REVIEW ARTICLE

Non-Cannabinoid Metabolites of *Cannabis sativa* with Therapeutic Potential

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Abstract: The Cannabis plant (*Cannabis sativa* L.) produces an estimated 545 chemical compounds of different biogenetic classes. In addition to economic value, many of these phytochemicals have medicinal and physiological activity. The plant is most popularly known for its two most prominent and most studied secondary metabolites—Δ^9-Tetrahydrocannabinol (Δ^9-THC) and Cannabidiol (CBD). Both Δ^9-THC and CBD have a wide therapeutic window across many ailments and form part of a class of secondary metabolites called cannabinoids—of which approximately over 104 exist. This review will focus on non-cannabinoid metabolites of *Cannabis sativa* that also have therapeutic potential, some of which share medicinal properties similar to those of cannabinoids. The most notable of these non-cannabinoid phytochemicals are flavonoids and terpenes. We will also discuss future directions in cannabis research and development of cannabis-based pharmaceuticals. Caflanone, a flavonoid molecule with selective activity against the human viruses including the coronavirus hCov-OC43 (Covid-19), and certain cancers, is one of the most promising non-cannabinoid molecules that is being advanced into clinical trials. As validated by thousands of years of the use of cannabis for medicinal purposes, vast anecdotal evidence abounds on the medicinal benefits of the plant. These benefits are attributed to the many phytochemicals in this plant, including non-cannabinoids. The most promising non-cannabinoids with potential to alleviate global disease burdens are discussed.

Keywords: cannabinoids; Δ^9-tetrahydrocannabinol, cannabidiol, non-cannabinoids, flavonoids; terpenes; secondary metabolites;

1. Introduction

A central Asian site of domestication of the cannabis plant is often cited [1]. The plant's medicinal value was first recorded in the Pen Ts'ao Ching, the Chinese pharmacopoeia—the world's oldest, compiled in the Han dynasty, first or second century A.D. [1]. The cannabis plant, its resin, and some derivatives of its compounds have been used in traditional eastern medicine. Uses include; for recreation, due to its hallucinogenic/hypnotic effects, for religious celebrations and meditative purposes; industrially for fibers, textiles and ropes, and medicinally as an analgesic anti-convulsant, antidiarrheal, sedative, relaxant, anxiolytic, antibacterial, antioxidant, and as treatment for tetanus, epilepsy and delirium tremens.

The Cannabis plant produces an estimated 545 [2] chemical compounds of different biogenetic classes [3]. The main biogenetic classes are shown table 1 below. These include primary metabolites, like amino acids, fatty acids, vitamins, sugars, and proteins, and secondary metabolites produced in trichomes, the cell's factory. Primary metabolites provide nutritional value. Secondary metabolites include approximately 120 terpenoids (61 monoterpenes, 52 sesquiterpenoids, and 5 triterpenoids [2], over 26 flavonoids [2], lignans, stilbenes and derivatives, alkaloids, and 20 steroids [2] dihydrophenanthrenes, glycoproteins, and dibenzyls [5, 6]. In addition to sharing analgesic, antimicrobial anti-cancer, anti-inflammatory, and neuroprotective properties, a majority also share anti-oxidant capabilities.

During many pathological conditions and diseases processes like age-related inflammatory and autoimmune diseases [7], asthma, atherosclerosis, cancer, chronic obstructive pulmonary disease, hypertension, ischemia/perfusion, diabetes, and HIV dementia [8], the cells of the body accumulate high levels of toxic reactive oxygen species (R.O.S.)/free radicals in comparison to antioxidants [9]. This imbalance can cause significant damage to cell structures [9]. Antioxidants mitigate excessively produced reactive oxygen species within the cells, and in doing so, reduce the oxidative stress in cells [10]. Antioxidants may therefore have therapeutic applicability against many human diseases including but not limited to cancer, viral infections, cardiovascular diseases and inflammatory diseases [10]. Natural antioxidants may also be revered due to their safer side effect profile compared to synthetic antioxidants used in preventative medicine and in the food industry [10].

The biosynthesis of the non-cannabinoids in cannabis is driven by pyruvate/acetyl-CoA for the terpenes via the plastidial deoxyxylulose phosphate/methyl-erythritol phosphate (DOXP/MEP) and cytoplasmic MVA pathways [2], and *p*-coumaril-CoA via the phenylpropanoid pathway [2] for flavonoids [2]. The synthesis of cannabinoids is via the precursor molecule Olivetolic Acid (OLA) and the polyketide pathway, and another precursor molecule, Geranyl Diphosphate (GPP) and the plastidial deoxyxylulose phosphate/methyl-erythritol phosphate (DOXP/MEP) pathway [2]. These processes are simplified in figure 1 below.
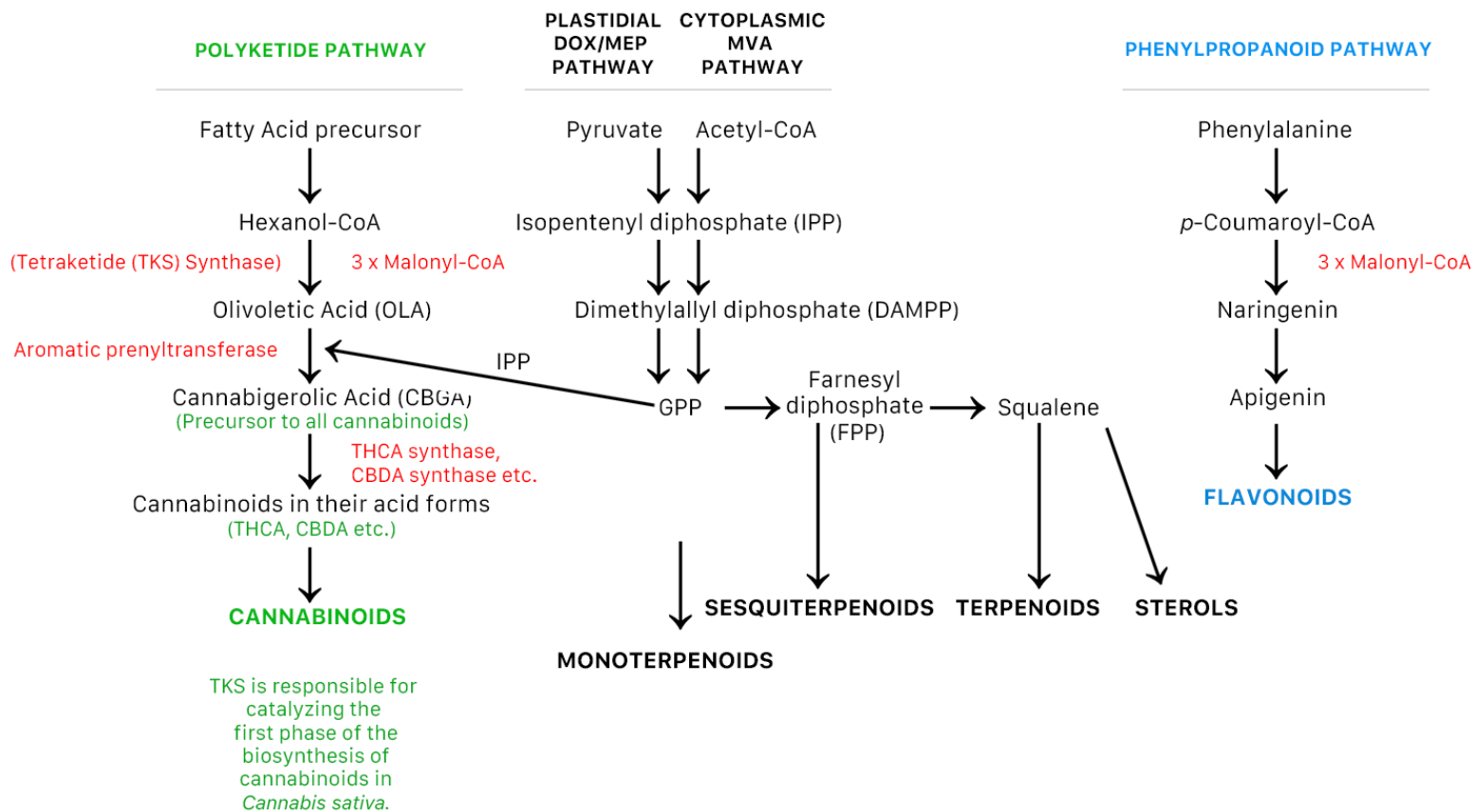
POLYKETIDE PATHWAY

