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Pharmacological Foundations of Cannabis Chemovars

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ABSTRACT

An advanced Mendelian Cannabis breeding program has been developed utilizing chemical markers to maximize the yield of phytocannabinoids and terpenoids with the aim to improve therapeutic efficacy and safety. Cannabis is often divided into several categories based on cannabinoid content. Type I, Δ^9-tetrahydrocannabinol-predominant, is the prevalent offering in both medical and recreational marketplaces. In recent years, the therapeutic benefits of cannabidiol have been better recognized, leading to the promotion of additional chemovars: Type II, Cannabis that contains both Δ^9-tetrahydrocannabinol and cannabidiol, and cannabidiol-predominant Type III Cannabis. While high-Δ^9-tetrahydrocannabinol and high-myrcene chemovars dominate markets, these may not be optimal for patients who require distinct chemical profiles to achieve symptomatic relief. Type II Cannabis chemovars that display cannabidiol- and terpenoid-rich profiles have the potential to improve both efficacy and minimize adverse events associated with Δ^9-tetrahydrocannabinol exposure. Cannabis samples were analyzed for cannabinoid and terpenoid content, and analytical results are presented via PhytoFacts, a patent-pending method of graphically displaying phytocannabinoid and terpenoid content, as well as scent, taste, and subjective therapeutic effect data. Examples from the breeding program are highlighted and include Type I, II, and III Cannabis chemovars, those highly potent in terpenoids in general, or single components, for example, limonene, pinene, terpinolene, and linalool. Additionally, it is demonstrated how Type I–III chemovars have been developed with conserved terpenoid proportions. Specific chemovars may produce enhanced analgesia, anti-inflammatory, anticonvulsant, antidepressant, and anti-anxiety effects, while simultaneously reducing sequelae of Δ^9-tetrahydrocannabinol such as panic, toxic psychosis, and short-term memory impairment.

Introduction

A proper exposition on any subject requires definitions, and this becomes critical in the case of Cannabis, where contentious debate is common and agreement on any point is frequently unattainable. This has certainly been the case with respect to the number of Cannabis species. Briefly speaking, *Cannabis sativa* L. Cannabaceae or "cultivated Cannabis" was probably initially described by Leonhart Fuchs in his *New Kreüterbuch* of 1542 [1], and this Latin binomial was adopted by Linnaeus in his comprehensive *Species Plantarum* in 1753 [2] to describe European hemp. Three decades later, Lamarck described a putative separate species, *Cannabis indica* Lamarck Cannabaceae from the subcontinent as a bushier and somewhat shorter plant with narrow leaflets [3], and the controversy over Cannabis species has remained without consensus ever since [4]. Particular taxonomic confusion arose in 1974 when Richard Schultes also described very compact, broad leaflet plants in Afghanistan as *C. indica* [5]. Other authorities such as Ernest Small championed a unitary species classification [6]. The argument takes on practical clinical implications contempo-

ABBREVIATIONS

CB_2	cannabinoid-two receptor
CBD	cannabidiol
CBDV	cannabidivarin
DAD	diode array detector
DEA	Drug Enforcement Administration
ECS	endocannabinoid system
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association
FID	flame ionization detector
GRAS	Generally Recognized As Safe
NIST	National Institute of Standards and Technology
RCT	randomized controlled trial
THC	Δ^9-tetrahydrocannabinol

raneously, as commercial designations of Cannabis as "*sativa*" or "*indica*" are commonly described as producing respectively a "head high" or "body high" in guidance to patients as to what variety to select for their treatment. Some have argued that such designations are woefully inadequate [4]. Creative solutions have been suggested, such as McPartland's preferred *Cannabis afghanica,* or the practical descriptive approach of Clarke and Merlin [7] combining morphology and purpose of use, e.g., broad-leaflet drug Cannabis and narrow-leaflet hemp.

Beyond the species controversy remains the issue of how we distinguish one plant from another based on its genetic or biochemical attributes. An unfortunate habit has developed in commerce to refer to Cannabis "strains." While this term may serve in microbiology to describe bacteria or viruses with certain attributes, it has no official standing in botany [8, 9]. Some authorities prefer "variety" or "cultivar", which was originally derived from "cultigen variety" [10]. However, some modern experts [11] argue that international plant nomenclature rules technically forbid such classification of Cannabis varieties because cultivars must be registered varieties. The illegality of Cannabis in most jurisdictions has thus restricted that classification to only a few examples. We recommend the alternative nomenclature of chemical varieties, or "chemovars," which emphasizes the unique biochemical attributes of particular Cannabis plants.

