Vapor pressure, vaping and corrections to misconceptions related to medical cannabis APIs physical properties and compositions

Aharon M Eyal[1], Dana Berneman Zeitouni[1], Dor Tal[1], Daniel Schlesinger[1], Noa Raz[1]*

[1] Bazelet Medical Cannabis Group, Or Akiva, Israel.
*. Corresponding author

Keywords
Terpenes, Cannabinoids, Vapor pressure, Boiling points, cannabinoids, Vaporization

Abstract

Introduction – Medical cannabis products contain dozens of Active Pharmaceutical Ingredients (APIs) resulting from the cannabis plant. However, their compositions and relative doses significantly change according to the production method. Products compositions are strongly dependent on processing steps conditions and on components evaporation during those steps. Review of the documentation presented to caregivers and to patients show erroneous data or misinterpretation of data related to the evaporation, e.g., cannabinoids boiling points, as well as confusions between terms, such as boiling, vaporization and evaporation.

Methods – Original and literature data were analyzed, comparing composition changes during various processing steps and correlating the extent of change to components vapor pressures at the corresponding temperature.

Results – Evaporation-related composition changes start at temperatures as low as those of drying and curing and become extensive during decarboxylation. The relative rate of components evaporation is determined by their relative vapor pressure and monoterpenes are lost first. On vaping, terpenes are inhaled before cannabinoids do.

Conclusions – Commercial medical cannabis products are deficient in terpenes, mainly monoterpenes, compared with the cannabis plants used to produce them. Terms such as “whole plant” and “full spectrum” are misleading since no product actually reflects the original cannabis plant composition. There are important implications for medical cannabis manufacturing and for the ability to make the most out of the terpenes API contribution. Medical cannabis products composition and product delivery are controlled by the relative vapor pressure of the various APIs. Quantitative data provided here can be used for improvement to reach better accuracy, reproducibility and preferred medical cannabis compositions.

Introduction

Unlike conventional drugs, most medical cannabis preparations contain multiple active pharmaceutical ingredients (APIs), including several cannabinoids and about twenty prevalent terpenes, all of which are considered to affect the results of the cannabis medical treatment. While the role of the main cannabinoids – THC and CBD – is studied for several decades[1,2], understanding the role of the terpenes in cannabis is still in its early stages [3–10]. The focus is not only on the effects of terpenes as such (their content is relatively small), but also on synergistic modulation of the cannabinoid's functionality, referred to as the entourage effect. The extent of that effect is still debated [5,11–16]

Many caregivers tend to think in terms of preferred strains or chemovars for treating particular indications. This also applies to oils produced from such strains. Terms like "whole plant" and "full spectrum" are often used to describe such oils[17–21]. Similarly, several cannabis clinical trials tested products characterized by strain name[5,22,23], rather than in terms of composition. Other commercial products, including ones used in many clinical studies, are characterized by the content of the main cannabinoids, but with no information about their terpenes content[17,19,20,24]. The Israeli regulator has specified products to be used for treating medical cannabis patients in Israel, all of which are characterized only by their content of THC, CBD and CBN[25].

This approach conflicts with a simple truth – the medical effect is determined by the doses of the main APIs in the formulation, independent of their source. The compositions of the medical cannabis products reflect inconsistency in inflorescences compositions and the effects of processing conditions[6,20,24,26–28]. The study here focuses on the changes in the composition during common steps of industrial manufacture of medical cannabis, such as drying and curing, extraction and decarboxylation. Given the volatility of some of the cannabis APIs, mainly the monoterpenes, the following deals more specifically with vaporization of APIs, with the parameters controlling it and with their implications for the final products' composition. Some of those implications extend to APIs provision during vaping. Also discussed are common misinterpretations of related physical data.

Materials:

Commercial medical cannabis extracts diluted in olive oil ("cannabis oils") and commercial inflorescences were purchased from authorized manufacturers in Israel. Cannabinoid's standards: Cannabinol (CBN), Cannabichromene (CBC), Cannabichromenic Acid (CBCA), Cannabigerolic acid (CBGA), Cannabigerol (CBG), Cannabidiolic acid (CBDA), Cannabidiol (CBD), Delta-9-Tetrahydrocannabinoic acid (THCA) and Delta-9-Tetrahydrocannabinol (THC) were purchased from Cerrilliant (Cerilliant Corporation, Round Rock, TX, USA). Cannabidivarin (CBDV), Cannabidivarinic Acid (CBDVA), Tetrahydrocannabivarin (THCV), and Delta-8-Tetrahydrocannabinol (Δ8-THC) were purchased from Restek (Bellefonte, PA, USA).
All terpene standards were purchased from Restek (Bellefonte, PA, USA), Catalog No.34095.
Ethanol for standard solutions and samples preparation was HPLC grade (J.T. Baker, USA).

Methods:

Vaping trials

Commercial cannabis inflorescences were ground using a coffee grinder (five pulses of 1 second each). About 200 mg doses of the ground material were vaporized using the Volcano Medic® vaporizer (Storz and Bickel, Tuttlingen, Germany) at selected temperatures and for

selected durations, all in three replicates. The inflorescence and the remaining materials after the vaporization were analyzed for their cannabinoids and terpenes content.