Fatty Acid precursor

↓

Hexanol-CoA

(Tetraketide (TKS) Synthase)   3 x Malonyl-CoA

Olivoletic Acid (OLA)

Aromatic prenyltransferase

Cannabigerolic Acid (CBGA)
(Precursor to all cannabinoids)

THCA synthase,
CBDA synthase etc.

↓

Cannabinoids in their acid forms
(THCA, CBDA etc.)

↓

CANNABINOIDS

TKS is responsible for
catalyzing the
first phase of the
biosynthesis of
cannabinoids in
Cannabis sativa.

PLASTIDIAL   CYTOPLASMIC
DOX/MEP   MVA
PATHWAY   PATHWAY

Pyruvate   Acetyl-CoA

↓   ↓

Isopentenyl diphosphate (IPP)

↓   ↓

Dimethylallyl diphosphate (DAMPP)

IPP   ↓   ↓

GPP → Farnesyl
diphosphate → Squalene
(FPP)

SESQUITERPENOIDS   TERPENOIDS   STEROLS

MONOTERPENOIDS

PHENYLPROPANOID PATHWAY

Phenylalanine

↓

p-Coumaroyl-CoA

3 x Malonyl-CoA

Naringenin

↓

Apigenin

↓

FLAVONOIDS

Figure 1. Synthesis of cannabinoids and non-cannabinoids [2]

Table 1 showing the main biogenetic classes of compounds produced by *Cannabis sativa* [11].

	Main Chemical Classes	Number of Compounds	Reference
1.	Terpenes	120	[11]
2.	Cannabinoids	66	[11]
3.	Hydrocarbons	50	[11]
4.	Sugars and related compounds	34	[11]
5.	Nitrogenous compounds	27	[11]
6.	Non-cannabinoid phenols	25	[11]
7.	Fatty acids	22	[11]
8.	Simple acids	21	[11]
9.	Flavonoids	21	[11]

In addition to having unique organoleptic properties [12], terpenes provide a wide range of therapeutic benefits to humans, secondary metabolites, particularly terpenes and flavonoids, play a primary role in a plant's defenses against hostile environments, herbivores and phytophagous insects.

The identified non-cannabinoid metabolites of cannabis are discussed in more detail in the ensuing sections.

2. Non-Cannabinoid Compounds

Cannabinoid and non-cannabinoid phytochemicals possess bioactive and protective properties that are beneficial to human health. In addition to cannabinoids, the Cannabis plant produces hundreds of non-cannabinoid secondary metabolites including approximately 120 terpenoids (61 monoterpenes, 52 sesquiterpenoids, and 5 triterpenoids [2], essential oils, over 26 flavonoids [2] lignans, stilbenoid derivatives, alkaloids, amino acids, spiro-indans, polyphenols, 20 steroids [2], diyhdrophenanthrenes, glycoproteins (like galactose, glucose, mannose and xylose), and dibenzyls [5, 6]. This list also includes a-cannabispiranol, chrysoeriol, 6-prenylapigenin, cannflavin A and b-acetyl cannabispiranol [13].

Flavonoids and terpenoids in particular, have a wide therapeutic window, including but not limited to cancer, inflammation, excessive reactive oxygen species in cells, and enhancement of neuroprotection. In addition to the phytochemicals mentioned below, a 2008 study by Radwan and colleagues identified and isolated six new non-cannabinoid phytochemicals from a high potency *Cannabis sativa* L. strain. These were 5-acetoxy-6-geranyl-3-n-pentyl-1,4-benzoquinone, 4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene, 4,7-dimethoxy-1,2,5-trihydroxyphenanthrene, cannflavin C, cb-sitosteryl-3-O-b-D-glucopyranoside-20-O-palmitate, and 4-hydroxy-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene [13]. The review below focuses on non-cannabinoids phytochemicals with therapeutic potential.

