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Minireview

Chemical constituents of marijuana: The complex mixture of natural cannabinoids

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Abstract

The cannabis plant (*Cannabis sativa* L.) and products thereof (such as marijuana, hashish and hash oil) have a long history of use both as a medicinal agent and intoxicant. Over the last few years there have been an active debate regarding the medicinal aspects of cannabis. Currently cannabis products are classified as Schedule I drugs under the Drug Enforcement Administration (DEA) Controlled Substances act, which means that the drug is only available for human use as an investigational drug.

In addition to the social aspects of the use of the drug and its abuse potential, the issue of approving it as a medicine is further complicated by the complexity of the chemical make up of the plant. This manuscript discusses the chemical constituents of the plant with particular emphasis on the cannabinoids as the class of compounds responsible for the drug's psychological properties.

Keywords: *Cannabis sativa*; Cannabis constituents; Marijuana; Cannabinoids

Contents

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Chemistry and constituents of *Cannabis sativa* L.

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, the most recent of which are those by Russo (2001, 2002) and ElSohly (2002).

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*-(6a*R*,10a*R*)-tetrahydrocannabinol (Δ^9-THC) being the most psychologically active constituent (Mechoulam and Gaoni, 1967a). 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 (Pate, 1999).

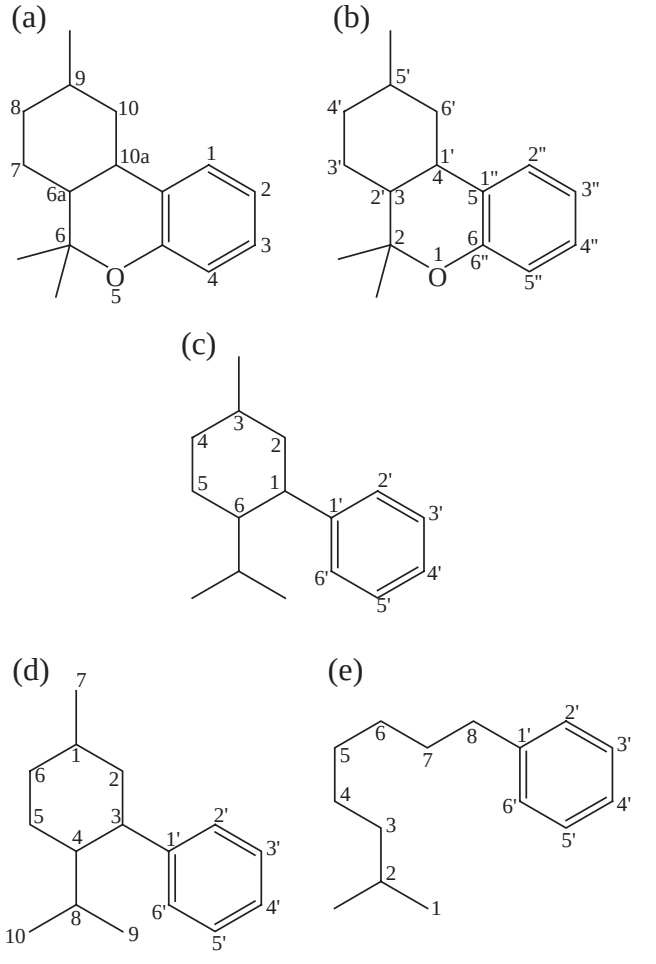

Fig. 1. Numbering of cannabinoids. (a) Dibenzopyran, (b) numbering used by Todd, (c) diphenyl, (d) monoterpene based on *p*-cymene and (e) monoterpene numbering.

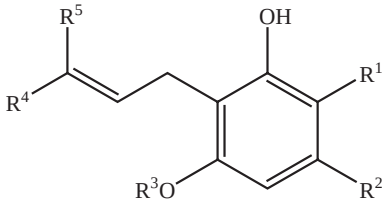

Fig. 2. CBG-type cannabinoids.

The total number of natural compounds identified in *C. sativa* L. in 1980 was 423 (Turner et al., 1980) and in 1995 was 483 (Ross and ElSohly, 1995). This review reports 6 new compounds; 4 new cannabinoids and 2 new flavonoids (Table 1).

