinese and Ayurvedic medicines, to the reasoning behind the isolation and structural elucidation of three phytocannabinoids and the spread of *Cannabis* throughout the world.

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1. Introduction

The plants of the genus *Cannabis* L., belonging to the *Cannabaceae* family, are usually described as consisting of only three species: *Cannabis sativa* L., *Cannabis indica* Lam., and *Cannabis ruderalis* Janisch. *Cannabis* is a genus of angiosperms, dioecious (male and female reproductive systems in separate plants, but, with some rarity, show bisexual inflorescences) and manifests an annual life cycle consisting of growth, blossoming, reproduction, and death in an interval of approximately one year [1-4].

Morphologically, they are herbaceous, erect, and reach one to six meters in height, depending on the species in question. *Cannabis* leaves, famous for their starry shape, have three to nine lobes, arranged in order of increasing size toward the middle axis of the leaf, and actinodromous venation. In particular, in the vast majority of the aerial part of *Cannabis there* are trichomes, glandular and nonglandular, which are important for the production and storage of phytocannabinoid compounds [1-6].

2. *Cannabis* in ancient times

Approximately 10.000 years ago, with the end of the Last Glacial Period, the climate of the planet became milder and drier, climatic conditions that favored the cultivation of plants for subsistence, which was crucial for the development of the agricultural phenomenon in the Neolithic Revolution. Domestication of wild plant and animal species, formerly wild, whose profits were obtained through gathering and hunting, resulted in the transition from the nomadic character to the establishment of fixed colonies, from which communities and cities would develop [7,8].

Along with rice, soy, barley, and millet, *Cannabis* is considered one of the five main grains by ancient people. The seeds found in *Cannabis* achenes, rich in proteins (such as albumin and edestin) and essential unsaturated fatty acids (such as linoleic and linolenic acids) served as food, input for other culinary purposes, and even soap production. Although *Cannabis* is not more commonly used in the constitution of the diet in certain communities in contemporary Nepal, for example, it is still used for such attributions [9-12].

The *Cannabis* stalks, in turn, after undergoing a process of decomposition by running water, gave rise to hemp, a malleable vegetable fiber that is easy to handle, durable, and resistant to water. Used in the creation of ropes for tools, mooring animals, sails, and rigging for boat building, the production of fabrics for clothing and protection, paper, and any other applicable

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purposes, this fibre has assumed an important role in daily life and the development of civilization throughout history [8,13].

To exemplify the long co-existence with hemp, ancestral archaeological relics date the use of this plant fiber as a fabric to approximately 8000 years before the common era (BCE) as a material in ancient Mesopotamia (present-day Iran and Iraq), and to 4000 years BCE and 3000 years BCE as a material for ropes in China and Kazakhstan, respectively. Impressively, until the beginning of the nineteenth century, it was estimated that around 80% of fabrics, candles, ropes, among other items, were produced from hemp [9,14-16].

Used as a stunner to facilitate the capture of fish, *Cannabis* is possibly the first plant to be cultivated for non-food purposes. The *Pen Ts'ao Ching* (the oldest pharmacopoeia in the world of Chinese origin and oral traditions, compiled around the 1st century but related to periods dating back to 2700 BCE) quotes that 'The Ma-fen *('fruit' of Cannabis)' if ingested in excess, it can cause the user to see demons.'.* Associated with the shamanistic culture of Central Asian natives, *Cannabis*, along with ginseng, was believed to help necromancers achieve premonitory powers and enlightenment of being [9,14].

The first people to use *Cannabis* as both a therapeutic and a narcotic tool were from the Indian region, circa 1000 years BCE, mainly because of its religious connotations. The two purposes were often linked. Described in the *Vedas* as one of the five sacred plants, it was believed to have arisen from a drop of *amrita* (sacred nectar) that fell from heaven onto the earth and was able to bring joy and freedom to those who used it [9,14].

The resin produced by trichomes and female flowers was known to have entheogenic properties; therefore, some parts of the plant were traditionally used in specific preparations. Three preparations were common: *bhang*, the least potent of the three, consisting of dried *Cannabis* leaves, something similar to modern day marijuana; *ganja*, made from unfertilized flowers to which the resin adheres; and *charas*, the equivalent of hashish, the most potent of all, made basically of pure resin [14,17,18].

