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Mini-review

CANNABIS TERPENES IN RELATION TO HUMAN HEALTH

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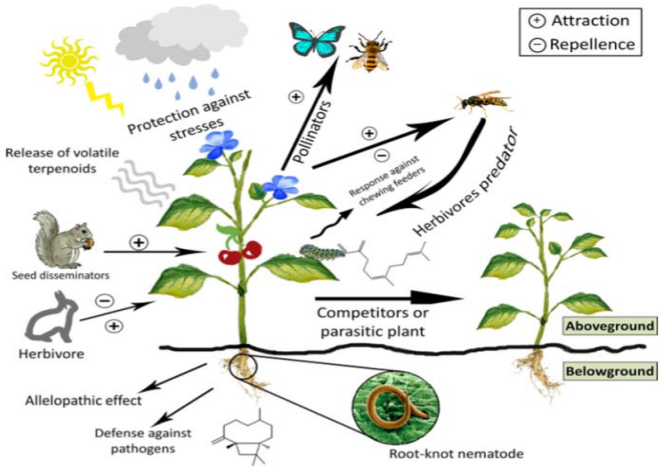
Terpenes and terpenoids form a large class of organic compounds, produced by numerous plants, including *Cannabis*, as secondary metabolites, together with cannabinoids, flavonoids, sterols, etc. They give the scent of the plants, as well as the fragrance of their extracts. In *Cannabis sativa* 110 terpenes and 121 terpenoids were described up to now, with myrcene and β-caryophyllene as the most prevalent mono and sesquiterpene, respectively. More than 30 genes are known to control the terpenes synthesis, through terpene synthases, less known. From here, a great variability of the relative content of tepenes has been described among *Cannabis* chemotypes, contributing to the modulation of some pharmacological actions, among the plant extracts. *Cannabis* terpenes have therapeutical potency, through independent actions, as well as through synergism or potentiation of the phytocannabinoids actions: antimicrobial and antiinflammatory properties, recently described analgesic effect, anticarcinogenic, antimutagenic, antiallergic, antihyperglycemic, antidepressive, anxiolytic, sedative effects, immunostimulating action, bronchodilator, increase of memory and concentration, active action on the main dermatological inflammatory diseases. The mini-review brings uptodate basic information referring to the chemical structure and classification of Cannabis terpenes, biosynthesis pathways, relative content variability, therapeutical effects.



INTRODUCTION

Cannabis sativa L. is a very potent plant, with an extremely rich metabolic profile. Although at present it is mainly perceived as a narcotic, it is also used since ancient times for its nutritional, medicinal and textile uses[1,2]. It is known that it has numerous active compounds representing different

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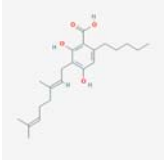
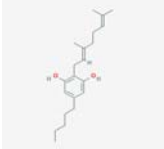
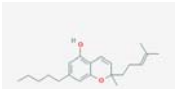
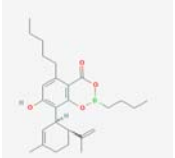
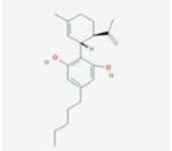
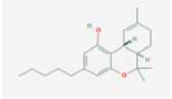
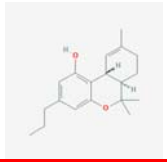
chemical classes. Some of them belong to primary metabolites, for example, amino acids, fatty acids and steroids, while cannabinoids, stilbenoids, flavonoids, steroids, lignans, terpenoids, and alkaloids belongs to secondary metabolites.[3] The name of secondary metabolites is due to the fact that they are formed due to the enzymatic resections of primary metabolites.

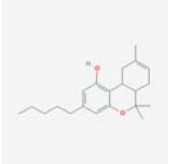
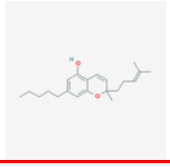
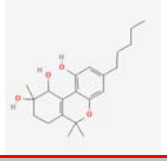
To date, *Cannabis sativa* L is known as a plant of about 1,600 chemical constituents, with more than 480 active compounds already been isolated, among which 180 belong to the cannabinoids family, and more than 150 are different terpenes.[4–6]

The phytocannabinoids identified so far, grouped in „structural families" or „classes" and their human effects are summarized in Table 1, next to the molecular formulas of some of them.

