CANNABIS

SCIENTIFIC AND SOCIETAL RELEVANCE

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AkiNik Publications
New Delhi

Published By: *AkiNik Publications*

AkiNik Publications
169, C-11, Sector - 3,
Rohini, Delhi-110085, India
Toll Free (India) – 18001234070

Authors: *Dr. Manash Pratim Sarma and Dr. Minakshi Bhattacharjee*

Edition: *1st*

Publication Year: *2020*

Pages: *124*

ISBN: *978-93-91216-80-1*

Book DOI: *https://doi.org/10.22271/ed.book.1286*

Price: *₹ 675/-*

Cannabis and Human

The oldest known written record on cannabis use comes from the Chinese Emperor Shen Nung in around 2727 B.C. There are also scriptures and records where ancient Greeks and Romans were also familiar with cannabis, while in the Middle East, use spread throughout the Islamic empire to North Africa. In 1545, cannabis spread to the western hemisphere where Spaniards imported it to Chile for its use as fibre. In North America cannabis, in the form of hemp, was grown on many plantations for use in rope, clothing and paper. In India, Ayurveda has too documented pharmacological uses of cannabis which lead to the fact that it was a plant of medicinal importance in ancient India too. Cannabis grows wild in the Himalayas, in India from Kashmir in the east to beyond Assam in the west, but also in Iran and all throughout Central and West Asia. (The Latin name 'Cannabis indica', later '*Cannabis sativa*' already suggests that cannabis grows, and is traditionally used in India.) Cannabis is nowadays cultivated mostly in the tropical and subtropical parts of India.

Cannabis has a long history of use in Ayurveda. Cannabis is known as bhaṅgā in Sanskrit. Cannabis is classified as a toxic substance by the ancient texts on Ayurvedic herbs, but it has been used in healing preparations after purification. It is mentioned in many of the ancient texts on Ayurveda like the Charaka Samhita, Sushruta Samhita, and Shargandhara Samhita.In traditional Indian medical texts, cannabis has first been mentioned a couple of thousand years ago in the Atharvaveda, whereas ayurvedic traditional texts do not mention this plant until the Middle Ages. The ayurvedic names of cannabis are "vijaya" - 'the one who conquers' and "siddhi" - 'subtle power', 'achievement'.Ayurveda differentiates between three therapeutic parts of the plant. They have somewhat different actions on the body, and are given separate names. Bhang is a name for the leaves of male and female plants, and in certain regions of India the name is also used for flowers of the male plant. The name ganja is given to the flowering tops of the female plant, and charas is the name for the plant resin, which naturally exudes from leaves, stems and fruits of plants that grow in the mountains between 2000 and 3000 m of altitude.

In Indian pharmacopeia, all parts of the plant are denoted as somewhat narcotic and different parts of the plant can also stimulate digestion, act as

analgesics, nervous system stimulants, can have sedative, spasmolytic, diuretic, to regulate high blood pressure and aphrodisiac actions.

The Anandakanda has a whole chapter dedicated to the herb, its toxicity, the procedure for purification, cultivation, preparation, and use. Anandakanda describes 9 successive stages of Cannabis toxicity. This text also prescribes various antidotal therapies to counter the toxic and narcotic effects of excessive use of Cannabis. About habitual, prolonged use of Cannabis it was mentioned that it leads towards disbalance of all three basic physiological forces in the body (as Ayurveda recognizes them) - vata, pitta, and kapha - and as the result of this disbalance chronically poor digestion, melancholy, sexual impotence, and body wasting.

Cannabis (Marijuana) is typically used recreationally for the mind-altering effects produced by the compound tetrahydrocannabinol (THC), which is present in the plant. Effects can vary greatly from person to person. Common effects include: Euphoria, relaxation, an altered perception of time, increased appetite, heightened sensory perception. However, some people may experience adverse effects, especially in higher doses. Such adverse effects include: Fear, distrust, panic, anxiety and other psychotic symptoms. It was also used for production of many fibre based commercial products throughout the world.

Dr. Manash Pratim Sarma

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Chapter - 1

Chemical Constituents of *Cannabis sativa* L. (Marijuana)

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Introduction

Marijuana is the crude drug derived from the plant *Cannabis sativa* L., a plant that is currently accepted as belonging to a family (Cannabaceae) that has only one genus (Cannabis) with only one species (sativa) that is highly variable. Cannabis has had a long history of use (over 5000 years) starting in Central and Northeast Asia with current use spreading worldwide as a recreational drug or as a medicine albeit unauthorized. Several historic reviews have been written on Cannabis use as a therapeutic drug [1, 2]. Cannabis is very complex in its chemistry due to the vast number of its constituents and their possible interaction with one another. These compounds represent almost all of the chemical classes, e.g., mono- and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids, among others. The best-known and the most specific class of Cannabis constituents is the C_{21} terpenophenolic cannabinoids, with (-)-Δ^9-trans-(6aR, 10aR)-tetrahydrocannabinol (Δ^9-THC) being the most psychologically active constituent [3]. The development of synthetic cannabinoids and the discovery of chemically different endogenous cannabinoid receptor ligands (endocannabinoids) have prompted the use of the term ‘‘phytocannabinoids’’ to describe these compounds [4]. The total number of natural compounds identified in *C. sativa* L. in 1980 was 423 [5], in 1995 was 483 [6] and in 2005 was 489 [7] (Table 1). These compounds altogether contribute to the unique pharmacological and toxicological properties of cannabis. The aim of the current review is to discuss the chemical constituents present in the plant and highlight the major class of compounds that are responsible for the drug’s psychosomatic properties.

Table 1: Constituents of *C. sativa* L. by chemical class

Chemical Class		1980	1995	2005
Cannabinoids	CBG Type	6	6	7
	CBC Type	4	4	5
	CBD Type	7	7	7
	Δ^9-THC Type	9	9	9
	Δ^8-THC Type	2	2	2
	CBL Type	3	3	3
	CBE Type	5	5	5
	CBN Type	6	7	7
	CBND Type	2	2	2
	CBT Type	6	9	9
	Misc Type	11	12	14
Nitrogenous compounds		20	27	27
Amino acids		18	18	18
Proteins, enzymes and glycoproteins		11	11	11
Sugars and related compounds		34	34	34
Hydrocarbons		50	50	50
Simple alcohols		7	7	7
Simple aldehydes		12	12	12
Simple ketones		13	13	13
Simple acids		20	20	20
Fatty acids		12	23	23
Simple esters and lactones		13	13	13
Steroids		11	11	11
Terpenes		103	120	120
Non-cannabinoid phenols		16	25	25
Flavonoids		19	21	23
Vitamins		1	1	1
Pigments		2	2	2
Elements		0	9	9
Total		423	483	489

1980	1995	2005
61	66	70

Chemical Constituents of *Cannabis sativa* L.

Cannabinoids

The typical C_{21} group of compounds present in *C. sativa* L. is known as cannabinoids and includes their analogs and transformation products [8]. The 70 known cannabinoids can be classified as follows:

Cannabigerol (CBG) type

Cannabigerol (CBG-C_5) was the first compound isolated from the resin of marijuana as a pure chemical substance. Although CBG-type compounds are inactive when compared to Δ^9-THC [9], they show considerable antibacterial activity against gram positive bacteria [10]. There are currently seven CBG-type compounds known (Figure 1 and Table 2). The most recently isolated compound, cannabinerolic acid, is the trans-isomer of cannabigerolic acid [11]. All other CBG-type compounds have cis-geometry.

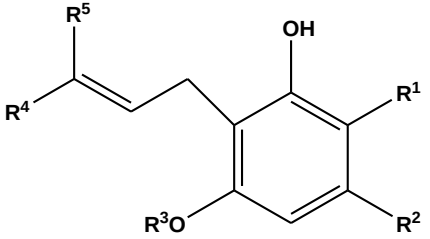

Fig 1: CBG-type cannabinoids

Table 2: CBG-type cannabinoids

Compound	Cis/trans	R^1	R^2	R^3	R^4	R^5
Cannabigerolic acid A [(E)-CBGA-C_5 A]	cis	COOH	n-C_5H_{11}	H	$(CH_2)_2CH=C(CH_3)_2$	Me
Cannabigerolic acid A monomethyl ether[(E)-CBGAM-C_5 A]	cis	COOH	n-C_5H_{11}	Me	$(CH_2)_2CH=C(CH_3)_2$	Me
Cannabigerol [(E)-CBG-C_5]	cis	H	n-C_5H_{11}	H	$(CH_2)_2CH=C(CH_3)_2$	Me
Cannabigerolic monomethyl ether[(E)-CBGM-C_5]	cis	H	n-C_5H_{11}	Me	$(CH_2)_2CH=C(CH_3)_2$	Me
Cannabigerovarinic acid A [(E)-CBGVA-C_3 A]	cis	COOH	n-C_3H_7	H	$(CH_2)_2CH=C(CH_3)_2$	Me
Cannabigerovarinic [(E)-CBGV-C_3]	cis	H	n-C_3H_7	H	$(CH_2)_2CH=C(CH_3)_2$	Me
Cannabinerolic acid A [(Z)-CBGA-C_5 A]	trans	COOH	n-C_5H_{11}	H	Me	$(CH_2)_2CH=C(CH_3)_2$

Cannabichromene (CBC) type

The discovery of cannabichromene (CBC-C_5) by Claussen *et al.* [12] and Gaoni and Mechoulam [13] occurred almost simultaneously and led to the discovery of other CBC-type compounds. Natural CBC-C_5 is thought to be racemic [14] and although the CBC acids, cannabichromenic acid and cannabichromevarinic acid, were reported to have optical activities of + 4.8° and -4.8° [15] in chloroform, respectively, they are also probably racemic [14]. It was also proven that both acids are the A acids on the basis of IR data and comparison with synthetic samples [15]. The isolation of the C_3-analog of CBC has been reported by two groups [16]. DeZeeuw *et al.* [16] identified the compound on the basis of GC-MS analysis and named it cannabivarichromene. They did not, however, state specifically that the C_3 side chain is n-propyl. They also did not report any optical activity. Shoyama *et al.* [15] named their isolated compound cannabichromevarin and indicated an n-propyl side chain. Morita and Ando [17] claimed the separation and identification of a CBC-C_3-type compound with a 4-methyl- 2-pentenyl side chain at C_2 (Figure 2 and Table 3) instead of a 4- methyl-3-pentenyl side chain as found in all the other know CBC-type compounds. The absolute configuration at C_2 has not yet been determined.

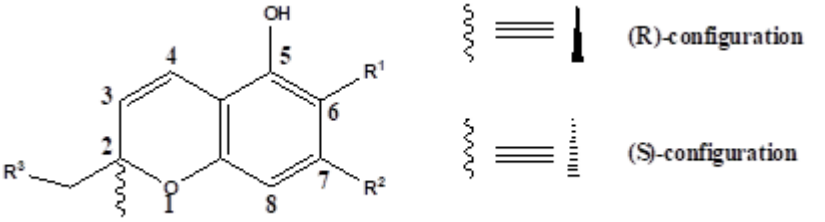

Fig 2: CBC-type cannabinoids

Table 3: CBC-type cannabinoids

Compound	R^1	R^2	R^3
(±)-Cannabichromenic acid (CBCA-C_5 A)	COOH	n-C_5H_{11}	$(CH_2)_2CH=C(CH_3)_2$
(±)-Cannabichromenic (CBC-C_5)	H	n-C_5H_{11}	$(CH_2)_2CH=C(CH_3)_2$
(±)-Cannabichromevarinic acid (CBCVA-C_3A)	COOH	n-C_3H_7	$(CH_2)_2CH=C(CH_3)_2$
(±)-Cannabichromevarinic (CBCV-C_3)	H	n/i-C_3H_7	$(CH_2)_2CH=C(CH_3)_2$
(±)-Cannabichromevarin (CBCV-C_3)	H	n-C_3H_7	$(CH_2)_2CH=C(CH_3)_2$
2-Methyl-2-(4-methyl-2-pentenyl)-7-propyl-2H-1-benzopyran-5-ol	H	n-C_3H_7	$(CH_2)_2CH=CHCH(CH_3)_2$

Cannabidiol (CBD) type

Cannabidiol was isolated in 1940 [18] and its absolute configuration established by synthesis of (-)-CBD as (-)-trans-(1R, 6R) [19]. The optical rotation of cannabidivarin was reported as $[\alpha]_D$-139.5° (chloroform) [20]. All of the known CBD-type cannabinoids have trans-(1R, 6R) (Figure 3 and Table 4) absolute configuration and presumably also negative optical rotation.

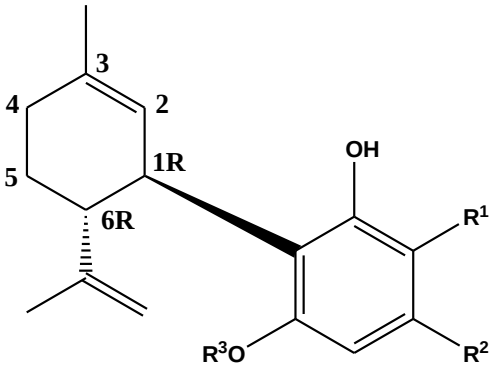

Fig 3: CBD-type cannabinoids

Table 4: CBD-type cannabinoids

Compound	R^1	R^2	R^3
Cannabidiolic acid (CBDA-C_5)	COOH	n-C_5H_{11}	H
(-)-Cannabidiol (CBD-C_5)	H	n-C_5H_{11}	H
Cannabidiol monomethyl ether (CBDM-C_5)	H	n-C_5H_{11}	Me
Cannabidiol-C_4 (CBD-C_4)	H	n-C_4H_9	H
Cannabidivarinic acid (CBDVA-C_3)	COOH	n-C_3H_7	H
(-)-Cannabidivarin (CBDV-C_3)	H	n-C_3H_7	H
Cannabidiorcol (CBD-C_1)	H	CH_3	H

(-)-Δ^9-trans-Tetrahydrocannabinol (Δ^9-THC) type

This type of Cannabinoids was first isolated by Gaoni and Mechoulam [21] and used NMR to assign the double bond position and the transconfiguration. They also reported an optical rotation of $[\alpha]_D$-140° (chloroform). The absolute configuration of tetrahydrocannabinol was determined to be trans-(6aR, 10aR) by comparison with D-(+)-glyceraldehyde and (-)-CBD [22]. Nine THC-type cannabinoids are known, although it is not certain if the C_4- and C_1-acids are the A and/or B acids (Figure 4 and Table 5).

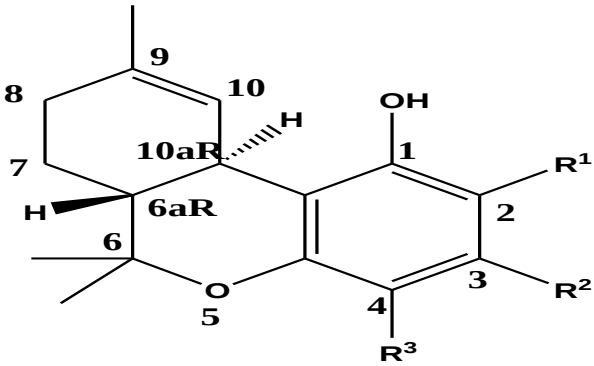

Fig 4: Δ^9-trans-THC-type cannabinoids

Table 5: Δ^9-trans-THC-type cannabinoids

Compounds	R^1	R^2	R^3
Tetrahydrocannabinolic acid A (Δ^9-THCA-C_5 A)	COOH	n-C_5H_{11}	H
Tetrahydrocannabinolic acid B (Δ^9-THCA-C_5 B)	H	n-C_5H_{11}	COOH
Tetrahydrocannabinolic (Δ^9-THCA-C_5)	H	n-C_5H_{11}	H
Tetrahydrocannabinolic acid-C_4 (Δ^9-THCA-C_4 A)	COOH	n-C_4H_9	H
Tetrahydrocannabinolic-C_4 (Δ^9-THC-C_4)	H	n-C_4H_9	H
Tetrahydrocannabivarinic acid A (Δ^9-THCVA-C_3 A)	COOH	n-C_3H_7	H
Tetrahydrocannabivarin (Δ^9-THCV-C_3)	H	n-C_3H_7	H
Tetrahydrocannabiorcolic acid A (Δ^9-THCOA-C_1 A)	COOH	CH_3	H
Tetrahydrocannabiorcol (Δ^9-THCO-C_1)	H	CH_3	H

(-)-Δ^8-trans-Tetrahydrocannabinol (Δ^8-THC) type

This group has only two compounds, namely (-)-Δ^8-trans-tetrahydrocannabinol and (-)-Δ^8-trans-tetrahydrocannabinolic acid A (Figure 5 and Table 6). They have the same absolute configuration as their Δ^9 counterparts, i.e. trans-(6aR, 10aR). Although no optical rotation data is available for Δ^8-THCA-C_5 A, synthetic Δ^8-trans-(6aR, 10aR)-THCVA-C_3 A has a reported value of $[\alpha]_D$-268° (chloroform) [15], indicating that the C_5-homolog should also have a negative optical rotation.

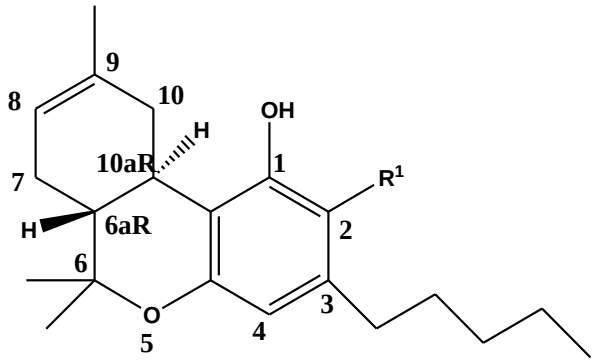

Fig 5: Δ^8-trans-THC-type cannabinoids

Table 6: Δ^8-trans-THC-type cannabinoids

Compound	R^1
(-)-Δ^8-trans-(6Ar, 10Ar)-Tetrahydrocannabinolic acid A (Δ^8-THCA-C_5 A)	COOH
(-)-Δ^8-trans-(6Ar, 10Ar)-Tetrahydrocannabinolic acid A (Δ^8-THC-C_5)	H

Cannabicyclol (CBL) type

Cannabicyclol (CBL-C_5) was first considered to have aTHC-type structure [23], and was therefore named THC III. It was isolated in 1967, renamed to cannabicyclol/cannabipinol and the structure revised [24]. The photochemical conversion of cannabichromene into cannabicyclol prompted another revision of the structure and speculation about the origin of the compound, i.e., if it is a naturally occurring compound or an artefact. Cannabicyclol from the crude plant material shows no apparent optical rotation, although an $[\alpha]_D$-3° was reported [25], and it could form as a result of natural irradiation in the plant or it could be an artefact formed in the crude extract [26]. This structure was finally confirmed as the correct structure by NMR [27] and X-ray analysis [28], although the absolute configuration is not yet known. Cannabicyclolic acid (CBLA-C_5 A) was first isolated asoptically inactive colorless prisms [29] and identified as the A acid of cannabicyclol by NMR analysis of its methyl ester and by comparison of the decarboxylation product with cannabicyclol. The photochemical conversion of CBCAC_5 A to CBLA-C_5 A was also demonstrated, and together with the fact that CBLA-C_5 A was observed to exist in larger amounts when Cannabis was harvested early in the vegetative phase [30] and stored as compared to when harvested in the reproductive phase, prompted the conclusion that CBLA-C_5 A is not a genuine substance but an artefact produced by natural irradiation of CBCA-C_5 A during storage [29]. Cannabicyclovarin (CBLV-C_3) was first detected by

GC-MS [31] and later isolated as optically inactive colorless needles [32]. Its structure was confirmed by comparison with synthetic CBLV-C_3 obtained by irradiation of CBCV-C_3.Only the relative configurations of these compounds are known (Figure 6 and Table 7).

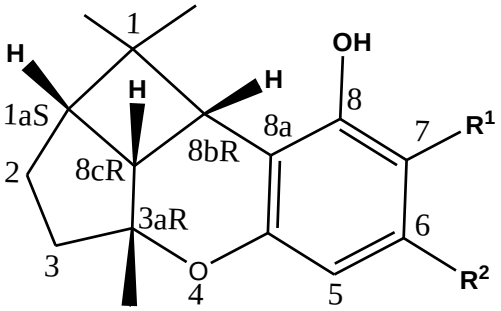

Fig 6: CBL-type cannabinoids

Table 7: CBL-type cannabinoids

Compound	R^1	R^2
(±) -(1aS, 3aR, 8bR, 8cR)-Cannabicyclolic acid (CBLA-C_5 A)	COOH	n-C_5H_{11}
(±) -(1aS, 3aR, 8bR, 8cR)-Cannabicyclol (CBL-C_5)	H	n-C_5H_{11}
(±) -(1aS, 3aR, 8bR, 8cR)-Cannabicyclovarin (CBLV-C_3)	H	n-C_3H_7

Cannabielsoin (CBE) type

The status of the CBE-type compounds (Table 8) as natural products has been questioned due to their infrequent identification and/or isolation from natural sources [33]. Also, they can be formed from the naturally occurring CBD and CBD acids by photo-oxidation [34] or pyrolysis [35]. In spite of these concerns, CBE and CBE acid (both the C_3 and the C_5homologues) have been reported to be natural products of *C. sativa* plant material or hashish on several occasions [35-37]. The first mention of cannabielsoin (CBE-C_5) in the literature occurs in 1973 [37], although no detail on the structure is given. The structure and absolute configuration were finally established by synthesizing CBE-C_5 using cannabidiol diacetate as starting material [38] and comparing it to cannabielsoin obtained by decarboxylation of natural cannabielsoin acid [35, 39]. No mention of optical rotation for these compounds could be found, but the methyl esters of both CBEA-C_5 acids displayed positive values in chloroform [34]. The absolute configurations for these compounds are (5aS, 6S, 9R, 9aR) (Figure 7).

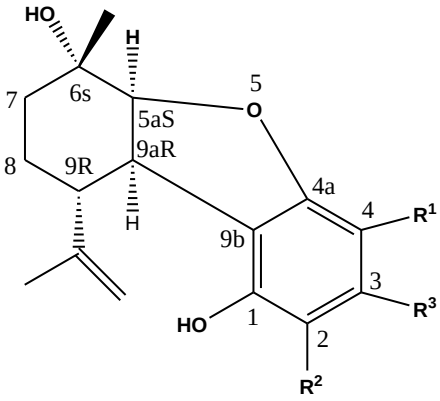

Fig 7: CBE-type cannabinoids

Table 8: CBE-type cannabinoids

Compound	R^1	R^2	R^3
(5aS, 6S, 9R, 9aR)-Cannabielsoic acid A (CBEA-C_5 A)	COOH	H	n-C_5H_{11}
(5aS, 6S, 9R, 9aR)-Cannabielsoic acid B (CBEA-C_5 B)	H	COOH	n-C_5H_{11}
(5aS, 6S, 9R, 9aR)-C_3-Cannabielsoic acid B (CBEA-C_3B)	H	COOH	n-C_3H_7
(5aS, 6S, 9R, 9aR)-Cannabielsoin (CBE-C_5)	H	H	n-C_3H_7
(5aS, 6S, 9R, 9aR)-C_3-Cannabielsoin (CBE-C_3)	H	H	n-C_3H_7

Cannabinol (CBN) type

CBN-type cannabinoids (Figure 8 and Table 9) are the fully aromatized derivatives of THC, and although they have been isolated from different cannabis extracts [40-42], they are thought of as artefacts. The concentration of CBN in cannabis products (marijuana, hashish and hash oil) increases during storage of these materials while the $\triangle^9$-THC concentration decreases, but at a different rate.

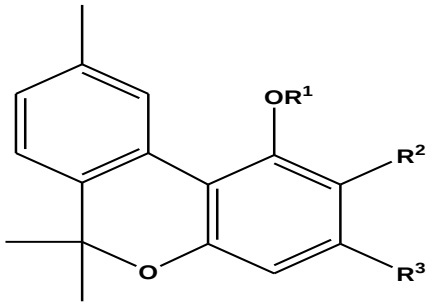

Fig 8: CBN-type cannabinoids

Table 9: CBN-type cannabinoids

Compound	R^1	R^2	R^3
Cannabinolic acid A (CBNA-C_5 A)	H	COOH	n-C_5H_{11}
Cannabinol (CBN-C_5)	H	H	n-C_5H_{11}
Cannabinol methyl ether (CBNM-C_5)	CH_3	H	n-C_5H_{11}
Cannabinol-C_4 (CBN-C_4)	H	H	n-C_4H_9
Cannabivarin (CBN-C_3)	H	H	n-C_3H_7
Cannabinol-C_2 (CBN-C_2)	H	H	C_2H_5
Cannabiorcol-C_1 (CBN-C_1)	H	H	CH_3

Cannabinodiol (CBND) type

CBND-type cannabinoids (Figure 9 and Table 10) are the fully aromatized derivatives of CBD. The first mention of these compounds appeared in 1972 [43, 44]. Van Ginneken *et al.* [43] named a compound isolated from hashish and identified by GC-MS cannabinodiol (R^1= n-C_5H_{11}). This assignment, however, was proven incorrect [45] after the total synthesis of cannabinodiol (CBND-C5). The compound isolated by Van Ginneken *et al.* [44] was determined to be cannabifuran (CBF-C_5) (Fig. 12b) and it was shown that the product from the photochemical conversion of cannabinol is cannabinodiol [46]. Therefore, all references in the literature vis-a`-vis CBND-type cannabinoids quoting Van Ginneken should be regarded with suspicion.