Due to numbing properties, its use ranged from more casual occasions such as weddings and family gatherings, festivals celebrating the coming of the seasons such as the *Holi* festival, to ceremonies of important religious nature such as *Durga Puja*. It is understood that marijuana is as significant and respected for these people as communion wine or sacred host is for Christians. For its other facets, ayurvedic medicine used *Cannabis* practically as a panacea: as an analgesic, anti-spasmodic, anticonvulsant, anti-inflammatory, aphrodisiac and anaphrodisiac, appetite stimulant, treatment of female tract diseases, abortifacient, inductor of childbirth, among several other applications [14,17-21].

Semitic people also knew about the psychoactive properties of *Cannabis* centuries before the Christian era, including the phases of early euphoria and late dysphoria caused using the plant. Its medicinal uses range from ointments for external injuries to oral preparations for various ailments and 'sicknesses of the spirit'. It was common in the Mesopotamian/ Persian region to use cannabis-based incense in certain social rituals, such as funerals, for example, which is even mentioned in the Aramaic version of the Old Testament of the Bible for aromatic and narcotic purposes. *Cannabis* is proposed to have been introduced to the African continent by Arab merchants before the 15th century [8,13,19].

3. *Cannabis* arrives in South America and 18th century Europe development

Through African slaves, mainly those from Angola, Brazil was the first location in South America to introduce the culture of *Cannabis.* The very term *maconha*, a term adopted in the Portuguese language to commonly refer to marijuana, has its origins in the native dialect of these populations trafficked to Brazil from Portugal. Common in rural areas in northeastern Brazil, *Cannabis* was used mainly in cultural and magical religious rituals, such as *catimbó*, to celebrate the deities believed by these populations, as well as for some therapeutic purposes, such as analgesia and antispasmodics. As it is associated with these more vulnerable ethnic racial groups, marijuana was known as the 'opium of the poor' and to this day has a pejorative and stereotyped connotation in Brazil [14,22-25].

Due to the demonization of herbal knowledge by the influence of the Catholic Church during the Middle Ages, the therapeutic properties of *Cannabis* were being hidden and omitted in European territories. Although some researchers have already cited the beneficial medicinal properties of the plant, such as the English John Parkinson, Robert Burton, and Nicholas Culpeper in the 17th century, until the 19th century, the use of *Cannabis* in Europe was predominantly like hemp and, to a lesser extent, seeds were used as food and a source of oils, or the plant in general as a homeopathic medicine [14,24].

With Napoleon's invasion of Egypt at the turn of the 18th to 19th century, three French army scientists, Isaac Silvestre de Sacy, Pierre-Charles Rouyer, and René-Nicolas Desgenettes, observed the use of hashish by local inhabitants and exported it to France to conduct experiments with the drug. Years later, around 1840, the psychiatrist Jacques-Joseph Moreau, after his studies in North Africa, also took *Cannabis* to France and tested different preparations on himself and his students to test its psychotomimetic properties, with the justification that he 'saw *in hashish, more specifically in its effects on mental abilities, a powerful and unique method to investigate the genesis of mental illness'.* Some notorious French people in Paris in the 1840s, such as the writers Alexandre Dumas, Charles Baudelaire, Théophile Gautier and Victor Hugo, were members of the so-called Club des Hashischins (hashish eaters club), which served as an object of study for Moreau. This, in some ways, contributed to the increase in the popularity of the drug and its use for hedonistic and recreational purposes [14,17,26].

In the United Kingdom, studies of the therapeutic properties of *Cannabis* arose from the work of Irish physician William Brooke O'Shaughnessy, professor of chemistry and materia medica in Calcutta, who noted the use of *Cannabis* in traditional Ayurvedic medicine, mainly as an antispasmodic. His observations on the effectiveness of *Cannabis* in the treatment of pain, convulsions, and vomiting resulting from infectious diseases such as rabies, tetanus, and cholera, diseases that were major public health problems in nineteenth-century Europe, were of great importance to Western medicine. The application of *Cannabis* as a hypnotic, sedative, analgesic, anticonvulsant, and in the symptomatic treatment of infectious diseases, now more widespread in Europe, led to its inclusion in the British (and later in the American) pharmacopoeia and is marketed in the form of tinctures, extracts, and tablets by large pharmaceutical laboratories in several countries, such as Merck, Burroughs Wellcome, among others [14,17,18,27,28].

At the same time, in Brazil, which had recently become independent of Portugal, with the repercussions of Moreau's research and that of French poets at the time, the popularity of *Cannabis* increased among the medical class of the country. What was previously almost restricted to use by African and indigenous slaves has now been adopted for therapeutic purposes by the white Brazilian society [23].