Table 1

Phytocannabinoids. Structural families and representatives with known actions. Adapted from[7-11]

Class Name	Compound with pharmacological known action	Pharmacological action
1. "**Cannabigerol**" type class (16 compounds)	Cannabigerolic Acid, CBGA 	Antibiotic
	Cannabigerol, CBG 	Antibiotic, antifungal, antiinflammatory, analgesic
2. "**Cannabichromene**" type class (9 compounds)	Cannabichromene, CBC 	Antiinflammatory, Antibiotic, antifunghi, analgesic
3. "**Cannabidiol**" type class (7 compounds)	Cannabidiolic Acid, CBDA 	Antibiotic,
	Cannabidiol, CBD 	Anxiolythic, antipsychotic, analgesic, antiinflammatory, antioxidant, antispasmodic
4. "**Delta-9- Tetrahydro- cannnabinol**" type class (23 compounds)	Tetrahydrocannabinol, THC 	Euphoriant Analgesic, Antiinflammatory, Antioxidant, antivomiting
	Delta-9- tetrahydrocannabivariv THCV 	Analgesic, euphorizing

5. "**Delta-8- Tetrahydro- cannnabinol**" type class (5 compounds)	Delta-8- Tetrahydro- cannnabinol 	Similar to THC, with weaker action
6. "**Cannabinol"** type class (11 compounds)	Cannabinol, CBN 	Sedative, antibiotic, anticonvulsivant, antiinflammatory
7. "**Cannabinodiol**" type class (2 compounds)	Cannabinodiol, CBND	Psychoactive
8. "**Cannabicyclol**" type class (3 compounds)	Cannabicyclol, CBL	Non-psychoactive
9. "**Cannabielsoin**" type class (5 compounds)	Cannabielsoin, CBE	Non-psychoactive
10. "**Cannabitriol**" type class (9 compounds)	Cannabitriol, CBT 	Anti breast cancer, through inhibitory activity on estrogen receptors-alpha,
11. "**Miscellaneous cannabinoids**" type class (30 compounds)		

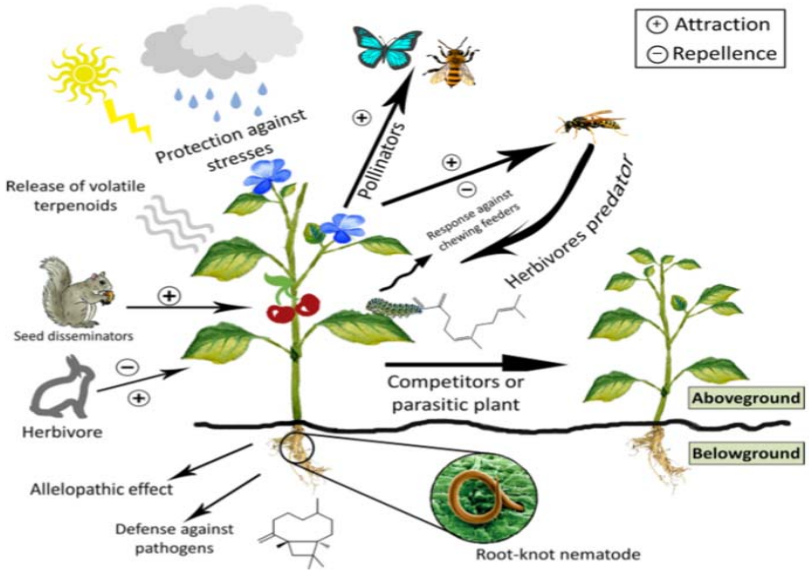


Fig. 1 – A summary of volatile mediated interactions between plants and their surrounding environment. Reproduced from.[11]

The combination of different secondary metabolites of varying concentrations is believed to increase the range of therapeutic properties – known as the "entourage effect".[7-9] Such interactions ocure among terpens or among phytocannabinoids in a cannabis full/broad spectrum extract, called intra-entourage effect, as well between a terpene and a phytocannabinoid, called inter-entourage effect.