2.1.1   *Terpenes and their derivatives, terpenoids.*

The word "terpene" was devised in 1866 by August Kekulé, a German organic chemist. Terpenes are hydrocarbons and are made up of isoprene units (5-carbon building blocks) [14], while terpenoids are an oxidized and denatured form of terpenes that differ in that they contain an additional functional group with oxygen [14]. They are not the same, despite being used synonymously. This oxidation occurs during the drying and curing processes when the plant is exposed to open air. Terpenes are typically classified by the number of isoprene units in the molecule. Isoterpene is the only hemiterpenes. Hemiterpenes and hemiterpenoids like prenol and isovaleric acid only have a single isoprene unit. Monoterpenes and monoterpenoids like pinene (most common terpene produced across plant species), limonene, myrcene, geraniol, and terpineol have two isoprene units. Sesquiterpenes and sesquiterpenoids like humulene and farnesol have three isoprene units. Triterpenes, like squalene—the precursors to all steroids [14], have six isoprene units. Sesquiterpenes and tetraterpenes have seven and eight isoprene units, respectively. Polyterpenes and norisoprenoids have multiple isoprene units in their molecule. **Figure 2** below shows structures of some terpenoids.
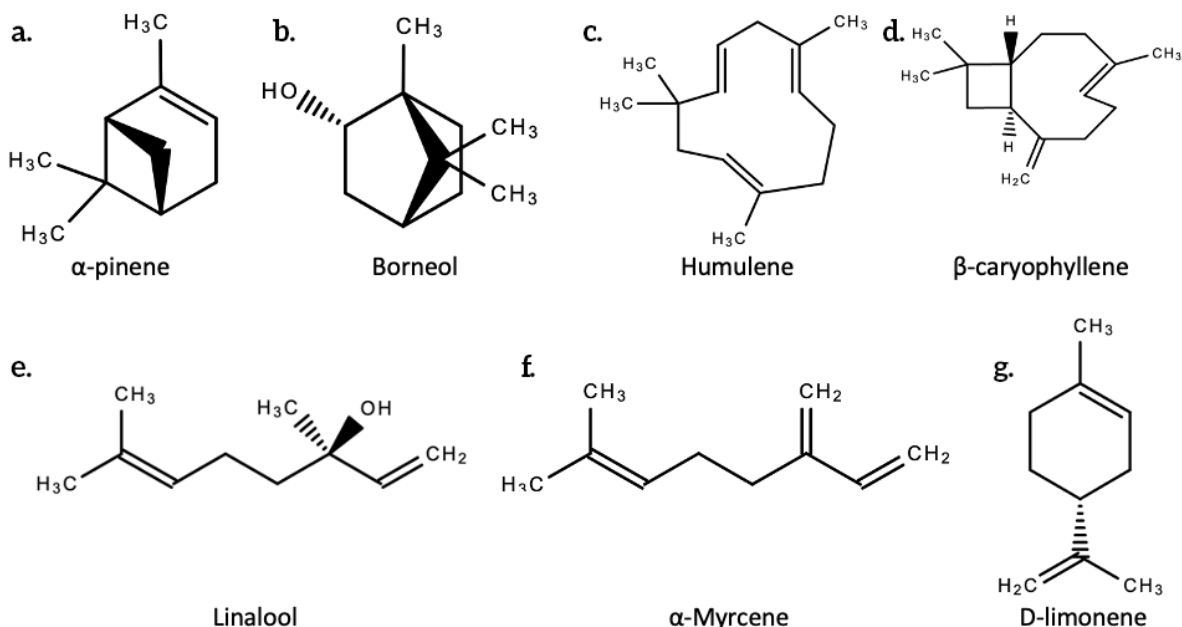
Figure 2. The chemical structures of some terpenoids.

Figure 1 above shows the biosynthetic pathway of terpenes and terpenoids, which are synthesized from an isoprenoid precursor Isopentenyl pyrophosphate (IPP). This is done so via the plastidial deoxyxylulose phosphate/methyl-erythritol phosphate (DOXP/MEP) pathway (monoterpenoids), and the Cytoplasmic Mevalonate (MVA) Pathway (sesquiterpenoids, triterpenoids, and sterols)[2]. Along with cannabinoids, terpenes are considered a main physiological marker of secondary metabolites [15, 16].

Terpenes are a large and diverse class of aromatic compounds responsible for the unique flavours and scents of many herbs and plants and phenotypic variation across plant species. Over 20,000 terpenes exist across plant species [17], and over 150 alone in the Cannabis plant [18]. This makes terpenes the largest classification of phytochemicals (Andre, Hausman, Guerriero, 2016). Their primary role in plants vary but, in some plants, may attract pollinators, and in others, deter herbivores and inhibit microbial growth.

The most common terpenes in cannabis include limonene, α-pinene, β-pinene, humulene, β-caryophyllene, linalool and myrcene [2]. Other common terpenes in cannabis include bisabool, borneol, camphene, geraniol, ocimene, terpineol, and valencene. These fall into the monoterpenoids and sesquiterpenoids categories. Refer to Table 2 below for examples of mono- and sesquiterpenoids profiled in a 2020 study by Jin and colleagues that profiled secondary metabolites in Cannabis inflorescences, leaves, stem bars, and roots for medicinal purposes [2].

Table 2. Examples of mono- and sesquiterpenoids profiled in Cannabis inflorescences, leaves, stem bars, and roots for medicinal purposes [2].

Monoterpenoids			Sesquiterpenoids	
α-pinene	Eucalyptol	Borneol	(-)-β-Elemene	Viridiflorol
Camphene	Ocimene	Terpinen-4-ol	β-Caryophyllene	(-)-Guaiol
Sabinene	γ-Terpinene	-Terpineol	Aromadendrene	(+)-Cedrol
(-)-β-pinene	Sabinene Hydrate	(+)-Dihydrocarvone	Trans- β-Farnesene	β-Eudesmol
β-Myrcene	Terpinolene	Nerol	α-Humulene	α-Bisabolol
α-Phellandrene	Frenchone	Pulegone	Valencene	
Δ 3-Carene	Linalool	Carvone	Ledene	
α-Terpinene	Frenchol	Geraniol	trans-Nerolidol	
p-Cymene	(-)-Isopulegol	Geranyl Acetate	Caryophyllene Oxide	
Limonene	Camphor		Globulol	

Terpenes provide aromatherapeutic benefits to humans including stress-, anxiety, and depression-relief, decongestion, and a general pharmacologically synergistic effect in combination with cannabinoids and flavonoids. As a result, terpenes are frequently used in cosmeceuticals, perfumes and beverage flavouring.

Terpenes and terpenoids are highly concentrated in the essential oils extracted from the Cannabis plant, and are also responsible for the therapeutic benefits that Essential Oils provide. A study by Piccaglia et al., 2016 explored the biological properties of some terpenes making up said essential oils extracted from the Cannabis plant (Table 3) by distillation and characterized by Gas Chromatography-Mass Spectrometry (GC-MS). Table 3 also shows the biological properties of other common terpenes found in cannabis.

Table 3 below shows the biological properties of some common terpenes in cannabis.

Terpene	Biological Property	References
Myrcene	Potent analgesic	[19]
	Anti-oxidant, neuroprotective, anti-inflammatory.	[20]
	Anticonvulsant	[21]
1,8-cineole	Increases cerebral blood flow and enhances cortical activity	[22]
Limonene	inhibits many species of bacteria and fungi – repellant.	[23]
	Anti-inflammatory, anti-oxidant, anti-viral, anti-diabetic, anti-cancer	[20]
	Anti-depressant; anticonvulsant	[21]
α-pinene & -pinene	Antimicrobial; repellant	[23]

	Bronchodilator; Anti-inflammatory	[20]
	Memory improvement/enhancement; acetylcholinesterase inhibitor	[21]
Linalool (Lavender scent)	Anxiolytic, anti-inflammatory; anti-microbial, anti-cancer, neuroprotective, Antidepressant	[20]
	Anti-influenza	[24]
	Sedative; Induces apoptosis in cancer cells	[21]
α-terpineol	Antimicrobial; repellant	[23]
	Anti-inflammatory	[25]
	Analgesic	[26]
	Nociception-inhibition	[26]
	Anti-convulsant	[27]
	Anti-Microbial	[21]
	Gastroprotective	[28]
Borneol	Antimicrobial; repellant	[23]
β- caryophyllene	Anti-inflammatory Analgesic	[20]
	Anti-spasmic in gut muscles	[21]
Humulene	Anti-allergy; anti-cancer	[20]
Ocimene	Antifungal; Antibacterial; Anti-oxidant; antiviral; anti-inflammatory	[29, 30, 31, 32, 33]

The Medical Cannabis Network also reports that a current study is being undertaken by researchers at the Israel Institute of Technology investigating the therapeutic efficacy of a cannabis terpene inhalant formulation in suppressing the immune system response against COVID-19.