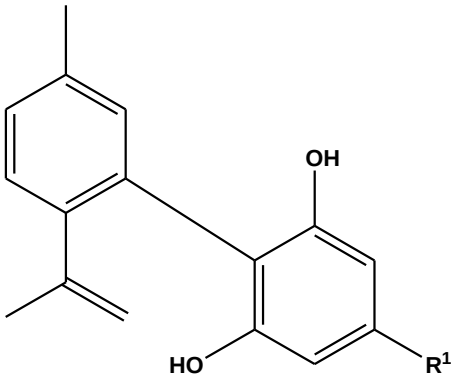

Fig 9: CBND-type cannabinoids

Table 10: CBND-type cannabinoids

Compound	R^1
Cannabinodiol (CBND-C_5)	n-C_5H_{11}
Cannabinodivarin (CBVD-C_3)	n-C_3H_7

Cannabitriol (CBT) type

Cannabitriol was first isolated by Obata and Ishikawa [47], the structure being determined by Chan *et al.* [48], who reported an $[\alpha]_D$ 107º(Figure 10 and Table 11). The isolation and characterization of (+)-cannabitriol [17] {$[\alpha]_D$ +7º} was followed by a single X-ray analysis of (±)-cannabitriol [49], confirming the structures of (+)- and (-)-cannabitriol, defining their relative configuration, and stating that all compounds previously named cannabitriol should be designated as trans-cannabitriol. The (±)-cis-isomer of (±)-trans-cannabitriol was isolated in 1978, but the individual (+)- and (-)-cis isomers have not been isolated separately [50]. The absolute configuration of these compounds has also not been determined. (±)-trans-Cannabitriol-C_3 and another CBT-C_3-homologueof unknown stereochemistry have been identified by GC-MS [51] in a 140-year-old ethanolic Cannabis extract. The C_{10}-ethoxy derivative ($[\alpha]_D$ – 10º) of (±)-trans cannabitriol-C_5 was isolated in 1977 [49] and the C_3-homologue was found by Harvey [52]. The 8,9-dihydroxy isomer of cannabitriol has been isolated as an optically inactive yellow oil [51], but the relative and absolute configurations are unknown. Harvey [52] also mentioned the presence of methyl-cannabitriol in the extract that he analyzed by select ion monitoring, but he did not give any further details, and therefore this C_1-homologue is not included as a known CBT type cannabinoid. Cannabidiolic acid tetrahydrocannabitriol ester (ester at C_9-OH) is the only reported ester of any naturally occurring cannabinoid [53].

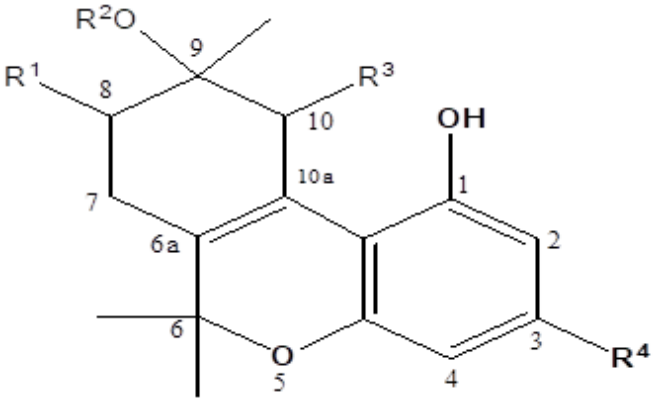

Fig 10: CBT-type cannabinoids

Table 11: CBT-type cannabinoids

Compound	R^1	R^2	R^3	R^4
(-)-trans-Cannabitriol [(-)-trans-CBT-C_5]	H	H	OH	n-C_5H_{11}
(+)-trans-Cannabitriol [(+)-trans-CBT-C_5]	H	H	OH	n-C_5H_{11}
(±)-cis-Cannabitriol [(±)-cis-CBT-C_5]	H	H	OH	n-C_5H_{11}
(±)-trans-Cannabitriol-C_3 [(±)-trans-CBT-C_3]	H	H	OH	n-C_3H_7
CBT-C_3-homologue	H	H	OH	C_3H_7
(-)-trans-10-Ethoxy-9-hydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol [(-)-trans-CBT-OEt-C_5]	H	H	OEt	n-C_5H_{11}
trans-10-Ethoxy-9-hydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol-C_3 [trans-CBT-OEt-C_3]	H	H	OEt	n-C_3H_7
8,9-Dihydroxy- $\Delta^{6a(10a)}$- tetrahydrocannabinol [8,9-Di-OH-CBT-C_5]	OH	H	H	n-C_5H_{11}
Cannabidiolic acid tetrahydrocannabitriol ester (CBDA-C_5 9-OH-CBT-C_5 ester)	H	CBDA-C_5 ester	OH	n-C_5H_{11}

Conclusion

Cannabis (*Cannabis sativa*, or hemp) is an annual herbaceous plant belonging to the Cannabaceae family has been used for multiple purposes (medicinal, recreational, seed oil and industrial fiber, etc.) for thousands of years. Its psychoactive and physiologically active constituents, known as cannabinoids, are found in the flowers (and to a lesser extent the leaves, and minimally in the stems, and seeds). The cannabinoids, primarily Δ^9-THC, are responsible for the plant's behavioral and psychotropic effects. There are also non-psychoactive cannabinoids such as cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) etc, which have several medicinal properties. The plant cannabis also contains other constituents which belong to diverse classes of natural products. Cannabis and the cannabinoids have potential medical applications in the treatment of a variety of serious illnesses.

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Chapter - 2

Societal Impact of Cannabis

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Introduction

Cannabis comes from the Hemp plant which is being used by many people in India since ancient times, presumably from the early Vedic era. Also referred to as Marijuana or weed, Cannabis is the most used illicit drug in the world. Cannabis or the Hemp plant is used for medical purposes. It is used in alleviating cancer and its pain and is also used in treating a rare disease called sickle cell anemia. It is used for ritual purposes in India since many Indians have the faith that Lord Shiva used Cannabis. During the Vedic period, Cannabis was used to make Soma, an intoxicating ritual drink that was praised in the Rig Veda. In the Atharva Veda, it is mentioned that people use to intake cannabis along with 5 other herbs and believed it as a sacred plant because it helped them to get relief from distress. Today, in many parts of India, it is used for commercial purposes in cloth, oil, food industries and used for spiritual purposes as well.

In 1930, the British government had ordered to stop the cultivation of cannabis which led to a drop in the cultivation. Even though, it had many good purposes it was on the list of the things which were banned by the Narcotic drugs and psychotropic substance act in the year 1985. Even though it was banned long back it is still found in some parts of India for only commercial purposes.

Places in which cannabis are found are

1) Jaisalmer
2) Pushkar
3) Noida
4) Mathura and
5) Varanasi
6) Parts of Meghalaya and Tripura

All India Institute of Medical Sciences (AIIMS) conducted a study in 2019 and reported that about 7.2 million Indians consumed cannabis in the financial year of 2018-19. The Ministry of Social Justice and Empowerment's survey reported that about 2.83% of Indians from the age group of 1—75 years (approximately 32million) were regular consumers of Cannabis Products. According to the World Health Organization reports, almost 3% of the world's adult population abuses cannabis.

City	Country	Consumption in Metric Tones
New York	USA	77.44
Karachi	Pakistan	41.95
New Delhi	India	38.26
LA, California	USA	36.06
Cairo	Egypt	32.59
Mumbai	India	32.38
London	UK	31.40

Source: ABCD 2018 Cannabis Price Index

According to the ABCD 2018 Cannabis Price Index Report, Two Indian cities rank among the Top seven highest Cannabis consuming cities in the world. India is also one of the cheapest places to buy Marijuana/Cannabis in the world. The price of Cannabis per gram ranges from Rs. 315 to Rs. 330 in New Delhi and Mumbai. Although Cannabis is Illegal in India, the Indian cities figure in the Top seven which is quite astonishing. Overall, The USA tops the list of highest consumers of Cannabis in the world, closely followed by Pakistan and India.

Intake of Cannabis/Marijuana can be done through various methods. It can be used as a consumable beverage. It can be used to brew tea or make shakes/lassis. Marijuana can be smoked by using hand-rolled cigarettes called Joints or Blunts. Cannabis can be mixed with food items like candies, brownies, fritters, laddoos, etc., and consumed.

The American Psychiatric Association's manual, DSM-5, has recently included Cannabis (Marijuana) Use Disorder, along with its symptoms and various diagnostic criteria for an addiction like – tolerance, withdrawal symptoms, cravings, etc.

Cannabis has huge repercussions on people, specifically the youths or youngsters in both rural and urban areas. The reason being that it is often easily accessible. The habit of cannabis consumption can creep up to youngsters as early as 11 years of age. Use of cannabis during adolescence can lead to altered brain development, a decline in cognitive function,

attentiveness, and memory, poor academic performance, decreased motivation, etc. Excessive use at this age may also lead to schizophrenia or other psychotic disorders. It can also affect youngsters' social life and cause social and interpersonal deficits. Cannabis or Marijuana can cause delinquent behavior, aggression, rebellion, and poor relationships with family, especially parents and siblings.

Impact of Marijuana/Cannabis on a Psychological and Social Level

- **Euphoria (mild or moderate)**: Intake of Cannabis can lead to mild or moderate levels of Euphoria and last for several hours.
- **Relaxation**: In popular culture, with its portrayals in films and television, Cannabis can be a source of achieving a state of relaxation regardless of the prior state of mind. It might hold for some users depending on the amount of intake but for the majority of people, the experience is quite contrasting. Cannabis strains can increase psychological activity, rather than slowing it down which can lead to anxiety or panic attacks.
- **Relief from Anxiety**: Although scientific research in this area is still sparse, it has been found that marijuana creates a calming experience that may temporarily relieve symptoms of anxiety for many people. Hence, they use it for self-medication. But prolonged use of cannabis can lead to Major Depressive Disorders/depression. Cannabis can also create psychological dependence and lead to addiction.
- **Time Perception Alteration**: The research on the effect of Cannabis on time perception alteration is sporadic. According to various reports, most cannabis users self-report the experience of a slowed time perception. Laboratory researchers have confirmed changes in the internal clock after the intake of cannabis, by depicting the irregular cerebellar blood flow and its relationship with distortion of time perception.
- **Hallucinations and mild Paranoia**: Intake of an excessive amount of Cannabis can lead to temporary Hallucinations lasting for several hours. For some people, high or long-term Cannabis intake/use can lead to mild or moderate levels of Paranoia.
- **Illusions (sometimes)**: Intake of Cannabis for a prolonged period can lead to temporary alterations of feelings, thoughts, or perceptions, also known as Illusions, lasting for several hours/days.

- **Impaired Cognitive Functioning**: Prolonged use of Cannabis may sometimes lead to impaired thoughts, sensations or feelings and can make way for psychotic disorders like schizophrenia.
- **Memory Disruption**: Various sources cite that Cannabis has been associated with memory loss. But the notion is largely anecdotal. Memory is split into two parts namely the short-term memory and the long-term memory. The immediate events are temporarily stored in short term memory, whereas in the long term memory, information is stored indefinitely. Current evidence shows that marijuana intoxication may temporarily alter or distort short-term memory processing. It is caused by compounds in cannabis that disrupt neural signaling while binding to the receptors responsible for memory in the brain. Interrupted short-term memory can impact learning, memory and can cause loss of interest or concentration problems.
- **Impaired motor control**: Prolonged use of Cannabis may sometimes lead to reduced activity in areas of the cerebellum, an area of the brain which is linked with motor control, coordination, and balance. Recent studies have pointed out that marijuana may change the way brain regions process information and communication. The changes may lead to impairments in the processing of cognitive and motor information and affect the ability to learn new motor skills.
- **Impaired Reaction Time**: Extensive smoking of marijuana may reduce the linear movement time significantly, according to some studies. This phenomenon may occur because of the reduced activity in the areas of the cerebellum which is associated with motor control, coordination, and balance.
- **Depression:** Various research suggests that heavy cannabis/marijuana smokers/users are diagnosed with depression more often than a non-smoker. Use of Cannabis may directly not induce depression but can trigger it when there are genetic, environmental, or other factors involved. So the bottom line is that Marijuana intake and depression accompany each other, but there is still no evidence that marijuana directly causes depression.

Other Impacts of Cannabis

Many people use toxic ways to escape reality. People in rural areas use it because they are in the belief that such practices will impress the almighty.

People using Cannabis usually have both psychological as well as social effects. It harms people. It is known as the antidepressant drug and it is very harmful as it slows down the central nervous system. People using cannabis have no control over their actions, emotions, and stay aloof, and like to stay in isolation most of the time. A high dosage of Cannabis also leads to a hallucination effect on the person who uses it. It is used by the people in the villages because the life of people in rural areas tends to be very hard. The villagers use this herb to reduce mental stress as well as physical pain.

Restoration of Cannabis cultivation or Hemp cultivation in fewer places in India has helped in the change in the social and economic status of the rural areas in India. Many people got employment and were uplifted from poverty. Cannabis cultivation does help in keeping the traditional knowledge and traditional practices of cultivation alive. In many rural areas, farmers and cultivators are still dependent on the traditional methods of cultivation and farming, so the restoration of cannabis cultivation has helped the cultivators to keep on using their traditional method and knowledge. Industries using cannabis for commercial purposes are seen as an important part of these farmers's everyday life.

As cannabis is legal in some parts of India and used only for commercial purpose, many industries are being set up in particular areas and it promises to give an income to those who cultivate and provides cannabis for that industry. Reverse migration is being seen as many villagers who are unable to find a job in the urban areas return to their villages as they got an opportunity to earn a stable economy through cultivation and provide a certain amount of cannabis to the industries.

Cultivation of Cannabis or hemp plant can also help in reducing or stopping deforestation of land. The land is a very fragile and important substance for the industries which are herb-based and cultivating the hemp plant can refresh the soil by restoring its fertility.

The restoration of Cannabis only for industrial use in India has a positive impact on rural society and the economy. It is also scientifically seen that cannabis can reduce plastic pollution as it is possible to make fully biodegradable plastic from the Hemp plant.

Conclusion

Irrespective of all the facts, Cannabis is an illicit drug in India. Even though it is illegal, it is cheap, easily accessible, and widely used by the citizens. It has a mythological value and is used for various Hindu rites and rituals. It is also used for commercial and medicinal purposes. However, it's

the younger generation that is getting affected in recent times, both psychologically and socially. It's time the Government makes some stricter laws to regulate the illicit use of cannabis and restrict its usage only for commercial and medicinal purposes as well as minimizes the negative impacts of the same in today's generation.

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Chapter - 3

Physiotherapy and Cannabis

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Introduction and definitions

Cannabis, also called Marijuana, which has a long history of human use. In Sanskrit, it is called Vijaya, and in Hindi known as Bhang. Sushruta Samhita mentioned bhang, a medicinal plant. The Indians are one of the earliest users of cannabis in history. It is also grown naturally in Persia, Southern Siberia, and China. Since its discovery, it has been used by millions of people for both inducing pleasures and pain management.

The use of harmful psychoactive substances is called substance abuse. It is one of the big problems confronting the modern world today especially among the youth. Cannabis is a psychoactive drug that alters perception. There has also been harmful use and dependence among the users of cannabis. Cannabis contains tetrahydrocannabinol (TCH), which is the chemical component causing the effects. Commonly in India bhang is ingested while Charas and ganja are mostly smoked.

There are an estimated 31 million users of Cannabis in India[1]. According to the data of National Drug Dependence Treatment Center, AIIMS, New Delhi, the prevalence of current cannabis use among the entire population 10-75 years), all males, all females, children's (10-17 years), adults (>18 years) is 2.8%, 5.0%, 0.6%, 0.9%, and 3.3% respectively. Overall, 0.25% of Indians use cannabis during a dependent pattern [1].

In India, Cannabis also called Bhang is legal in many states, and Charas and Ganja which are considered illegal as per the International drug conventions and also as per Indian law (NDPS Act, 1985).

Legal Aspects: India & Abroad

In 1838, 1871, and 1877 various attempts at criminalizing cannabis in British India were made and introduced [2]. International treaty Single Convention on Narcotic Drugs 1961 classed cannabis with hard drugs.

During the talks, the Indian delegation opposed its intolerance to the social and religious customs of India. As a settlement, the Indian Government assured to limit the export of Indian hemp, and the final draft of the treaty defined cannabis as [3]:

"Cannabis" means the flowering of the cannabis plant in which the seeds and leaves are excluded when not accompanied by the tops from which the resin has not been extracted, by whatever name they will be designated.

Bhang was overlooked from the definition of "cannabis" which allowed Indians to hold on to the consumption of bhang during Holi. The treaty also gave India 25 years to crack down on recreational drugs. Towards the top of this exemption period, the Indian government passed the Narcotic Drugs and Psychotropic Substances Act in 1985 [4].

The sale and gathering of cannabin and flowers are banned by NDPS, but allowed the utilization of the leaves and seeds, allowing the states to manage the latter. Cannabis is considered as a source of biomass, fiber, and high-value oil according to The National Policy on Narcotic Drugs & Psychotropic Substances. The government of India facilitates the cultivation of cannabis with low THC content for the research field [5].

Although NDPS allows the utilization of bhang, different states in the country have their own laws for restricting its use. In some states, only authorized dealers are allowed to sell bhang. Some states even have rules about the utmost amount of bhang one person can carry and therefore the minimum age of the customer [6]. Sale, purchase, possession, and consumption of ganja and bhang in Assam are illegal as per The Assam Ganja and Bhang Prohibition Act, 1958 [7]. While in Maharastra you can't manufacture, possess, and consume bhang or bhang-containing substances without a license [8].

The legalization of bhang is done by removing it from the list of "intoxicating drugs" covered by the Gujarat Prohibition Act, Gujrat [9]. Numerous efforts were done to re-legalize cannabis in India, with the holding of medical conferences in different parts of India like Bangalore, Pune, Mumbai, and Delhi by the good Legalization Movement. Many articles and programs were conducted within the popular media have also begun to seem to push for a change in cannabis laws.

Prominent leaders like Maneka Gandhi, Viki Vaurora, and Shashi Tharoor advocated the legalization of cannabis on the basis of health benefits under medical grounds [10, 11, 12, 13]. Back in July 2019, a petition was filed by the Great Legalization Movement Trust, challenging the ban on cannabis

which the Delhi High Court agreed to hear. The general public interest litigation argues that group cannabis with other compound medications under the NDPS Act is "random, unscientific and unreasonable" [14].

The Central Council for Research in Ayurvedic Sciences (CCRAS), a research body under the Ministry of AYUSH, announced the outcome of the initial clinical study in India on the use of cannabis as a restorative medication for cancer patients around 25 November 2018. Gujarat Ayurved University, Jamnagar, in collaboration with the Tata Memorial Hospital in Mumbai conducted the pilot study on patients undergoing treatment for cancer. CCRAS Director General Vaidya K.S. Dhiman stated that "cannabis leaves-based drugs have been found successful in alleviating pain and other symptoms in cancer patients post-chemo and radiotherapy in a pilot study conducted earlier that season [15]".

In November 2018 Bombay Hemp Company (BOHECO) collaborated with CSIR and hosted a conference "Cannabis R&D in India: A Scientific, Medical and Legal Perspective" to promote the use of cannabis-based medicines in Delhi [16]. On the very same day, the Indian Institute of Integrative Medicine (IIIM) of this CSIR announced that they were working on the development of three cannabis-based medicines to cure cancer, epilepsy, and sickle-cell anemia [17, 18]. Under the Act of NDPS, penalties vary depending upon the amount of cannabis and act of criminalization, following are few· Segment 20 Of the NDPS Act, 1985 arrangements with the offenses related not exclusively to the utilization yet additionally development, ownership, use, deal/buy, import/fare, transportation, and warehousing of cannabis, aside from clinical or logical purposes.

The penalty for producing, fabricating, having, selling, buying, moving, bringing in between State, sends out between State, or utilizing cannabis is as per the following: For little amount: Rigorous detainment for a term that may reach out to a half year or a fine that may stretch out to Rs 10,000, or both. For more than a little amount however lesser than business amount: Rigorous detainment may stretch out to 10 years with a fine that may reach out to Rs 1 lakh. For business (commercial) amount: Rigorous detainment won't be under 10 years, yet may reach out to 20 years and a fine of at least Rs 1 lakh (which can be stretched out to two lakhs). For Juveniles: There is a different law for adolescents (Section 18 of Juvenile Justice Act) and those under 18 who cannot be punished under the NDPS Act.

Clinical manifestation

Depending upon the route of administration, Intoxication depends on

whether cannabis is inhaled or ingested. It may take a few minutes during inhalation and a few hours if ingested. The disorder shows clinically huge maladaptive conduct or mental changes. The magnitude of these changes varies widely, depending upon the dose of THC and the subject using cannabis. The duration of subjective intoxication is typically three to four hours, if inhaled, and is prolonged with oral ingestion because of continued slow absorption from the gut [19, 20]. Ingestion of cannabis typically leads to feeling "high," marked by a euphoric, pleasurable feeling and also a decrease in anxiety, alertness, depression, and tension. Nonetheless, dysphoric responses might be joined by social withdrawal.

The subject may have perceptual changes like colors are brighter and music is more vivid. Time perception may also be distorted. They may perceive time is faster than clock time. Spatial perception can also be distorted and high doses or potent cannabis products may cause hallucinations [20]. Cannabis use diminishes response time and impedes focus, transient memory, and decreases the ability to perform the risk assessment [20]. These effects are additive when cannabis is used in conjunction with other central nervous system depressants. Acute cannabis abuse also impairs motor function and coordination and disturbs the ability to complete critical tasks that require individual attention.

Impairment of mental function, motor coordination, and decision making lasts much more duration in comparison to the transient feeling of "high." Psychomotor impairment lasts for 12 to 24 hours. It is due to the accumulation of marijuana in fat tissue, slow release of THC from fatty tissue stores, and enterohepatic recirculation [21]. However, a marijuana user may think that he or she is no longer impaired several hours after the acute mood-altering effects have resolved.

Acute psychomotor impairments interfere with the ability to operate other heavy machineries such as automobiles, trains, and motorcycles, and there is evidence that cannabis intoxication increases the risk of traffic accidents. Drivers using cannabis are much more prone to accidents as compared to drivers who do not use any drugs or alcohol [22]. The signs of cannabis intoxication are Tachycardia, Increased blood pressure, tachypnoea, Conjunctival injection (red-eye), Dry mouth and increased appetite Chronic heavy use may lead to a loss of pleasurable effects during cannabis use and a corresponding increase in dysphoric effects. Drug testing — Drug testing is useful for monitoring the progress of treatment and early detection of relapse [23].

Urine, blood, oral fluid, and hair can all be tested for cannabinoid metabolites [24]. Among this Urine testing is the commonest, which is generally less expensive, is widely available and as these tests are vulnerable to cheating, the samples are collected under direct observation. A positive urine test only shows the past use and therefore it cannot be used in the diagnosis of intoxication, abuse, or dependence, because cannabinoid metabolites are highly lipophilic, and they remain in the body fluids for long periods of time and also are excreted slowly, so urine tests for remain positive even after discontinuation of cannabis for up to:

- For casual cannabis user 7 to 10 days
- For heavy user 2 to 4 weeks
- Months in a chronic heavy user

Prescribed medicine like dronabinol for treating nausea induced in patients by chemotherapy or for the HIV wasting syndrome will also test positive for delta-9-tetrahydrocannabinol (THC) but urine drug testing can be done to differentiate smoked marijuana from oral dronabinol which need to specifically request on the drug screen [25].

Sweat patch testing is another means of assessing the use of marijuana and is more resistant to cheating compared to urine tests because if the patch is removed once, the edges become disfigured which can be easily identified by the clinician. The patch can be worn for a few hours to a few weeks, after which it falls off. While the subject worns it collects prospective evidence of cannabis compared to the retrospective data collected by other types of testing. The patch should be removed under direct observation and is sent to a laboratory for testing [24].

Patients testing positive may deny the use and claim the result is a false positive. However, But regardless of the specimen tested (urine, blood, oral fluid, hair, or sweat) clinical laboratories follow certain standard tests that eliminate the possibility of false-positive results [24]. Testing begins with a highly sensitive immunoassay screening test. Highly specific confirmation tests, such as a gas chromatography/mass spectrometry test are done to confirm if the results are found positive in the screening.

Differential diagnosis: Intoxication, abuse, and dependence due to other substances may mimic syndromes caused by cannabis. Besides, symptoms of psychiatric disorders not involving substances can overlap with symptoms of cannabis disorders, Therefore a proper diagnostic evaluation is needed to ascertain which disorder is present and specific treatment can be directed [19]. Mental problems, including other substance use disorders that

look like cannabis issues, can likewise happen related to cannabis dependence disorders.

Acute cannabis intoxication

The cannabis intoxication can resemble significant maladaptive behavioral or psychological changes that occur during intoxication due to other substances

- **Alcohol, sedatives, hypnotics, or anxiolytics:** Impaired judgment and motor coordination are common due to abuse of substances like alcohol, sedatives, hypnotics, anxiolytics, or cannabis. They are distinguished by the occurrence of nystagmus, ataxia, suppressed appetite, and increased aggressive behavior is also observed.
- **Hallucinogen:** The symptoms like motor coordination, impaired judgment, paranoia, tachycardia, and anxiety which can occur in hallucinogen and cannabis intoxication. Its intoxication can be distinguished by more prominent perceptual disturbances, tremors, diaphoresis, and papillary dilation.
- **Phencyclidine:** It is much more likely to cause nystagmus, ataxia, an increase in blood pressure, and aggressive behavior. Phencyclidine and Cannabis intoxication may result in impairment of higher mental functions like judgment making and tachycardia.