At the beginning of the twentieth century, with the fluctuating interpersonal therapeutic efficacy of *Cannabis*-based products, their composition with uncertain and poorly standardized doses, psychoactive effects, fear of an 'outbreak' of *Cannabis* abuse, and the emergence of effective drugs containing well-defined active ingredients and for the same clinical indications as *Cannabis,* such as aspirin and vaccines for infectious diseases, the popularity of *Cannabis* decreased [14,18].

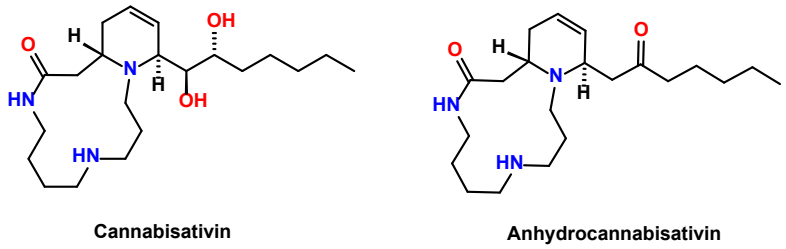

Figure 1. Chemical structures of cannabisativin and anhydrocannabisativin.

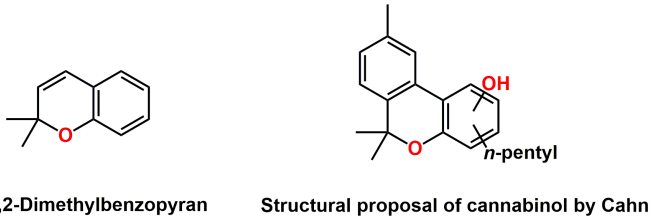

Figure 2. 2,2-Dimethylbenzopyran ring system and tricyclic structure of cannabinol proposed by Cahn.

4. Before 1900 and early 1900s: The first chemical impressions

Despite the ancient use of *Cannabis* over the millennia in different regions of the world and the fact that some characteristics of its active principles were already known, the causal factors of the psychosomatic effects of the plant were only clarified much more recently, in the twentieth century [29,30]. In the north of the African continent, it was a common traditional preparation of the plant, similar to the enfleurage process, in which leaves and flowers were placed in a mixture of water and butter and then the layer of butter was removed and used for convenience purposes. This "capture" of the therapeutic and recreational effects of *Cannabis* by butter already indicated the lipophilic nature of its biologically active components [17].

It was also observed, in the second half of the nineteenth century, that the psychoactive component of *Cannabis* was not an alkaloid, a phytochemical class that gained popularity due to tobacco nicotine, opium morphine, and other phytocomponents known at the time. Some *Cannabis* alkaloids were found through extraction and purification techniques of plant extracts, such as cannabisativin and anhydrocannabisativin, derived from spermidine, whose structures were only elucidated in the 1970s (Figure 1). However, due to their low concentrations in plant matter and their low activity when administered in an animal model, the idea that these compounds were responsible for the pharmacological effect was discredited [29,30].

At the turn of the twentieth century, a biologically very active reddish oil was obtained from the distillation process of *charas* samples (*Cannabis* resin preparation), with activity compatible with the pharmacological outcomes expected from the use of the plant. From the oil, identified as a mixture, a crystal was isolated after acetylation, which, when subjected to subsequent hydrolysis, gave rise to a phenol whose molecular formula was compatible with $C_{21}H_{26}O_2$. This compound, named cannabinol, was assumed to be the active principle responsible for the psychosomatic response resulting from the use of the plant. However, *in vivo* tests with rabbits showed that cannabinol had too weak activity to be, in fact, the chemical species behind the psychoactivity of *Cannabis* [30-33].

The English chemist Robert Sidney Cahn, in the early 1930s, contributed enormously to the structural proposal of cannabinol. After a few decades of failed and/or inconclusive attempts to further isolate and elucidate the compound, using a rigorous scientific method of synthesis and analytical experiments with 2,2-dimethylbenzopyran ring systems, a fused tricyclic structure was proposed, one of the rings being a pyran heterocycle, but the positions of the hydroxyl and *n*-pentyl substituents remained uncertain (Figure 2) [31,33-36].

As other phenols were identified in qualitative analytical tests of the resin extract, subsequent studies were carried out and a crystalline derivative was isolated after reaction with 3,5-dinitrobenzoyl chloride, suggesting the presence of a diphenolic compound as a precursor (later confirmed by other qualitative methods). After ammonolysis of the ester formed, a compound was identified whose molecular formula was compatible with $C_{21}H_{30}O_2$ or $C_{21}H_{32}O_2$ (it was not possible to distinguish using the analytical methods available at the time) [33,37].