HPLC and GC analysis

High Performance Liquid chromatography

The analysis of cannabinoids was carried out on HPLC Waters PDA 2996, equipped with a pump, autosampler, column-oven, and a Photodiode Array detector (PDA). The analytical balance is Mettler Toledo MS205DU. The method was developed by Bazelet and is based on HPLC reverse phase separation with HPLC column type C18 and UV detection. The method is fully validated for 12 cannabinoids (see in materials) with requirements of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines[29], Israeli Medical Cannabis Agency (IMCA), European Pharmacopoeia (EP)[30] and the United States Pharmacopeia (USP). The method range is 0.1% - 120.0% of the nominal working concentration, proved by linearity, precision and accuracy studies. The Limit of Quantitation of the method is 0.1%. Total cannabinoids is calculated as if all of the cannabinoids are in their decarboxylated form.

Gas Chromatography

Terpene's analysis was carried out on Agilent Technologies GC system model 6890N equipped with FID detector. A CTC autosampler (Pal RTC, CTC analytics, Switzerland) was used. The column was ZB-624plus 30m X 0.25 mm X 1.40µm with He as carrier at 1.2 mL/min constant flow. The method, developed in Bazelet to determine 19 terpenes likely to be present in cannabis. The method is fully validated according to the requirements of ICH guidelines, EP and USP. The range of the method is 200 ppm – 4000 ppm, proved by linearity, precision and accuracy studies. The Limit of Quantitation of this method is 200 ppm. Due to a lack in standards the content of all unidentified terpenes was estimated by calculating their area from a-Humulene response factor. The terpenes that are not fully identified are presented by their retention time (RT).

Results and Discussion:

Prevalent terpenes and their content in inflorescences and in extracts

Inflorescences of chemovars grown in Israel were analyzed for their cannabinoids and terpenes contents. Table 1 presents for each terpene ranges of concentration and of terpenes to total cannabinoids ratios. Table 2 presents similar data for commercial medical cannabis "oils" – cannabis extracts diluted in vegetable oils.

The majority of the identified terpenes belong to one of four groups – monoterpenes, monoterpenoids, sesquiterpenes and sesquiterpenoids, see Table 3. The total inflorescence terpenes content varies much between different chemovars, about 0.3% to about 2.3%, and the most prevalent ones are myrcene, α-humulene, β -caryophyllene and β-pinene, which is in good agreement with literature results[5,6]. Lower terpene contents were found in the commercial oils, which are particularly low in monoterpenes.

Vaporization, boiling, boiling points and evaporation

The boiling points of some of the cannabis terpenes are shown in Table 3. Unless differently specified, the term boiling point refers to the temperature of boiling at atmospheric pressure, also termed normal boiling point. Typically, the boiling points increase in the following sequence: monoterpenes, monoterpenoids, sesquiterpenes and sesquiterpenoids.

It is well known that terpenes are volatile and that the characteristic aroma of different chemovars is determined by some of the more volatile terpenes[31]. Also known is that some of the terpenes are lost due to vaporization during processing and that the extent of monoterpenes loss is greater than that of sesquiterpenes[32,33]. Yet, there is much erroneous data and misinterpretation of data related to the boiling points of cannabinoids and of some terpenes. For example, dozens of documents and websites report that the boiling point of THC is 155-157°C and that that of CBD is between 160°C and 180°C[34], while the actual (normal-) boiling points are markedly higher as detailed in the following. Similarly, the boiling point of β-caryophyllene is shown in many publications as 119°C or 130°C[34], while the actual boiling point is about 263°C[35]. Also, in some cases, the terms boiling, vaporization and evaporation are confused. These aspects are briefly discussed here, based on the vapor pressure property of the involved compounds.

The vapor pressure is the pressure exerted by a vapor in thermodynamic equilibrium with the liquid phase[36]. At a given temperature, more volatile liquids have higher vapor pressures. The vapor pressure increases non-linearly with the temperature, according to the Clausius-Clapeyron equation[37]. Figure 1 presents vapor pressures dependency on temperature for some of the terpenes, based on this equation. The temperature at which the vapor pressure of a compound reaches the atmospheric pressure (760 torr, 100KPa) is the boiling point of that compound, also referred to as the normal boiling point. At this temperature, the vapor pressure becomes sufficiently high to overcome the atmospheric pressure and to lift the liquid to form bubbles, which is referred to as boiling. Under vacuum, lower temperatures are sufficient to bring the vapor pressure to the external one, so that at high vacuum of 0.05 torr, THC boils at about 155°C.

There is no practical direct way of measuring the temperature at which the vapor pressures of THC and CBD reach normal room pressure (about 760 torr), since at such elevated temperatures, these cannabinoids are instable and decompose. The normal boiling points can, however, be estimated by extrapolating vapor pressure at lower temperatures, using the Clausius-Clapeyron equation. For example, the vapor pressures of THC at 155°C and 190°C are about 0.05 torr and 0.3 torr, respectively, leading to boiling points higher than 400°C, in agreement with the results of McClements et al., Umnahanant et al and Lovestead and Bruno[38–40].

