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THE PHYTOCANNABINOIDES FROM *CANNABIS SATIVA* L. AN OVERVIEW

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Abstract: *Cannabis sativa* is among the first cultivated plants for producing fibres from the stalks and consumption of the seeds. Later, the medicinal properties were discovered. The oldest written record of using cannabis for the medicinal and recreational purposes is from China. Over the time many experimental researches were carried out that emphasize the importance of cannabinoids for human health. The present paper focused to present an overview of the main cannabinoids synthetized in cannabis plant and their medicinal and therapeutic effects. Cannabis has a complex chemical composition including besides cannabinoids (over 100), also terpenoids, sugars, alkaloids, quinones and stilbenoids. Of major importance are two compounds tetrahydrocannabinol (THC) and cannabidiol (CBD). Over the time different researches pointed out the beneficial effect of cannabinoids on a wide range of diseases such as epilepsy, neurological diseases, mental conditions like anxiety and depression, chronic pains and certain forms of cancer. In addition to the important advantages it must be also paid attention to the psychoactive action of the certain cannabinoids that may produce cognitive disturbances, attention disorders, sever panic, can affect the short-term memory, and slow the reaction time. This deficits induced usually by THC can be moderate by using CBD which reduce the psychoactive effect. Considering the similar profile of cannabinoids to other medication, care must be taken to interaction with other drugs and medical conditions.

***Keywords*:** cannabichromene, cannabicyclol, cannabidiol, cannabielsoin, cannabigerol, cannabinodiol, cannabinol, cannabitriol, tetrahydrocannabinol.

Introduction

Hemp is an annual plant belonging to the *Cannabaceae* family, with dioecious and monoecious varieties (Sakamoto *et al*., 1998). Genus *Cannabis* has just one species *Cannabis sativa* L. divided into three subtypes *sativa*, *indica* and *ruderalis*. *Cannabis sativa* was among the first cultivated species (Meccariello and Chianese, 2016). The plant is considered to be originated in

Central Asia where it is believed to have been domesticated for over 6,000 years ago (Mandolino, 2007). First uses of cannabis were for producing fibres from the stalks and consumption of the seeds. Later, the medicinal properties were discovered. The oldest written record of using cannabis for the medicinal purposes is from China, where the 'father of Chinese Medicine', the Chinese emperor Shen Nung in 2,727 BC, using himself as a test subject, investigated cannabis for its medicinal potential along with other vegetable, animal and mineral sources (Parker, 2017). The first report of using cannabis in recreational purpose was also the Chinese (Abel, 1980) (Figure 1), and India was the first culture using cannabis in social and religious purposes (Parker, 2017).

Figure 1. Using cannabis plant for recreational purpose in Ancient China
(Source: https://www.ancient-origins.net sites/default/files
/field/image/High-Times-in-Ancient-China.jpg)

The Western medicine introduced cannabis treatment in 1839 when the surgeon William Brooke O'Shaughnessy prescribes it for analgesic, sedative, anti-inflamatory, anti-spasmodic and anti-convulsant effects (Parker, 2017). After Abrams and Guzman (2015), Queen Victoria chooses cannabis for the treatment of her menstrual pain. Important French figures like the great poet Charles Baudelaire, the writer Theophile Gautier and the famous psychiatrist Jacques-Joseph Moreau mentioned the psychological effects of cannabis (Mechoulam and Hanus, 2000). Over the time many experimental researches were carried out that emphasize the importance of cannabinoids for human health. Considering the aforementioned, the present

paper focused to present an overview of the main cannabinoids synthetized in cannabis plant and their medicinal and therapeutic effects.

Cannabinoids of Hemp

'Cannabinoid' is the term meaning a set of oxygen-containing C_{21} aromatic hydrocarbon compounds (Pertwee, 2005). Even though initially this label referred only to the compounds produced naturally by the hemp plant, nowadays the term is used more broadly, encompassing both types of cannabinoids, natural and synthetic. Currently there are three different groups of cannabinoids: phytocannabinoids (synthetized by the cannabis plant), endocannabinoids (produced by the animal and human body), and synthetic cannabinoids (generated in laboratory). Synthetic cannabinoids mimic the effect of the natural ones and have an identical ('dronabinol') or similar ('nabilone') structure of THC (Freeman *et al*., 2019).