Primary mental disorders — acute adverse reactions may arise during cannabis intoxication, which can resemble clinical features of many psychiatric disorders not involving substances. These include

- Panic disorder
- Generalized anxiety disorder
- Major depressive disorder
- Bipolar I or II disorder
- Schizophrenia, paranoid type

These disorders are distinguished by the absence of tachycardia and injected conjunctivas that occur with cannabis intoxication usually a negative urine drug screen may help make the diagnosis.

Cannabis abuse and dependence — chronic use of cannabis shows symptoms similar to dysthymic disorder, which may involve depressed mood, occupational and functioning impairment of social. A urine drug screen can help make the diagnosis.

Polysubstance dependence — It also includes the diagnosis of polysubstance dependence for patients who repeatedly use three or more substances (not including caffeine and nicotine) during the same 12 month period, with no one substance predominating. In addition, dependence criteria are met for substances as a group, but not for anyone specific substance.

"Exercise" An Adjunct tool in addiction rehabilitation

Exercise helps to conquer addiction. In an article by Psychiatrist Claire Twark in Harvard Health Publishing said that she has discovered exercise helps to distract her patients. She added that workouts add structure to the daily routine which helps the patients with forming positive social changes and help cure depression and anxiety together with other remedies [26].

The above-mentioned truth is also backed by a small Danish pilot research by Kirsten Kaya Roessler in people who investigated a workout program offered to 38 men and women who misused a variety of substances, such as opioids, cannabis, amphetamines, and cocaine. Participants agreed to take part in group exercise three times a week for just two to six months. Twenty people completed the intervention. When reassessed annually later, five documented abstinence and 10 reported that they had decreased their material use [27].

"Exercise" as a potent treatment for drug misuse. Various studies hold the simple fact that several behavioral and neurobiological consequences of exercise that could cause its protective effects in the decrease of compulsive patterns of drug intake in clinical and at-risk populations [28].

Exercise serves alternatively as, non-drug reinforce to reduce drug self-administration. The capability of alternative non-drug reinforces to attenuate measures of medication self-administration has been well-described in the literature and may take the form of consumable, possessional, or activity-based stimuli (Carroll, 1993; Higgins, 1997) [29, 30].

Exercise may also reduce drug self-administration by reducing co morbid risk factors that are related to substance use disorders. There's a huge body of literature suggesting that exercise decreases measures of depression and anxiety in human populations [31] (Herring *et al*, 2010 (A6); Perraton *et al*., 2010 [32] (A7)), both of which are risk factors for substance use and misuse (Swendsen and Merikangas, 2000 [33]; Castle, 2008 [34]).

Exercise also normalizes the behavioral and neurobiological consequences of prolonged stress in lab animals (Haack *et al*., 2008; Marais

et al., 2009), which can be another risk factor for substance abuse in people. Exercise may thus be producing some of its protective effects in animal models by reducing negative affective conditions that serve to initiate, maintain, and accelerate medication self-administration [28].

One additional mechanism by which exercise can govern medication self-administration and drug-seeking behavior is by producing neuroanatomical changes through neurogenesis and gliogenesis. Aerobic exercise induces neurogenesis in several regions of the hippocampus (Rhodes *et al*., 2003; Uda *et al*., 2006). Reductions in hippocampal neurogenesis have been implicated in drug self-administration (Noonan *et al*., 2010); and by extension, exercise can enhance the capability of this arrangement to buffer compulsive patterns of drug intake. Aerobic exercise increases gliogenesis in the prefrontal cortex of rats (Mandyam *et al*., 2007), and exercise has positive impacts on prefrontal-dependent behavior in humans (Little *et al*., 2006; Yanagisawa *et al*., 2010).

Although cannabis is one of the most widely used banned substances; individuals diagnosed with cannabis use disorder have few well-researched, affordable treatment options available to them. Exercises can be said to have great potential as an adjunctive treatment for individuals with cannabis use disorder. Cannabis dependence is a significant public health problem and as there are no approved medications for this condition, management must rely on behavioral approaches empirically complemented by such lifestyle changes as exercise.

Jessica G Irons *et al*. (2014) reported that increasing physical activity may be helpful in individuals with cannabis dependence who are engaged in a cessation attempt [35]. A recent study states that Moderate-intensity aerobic exercise may reduce the sleep disturbances associated with cannabis withdrawal (Denielle McCartney *et al*. 2020) [36]. A study was done on 14 cannabis-dependent adults by Maciej S Buchowski *et al*. with aerobic exercises (10 supervised 30-min treadmill exercise sessions standardized using heart rate (HR) monitoring (60–70% HR reserve over 2 weeks.). Within the run-in period, the daily use of cannabis was 5.9 joints per day. The results indicated that Average cannabis use levels within the exercise (2.8 joints,) and follow-up (4.1 joints,) periods were lower than during the run-in period. The above statements back the fact that Supervised Aerobic exercises are found to be helpful in the management of cannabis dependency [37].

Angelique G. Brellenthin and Kelli F Koltyn in their study “Exercise as an Adjunctive Treatment for Cannabis Use Disorder” concluded that heavy

cannabis use may dysregulate the endogenous cannabinoid system, which has implications for several psychobiological processes that interact with the endocannabinoid system such as reward processing and the stress response. Given that exercise is a potent activator of the endocannabinoid system, it is mechanistically plausible that exercise could be an optimal method to supplement cessation efforts by reducing psychophysical withdrawal, managing stress, and attenuating drug cravings [38]. Exercise can be a fantastic tool for those who are in recovery for a lot of reasons.

Improves sleep pattern: Exercising regularly leads to improved sleep patterns. When a person sleeps better and feels rested their overall wellbeing improves.

Exercise can make one feel good: The process of exercising releases several hormones like Endorphins, serotonin, and dopamine in the brain that help someone feel better and generate an overall sense of well-being.

Time utilization keeps the patient active: During addiction recovery, it is usually a fantastic idea to remain active, particularly in the beginning phases. Exercising regularly is a great way to stay busy.

Helps in Healing the Body; cardiovascular health improves with regular exercise which leads to a decreased chance of developing hypertension, high cholesterol, and heart disease. Exercise boosts the immune system and has been demonstrated to help improve mental health and decrease the chance of developing Alzheimer's later on in life.

Regular Workout Routines Provide Structure: A life of active addiction usually does not comprise much arrangement. An important element of recovery is growing healthy habits and patterns. Physical exercise boosts Self-Confidence: Another extra benefit of exercise is an improved sense of self-confidence. When folks take good care of their body they generally feel much better about themselves than when they do not. Increased the rate of success for Living a Quality Life. Different studies have demonstrated that people who are in the recovery phase who exercise regularly have higher success rates of living a quality life, when taking into consideration that regular exercise helps with stress reduction, enhances sleep, an increased sense of overall wellbeing.

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Chapter - 4

Domestication of *Cannabis* and Its Future Prospects

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Introduction

Cannabis refers to a group of three plants with psychoactive properties, known as *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Among them the most widely cultivated species is *Cannabis sativa* (L) (UNODC-2016 & WHO-2013 [1, 2]) Well drained soils, adequate sunlight, warmth and moisture are most essential parameters for proper grow of this plant and this is the reason that most naturally growing populations are found seasonally across accommodating northern temperate latitudes [3-7] (Merlin, M. D. 1972; Clarke, R. C. 1977; Clarke, R.C. and Merlin, M. D. 2013; Clarke, R. C. 1981; Small, E. 2015). Within this temperate latitude area around the northern hemisphere only the seminal uses, early cultivation, worldwide dissemination and eventual domestication of this plant all began in course of time [8] (Clarke, R.C. and Merlin, M. D. 2016).

During the last few decades the presence of psychoactive compounds in *Cannabis* attracted many scientists' attention towards this plant around the world [9] (Meijer, EPM de 1993). For the biological function of the cannabinoid containing resin for the plant itself, several theories had been proposed by many. Krejci (1970) [10] had suggested a relation with antibiotic activity; Schultes (1970) [11] for drought and heat tolerance and as a result it was believed that warm, dry and windy conditions induce higher densities of resin glands where biosynthesis of cannabinoids takes place. It has also been estimated that when grown in a continental climate there is higher contents of cannabinoids than in a maritime climate in the same populations [12] (Murari G., S. Lombardi, A.M. Puccini & R. de Sanctis, 1983).

Ecology and botany of the plant

The *Cannabis* plant produces either male (pollen) or female (seed) flowers and hence is dioecious in nature. The monoeciuos characteristic is

very rare in this plant. Air pollination is the major characteristics of this plant spp. wind pollination, dioecious sexuality, and X/Y sexual inheritance are each relatively rare in plants, y*et al*l three are characteristics of *Cannabis* [8] (Clarke, R.C. and Merlin, M. D. 2016). This plant sp. grows and develops within their annual life cycle of sexual reproduction. Clarke and Merlin (2016) had also stated that the moistened seeds germinate as spring weather warms, and juvenile plants grow rapidly through the summer. Fast-growing juvenile plants appear much alike, but as autumn day length decreases, populations begin to flower and plants express individual phenotypic differences. Male plants within a single population are often slightly taller than female plants. Male flowers hang from branches with few leaflets and are exposed to the wind (which facilitates pollen dispersal), whereas flowers on female plants are tightly clustered with small leaflets to trap male pollen grains that fertilize the female ovules. Soon after males shed their pollen they die. Before the arrival of killing frosts, the fertilized female plants ripen viable seeds. These disseminules fall to the ground via the wind or feeding birds and other animals that disperse the seeds inadvertently; and then they overwinter in the soil ready to initiate another life cycle the following spring.

As mentioned earlier, the Cannabis favors a mild climate with sufficient water and sunlight. Cannabis thrives on the nutrient-rich dump heaps near human occupation and has readily apparent agronomic traits, and it was therefore pre adapted to cultivation (Anderson, 1967; Merlin, 1972; Clarke and Merlin, 2013). Annual plants of this genus branch freely when cultivated in open areas; when grown in dense stands, they suppress branching, forming a single central stalk (Iltis, 1983). This naturally adapts Cannabis to high density sowing for fibre production, as well as low density plantings that encourage branching and flower formation for seed and drug production.

Diversity of *Cannabis* and its domestication

The main determinant factor for the phenotype of any plant is the environmental factors along with the genetic set up of that plant sp. So, under the pressure of natural selection within the diverse environments into which the Cannabis were introduced, genetically and phenotypically diverse varieties of Cannabis had been evolved and were further selected by humans for higher yield of fibre, seeds or drug products (Clarke and Merlin (2016). It was Karl Hillig (2004a, b & 2005), who set the stage for understanding the evolution of *Cannabis* by encompassing a wider geographical range and diversity of population states than earlier efforts. Though not all, but many taxonomists considered cannabis to be a polytypic genus consisting of two extant species viz. *Cannabis sativa* and *Cannabis indica*. As stated by Clarke

and Merlin (2013) and Small (2015), based on natural origins and associations with humans, taxonomists have recognized three more populations of this plant spp. namely those that are truly wild, those that are cultivated and those that are feral escapes which grow spontaneously in areas associated with and often disturbed by humans. Clarke and Merlin (2013) on the basis of archaeological and historical records as suggested by Hillig's chemotaxonomic research had published the names and acronyms that confining the geographical and cultural groupings as an aid to understand the roles of differing the gene pools in the domestication history of Cannabis.

Now, in case of domestication processes like isolation, artificial selection and inbreeding that imposed by humans suffered a limited genetic diversity, whereas natural out crossing and genome-mixing have encouraged genetic diversity. So the question still remains that during cultivation and breeding, how Cannabis evolved towards domestication, as opposed to remnant wild populations and feral escapes that evolved under natural selective pressures alone? It is only because of the easily growing nature and being the multi-use plant human included this plant in most priority list for cultivation where they encountered this versatile resource (Clarke and Merlin (2016). As a result of cultivating this plant from their local origin where they show the traits that are differ from the norms, human unwittingly initiated the process of domestication and such artificial selection of this plant with varying products of better quality and higher quantity favours the domestication of this plant over natural selection. Moreover, during the domestication process, hybrid offspring are artificially selected which leads to novel combinations of traits than that of the parents.

Clarke and Merlin (2016) also stated that during domestication, traits more frequently diverge from the wild condition by bidirectional or two-way evolution via disruptive selection—again resulting in a continuum of phenotypes, but with the median wild condition lying between two domesticated extremes (e.g., stalk internode length and branching pattern, variations in cannabinoid content, and timing of maturation). Disruptive selection occurs when natural selection of wild populations favours certain environmentally adaptive traits, whereas artificial selection of cultivated crops favours a certain plant product, and leads to strong evolutionary consequences during the domestication process. Natural evolutionary determinants were important before humans started using and spreading Cannabis, and natural selection will always play a role in its evolution. Domestication may have had more profound effects on the evolution of the functional physiology of Cannabis rather than its anatomical physical traits,

and perhaps plants of this genus were so well pre adapted for agriculture that few morphological changes were required. Nevertheless, human selection during domestication has had by far the greatest influence on changes in Cannabis phenotypes, both morphological and physiological. This process accelerated during the last half of the twentieth century as industrial hemp and marijuana breeders developed new cultivars through vigorous artificial selection.

Geographical distribution and Germplasms of Cannabis

It has been reported that the origin of Cannabis is supposed to be though in Central Asia, Sharma (1979) stated that truly and nearly wild populations still occur in Himalaya. Purseglove (1974) mentioned that the ancient times cultivation had taken place in Asia and Europe while Haney and Bazzaz (1970) stated that the genus widely occurs in Africa too. The domestication status ranges from truly wild to naturalized, landraces, breeders material (mutants, inbred populations) and cross-bred cultivar (up to hybrid F_1 cultivar) (Meijer, E.P.M, de & L.C.P. Keizer, 1994). As stated by Hoffmann (1961) until the 1950s, fibre hemp strains were usually derived from indigenous landraces by selection. Well-performing exotic strains were frequently imported and adapted to local conditions or used for cross-breeding. Between 1940 and 1960 breeding in many countries were aimed at monoecious cultivars (Dempsey, 1975). Heterosis breeding became important in Hungary in the late 1950s. On the other hand, the drug producing Cannabis landraces are maintained by many countries like Afghanistan, Thailand, India, Nepal and Netherlands and also they are commercializing some strains of Cannabis for the same purpose (Clarke-1981 and Cherniak-1982).

Only a few gene banks stored the *Cannabis* germplasms. Collection occurs mainly in connection with recently abandoned or current fibre hemp breeding. The Vavilo Institute (St. Petersburg, Russia) have the largest collections of 400 accessions of *Cannabis* (Lemshev *et al*., 1994) which is followed by the Hungarian gene bank stores about 70 accessions. The gene banks of Germany, Turkey and Japan have the collection of up to 20 accessions while some botanical gardens maintain a few accessions. Availability of number of accessions is very limited in comparison to other crops and also is generally poorly documented. Maintenance of *Cannabis* germplasms is very difficult as the environmental conditions easily affect them. There are many reports on changes in cannabinoid properties and plants habits after a few generations under altered conditions (Hakim *et al*., 1986 and Tschaneff, 1959). Therefore, special caution during multiplication

is required in order to specific properties. Selection for a desired phenotype in commercial cultivars usually takes place during outdoor multiplications and keeps a distance of at least one km between multiplication fields to avoid introgression. On the other hand multiplication of exotic accessions should be organized indoors to allow development of seeds in every female plant.

Besides the cultivars the seeds are also kept in gene bank to reproduce in ideal conditions when any *Cannabis* landrace is not reproducing in every five or ten years. In the last 50 years it has been noticed that the genetic diversity of the cannabis genome dwindle away. Indeed, the vast majority of the landraces may already be extinct, and for that reason we must be careful to preserve and multiply what remains as stated by R. C. Clarke and M. D. Merlin (2016). They also stated that, given the importance of Cannabis as a traditional as well as present-day crop plant, the biodiversity of this genus (particularly among the drug cultivars) is sorely under-represented in seed banks, especially in light of recent research interest in medical Cannabis and also when we take this lack of diversity into account, in light of genetic impurity and low seed numbers, there really is no reliable reserve of Cannabis seeds.

The primary goal of germplasms preservation is the conservation of the entire genome of each population while the secondary goal of genetic preservation is to reproduce the accessions in sufficient quantities to maintain a reserve for future reproductions and public distribution (Crossa *et al*, 1993). On the other hand Watson and Clarke, 1997 had stated that common goal of Cannabis breeders should be establishing a more comprehensive core collection of Cannabis seed accessions that have been exhaustively characterized agronomically in the field, and on molecular levels, genetically and chemically, in the laboratory. Only then, can we see what diversity really is available for researchers to work with in the future. This core collection should be maintained with optimal reproduction and storage methodology, and individual accession evaluations should be made accessible to breeders.

Future Prospects

Watson and Clarke, 1997 had stated that common goal of Cannabis breeders should be establishing a more comprehensive core collection of Cannabis seed accessions that have been exhaustively characterized agronomically in the field, and on molecular levels, genetically and chemically, in the laboratory. Only then, can we see what diversity really is

available for researchers to work with in the future. This core collection should be maintained with optimal reproduction and storage methodology, and individual accession evaluations should be made accessible to breeders. It has also been.

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Chapter - 5

Adverse Effects Associated with Cannabis Use for Medical Problems

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Adverse Effects Associated with Cannabis Use for Medical Problems

While not 100 percent risk free, cannabis is amazingly short on side effects. With acute use, most undesirable effects are caused by delta-9 THC, and they are dose related; the higher the amount of THC, the greater the possibility of experiencing an adverse reaction. Some common side effects associated with THC use are dry mouth, dry eyes, reddened eyes, slow pupil response to light, and decreased eye-blink rate. Any adverse effects from too high a dose of THC will resolve once the THC is metabolized and eliminated.

Lethal dose

Although there is an abundance of cannabinoids receptors in the brain, unlike opiates, there is a paucity of receptors in the area of the brain that controls heart rate and respirations. Therefore, none of the direct adverse effects caused by THC are life threatening. It is not possible to consume or inhale enough cannabis to reach the lethal dose—which is approximately 15,000 times higher than the therapeutic dose. According to the Oregon Institute for Cannabis Therapeutics, a nonlethal dose of 92 milligrams per kilogram of THC given intravenously to monkeys is equal to a 154-pound person smoking 3 *pounds* of 1percent cannabis at one time. This would be more than 1 million times the minimal effective dose and 250,000 times the usual smoked dose. The same person would have to eat 10 pounds of 5 percent hashish at one time to achieve similar nonlethal blood levels. In comparison, doubling an insulin dose or achieving a blood alcohol concentration of 0.4 percent can result in death. The DEA estimates that a person would have to smoke 1,500 pounds of cannabis in 15 minutes to be lethal.

Poor metabolizers

Poor metabolizers are people who are genetically predisposed to clear medications from their system at a slower rate than the average person. Patients who are poor metabolizes of THC or who are on medications that slow down the metabolism of THC are at increased risk of experiencing undesirable effects at doses that are lower than what would be expected to cause problems. Patients with a history of experiencing many side effects from a variety of medications should consider pharmacogenomics testing. This is usually a saliva test that assesses the activity of enzymes in the liver that are used to metabolize medications. The results of these tests can be helpful in dosing not only cannabis but also other medications that might benefit a patient's condition.

Some medications can interfere with the metabolism of THC by inhibiting the necessary liver enzymes. Taking these medications in close proximity to a cannabis dose may result in higher-than-expected blood levels. While this list is not exhaustive, they include antifungal medications like ketoconazole, fluconazole, and metronidazole; fluoxetine; cimetidine; and erythromycin.

While cannabidiol (CBD) does not cause intoxicating effects, high doses can cause sedation, diarrhea, and decreased appetite. Medications that can interfere with CBD metabolism include clopidogrel (Plavix), cimetidine, citalopram (Celexa), delavirdine (Rescriptor), efavirenz, felbamate, fluconazole (Diflucan), fluoxetine (Prozac), fluvastatin, fluvoxamine (Luvox), indomethacin (Indocin), isoniazid, ketoconazole, lansoprazole (Prevacid), lovastatin (Mevacor), metronidazole (Flagyl), modafinil (Provigil), paroxetine (Paxil), probenecid, omeprazole (Prilosec), oxcarbazepine (Trileptal), sulfamethoxazole, sertraline (Zoloft), ticlodipine (Ticlid), and topiramate (Topamax).

Using edibles increases the risk of side effects. One of the reasons is that absorption of cannabinoids from the gastrointestinal tract is very unpredictable. A patient might absorb a small portion of a large dose and experience relief and, on another day, take the same dose, absorb a lot more, and feel the undesirable effects of THC. Sometimes the amount of time needed to absorb the medicine is longer than usual, and thinking that they have not taken enough, a patient may take an additional dose, only for everything to kick in hours later. The side effects most often encountered are anxiety, paranoia, nausea, and sedation, as well as effects on the nervous system that impair memory, balance, reaction time, and dizziness.

Intoxication

The intoxicating effect of THC can cause euphoria and enhanced sensory perception—colors may appear to be more vivid, and vision and hearing may sharpen. There may be impaired balance and coordination, and reaction times may be slower. Some varieties of cannabis are energizing and motivating, which can be a benefit; while others may cause sedation. The intoxicating effect associated with THC can be an adverse effect or a benefit, depending on the condition and goals of the patient. For patients in severe pain, the altered mentation can add to their relief and take their minds off of their discomfort. For others, it can be an annoyance or cause psychic discomfort. Some patients are very sensitive to THC and have described out-of- body experiences. Many of the side effects associated with cannabis use can be avoided by starting with a very low dose and gradually increasing until the desired response is reached, utilizing a mode of delivery that slows the delivery of THC to the brain, and using plant varieties that have enough CBD to dampen the intoxicating effects of THC.

Impaired driving

Cannabis slows reaction time and impairs short-term memory. With intoxication, fine- and gross-motor coordination are impaired, resulting in clumsiness, and sense of time is altered. All of these things can impair driving. THC concentrations of two to five nano grams per milliliter are associated with Substantial driving impairment. Studies show that cannabis users attempt to Compensate by driving more slowly and allowing for more distance between them and the preceding vehicle. When paired with alcohol, lane weaving becomes more problematic. Studies have shown that 10 percent of fatal motor vehicle accidents have evidence of cannabis use, and 70 to 90 percent of that also has elevated blood alcohol levels. Combining alcohol with cannabis and Driving is dangerous. Cannabis use alone doubles the risk of having an accident. The Insurance Institute for Highway Safety looked at rates of collision claims in Colorado, Oregon, and Washington after recreational cannabis was legalized and reported a 3 percent increase. Another study in the *American Journal of Public Health* reported no increase in fatalities. Nevertheless, driving is not advised if you are impaired by THC. I advise patients to use a CBD: THC balanced variety of cannabis for daytime use and limit THC-rich strains for evenings when they are in for the night. In legal terms, driving under the influence of cannabis is no different than driving under the influence of alcohol, and if caught, you will be arrested.

Psychosis

CBD and low doses of THC have antipsychotic effects; however, because of the biphasic effect of cannabis, THC at high doses can cause hallucinations in some patients. This is not a permanent condition, nor should it be construed as the emergence of schizophrenia or a psychotic illness. The symptoms will cease once the THC level is metabolized and eliminated. It was once thought that cannabis could induce psychotic illnesses like schizophrenia, but that has not been proven and is no longer thought to be the case, except in people who are genetically predisposed to develop schizophrenia.

Anxiety and paranoia

At low doses, THC lowers anxiety; however, at high doses or in patients who are sensitive, THC can precipitate anxiety and paranoia. When highly concentrated waxes, shatters, and vape oils are used, it is very difficult to control the dose, so this type of reaction is likely to occur, especially in cannabis-native and elderly patients.

Gastrointestinal effects

Nausea and vomiting are the more common side effects associated with too much THC. These are typically transient symptoms that resolve once the THC is metabolized and blood levels are lowered. While low to moderate doses of CBD regulate gastrointestinal motility and relieve constipation or diarrhea, excessively high doses of CBD can cause diarrhea. Although CBD lowers gastric acidity and often improves symptoms related to gastroesophageal reflux disorder (GERD), it can also lower gastroesophageal sphincter tone, which may make symptoms worse. In my clinical experience, it is more likely to improve symptoms associated with reflux but is something to consider if GERD symptoms increase while taking CBD.

Sedation

This can be a benefit for insomniacs but a negative side effect if daytime alertness is impaired. This can be caused by both THC- and CBD-dominant varieties. Terpenes like myrcene and linalool are relaxing and may contribute to this effect. CBD in low doses can be energizing and may interfere with falling asleep if taken too late in the day. At higher doses, CBD tends to be sedating. There are patients, however, who experience sedation with CBD even at relatively low doses. This typically goes away with continued use. Cannabis that has been sitting around for a while may have higher levels of CBN, a metabolite of THC. CBN is sedating and often found in varieties of cannabis known to help patients fall asleep and stay asleep.

Appetite

The effect of cannabis on the appetite can be an adverse effect or a benefit, depending on the condition of patient. THC stimulates the appetite; CBD suppresses the appetite.

Cardiovascular effects

While cannabis does not have an effect on heart rate and blood pressure in all patients, THC can be associated with an increase in heart rate in patients new to cannabis or who take too high a dose. Blood pressure is typically not affected.

THC can be associated with lowering of heart rate and blood pressure after long-term use. This can potentially cause dizziness or even fainting in patients whose normal systolic pressure is less than 100. Patients on medication for hypertension should monitor their pressure when using cannabis over time. If the pressures decline significantly, an adjustment in the dose of their medication might be warranted. I have seen patients whose blood pressures have normalized with the use of THC over time.

Changes in heart rate could be problematic for patients who have an uncontrolled arrhythmia, when the rate is either too high or too low. Patients with histories of arrhythmias controlled by medication, surgery, or pacemaker appear to tolerate cannabis without incident. I have followed patients with other cardiac problems, such as congestive heart failure and abnormal ejection fractions, who also do not appear to suffer any ill effects.