The term vaporization refers to any form of converting liquid to gas, including at temperatures below the boiling point (as in cannabis inflorescence drying at ambient temperature). Such vaporization below the boiling point is termed evaporation. At a given temperature, compounds with different boiling points vaporize at different rates. The relative rate of vaporization depends on the corresponding vapor pressure. Calculated vapor pressures at various temperatures are added in Table 3. This data shows that a relatively small difference in the boiling point may result in a significant difference in the vapor pressure so that, for example, at 20°C, the rate of α-pinene evaporation is about 3 times greater than that of limonene.

The following sections deal with vaporization and evaporation of cannabinoids and terpenes at various stages of cannabis processing and administration.

Terpenes loss on drying and curing at about the ambient temperature

Harvested cannabis inflorescences typically contains about 80% moisture and goes through post-harvest drying and curing. Various manufacturers adopt different drying methods, characterized among others by different treatment durations ranging from few weeks to a couple of months. Although conducted at relatively low temperatures, some terpenes evaporation takes place.

Hanus and Hod's[5] Tables 24 and 25 present the prevalent terpenes of chemotype Pandora's Box in fresh and in dry forms, normalized to the most prevalent terpene in each case (terpinolene and β-caryophyllene, respectively). In Table 4, we have recalculated the terpene contents for both the fresh and the dried forms relatively to the content of β-caryophyllene in each. It shows that, as a result of drying, out of the two main monoterpenes, β-myrcene disappears from the most prevalent terpenes, and the terpinolene/β-caryophyllene ratio drops by more than a factor of 3. For most sesquiterpenes, however, changes are small. Similar observations were reported by Ross and ElSlsohly 1996[41]. These results are in agreement with the calculated vapor pressures in Table 3, showing that, at ambient temperature, the vapor pressure of β-myrcene is about 80 times greater than that of β-caryophyllene.

Thus, even dried inflorescences, with no further processing, do not reflect properly the terpene content of the cannabis plant, nor the monoterpenes to sesquiterpene ratio or the terpenes/cannabinoids ratios. Differently put, dried inflorescence in whatever form it was dried, is already not a "full spectrum" composition.

Evaporation during sterilization

A common step in cannabis processing involves sterilization or pasteurization in order to reduce the bacterial and fungal count. Methods used include β- or gamma-irradiation, steam treatment and radio-frequency treatment[42], some of which involves heating the inflorescence to at least about 60°C[43]. Steam treatment also requires a follow-up drying step. Terpenes evaporate according to their vapor pressure at the corresponding temperature[43], unless the treatment is conducted in a sealed package capable of withstanding the heating-generated pressure.

Terpenes and cannabinoids in extracts exposed to temperatures of up to 49°C

Sexton et al. [31], present data for cannabinoids and terpenes content of six cannabis chemovars inflorescences and of extracts generated from their trim. Extracts were produced by extracting with super-critical CO2 in a closed-loop system for 6 hours. The temperatures of the extractor, of the separator and of the condenser were 43°C, 60°C and 4°C, respectively. Extraction pressure was 1850 psi. After separating the CO2 in the separator, the concentrated extract was treated in a vacuum oven for 24 hours at a reduced pressure and at 49°C for the removal of residual water. Additionally, the authors presented for each reported component the ratios between its concentration in the extract, on the one hand, and in the flowers, on the other. The conclusion reached was that the extraction protocol enhances the potency of both cannabinoids and terpenoids, but in a different fashion [31].

From Sexton et. al.'s[31] data, we have calculated for each terpene the terpene to total cannabinoids weight/weight ratios in both the flower (Rf) and the extract (Re). Also calculated was Rp = Re/Rf. Rp magnitude is determined mainly by two parameters: (i) extraction selectivity[11,27,32,44] and (ii) components loss to evaporation. Consider first a theoretical terpene with volatility so low that no loss of it takes place during processing, so that Rp is solely determined by extraction selectivity. In such case, Rp >1 indicates higher selectivity to terpenes over cannabinoids and a relatively low cannabinoids extraction yield. For example, in case the terpene is completely extracted, Rp of 1.8 and 2.7 would correspond to cannabinoids extraction yields of 56% and 37%, respectively, which are far too low for an industrial operation.

In Figures 2a-2f we present for each chemovar the calculated Rp values and their dependencies on the terpene boiling points. A good correlation is found, indicating that the main contributor to the difference between the extracts and the inflorescences in Sexton's work is evaporation, mostly taking place during the dewatering step. This assumption is supported by the data in Table 3, presenting the estimated vapor pressures of the various terpenes at 49°C. Accordingly, the evaporation rates α-pinene and linalool are about 190 times and about 11 times greater, respectively, than that of α-humulene.
In summary, while solvent selectivity might play a role, if showing high preference to cannabinoids over terpenes, the change in the terpenes/cannabinoids ratio in the extract compared with that of the plant material source is mainly dependent on the volatility of the terpenes, more specifically on their vapor pressure at the treatment temperature. Even at the relatively low temperature of Sexton's method, volatile terpenes are lost at a rate of 70-95%. At the same time, the non-volatile terpenes are mostly preserved. Using different solvents with different boiling points may change the extent of removal[45], but not the main outcome: reduction in the extract of the overall proportion of the terpenes, in the monoterpenes/cannabinoids ratio and in the monoterpenes/sesquiterpenes ratio.