Terpenes are responsible for the odor and flavor of the different *Cannabis* species. They are playing an important role in plant life through plant defenses, by attracting pollinators and through different interactions between the plants and their environment (Figure 1). They are important because of their enormous applications in the pharmaceutical, food and cosmetics industries.[10]

Table 2

Examples of terpenes and terpenoids from *Canabis sativa* L., adapted from [13]

	Terpenes	**Terpenoids**
C10	●Beta-myrcene (acyclic, C10H16) ●Alpha-phellandrene (monocyclic, C10H16) ●Alpha-pinene (bicyclic, C10H16) ●Tricyclene (tricyclic, C10H16)	●Linalool (acyclic, C10H18O) ●Cis-linalool oxide (monocyclic, C10H18O2) ●Cis-sabiene hydrate (bicyclic, C10H18O)
C15	●Cis-Beta-farnesene (acyclic, C15H24) ●Alpha-humulene (monocyclic, C15H24) ●Beta-caryophyllene (bicyclic, C15H24) ●Alpha- cubebene (tricyclic, C15H24)	●Cis-nerolidol (acyclic, C15H26O) ●Humulene epoxide II (monocyclic, C15H24O) ●Sesquicineole (bicyclic, C15H26O) ●Epi-cubebol (tricyclic, C15H26O)
C20	m-camphorene (monocyclic, C20H32)	●Phytol (acyclic, C20H40O)
C30	●squalene (acyclic, C30H50)	●sitostanol (tetracyclic, C29H52O) ●friedelin (pentacyclic, C30H50O)

(1) Terpenes: Chemical structure. Classification

Terpenes are hydrocarbons consisting of repeated unit of isoprene, through ”head-tail” connections (in the case of mono-, sesqui-, di-, and sesterpenes) or it associates ”head-tail” connections with ”head-head” ones (in triterpenes and carotenoids/ tetraterpenes).[11] The name of terpenes was suggested by Kekule for hydrocarbon in 1866.[12]

Terpenes are classified in families, according to the number of isoprene unit repetition: hemiterpenes (1 unit, 5 Carbon atoms), monoterpenes (2 units, 10 Carbon atoms), sesquiterpenes (3 units, 15 Carbon atoms), diterpenes (4 units, 20 Carbon atoms), Sesterpenes (5 units, 25 Carbon atoms), triterpenes (6 units, 30 Carbon atoms), carotenoids (8 units, 40 Carbon atoms), gums (more than 100 units, more than 500 Carbon atoms).[13]

Terpenoids are modified terpene classes, which contain oxygen atoms, thus resulting alcohols, aldehydes or ketones. According to Hanus/Hod, 2020, in *Cannabis sativa* 110 terpenes and 121 terpenoids were described up to now, representative examples are included in Table 2.[13]

(2) Terpenes and terpenoids profiles in *Canabis sativa* L

Monoterpene myrcene is the smallest and most prevalent terpene, found in most varieties of *Cannabis*, while among the sesquiterpenes of the plant, β-caryophyllene is the most prevalent and the only terpene that is known to interfere with the human endocannabinoid system.[14]

In *Cannabis* plants, terpenes and terpenoids reach their highest concentration, together with cannabinoids, in the resin secreted by glandular trichromes that cover the inflorescence of female non-fertilized plants.[15] The absolute quantity of terpenes in the living plant and especially the profile of terpenes is a variable aspect, the genetic determinant being strongly superior to the environment conditions (climate, fertilizer, plant age)[16-18] Consequently, each cannabis strain has its own terpenoid profile, that differs both qualitatively and quantitatively from that of other strains, due to their relative amounts and the assemblage of the given terpenes present.[19] Variations in the terpene profile can also be found in different growth stages (*e.g.* in the vegetative stage the proportion of monoterpenes is much lower than in the flowering stage).[20] The profile of terpenes is especially sensitive to the environment conditions after harvesting (the heat and light conditions during preservation and processing).[17]

Three species have innitialy been described in *Cannabis* plants (Figure 2): *Cannabis sativa Linnaeus* (by the suedish botanist Carl Linnaeus in 1750), *Cannabis indica Lamarck (*by the French naturalist Jean Baptiste Lamarck in 1785), and *Cannabis ruderalis* (by the rusian botanist D.E. Janichevsky in the XXth century).[21, 22] It is accepted today *that sativa, indica and ruderalis* plants are subvarietes of *Cannabis sativa L.* The s*ativa* subvariety (known as hemp) has a low content of THC and terpenes as well, while the *indica* subvariety (known as marijuana) has a high content of THC and terpenes.[23]