2.2   Phenolic Compounds in Cannabis sativa

Polyphenols, also known as phenylpropanoids, are a class of over 10,000 chemical compounds that have phenyl groups/rings (C_6H_5). A phenyl ring consists of a 6-carbon structure formed on a hexagonal plane. Five of these carbon atoms are each individually bonded to hydrogen atoms (Figure 3a).

A 2020 study by Izzo and colleagues analyzed some phenolic compounds in Cannabis sativa L. inflorescences using UHPLC-Q-Orbitrap HRMS (Ultra-High-Performance Liquid Chromatography-Quadruple-Orbitrap High-Resolution Mass Spectrometry). Table 4 below lists some of the phenolic compounds investigated. Cannabisin A, B and C were the predominant lignanamides identified [34].

Table 4. List of Phenolic Compounds in Commercial *Cannabis sativa* [34].

Flavonols	Phenolic Amides	Flavones	Phenolic acids
Catechin	N-trans-Caffeoyltyramine	Cannflavin A	Hydroxycinnamic acids
Epicatechin	Flavonoids	Cannflavin B	Chlorogenic acid
Flavonone	Flavonol	Luteolin-7-O-glucoside	Caffeic acid
Naringenin	Rutin	Apigenin-7-O-glucoside	p-Coumaric acid
Lignanamides	Quercetin-3-glucoside	Luteolin	Ferulic Acid
Cannabisin A	Kaempferol-3-O-glucoside	Apigenin	
Cannabisin B	Quercetin		
Cannabisin C	Kaempferol		

2.3   Flavonoids

Flavonoids are a large family of polyphenolic plant compounds that naturally occur in fruits, vegetables, chocolate, and beverages like wine and tea.

There are six classes of flavonoids including anthocyanidins, flavan-3-ols, flavonols, flavanones, flavones, and isoflavones. Chemically, flavonoids have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B), and a heterocyclic ring. This carbon structure can be abbreviated C6-C3-C6. **Figure 3** below shows the structures of some flavonoids.

a. Cannflavin A

b. Cannflavin B

c. Flavone

d. Luteolin
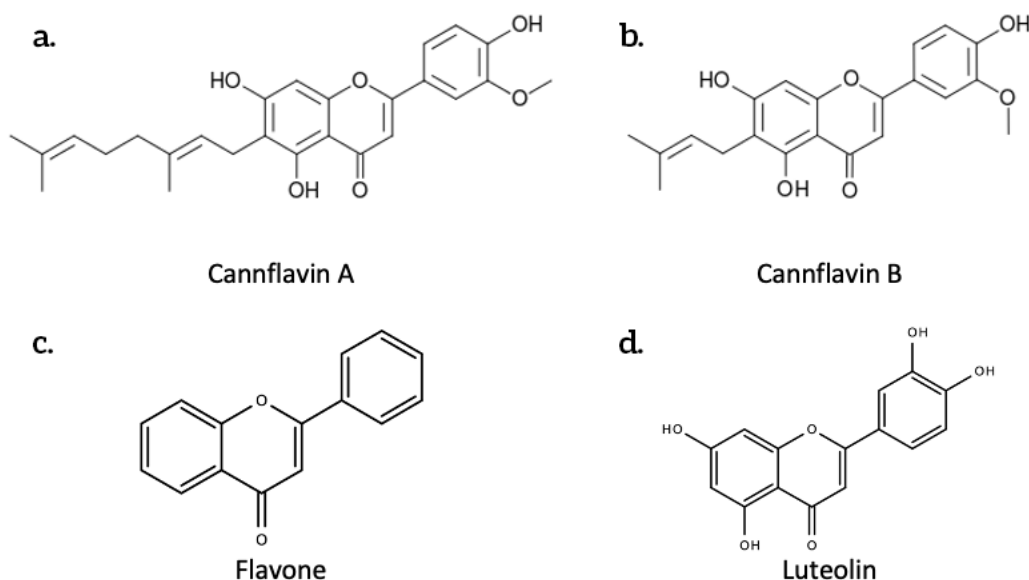
Figure 3. Chemical structures of some flavonoids.

Flavonoids are found in a wide range of plants and may act as physiological regulators, cell-cycle inhibitors and/or chemical messengers. They are also responsible for plant pigmentation (flower coloration to attract pollinator animals/insects), UV filtration/protection, and symbiotic nitrogen fixation.

Flavonoids provide color, flavour and aroma. These class of compounds also have anti-cancer, antioxidant, antithrombogenic, antidiabetic and neuroprotective activities via modulation of a number of cell-signaling cascades.

A 2016 study by Bertoia and colleagues explored the relationship between dietary flavonoid intake (of flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, and flavonoid polymers) and weight change at 4-year intervals between 1986 and 2011 of 124,086 men and women. In conclusion of this study, intake of foods rich in flavonols, flavan-3-ols, anthocyanins, and flavonoid polymers, inversely related to weight gain. Anthocyanidins had the greatest negative correlation with weight maintenance [35]. See tables 5 and 6 below for some biological properties of some common classes of flavonoids.

Table 5 showing biological properties of some common classes of flavonoids.

Flavonoid	Biological Property	
Flavonols (E.g. Quercetin & Kaempferol)	Antioxidant; Cardioprotective	[36]
Flavanones	Antioxidant; Anti-cancer; Anti-inflammatory	[36]
Isoflavonoids	Phytoestrogenic (mimic the hormone estrogen); Hormone balance and metabolism.	[36]
Anthocyanins (responsible for a plant's unique colour)	Antioxidant and Anti-inflammatory.	[36]

Over 20 different flavonoids have been identified in Cannabis, most of which fall into flavonol and flavone group [2]. One such flavonoid is Cannflavin A, which is considered to be 30 times more effective than Aspirin at inhibiting prostaglandin E2, a significant modulator of inflammation [37]. Cannflavin B is also an inhibitor of prostaglandin E2 [38].