Terpenes and cannabinoids in decarboxylated inflorescence

According to a processing method, decarboxylation is conducted in the inflorescences prior to the extraction step [6]. Romano and Hazekamp (2013)[45] have tested two methods of decarboxylating inflorescence of the variety Bedrocan: 5 minutes in a water bath at 98-100 °C and 30 minutes in an oven at 145 °C. The decarboxylation efficiency of the former was small, but it still involved the loss of about one half of the main monoterpenes. Loss of sesquiterpenes at these conditions was smaller, but was nearly complete at 145 °C.
Shapira et al.[7] reported terpenes content of three chemovar inflorescences prior to decarboxylation and after it. Decarboxylation involved keeping in an oven at 130°C for 1 hour. Shapira et. al[7] did not report the cannabinoids concentrations so that they cannot be used as the non-volatile reference here. Instead, we have used for the calculations the content of each terpene relative to that of β-caryophyllene prior to decarboxylation (R(C) and after it (R(ADC). Table 5 presents the ratio of these ratios, Rd=R(ADC)/R(C), for Shapira's three chemovars.

The results clearly show that the decarboxylated flowers are depleted in monoterpenes and in monoterpenoids compared with the sesquiterpene β-caryophyllene. The extent of that depletion depends on the boiling points and on the vapor pressures at the decarboxylation temperature (130°C). According to the data in Table 3, at that temperature, the evaporation rates of β-pinene and α-terpineol are about 900 times and about 100 times greater, respectively, than that of α-bisabolol.

Terpenes and cannabinoids ingestion on using vaporizers at 180°C to 220°C

Vaporization also plays an important role in using vaporizers ("vaping") to deliver the cannabis APIs – cannabinoids and terpenes – from cannabis inflorescence. Ground inflorescence is heated in dedicated vaporizers for few minutes and the formed vapors are inhaled. In most vaporizers, the vapors are inhaled directly, while in others, the vapors are collected in a kind of a balloon and then inhaled from it. Many forms and designs of vaporizers exist on the market, with prices ranging from a few USD to almost 1000 USD. The recommended operation temperature is typically 160-220°C, or more specifically, about 180°C. This temperature is more than 200°C under the normal boiling points of THC and CBD.

Lanz et al.[46] have compared vaporization of cannabis in five commercial vaporizers, all of which were operated at 210°C for 3 minutes. Vaporization extent was 55%-83% for THC and 46%-70% for CBD. No data was provided for terpenes vaporization. In order to compare terpenes vaporization to that of cannabinoids, we have conducted a trial operating a Volcano vaporizer (one of the five used by Lanz et. al.) at 180°C to 220°C, for durations extending from 20 seconds to 180 seconds.

Table 6 presents THCA, THC and total THC concentrations before heating and in the residues after it. On temperature elevation, the acid-form cannabinoids, e.g., THCA and CBDA, decarboxylate to the neutral derivates, e.g., THC and CBD. According to Table 6, at the conditions of the trial here, decarboxylation approaches completion within 40 seconds at 180°C and is practically completed within 20 seconds at 220°C. Next, these neutral cannabinoids evaporate at a rate dependent on the operating temperature. Here, 34% and 50% of the THC evaporate within 20 and 40 seconds, respectively, at 220°C, but only 10% and 20%, respectively at 180°C, which is in good agreement with the corresponding vapor pressures. According to the Clausius-Clapeyron equation, compared to vaping at 160°C, the evaporation rate of THC at 180°C, 200°C and 220°C are about 3 times, 8.4 times and 19.4 times greater, i.e., increasing by a factor of nearly 3 per 20°C of temperature elevation. Extrapolating the results in Tabe 6 shows that, at the conditions used here, at 180°C, more than three minutes are required for approaching complete evaporation of the THC.

Figure 3 present the terpenes content of the starting inflorescence and of that inflorescence after 20 seconds and 40 seconds at 180°C. Monoterpenes and monoterpenoids are mostly evaporated and the sesquiterpenes and sesquiterpenoids are markedly evaporated, before there is significant evaporation of THC. As can be concluded from Table 3, monoterpenes and monoterpenoids reach boiling at the temperature of vaporizers operation or approach it, while others terpenes have high vapor pressures, resulting in high rates of evaporation. Thus, for example, the rates of vaporization at 180°C of bisabolol (sesquiterpenoid), β-caryophyllene (sesquiterpene), linalool (monoterpenoid), and myrcene (monoterpene) are about 23, 380, 2200, and > 3500 times greater than that of THC.

It is important to note that, while the data reported here applies to the composition of the vapors formed in the vaporizer, the composition of the inhaled vapors may differ. That is since the formed vapors cool down to some extent before being actually inhaled. On cooling, the cannabinoids (and possibly also some high-boiling terpenes) condense to small droplets. Those droplets may partially adsorb on the cooler parts of the vaporizer or stay within the balloon, when one is used. As a result, the proportion of the low-boiling terpenes in the actually inhaled vapors is even higher than that in the vaporizer-formed vapors.

These data and analysis show that, in using a vaporizer at recommended conditions, in total, the inhaled terpenes to cannabinoids ratio is greater than that in the inflorescence. Potentially more importantly, the vast majority of the terpenes are inhaled before a significant fraction of the cannabinoids is received. It is not clear yet what are the implications of this time difference for the entourage effect.