Cannabinoids: 70 known (4 new)

The typical C_{21} group of compounds present in *C. sativa* L. is known as cannabinoids and includes their analogs and transformation products (Razdan, 1987). Five different numbering systems have been used for the cannabinoids (Fig. 1; Eddy, 1965). Compounds in this review will be numbered according to these systems, or if needed, by using the Chemical Abstract Index numbering. The 70 known cannabinoids can be classified as follows:

Cannabigerol (CBG) type: 7 known (1 new)

Cannabigerol (CBG-C_5) was the first compound isolated from the resin of marijuana as a pure chemical substance (Gaoni and Mechoulam, 1964a). Although CBG-type compounds are inactive when compared to Δ^9-THC (Grunfeld and Edery, 1969; Mechoulam et al., 1970), they show considerable antibacterial activity against gram positive bacteria (Mechoulam and Gaoni, 1965). There are currently seven CBG-type compounds known (Table 2; Fig. 2). The most recently isolated

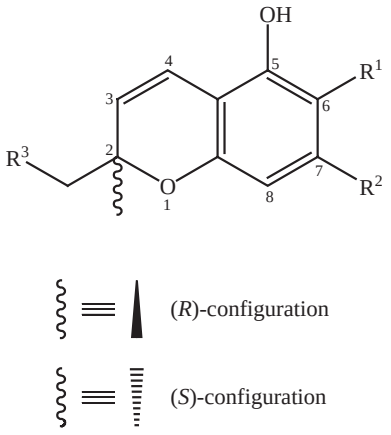

Fig. 3. CBC-type cannabinoids.

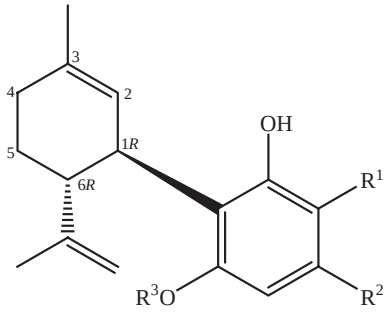

Fig. 4. CBD-type cannabinoids.

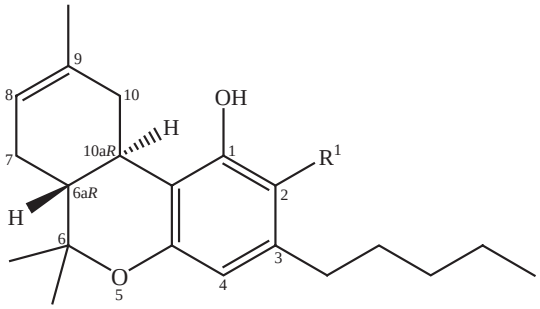

Fig. 6. Δ^8-*trans*-THC-type cannabinoids.

compound, cannabinerolic acid, is the *trans*-isomer of cannabigerolic acid (Taura et al., 1995). All other CBG-type compounds have *cis*-geometry.

Cannabichromene (CBC) type: 5 known (1 new)

The discovery of cannabichromene (CBC-C_5) by Claussen et al. (1966) and Gaoni and Mechoulam (1966) occurred almost simultaneously and led to the discovery of other CBC-type compounds.

Although the number of known CBC-type compounds were given as five in a review article in 1995 (Ross and ElSohly, 1995), the 1980 review article (Turner et al., 1980) only indicated four. Since there were no new CBC-type compounds reported in the 1995 review, it seems that the number reported in 1995 was in error and the correct number should have been four.

Natural CBC-C_5 is thought to be racemic (Gaoni and Mechoulam, 1971; Yamaguchi et al., 1995), and although the CBC acids, cannabichromenic acid and cannabichromevarinic acid, were reported to have optical activities of +4.8° (Shoyama et al., 1968) and −4.8° (Shoyama et al., 1977) in chloroform, respectively, they are also probably racemic (Gaoni and Mechoulam, 1971). It was also proven that both acids are the A acids on the basis of IR data and comparison with synthetic samples (Shoyama et al., 1968, 1977).