Cannabis plant has a very complex chemical composition including besides cannabinoids, also terpenoids, sugars, alkaloids, quinones and stilbenoids (Mandrioli *et al*., 2019). After Freeman *et al*. (2019), there are at least 144 cannabinoids naturally synthetized by the cannabis plant, all being known as phytocannabinoids. These are the secondary metabolites without a proper role in plant growing, but important for the immune system due to their fight against parasite, pests, insects and predators. The concentration of cannabinoids in a plant or a tissue is determined by the presence or absence of trichomes, the small structures where cannabinoids are synthetized and isolated (Potter, 2014). In the cannabis plant were identified eleven types of cannabinoids (Mechoulam, 2005; ElSohly and Gul, 2014), as they can be seen in table 1.

Table 1

Cannabinoids from the cannabis plant

Cannabinoid	Abbreviation	3D Structure
Delta 9-tetrahydrocannabinol	Δ9-THC	Figure 2
Delta 8-tetrahydrocannabinol	Δ8-THC	Figure 3
Cannabidiol	CBD	Figure 4
Cannabigerol	CBG	Figure 5
Cannabinol	CBN	Figure 6
Cannabinodiol	CBND	Figure 7A
Cannabitriol	CBT	Figure 7B
Cannabielsoin	CBE	Figure 7C
Cannabicyclol	CBL	Figure 7D
Cannabichromene	CBC	Figure 7E
Miscellaneous cannabinoids		

Depending on the ratio between the two most important cannabinoids, Δ^9-THC and CBD, cannabis plants are classified in three different groups (Hilling and Mahlberg, 2004):

- 'drug type' plants with Δ^9-THC/CBD > 1;
- 'intermediate type' plants when Δ^9-THC/CBD = 1;
- 'fibre type' plants with Δ^9-THC/CBD < 1.

Tetrahydrocannabinol (THC). The psychoactive cannabinoid

Δ^9-tetrahydrocannabinol (Figure 2) was discovered in 1964 by Yehiel Gaoni and Raphael Mechoulam, two chemists from the Hebrew University of Jerusalem (Parker, 2017). That is when scientific research on this cannabinoid began, even though its recreational effects were known long before. THC is the cannabinoid which acts on the brain and produces the psychoactive effect.

Δ^9-THC is mainly use for its orexigenic and antiemetic properties. Oral administration of this cannabinoid was efficient for patients with muscle spasticity (Zajicek *et al.*, 2005), painfull spams, bladder dysfunction or Tourette syndrome (Koppel *et al.*, 2014). Also, the analogue synthetic cannabinoids ('dronabinol' with identical structure of THC and 'nabilone' with similar structure) are being used in special cases such of nausea and vomiting of people who are following chemotherapy treatment, or to AIDS patients for losing weight (Freeman *et al.*, 2019).

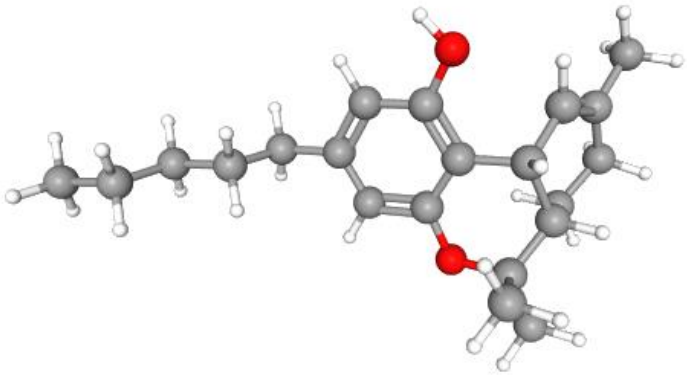

Figure 2. Structure in 3D of Δ9-tetrahydrocannabinol ($C_{21}H_{30}O_2$)
(Source: NCBI, 2020a)

The other active THC of cannabis plant is Δ^8- tetrahydrocannabinol (Figure 3), little bit less potent than Δ^9-THC, but being also a psychoactive compound (Meccariello and Chianese, 2016). Δ^8-THC is considered to be about 30% less psychotropic than Δ^9-THC (Etter, 2019). The structure is similar to Δ^9-THC excepting the double bond on the eight carbon, with analgesic, antiemetic, orexigenic, anxiolityc and neuroprotective properties (Etter, 2019). The research of Munson *et al*. (1975) demonstrates the Δ^8-THC potential to reduce the size of cancer tumours.