Another major flavonoid derived from Cannabis is Caflanone. In recent studies, caflanone demonstrated activity against the human coronavirus hCov-OC43 (Covid-19) belonging to clade b of the genus Betacoronavirus same as SARS-COV-2 [38]. *In vitro*, caflanone inhibited the hCov-OC43 human Coronavirus with an EC50 of 0.42 μM [39]. *In silico* studies showed that caflanone may act by inhibiting the Angiotensin-converting enzyme 2 (ACE2) receptor found in the lung and respiratory tract, and used by the virus during cell entry and infection. Caflanone was also shown to have strong binding affinity to two of the proteases (PLpro & 3CLpro) are vital to the replication of SARS-COV-2 in humans, thereby inhibiting viral entry to and/or replication within human cell [39]. Figure 4 shows the main interactions of

caflanone with the proteins ACE2 (catalytic site/zinc metallopeptidase domain), Glu375, Glu402, ZN803, HIS374, Phe274 and Arg 273 [39]. The docking/binding studies results below show that the phytoantiviral flavonoids (Hesperetin, Myricetin, Linebacker, and Caflanone) could bind equally or more effectively than Chloroquine (CLQ), another investigation drug for SARS-COV-2 [39] (Figure 5).
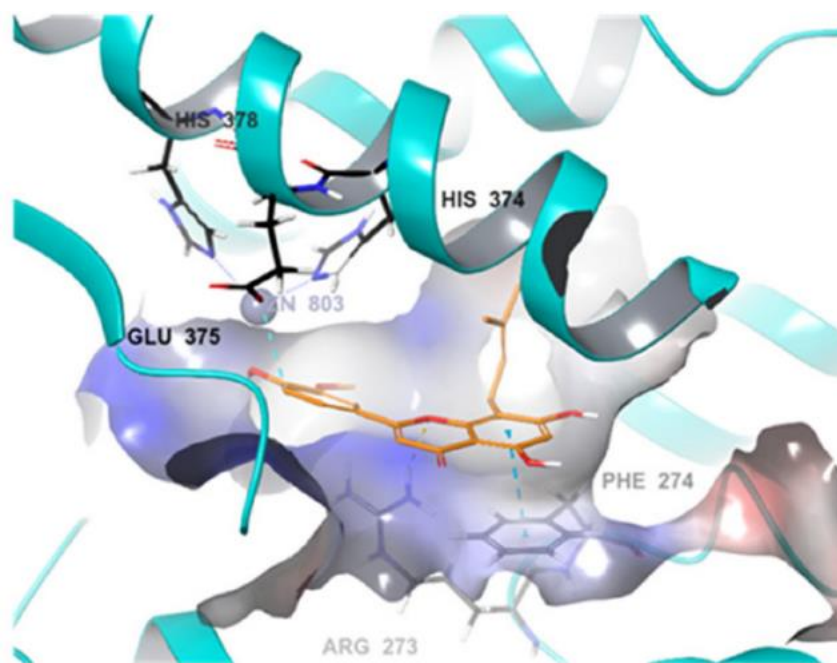

Figure 4. The main protein interactions of caflanone [39]. Reproduced with permission from Wilfred Ngwa, *Potential of Flavonoid-Inspired Phytomedicines against COVID-19*; published by *Molecules* Open-Access Journal, June 11, 2020.

Binding Energy (kcal/mol)

Hesperetin	Myricetin	Linebacker	Caflanone	Chloroquine	Chloroquine
-9.1	-8.9	-9.2	-7.9	-4.1	-4.7
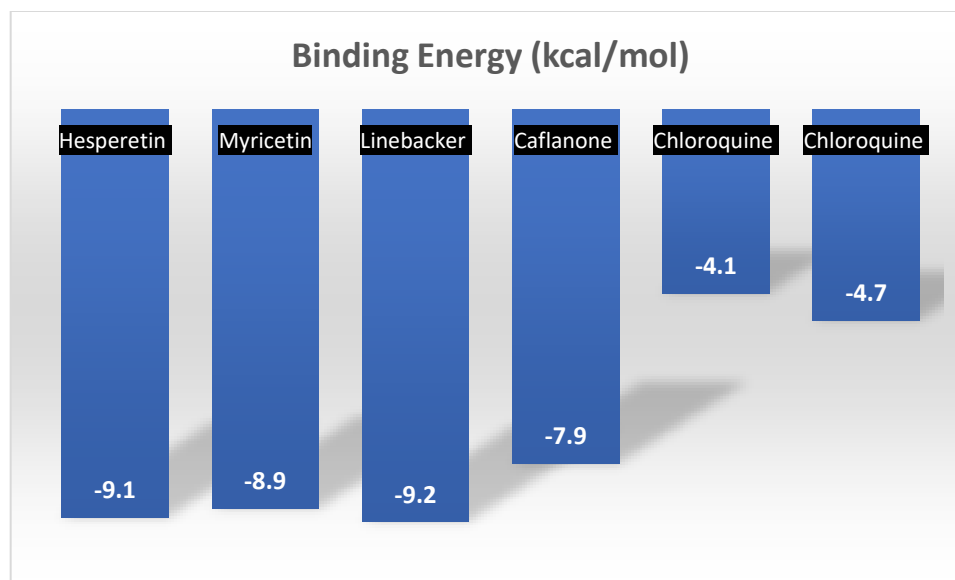
Figure 5. A comparison of the docking/binding studies results between the phytoantiviral flavonoids Hesperetin, Myricetin, Linebacker, and Caflanone [39].

Table 6. showing more therapeutic benefits of flavonoids.

Therapeutic window/benefits of flavonoids	Patent Number
Flavonoid derivatives targeting kinases, sirtuins and oncogenic agents for the treatment of cancers.	[40, 41]
Agent containing flavonoid derivatives for treating cancer and inflammation.	[42]
Therapeutic agents containing cannabis flavonoid derivative for ocular disorders.	[43]
Therapeutic agents containing cannabis flavonoid derivatives for the prevention and treatment of neurodegenerative disorders.	[44]
Pi 4-kinase inhibitor as a therapeutic for viral hepatitis, cancer, malaria. autoimmune disorders and inflammation, and a radiosensitizer and immunosuppressant.	[45]
Therapeutic antiviral agents containing cannabis cannabinoid derivatives.	[46]