The isolation of the C_3-analog of CBC has been reported by two groups (De Zeeuw et al., 1973; Shoyama et al., 1975). De Zeeuw et al. 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, which caused some confusion, since the structure in the Chemical Abstracts (# 136452s) is drawn with an isopropyl side chain. They also did not report any optical activity. Shoyama et al. named their isolated compound cannabichromevarin and indicated an *n*-propyl side chain and optical rotation of $[\alpha]_D$ +58° (chloroform).

Morita and Ando (1984) claimed the separation and identification of a CBC-C_3-type compound with a 4-methyl-2-pentenyl side chain at C2 (Fig. 3; Table 3) in stead of a 4-methyl-3-pentenyl side chain as found in all the other know CBC-type compounds. This is the only reference to this compound found in the literature and is probable due to a misinterpretation. The addition of this compound, however, takes the total number of known CBC-type compounds to five (Table 3).

The absolute configuration at C2 has not yet been determined.

Cannabidiol (CBD) type: 7 known

Cannabidiol was isolated in 1940 (Adams et al., 1940) and its absolute configuration established by synthesis of (−)-CBD as (−)-*trans*-(1*R*,6*R*) (Petrzilka et al., 1969). The optical rotation of cannabidivarin was reported as $[\alpha]_D$ −139.5° (chloroform) (Vollner et al., 1969). All of the known CBD-type cannabinoids (Table 4) have *trans*-(1*R*,6*R*) (Fig. 4) absolute configuration and presumably also negative optical rotation.

(−)-Δ^9-trans-Tetrahydrocannabinol (Δ^9-THC) type: 9 known

The structure of tetrahydrocannabinol was unknown until Gaoni and Mechoulam (1964b) isolated Δ^9-THC and used NMR to assign the double bond position and the *trans*-configuration. They also reported an optical rotation of $[\alpha]_D$

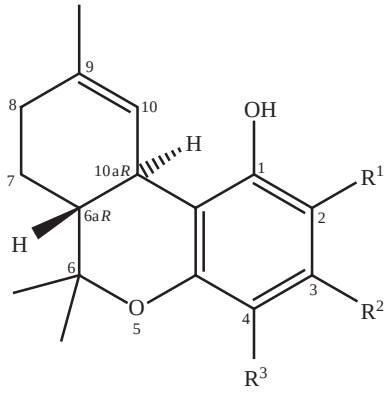

Fig. 5. Δ^9-*trans*-THC-type cannabinoids.

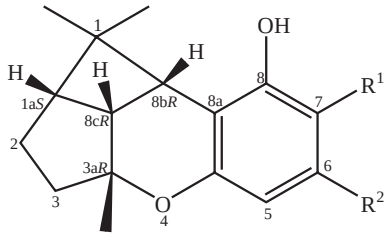

Fig. 7. CBL-type cannabinoids.

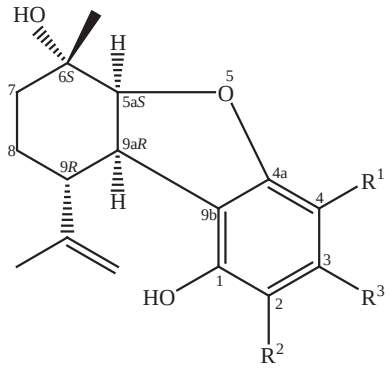

Fig. 8. CBE-type cannabinoids.

−140° (chloroform). The absolute configuration of tetrahydrocannabinol was determined to be *trans*-(6a*R*,10a*R*) by comparison with D-(+)-glyceraldehyde and (−)-CBD (Mechoulam and Gaoni, 1967b). 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 (Table 5; Fig. 5).

(−)-Δ⁸-trans-Tetrahydrocannabinol (Δ⁸-THC) type: 2 known

This group has only two compounds, namely (−)-Δ^8-*trans*-tetrahydrocannabinol and (−)-Δ^8-*trans*-tetrahydrocannabinolic acid A (Table 6; Fig. 6). They have the same absolute configuration as their Δ^9 counterparts, i.e. *trans*-(6a*R*,10a*R*). Although no optical rotation data is available for Δ^8-THCA-C_5 A, synthetic Δ^8-*trans*-(6a*R*,10a*R*)-THCVA-C_3 A has a reported value of $[\alpha]_D$ −268° (chloroform) (Shoyama et al., 1977), indicating that the C_5-homolog should also have a negative optical rotation.