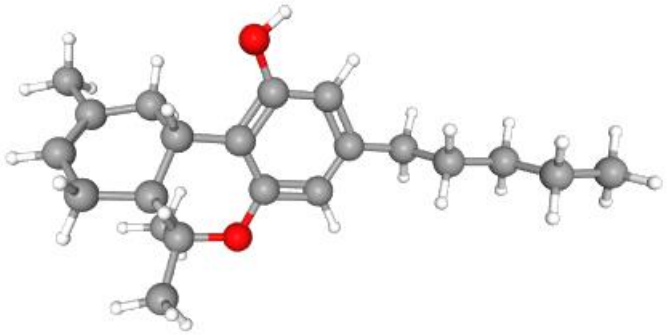

Figure 3. Structure in 3D of Δ8-tetrahydrocannabinol ($C_{21}H_{30}O_2$)
(Source: NCBI, 2020b)

THC as the main psychoactive component of the cannabis plant may produce cognitive disturbances in humans, affecting the short-term memory, slowing reaction time, attention disorders, and incoordination, sever panic. In case of vulnerable people or in young consumers, cannabis may induce chronic psychosis such as schizophrenia (Hall and Solowij, 1998; Johns, 2001; Henquet *et al*., 2005). There were reports that using CBD can protect against the deficits induced by THC; it seems that cannabidiol reduces the psychotic effect of THC (Parker, 2017).

Analysing the cannabis plant, roots and seeds are totally free of THC, stems have very low concentration and the upper leaves contain 2-3% more THC than the lower leaves. The highest percent of THC (up to 25%) is found in the female unpollinated floret.

Cannabidiol (CBD). The medicinal cannabinoid

Neurodegenerative diseases (Parkinson, Huntington, Alzheimer, multiple sclerosis, amyotrophic lateral sclerosis and cerebral ischemia) are disorders with the highest incidence in the populations worldwide (Giaccoppo *et al*., 2014). Fagan and Campbell (2014) demonstrated that in the case of many neurodegenerative diseases, the endocannabinoid system is altered; therefore it is considered a healthy opportunity the use of

cannabinoids (Giaccoppo *et al*., 2014) (table 2). CBD (Figure 4) is one of the most abundant compounds in cannabis plants, but without the psychoactive effect (NHA, 2019).

Table 1.

Therapeutic targets for cannabinoid medicines

Disease	Therapeutic Cannabinoids	Therapeutic Targets
Parkinson Disease	Δ9-THC	Tremor
	CBD	Dystonia and discinesia
	WIN 55,212-2 + SR141716A	Akinesia
	Δ9-THCV	Diskinesia
Huntington Disease	Δ9-THC	Hyperkinesia and choreic movements
	CBG	Hyperkinesia
	Δ9-THC+ CBD	Hyperkinesia and choreic movements
	HU210 and WIN55,212-2	Hyperkinesia
Alzheimer Disease	Δ9-THC	Behavior disorders and motor impairment
	CBD	Learning behavior
	WIN 55,212-2	Cognitive impairment
	Δ9-THC + CBD	Memory and learning impairment
	SYNTHETIC Δ9-THC (Dronabinol)	Nocturnal motor activity, agitation and anorexia
Multiple Sclerosis	Δ9-THC	Spasticity
	HU210 and WIN 55,212-2	Tremor and spasticity
	JWH-133	Tremor and spasticity
	CB52	Motor impairment
	SYNTHETIC Δ9-THC	Neuropathic pain
	Δ9-THC+ CBD	Spasticity, neuropathic pain and bladder dysfunction
Amyotrophic lateral sclerosis	Δ9-THC	Motor impairment and spasticity
	WIN 55,212-2	Tremor and motor impairment
	AM1241	Tremor and motor impairment
	Δ9-THC + CBD	Motor impairment
Cerebral Ischemia and Hypoxia	CBD	Reduction of brain edema, cerebral hemodynamic impairment and seizures
Epilepsy	CBD	Convulsions
	CBDV	Convulsions
	Δ9-THCV	Convulsions

Source: Giacoppo *et al*. (2014)

Different researches highlights the beneficial effect of CBD on epilepsy (Fattore, 2015) and neurological diseases (Giacoppo *et al*., 2014), mental conditions such as anxiety and depression (Maroon and Boost, 2018), chronic pains (National Academies of Sciences, Engineering, and Medicine, 2017) and certain forms of cancer (Śledziński *et al*., 2018).