With the strong indication of the presence of an *n*-pentyl group in a phenolic ring in the new molecule, supported by qualitative tests and by the assumption that it would be derived from olivetol (*n*-pentylresorcinol), thus preserving the same substitution pattern of the aromatic portion, cannabinol would originate from the condensation of a terpenoid nucleus with olivetol. This reasoning thus allowed the elucidation of the structure that would be different from that initially attributed to cannabinol, since in this case, because of the presence of two phenolic hydroxyls, the existence of a pyran ring in the new molecule was excluded. The proposed diphenol was then named cannabidiol (CBD). However, the position of unsaturation in the alicyclic portion of the molecule remained uncertain (Figure 2) [37-41].

Both cannabinol and CBD did not show the characteristic activity of the use of *Cannabis* in animal models, and the active principle (or active principles) responsible for this activity remained unclear. However, some experimental observations carried out by groups of researchers resulted in important discoveries. In the field of phytochemistry, Haagen-Smit and collaborators isolated a crystal from *Cannabis*, with an unidentified chemical structure, which showed the classical activity of the plant in a canine model. In the context of synthetic organic chemistry, Adams and collaborators and Todd, Ghosh, and Wilkinson identified tetrahydrocannabinoid compounds, derived from the cyclization of CBD in an acidic medium and an intermediate of cannabinol synthesis, respectively, which showed potent psychoactive activity in a canine model [31,36,42].

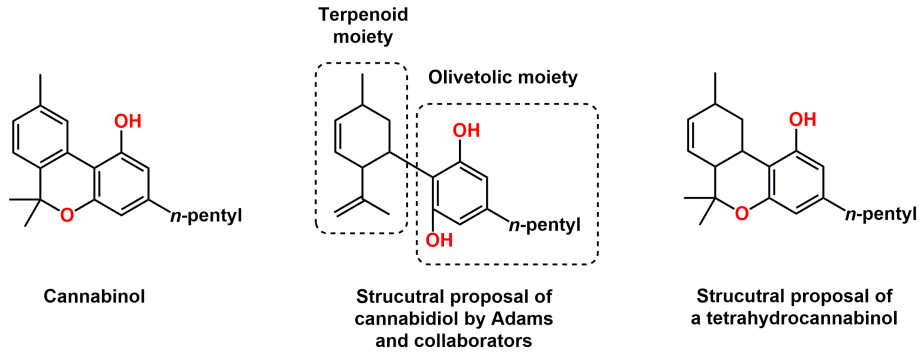

Figure 3. Chemical structure of cannabinol and structural proposals of cannabidiol and tetrahydrocannabinol.

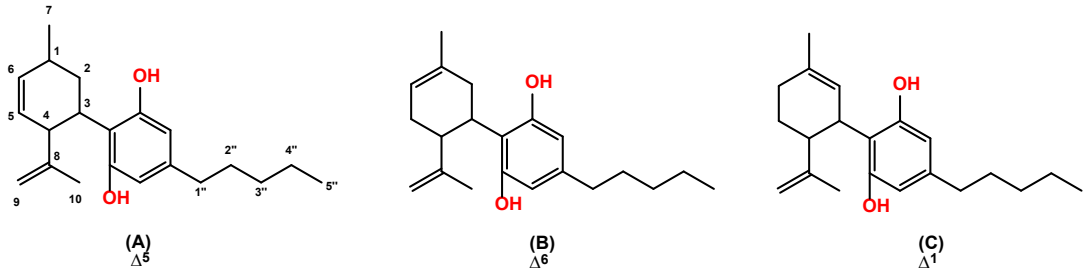

Figure 4. Possible insaturation positions in the terpenoid moiety in cannabidiol.