Conclusion

Any post-harvest processing step changes the composition of the cannabis product, even if conducted at relatively low temperatures such as in drying and curing. Industrial medical cannabis products, at least the vast majority of them, are therefore different from the harvested inflorescence and as such are not “whole plant” or “full spectrum” ones. The administered products are depleted in terpenes compared to the inflorescence at harvest, particularly with regards to monoterpenes and monoterpenoids. Since cannabinoids and sesquiterpenes do not show marked evaporation during processing, the ratios of monoterpenes to cannabinoids and monoterpenes to sesquiterpenes drop drastically, with potential important implications for the entourage effect.

The vapor pressure changes non-linearly with the temperature so that small variations in temperature have strong impacts. Thus, the rate of evaporation of myrcene during decarboxylation at 120^{o}C is about 2.1 times greater than that at 100^{o}C, while for THC the rate at 120^{o}C is 4.3 times greater than that at 100^{o}C. Uniform heating of inflorescences is practically impossible in industrial operations, processing batches of dozens of kilograms of solid material with varying bulk densities. Combined with the strong dependence of the vapor pressure on the temperature, this means that the composition of the industrial products is not uniform and is not reproducible between batches.

The normal boiling point of the cannabinoids is much higher than what is usually considered, i.e., above 400^{o}C, rather than about 160^{o}C, as mistakenly stated in many users’ publications. Yet, cannabinoids evaporation at the temperatures of vaporizers operation is feasible. It is important to note however, that terpenes, particularly monoterpenes, are mostly inhaled before the cannabinoids are.

These findings and analyses have important implications for producers, caregivers and users of medical cannabis in the form of cigarettes or via vaporizer. There is much room for improvement to reach accuracy, reproducibility and preferred medical cannabis compositions, making the most of the entourage effect. The analysis here provides tools for reaching such improvements.

Acknowledgments: The authors thank Inna Perutski and Noam Huppert for HPLC and GC analyses.

Authorship confirmation statement: All authors have read and agreed to the published version of the manuscript.

***Authors disclosure statements*:** All authors are employers in Bazelet group, a medical cannabis manufacture in Israel

***Funding statement*:** No direct funding was received for this paper.

References

1. ElSohly MA, Chandra S, Radwan M, et al. A Comprehensive Review of Cannabis Potency in the United States in the Last Decade. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2021;6:603–606.

2. Pertwee RG. Cannabinoid pharmacology: The first 66 years. *Br J Pharmacol*. 2006;147.

3. Mechoulam R, Hanuš LO, Pertwee R, et al. Early phytocannabinoid chemistry to endocannabinoids and beyond. *Nat Rev Neurosci*. 2014;15:757–764.

4. Hanuš LO, Meyer SM, Muñoz E, et al. Phytocannabinoids: A unified critical inventory. *Nat Prod Rep*. 2016;33:1357–1392.

5. Hanuš LO, Hod Y. Terpenes/Terpenoids in Cannabis: Are They Important? *Med Cannabis Cannabinoids*. 2020;3:25–60.

6. Ternelli M, Brighenti V, Anceschi L, et al. Innovative methods for the preparation of medical Cannabis oils with a high content of both cannabinoids and terpenes. *J Pharm Biomed Anal*. 2020;186:113296.

7. Shapira A, Berman P, Futoran K, et al. Tandem Mass Spectrometric Quantification of 93 Terpenoids in Cannabis Using Static Headspace Injections. *Anal Chem*. 2019;91:11425–11432.

8. Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. 1st ed. Elsevier Inc.; 2017.

9. Russo EB. The case for the entourage effect and conventional breeding of clinical cannabis: No “Strain,” no gain. *Front Plant Sci*. 2019;9:1–8.

10. Russo EB. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163:1344–1364.

11. Namdar D, Voet H, Ajjampura V, et al. Terpenoids and phytocannabinoids co-produced in cannabis sativa strains show specific interaction for ell cytotoxic activity. *Molecules*. 2019;24.

12. Kamal BS, Kamal F, Lantela DE. Cannabis and the Anxiety of Fragmentation—A Systems Approach for Finding an Anxiolytic Cannabis Chemotype. *Front Neurosci*. 2018;12.

13. Nuutinen T. Medicinal properties of terpenes found in Cannabis sativa and Humulus lupulus. *Eur J Med Chem*. 2018;157:198–228.

14. Santiago M, Sachdev S, Arnold JC, et al. Absence of Entourage : Terpenoids Commonly Found in Cannabis sativa Do Not Modulate the Functional Activity of D 9 -THC at Human CB 1 and CB 2 Receptors. 2019;4:165–176.

15. Koltai H, Namdar D. Cannabis Phytomolecule "Entourage": From Domestication to Medical Use. *Trends Plant Sci*. 2020;25:976–984.

16. LaVigne JE, Hecksel R, Keresztes A, et al. Cannabis sativa terpenes are cannabimimetic and selectively enhance cannabinoid activity. *Sci Rep*. 2021;11:1–15.

17. Aran A, Harel M, Cassuto H, et al. Cannabinoid treatment for autism: a proof-of-concept randomized trial. *Mol Autism*. 2021;12:1–11.