Cannabis growers have produced a large number of hibrids, of these native subspecies, which they group and express as the following biotypes: “pure sativa”, “mostly sativa”, “sativa/indica hybrid”, “mostly indica”, “pure indica”, “ruderalis hybrid”. The relativ content in terpenes (% myrcene, % limonen, % pinene, etc) is stable among the plants of the same biotype, but it vary from one biotype to another, being genetically determined. Due to this stable terpene profile

inside each cannabis biotype, some terpenes have been used as biomarkers of the plants, when they are found to have the same content in cannabinoids. As such, they allow to make the difference between medical and recreational strains, as well to detect strains resistant to insects (the volatile monoterpenes in inflorescences showed repellent action, mostly limonene and alpha-pinene), or to select plants resistant to the attack of herbivores (the bitter sesquiterpenes in cannabis leaves remove the herbivores).

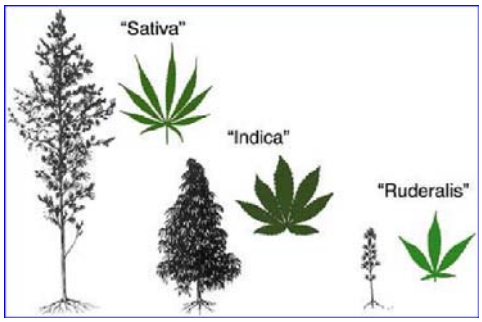


Fig. 2 – Morphological differences among the 3 subvarieties of *Cannabis sativa L*. Reproduced from.[24]

There are scientists who promote sesquiterpenes as suitable biomarkers of cannabis cultivars; others sustain even several monoterpenes might have this quality. As such, in cannabis „mostly indica" beta-myrcene, followed by limonene and alpha-pinene dominates, while in "mostly sativa" plants the dominancy is of alpha-terpinolene or alpha-pinene or beta-myrcenes, followed by alpha-terpinolenes or trans-beta-ocimenes.[25]

For a better understanding of the medicinal properties of the *Cannabis sativa L* plant, a new classification aside from the botanical one, has been developing from 1973 until 2004, based on a range of potentially active constituents, among which the most important are cannabinoids and terpenoids. Instead of the designation of "strain" or "cultivar", the term "chemovar" or "chemotype" is used, as suggestive for the chemical profile of phytocannabinoids and terpenes in flowers[26]. To date, 5 chemotypes have been defined for *Cannabis sativa L*, reffering to the ratio CBD: THC in each plant, while the accompanying terpenes of each type, still need an ongoing research:[27-30]

Chemotype **I**: THC-dominant with a concentration of >0.3% and CBD content of <0.5%. It has no medical use;

Chemotype **II** – contains CBD and THC in varying moderate concentrations, CBD more than THC. This chemotype allows therapeutic benefits, while mitigate unwanted intoxication with THC;

Chemotype **III** – CBD-dominant with low THC content (up to 1%), that provides little to no intoxication.

In Europe, only plants with THC less than 0.3% are regulated, of this type. It is a medicinal use type, too;

Chemotype **IV**, a type III, rich in Cannabigerol (CBG). CBG has demonstrated potential therapeutic benefits, ranging from appetite stimulation to reduction in neuroinflammation and increased neuroprotection, in mouse models;

Chemotype **V** – refers to *Cannabis* plants that produce little to no cannabinoid content. The usefulness of this chemotype is still sought.