2.4 Fatty Acids of Cannabis seeds

Fatty acids have high nutritional value. They are a class of molecules made up of a chain of carbon atoms bonded with hydrogen atoms, with a function carboxyl group (-COOH) attached to a terminal end. It is this functional group that participates in chemical reactions that allow fatty acids to perform their physiological roles. Figure 5 below shows the structure of some fatty acids. These roles include: providing insulation, storing and providing energy for cells

in the absence of glucose, providing the precursor (cholesterol) for the production of hormones and intracellular membranes (estrogen, testosterone, vitamin D hormone, steroids, and prostaglandins), forming the building blocks of glycolipids and phospholipids which form the cell membrane and subcellular membrane, transporting fat soluble vitamins (A, D, E and K) , and modifying proteins. Many of these fatty acids have nutritional and pharmaceutical potential [47].
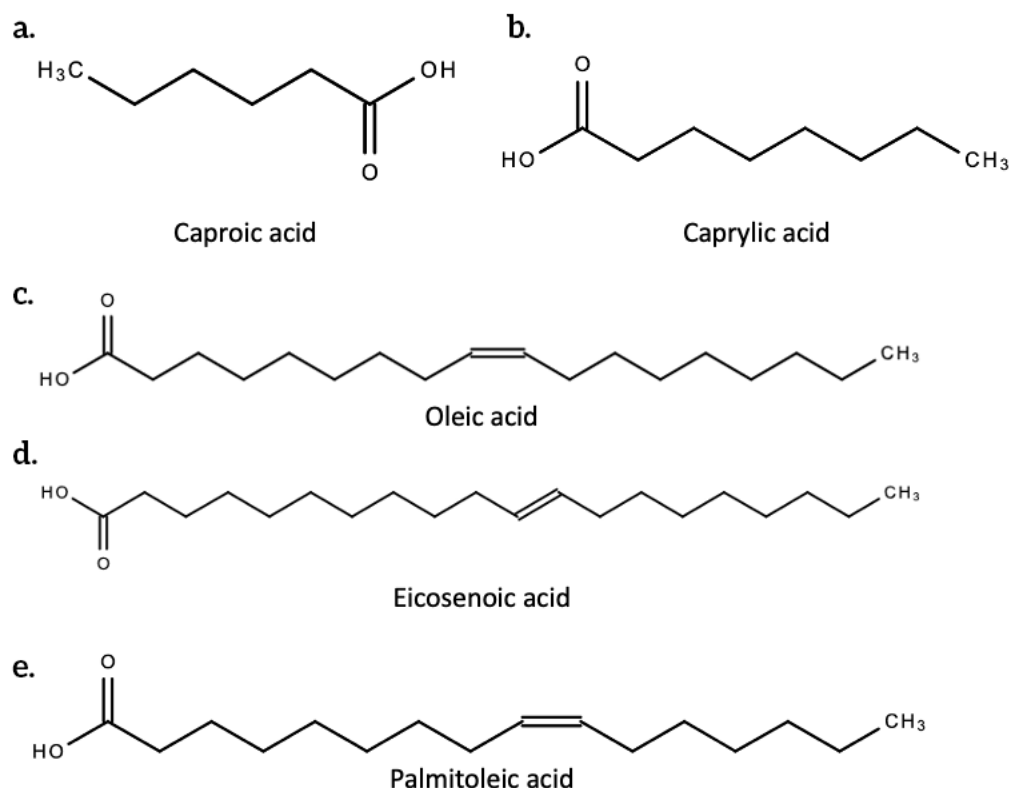

Figure 6. The structure of some fatty acids found in *Cannabis sativa*.

A 1996 study by Ross and colleagues explored the composition of fatty acids present in the lipid matter of [commercial] cannabis seeds from different countries. Some fatty acids in commercial *Cannabis sativa* (seeds) include caproic acid, caprylic acid, myristic acid, palmitoleic acid, palmitic acid, margaric acid, oleic acid, linolenic acid, isolinolenic acid, linoleic acid, stearic acid, eicosenoic acid, arachidic acid, isoarachidic acid, and behenic acid [48].

It should also be noted that *Cannabis sativa* seeds, particularly those of the hemp variety, typically have nutritional value. The seed is made up of approximately 25% high-quality protein and 35% fat [49]. Table 8 below lists some vitamins, minerals and macronutrients found in *Cannabis sativa* seeds. Hemp oil extracted from the seed contain significant concentrations of fatty acids (particularly omega-6 fatty acids), vitamin C [50][51], thiamine [50][51], riboflavin [50][51], vitamin E [50][51], minerals like calcium [50], magnesium [50][51], potassium [50][51], phosphorus [50][51], iron [50][51]. Zinc [50][51], sodium [50][51], copper [51], and macronutrients likes fat [50], carbs [50], fiber [50], and protein [50].

It should also be noted that *Cannabis sativa* seeds, particularly those of the hemp variety, typically have nutritional value. The seed is made up of approximately 25% high-quality protein and 35% fat [49]. Hemp oil extracted from the seed contain significant concentrations of fatty acids (particularly omega-6 fatty acids) and vitamin E, in addition to several minerals, vitamins and macronutrients (listed in table 7).

Table 7. Examples of vitamins, minerals and macronutrients produced *by Cannabis sativa* seeds [50]

Vitamins	Minerals	Macronutrients
C	Calcium	Fat
Thiamine	Iron	Carbs
Riboflavin	Magnesium	Fiber
Niacin	Phosphorus	Protein
B-6	Potassium	kJ:2313
Folate	Sodium	
A	Zinc	
E		

In comparison to other popular and nutritionally-rich edible oils like canola, sunflower, pumpkin and soybean, only hemp oil provides the optimal ratio (3:1) of omega-6 fatty acid (Linolic Acid) and omega-3- fatty acids (Alpha-linolenic acid), along with Gamma linolenic acid (GLA) and Stearidonic Acid (SDA) [49]. See Figure 7 for a comparison of composition of Edible plant oils.
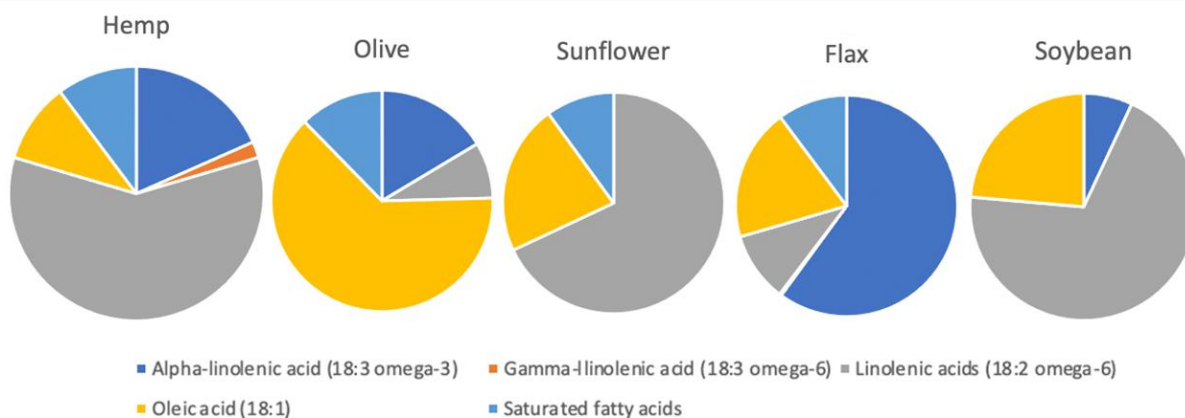
Figure 7. Comparison of fatty-acid composition of edible plant oils [49].