Cannabicyclol (CBL) type: 3 known

Cannabicyclol (CBL-C_5) was first considered to have a THC-type structure (Korte and Sieper, 1964), and was therefore named THC III. It was isolated in 1967, renamed to cannabicyclol/cannabipinol and the structure revised (Mechoulam and Gaoni, 1967a; Claussen et al., 1968; Crombie and Ponsford, 1968). 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.

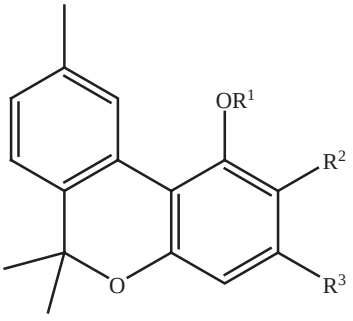

Fig. 9. CBN-type cannabinoids.

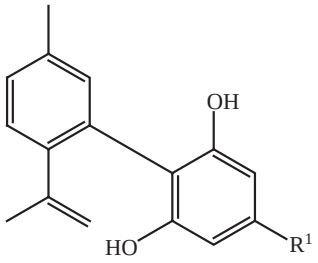

Fig. 10. CBND-type cannabinoids.

Cannabicyclol from the crude plant material shows no apparent optical rotation, although an $[\alpha]_D$ −3° was reported (Claussen et al., 1968), and it could form as a result of natural irradiation in the plant or it could be an artifact formed in the crude extract (Crombie et al., 1968; Crombie and Ponsford, 1971). This structure was finally confirmed as the correct structure by NMR (Kane, 1971) and X-ray analysis (Whiting et al., 1970), although the absolute configuration is not yet known.

Cannabicyclolic acid (CBLA-C_5 A) was first isolated as optically inactive colorless prisms by Shoyama et al. (1972) 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 CBCA-C_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 (Shoyama et al., 1968) 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 artifact produced by natural irradiation of CBCA-C_5 A during storage (Shoyama et al., 1972).

Cannabicyclovarin (CBLV-C_3) was first detected by GC-MS (Vree et al., 1972a) and later isolated as optically inactive colorless needles (Shoyama et al., 1981). 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 (Table 7; Fig. 7).

Cannabielsoin (CBE) type: 5 known

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 (Hartsel et al.,

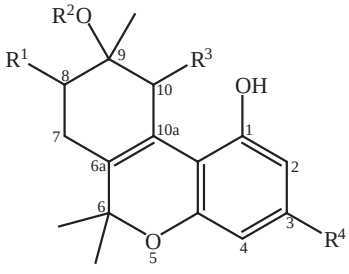

Fig. 11. CBT-type cannabinoids.