18. Marinotti O, Sarill M. Differentiating Full-Spectrum Hemp Extracts from CBD Isolates: Implications for Policy, Safety and Science. *J Diet Suppl*. 2020;17:517–526.

19. Maayah ZH, Takahara S, Ferdaoussi M, et al. The anti-inflammatory and analgesic effects of formulated full-spectrum cannabis extract in the treatment of neuropathic pain associated with multiple sclerosis. *Inflamm Res*. 2020;69:549–558.

20. Nahler G, Jones TM, Russo EB. Cannabidiol and Contributions of Major Hemp Phytocompounds to the "Entourage Effect"; Possible Mechanisms. *Altern Complement Integr Med*. 2019;5:1–16.

21. Maayah ZH, Takahara S, Ferdaoussi M, et al. The molecular mechanisms that underpin the biological benefits of full-spectrum

cannabis extract in the treatment of neuropathic pain and inflammation. *Biochim Biophys Acta - Mol Basis Dis*. 2020;1866:165771.

22. Gallily R, Yekhtin Z. Avidekel Cannabis extracts and cannabidiol are as efficient as Copaxone in suppressing EAE in SJL/J mice. *Inflammopharmacology*. 2019;27:167–173.

23. Baron EP, Lucas P, Eades J, et al. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain*. 2018;19.

24. Potter DJ. A review of the cultivation and processing of cannabis (*Cannabis sativa* L.) for production of prescription medicines in the UK. *Drug Test Anal*. 2014;6:31–38.

25. Landschaft Y, Albo B, Mechoulam R, et al. Medical Cannabis. 3rd ed. Israeli Medical Cannabis Agency, Ministry of health; 2019. https://www.health.gov.il/hozer/mmk154_2016.pdf

26. Vitetta L, Sikali JF. Comment on: Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in patients with chronic pain. *Can J Anesth*. 2021. doi:10.1007/s12630-021-02078-z

27. Namdar D, Mazuz M, Ion A, et al. Variation in the compositions of cannabinoid and terpenoids in *Cannabis sativa* derived from inflorescence position along the stem and extraction methods. *Ind Crops Prod*. 2018;113:376–382.

28. Lazarjani MP, Young O, Kebede L, et al. Processing and extraction methods of medicinal cannabis: a narrative review. *J Cannabis Res*. 2021;3.

29. Guideline ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2019.

30. Europe. C of, Commission. EP, Healthcare. ED for the Q of M&. European pharmacopoeia. Strasbourg: Council Of Europe : European Directorate for the Quality of Medicines and Healthcare; 2010.

31. Sexton M, Shelton K, Haley P, et al. Evaluation of cannabinoid and terpenoid content: Cannabis flower compared to supercritical

CO 2 concentrate. *Planta Med*. 2018;84:E3.

32. Milay L, Berman P, Shapira A, et al. Metabolic Profiling of Cannabis Secondary Metabolites for Evaluation of Optimal Postharvest Storage Conditions. *Front Plant Sci*. 2020;11:1–15.

33. Casano S, Grassi G, Martini V, et al. Variations in terpene profiles of different strains of Cannabis sativa L. *Acta Hortic*. 2011;925:115–122.

34. McPartland JM, Russo EB. Cannabis and Cannabis extracts: Greater than the sum of their parts? *Cannabis Ther HIV/AIDS*. 2012;1:103–132.

35. Sharma C, M. Al Kaabi J, M. Nurulain S, et al. Polypharmacological Properties and Therapeutic Potential of β-Caryophyllene: A Dietary Phytocannabinoid of Pharmaceutical Promise. *Curr Pharm Des*. 2016;22:3237–3264.

36. Růžička K, Fulem M, Růžička V. Vapor Pressure of Organic Compounds. Measurement and Correlation. 2008.

37. Salzman WR. Clapeyron and Clausius-Clapeyron Equations. *Chem Thermodyn Univ Arizona, Tucson*. 2001.

38. Lovestead TM, Bruno TJ. Determination of cannabinoid vapor pressures to aid in vapor phase detection of intoxication. *Forensic Chem*. 2017;5:79–85.

39. McClements DJ. Enhancing Efficacy, Performance, and Reliability of Cannabis Edibles: Insights from Lipid Bioavailability Studies. *Annu Rev Food Sci Technol*. 2020;11:45–70.

40. Umnahanant P, Zafar A, Kankala V, et al. Vapor pressure and vaporization enthalpy studies of (+)-longifolene, (–)-isolongifolene and B-myrcene by correlation gas chromatography. *J Chem Thermodyn*. 2019;131:583–591.

41. Ross SA, Elsohly MA. The volatile oil composition of fresh and air-dried buds of Cannabis sativa. *J Nat Prod*. 1996;59:49–51.

42. Jerushalmi S, Maymon M, Dombrovsky A, et al. Effects of cold plasma, gamma and e-beam irradiations on reduction of fungal

colony forming unit levels in medical cannabis inflorescences. *J Cannabis Res*. 2020;2:0–11.

43. Jerushalmi S, Maymon M, Dombrovsky A, et al. Effects of steam sterilization on reduction of fungal colony forming units, cannabinoids and terpene levels in medical cannabis inflorescences. *Sci Rep*. 2021;11:1–13.