2.5   Alkaloids in Cannabis

In 1876 Preobrajensky claimed to find nicotine in cannabis resin (hashish) from Uzbekistan in 1876 [52]. This was later rejected on the basis that cannabis users from that part of the world tend to mix the resin with tobacco before smoking. This made it likely that the presence of nicotine was due to the tobacco. In later 1881 at the British Pharmaceutical Conference, Siebold and Bradbury reported on the isolation of the alkaloid Cannabinine [53]. Two years later in 1883, Hay isolated Tetanocannabin, another biologically active alkaloid. It was so called because it produced strychnine-like convulsions in frogs [54]. In 1986, even Merck (of Darmstadt) began marketing and advertising a "Cannabine Alkaloid" product [55].

Alkaloids are a class of hetero-cyclical organic compounds that contain one or more nitrogen atom. They may also contain an oxygen, sulfur, chlorine, bromine, or phosphorus atom attached to the molecule. They are most associated with plants, but are also produced by microorganisms and animals [56]. In plants, alkaloids are a form of chemical defense against herbivores. Many alkaloids are pharmacologically active. In fact, alkaloids make up about 60% of plant-derived drugs [57]. On the same tangent, dndogenous indole alkaloids have been confirmed in hemp [58].

Alkaloids have a variety of therapeutic applications as analgesics, anti-bacterial, anti-cancer, antiarrythmic, anti-asthma agents, antimalarials, anticholinergics, bronchodilatory, laxative, miotic, oxytocic, vasodilatory, psycotropic, and stimulating agents. This class of compounds include morphine, cocaine, nicotine, caffeine, quinine, ephedrine, among others.

Cannabinaceous alkaloids are alkaloids produced by *Cannabis sativa*. These include, but are not limited to Cannabisativine and Anhydrocannabisativine [59].

A 1971 study by Klein and colleagues investigated the constituents of alkaloids mixtures extracted from Cannabis plants and reported the isolated of four alkaloids, namely Cannabimines A-D [60]. It was also noted that both Cannabimine A and Anyhrocannabisativine (isolated in 1976) share the same molecular formular ($C_{21}H_{37}N_3O_2$) [59].

Cannabisativine was the first cannabinaceuous alkaloid to be fully identified. It was isolated in 1975 in Mississippi, from the roots of a Mexican variant of *Cannabis sativa* [61]. See **Figure 8** below. These alkaloids demonstrated antiparasitic, antipyretic, antiemetic, antitumor, diuretic and analgesic properties [62]. In a 2004 study, Kuethe and Comins were able to achieve total asymmetric synthesis of cannabisativine with a high degree of stereo control [63].
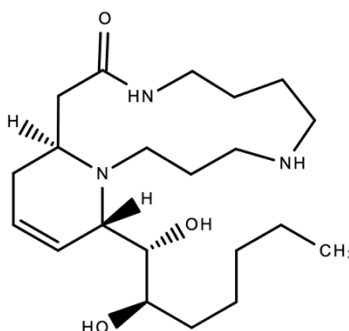

Figure 8. Chemical structure of Cannabisativine, the first cannabinaceuous alkaloid to be fully identified.

2.6   Lignanamides and phenolic acids

Lignanamides are another example of naturally-occurring, non-cannabinoid secondary metabolites with bioactivity. This class of phytochemicals produced in cannabis include Cannabisin A-G, and Grossamide [64].

These phytochemicals are powerful anticancer, antitumor, antiviral, antioxidant, antidiabetic, cardiovascular, cytotoxic, antineoplastic, anti-inflammatory, anti-obesity, analgesic, antihyperlipidemic and anti-hyperlipidemic agents [64], and they also inhibit Acetylcholinesterase inhibitory [65]. In this 2015 study by Yan and colleagues, four new lignanamides were also isolated from the hemp seed. These were Cannabisin M, Cannabisin N, Cannabisin O, and 3,3'-demethyl-heliotropamide [65]. Cannabisins are unique to the Cannabis plant. It should also be noted that phenolic amides share these bioactive properties [65].

2.7   Amino Acids

Amino acids are the building blocks of proteins which carry out a multiple biological functions in the body including energy production, fat metabolism, muscle metabolism, immune system function, response and maintenance, the synthesis of enzymes, hormones and neurotransmitters, tissue growth, nutrient absorption, sleep-wake cycles, regulation of blood sugar levels, hemoglobin production, digestion, and sexual function [66]. The amino acid molecule consists of a central carbon atom, an amino group (-NH2), a function R group side chain that defines the chemical properties of that specific amino acid, and a carboxyl group (COOH) [67]. Refer to **Figure 9** below for the chemical structure of an amino acid.
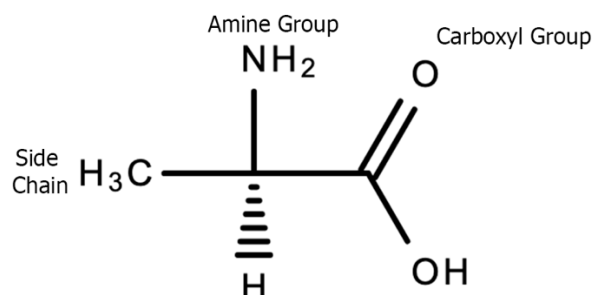

Figure 9. The basic structure of Alanine, an amino acid.

Cannabis sativa (hemp) seeds contain eight of the nine essential amino acids. These include histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, and valine. Tryptophan, from which serotonin (the "happy" neurotransmitter), is not produced in the *Cannabis sativa* plant. In fact, a 2007 study by Bambico and colleagues suggests that cannabinoids (THC, CBD) may exhibit potent antidepressant properties at low doses, and depressant properties at high doses [68]. This may explain the depressant properties of Cannabis at certain doses. Essential amino acids are defined as those that cannot be synthesized in our bodies, but instead have to be obtained through food. A 2014 study by Audu, Ofojekwu, Ujah & Ajima suggest that amino acids might be most concentrated within the leaves

of the *Cannabis sativa* plant [69]. This is understandable because trichomes (the cell's factory) are most concentrated in the leaves of plant.

Hempseed protein is unique within the plant kingdom because it contains the highest composition (65%) of the globulin edistin which make up many enzymes, antibodies, and hormones in the body [70].

2.8 Stilbenes and stilbenoids

Stilbenes (and their derivatives) are naturally occurring polyphenolic phytochemicals that, aside from being a form of herbivore- and disease-resistance mechanisms for many lower and higher plants in the plant kingdom [71], have a wide range of biological activity and medicinal value to humans [72]. Stilbenoids are stilbene derivates that have been hydroxylated [73].
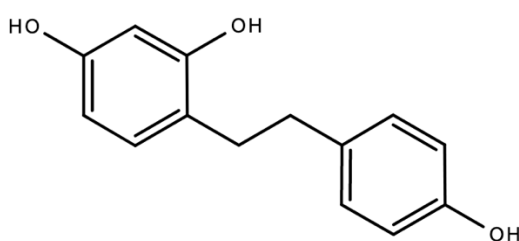
Figure 10. Chemical structure of Dihydroresveratrol, a hydroxylated stilbene derivative.