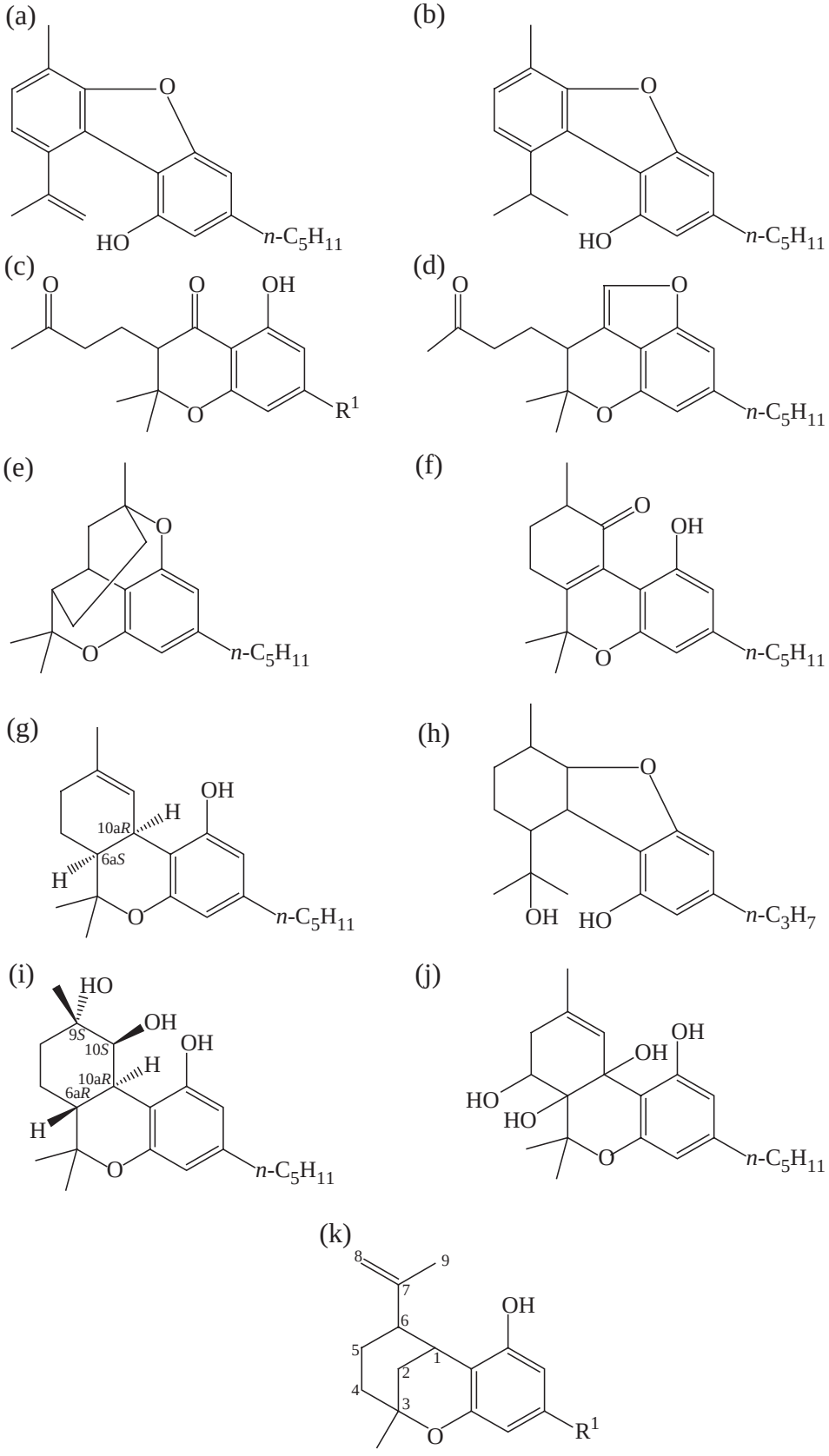

Fig. 12. Miscellaneous-type cannabinoids (see Table 12).

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

Chemical Class	1980	1995	2005	Table	Figure
Cannabinoids	61	66[3]	70	1–12	1–12
CBG type	6	6	7	2	2
CBC type	4	4	5	3	3
CBD type	7	7	7	4	4
Δ^9-THC type	9	9	9	5	5
Δ^8-THC type	2	2	2	6	6
CBL type	3	3	3	7	7
CBE type	5	5	5	8	8
CBN type	6	7	7	9	9
CBND type	2	2	2	10	10
CBT type	6	9	9	11	11
Misc type	11	12	14	12	12
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[1]	483[2]	489	–	–

[1]The total given in the 1980 review was 421. The 2 glycoproteins of unknown structures, however, make the total 423.
[2]The simple acids and fatty acids in the 1995 review are given as 21 and 22, respectively. They should, however, be 20 and 23, respectively, which leaves the total unchanged.
[3]The CBC-and miscellaneous-type cannabinoids in the 1995 review are given as 5 and 11, respectively. They should, however, be 4 and 12, respectively, which leaves the total unchanged.

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

1983). Also, they can be formed from the naturally occurring CBD and CBD acids by photo-oxidation (Shani and Mechoulam, 1974) or pyrolysis (Küppers et al., 1973). In spite of these concerns, CBE and CBE acid (both the C_3 and the C_5 homologues) have been reported to be natural products of *C. sativa* plant material or hashish on several occasions (Shani and Mechoulam, 1974; Küppers et al., 1973; Grote and Spiteller, 1978a; Bercht et al., 1973).