The use of cannabis in patients with severe cardiac instability should be avoided or done with great caution. For patients with hypo perfusion issues, which is poor delivery of blood to the heart muscle from severe atherosclerotic disease or decreased cardiac output, lowering blood pressure or heart rate could further decrease the delivery of oxygen to the muscle and cause an ischemic event, or heart attack. While THC might not be the best choice in these patients, studies have shown that patients using CBD benefit from its antioxidant and cardio protective effects, which have been shown in animal models to minimize the area of ischemic damage to the heart muscle. I encourage patients with heart disease to use high-CBD varieties with very little THC.

Respiratory effects

Respiratory symptoms can arise, not from the plant itself, but from mechanical irritation to the airways from smoking and vaporizing. Inhaling cannabis can also cause increased mucous production and cough.

In contrast to the smoking of tobacco leaf, it has not been established that smoking cannabis is associated with an increased risk of lung cancer or chronic obstructive pulmonary disease (COPD). It is not known whether the anti- inflammatory, bronchodilator, and antitumor properties play a part. That being said, the products of combustion from burning cannabis are carcinogenic, and the amounts of tar delivered to the lungs is high. I do not typically recommend inhalation as a mode of delivery unless the patient has a condition that demands a rapid onset of action; if that's the case, I recommend vaporizing instead of smoking. Otherwise, there are other delivery systems—tinctures, lozenges, and transversal—that are not associated with these side effects. Generally, any symptoms that arise from vaporizing or smoking cannabis resolve once another method of delivery is used.

Infection

Cannabis is not an immunosuppressant; therefore, it does not cause patients to be more susceptible to infection. Cannabis *modulates* the autoimmune system by increasing and decreasing various proinflammatory mediators like tumor necrotic factor (TNF), interferon (INF), and leukokinins (IL), thereby having the ability to mitigate some of the symptoms caused by autoimmune conditions like myasthenia gravis and lupus.

Any cannabis plant, and especially community-acquired cannabis, if contaminated with pathogenic molds and bacteria can cause respiratory infections. This is of special concern for patients with compromised immune Systems. Researchers at the University of California, Davis, identified multiple organisms in medical cannabis plants that can cause serious infection in patients with AIDS, leukemia, or lymphoma or those receiving immunosuppressive therapy for other medical conditions.

Fertility

The endocannabinoid system plays a significant role in the reproductive tract, as well. Receptors and endocannabinoid are found throughout the system—from an area of the brain called the hypothalamus that controls the production of sex and reproductive hormones, down to the Leydig and Sertoli cells in the testes and sperm.

It has been well documented that testosterone and the female follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin levels are reduced with heavy THC-rich cannabis use. Low levels of these hormones can negatively affect sperm production and sperm motility.

Studies have found Down regulation, or decreased synthesis, of anandamide and 2-AG in the sperm of infertile men and, in women with histories of early spontaneous abortions, decreased fatty acid amide hydrolase (FAAH, the enzyme that metabolizes anandamide) activity in maternal lymphocytes.

Pregnancy

Pregnant women have certainly used cannabis, and there are studies with contradictory conclusions. A 2011–2013 Australian study of 344 Aboriginal women found that those who used cannabis during pregnancy were more likely to have smaller babies and more likely to give birth to babies with low birth Weights or babies that was small for gestational age. However, this study was not able to assess doses or control for use of alcohol or other drugs.

In 2016, researchers at the University of Arizona reviewed 24 studies on cannabis use in pregnancy. They concluded that infants of women who used cannabis during pregnancy had an increased incidence of low birth weight and increased risk of being admitted to the neonatal intensive care unit compared to mothers who didn't use cannabis during their pregnancies. Again, most of the studies were not able to exclude concurrent alcohol or tobacco use. The four- year retrospective study of 8,138 women found that 8.4 percent of the subjects used cannabis during pregnancy. The women using cannabis tended to be Younger, African American, and with poor prenatal care. They were also more likely to use tobacco, alcohol, and other drugs. When results were adjusted for race, tobacco, alcohol, and other drugs, poor neonatal outcome was not significantly higher among those who used cannabis during pregnancy.

Neonatal outcome does not always predict long-term consequences of behavior and exposures during pregnancy. Until future studies are able to show that cannabis has no effect on birth weight, perinatal health, fetal neurodevelopment, childhood developmental milestones, and other sequelae.

Testicular cancer

In earlier studies, there appeared to be an association with increased risk of testicular cancer and heavy cannabis use in younger men. However, a 2015 systematic review of the literature did not conclude that there was a strong association with cannabis smoking and testicular cancer. The association between heavy cannabis use and testicular cancer remains inconclusive.

Tolerance

Tolerance occurs when cannabis is used over an extended period of time, especially at high doses. When the endocannabinoid system sees a lot of cannabinoids, it interprets the high levels as an indication to down regulate, or shut down, cannabinoids receptors. When the system is down regulated, it takes higher doses to achieve similar effects. This occurs in different areas of the brain at different rates. For example, the effect of THC on memory loss in chronic cannabis users tends to improve with time, but the experience of the euphoric high continues. If the tolerance were the same throughout the brain, then memory would no longer be affected and the euphoric response would go away, but that does not happen. When health-care providers treat pain with NSAIDs, opiates, and other types of medication, the doses are gradually increased if previous doses no longer are effective. With cannabis, the approach to tolerance is just the opposite. If patients discontinue using cannabis for a short period of time, a mere three or four days, then the system will increase the number of receptors to make up for the lower levels of cannabinoids.

I suggest to patients that they not medicate every day if they have an alternative medication to use on off days. I also recommend that they use the lowest dose necessary to alleviate their symptoms. Just doing these two things often prevents tolerance from developing. If after time they feel that the dose they have been using is no longer effective, then it may be time to stop cannabis use for three or four days and then start back at a dose that is about a third of the previous dose. More times than not, that new dose is actually lower, not higher, than the dose that was no longer effective.

Nervous system

Lethargy; slowed reaction time; dysphasia; dizziness; altered sense of time; and impaired balance, coordination, short-term and episodic memory, problem- solving skills, and focus can occur with higher doses of THC. It is important for patients to note that they are not experiencing any of these effects before deciding to drive, operate any type of machinery, or make legal decisions. These side effects will also increase the risk of a patient falling and must be taken into consideration when recommending cannabis to elderly patients or patients with impaired balance.

There is data to suggest that excessive use of high doses of delta-9 THC over prolonged periods affects episodic memory and has a negative impact on a person’s ability to take on new information (e.g., the loss of IQ points); there are also studies that refute this. Again, these adverse effects have not been Identified in those who use cannabis in low to moderate doses for

medical reasons and is more commonly ascribed to long-term, heavy recreational use. When these adverse cognitive effects do occur, studies indicate that they resolve with subsequent abstinence.

CBD does not cause these effects, and patients using CBD-dominant varieties of cannabis, even with moderate amounts of THC, do not typically experience mental impairment. CBD's Neuroprotective properties may protect against the neurotoxicity of THC. Every person is different, however, and some patients experience mental impairment, even when CBD is present. You also have to keep in mind that mistakes happen. You may have a product that has more THC in it than is recorded on the label. Always try a new product, even if it has the same name or cannabinoids profile, at a time when you will not need to drive, operate heavy or dangerous equipment, or make legal decisions. Less common but possible side effects from THC include changes in blood pressure or heart rate and hallucinations.

Neuro-developmental

Cannabis has an exceedingly high safety profile. There are very few documented side effects associated with cannabis use; those pertain to a dose response to delta-9 THC. One large concern expressed in ant cannabis legislation and by the American Academy of Pediatrics has been that legalization would increase access and use for adolescents, whose brains are still developing and are at increased risk of neurodevelopment changes—impaired short-term memory and decreased concentration, attention span, and problem-solving skills, all of which interfere with learning. Another concern is alterations in motor control, coordination, judgment, reaction time, and tracking ability, which have the potential to increase the incidence of motor vehicle and other types of accidents.

Interestingly, since the legalization of medical cannabis at state levels, adolescent cannabis use and prevalence of cannabis use disorder in adolescents has gone down. According to the Substance Abuse and Mental Health Services Administration's December 2015 report, teen use of cannabis in all 50 states did not change except in three states—Ohio, Hawaii, and Rhode Island—where teen. Use decreased. According to the Colorado Department of Health 2015 Healthy Kids Colorado survey, 21.2 percent of adolescents used marijuana in 2015, two full years after cannabis became legal for medical use, down from 25 percent in 2009, before medical use was legalized. It is also noteworthy that cannabis use among adolescents in Colorado is just below the national average of 21.7percent.

In 2013, the National Institute on Drug Abuse published a statement on

adolescent cannabis use: “Regular marijuana use in adolescence is part of a cluster of behaviors that can produce enduring detrimental effects and alter the trajectory of a young person’s life—thwarting his or her potential. Beyond potentially lowering IQ, teen marijuana use is linked to school dropout, other drug use, mental health problems, etc.” Synaptic remodeling and pruning continues in humans until about age 25. The brain is laying down needed pathways and clearing away those that are not necessary. There is equivocal evidence that delta-9 THC has a negative effect on this process. Magnetic resonance imaging studies have shown reductions in the volumes of the hippocampus, amygdale, and cerebellum in long-term, heavy, recreational users of THC when compared to nonusers. And it has also been shown that users who started before the age of 17 have a smaller ratio of cortical gray to white matter in the brain. This phenomenon has not been described in patients whose doses are typical for medical use. While these studies implicate the chronic use of cannabis in deleterious effects on the morphology of brain structures that control emotion, memory, learning, and executive function, there is contradictory evidence that it does not.

I believe that there can be long-term neurological consequences associated with chronic cannabis use, but from my clinical experience, it appears to be most pronounced in patients who are using cannabis as an intoxicant and at higher and more frequent doses. In some patients, it has affected their lives negatively with regard to legal problems or job loss because they tested positive for drugs. There are many patients, however, working in areas where drug testing is not a factor, and they do not have any apparent issues. Three psychiatric disorders commonly seen in pediatrics—obsessive- compulsive disorder, attention deficit disorder, and Tourette syndrome—are characterized by abnormal functioning of the neural pathways that connect the frontal lobe with the basal ganglia, resulting in impaired self-regulation. These happen to be three conditions that have been reported, anecdotally, to respond to cannabis therapy. We must consider that abnormalities in this area of the brain may influence why some adolescents choose to use cannabis at an early age.

We are still faced with what comes first: the proverbial chicken or egg? Does early use of cannabis cause abnormalities in the developing brain, or do abnormalities in the developing brain lead to early cannabis self-medication? I don’t think these questions have been adequately addressed. They will be difficult to answer as long as cannabis’s Schedule I status impedes research focused on benefits. As it stands, the only research on cannabis that can be conducted by the National Institute on Drug Abuse has to be focused on demonstrating that its use is detrimental. Until these

questions are answered, I think we have to rethink our approach to young people who experiment with cannabis and consider that perhaps there is an underlying issue that leads them to seek relief from an illegal substance. Such adolescents should be evaluated, diagnosed, and treated, not punished. We also have to continue to consider that there may be detrimental effects on neurodevelopment and carefully weigh the risks and benefits when making recommendations for adolescents and young adults. The current evidence suggests that neurodevelopment impairment from cannabis is related to chronic and heavy use of THC.

It stands to reason that some behavior issues may lead to experimentation with drugs and that cannabis, being readily available, as are alcohol and tobacco, is easily acquired by this population. Prior assertions that cannabis use in and of itself leads to the use of more dangerous drugs have certainly been dispelled. There has been no establishment of cause and effect. The 2013 statement issued by the director of the National Institute on Drug Abuse would lead one to believe that cannabis causes the behavior, but it is well known that people who abuse drugs start with substances that are readily available. Those substances are usually cigarettes, alcohol, and marijuana. Given that, one could say that tobacco use in adolescence leads to drug abuse later in life. One also has to consider that people who may be more impulsive or more willing to take such risks as using illegal substances could possibly be doing so because of structural or petrochemical differences in the brain. While the jury is still out on the long- term effects of chronic exposure to cannabis, there is not much doubt that THC has an effect on short-term and episodic memory, time perception, sensory perception, and coordination and that the risks of these side effects must be outweighed by the benefits of its use.

Drug interactions

Just like any other medication, it is important to know which medications might affect cannabis metabolism and which medications might be affected by the use of cannabis. When medications are absorbed from the gastrointestinal tract, they are metabolized in the liver by an enzyme system known as cytochrome P450. When a medication is metabolized at a slower-than-expected rate, the normal doses that are usually well tolerated can cause higher-than-expected blood levels and can lead to undesirable side effects. Another consideration is that, with some medications, it is the metabolite, not the drug itself, which is the active agent. In those cases, if cannabis interferes with the metabolism, there will be lower-than- expected levels of the active agent. This may result in sub therapeutic levels, decreased efficacy, or exacerbation of symptoms.

When cannabis is swallowed, eaten, or given via an indwelling catheter in the stomach or feeding tube, it is absorbed from the intestines and goes to the liver, where the enzymes metabolize the drug. This is referred to as the hepatic first pass. Different components of cannabis are metabolized by different enzymes.

CBD is metabolized by CYP3A4 and CYP2C19; THC is metabolized by CYP3A4 and CYP2C9. When CBD is metabolized, a lot of CYP3A4 is used up—leaving little to metabolize other medications. When patients take other medications that need CYP3A4 too closely to CBD, there may not be enough enzymes left to adequately metabolize other drugs. The enzyme 3A4 is used to metabolize approximately 65 percent of the medications for which health-care providers write prescriptions, as well as many over-the-counter medications. Because CBD, in particular, uses up a lot of that enzyme, if it is taken in close.

Proximity to medications that need that enzyme, it can cause higher plasma levels than expected. This is especially important when patients are taking medications like antidepressants, blood thinners, and cholesterol-lowering medications like statins. CBD can increase the sedative effect and mental confusion of benzodiazepines and can be a problem for elderly patients and those who have an increased risk of falling due to physical or mental limitations. However, taking cannabis in close proximity to benzodiazepines does not increase the risk of respiratory depression as is the case when opiates are taken with such benzodiazepines as alprazolam and diazepam.

THC uses CYP3A4 and CYP2C9 but not to the extent that CBD uses CYP3A4. THC also induces or activates the CYP1A2 enzyme. When this enzyme is activated, serum levels of the medications metabolized by that enzyme may be lower than expected. Some of the medications metabolized by this enzyme are chlorpromazine, clozapine, cyclobenzaprine, olanzapine, duloxetine, haloperidol, and naproxen. Delta-9 THC also has a significant additive effect when combined with alcohol and barbiturates.

While cannabis may not affect all of the medications in these classes, when in doubt, I advise spacing cannabis one and a half to two hours from the tricyclic antidepressants, MAO inhibitors, antiepilepsy drugs, benzodiazepines, statins, proton pump inhibitors, beta blockers, and anticoagulants. This is especially important when taking medications that use more than one of these enzymes for metabolic clearance.

It has been documented that valproic acid (Depakote) and clobazam

(Onfi) levels can be affected by CBD. Levels of any antiepilepsy drugs should be monitored, and especially when taking clobazam.

While taking these medications is not a contraindication to using cannabis products, and many people who use cannabis do not experience adverse effects from medications, it is best to err on the side of caution and space your medication when possible. The appendix at the end of this book lists some Known medication interactions but should not be considered complete. There may be other medications that are metabolized by these enzymes that are not listed. Your recommending physician or provider should review your medication list and make note of any that should be taken two hours from your cannabis dose.

There are also medications that can interfere with the metabolism of THC and CBD (see appendix). These medications can increase the plasma levels of cannabis. Medications that inhibit 3A4 may increase levels of both CBD and delta-9 THC. Inhibitors of 2C9 may increase levels of CBD, and inhibitors of 2C19 may interfere with the metabolism of delta-9 THC and increase its plasma levels, which will increase the risk of adverse effects.

Particular care must be taken when giving CBD to seizure patients. Having followed many patients who are taking multiple medications, I have not seen many problems with drug interactions, but fluctuations in plasma levels do occur in either direction. Watch for increases with Depakote, Unfit, Keppra, felbamate, topiramate, and Phenobarbital levels and decreases with lamotrigine, clonazepam, lacosamide, and rufinamide levels. But remember, levels can Fluctuate in either direction.

Possible consequences of overuse

Substance Use Disorder

Substance use disorder is far more prevalent than cannabis addiction and can affect as many as 30 percent of people who use cannabis. Cannabis use disorder and addiction are most common in young males between the ages of 18 and 30, and given the widespread availability of cannabis with high concentrations of THC, I suspect it is underreported. People who use cannabis at these high concentrations may be seeking the euphoric effect of the plant and may not be using cannabis for medical conditions. Patients suffering from bipolar affective disorder are at increased risk of developing a substance use disorder, so care should be taken to use low-THC varieties along with careful monitoring by the patient's mental-health provider.

Symptoms of substance use disorder include

- taking larger amounts of a substance or for longer than intended;
- repeatedly failing to use less or quit;
- dedicating a lot of time to acquiring or using;
- having cravings or urges;
- giving up activities in order to use the substance;
- continuing to use the substance even when it is causing problems with work, school, or home life;
- using the substance even if it puts you in dangerous situations;
- having physical or psychological problems caused or made worse by the substance;
- needing more of the substance to get the effect you want; and
- Having withdrawal symptoms that are relieved by using the substance.

Substance use disorder is rated mild if the patient has two to three symptoms, moderate with four to five symptoms, and severe with six or more symptoms. The amount and frequency of THC use is directly proportionate to the Likelihood of cannabis use becoming a problem; frequently using high doses increases your risk. Medical cannabis dispensaries commonly sell highly concentrated waxes, shatters, budders, and other products that can have THC concentrations as high as 96 percent. Cannabis flower concentrations are also high, at 10 to 26 percent; in contrast, the average THC content in confiscated Cannabis in the 1990s was about 3.7 percent. Cannabis, especially THC, works better for most ailments at low to moderate doses, so there is no reason to use high-THC-concentration products. Using small doses of a tincture two to four times a day or vaporizing less than an ounce of flower per month with breaks here and there is not likely to cause tolerance, dependence, or addiction. This is not to say that some patients require higher doses to alleviate their symptoms, but it's important to use the least amount necessary.

Cannabis addiction rates are at about 9 to 10 percent and are considered relatively low when compared to other substances that commonly cause addiction, like caffeine, tobacco, and alcohol. For chronic pain patients, THC is relatively ineffective at high doses, and the patients who need high doses

probably have either developed tolerance or may be rapid metabolizes, meaning that they metabolize cannabis at such a rapid rate that it takes higher-than-usual doses to obtain a therapeutic blood level. In 1994, Jack Henning field of the National Institute on Drug Abuse and Neal L. Benowitz at the University of California, San Francisco, conducted a study on nicotine addiction. They ranked six commonly abused drugs in order of severity according to five criteria: dependence, withdrawal, reinforcement, tolerance, and Intoxication. Cannabis ranked sixth, or the least likely to cause either serious withdrawal symptoms or dependence, when compared to alcohol, nicotine, heroin, cocaine, and caffeine. Cannabis users who are males between the ages of 18 and 24 have the greatest risk of becoming addicted, and that rate has remained at about 9 percent.

A motivational Syndrome

This syndrome is just what it says: Patients are complacent and unmotivated. While this is seen clinically in some heavy cannabis users, causality has not been established, meaning it has not been determined if patients with this condition turn to cannabis or if cannabis causes the problem. It has been described in patients with cannabis use disorder and depression and as a side effect of serotonin reuptake inhibitors. This is another possible effect of overuse and has not been described as an adverse consequence of medicinal use.

Cannabinoid Hyperemesis Syndrome

Chronic nausea and vomiting can be a symptom of cannabinoids hyper emesis syndrome. This syndrome is typically seen in young men who are recreational users or are self-medicating and is a consequence of using large amounts of cannabis over an extended period of time. This is not considered an adverse effect of medical use but a symptom of cannabis use disorder. Patients with this condition typically find relief from the nausea by taking frequent hot showers. It is thought that activation of the heat receptors (TRPV1) in the skin play a role in alleviating the symptoms. Capsaicin cream, which also activates those heat receptors, has also been found to be effective in alleviating these symptoms. Patients with this condition will improve if they abstain from using cannabis.

Summary

When cannabis varieties that contain both CBD and THC are started at low doses and gradually increased until symptoms are alleviated, it is usually very well tolerated and with minimal or no adverse effects. Adverse effects are typically associated with high-THC doses, which will resolve once the

THC is metabolized and eliminated. With the possible exception of excessive use, particularly in young, heavy cannabis users, the adverse effects associated with THC are not permanent. CBD and THC synergize each other's beneficial effects, and CBD mitigates the intoxicating effect of THC while also preventing THC's effect on memory, balance, reaction time, and coordination.

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Chapter - 6

Cannabis: The Journey from Medicine to Intoxicant and Back Again

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Cannabis: The Journey from Medicine to Intoxicant and Back Again

There was a time when American doctors were able to write prescriptions for cannabis extracts, called tinctures, and salves to treat ailments like migraines, parasites, seizures, pain, and melancholy. It was not a perfect medicine. Dosing could be challenging because no one knew exactly why or how it worked, but most of the time it did work. Except for occasions when a patient was given a vial of cannabis tincture that was stronger than expected and experienced the effects of too much Δ-9-tetrahydrocannabinol (THC), it was safe—so safe, in fact, that no one died. It is important for both patients and health-care providers to have an understanding of the history of cannabis as a medicine and intoxicant and the series of events that led to every type of the cannabis plant, both fibrous and drug type, to be declared an international public menace and relegated to an illegal, black-market, recreational street drug. With some awareness of the politically and financially motivated efforts to remove cannabis from the physician's toolbox, I think you just might have a better appreciation for this effective and remarkably safe medicinal.

Agricultural Beginnings

Although human beings emerged about 250,000 years ago, according to archeological evidence, agriculture is a relatively modern invention, at only about 12,000 years old, with some tantalizing evidence of plant cultivation as early as 23,000 years ago. Prior to cultivation, humans were hunters and Gatherers, foraging wild berries and plants and following the migratory paths of wild animals. Cultivation was one of the first things that set man apart from other creatures inhabiting the earth. It was man's first attempt at

manipulating the environment to suit his needs, and it was the necessary first step toward many technological advances.

Cannabis is certainly one of the first, and perhaps the oldest, cultivated plant, and it played an important role in mankind's beginnings. Cannabis hemp cord was identified in pottery in a Taiwanese village site dating back at least 10,000 years. Cannabis seeds and oil were used for food in China as early as 6,000 BC, and 4,000 years before the birth of Christ, hemp fibers were used for textiles in China and Turkestan.

Ancient Medicine

Cannabis, called má, is one of the 50 fundamental herbs of Chinese medicine. Pharmacologist Emperor Shen Nung wrote a book on treatment methods in 2737 BC, which included the medical benefits of má. The *Pen Ts'ao Ching*, written in 1 AD, is based on traditions from the time of Shen Nung and is the oldest known pharmacopoeia. Cannabis was recommended for more than 100 conditions, including gout, malaria, poor memory, and rheumatism. Hua Tuo (140–208 AD) is credited with being the first healer to use cannabis as an anesthetic. He mixed pulverized cannabis plants with wine and acupuncture to locally and systemically anesthetize patients for wound cleaning and pain control.

In 1993, a 2,500-year-old mummy was discovered in the permafrost of Ukok Plateau in the Altai Mountains of eastern Russia near the Chinese border, an especially cold and dry region. With the inadvertent help of grave robbers, whose disturbance of her tomb allowed water to enter and freeze, the Siberian Ice Maiden (also known as the Princess of Ukok) was so well preserved that even her elaborate tattoos were intact. Anthropologists were able to ascertain what medical conditions she suffered from. MRI scans revealed that the young woman had a malignant tumor in the right breast, with metastasis to the right axillary lymph nodes and spine. The scans also showed that she suffered from osteomyelitis, an infection in the bone, and a skull fracture and other injuries, including a dislocated right hip, consistent with possibly falling off a horse.

This 20-something-year-old was obviously a person of significant stature and prestige. Her coffin was elongated to accommodate a three-foot headdress. Also in the burial chamber (or kurgan, of the Pazyryk culture) were two small tables with serving trays holding horsemeat, mutton, yogurt, coriander seeds, a beverage—and a pouch containing cannabis. While we don't know for sure that she used cannabis to control the excruciating pain she must have experienced, it's highly likely that she did.

There has been much debate over a passage in the Old Testament in which God gives Moses the recipe for holy anointing oil, often translated as "sweet calamus." Exodus 30:23–25 reads, Take thou also unto thee principal spices, of pure myrrh five hundred shekels, and of sweet cinnamon half so much, even two hundred and fifty shekels, and of *kaneh bosem* two hundred and fifty shekels. And of cassia five hundred shekels, after the shekel of the sanctuary, and of oil olive and hin. And thou shalt make it an oil of holy ointment, an ointment compound after the art of the apothecary: it shall be holy anointing oil.

In 1937, Sula Benet, a Polish anthropologist and professor at Hunter College who specialized in longevity and Eastern European culture, wrote that the Hebrew word *kaneh* means both "hemp" and "reed." I also spoke with a physician from the Israeli Ministry of Health, who asserted that *Kaneh-bos* (singular) translates to "aromatic cane" and that; indeed, the Hebrew term *kaneh bosem* found here means "cannabis" and was an ingredient in holy anointing oil.

Ibn Sina (b. 980), the Persian philosopher and scientist, is best known as the physician who wrote *The Canon of Medicine*, probably the most advanced scientific medical textbook available in its day. Written in Arabic, the *Canon* was translated into European languages and was widely used as a reference in Western universities until well into the seventeenth century. *The Canon of Medicine* makes various references to "Kunnabis" in the treatment of ear infections, skin rashes, and inflammation. In addition, it warns of the problem of using too many leaves.