When a chemotype is analyzed, it is recommended at least five of the most commonly abundant terpenes to be evaluated: a sesquiterpene, β-caryophyllene and four monoterpenes: D-limonene, β-myrcene, α-pinene, and γ-terpinolene.[31] An example of association "chemotype – terpenes profile" is reproduced in Figure 3. In plants with prevalent content of CBD or THC, certain sets of terpenes resulted to accompany the main cannabinoid, each terpene of the set, with more or less probability, as Figure 3 expresses.[21, 32]

(3) Terpenes Biosynthesis in *Canabis sativa* L

Most terpenes that are identified in *Cannabis* are hydrocarbons, directly produced, through the catalytic action of the terpesynthase enzymes, while more complex molecules need cytochrome P450's action. The chemical diversity of terpenes identified in *Cannabis* corresponds to the chemical diversity of terpesynthases (CsTPS) that are codified in the genes of cannabis enzyme family.
Terpenes identified in cannabis resin are produced through an isoprenoid biosynthetic system, that has its origin in 2 synthesis pathways:

(1) **the mevalonic acid pathway** (MEV), ocures in cytosol, resulting sesquiterpenes and triterpenes and

(2) **the methylerythritol phosphate pathway** (MEP), ocures in plastides, resulting mono, di and tetraterpenes.

Monoterpenes and cannabinoids have a common precursor, namely an isoprenoid C10, geranyl diphosphate (GPP, C_{10}), while sesquiterpenes are released by isoprenoid C15, farnesyl diphosphate (FPP, C_{15}) (Figure 4).[33, 34]

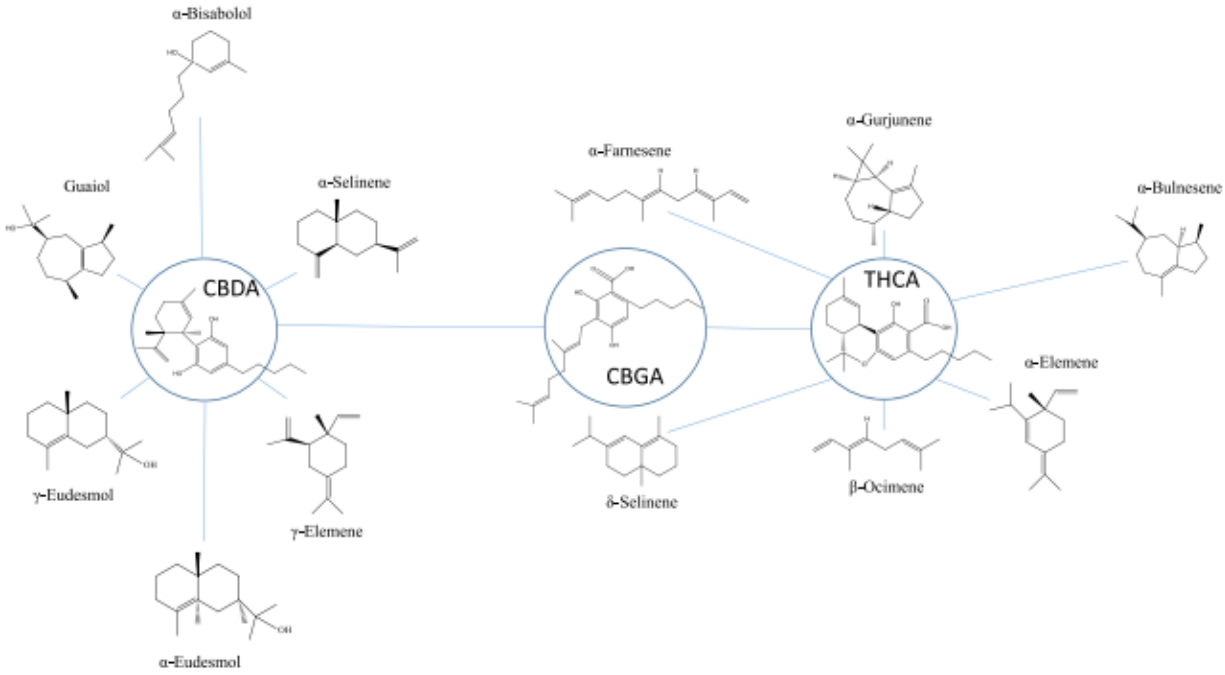


Fig. 3 – Schematic description of the correlation between THCA or CBDA and specific sets of terpenes. Principle components analysis (PCA) was used. The length of the lines between compounds represents the statistical correlation distance between the components. Abbreviations: CBDA, cannabidiolic acid; THCA, Δ9-tetrahydrocannabinolic acid. Reproduced from.[34]