44. Moreno-Sanz G, Vera CF, Sánchez-Carnerero C, et al. Biological Activity of Cannabis sativa L. extracts critically depends on solvent polarity and decarboxylation. *Separations*. 2020;7:1–16.

45. Romano LL, Hazekamp A. Cannabis Oil: chemical evaluation of an upcoming cannabis-based medicine. *Cannabinoids*. 2013;1:1–11.

46. Lanz C, Mattsson J, Soydaner U, et al. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS One*. 2016;11.

Table 1: Ranges for terpenes concentrations and for terpenes to cannabinoids ratios in inflorescences of *Cannabis Sativa* L. chemovars grown in Israel. Terpenes that are not fully identified are presented by their retention time (RT). Total THC concentrations ranged up to about 25% and those of total CBD, up to 15%.

Blank cells are when the cannabinoids concentration is missing.

Group	Compound	Min (ppm)	Max (ppm)	Min (mg/g TC)	Max (mg/g TC)
Monoterpenes	a-Pinene	94	5185	0.47	21.4
	Camphene	57	207	0.30	0.55
	Sabinene	260	260	1.30	1.44
	b-Pinene	121	6700	0.81	33.5
	Myrcene	266	9053	2.22	35.1
	delta-3-Carene	383	383		
	Carene	142	1106	1.12	7.42
	Ocimene	121	2343	0.93	5.12
	Limonene	142	3663	1.12	18.0
	p-Cymene	1885	1885		
	gamma-Terpinene	101	378	0.77	2.75
	Terpinolene	201	1192	1.34	3.64
Other terpenes	Linalool	176	2020	1.21	10.1
	RT 13.0	91	697	0.54	4.08
	RT 14.7	129	373	1.00	2.66
	RT 19.0	135	1219	1.17	6.77
	Isopulegol	1439	1439		
	b-Caryophyllene	533	6778	3.44	26.8
	a-Humulene	196	7132	1.19	10.1
	Nerolidol	105	1210	0.62	6.05
	RT 20.4	61	1681	0.47	11.2
	RT 20.5	74	332	0.62	1.84
	RT 20.7	88	785	0.86	4.36

	RT 20.8	50	247	0.38	1.65
	RT 20.9	55	732	0.69	4.07
	RT 21.0	189	1446	2.06	9.64
	RT 21.1	230	2022	2.67	13.5
	Guaiol	97	1890	0.66	10.1
	Eudesmol	93	1366	0.81	7.99
	Bisabolol	117	2768	0.78	16.2
Total terpens		3060	23382	28.9	130

Table 2: Concentration ranges of cannabinoids, monoterpenes and other terpenes (monoterpenoids, sesquiterpene and sesquiterpenoid) found in commercial cannabis oil. Terpenes that are not fully identified are presented by their retention time (RT). Total THC concentrations ranged up to about 20% and those of total CBD, up to 28%.

Category	Compound	Min (ppm)	Max (ppm)	Min (mg/g TC)	Max (mg/g TC)
Monoterpenes	a-Pinene	3032	3032	19.3	19.3
	Myrcene	219	380	0.76	2.11
	Limonene	71	2103	0.34	13.4
	Terpinolene	1469	1469	9.36	9.36
Other terpenes	Linalool	165	653	0.57	2.92
	RT 19.0	348	348	2.22	2.22
	Isopulegol	228	242	0.92	1.29
	b-Caryophyllene	686	4833	2.37	20.8
	a-Humulene	249	1392	0.86	6.08
	Nerolidol	74	689	0.26	3.65
	RT 20.4	1122	2448	8.83	9.83
	RT 20.8	202	424	1.59	1.88
	RT 20.9	338	716	2.66	3.27
	RT 21.0	1124	2299	8.85	11.0
	RT 21.1	1430	3028	11.3	14.6
	Guaiol	206	1725	1.33	5.95
	Eudesmol	127	437	1.00	1.76
	Bisabolol	301	2264	1.12	9.09
Total terpenes		2995	19590	250031	580016

Table 3: Cannabinoids and terpenes normal boiling points and their vapor pressures at several temperatures