Cannabis (*Vijaya* in Sanskrit) is indigenous to India and is found in more than 80 traditional Ayurvedic formulas. It is recognized as a powerful herb with the ability to both heal and poison and is recommended in only very small doses and always in combination with herbs that balance its effects. It is used to treat pain, digestive disorders, and dysentery and to enhance sexuality. It is known to improve digestion; relieve anxiety; and treat glaucoma, swelling, and diabetes. Its dry, hot, and penetrating qualities are said to have a long-term negative impact on reproductive tissue, and "overuse can lead to dry, weak, brittle tissues." In fact, excessive cannabis use can affect sexual hormone production in both men and women and can negatively affect fertility.

The Materia Medica of Indian Herbalism, published in 1841, notes that long- term consequences of cannabis use can include indigestion, tissue depletion, melancholia, and impotence. Excessive doses can cause "mental

exaltation, intoxication, a sense of double consciousness, memory loss and gloominess." It is known as a tamasic drug, which means that, if used in excess, it could dull the mind, affect memory, and cause spiritual confusion. In Ayurveda, the patient is discouraged from smoking because the qualities of smoke are heating, penetrating, and drying. They are encouraged to use cannabis as an edible and along with other herbs or foods to make it less damaging. It is thought that milk balances the negative qualities of cannabis. Traditionally bhang, a cannabis milkshake consumed during certain Hindu festivals, is made by boiling leaves in milk with dates, sugar, saffron, cardamom, rose petals, and almond meal.

Western Medicine

Dr. William Brooke O'Shaughnessy (b. 1809) was an Irish physician, surgeon, and chemist who, in addition to his work with cannabis, would later lay the groundwork for intravenous fluid and electrolyte replacement in the treatment of cholera. After graduating from the University of Edinburgh in 1829, he joined the British East India Company in 1833 and moved to Calcutta. There, he served on the committee of the Materia Medica and later as chemical examiner, developing methods for forensic studies to detect arsenic poisoning and other botanical poisons. He was a member of the Medical and Physical Society of Calcutta, where he published one of his first papers on the medical application of cannabis, "Case of Tetanus, Cured by a Preparation of Hemp (the Cannabis Indica)," in 1839. In 1841, O'Shaughnessy returned to England, where he introduced the use of cannabis to Western (European) medicine.

Dr. O'Shaughnessy wrote of his successful treatment with cannabis in "On the Preparations of the Indian Hemp, or Gunjah," published in the *Provincial Medical Journal*, which included "Their Effects on the Animal System in Health, and Their Utility in the Treatment of Tetanus and Other Convulsive Diseases," "Cases of Rheumatism Treated by Hemp," "Case of Hydrophobia [Rabies]," "Use in Cholera," "Use in Tetanus," and "Case of Infantile Convulsions." I have been particularly taken with Dr. O'Shaughnessy account of the baby girl with infantile spasms. He meticulously chronicled the condition of the baby and the devastating effects of the constant seizing. His description of how he gradually increased, or titrated, the dose until her body responded to the medicine parallels much of what parents and cannabis clinicians of today have found. In his article, the infant responds at first, but at a later date, the spasms start again. Again, he administered the cannabis tincture, slowly increasing the dose, but he had to give a lot more than the first time. He marveled that the amount needed by

the baby was on par with the dose a much older person had taken during an experiment and that, while that amount was intoxicating to the young adult, it did not appear to have any deleterious effects on the baby. It so beautifully illustrates how each batch of medicine may be slightly different, how younger people appear to tolerate much higher doses than do older people, and how every person responds to cannabis differently—all important things to consider when recommending dosing.

The New World

Hemp was such a valued commodity and had so many uses that it was a required crop in the 13 original colonies. It was used as food and to make cloth and rope. In times of shortage, one could be jailed for failing to grow *Cannabis sativa*.

It was also recognized for its medical benefits and was added to the list of approved drugs and treatments, the US Pharmacopoeia, in 1850. Companies like Eli Lilly, Park Davis, and E. and Wm. S. Merrell produced cannabis tinctures that were commonly prescribed for migraines, melancholia, pain, muscle spasms, and seizures. While it was widely used during the second half of the nineteenth century, it began to fall out of favor with the advent of pharmaceutical tablets like aspirin and morphine, which were much easier to dose. Produced as a tincture (a plant extract in alcohol or oil), it was impossible to know the concentration of the psychoactive component, THC, so it was not uncommon for patients to take too high a dose and suffer the adverse effects— dizziness, mental confusion, anxiety, and paranoia.

Twentieth- and Twenty-first-century medicine, regulations, and politics

Pure Food and Drugs Act of 1906

During this period, excessive opium and cocaine use was creating problems with addiction. These substances were used in products from Coca-Cola to bogus patent medicines for coughs, pain, and discomfort associated with tuberculosis to even teething medicine for babies. As the addiction problem grew, medicines thought to be less addicting than morphine, like heroin (later found to be more Addicting), were developed and prescribed.

As a result, there was an increased social concern that the public was unknowingly using addictive substances. In 1906, the federal Pure Food and Drugs Act was passed for the purpose of "preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious

foods, drugs, medicines, and liquors" and required that the "quantity of any alcohol, morphine, opium, cocaine, heroin, alpha or beta cocaine, chloroform, cannabis indicia, chloral hydrate, or acetanilide, or any derivative or preparation of any Such substances contained therein" be present on the label. With that, the bottles of cannabis tinctures identified the variety of cannabis, the suggested dose, warnings, and sometimes a skull and crossbones symbol, with instructions on what to do for accidental poisonings. Quite naturally, this was cause for concern for some patients. Around this time, there was also a growing sentiment against any type of intoxicant, including alcohol, and the temperance movement was in full swing. The Eighteenth Amendment was ratified in 1919 and remained in effect for 14 years, until it was repealed in 1933.

William Randolph Hearst and the "Mexican Problem"

Many Mexican laborers and migrant workers used cannabis to relieve stress, without the hangover associated with alcohol. It was also used by the soldiers in Pancho Villa's army during the Mexican Revolution (1910–1920). Newspaper magnate William Randolph Hearst was known to have a particular hatred for Mexicans and Mexican Americans, possibly fueled by the loss of 800,000 acres of timberland to Pancho Villa during the Mexican Revolution. He used his newspapers to portray Mexicans as lazy, violent, marijuana-smoking degenerates who stole jobs from white Americans. After the 1929 stock market crash, Americans were faced with the massive unemployment of the Great Depression, and Hearst's racist propaganda fueled the growing anti-immigrant sentiment by citizens who believed that these foreigners were taking their jobs away. Prior to the federal ban that occurred in the 1930s, states with larger Mexican populations, like California (1913), Wyoming (1915), Texas (1919), Arkansas (1923), Iowa (1923), Nevada (1923), Oregon (1923), Washington (1923), Montana (1927), and Nebraska (1927), had made recreational use of cannabis illegal. These laws tended to be specifically targeted against the Mexican American population. The *Butte Montana Standard* reported a legislator's comment: "When some beet field peon takes a few traces of this stuff . . . he thinks he has just been elected president of Mexico, so he starts out to execute all his political enemies."

The Decorticator and the Anti hemp Campaign

In 1919, George W. Schlichten patented a newly designed decorticator, a machine that could strip the fiber from any plant without first having to soak the plant. It was the first time hemp could be processed efficiently at an

industrial level, and it didn't take long before the potential for hemp to be used in paper and other products on a large scale was realized. Hemp was also used to make canvas, sails, paint, rope, and clothing. In the late 1920s, Lammot du Pont began working on polymers to make plastics like neoprene and synthetic rubber and in 1935 introduced his new synthetic fiber, nylon. It has been speculated that mass- producing products from hemp would seriously affect the value of timberland owned by Hearst and others and the synthetic paints and fibers produced by du Pont.

Harry J. Anslinger and the Federal Bureau of Narcotics

In 1930, Harry J. Anslinger was appointed commissioner of the US Treasury Department's newly founded Federal Bureau of Narcotics by financier, Andrew Mellon, his wife's uncle. Anslinger built his career on alcohol prohibition and enforcement and supported the criminalization of drugs, but prior to 1930, Anslinger had voiced a different assessment of cannabis—that it was not a problem and that it did not harm people. However, some believe that, with the end of alcohol prohibition in 1933, he was in need of a new substance to police and control, so cannabis became the target. Thus began the campaign of distortions, mistruths, and lies about the effects of cannabis, supported by mass media and the yellow journalism of William Randolph Hearst: By the tons it is coming into this country—the deadly, dreadful poison that racks and tears not only the body, but the very heart and soul of every human being who once becomes a slave to it in any of its cruel and devastating forms. . . . Marihuana is a short cut to the insane asylum. Smoke marihuana cigarettes for a month and what was once your brain will be nothing but a storehouse of horrid specters. Hasheesh makes a murderer who kills for the love of killing out of the mildest mannered man who ever laughed at the idea that any habit could ever get him. He, more than any other figure, waged a vigorous, vicious, and racially charged campaign against marijuana. Propaganda around the country included statements like: There are 100,000 total marijuana smokers in the United States, and most are Negroes, Hispanics, Filipinos and entertainers. Marijuana, a weird "jazz weed" frequently used by Mexican drug addicts, is the source of much crime in the Southwest.

A reefer is a cigarette made of marijuana and marijuana is a narcotic weed introduced from Mexico to palliate the jittery nerves of hi-de-do Harlemites— especially, it seems, the nerves of bandsmen. Marijuana is taken by musicians. And I'm not speaking about good musicians, but the jazz type. Because there was no scientific or clinical evidence that cannabis was addictive or dangerous, and it did not, at the time, pose any major social

problems, what was the motivation? What was it about cannabis that made it such a menace?

In 1931, du Pont started to manufacture neoprene, a synthetic rubber, and then began to work on a synthetic fiber that could replace silk. Nylon was eventually introduced to the market in 1935, and in 1938, du Pont received the patent. There are various theories on the motivation behind Anslinger's frenzied attack on cannabis. Some believe it was driven by racial hatred, plain and simple. Others suspect that he was encouraged by Mellon to remove hemp as a possible competitor to du Pont's new synthetic fiber. There is no proof of any orchestrated conspiracy, but Mellon was also the financier backing du Pont. And others have concluded that it was simply a career move to keep the bureau that so vigorously policed alcohol relevant and, most importantly, funded.

Newspapers continued to write articles characterizing Mexicans as frenzied, violent attackers, fueled by smoking marijuana. A 1935 *Los Angeles Times* article reported, "When a Mexican of the lower class runs amuck, tries to snip off the ears of his wife with the carving knife, cut the throat of his compare, and it takes six to eight burly American policemen to get him to jail—when those things happen, I say it is as clear as day that the little chap, who otherwise, would be no stronger than a cat, has been smoking marihuana."

Marihuana Tax Act of 1937

In the 1937 congressional hearings, which would ultimately decide the fate of? Cannabis as a medicine, there was only one person who testified on its behalf. Dr. William Woodward, legislative counsel for the American Medical Association, began by stating that the word *marijuana* was not recognized by the medical profession, and most did not realize that it was indeed cannabis that was the substance in question. He also challenged the claims that cannabis caused addiction, insanity, violence, and death: There is nothing in the medicinal use of Cannabis that has any relation to Cannabis addiction. I use the word "Cannabis" in preference to the word "marihuana," because Cannabis is the correct term for describing the plant and its products. The term "marihuana" is a mongrel word that has crept into this country over the Mexican border and has no general meaning, except as it relates to the use of Cannabis preparations for smoking. It is not recognized in medicine, and I might say that it is hardly recognized even in the Treasury Department. He went on to explain that cannabis had largely fallen out of favor and was not overprescribed. As medicines like aspirin and morphine

were introduced into the US Pharmacopeia, the uncertainties of dosing made prescribing cannabis less popular with the doctors of the era. While they still prescribed it, they were turning more and more to the convenient pills being made available: I say the medicinal use of Cannabis has nothing to do with Cannabis or marihuana addiction. In all that you have heard here thus far, no mention has been made of any excessive use of the drug by any doctor or its excessive distribution by any pharmacist. And yet the burden of this bill is placed heavily on the doctors and pharmacists of the country; and I may say very heavily, most heavily, possibly of all, on the farmers of the country.

The medicinal use has greatly decreased. The drug is very seldom used. That is partially because of the uncertainty of the effects of the drug. That uncertainty has heretofore been attributed to variations in the potency of the preparations as coming from particular plants; the variations in the potency of the drug as coming from particular plants undoubtedly depends on variations in the ingredients of which the resin of the plant is made up. To say, however, as has been proposed here, that the use of the drug should be prevented by a prohibitive tax, loses sight of the fact that future investigation may show that there are substantial medical uses for Cannabis. So what caused an ancient medicinal that was still used in other parts of the world, was added to the US Pharmacopeia in 1850, and was prescribed by Western physicians in England and the United States to be outlawed? Why was this medicinal, effective in treating seizures, chronic pain, melancholia, parasites, asthma, and menstrual cramps, stricken not only from the United States but also from virtually every country on the planet? It was probably not one single thing but a series of events and circumstances that led to the prohibition of cannabis.

While cannabis was found to be an effective treatment for many conditions, physicians and scientists did not know how or why it worked. One thing they did know was that dosing could be an issue. When prescribing the tinctures, it was not uncommon for a patient to experience adverse side effects like dizziness, altered mutation, nausea, vomiting, or excessive sedation. As we now know, the cannabinoids production varies from plant to plant, and then drops of one batch might be therapeutic, but ten drops of the next batch might have a much higher content of THC and sicken the patient. With pills, doctors were able to prescribe the amount of medication, confident that the dose would not make the patient sick. Thus, the use of medicinal cannabis began to decline, not because it was ineffective or dangerous, but because medications in pill form were more predictable.

The LaGuardia Committee Report

In 1944, New York mayor Fiorello La Guardia consulted with the New York Academy of Medicine. He was well aware of the reports made public by Anslinger, Hearst, and others. What they described with cannabis did not match what he had heard about when serving in Congress. There, he learned of cannabis use by soldiers in Panama, which was described by the Army Board of Inquiry as relatively harmless. At the suggestion of the Academy of Medicine, La Guardia appointed a committee to conduct a social and scientific investigation of cannabis use. While La Guardia did not advocate cannabis use in excess, he hoped that the report might justify an amendment to existing federal law and that further research be done into the possible therapeutic value of cannabis in treating drug addiction.

The study documented that, under the influence of cannabis, subjects did not display statistically significant changes in behavior, the effects were not always related to the amount used, and that the effects at low doses tended to be opposite the effects at higher doses. It was also noted that subjects showed decreased motivation and objectivity, were less aggressive, and were more self- confident, which was thought to be a function of increased relaxation and disinhibition. It was noted that higher doses were associated with less-desirable effects, including anxiety, paranoia, and nausea. Most interestingly, the study compared the personality traits in chronic cannabis users with subjects who did not use cannabis: When the productions of the unrigged marihuana user are studied, certain personality traits which serve to differentiate him from the non-user and from the "average" individual can be discerned. As a group the marihuana users studied here were either inhibited emotionally or turned in on themselves, making little response to stimuli in the world about them. People with this type of personality generally have difficulty adjusting to others and are not at ease in social situations. This withdrawal from social contacts apparently finds little compensatory or sublimating activity elsewhere. These subjects did not have a desire or urge to occupy themselves creatively in a manner that might prove socially useful. They showed a tendency to drift along in passive fashion and gave a good portion of their attention to relatively unimportant matters. These men were poorly adjusted, lonely and insecure. As indicated by their history they seldom achieved good heterosexual adjustment. This description brings to mind traits noted in patients with Asperger's syndrome, which is a condition on the autism spectrum. It is characterized by impairment in social interaction; poor or nonexistent peer relationships; severe social anxiety; restricted patterns of behaviors; and intense interests in narrow, esoteric subjects. It is more common in males than females.

The committee's conclusions in 1944 contradicted the misinformation propagated in the campaign waged by Hearst and Anslinger. Further, marijuana was used mostly by minorities and was not a nidus for criminal behavior:

From the foregoing study the following conclusions are drawn

- Marihuana is used extensively in the Borough of Manhattan but the problem is not as acute as it is reported to be in other sections of the United States.
- The introduction of marihuana into this area is recent as compared to other localities.
- The cost of marihuana is low and therefore within the purchasing power of most persons.
- The distribution and use of marihuana is cantered in Harlem.
- The majority of marihuana smokers are Negroes and Latin Americans.
- The consensus among marihuana smokers is that the use of the drug creates a definite feeling of adequacy.
- The practice of smoking marihuana does not lead to addiction in the medical sense of the word.
- The sale and distribution of marihuana is not under the control of any single organized group.
- The use of marihuana does not lead to morphine or heroin or cocaine addiction and no effort is made to create a market for these narcotics by stimulating the practice of marihuana smoking.
- Marihuana is not the determining factor in the commission of major crimes.
- Marihuana smoking is not widespread among school children.
- Juvenile delinquency is not associated with the practice of smoking marihuana.
- The publicity concerning the catastrophic effects of marihuana smoking in New York City is unfounded.

Single Convention on Narcotic Drugs

The Single Convention on Narcotic Drugs of 1961 is an international treaty between 154 nations to prohibit the production and supply of narcotics not licensed for medical treatment and research. Its purpose was to add synthetic opioids that had been developed since the Paris Convention of 1931, which controlled opium, morphine, heroin, coca, and cocaine. It was here that cannabis was added to the list of internationally controlled substances.

Nixon's War on Drugs

Under President Richard Nixon (1969–1974), Congress passed the Comprehensive Drug Abuse Prevention and Control Act of 1970, which regulates the manufacture, importation, possession, use, and distribution of certain substances. The Controlled Substances Act, Title II of the Comprehensive Drug Abuse Prevention and Control Act, puts drugs into one of five classifications. As schedule levels for medications go up, the theoretical risk of abuse goes down. Schedule I is defined as substances having *a high potential for abuse, no accredited medical use, and a lack of accepted safety*. Cannabis, or marijuana and any substance derived from its flower or leaves, is classified as Schedule I, as are heroin, LSD, MDMA (Ecstasy), mescaline, and peyote. Synthetic THC capsules, the exact same THC molecule found in the cannabis plant, were approved by the FDA and introduced to the market in 1986 as a Schedule II medication. Dronabinol was reclassified in 1999 to Schedule III.

Just like Anslinger, Nixon waged a "war on drugs" based on what appears to be cultural and racial prejudice and misinformation. Dead set on instituting a policy that paid little attention to facts or science, Nixon requested a study that would support his conclusion that the use of marijuana was dangerous and should not be legalized. Former Pennsylvania governor Raymond P. Schafer headed the National Commission on Marihuana and Drug Abuse. Among its members were physicians, bipartisan representation from the US Senate and the House of Representatives, an attorney, a college president, a television producer, a university pharmacy department chairman, and a law school dean.Instead of finding evidence to support continued prohibition, the commission found that marijuana users were not a threat to society but were, in fact, "timid, drowsy, and passive" and recommended in 1972 that marijuana should be decriminalized. Nixon ignored their findings. Instead, it was opposed in 1974 by the recommendations of a congressional subcommittee chaired by conservative Democrat Senator James Eastland from Mississippi.

In 1994, Dan Baum, a writer for *Harper's Magazine*, reportedly had a conversation with Nixon's domestic policy adviser, John Ehrlichman: You want to know what this was really all about? The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. You understand what I'm saying? We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.

The Obama-Era Enforcement Policies

The Cole Memo was written in 2013 by US Deputy Attorney General James M. Cole and sent to US attorneys. It stated that they should prioritize their focus on cannabis enforcement to distribution to minors and criminal and gang activity. They should also prevent diversion from legal to illegal states, authorized Activity from being used as a front for trafficking, drugged driving, growing marijuana on public lands, and use and possession on federal property. Attorneys should refrain from prosecuting state-approved cannabis businesses as long as they comply with their state's cannabis regulations. As part of the 2014 Farm Bill, legislation was passed legalizing *cannabisSativa* L., the fiber or industrial-type plant with less than 0.3 percent THC. State- licensed growers are allowed to grow, process, and sell products from this plant as part of a state's sanctioned research program. It is through these state programs that online and retail hemp-derived cannabidiol (CBD) products are produced.

Rohrabacher-Blumenauer Amendment

The Rohrabacher-Blumenauer Amendment (also the Rohrabacher-Farr Amendment), first introduced in 2001 by Dana Rohrabacher (R-CA), Maurice Hinchey (D-NY), and Sam Farr (D-CA), forbids the Justice Department from using federal funds to interfere with a state's medical cannabis program. It passed in 2014, after six prior failed attempts as part of an omnibus spending bill. Currently the amendment has to be renewed with each new budget bill.

Attorney General Sessions

In the spring of 2017, former senator and newly appointed attorney general Jefferson Sessions (R-MS) wrote a letter to Congress requesting a repeal of the Rohrabacher-Blumenauer Amendment: [It would] inhibit [the

Justice Department's] authority to enforce the Controlled Substances Act. I believe it would be unwise for Congress to restrict the discretion of the Department to fund particular prosecutions, particularly in the midst of an historic drug epidemic and potentially long- term uptick in violent crime. The Department must be in a position to use all laws available to combat the transnational drug organizations and dangerous drug traffickers who threaten American lives.

In response to the Sessions letter, Senators Cory Booker (D-NJ), Kristen Gillibrand (D-NY), Mike Lee (R-UT), and Rand Paul (R-KY) reintroduced the CARERS Act, which initially stalled after being introduced in 2015. This bipartisan act would allow the possession, production, and distribution of Medical marijuana in states that have legalized it. It would also allow Veterans Administration doctors to recommend it to their patients in those states where it is legal; improve access to cannabis for medical research; and reschedule CBD, the major no psychoactive component of the plant.

On January 4, 2018, the attorney general rescinded the Cole Memo. This, according to some, has opened the door to federal policing in states that (1) have medical cannabis programs, where a patient must have a doctor's recommendation to use cannabis legally; (2) have decriminalized cannabis use (it is illegal, but if caught, offenders may have to pay a fine on par with running a red light); and (3) have legalized adult-use recreational cannabis for anyone over the age of 21. As for now, the Rohrabacher-Blumenauer Amendment protects medical cannabis programs that are run in compliance with state regulations but not recreational or adult use. While there are concerns about federal interference from officials and cannabis business owners in states with legalized recreational cannabis and users in states that have decriminalized cannabis use, many believe this move by the Justice Department will serve as motivation for states without formal programs in place to increase their efforts to pass medical cannabis legislation.

Summary

The current historic drug epidemic has nothing to do with cannabis. The rise in drug-related deaths is caused by increased access to opiates and benzodiazepines, the combination that accounts for the majority of prescription drug overdoses—access that begins in the doctor's office when patients are prescribed these medications for chronic pain. For some, their pain has resolved, and the drugs remain in the medicine cabinet for other family members to access; for others, it marks the beginning of addiction. A 2014 study published in the *Journal of the American Medical Association*

showed that opiate-related overdose death rates had declined by as much as 24.8 percent in states with legal medical cannabis.

After the 2014 legalization of small amounts of cannabis for recreational use in Colorado, violent crime rates in Denver fell 6.9 percent in the first quarter of 2014 compared to the prior year, and property crime dropped by 11.1 percent. A study published in 2014 by researchers at the University of Texas at Dallas concluded that legalization of cannabis does not correlate with an increase in violent or property crime and may actually reduce it as well as reduce alcohol consumption, which *is* associated with an increase in violent crime. Since the Legalization of medical cannabis, marijuana trafficking by Mexican drug cartels has decreased significantly, just as bootlegging disappeared after the end of alcohol prohibition.

It is important for patients and health-care providers to understand that the Reasons for cannabis being made illegal were based on, what some would argue, economic and sociopolitical issues, not science and medicine. The energy spent on making and keeping it an illegal, schedule I substance is grossly disproportionate to the adverse effects attributed to the plant.

As of June 2017, cannabis is legal for medical use in 29 states, the District of Columbia, and 2 US territories: Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, the District of Columbia, Guam, Florida, Hawaii, Illinois, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Pennsylvania, Puerto Rico, Rhode Island, Vermont, and Washington. An additional 17 states have restrictive CBD-only laws in effect: Alabama, Georgia, Indiana, Iowa, Kentucky, Mississippi, Missouri, North Carolina, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Wisconsin, and Wyoming. Only in two of these, Alabama and Missouri, is it possible to obtain CBD without breaking state or federal law. Nebraska is an industrial hemp state, and residents are allowed to use hemp- derived CBD, but Kansas and Idaho are not, so those residents have no legal access at the state level to cannabis of any kind. Cannabis is no longer considered a gateway drug. According to the CDC, persons addicted to alcohol are two times more likely to also be addicted to heroin, while those addicted to marijuana are three times more likely. In contrast, individuals addicted to cocaine are 15 times more likely to be addicted to heroin, and those addicted to prescription drugs are 40 times more likely to have a heroin addiction. Alcohol, cocaine (commonly used by ENT and plastic surgeons to control bleeding in the operating room), and obviously prescription drugs are all

legal. Cannabis has anti-inflammatory, analgesic, anxiolytic, antipsychotic, antitumor, antispasmodic, and antidepressant effects. It has been proven effective in treating seizures and neuropathic pain in double-blind, placebo-controlled, multicenter studies, where they can research the effects on large numbers of patients, and neither the patient nor the researcher knows who is being treated with cannabis, in order to remove any bias or preconceptions of the part of patients and researchers. It has a relatively low potential for addiction (6 to 9 percent versus 13 to 18 percent for alcohol). Unlike alcohol, cannabis has a lethal dose so high that it's impossible for a person to inhale or ingest it, and it has no known long-term health consequences other than possible effects on memory and cognition in heavy users who start at a young age.