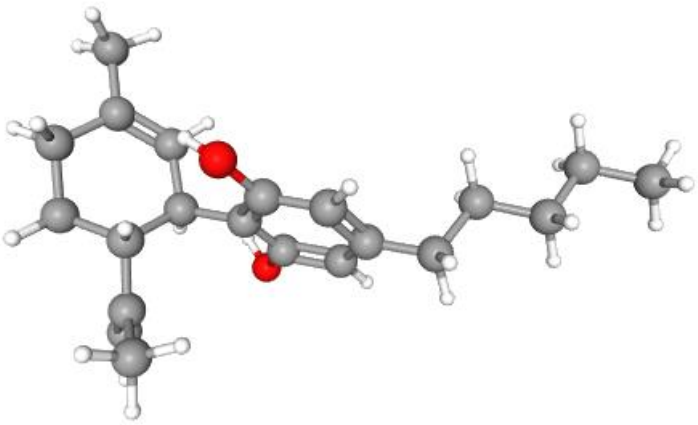

Figure 4. Structure in 3D of cannabidiol ($C_{21}H_{30}O_2$)
(Source: NCBI, 2020c)

CBD has a very complex profile similar to other medication, so there is the possibility to interact with other drugs and medical conditions. Therefore, great care must be taken to potentially adverse drug events (Brown and Winterstein, 2019). Side effects of using cannabidiol in clinical trials were reported by Brown and Winterstein (2019) as somnolence, fatigue, diarrhea, sleep disturbance and insomnia, decreased appetite etc. At higher doses than recommended may occur stronger side effects like toxicity, embryo-fetal mortality, spermatogenesis reduction, hepatocellular injuries or hypotension (Huestis *et al*., 2019).

Cannabigerol (CBG). The parent molecule

CBG (Figure 5) is the molecule from which are synthetized the others cannabinoids; it is known as the 'parent molecule' (Morales *et al*., 2017). During the growing season of the plant, CBG is mainly converted into the others cannabinoids, so in the plant remains very low level, about 1% (Aizpurua-Olaizola *et al*., 2016). It seems that cannabigerol has anti-inflammatory properties for the bowel disease (Borrelli *et al*., 2013) and an

antibacterial action (Appendino *et al*., 2008), antioxidant role, appetite enhancer and is a neuroprotective agent (NCBI, 2020d).

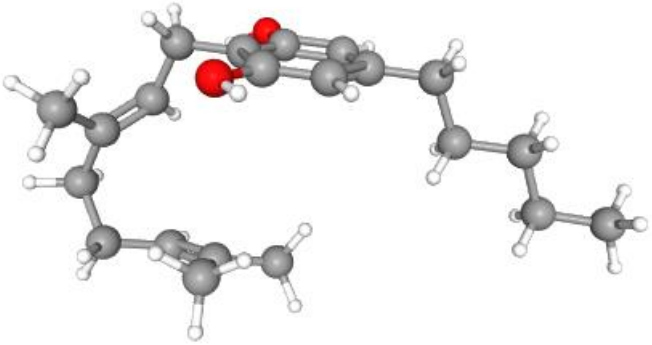

Figure 5. Structure in 3D of cannabigerol ($C_{21}H_{32}O_2$)
(Source: NCBI, 2020d)

Cannabinol (CBN)

Unlike the other cannabinoids, CBN (Figure 6) is not synthetized from the parent molecule, cannabigerol, but it is derived from the degradation of THC and mainly is found in mature plants (Andre *et al*., 2016). Currently, CBN is limited in some special cases, such as stimulating the appetite in HIV-positive patients or treat the spasticity in adult patients with multiple sclerosis (Lynch and Ware, 2015).

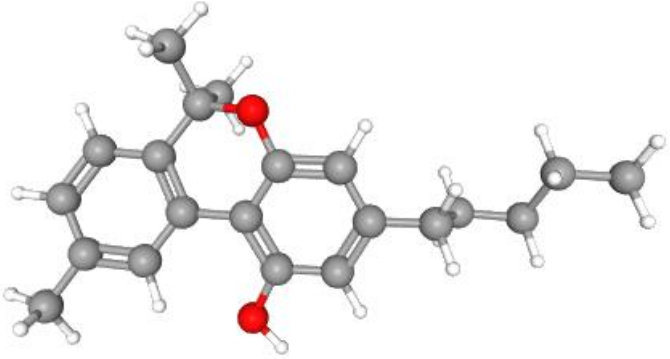

Figure 6. Structure in 3D of cannabinol ($C_{21}H_{26}O_2$)
(Source: NCBI, 2020e)

The other cannabinoids

In addition of the cannabinoids presented above in the cannabis plant were found low concentrations of cannabinodiol or cannabidinodiol (CBND) (Figure 7A), a cannabinoid with psychoactive effects (Lewis *et al*., 2017); cannabitriol (CBT), psychoactive compound with a similar structure of THC (Figure 7B); cannabielsoin (CBE), a non-psychoactive cannabinoid derivate from CBD (Figure 7C); cannabicyclol (CBL) (Figure 7D), a non-psyhoactive element following degradation of cannabichromene due to irradion; and, cannabichromene (CBC) a major non-psychotropic phytocannabinoid (Figure 7E) that potentiates some effects of tetrahydrocannabinol and have moderate anti-inflammatory and antinociceptive effects (Udoh *et al*., 2019).