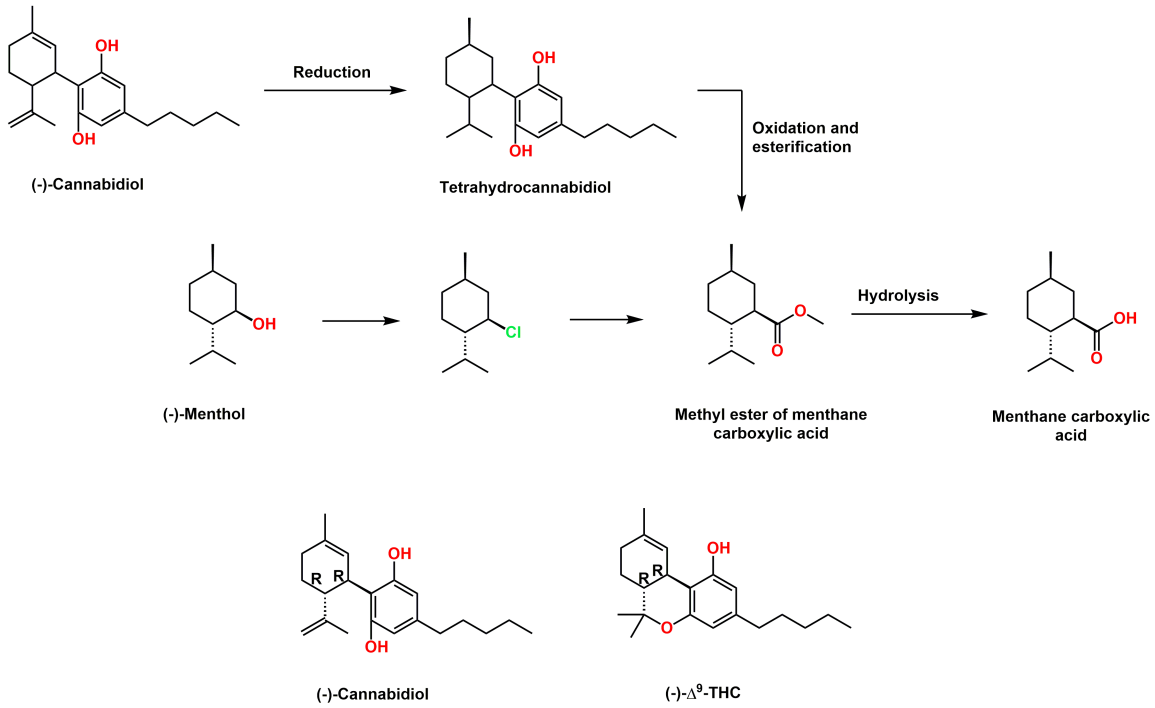

Figure 5. Steps for obtaining menthanecarboxylic acid and its methyl ester from (-)-CBD and (-)-menthol. Absolute configurations of CBD and Δ⁹-THC.

5. The second half of the 20th century: The elucidation of cannabidiol and Δ⁹-tetrahydrocannabinol

However, the position of the double bond in the terpenoid nucleus of these tetrahydrocannabinoids, as in the CBD, remains uncertain. It was assumed that the composition of the red oil extracted from *Cannabis* would be a very rich mixture of chemically related compounds, such as cannabinol, CBD, and a variety of tetrahydrocannabinol isomers, and perhaps even several other uncorrelated substances from other phyto-chemical classes, and that the psychoactivity characteristic of plant use would result from this mixture [37,39,43].

Despite the great efforts of brilliant scientists in the first half of the 20th century, such as Robert Sidney Cahn, Roger Adams, Alexander Todd, Krejčí and Šantavý and others, the only compound complete and correctly elucidated structurally until the beginning of the 1960s was cannabinol, which until then was considered devoid of pharmacological activity (later it was found to display very low psychoactivity).