One has to ask, why is this plant schedule? It is my hope that, as you read about the many benefits of cannabis and its remarkably low toxicity profile and learn how to use it in a manner that is not impairing, you might consider it as a safe and effective alternative or addition to your therapeutic program to achieve better health and well-being.

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Chapter - 7

Pharmacological and Therapeutical Aspects of Cannabis

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Introduction

Cannabis, also known as marijuana or ganja, is the most controversial plant in the history of mankind, obtained from the biological source *Cannabis sativa* Linn. Or Cannabis Indica, belongs to the family of Cannabinaceae. The plant is most popular due to its recreational as well as medicinal use. Cannabis is produced in nearly every country worldwide, and is the most widely produced illicit drug. The countries like Mexico, Colombia, Jamaica and USA are the highest producer of this plant; followed by Morocco, Afghanistan, South Africa, Lesotho, Swaziland, Malawi, Nigeria, Ghana, Senegal, Gambia, Kenya, Tanzania and Pakistan. It contains 421 substances of 18 chemical types. Out of which the most significant compound is δ- 9-tetrahydrocannabinol, which causes several effects, both in the Central Nervous System and in several peripheral locations in the organism. The plants are mostly grow at warm and tropical climates& cultivated throughout the world. The global cannabis cultivation market size was valued around USD 123.9 billion in the year 2019 and is expected to grow at a compound annual growth rate of 14.3% from 2020 to 2027. Growing legalization and the adoption of cannabis for the treatment of chronic diseases are the key factors that driving the growth of the market.

Cannabis Pharmacology

Pharmacokinetics

THC-tetrahydrocannabinol the major bioactive component that shows rapid absorption in blood stream followed by faster distribution in different tissues, organs including brain. It shows higher bioavailability when administered through pulmonary route rather than oral route. Cannabinoids another major bioactive present in cannabis are very lipid soluble and preferably accumulate in fatty tissues after absorption and reaching peak concentrations in 72-96 hours followed by a slow release into different organ

and tissues of the body, including brain. Total body clearance of Cannabinoids may take 30 days after single dose admiration. The metabolism of cannabinoids results more than 20 metabolites, most of them follows hydrophilic in nature and excreted through urine. A few metabolites are reabsorbed and initiate prolong action. Further, as per the reported literature most of the THC are excreted through the feces (65%) and approximately 30% of the THC is eliminated in the urine as conjugated glucuronic acids and hydroxylated metabolites.

Pharmacodynamics

The Pharmacological effects and therapeutic responses of cannabinoid compounds are mainly depend on its attachment and activation of cannabinoid receptors that was discovered by Davene *et al*. in the year 1988 and later Munro *et al*. identify the CB2 receptor intheyear1993.Most of the bioactive phytochemicals obtained from cannabis are reported to act on CB1 and CB2 receptors. Both of these receptors are coupled through inhibiting G proteins (Gi proteins), negatively to adenylate cyclase and positively to mitogen-activated protein kinase. Activation of Gi proteins causes inhibition of adenylate cyclase, thus inhibiting the conversion of AMP to cyclic AMP. On the other hand CB1 receptors are also coupled to ion channels through Gi/o, negatively to N-type and P/Q-typecalcium channels and inwardly rectifying potassium channels. They may also mobilize arachidonic acid and close serotonin (5-HT3) receptor ion channels, and someCB1 receptors are negatively coupled to M-type potassium channels. It is also reported that under certain conditions, they may also activate adenylate cyclase through stimulating G proteins (Gs proteins).CB1 receptors are found mainly on neurons in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them endocrine glands, leucocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts.CB2 receptors occur principally in immune cells, e.g. leucocytes, spleen and tonsils and there is markedly more availability of mRNA forCB2 than for CB1 in the immune system. Most of the cannabis obtained derivatives mainly increases the release of dopamine from the nucleus accumbens and prefrontal cortex, which is produce euphoric effect.

Bioactive phytochemical of cannabis & their medicinal use

Tetrahydrocannabinol (THC): The mostly available phytochemical found in cannabis, and are responsible for the psychoactive effects, including changes in human cognition and perception (Hofmann and Frazier, 2013). THC are reported exerts a wide variety of therapeutic effects, its primarily act as a partial agonist of CB1 receptors, CB2 receptors which are mainly

present in CNS (Central nervous system) &cells of the immune system. THC shows anticonvulsant effects which is suggested to act on CB1 receptors and may serve as potential constituent in epilepsy (Consroe *et al*., 1982; Wallace *et al*., 2001). (Detyniecki and Hirsch, 2015). Moreover it play vital role in management and treatment of several diseases includes Neurodegenerative Diseases (Neuroprotection, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Tourette syndrome, Parkinson's disease), antitumor effect, Cancer palliation, Analgesic effect.

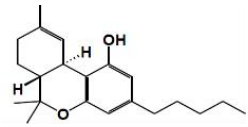
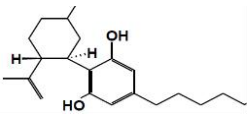
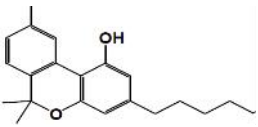
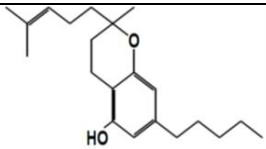
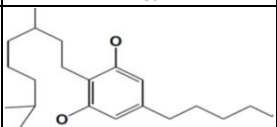
Cannabidiol (CBD): It is the major form of phyto-cannabinoid derived from cannabisthat has wider therapeutic potentials like anticonvulsant, anti-inflammatory, antioxidant effects and anti tumorigenic activities. It's having a low affinity for CB1 and CB2 receptor, and also reported to have partial affinity towards serotonin 5-HT1A receptor and allosteric modulation of opioids receptors. CBD reaches maximum plasma concentration between 0 and 2 hrs and get metabolized in liver as well as intestine. They are found to be effective against epilepsy. In the year 2018 FDA has approved the medicinal use of CBD for the children and aged patients who suffer from the seizure disorders Lennox-Gastaut syndrome and Dravet syndrome.

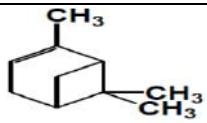
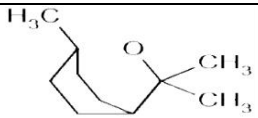
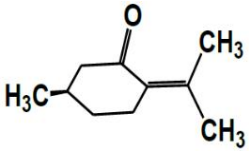
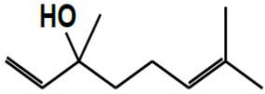
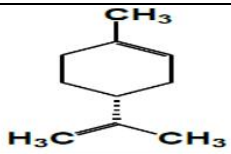
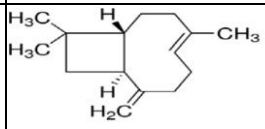
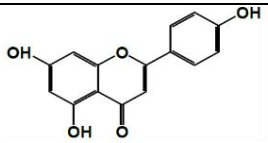
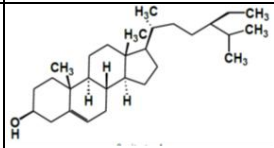
Cannabinol (**CBN**): It is a mildly psychoactive cannabinoid found only in trace amounts in aged cannabis. CBN acts as a partial agonist at CB1 receptors, but has a civic affinity for CB2 receptors; without ban, it has lower affinities relative to THC. Unlike other cannabinoids, CBN does not come directly from cannabigerol (CBG) or cannabigerolic acid (CBGA), but is the degraded product of tetrahydrocannabinolic acid (THCA). If cannabis is exposed to air or ultraviolet light (for example, sunlight) over a long period of time, THCA will convert to cannabinolic acid (CBNA). CBN is then formed by decarboxylation of CBNA.

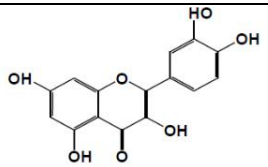
Cannabichromene (CBC): The second most abundant found cannabinoids known as phytocannabinoids. It is having structural similarity to the other natural cannabinoids, including tetrahydrocannabinol (THC), tetrahydrocannabivarin (THCV), cannabidiol (CBD), and cannabinol (CBN). CBC reported to have antinociception and anti-inflammatory effects on rodents. CBC can interact with transient receptor potential (TRP) cation channels that inhibit endocannabinoid inactivation, and stimulate CB2 receptors (Ki ~ 100 nm), but it does not have significant activity at CB1 receptors (Ki > 1 μM). It possesses poor affinity to the CB1 receptor. CBC can relieve pain, potentiate the analgesic effects of THC, ameliorate-induced colonic inflammation, and paw edema by demonstrably inhibiting macrophage and MAGL activity.

Cannabigerol (CBG): CBG is one of the important cannabinoids with several medicinal values found in different species of cannabis in very little quantity. It is having less affinity towards CB1 receptor. It has shown therapeutic effects includes analgesic and anti-inflammatory, inhibit platelet aggregation, reduction in intraocular pressure etc. it also showed a significant antitumor effects.

Table 1: Major Phytochemicals present in cannabis and its reported medicinal Uses

S. No.	Phytochemicals reported to be present in cannabis	Chemical Structure	Medicinal Use	Reference
1	THC- tetrahydrocannabinol	 $C_{21}H_{30}O_2$	Antioxidant, Analgesic Anticonvulsant Anti-inflammatory Antiemetic, Ephoriant	1
2	CBD- Cannabidiol	 $C_{21}H_{30}O_2$	Analgesic, Anticonvulsant Antitumorigenic Neuroprotective Immune modulation Antioxidant Anti-inflammatory Antipsychotic Anxiolytic Antispasmodic	1
3	CBN- Cannabinol	 $C_{21}H_{26}O_2$	Antibiotic Psychoactive properties Sedative Oxidant	2
4	CBC- Cannabichromene	 $C_{21}H_{30}O_2$	Antibiotic Anti-inflammatory Antifungal	2
5	CBG- Cannabigerol	 $C_{21}H_{32}O_2$	Antibiotic Antifungal Anti-inflammatory	2

6	α- pinene	 **$C_{10}H_{16}$**	Anti-inflammatory Stimulant Antibiotics Antineoplastic	3
7	1,8-Cineole (eucalyptol)	 **$C_{10}H_{18}O$**	Anti-inflammatory Antibiotics Antiviral Stimulant	3
8	Pulegone	 **$C_{10}H_{16}O$**	Sedative Antipyretic Memory booster	2
9	Linalool	 **$C_{10}H_{18}O$**	Sedative Antidepressant Anxiolytic	1
10	d- limonene	 **$C_{10}H_{16}$**	Antidepressant Cannabinoid agonist Anti- mutagenic	1
11	β – Caryophyllene	 **$C_{15}H_{24}$**	Anti-inflammatory Antimalarial	3
12	Apigenin	 **$C_{16}H_{10}O_5$**	Anti-inflammatory Axiolytic Estrogenic	2
13	β- Sitosterol	 **$C_{29}H_{50}O$**	Anti-inflammatory	2

14	Quercetin	 $C_{15}H_{10}O_7$	Antioxidant Antiviral Antineoplastic	2

The medicinal values and therapeutic benefits of cannabis are well described in various reputed classical ancient literatures. A century before it was happened to be a licensed medicine in the United States, after that it was removed by American Medical Association and the U.S. Pharmacopeia. The renewed interest in the therapeutic effects of cannabis emanates from the movement that began 30 years ago to make cannabis available as a medicine to patients with a variety of conditions. It was in 1996 that Arizona and California first passed medicinal cannabis legislation, although Arizona later rescinded the approval, so it would be California that paved the way.

Relief from chronic pain is by far the most common condition cited by patients for the medical use of cannabis. Ilagan *et al*. (2013) reported in his study that 87 percent of participants were seeking medical marijuana for pain relief. Further Cancer a disease characterized by an abnormal, unfettered division of cells; a biological disorder that often results in tumour growth. It is one of the leading causes of mortality of the world. Literature revel the fact that there is evidence to suggest that cannabinoids may play a role in the cancer regulation processes. Nausea and vomiting are the most common side effects of most of the cytotoxic chemotherapy agents. A number of pharmaceutical interventions in various drug classes have been approved for the treatment of chemotherapy-induced nausea and vomiting. Among this cannabinoid medications, nabilone and dronabinol were initially approved in 1985 for the management of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional antiemetic treatments. Literature reported that Cannabinoids played an effective role in treatment of anorexia and weight loss occurs due to HIV/AIDS, & Cancer. Further, cannabinoids also reported to have potential therapeutic effect in patients with Irritable Bowel Syndrome (IBS). Epilepsy is a disorder that affects an estimated 7.35 million patents, across the world throughout the all age group. Cannabis plays a vital role in the management of epilepsy. Many more disease conditions are reported to get addressed by means of bioactive phyto-medicines present in cannabis.

Recent status of research on cannabis

Sl. No.	Pharmaceutical dosage form	Active phytochemicals	Present status	Medicinal Use
1	Solid oral dosage form	CBD-Cannabidiol	Clinical Trails	Treatment of Solid Crohn's disease, GVHD
2	Self-emulsifying drug delivery systems	Tetrahydro - cannabinol	Preclinical study	Improving dissolution, stability
3	Liquid oral dosage form	THC-glycosides	Clinical trials	resistant inflammatory bowel disease Inflammation
4	Topical gel, cream	Phyto-cannabinoids	Preclinical	dermatitis Inflammation, Arthritis, Oedema, Rheumatic diseases
5	Ocular ointment	THC analogue	Formulation and development	Glaucoma Reduce intraocular pressure
6	Oil, spray, cream	CBD-Cannabidiol	Clinical treatment	Epidermiolysis bullosa Pain, blistering
7	Chewing-gum	THC : CBD = 1:1	Preclinical	Pain, spasticity, dementia etc

Commercially available approved medicinal product of cannabis:

Sl. No.	Brand name & API	Name of the manufacturer	Medicinal Use	Type of dosage form
1	Epidiolex & CBD-Cannabidiol	GW Research Ltd	epilepsy, Lennox-Gastaut syndrome and Dravet syndrome	Liquid oral
2	Dronabinol (Marinoland Syndros) & tetrahydro cannabinol	Solvay Pharmaceuticals	Nausea, Vomiting Caused due to cancer chemotherapy & effective against loss of appetite and weight loss in people with HIV infection.	Liquid oral
3	Cesamet (Nabilone) & tetrahydrocannabinol (THC)	Valeant Pharmaceuticals	Nausea, pain, anti-emetic	Liquid oral
4	Sativex (Nabiximols) & combonation of tetrahydrocannabinol and CBD-Cannabidiol	GW Research Ltd	Neuropathic pain, spasticity, overactive bladder,	Mouth Spray

Biological responses generated by Cannabis and its bioactive derivatives

Sl. No	Disease states/health issues	Possible therapeutic / biological response
1	Multiple sclerosis	Psychoactive effects, may induce acute psychosis, anti-inflammatory, and neuroprotective
2.	Spinal cord injury	Inflammation, pain anxiety
3	Spinal cord disease	pain and spasticity
4	Cancer	They can induce cell cycle arrest, promote apoptosis, and inhibit proliferation, migration and angiogenesis in tumor cells
5	HIV/AIDS	Smoking marijuana relieves neuropathic pain, In AIDS patient
6	Arthritis	CBD oil contains extracts from cannabis plants. Some people use CBD oil to relieve pain associated with chronic conditions, such as arthritis.
7	Epilepsy	Anti-seizure, antipsychotic, neuroprotective, antidepressant and anxiolytic.
8	Schizophrenia	In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders
9	Post-traumatic stress disorder	Canabinoids have defective treatment on PTST disorder. It has no effect on sleep quality and quantity
10	Sleep disorder	Effective treatment for improving sleep
11	Depression	It relieves from persistent depressive disorder, major depressive disorder, premenstrual dysphoric disorder)
12	Anxiety	Cannabidol improved anxiety symptom Cannabidiol was associated with a greater improvement on the anxiety factor of a 100-point visual analogue mood scale
13	Chronic pain	medical cannabis use in pain patients was associated with a 64 percent reduction in opioid use
14	Anorexia nervosa	Oral cannabinoids being able to increase weight in patients with the HIV-associated wasting syndrome and anorexia nervosa. No benefit has been demonstrated in cancer-associated anorexia-cachexia syndrome.
15	Multiple sclerosis	Muscle spasming, vision and sensation problems, and balance problems, which cannabis can help to dramatically improve.

16	Muscle spasm	Muscle elasticity, spinal cord problems are cured by the cannabis
17	Nausea	CBD might help quell nausea because it interacts with serotonin receptors.
18	wasting syndrome	Cachexia is a common term for the wasting symptoms which may appear in almost every chronic illness, such as AIDS, tuberculosis, and cancer. Cancer cachexia (CCA) is a result of the interaction between the host and the tumor, mainly manifested in short-term wasting, malnutrition, and so on. Due to the chronic food shortages, absorption dysfunction and metabolic disorders, all of these eventually lead to hypo immunity, organ failure, and higher susceptibility to pathogenic microorganisms.

Summary

Cannabis is an ancient plant that remained controversial in terms of its applicability on the mankind. Although it was abundantly utilized for the recreation purpose for a decade, but the existing literature, research findings explored the promising health benefits of the plant. Its role against diseases like epilepsy as (anti-seizure, antipsychotic, neuroprotective, antidepressant and anxiolytic), Pain management, overcome the side effects of cancer; HIVs, etc. are reported as extraordinary. Extensive research activities are going on across the world to explore more unknown potential of cannabis plant. Although the legal obligations are still applies against cannabis production but looking towards its health benefits an medicinal use this plants cultivated

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Chapter - 8

A Review on Cannabis: Its Benefits for Human Health

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Abstract

Cannabis refers to a group of plants with psychoactive properties. Cannabis is an herbal drug that is made from the Cannabis plant. It contains chemicals called cannabinoids. Cannabinoids are found in the highest levels in the leaves and flowers of cannabis. In these review paper, we have shown uses of cannabis in treating some health ailments and its potential to cure certain diseases. The objective of this review paper is to show the potential health implications of cannabis.

Keywords: Cannabis, Health Benefits, Medicinal, Phytochemical, Nutraceutical

Introduction: *Cannabis sativa spp.*, a natural resource which has been cultivated since ages is utilized in the form of food supplements, textiles, building materials, body care products, food as well as medicines (Hartsel A. Joshua *et al.,* 2016). *Cannabis sativa* L. is an important herbaceous species used in traditional medicine, which originated from Central Asia. It has numerous applications, is rich in phytochemicals as well as abundant in cellulosic and woody fibers (Andre, C. M. *et al.,* 2016). There has been expanded interest in the part of cannabis for treating ailments. There are both potential therapeutic uses for and potential health risks of using cannabis. A chemical called delta-9-tetrahydrocannabinol (THC) is responsible for the way your brain and body respond to cannabis. While it is used by some for therapeutic purposes, there are short and long-term physical and mental health effects that can be harmful (Bhattacharyya *et al.*, 2010).

The different properties and health benefits of Cannabis are briefly reviewed as mentioned below:

Properties of different parts of Cannabis: Cannabis has been used for its food, fiber and medicine purpose since historical times (Kuddus M. *et al.*,

2013). It has been seen that there is growing interest in the wide range of medical usage of cannabis and its constituents in recent decades (Abuhasira, R. *et al.,* 2018).

Farinon, B *et al.,* (2016) conducted a study on "The Seed of Industrial Hemp (*Cannabis sativa* L.): Nutritional Quality and Potential Functionality for Human Health and Nutrition" with the goal to examine the scientific literature with concern to the nutritional as well as functional properties of hempseeds.

A cannabinoid, Δ^9-THC is produced mainly in the leaves and flower buds of the plant. After the discovery of the chemical structure of its major active constituent, Δ^9-tetrahydrocannabinol (Δ^9-THC), Cannabis (*Cannabis sativa*, or hemp) and its constituents, particularly the cannabinoids have been the pivot of extensive chemical and biological research for nearly half a century. Various medicinal functions are found in other non-psychoactive cannabinoids also such as cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG), along with other non-cannabinoid constituents which belong to diverse classes of natural products (ElSohly, M. A. *et al.,* 2017)

A study was conducted by Lewis, M. A. *et al.,* 2018 on "Pharmacological foundations of Cannabis Chemovars". Through the study, an advanced Mendelian Cannabis breeding program was developed which used chemical markers to improve therapeutic effectiveness and safety, for the maximum yield of phytocannabinoids and terpenoids. Based on the amount of cannabinoid present, cannabis is divided into several categories. In both medical and recreational marketplaces, the prevalent offering is Type I, Δ9- tetrahydrocannabinol-predominant. Currently, the therapeutic potential of cannabidiol has been recognized leading to the promotion of additional chemovars: Type II, Cannabis containing both Δ9-tetrahydrocannabinol and cannabidiol, and cannabidiol-predominant Type III Cannabis. From the breeding program, it was significantly shown that those highly potent in terpenoids, or single components such as limonene, pinene, terpinolene and linalool include Type I, II, and III Cannabis chemovars.

Cannabis and its health implications

At present, the most prevalent and consumed illicit drug in the world is cannabis with global numbers of users approaching 182.5 million (3.8% of global population) (Goyal H. *et al.,* 2017).The use of cannabis is relatively common and widespread. In most regions of the world, demand by cannabis users for treatment has been increasing. Some countries have also decriminalised or legalised use of cannabis (Nielsen S *et al.,* 2019). The

extensive use of cannabis has been prevailing since centuries for medical purposes. Policies regarding medical and recreational cannabis have been implemented by different countries. For pain relieving purposes, Cannabis pharmacotherapy has been used by an increasing population. Modest evidence was found which supported the use of cannabinoid pharmacotherapy for pain by a recent meta-analysis of clinical trials of cannabis and cannabinoids for pain (Hill, K. P. *et al.,* 2017).

Currently, the medicinal properties of cannabis as well as cannabinoids have been discovered. Cannabis and the cannabinoids have some potential applications in treating a number of serious illnesses, such as glaucoma, depression, neuralgia, multiple sclerosis, Alzheimer's, and also in alleviation of symptoms of HIV/AIDS and cancer (ElSohly, M. A. *et al.,* 2017)

A study conducted by Weston-Green, K. (2019) on "The United Chemicals of Cannabis: Beneficial Effects of Cannabis Phytochemicals on the Brain and Cognition" revealed that in multiple states of cognitive impairment, there is beneficial treatment effects of cannabidiol (CBD), isolated from the cannabis plant which is a major non-intoxicating compound. The study also found that the treatment of schizophrenic symptoms and cognitive deficits can be treated by CBD.

Relief from chronic pain is one of the most common condition cited by patients for the medical use of cannabis. Several research has suggested that cannibis is as effective as opioids for chronic pain relief. According to some research, it is as effective as opioids, which are among the most potent pain-relieving drugs. Ilgen *et al.,* (2013) reported that 87 percent of participants in their study were seeking medical marijuana for pain relief. In addition, there is evidence that some individuals are replacing the use of conventional pain medications with cannabis. For example, one study reported that patrons of a medical marijuana dispensary used medical cannabis in pain patients and that was associated with a 64 percent reduction in opioid use (Boehnke *et al.*, 2016).

Cancer is a broad term used to describe a wide range of related diseases that are characterized by an abnormal, unregulated division of cells; it is a biological disorder that often results in tumour growth (NCI, 2015). Several studies suggest that cannabis are beneficial for cancer treatment, however many researchers have reported that there are insufficient evidence of cannabis and its association with cancer (National Academies Press (US); 2017).

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder commonly associated with symptoms of abdominal cramping and changes in bowel movement patterns. Individuals with Crohn's disease or ulcerative colitis can find some relief with the use of cannabis. THC and cannabidiol are known to help enhance immune response while also interact with cells that play a vital role in the functioning of the gut. Cannabis helps block off bacteria and other compounds that cause inflammation in the intestines (Healtheuropa, 2019).

The need and tolerance of cannabis depends on prior experience of patient and underlying cannabinoid tone. Cannabis medicine has adverse events which pertain primarily to THC and to avoid psychoactive sequelae and development of tolerance, the total daily dose-equivalent should generally be limited to 30 mg/day or less, preferably in conjunction with CBD. (MacCallum, C. A., & Russo, E. B., 2018).A study was conducted by Dickson, B. *et al.,* (2018) on "Recommendations from Cannabis dispensaries about first-trimester cannabis use". The proportion of marijuana dispensaries which recommended a cannabis product to be used during pregnancy was the primary outcome of the study. Secondary outcomes of the study revealed proportion which endorsed the use of cannabis as safe during the period of pregnancy, recommendations of specific product and encouraging discussion with a health care provider. In the United States, medicolegal realities are rapidly evolving surrounding "medical marijuana" or "medical cannabis". Information or certification for medical cannabis are being increasingly asked by patients to clinicians. (Ebbert, J. O., 2018).

Conclusion and Recommendation: There is evidence that demonstrates both the harms and health benefits of cannabis. However, potential medicinal benefits of cannabis in several ailments have been found by researchers in the past few years suggesting cannabis to be one of the most promising medicinal plants. But to establish the medicinal use of cannabis, more in-depth research must be done which provides evidence of its proper medicinal use.

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Chapter - 9

Phytochemical Analysis of Selected Cannabis from Northeast India

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Abstract

The Cannabis plant commonly is known for its viable psychoactive substance. In India it is served in religious functions. Cannabinoids in the cannabis plant include delta-9-tetrahydrocannabinol (THC), Cannabidiol (CBD), and cannabinol (CBN). THC is the primary psychoactive compound, with CBD, and it is a non-psychoactive compound. Despite of being an psychoactive compounds it has many medicinal effect, such as, treatment of various diseases and other health problem such as HIV/AIDS, glaucoma, treatment of pain, eye problem, muscle spasticity, convulsion, asthma, insomnia, hypertension, depression etc.