A 2004 study by El-Feraly isolated, characterized and synthesized dihydroresveratrol (3,5,4'-Trihydroxybibenzyl), a metabolite derivative of resveratrol, a dihydrostilbenoid, from *Cannabis sativa* (Figure 10 above) [74]. A 2019 study by Giménez-Bastida and colleagues reported that dihydroresveratrol and other metabolite derivatives of resveratrol, induced senescence in breast cancer cells [75].

Nineteen stilbenoids unique to the Cannabis plant were identified in a 1995 study by Ross and ElSohly [5]. These can be divided into three main structural classes: eleven spiroindans, eight dihydrostilbenes/bibenzyls, five phenanthrenes and prenylated, geranylated and glycosydated derivates [3]. Table 9 below is a list of these compounds.

Denbinoben, first isolated in a 2008 study by Sànchez-Duffhues, is reported to have beneficial bioactive properties to human health as an anti-HIV, antioxidant, anti-tumor, and inhibitor of platelet aggregation [76]. The structure of Denbinoben is shown in figure 11 below.

Table 9 some stilbenes and their derivatives found in *Cannabis sativa.*

Spiroindans	Eight Dihydrostilbenes/bibenzyls	Phenanthrenes and derivates.
1. Cannabispirone	**a. Prenylated**	1. 9,10-
2. Cannabispirenone-A	i. 3,4'-dihydroxy-5,3'-	dihydrophenanthrene
3. Isocannabispirenone	dimethoxy-5'	i. cannithrene-1
4. Isocannabispiradienone	isoprenyl	ii. cannithrene-2
5. Cannabispirenone-B	ii. Canniprene	

6. β-cannabispiranol
7. α-cannabispiranol
8. Acetyl cannabispirol

Cyclohexane Spirans
9. 5,7-dihydroxyindan-1-spiro-cyclohexane
10. 7-hydroxy-5-methoxyindan-1-spiro-ciclohexane
11. 5-hydroxy-7-methoxyindan-1-spiro-ciclohexane

iii. Cannabistilbene I,
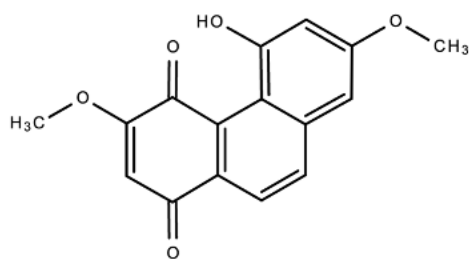iv. Cannabistilbene IIa
v. Cannabistilbene IIb
b. Non-prenylated
i. 3,4'-dihydroxy-5-methoxy bibenzyl
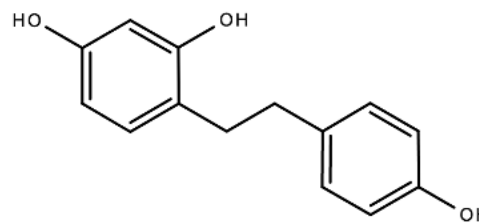ii. 3,3'-dihydroxy-5,4'-dimethoxy bibenzyl
iii. Dihydroresveratrol

2. 4,7-dimethoxy-1,2,5-trihydroxyphenanthrene
3. 4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene
4. 4-hydroxy-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene
5. Denbinobin (5-hydroxy-3,7-dimethoxy-1,4-phenanthrenequinone)

Denbinobin (5-hydroxy-3,7-dimethoxy-1,4-phenanthrenequinone)

Dihydroresveratrol
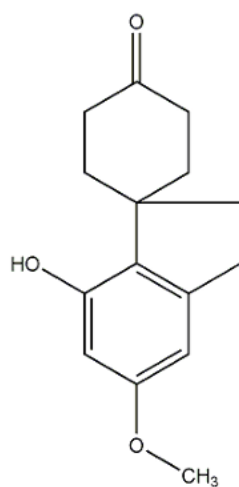
Cannabispirone
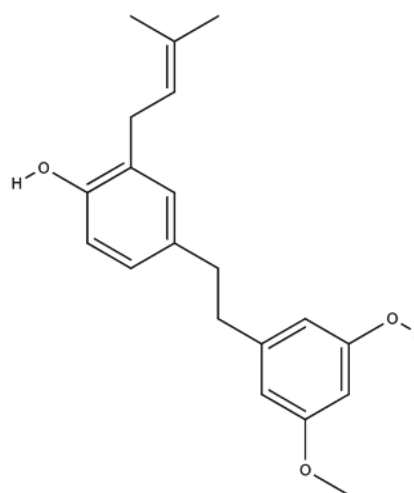
Cannabistilbene I

Figure 11. The chemical structures of some stilbenes and their derivates found in *Cannabis sativa*.

3. Conclusion and future prospects

The Cannabis plant produces an estimated 545 cannabinoid and non-cannabinoid phytochemicals of great economic and medicinal value [1]. These include some 104 cannabinoids (including CBD, Δ^9-THC, and CBG), 120 terpenoids, over 26 flavonoids [1], lignans, phenolic amides, amino acids, nitrogenous compounds, steroids, fatty acids, alkaloids, stilbenes, vitamins, minerals and other phytochemicals. These phytochemicals are produced in virtually all areas of the plant (root, leaves, stem). The aforementioned Cannabinoids and non-cannabinoid secondary metabolites are produced primarily in the trichomes of the Cannabis plant [77].

Cannabinoid and non-cannabinoid secondary metabolites have wide therapeutic application across many ailments including different types of cancers, diabetes, cardiovascular disorders, neurodegenerative disorders, inflammation-related diseases, and viral infections. Unlike THC, one of the most studied cannabinoids, the majority of these phytochemicals are non-psychotropic. This means they will not produce the psychoactive effects produced by THC, but will still have therapeutic benefit.

A majority of these phytochemicals require further in-depth characterization for their therapeutic efficacy and safety. There is also the need for a more rigorous standardization of cannabis cultivation practices so as to ensure consistent reproducibility of the profiles of secondary metabolites like terpenes. The ability to reconstruct synthetic pathways, elucidate regulatory mechanism involved in the production of secondary metabolites, and establishing genomic, metabolomic, transcriptomic maps/"fingerprints" of said secondary metabolites will allow drug-manufacturers to produce more targeted drugs [78].

There is a need for more systematic botanical, physicochemical and chemical analyses of the Cannabis plant. Further research is required to determine the efficacy, dosage standards, optimum extraction methods/solvents, cytotoxicity/hepatoxicity, pharmacokinetics, molecular mechanisms of action, phytoantiviral screening methods, and drug interactions for many phytochemicals in the Cannabis plant.

18

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