				Vapor pressure (Torr)			
Category	Compound	Formula	Boiling point (°C)	20°C	49°C	130°C	180°C
Cannabinoids	THC	$C_{21}H_{30}O_2$	425	5.24E-07	1.38E-05	1.07E-02	1.97E-01
	CBD	$C_{21}H_{26}O_2$	463.9	6.31E-06	1.02E-04	2.89E-02	3.45E-01
Monoterpenes	α-pinene	$C_{10}H_{16}$	155	3.57E+00	1.65E+01	3.69E+02	1.44E+03
	Sabinene	$C_{10}H_{16}$	163	1.92E+00	9.83E+00	2.72E+02	1.17E+03
	β-pinene	$C_{10}H_{16}$	166	2.18E+00	1.06E+01	2.66E+02	1.09E+03
	β-Myrcene	$C_{10}H_{16}$	168	1.69E+00	8.72E+00	2.43E+02	1.05E+03
	D-limonene	$C_{10}H_{16}$	176	1.13E+00	6.12E+00	1.88E+02	8.47E+02
	Terpinolene	$C_{10}H_{16}$	185	7.99E-01	4.44E+00	1.44E+02	6.65E+02
Monoterpenoids	Linalool	$C_{10}H_{18}O$	198	1.15E-01	9.36E-01	6.60E+01	4.27E+02
	Fenchyl alcohol	$C_{10}H_{18}O$	201	7.54E-02	6.63E-01	5.48E+01	3.81E+02
	α-terpineol	$C_{10}H_{18}O$	217	3.01E-02	2.92E-01	2.93E+01	2.22E+02
Sesquiterpenes	β-caryophyllene	$C_{15}H_{24}$	263	2.12E-02	1.70E-01	1.17E+01	7.48E+01
	α-humulene	$C_{15}H_{24}$	276	1.00E-02	8.77E-02	7.19E+00	4.98E+01
	selina-3,7(11)-diene	$C_{15}H_{24}$	282	1.17E-02	9.71E-02	7.10E+00	4.67E+01
sesquiterpenoid	Guaiol	$C_{15}H_{26}O$	290	8.99E-05	1.80E-03	7.86E-01	1.13E+01
	Alpha-eudesmol	$C_{15}H_{28}O$	295	4.98E-05	9.55E-04	3.86E-01	5.37E+00
	α-bisabolol	$C_{15}H_{26}O$	314	2.24E-05	5.05E-04	2.84E-01	4.57E+00

Table 4: The content of the most prevelant terpenes in the fresh and in dried Pandora's Box inflorescences, relative to their beta-caryophyllene content. (Recalculation of Hanus and Hod[5], tables 24 and 25 beta-caryophyllene content).

Terpene	Fresh	Dried
Beta-caryophyllene	100	100
Terpinolene	116.0	37.2
Alpha-humulene	40.0	35.9
Gama-elemene (257)	26.2	30.8
Selina-3,7(11)-diene	17.6	20.6
Beta-myrcene	15.1	
Germacrene B	13.2	10.4
Alpha-cadinene (271)	12.9	
Bulnesol	11.6	15.4
10-epi-gama-eudesmol (300)		14.7
Alpha-eudesmol		10.8
Guaiol		10.5

Table 5: Rd = R(DAC)/R(C) calculated from the data of Sahpira et al.[7] report. Blank cells are below level of quantification

Terpene	Rd (type I)	Rd (type II)	Rd (type III)
Alpha-pinene	0.17		0.013
Sabinene	0.05		
Beta-pinene			
Beta-myrcene	0.04		0.05
Limonene	0.39	0.45	0.46
Linalool	0.43	0.58	0.47
Alpha-fenchol	0.40	0.38	0.41
Alpha-terpineol	0.50	0.47	0.43
Beta-caryophyllene	1	1	1
Alpha-humulene	1.04	1.08	0.95
Ledene	1.04	1.09	0.81
Valencene	1.08	1.07	0.98

Table 6: THCA, THC and total THC concentration found in ground inflorescence before and after heating in a Vulcano vaporizer at several temperatures for several durations.

Temperature (°C)	Time (Seconds)	%THC (w/w)	%THCA (w/w)	%TotalTHC (w/w)	Total THC (Mg)	degree of evaporation	N
Before heating		0.80 ± 0.02	15.6 ± 0.19	14.5 ± 0.15	30.0 ± 0.65	0%	6
180	**20**	9.77 ± 0.92	7.57 ± 0.78	16.4 ± 0.37	27.2 ± 0.12	-9%	3
	40	13.9 ± 0.57	1.37 ± 0.05	15.1 ± 0.52	23.8 ± 1.18	-21%	3
	60	13.1 ± 0.19	0.97 ± 0.10	14.0 ± 0.17	23.3 ± 0.29	-22%	3
	90	11.6 ± 0.31	0.33 ± 0.03	11.9 ± 0.29	19.7 ± 0.43	-34%	3
	120	10.3 ± 0.21	0.50 ± 0.24	10.7 ± 0.32	16.8 ± 0.47	-44%	3
	180	7.07 ± 0.16	0.03 ± 0.03	7.10 ± 0.15	10.3 ± 0.27	-66%	3
200	**20**	12.7 ± 0.35	1.87 ± 0.64	14.4 ± 0.23	24.2 ± 0.52	-19%	3
	40	11.2 ± 0.35	0.27 ± 0.07	11.4 ± 0.41	18.3 ± 0.84	-39%	3
Before heating		2.20 ± 0.03	7.10 ± 0.05	8.4 ± 0.07	16.8 ± 0.17	0.0%	3
220	**20**	6.52 ± 0.05	0.13 ± 0.11	6.6 ± 0.08	11.0 ± 0.34	-34.2%	3
	40	5.29 ± 0.28	0.00 ± 0.00	5.3 ± 0.28	8.33 ± 0.55	-50.3%	3

Figures legends:

Figure 1: Vapor pressures of some terpenes at various temperatures, based on Clausius-Clapeyron equation.

Figure 2: A correlation between the ratio of terpenes in extract (C) and flower (F) of some cannabis strains and terpenes boiling point.

Figure 3: Terpenes concentration measured in *Cannabis Sativa* L. inflorescence before and after vaporize at 180 0C for 20 and 40 seconds.