The current studied was undertaken for phytochemical analysis, estimation of protein, and evaluation of Antioxidant and Antimicrobial activity of the studied plant against *S.aureus* and *E.coli*. Standard protocol had followed for analyzing phytochemicals. And from the result it was concluded that there are many bioactive phytochemicals present in the extracted plant. The reported phytochemicals are phenol, terpenoids, steroids, saponin, tannin, glycosides, carbohydrate and proteins. Various extract were prepared out of which protein concentration was evaluated for methanol and chloroform and was compared. The antimicrobial activity were evaluated and a recommendable zone of inhibition was seen in methanol extract.

Keywords: *Cannabis sativa, Cannabinol, Cannabidiol, Tetrahydrocannabinol, Antimicrobial* activity, *S.aureus, E.coli*, Antioxidant activity, Phytochemical analysis.

Abbreviation: None

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

Introduction

The hemp plant that grows worldwide, *Cannabis sativa*, is commonly known as marijuana. Today, the cannabis plant is widely regarded as a viable psychoactive drug, with previous reports of cannabis use materializing over 10,000 years ago. Cannabis later spread through Asian countries and was introduced in India, and is used in religious functions [1]. It gives the plant the security and respect that cultural or religious recognition engenders.

Cannabis use for recreation and as enticing characteristics of cannabis and hashish, cannabis usage as a drug has not been widespread in Europe immediately. Despite its psychoactive effects in Europe, the enticing characteristics of Marijuana did not arise until the 1960s, when it was reintroduced, among others, by visitors from the USA [2].

Cannabinoids include delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) at the cannabis plant. THC is the main psychoactive agent of CBD, and the latter is non-psychoactive. THC exists at concentrations that are higher than CBD. *Cannabis sativa*'s established chemical composition is ever-changing. And new constituents of non-cannabinoids and cannabinoids are often discovered in the plant [3].

Cannabidiol (CBD), a major component of cannabis, has soporific properties and clinical trials have indicated rising anxiety and other psychological side effects that THC encourages. CBD effectively destroys high-potency bacteria and cannabis can have less microbial contamination than other medicinal plants (herbs); an significant factor for individuals with immune-compromise. Materials work in *C. sativa* components (leaves, seeds, fruits and bark) differ depending on the mode of operation, both added directly or in solvent extract form. Sativa has analgesic, antiemetic, anti-inflammatory, sedative, anticonvulsant and laxative activities and clinical trials have shown its efficacy in alleviating nausea and vomiting during chemotherapy treatment of cancer [4].

Indian cannabis has been extensively used for the diagnosis of diseases and other health issues such as HIV/AIDS, glaucoma, pain relief, eye disorders, muscle spasticity, epilepsy, asthma, insomenia, hypertension, depression etc. [9] In addition, cannabis was consumed for relaxation. Cannabis is also used for shampoos and other cosmetic purposes. In fact, the production of cannabis is a lucrative industry that yields significant local and foreign profits to farmers and marketers [10].

Indian marijuana is the most misrepresented and despised herb in recent times, given its widespread uses. Hatred has been so prevalent around the world that millions of dollars have been spent on dispatching this important crop production. Hundreds of hectares of Indian hemp had been burned, and this crop's growers, marketers, dealers and consumers were arrested and imprisoned. Also, people who don't know anything about the usefulness of the crop were inelegant in hating it [11].

Cannabis distribution worldwide

Cannabis in India

Since 2000 BCE cannabis has been used in India. Common words for cannabis preparations in Indian culture include Charas (resins), Ganja (flower), and Bhang (seeds and leaves). In 1961 the Single Conventional international convention on Narcotic Drugs thumped cannabis as hard drugs. The official source rejected its hostility against India's social and religious customs. Thus the Indian government negotiated and agreed to restrict Indian Hemp exports. This enabled India to continue the tradition of consuming Bhang in holiday. The Narcotic Drugs and Psychotropic Product Act (NDPS) had been passed in 1985 by Indian government. NDPS restricted the manufacture and scale of cannabis resins and flowers, but permitted the use of leaves and seeds, allowing the government to control the latter.

Cannabis in other countries

Cannabis is used all over the world but its legalization is at stake. Many nations, such as South America, allow adults to acquire up to 40 grams of marijuana from licensed pharmacies per month. In Canada, the federal government launched the Cannabis Act, which enables individuals aged 18 years and older to purchase and use marijuana.

Cannabis in northeast

Marijuana in northeast, Manipur has been regarded as the country's best herb. Manipur 's numerous districts such as Ukhrul have been under the weed cultivation microscope. Other north-eastern states such as Assam and Meghalaya are also a mass weed cultivator.

Medical utility of *Cannabis sativa* (Marijuana)

Cannabis sativa's medicinal value has been understated and therefore abandoned. It states negative aspect, for medical use or other uses of this commercial crop, which has been interpreted thus leading to its rejection to the detriment of its value to humanity. Cannabis has a long history, with the earliest evidence attributed to Shen Nung in twenty-eight for its medicinal

and health use. Shen Nung professes cannabis use in China for his medical advantages during that time. Shen Nung, a legendary Chinese emperor and pharmacist, asserted that cannabis was used in China for its sedative properties, pain treatment and general psychoactive effects during this period [12].

Cannabis can be delivered by smoking, since that's how it is ingested by most medical users. In clinical trials such products are most commonly systematized in their THC content. THC, or delta-9-tetrahydrocannabinol, is the most important pharmacological and toxicological component contained in cannabis that has created countless animal and human effects. THC's most well-established opiate effect is the suppression of vomiting and diarrhea caused by chemotherapy in patients with cancer. Pure THC can be chemically synthesized or derived from natural sources. THC represents a group of closely related compound, cannabinoids and is commonly considered to be Cannabis' primary psychoactive components. Over 100 cannabinoids have been identified, but only a few of the major cannabinoids have been categorized for biological activities, like cannabidiol and cannabinol (CBN) [13].

The FDA regulates two cannabinoids, which can thus be legally sold under federal law in the United States. Another, Dronabinol, comprises THC trans-isomer soluble in sesame oil that is found in a gelatin capsule. In this drug the THC is extracted synthetically. The medication is FDA approved for conditions, chemotherapy-induced nausea and vomiting (CINV) and anorexia in patients with the acquired immunodeficiency syndrome related to weight loss. The second, Nabilone, is a psychoactive chemical which mimics THC’s action. It is approved by the FDA to treat CINV. Both drugs are available in capsule form only. Nabilone is classified as a prescription drug under Schedule II while dronabinol is classified as a controlled drug under Schedule III. The effectiveness of these medications for the treatment of acute nausea and vomiting is limited by the need for oral treatment and stomach ingestion, as well as the length of time needed to achieve plasma peaks [14].

Today marijuana's medicinal applications are far more constrained. For the most part, in conventional treatment efforts, pharmaceutical products such as Levontradol, Nabilone, and Marinol have been used which chemically mimic the cannabinoids. These synthetics have been used as they provide a more stable way of providing the active materials of tetrahydrocannabinol, synthetics may provide a better solution. But it was cannabis THC that opened the way to synthesis. And there is a rapid impact when marijuana is smoked, rather than when synthetic oral THC is asked to take. Therefore, cannabis is more effective in its natural form.

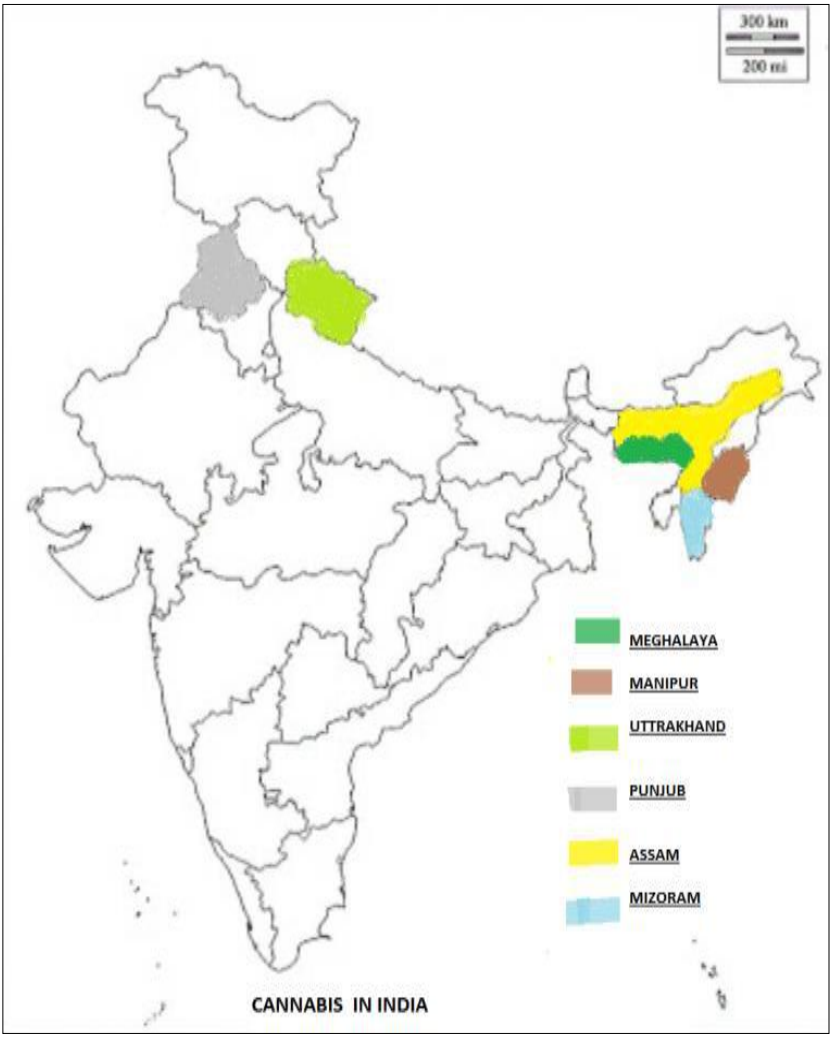


Fig 1: Cannabis in India. (Internet Sources)

Botanical name: *Cannabis sativa* Linne

Fig 2: Plant of *Cannabis sativa*

Taxonomical classification

According to the botanical classification, the plant is classified as follows

Table 1: Taxonomical classification of *Cannabis sativa*

Kingdom	*Plantae*
Division	Tracheophyta
Class	Angiospermae
Order	Urticales
Family	Cannabaceae
Genus	*Cannabis*
Species	*Sativa linne*

Review of literature

Audu *et al*., conducted the study on Phytochemical, proximate composition, amino acid profile and characterization of Marijuana (*Cannabis sativa* L.). The phytochemical and proximate compositions, amino acid profile and characterization of *Cannabis sativa* leaves, stem and seeds were conducted to provide baseline information on its potent in feed materials for its subsequent utilization in supplementing fish nutrition in aquaculture. Phytochemical analysis of the leaves revealed the presence of alkaloids, flavonoids, cardiac glycosides, resins, terpins and steroids while the proximate composition had elevated levels of 6.87% moisture, 23% crude protein, 19.97% lipid and 11.8% Ash; 18.95% fibre and 39.70% NFE in the stem and 25.36% crude fiber content in seeds. *C. sativa* leaf contains 9

Essential Amino Acids (EAA), which have good concentration of methionine and lysine. Characterization of the leaf extracts revealed six clearly-pigmented spots with the highest travelled as cannabinol (CBN). The implications of these findings indicate that *C. sativa* has potential inclusion in fish feeds requirement, ameliorating stress conditions during handling, sampling and transportation as well as possible utilization to anesthetize fish going by the array of the bioactive compounds present in the crude leaf extracts of the plant.

Ayenigbara, studied the medical utility of *Cannabis sativa*. *Cannabis sativa* (Marijuana) is a crop which is grown all over the world. The plant is one of the most hated, maligned and detested anywhere in the world and huge sums of money and efforts are being expended to annihilate its production, distribution marketing and consumption. *Cannabis sativa* is erroneously believed to cause deleterious health problems among other controversies. However, studies have shown that this plant, apart from being regarded as one of the five sacred crops, has a lot of medicinal, recreational, commercial and social uses.

Huestis *et al*., conducted the study on cannabinoids concentration in hair from documented cannabis users. Fifty-three head hair specimen were collected from 38 males with a history of cannabis use documented by questionnaire, urinalysis and controlled, double blind administration of tetrahydrocannabinol (THC) is an institutional review board approved protocol. The subjects completed a questionnaire indicating daily use was also documented by positive cannabinoids urinalysis, a hair specimen was collected from each subject and they were admitted to a closed research unit.

Arno Hazekamp *et al*., 2010, studied about, Review on clinical studies with cannabis and cannabinoids 2005-2009. To date, a large number of controlled clinical trials have been done evaluating the therapeutic applications of cannabis and cannabis-based preparations. In 2006, an excellent review was published, discussing the clinical trials performed in the period 1975 to June 2005 [Ben Amar 2006]. The current review reports on the more recent clinical data available. A systematic search was performed in the scientific database of PubMed, focused on clinical studies that were randomized, (double) blinded, and placebo-controlled. The period screened was from July 1, 2005 up to August 1, 2009. The key words used were: cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador and Sativex. For the final selection, only properly controlled clinical trials were retained. Open-label studies were excluded, except if they were a direct

continuation of a study discussed here. Thirty-seven controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Based on the clinical results, cannabinoids present an interesting therapeutic potential mainly as analgesics in chronic neuropathic pain, appetite stimulants in debilitating diseases (cancer and AIDS), as well as in the treatment of multiple sclerosis.

Joan L. Kramer, MD, studied on, Medical Marijuana for Cancer, Marijuana has been used for centuries, and interest in its medicinal properties has been increasing in recent years. Investigations into these medicinal properties has led to the development of cannabinoid pharmaceuticals such as dronabinol, nabilone, and nabiximols. Dronabinol is best studied in the treatment of nausea secondary to cancer chemotherapy and anorexia associated with weight loss in patients with acquired immune deficiency syndrome, and is approved by the US Food and Drug Administration for those indications. Nabilone has been best studied for the treatment of nausea secondary to cancer chemotherapy. There are also limited studies of these drugs for other conditions. Nabiximols is only available in the United States through clinical trials, but is used in Canada and the United Kingdom for the treatment of spasticity secondary to multiple sclerosis and pain. Studies of marijuana have concentrated on nausea, appetite, and pain. This article will review the literature regarding the medical use of marijuana and these cannabinoid pharmaceuticals (with emphasis on indications relevant to oncology), as well as available information regarding adverse effects of marijuana use. CA Cancer J Clin 2015;65:109-122. V C 2014 American Cancer Society.

Ethan B. Russo *et al*., 2008, studied on, Phytochemical and genetic analyses of ancient cannabis from Central Asia. The Yanghai Tombs near Turpan, Xinjiang-Uighur Autonomous Region, China have recently been excavated to reveal the 2700-year-old grave of a Caucasoid shaman whose accoutrements included a large cache of cannabis, superbly preserved by climatic and burial conditions. A multidisciplinary international team demonstrated through botanical examination, phytochemical investigation, and genetic deoxyribonucleic acid analysis by polymerase chain reaction that this material contained tetrahydrocannabinol, the psychoactive component of cannabis, its oxidative degradation product, cannabinol, other metabolites, and its synthetic enzyme, tetrahydrocannabinolic acid synthase, as well as a

novel genetic variant with two single nucleotide polymorphisms. The cannabis was presumably employed by this culture as a medicinal or psychoactive agent, or an aid to divination. To our knowledge, these investigations provide the oldest documentation of cannabis as a pharmacologically active agent, and contribute to the medical and archaeological record of this pre-Silk Road culture.

Marilyn A. Huestis *et al*., 2007, studied on, Cannabinoid Concentrations in Hair from Documented Cannabis Users. fifty-three head hair specimens were collected from 38 males with a history of cannabis use documented by questionnaire, urinalysis and controlled, double blind administration of Δ9tetrahydrocannabinol (THC) in an institutional review board approved protocol. The subjects completed a questionnaire indicating daily cannabis use (N = 18) or non-daily use, i.e. 1 to 5 cannabis cigarettes per week, (N = 20). Drug use was also documented by a positive cannabinoid urinalysis, a hair specimen was collected from each subject and they were admitted to a closed research unit. Additional hair specimens were collected following smoking of two 2.7% THC cigarettes (N = 13) or multiple oral doses totaling 116 mg THC (N = 2). Cannabinoid concentrations in all hair specimens were determined by ELISA and GCMSMS. Pre- and post dose detection rates did not differ statistically, therefore, all 53 specimens were considered as one group for further comparisons. Nineteen specimens (36%) had no detectable THC or 11-nor-9-carboxy-THC (THCCOOH) at the GCMSMS limits of quantification (LOQ) of 1.0 and 0.1 pg/mg hair, respectively. Two specimens (3.8%) had measurable THC only, 14 (26%) THCCOOH only, and 18 (34%) both cannabinoids. Detection rates were significantly different ($p < 0.05$, Fishers' exact test) between daily cannabis users (85%) and non-daily users (52%). There was no difference in detection rates between African American and Caucasian subjects ($p > 0.3$, Fisher's exact test). For specimens with detectable cannabinoids, concentrations ranged from 3.4 to > 100 pg THC/mg and 0.10 to 7.3 pg THCCOOH/ mg hair. THC and THCCOOH concentrations were positively correlated ($r = 0.38$, $p < 0.01$, Pearson's product moment correlation). Using an immunoassay cutoff concentration of 5 pg THC equivalents/ mg hair, 83% of specimens that screened positive were confirmed by GCMSMS at a cutoff concentration of 0.1 pg THCCOOH/mg hair.

Esra M.M. Ali. *et al*., 2011, studied on Antimicrobial Activity of *Cannabis sativa* L. The oil of the seeds, petroleum ether and methanol extracts of the whole plant of *Cannabis sativa* belonging to the family Cannabinaceae were screened for their antimicrobial activity against two

Gram positive organisms (Bacillus subtilis, Staphylococcus aureus), two Gram negative organisms (Escherichia coli, Pseudomonas aeruginosa) and two fungi namely Aspergillus niger and Candida albicans using the cup plate agar diffusion method. The oil of the seeds of *Cannabis sativa* exerted pronounced antibacterial activity (21 - 28 mm) against Bacillus subtilis and Staphylococcus aureus, moderate activity (15 mm) against Escherichia coli and high activity (16 mm) against Pseudomonas aeruginosa and inactive against the two fungi tested. The petroleum ether extract of the whole plant exhibited pronounced antibacterial activity (23 - 28 mm) against both Bacillus subtilis and Staphylococcus aureus organisms, high activity (16 mm) against Escherichia coli and inactive against Pseudomonas aeruginosa and both fungi. The methanol extract of the whole plant showed also pronounced antibacterial activity (29 mm) against Bacillus subtilis, low activity (12 mm) against Staphylococcus aureus and high activity (16 - 18 mm) against both Gram negative organisms, inactive against Aspergillus niger and low activity (13 mm) against Candida albicans. The minimum inhibitory concentrations of *Cannabis sativa* methanol extracts of the seeds and the whole plant against the standard organisms were determined using the agar plate dilution method. The standard organisms were tested against reference antibacterial and antifungal drugs and the results were compared with the activity of the extracts.

Istok Nahtigal *et al*., 2016, study about, The pharmacological properties of cannabis. The efforts to understand the nature of how the consumption of cannabis affects the human body are ongoing, complex, and multifaceted. Documentation on the use of cannabis dates back thousands of years; however, it is only now with the recent softening of legal restrictions that modern research approaches have been able to initiate an appropriate level of detailed investigations. For clinicians, researchers and policy makers, this chapter reviews the general structure of cannabinoids, the current understanding of cannabinoids on cellular systems, the difference between inhalation and oral consumption on cannabinoid bioavailability, the variance among purified cannabinoids versus whole plant extract, and the potential activities of another prominent family of secondary metabolites found in cannabis, the terpenes.

Sabrina Giacoppo. *et al*., 2014, study on, Cannabinoids: New Promising Agents in the Treatment of Neurological Diseases. Nowadays, *Cannabis sativa* is considered the most extensively used narcotic. Nevertheless, this fame obscures its traditional employ in native medicine of South Africa, South America, Turkey, Egypt and in many regions of Asia as a therapeutic

drug. In fact, the use of compounds containing Cannabis and their introduction in clinical practice is still controversial and strongly limited by unavoidable psychotropic effects. So, overcoming these adverse effects represents the main open question on the utilization of cannabinoids as new drugs for treatment of several pathologies. To date, therapeutic use of cannabinoid extracts is prescribed in patients with glaucoma, in the control of chemotherapy-related vomiting and nausea, for appetite stimulation in patients with anorexia-cachexia syndrome by HIV, and for the treatment of multiple sclerosis symptoms. Recently, researcher efforts are aimed to employ the therapeutic potentials of *Cannabis sativa* in the modulation of cannabinoid receptor activity within the central nervous system, particularly for the treatment of neurodegenerative diseases, as well as psychiatric and non-psychiatric disorders. This review evaluates the most recent available data on cannabinoids utilization in experimental and clinical studies, and highlights their beneficial effects in the prevention of the main neurological diseases and for the clinical treatment of symptoms with them correlated.

T.S. Geetha and N.Geetha (2014), performed phytochemical screening, quantitative analysis of primary and secondary metabolites of *Cymbopogan citratus* (DC), leaves from Kodaikanal hills, Tamil Nadu. The results obtained indicates that the species have the potential to act as a source of useful drugs because of presence of various phytochemical components such as carbohydrate, protein, lipids, phenols, flavonoids and tannin.

AIMS and objective

1. Phytochemical analysis of selected sample by following various phytochemical tests.
2. To estimation of protein by Lowry's method.
3. To determine the Antioxidant activity of the selected plant
4. To determine the Antimicrobial activity of the plant.
5. Quantitative analysis of the sample by FTIR and GC/MS.

Materials & methods

Sample collection

The *Cannabis sativa* plants were collected from various region of Guwahati. The leaf part of the plants was separated from the plant after collection and it was then shade dried. The dried plant leaf was ground in powdered form and stored in an air tight container.

Extracting process

- **Water extract:** 10 gm of air-dried plant extract powder was taken in 100ml of distilled water for 72hours in dark. After that it was stored in refrigerator for further use.
- **Methanol extract:** 46gm of air-dried extract powder was taken in 350ml of methanol in soxhlet apparatus and then the extract was allowed to evaporate till dryness. The dried extract was then stored in refrigerator for further use.
- **Chloroform extract:** 38gm of air dried extract powder was taken in 300ml of chloroform in soxhlet apparatus and then the extract was allowed to evaporate till dryness. The dried extract was then stored in refrigerator for further use.

Phytochemical analysis

After the successful extraction of the plant, the resulted extract was subjected to various phytochemical screening. Qualitative analysis was performed to detect the presence of various bioactive metabolites by using standard protocols.

Detection of carbohydrate

a) Molish's reagent: Aqueous or alcoholic solution of substances+ 10% alcoholic solution of α-napthol, shake well then added concentrated sulfuric acid along the side of the tube. A violet ring at the junction of two liquid confirmed the presence of carbohydrate.

b) Fehling's reagent: 2ml of Fehling's solution A + 2ml of Fehling's solution B + 2ml of extract. Boiled, brick red precipitate appeared indicating reducing sugar present.

c) Barfoed's reagent: 2ml of extract + 2ml of Barfoed's reagent. Boiled, yellow precipitate appeared then reducing sugar present.

d) Benedict's solution: 5ml of Benedict reagent + 3ml of test solution mixed well then boil in water bath. If appearance of brick red ppt. at the bottom of the test tube then monosaccharides are present.

Detection of protein

a) Xanthoproteic test: the extract treated with few drops of conc. Nitric acid solution. Formation of yellow color indicates the presence of protein.

Detection of glycoside

a) Liebermann's test: 2ml of the organic extract was dissolved in 2ml of chloroform and 2ml of acetic acid was added and the solution cooled well in ice. Sulphuric acid was then added carefully. A color change from violet to blue to green indicates the presence of steroid nucleus.

b) Salkowski test: 2ml of each extract was dissolved in 2ml of chloroform. 2ml of sulphuric acid was added carefully and shaken gently. A reddish brown color indicates the presence of steroid ring.

Detection of tanin

a) Deposition of red precipitate when extract of each plant sample was boiled with 1% aqueous Hydrochloric acid was taken as an evidence for the presence of phlobatanins.

Detection of saponin

a) 5ml of extract was shaken vigorously with 5ml of distilled water in a test tube and warmed. The formation of stable form was taken as an indication for presence of 107aponins. The frothing was mixed with 3 drops of olive oil and shaken vigorously and then emulsion was formed.

b) Foam test: small amount of extract was shaken with little quantity of water. If foam produced persists for ten min it indicates the presence of 107aponins.

Detection of flavonoids

a) 2ml of dilute sodium hydroxide was added to 2ml of extract. The appearance of yellow color indicates the presence of flavonoids.

b) Flavonoids give a dull green/reddish brown color on treatment with ferric chloride solution.

Detection of steroids

a) Liebermann's test: 2ml of the organic extract was dissolved in 2ml of chloroform and 2ml of acetic acid was added and the solution cooled well in ice. Sulphuric acid was then added carefully. A color change from violet to blue to green indicates the presence of steroid nucleus.

b) Salkowski test: 2ml of each extract was dissolved in 2ml of chloroform. 2ml of sulphuric acid was added carefully and shaken gently. A reddish brown color indicates the presence of steroid ring.

Detection of terpenoids

a) Carr-Price reagent (20% antimony chloride in chloroform): Terpenoid gives deep blue color when treated in chloroform solution with either conc. Sulphuric acid or antimony chloride.