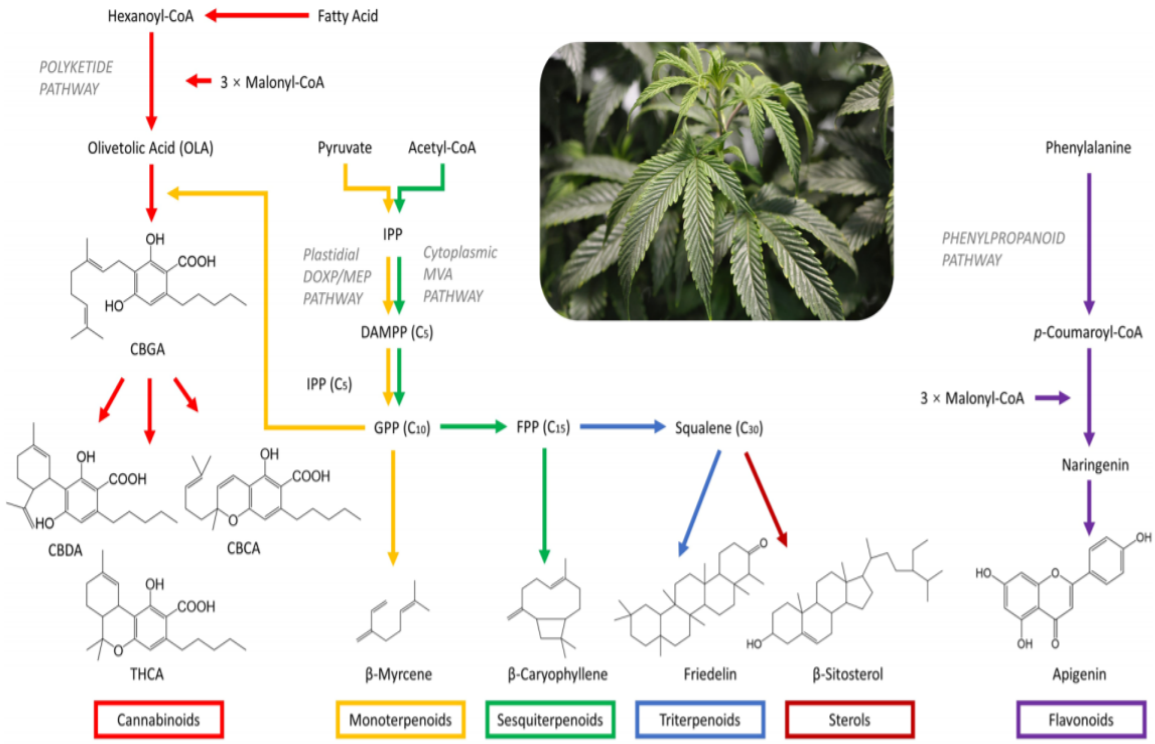


Fig. 4 – Schematic view of the biosynthetic pathways leading to the *Cannabis* secondary metabolites. Reproduced from.[36]

The terpenes synthesis is catalised by monoterpene-synthetase (mono-TPS) and sesquiterpenes synthetase (sesqui-TPS). More than 30 genes of *Cannabis* TPS (CsTPS) were identified. Only nine of them have been functionally characterized, having a multi-product nature.

The variability of the genetic structure in the CsTPS family and the variation of the expression of CsTPS genes may explain the variation of the

terpene profile. Gene expression may change during the plant growth, or under the influence of environmental factors.

There are terpenes detected in cannabis that may appear through non-enzymatic mechanisms, due to the oxidation, high temperature or UV radiations, during the storage or processing stages. These non-enzymatic changes may cause a level of variation, independent of the plant metabolism. Variations of terpenes, especially in the case of volatile monoterpenes, may occur when processing the dried plants.[35-38]

(4) *Cannabis* sativa L. terpenes: therapeutical effects

The unquestionable element that can be attributed to terpenes is the specific aroma for volatile monoterpenoids and sesquiterpenoids. According to the profile of cannabis terpenoids, different aromas for various types of cannabis may be induced.[39] Terpenoids may directly elicit physiological effects, modulate cannabinoid responses or reduce their undesired side effects. As to their independent therapeutical effects (studies on animals and humans), the following can be listed: antimutagenic, antidiabetic, analgesic, antiinflammatory, in acute inflammations, unlike cannabinoids, efficient in chronic inflammations,[40] antiallergic, antioxidative, antitumoral, anxiolythic and neuroprotector.[41,42] Examples of independent therapeutical effects of the best known terpenes are presented in Table 3. The minimum concentration of terpenes in the full spectrum cannabis extract, required for their functions to be effective, is above 0.05% v/w.[43-45]