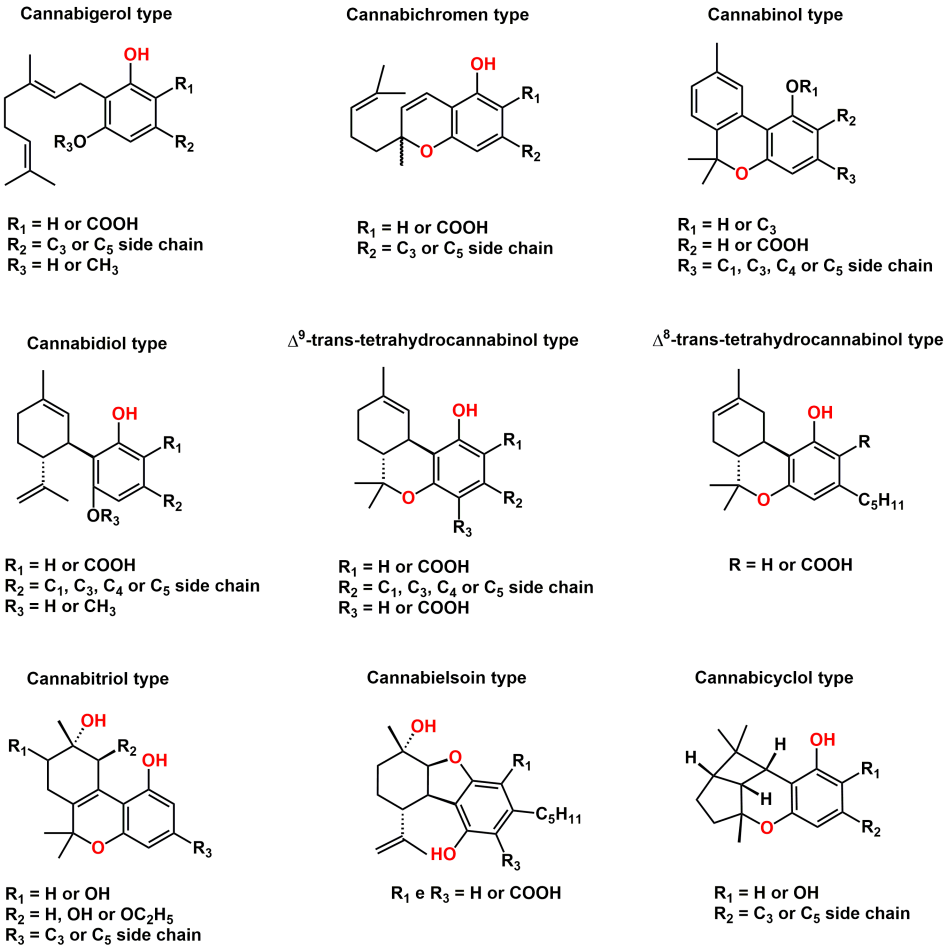

Figure 6. Most common phytocannabinoid classes.

Lack of knowledge about the exact structure of other phytocannabinoids proved to be an obstacle in the continuation of pharmacological tests with CBD and tetrahydrocannabinoids, which require well-established materials and methods for the observation and interpretation of reliable results [3,44-47].

From the ultraviolet spectral data obtained by Adams *et al*. in the 1940s, it was known that CBD did not have a double bond conjugated to the aromatic ring derived from olivetol or to the terminal alkene, therefore, only three positions would be possible for unsaturation, as shown in Figure 3 [39,45].

In the early 1960s, Raphael Mechoulam and Youval Shvo masterfully used the analytical technique of hydrogen nuclear magnetic resonance (^{1}H NMR) to finally assign the position of unsaturation in the terpenoid nucleus. These authors verified that the ^{1}H NMR spectrum of CBD presented only three signals related to olefinic hydrogens, two of them assigned to the exocyclic alkene and one attributed to the endocyclic double bond. This information, together with the presence of singlets corresponding to the hydrogens of two methyl groups bonded to the *sp*^{2} hybridized carbon and the only one corresponding to a methyl group linked to a saturated chain, is indicated in Figure 4 as carbons 7 (δ 1.68 ppm), 10 (δ 1.80 ppm) and 5'' (δ 0.88 ppm), respectively, served as the basis to exclude the structural proposal (A), with unsaturation Δ^5 [45].

In the ^{1}H NMR spectrum of the CBD was observed, at δ 3.85 ppm, a doublet (*J* = 11 Hz) and, similarly, a signal at δ 3.58 ppm was observed in the spectrum of the dinitro benzoate ester derivative (modifications in the phenolic hydroxyls) of the CBD, both corresponding to H-3. The value of the chemical shift for H-3 is indicative of a proton neighboring the double bond, which corroborates the hypothesis of structure C (Figure 4), with unsaturation Δ^1, to be the correct one. The presence of Δ^1 unsaturation by anisotropy may lead to a deshielding of the neighboring hydrogen nucleus, i.e., to a downfield shift to the H-3 resonance. Further evidence of the Δ^1 position of the alicyclic olefin of CBD was obtained through the spectrum of a derivative of CBD containing the saturated terpene ring. In this case, the signal corresponding to hydrogen H-3 is at δ 2.60 ppm, typical of hydrogen bonded to benzylic carbon, demonstrating the presence of an unsaturation close to carbon 3 in the original molecule [45].

Another need regarding the structural determination studies of phytocannabinoids in addition to the olefin position was the elucidation of configuration of chiral centers, in order to have, in fact, the fully elucidated structure of both CBD and the main compound reported as responsible for psychoactivity, Δ^9-tetrahydrocannabinol (Δ^9-THC, reported at the time as Δ^1-tetrahydrocannabinol due to naming and atom numbering conventions) [46,48].