The first mention of cannabielsoin (CBE-C_5) in the literature occurs in 1973 (Bercht et al., 1973), although no detail on the structure is given. The structure and absolute configuration was finally established by synthesizing CBE-C_5 using cannabidiol diacetate as starting material (Uliss et al., 1974) and comparing it to cannabielsoin obtained by decarboxylation of natural cannabielsoin acid (Shani and Mechoulam, 1970; Küppers et al., 1973). 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 (Shani and Mechoulam, 1974).

The absolute configurations for these compounds are (5a*S*,6*S*,9*R*,9a*R*) (Fig. 8).

Cannabinol (CBN) type: 7 known

CBN-type cannabinoids (Table 9; Fig. 9) are the fully aromatized derivatives of THC, and although they have been isolated from different cannabis extracts (Wood et al., 1896;

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
Cannabigerol 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
Cannabigerovarin [(*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	$(CH_2)_2CH{=}C(CH_3)_2$

Table 3
CBC-type cannabinoids

Compound	R^1	R^2	R^3
(±)-Cannabichromenic acid (CBCA-C_5 A)	COOH	n-C_5H_{11}	$(CH_2)_2CH{=}C(CH_3)_2$
(±)-Cannabichromene (CBC-C_5)	H	n-C_5H_{11}	$(CH_2)_2CH{=}C(CH_3)_2$
(±)-Cannabichromevarinic acid (CBCVA-C_3 A)	COOH	n-C_3H_7	$(CH_2)_2CH{=}C(CH_3)_2$
(±)-Cannabivarichromene (CBCV-C_3/CBCV-$^iC_3$)	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-2*H*-1-benzopyran-5-ol	H	n-C_3H_7	$CH_2CH{=}CHCH(CH_3)_2$

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

Compound	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
Tetrahydrocannabinol (Δ^9-THC-C_5)	H	*n*-C_5H_{11}	H
Tetrahydrocannabinolic acid-C_4 (Δ^9-THCA-C_4 A and/or B)	COOH or H	*n*-C_4H_9	H or COOH
Tetrahydrocannabinol-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 (Δ^9-THCOA-C_1 A and/or B)	COOH or H	CH_3	H or COOH
Tetrahydrocannabiorcol (Δ^9-THCO-C_1)	H	CH_3	H

Mechoulam and Gaoni, 1965; Bercht et al., 1973; Harvey, 1976), they are thought of as artifacts. The concentration of CBN in cannabis products (marijuana, hashish and hash oil) increases during storage of these materials while the Δ^9-THC concentration decreases, but at a different rate.

Cannabinodiol (CBND) type: 2 known

CBND-type cannabinoids (Table 10; Fig. 10) are the fully aromatized derivatives of CBD. The first mention of these compounds appeared in 1972 (Van Ginneken et al., 1972; Vree et al., 1972b). Van Ginneken et al. named a compound isolated from hashish and identified by GC-MS cannabinodiol (Fig. 10, R^1=*n*-C_5H_{11}). This assignment, however, was proven incorrect (Lousberg et al., 1977) after the total synthesis of cannabinodiol (CBND-C_5). The compound isolated by Van Ginneken et al. 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 (Bowd et al., 1975). Therefore, all references in the literature vis-à-vis CBND-type cannabinoids quoting Van Ginneken should be regarded with suspicion.

Cannabitriol (CBT) type: 9 known

Cannabitriol was first isolated by Obata and Ishikawa (1966), the structure being determined by Chan et al. (1976), who reported an $[\alpha]_D$ −107° (Table 11; Fig. 11). The isolation and characterization of (+)-cannabitriol (ElSohly et al., 1977){$[\alpha]_D$ +7°} was followed by a single X-ray analysis of (±)-cannabitriol (McPhail et al., 1984), 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 (ElSohly et al., 1978), but the individual (+)- and (−)-*cis*-isomers have not been isolated separately. The absolute configuration of these compounds has also not been determined.