More and more studies have been published on the synergistic and/ or entourage actions of terpenes and cannabinoids, when they are used in natural cannabis full-spectrum and broad-spectrum products.[46] Subsequent, Russo developed the term of "botanical synergy", in which a dominant, active molecule is supported by other plant derivatives as cannabinoids, terpenes, flavonoids and other inactive substances, to achieve a maximal pharmacological effect.[47] The potentiation between different compounds of the same structural family (terpenes, flavonoids, cannabinoids) is called "intra-entourage",[48] while between cannabinoids and terpenes "inter-entourage".[49] In the scientific literature it is stated that although terpenes in the extracts from cannabis inflorescence have low concentrations, their contribution to the therapeutic effect of the cannabinoids may be significant. It is also considered that terpenes enhance the mood stabilizing effects of the two main cannabinoids, THC and CBD. *Cannabis indica* L. strains, are rich in THC and myrcene, too. Myrcene induces relaxation and decreases the anxiety given by THC. *Cannabis sativa* L. strains are mostly rich in limonene and other terpenes, that induce alertness.[21]

There are evidences that certain monoterpenes block the forming of tumors or inhibit the *in vivo* progression of the tumor cells cycle in rats. Similarly, cannabinoids may inhibit the forming of malignant tumors in animals. It is suggested that the cannabis extract with a combination of cannabinoids and terpenes may have anticancerous properties.[50-53] An alcoholic extract from fresh *Cannabis*, rich in THC, associated in turn with 5 types of terpenes (beta-caryophyllene, humulene, nerolidol, linalool, sibeta-pirene) showed a stronger antitumoral activity than the pure THC, without any of the 5 terpenes having independent antitumor action.[9]

Some medicinal properties may vary, from one *Cannabis* variety to another, due to the active role the terpenes and flavonoids play, summing with (synergism) or potentiating (entourage effect) the cannabinoids actions, on one hand; on the other hand, because of different terpenes profiles, in different cannabis chemotypes.[8, 54] Table 4 presents examples of terpenes and phytocannabinoids and their synergistic actions,[8] in *Cannabis sativa* plants.

The National Academy of Sciences, Engineering, and Medicine's 2017 publication, "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research"[55] provided a significant contribution by synthesizing the existing evidence base for the therapeutic use of cannabis. Among the multiple effects of the medical use of *cannabis* plant one can include: analgesic,[56] anti-vomiting, anti-nausea, antiepileptic (Dravet and Lennox-Gastaut syndromes), antipsychotic, antidiabetic, neuroprotective, antiinflammatory[57] and immunomodulatory properties,[58] muscle relaxant (Parkinson's disease, multiple sclerosis, Huntington's disease)[59] anti-arthritic, anti-anxiety, antiglaucoma action, Alzheimer's disease and dementia, as well as anti-tumoral properties.[60-62] In this context, more clinical research is needed, to define the influence of terpene profiles on the pharmacology of a cannabis product, for specific conditions.

Table 3

Therapeutic, independent effects of the best known terpenes in plants. Reproduced from[63]