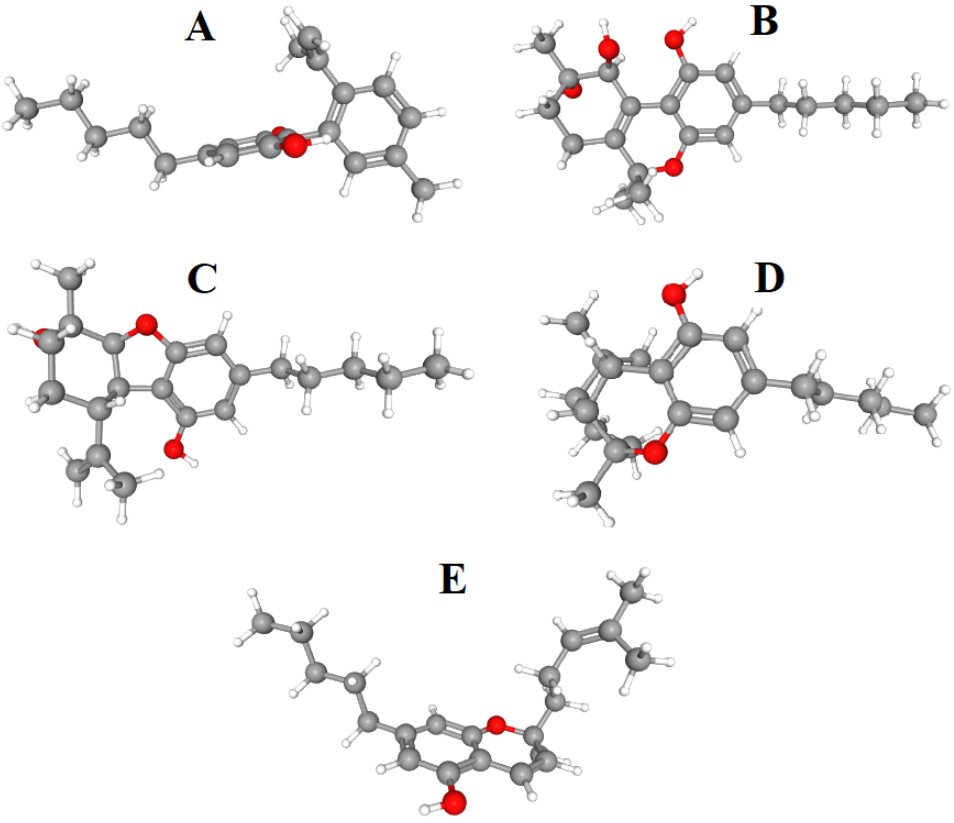

Figure 7. Structure in 3D of A - cannabidinodiol ($C_{21}H_{26}O_2$); B - cannabitriol ($C_{21}H_{30}O_4$); C - cannabielsoin ($C_{21}H_{30}O_3$); D - cannabicyclol ($C_{21}H_{30}O_2$); E - cannabichromene ($C_{21}H_{30}O_2$)
(Source: NCBI, 2020f-j)

Conclusions

Cannabis plant naturally synthetize over 100 cannabinoids grouped into eleven types, of major importance for human health being the psychoactive component tetrahydrocannabinol (THC) and cannabidiol (CBD) the non-psychoactive compound. Over the time different researches pointed out the beneficial effect of cannabinoids on a wide range of diseases such as epilepsy, neurological diseases, mental conditions like anxiety and depression, chronic pains and certain forms of cancer. In addition to the important advantages, it must be also paid attention to the psychoactive action of the certain cannabinoids that may produce cognitive disturbances, attention disorders, sever panic, can affect the short-term memory, and slow the reaction time. This deficits induced usually by THC can be moderate by using CBD which reduce the psychoactive effect. Considering the similar profile of cannabinoids to other medication, care must be taken to interaction with other drugs and medical conditions.

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