Based on the results of Adams and collaborators from the 1940s, Mechoulam and Gaoni used the same methodology to compare CBD and specific derivatives with molecules with already well-defined stereochemistry. After reduction of (–)-CBD, the natural form of the phytocannabinoid, a tetrahydrocannabidiol was obtained (more specifically, a mixture of epimers of the carbon at the C-1 position, separated by chromatographic techniques), which after oxidation and esterification afforded the menthanecarboxylic acid methyl ester.

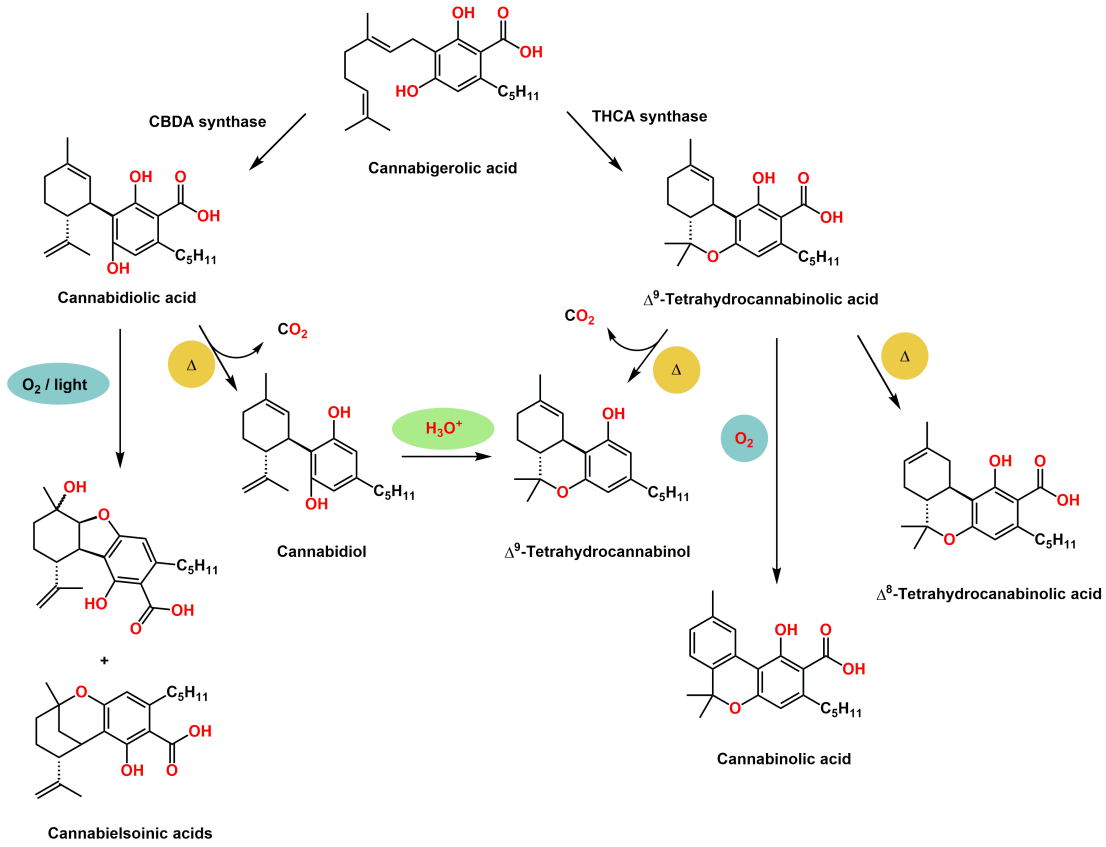

Figure 7. Examples of conversion between phytocannabinoids.

The resulting methyl ester was subsequently hydrolyzed to the corresponding carboxylic acid, as shown in Figure 5. At the same time, from (–)-menthol, a chemically well-established monoterpene in terms of its configuration, the same menthane-carboxylic acid methyl ester, followed by the corresponding acid were synthesized (Figure 5). Both the ester and the acid obtained from (–)-CBD presented physicochemical and spectrometric data identical to those obtained from (–)-menthol, such as infrared and NMR spectra, specific rotation and retention factors in thin layer chromatography, being possible to categorically establish the configurations of the asymmetric carbons of CBD, later confirmed by X-ray crystallography [46,49,50].

As already observed by several researchers, Δ^9-THC could be obtained from CBD as a cyclization product, therefore, it was postulated that the configuration of the chiral carbons would be the same as the starting material, which was later confirmed by total synthesis [46,49].