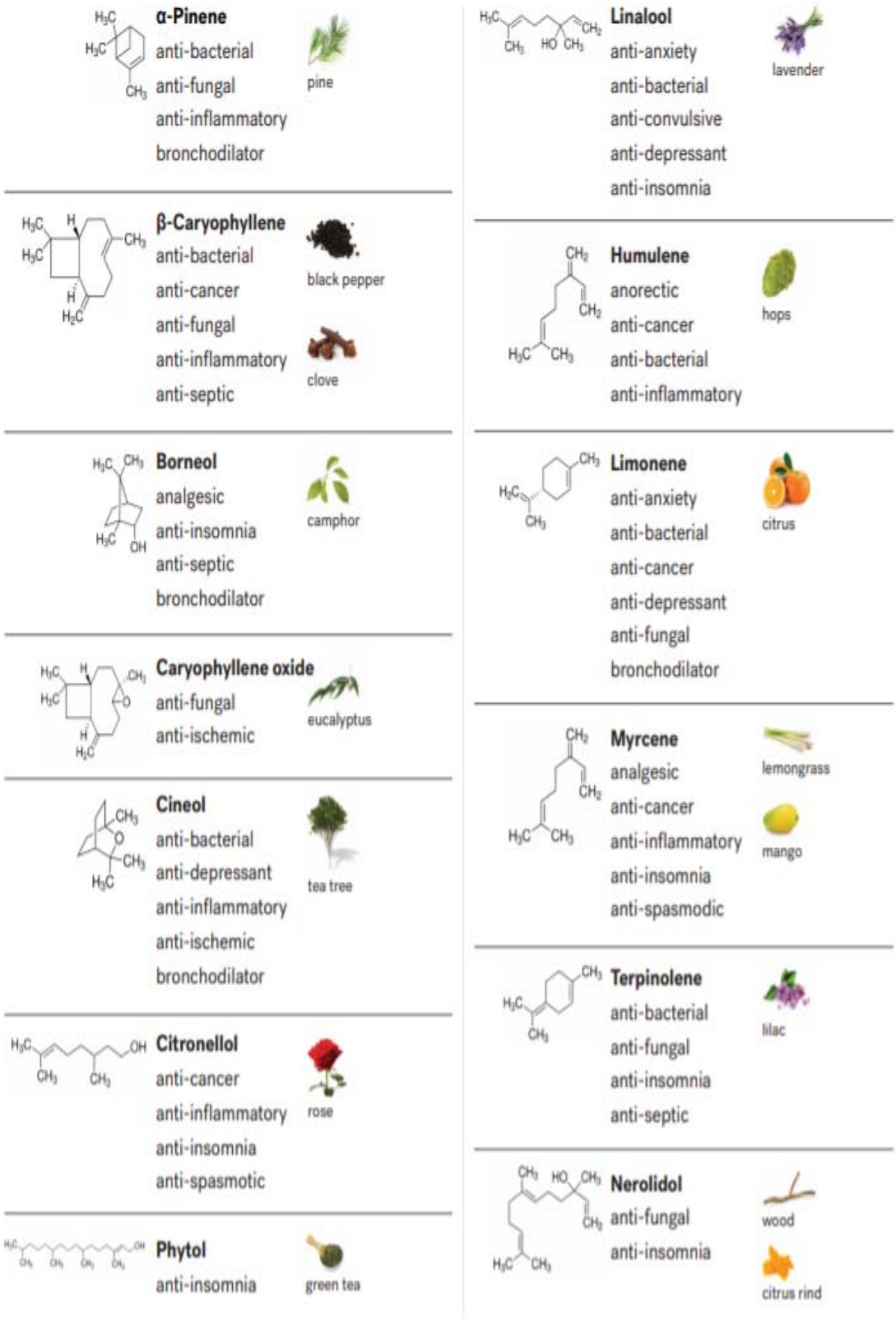


Table 4

Synergistic actions of terpenes of *Cannabis sativa* and phytocannabinoids

		phytocannabinois		
		THC	**CBD**	**CBG**
Terpenes	***Limonenes***	gastroesophageal anti-reflux	immunostimulating by inhalation, anxiolythic, antiacne, breast cancer cell apoptosis	
	Alpha-pinenes	Bronchodilator effect	antiinflammatory effect, via Prostaglandin E1	
	Beta-myrcenes	sedative, muscle-relaxing and hypnotic effects	anticarcinogenesis effect induced by aflatoxin, antiinflammatory effect via Prostaglandin E2	anticarcinogenesis effect induced by aflatoxin

CONCLUSIONS

Non-phytocannabinoid constituents of *Cannabis sativa* are now giving birth to a new and promising area of research. In the past, the only argument for identifying the profile of terpenes in cannabis was to improve canine training aids in illicit drug detection.[64] At present it is known that terpenes can enhance, through synergistic or potentiation actions, the feeling of relaxation, stress relief, energy boost, given by cannabinoids, as well as their pharmaceutical functions.[65, 66] This mini-review brings to the attention of the professionals in the medical system a topic that we can no longer afford not to delve into.

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