Detection of phenolic compounds

a) The intense green, purple, blue or black color many of them gives in solution when 1% aqueous or alcoholic ferric chloride is added. This procedure is modified by using a fresh aqueous mixture of 1% ferric chloride and 1% potassium ferricyanide.

Protein estimation by lowry's method

- Lowry's reagent or alkaline copper sulfate solution:

Solution A: 2% sodium carbonate in 0.1N NaOH and solution B: 0.5% copper sulfate solution in 1% sodium potassium tartarate solution.

Mix 50ml of solution A with 1ml of Solution B.

- Folin-ciocalteau reagent
- Standard protein solution: dissolve 200mg of BSA in 100ml distilled water in a flask.

    a) Pipette out into a series of tubes 0.2,0.4,0.6,0.8, and 1.0 ml of protein solution and make up the total volume to 1ml with addition of water.

    b) To each tube 5ml of the alkaline-copper sulfate solution in pipette out, mixed well and allowed to standard at room temperature for 10-15min.

    c) 0.5ml of the reagent in pipettes out into each tube, mixing rapidly after each addition.

    d) The tubes are left as such for 30min and the blue colour formed is measured at 700nm

    e) Prepare a blank with 1ml of distilled water, instead of protein solution and with 1ml of unknown solution and proceeds as per standards.

Prepare a calibration curve with mg of protein present in a given unknown sample.

Antioxidant activity

Requirement

- Preparation of 40µl, 70µl, 100µl and 130µl conc. Of sample
- 100ml methanol
- 0.1µM of DPPH

DPPH scavenging assay

The antioxidant activity of methanol and chloroform extract of the plant material was assayed according to the method of Kaur et.al (2012). DPPH (2,2-diphenyl picryl hydrazyl). The commercially available stable free radical that is purple in colour. When DPPH in incubation time, the purple colour converted into yellow colour. The preparation of test extracts with concentration of 1000µg/ml by dissolving 20mg of the methanol and chloroform extract and made up the volume 20ml by methanol or water. Different concentration of plant extracts (40µg/ml-130µg/ml) was added and the volume was made 1ml with distilled water after that added 2ml of methanolic DPPH solution and final volume is made up 3ml. the adsorbance was determined by absorption at 517nm after 30 min against a blank solution containing methanol without DPPH. The DPPH radical scavenging assay of the different cannabis sample extract was calculated by the formula.

$$\%\text{inhibition} = \frac{A\,control - A\,sample}{A\,control} \times 100$$

Antimicrobial activity

Antimicrobial activity of the extract was determined by the agar disc diffusion method. *S.aureus* bacteria were grown on blood agar media and *E.coli* on nutrient agar, both at 37℃ for 24 hours. Several colonies of overnight cultured bacteria were transferred into nutrient broth and the density was adjusted to McFarland standard 0.5, or approximately equivalent to 10^8 CFU/ml. the density-adjusted bacteria were swabbed on Mueller Hinton Agar (MHA). The extract (methanol and chloroform) were dissolved by 20% dimethyl sulfoxide (DMSO). To test each extract sterile filter paper discs of 6mm in diameter were placed on MHA plates. Sample of each extract (methanol and chloroform) were applied to individual disc separately. 20% DMSO was applied to other discs as negative control. Penicillin disc served as positive control. The plates were then incubated an aerobically for 24 hrs at 37℃. Antibacterial activity was evaluated by measuring the diameter of inhibition zones.

Test microorganisms

Stephylococcus aureus, and, *E. coli*

Qualitative and quantitative analysis

Sample extracted from *Cannabis sativa* in solvent methanol was send for GC-MS and FTIR, in Biotech Park, Guwahati.

Observation and results

Extract yield

Table 2: Extract yield

Sl No.	Area from where saple is collected	Solvent	Colour of the extract	Yield of the extract (gm)	Yield % (% ww)
1	Panikhaiti	Methanol	Green	6gm	12.6%
2	Hatisila	chloroform	Green	4.5 gm	11.25%

Phytochemical test

Methanol extract

Detection of carbohydrates

Table 3: Detection of carbohydrates for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Molish's test	Carbohydrates	*
Fehling's test	Reducing sugar	*
Barfoed's test	Monosaccharides	+
Benedict's test	Reducing sugar	+

Detection of protein

Table 4: Detection of protein for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Xanthoproteic test	Protein	*

Detection of glycoside

Table 5: Detection of glycoside for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Liebermann's test	Glycoside	*
Salkowski's test	Glycoside	+

Detection of tannin

Table 6: Detection of tannin for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Test for phlobatannis	phlobatannis	+

Detection of saponin

Table 7: Detection of saponin for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Olive oil test	Saponin	+
Foam test	Saponin	+

Detection of flavonoids

Table 8: Detection of flavonoids for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Sodium hydroxide	Flavonoids	-
Ferric chloride	Flavonoids	+

Detection of steroids

Table 9: Detection of steroids for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Liebermann’s test	Glycoside	*
Salkowski’s test	Glycoside	+

Detection of terpenoids

Table 10: Detection of terpenoids for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Carr-price reagent test	Terpenoids	+

Detection of phenolic compounds

Table 11: Detection of phenolic compound for methanol extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Ferric chloride test	Phenolic componds	+

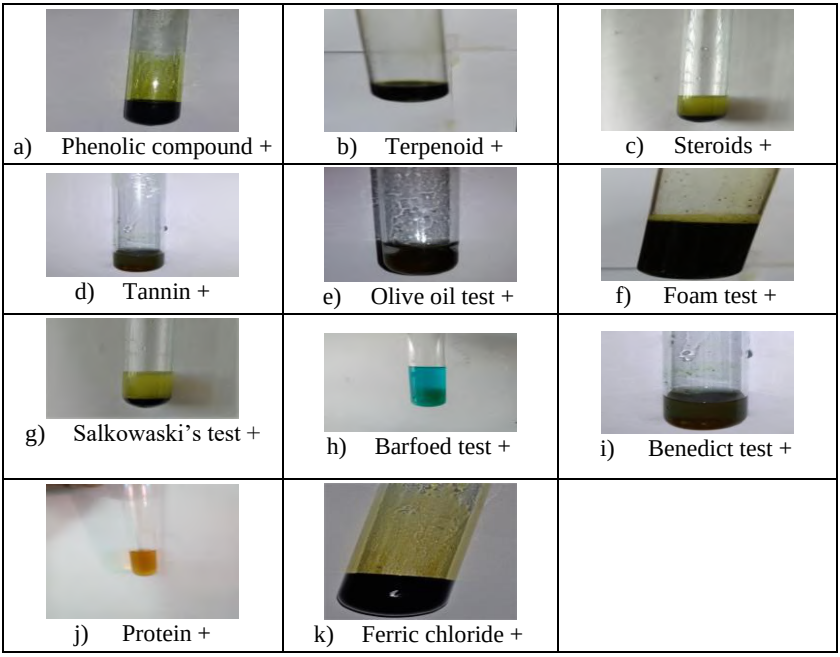


Fig 3: Phytochemical test results. Key words (+) = positive. The reported results shows, presence of Phenolic compounds, Terpenoids, Steroids, Protein, Salkowaski's test confirms the presence of glycosides, olive oil test and foam test confirms the presence of Saponin, Barfoed test and Benedict test confirms the presence of Carbohydrates, ferric chloride test confirms Flavonoids.

Chloroform extract

Detection of cabohydrates

Table 12: Detection of protein for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Molish's test	Carbohydrates	+
Fehling's test	Reducing sugar	*
Barfoed's test	Monosaccharides	+
Benedict's test	Reducing sugar	+

Detection of protein

Table 13: Detection of protein for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Xanthoproteic test	Protein	+

Detection of glycoside

Table 14: Detection of glycoside for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Liebermann's test	Glycoside	-
Salkowski's test	Glycoside	+

Detection of tannin

Table 15: Detection of tannin for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Test for phlobatannis	Phlobatannis	+

Detection of saponin

Table 16: Detection of saponin for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Olive oil test	Saponin	+
Foam test	Saponin	+

Detection of flavonoids

Table 17: Detection of flavonoids for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Sodium hydroxide	Flavonoids	-
Ferric chloride	Flavonoids	-

Detection of steroids

Table 18: Detection of steroids for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Liebermann's test	Glycoside	-
Salkowski's test	Glycoside	+

Detection of terpenoids

Table 19: Detection of terpenoids for chloroform extract, key words (+) = positive, (-) = negative, (*) = Result not found

Test	Inference	Result
Carr-price reagent test	Terpenoids	+

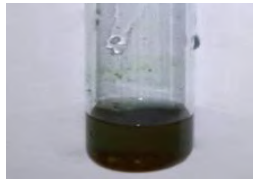
Detection of phenolic compounds

Table 20: Detection of phenolic compound for chloroform extract, key words (+) = positive, (-) = negative, (*) =

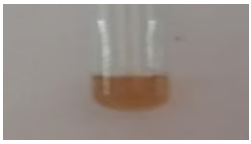
Test	Inference	Result
Ferric chloride test	Phenolic componds	+

a) Barfoed test +

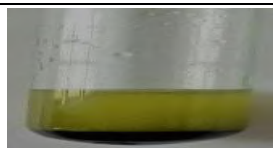
b) Molish's test



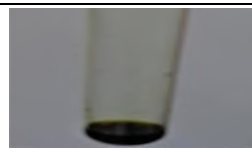
c) Benedict test+



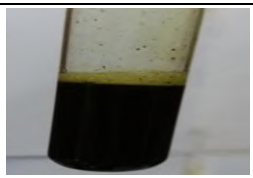
d) Protein +



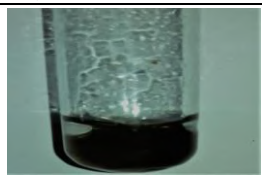
e) Salkowaski's test



f) Tannin +

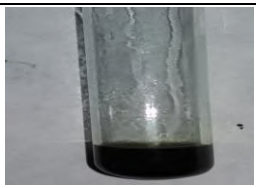


g) Foam test +



h) Olive oil test +

i) Flavonoids +



j) Phenol +

Fig 4: Phytochemical test results. Key words (+) = positive. the reported results shows, presence of Phenolic compounds, Terpenoids, Steroids, Protein, Salkowaski's test confirms the presence of glycosides, olive oil test and foam test confirms the presence of Saponin, Barfoed test, Molish's test and Benedict test confirms the presence of Carbohydrates, ferric chloride test confirms Flavonoids.

Protein estimation by lowry's method

Table 21: Estimation of protein by Lowry's method, in which the absorbance of methanol extract is 0.774mg/ml and absorbance of chloroform extract is 0.43mg/ml.

Concentration	O.D(650nm)
0.2ml	0.22
0.4ml	0.44
0.6ml	0.7
0.8ml	0.92
1.0ml	1.14
Blank	0.00
Methanol extract	0.774
Chloroform extract	0.43

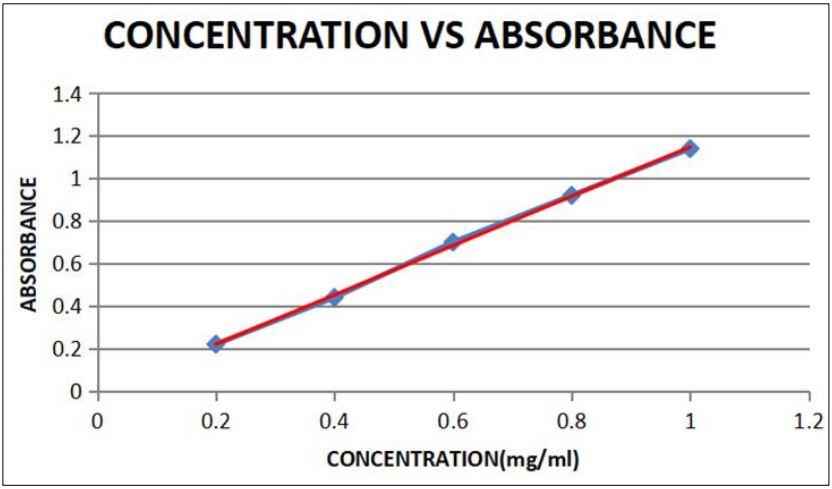


Fig 5: Graphical representation to estimate protein from Lowry's method, methanol have absorbance of 0.774nm and the concentration of the sample is 0.68mg/ml and chloroform have absorbance of 0.43nm and the concentration of the sample is 0.38mg/ml. therefore it can be concluded that the protein concentration of methanol extract i.e., 0.63mg/ml more than chloroform extract.

Antioxidant activity by DPPH

Methanol extract

Table 22: DPPH scavenging assay %inhibition:

Concentration Of Sample	**Absorbance**
40µl	0.337
70 µl	0.334

100µl	0.309
130 µl	0.300

Table 23: %inhibition for methanol extract, The result indicates that the antioxidant property in methanol extract was 64% in 130 µl of concentration

Concentration of sample	Methanol extract sample
40 µl	59.44%
70 µl	60%
100 µl	63%
130 µl	64%

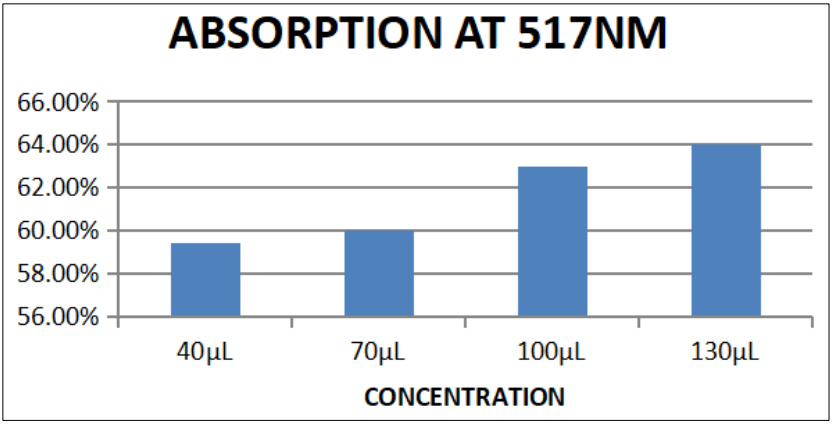


Fig 6: Graphical representation of % inhibition of methanol extract

Chloroform extract

Table 24: DPPH scavenging assay %inhibition:

Concentration of sample	Absorbance (715µl)
40 µl	0.413
70 µl	0.367
100 µl	0.377
130 µl	0.380

Table 25: %inhibition for choloform extract. The result indicates that the antioxidant property in methanol extract was 55.8% in 70 µl of concentration

Concentration of sample	Chloroform extract sample
40 µl	50.3%
70 µl	55.8%
100 µl	54.63%
130 µl	54.27%

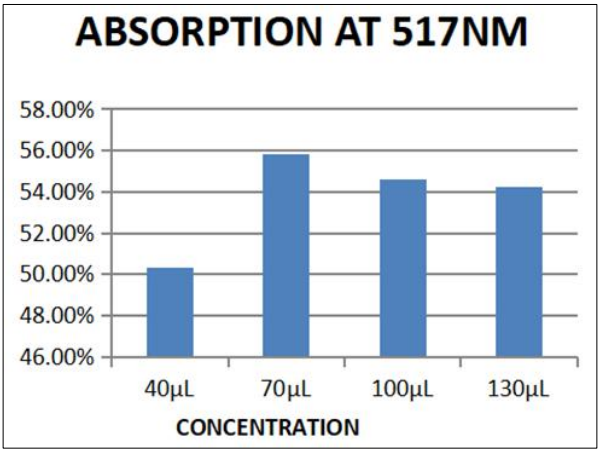


Fig 7: Graphical representation of % inhibition of chloroform extract.

Antimicrobial activity

Evaluation of the extract against *S. aureus*

Methanol extract: The highest antimicrobial activity against *S.aureus* in Mueller-Hinton Agar was shown by methanol extract, with a zone of inhibition of 14mm.

Chloroform extract: It was found that chloroform extract have effect on *S.aureus* with zone of inhibition of 11mm.

Evaluation of the extract against *E.coli*

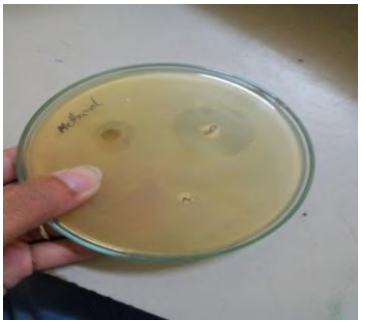
Methanol extract: Methanol extract was found to have the highest effect on *E.coli*. The zone of inhibition was found to be 12mm.

Chloroform extract: The zone of inhibition for chloroform extract was found to be 10mm against *E.coli* on MHA media.

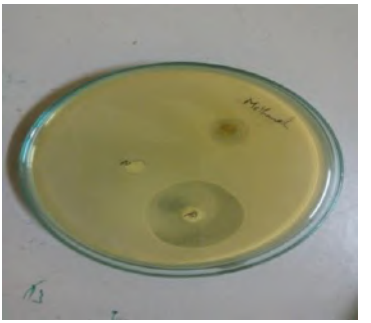
Antimicrobial evaluation

Table 26: Antimicrobial evaluation of extract of *Cannabis sativa*. The zone of inhibition was measured in millimeter and it was found to be 14mm and 12mm for methanol extract and 11 and 10mm for chloroform extract against *S.aureus* and *E.coli*. Hence, methanol extract shows highest possibility of using as a bio-control against pathogen.

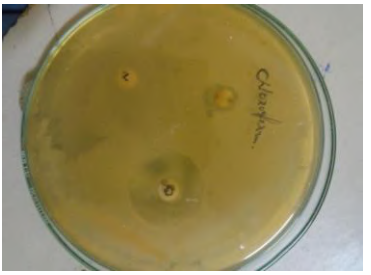
Test organisms	Media	Inhibition zone(mm)	
		methanol	chloroform
Staphylococcus aureus	MHA	14	11
E.coli	MHA	12	10



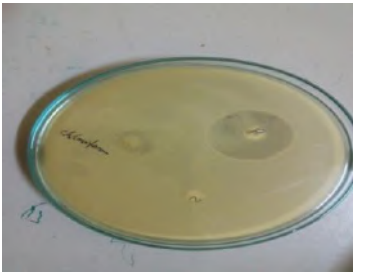
1. Zone of inhibition against *S.aureus* is 14mm



2. Zone of inhibition against *E.coli* is 12mm



3. Zone of inhibition against *S.aureus* is 11mm



4. Zone of inhibition against *E.coli* is 10mm

Fig 8: Antimicrobial test result. a) And b), shows ZOI of 14 and 12mm against *S.aureus* and *E.coli.* Whereas, c) and d), shows ZOI of 14 and 12mm against *S.aureus* and *E.coli.*

Result for FTIR

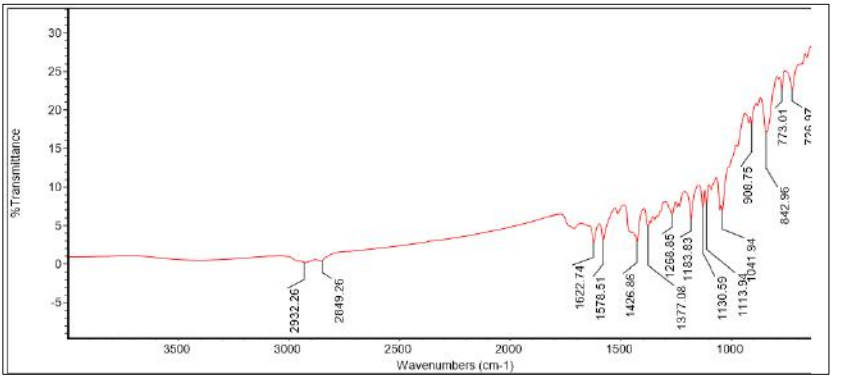


Fig 9: FTIR result. The FTIR result is compared with literature review of tetrahydrocannabinol, and the FTIR result is same as the literature review. Hence it can be concluded that the sample contain the pure compounds i.e., Tetrahydrocannabinol.

Table 27: The result shows CH stretching, C=C stretching, C-H bending, S=O stretching, C-O stretching, C-Cl stretching, C-H bending, and C=C bending.

Absorption(S)(CM^{-1})	Functional Group
2932.26	CH stretching
2849.26	CH stretching
1622.75	C=C stretching
1377.08	C-H bending
1268.83	N-O stretching
1183.83	S=O stretching
1130.59	C-O stretching
908.75	C=C stretching
842.96	C-Cl stretching
773.01	C-H bending
726.97	C=C bending

Result for GC

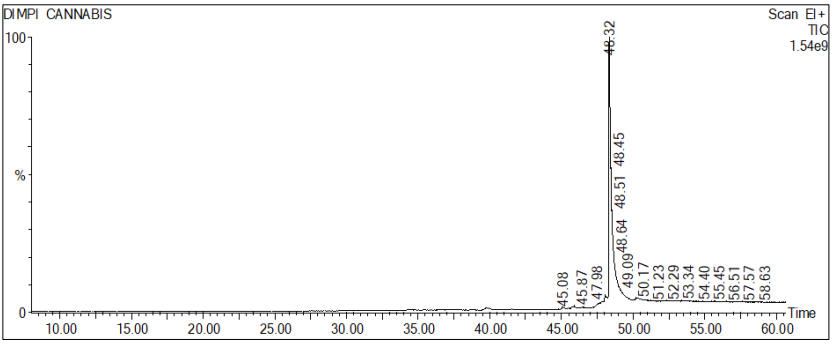


Fig 10: Result of GC, Shows the pick of 48.32, which conclude it was the pure compound of the sample i.e., Tetrahydrocannabinol.

Discussion

The *Cannabis sativa* leaves were exposed to methanol and chloroform extraction. The leaf extract was tested for phytochemical content, Lowry's method of estimating the protein, and antimicrobial and antioxidant activity assessment. Many phytochemical constituents were contained in the sample.

From a 45gm sample, the yield percentage of the extract was easily found to be maximum in methanol i.e., 6gm, followed by chloroform extract i.e., 4.5 gm. The yield from 10 gm of sample for Aqueous extract was found to be 5gm by cold extract method.

The Phytochemical analysis of this plant showed the presence of various active components like flavonoids, saponins, glycoside, steroids, carbohydrates and proteins which are in accordance to a previous study by Audu *et al.,* 2014.

The maximum protein concentration in methanol extract is 0.68mg / ml, and the protein concentration for chloroform extract is 0.38mg/ml, as measured by the Lowry test. These findings suggest that the methanol extract protein concentration is higher than that of the chloroform extract.

Through this method, the knowledge gathered from conventional cultures about the plant's usage was coupled with the laboratory studies. Antimicrobial activity has been recorded when the inhibition zone is larger than 3 mm. Different canabis extract species examined had antibacterial activity against *S.aureus* and *E.coli.* Heavy antibacterial activity in methanol extract of plant against *S.aureus* and *E.coli*, in similar line as reported by Ali *et al*., 2012.Inhibition zone for methanol extract against *S.aureus* and *E.coli* were recorded to be 14mm and 12mm on MHA respectively. A notable antimicrobial activity was also seen in chloroform extract.

The scientific and dietary literature commonly dicusses free radicals and antioxidants. Antioxidant is designed to prevent formation and to counteract the activities of reactive oxygen and nitrogen species, which are created *in vivo* and cause DNA, lipids, proteins and other biomolecules to damage. The highest % inhibition in methanol extract was 64% in concentration 130µl and in chloroform extract the highest %inhibition was 55.8% in 70µl concentration. Therefore the result indicated the possibility of using the methanol extract shows maximum of 64% of antioxidant property (130µl). Hence, the results showed the validity and clinical use of methanol extract of *Cannabis sativa* in the control of antioxidant activity (Remella *et al*., 2015)

FTIR spectra were recorded in the scan range of400-4,000 cm^{-1} with a resolution in Thermo Scientific Nicolet iS50 FT-IR Spectrometer. Fourier Transform Infrared Spectrophotometer is the most solid instrument for recognizing the functional groups of the microbial samples which gave some important evidence for functional behaviour of the compounds especially for comparison with past studies. The stretching frequencies at 2932 and 2849cm^{-1} indicate the presence of aromatic rings which appeared for the stretching frequency of aromatic CH units. The carbonyl stretching frequency for the C=O unit has appeared at 1623 cm^{-1} and the stretching frequency of C=C for aromatic rings appeared at 1578cm^{-1}. The stretching frequency around 1183 cm -1 indicates the presence of the C-O unit which is present in the carboxylate group.

Conclusion

In the present study the Phytochemical screening for *Cannabis sativa* show the presence of active compounds like steroids, terpenoids, flavonoids, glycosides, carbohydrate, and protein from methanol and chloroform extract. The term phytochemicals refers to the wide varieties of compounds made by plants and is mainly used to describe those compounds that may affect human health.

On the basis of Antimicrobial assay the study, Methanol extract of *Cannabis sativa*, showed a notable antimicrobial effect against *S.aurues and E.coli*. The effective result of the methanolic root extract was probably because of the combination of compounds extracted in methanol.

On the basis of the antioxidant activity of *Cannabis sativa* was found. These findings suggest that the selected phytoextract possess antioxidant properties and can be used for scavenger of free radicals that are found inside human body. Antioxidant activity was confirmed by the selected plant and the result reveal the extract showed its efficacy for scavenger free radicals.

Analyzing phytochemicals, with antimicrobial and antioxidants activity in plants will provide information, how effective the plant is medicinally. The compounds extracted from the various solvent may be used in further studies for isolation and characterization discovery of major bioactive products may serve in new drug formation and lead to the development of new pharmaceuticals products.

And finally the sample send for FTIR and GC-MS test concluded that the compound in the sample is Tetrahydrocannabinol.

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