(±)-*trans*-Cannabitriol-C_3 and another CBT-C_3-homologue of unknown stereochemistry have been identified by GC-MS (Harvey, 1985) in a 140 year old ethanolic *Cannabis* extract.

The C10-ethoxy derivative ($[\alpha]_D$ −10°) of (±)-*trans*-cannabitriol-C_5 was isolated in 1977 (ElSohly et al., 1977) and the C_3-homologue was found by Harvey (1985).

The 8,9-dihydroxy isomer of cannabitriol has been isolated as an optically inactive yellow oil (ElSohly et al., 1978), but the relative and absolute configurations are unknown.

Harvey (1985) also mentioned the presence of methyl-cannabitriol in the extract that he analyzed by select ion

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

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

Table 7
CBL-type cannabinoids

Compound	R^1	R^2
(±)-(1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclolic acid (CBLA-C_5 A)	COOH	*n*-C_5H_{11}
(±)-(1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclol (CBL-C_5)	H	*n*-C_5H_{11}
(±)-(1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclovarin (CBLV-C_3)	H	*n*-C_3H_7

Table 8
CBE-type cannabinoids

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

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

Table 10
CBND-type cannabinoids

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

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 C9-OH) is the only reported ester of any naturally occurring cannabinoid (Von Spulak et al., 1968).

Miscellaneous types: 14 known (2 new)

The 1980 review (Turner et al., 1980) and the 1995 review (Ross and ElSohly, 1995) reported 11 miscellaneous type cannabinoids (Table 12; Fig. 12). However, the last review described one new miscellaneous type, indicating that the actual number in 1995 should have been 12.

Dehydrocannabifuran (DCBF-C_5), cannabifuran (CBF-C_5), cannabichromanone (CBCN-C_5) and 10-oxo-$\Delta^{6a(10a)}$-tetrahydrocannabinol (OTHC) (Friedrich-Fiechtl and Spiteller, 1975) were isolated in 1975 and followed by the isolation of cannabichromanone-C_3 (CBCN-C_3) (Grote and Spiteller, 1978a) and cannabicoumaronone-C_5 (CBCON-C_5) (Grote and Spiteller, 1978b). The absolute configurations of these compounds are not known.

Cannabicitran (CBT-C_5) was first synthesized and named citrylidene-cannabis (Crombie and Ponsford, 1971), and then isolated (Bercht et al., 1974) from Lebanese hashish. The absolute configuration of cannabicitran is not known.

(−)-Δ^9-*cis*-(6a*S*,10a*R*)-Tetrahydrocannabinol [(−)-*cis*-Δ^9-THC-C_5], the *cis*-isomer of Δ^9-THC, was found as a major contaminant in samples of confiscated marijuana (Smith and Kempfert, 1977). The (+)-enantiomer and the racemic mixture of the *cis*-isomer have not been isolated.

Cannabiglendol-C_3 (8-hydroxy-isohexahydrocannabivarin or OH-*iso*-HHCV-C_3) was isolated from an Indian *Cannabis* variant grown in Mississippi (Turner et al., 1981) and identified by spectral means and by comparison to the synthetic C_5-homolgue.

Table 12
Miscellaneous-type cannabinoids

Compound	Fig. 12	R^1
Dehydrocannabifuran (DCBF-C_5)	(a)	–
Cannabifuran (CBF-C_5)	(b)	–
Cannabichromanone (CBCN-C_5)	(c)	n-C_5H_{11}
Cannabichromanone-C_3 (CBCN-C_3)	(c)	n-C_3H_7
Cannabicoumaronone-C_5 (CBCON-C_5)	(d)	–
Cannabicitran (CBT-C_5)	(e)	–
10-Oxo-$\Delta^{6a(10a)}$-Tetrahydrocannabinol (OTHC)	(f)	–
(−)-Δ^9-(6aS,10aR-*cis*)-Tetrahydrocannabinol [(−)-*cis*-Δ^9-THC-C_5]	(g)	–
Cannabiglendol-C_3 (OH-*iso*-HHCV-C_3)	(h)	–
(−)-(6a*R*,9*S*,10*S*,10a*R*)-9,10-Dihydroxyhexahydrocannabinol [(−)-Cannabiripsol-C_5]	(i)	–
(−)-6a,7,10a-Trihydroxy-Δ^9-tetrahydrocannabinol [(−)-Cannabitetrol]	(j)	–
(±)-Δ^7-*cis*-(1*R*,3*R*,6*S*)-Isotetrahydrocannabivarin-C_3	(k)	n-C_3H_7
(−)-Δ^7-*trans*-(1*R*,3*R*,6*R*)-Isotetrahydrocannabivarin-C_3	(k)	n-C_3H_7
(−)-Δ^7-*trans*-(1*R*,3*R*,6*R*)-Isotetrahydrocannabinol-C_5	(k)	n-C_5H_{11}