6. Other phytocomponents from *Cannabis*

With the advent of more modern and precise extraction, purification and analysis techniques, over the decades, it has been possible to carry out the isolation and characterization of several molecules belonging to different chemical classes in *Cannabis*, both in the resin and in other parts of the plant body, such as stem, leaves, and seeds. Hundreds of primary and secondary metabolites such as terpenes, heteroside, flavonoids, sugars, proteins, enzymes, glycoproteins, hydrocarbons as well as fatty acids, vitamins, pigments, among others, have been described in works investigating the chemical components present in this millennium-old plant. Among these classes, phytocannabinoids, found in their neutral or acidic forms, add up to more than 80 different compounds, grouped into types, as shown in Figure 6, in addition to miscellaneous types that structurally diverge from the most commonly found [3,51-53].

Many phyto-cannabinoids are metabolites of the same biosynthetic pathway, some being interconvertible when subjected to certain reaction conditions, both in the microenvironment of plant cells and in external conditions related to enzymatic catalysis, temperature, pH, oxygen, and light incidence (Figure 7) [3,4,54].

Admiring the great diversity and biochemical complexity present in just one plant species makes us feel humble before the universe of biomolecules present in living beings that surround us. Extensive and laborious work has been, and will always be done to understand and elucidate the structure of the molecules that have accompanied us for millennia. But, fortunately, contact with these sources of natural secrets in this ocean of ignorance encourages us to always look for more ways to understand our surroundings. Many of these molecules are potentially useful for human use, either as a drug or for any other reasonable purpose, many potentially toxic, and many more that we may never know about.

Interestingly, the study of *Cannabis* enabled us to understand not only the physiology and biochemistry of the plant, but also our own physiology and allowed the development of drugs for clinical conditions that often seemed insurmountable.

7. Legality marks after the 1900s and contemporaneity

In 1937, the Marihuana Tax Act was introduced in the United States by the National Narcotics Service, a government department. This prohibitionist measure created a rigorous bureaucracy that subjected the payment of very high amounts of money for medicinal, industrial, and any other uses of *Cannabis*. Years later, *Cannabis* was removed from the

American pharmacopoeia and entered the list of drugs of abuse [14,18].

The hedonistic purposes of *Cannabis* and other narcotics, such as opioids, stimulants, and psychedelics, gained great strength in the second half of the 20th century. This was mainly due to cultural and even religious movements, such as jazz, blues, the hippie movement, Rastafarian, the recovery of literature from the previous century, and rock'n roll, starring famous artists such as Bob Marley, Janis Joplin, Jimi Hendrix, The Beatles and The Doors, whose works influenced popular culture to this day. Contextualized by a scenario of unrest and political discontent in a century marked by wars, members of these movements adopted the discourse of spreading peace, love, the use of drugs of abuse, and controversial postures for the time as a form of counterculture, as a protest [55-60].

Currently, some locations have already decriminalized the recreational use of *Cannabis,* such as South Africa, Canada, Georgia, and Uruguay, and some states in the United States, such as California, Washington, and Colorado. Some licensed establishments in the Netherlands are also authorised to market products containing the plant. Several other countries, such as Germany, United Kingdom, Chile, New Zealand, and Brazil, among others, authorize the sale of *Cannabis*-based products for medicinal purposes [61-64].

Efforts to deconstruct the stigma, legalize the use of the plant, and explore potential therapeutics have been placed in focus over the last six decades, due to discoveries related to the active principles of *Cannabis* in the 1960s and its promising developments for contemporary medicine.

8. Conclusion

Used for millennia as a food, fiber production and religious, therapeutic, and recreational instrument, a source of phytocompounds with proven efficacy for clinical conditions of difficult management, its planting, cultivation, use and acquisition are today prohibited - even for researchers who intend to work with this plant! - in the vast majority of countries. Recent efforts try to decriminalize the use of the drug and to expand the medical use and access to patients of *Cannabis*-based drugs through legislation, but despite successes around the world, it still finds its hindrances. *Cannabis* is perhaps one of the greatest controversies in contemporary humanity.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Conceptualization: Gabriel Vitor de Lima Marques; Methodology: Gabriel Vitor de Lima Marques; Investigation: Gabriel Vitor de Lima Marques; Data Curation: Gabriel Vitor de Lima Marques; Writing - Original Draft: Gabriel Vitor de Lima Marques; Writing - Review and Editing: Renata Barbosa de Oliveira; Visualization: Gabriel Vitor de Lima Marques, Renata Barbosa de Oliveira; Supervision: Renata Barbosa de Oliveira; Project Administration: Renata Barbosa de Oliveira.

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