(−)-Cannabiripsol-C_5 [(−)-CBR-C_5)] was isolated from a South African *Cannabis* variant (Boeren et al., 1979). Spectral analysis indicated that the isolated compound might be the dihydro-derivative of 9,10-dihydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol. Since this compound has four chiral centers, 16 stereoisomers would be possible, but the assumption that the stereochemistry at C6a and C10a was the same as for naturally occurring Δ^9-THC, only left four stereoisomers. Synthesis of these four isomers showed that cannabiripsol-C_5 is in fact (−)-(6a*R*,9*S*,10*S*,10a*R*)-9,10-dihydroxyhexahydrocannabinol.

When using an electronic database such as SciFinder Scholar® to research the cannabinoids, two cannabiripsol-type compounds are listed that might cause confusion. These two compounds, namely cannabiripsol-C_5 [CAS 99623-72-0] and cannabiripsol-C_3 [CAS 99623-73-1], both given without stereochemistry and both referencing the same publication (Harvey, 1985) are probably mistakes, since careful review of this article reveals a mistake in one of the structures (IIIa and IIIb). This structure should have a double bond between C6a and C10a, making it 9,10-dihydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol-type compounds and not cannabiripsol-type compounds.

(−)-Cannabitetrol [(−)-6a,7,10a-trihydroxy-Δ^9-tetrahydrocannabinol] was isolated and identified by ElSohly et al. (1984), reporting an $[\alpha]_D$ −51°. The absolute configuration of this compound is unknown.

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 (unknown stereochemistry)	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-$\Delta^{6a(10a)}$- tetrahydrocannabivarin-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-C5 ester)	H	CBDA-C_5 ester	OH	n-C_5H_{11}

The 1995 review (Ross and ElSohly, 1995) contained one new miscellaneous-type cannabinoid, namely (±)-Δ^7-*cis*-isotetrahydrocannabivarin-C_3 (Shoyama et al., 1981). NMR suggested that the vicinal protons C1-H and C6-H are *cis*, based on a coupling constant ($^3J_{1,6}$=6 Hz) and analysis of the Dreiding model. This would indicate a relative configuration of 1,2-*cis*-(1*R*,3*R*,6*S*).

The GC-MS analysis of hashish oil (Morita and Ando, 1984) led to the identification of (−)-Δ^7-*trans*-(1*R*,3*R*,6*R*)-isotetrahydrocannabivarin-C_3 and (−)-Δ^7-*trans*-(1*R*,3*R*,6*R*)-isotetrahydrocannabinol-C_5, although no apparent justification for the absolute configurations are given.

Other constituents: 419 known (2 new)

The following chemical classes (number known) has been identified in marijuana: nitrogenous compounds (27), amino acids (18), proteins (3), enzymes (6), glycoproteins (2), sugars and related compounds (34), hydrocarbons (50), simple alcohols (7), simple aldehydes (12), simple ketones (13), simple acids (20), fatty acids (23), simple esters (12), lactones (1), steroids (11), terpenes (120), non-cannabinoid phenols (25), flavonoids [23, including 2 new flavonol glycosides, namely kaempferol 3-*O*-sophoroside and quercetin 3-*O*-sophoroside, isolated from pollen grain collected from male plants of *C. sativa* L. (Ross et al., 2005)], vitamins (1), pigments (2) and elements (9) (Turner et al., 1980; Ross and ElSohly, 1995).

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