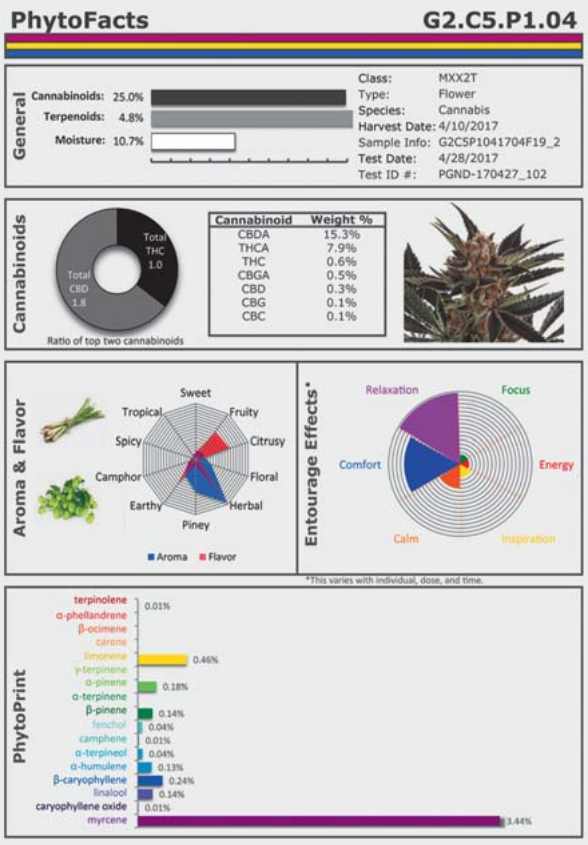
Cannabis is often divided into several categories based on cannabinoid content: Type I, THC-predominant, is the prevalent offering in both medical and recreational marketplaces. In recent years, the therapeutic benefits of CBD have been better recognized, leading to the promotion of additional chemovars: Type II Cannabis that contains both THC and CBD, and CBD-predominant Type III Cannabis. While high-THC and high-myrcene chemovars dominate markets, these may not be optimal for patients who require distinctly different biochemical profiles to achieve symptomatic relief. Type II and III Cannabis chemovars that display CBD- and terpenoid-rich profiles have the potential to improve both the efficacy of THC and minimize adverse events associated with it.

Certain biochemical differentiation factors in Cannabis beyond the phytocannabinoids have already been identified. In successive decades, various investigators have noted that terpenoid content, and not cannabinoid ratios, provide the clearest demarcation between chemovars [12, 13]. The bulk of Cannabis terpenoids are produced in glandular trichomes of the unfertilized female flowering tops, the same primary source of phytocannabinoid production. As many as 200 different terpenoids have been isolated in Cannabis and their composition is primarily genetically rather than environmentally determined. Despite seemingly low concentrations in a preparation, terpenoids are quite potent and are productive in behavioral effects to increase or decrease activity levels in rodents, even when observed serum levels are low or negligible [14]. Terpenoid concentrations in Cannabis flowers were previously commonly in the 1% range, with up to 10% within trichomes [15], but this situation has changed in recent decades due to selective breeding such that flower concentrations of 3.5% or more are observed currently [16]. The ecological roles and pharmacological effects of terpenoids supporting herbal synergy in Cannabis have been previously extensively reviewed [17–20], and readers are referred to these sources for additional insight.

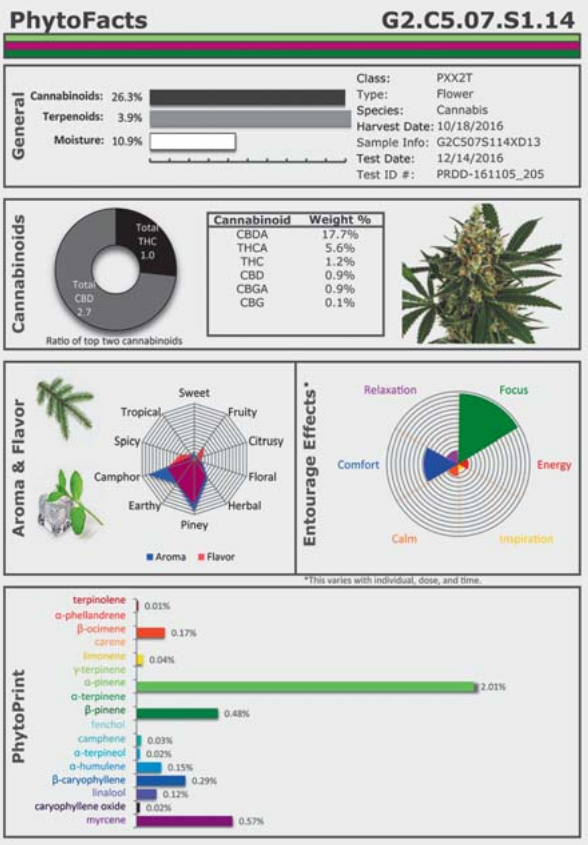
All the terpenoids discussed herein are GRAS by the US FDA and/or are approved as food additives by the FEMA. According to a recent publication [21], 50 Cannabis terpenes are routinely encountered in North American chemovars, but 17 are most common. Of these, several predominate to form eight "Terpene Super Classes": myrcene, terpinolene, ocimene, limonene, α-pinene, humulene, linalool, and β-caryophyllene. Similarly, Fischedick [22] analyzed Cannabis samples from a single California Cannabis dispensary over the course of a year, and identified five terpenoid groups based on predominant content: myrcene, terpinolene, myrcene/limonene, β-caryophyllene, and bisabolol. Recently, for the first time, several terpene synthases in Cannabis have been identified and observed to be promiscuous in their production of substrates [23], but the mechanisms underlying regulation of terpenoid synthesis in Cannabis remain to be elucidated.

The current study will introduce a new method of Cannabis classification and analysis named PhytoFacts (*vide infra,* Materials and Methods, https://phytofacts.info), and provide examples of distinct chemovars developed with a planned Mendelian breeding regimen utilizing chemical markers to isolate both terpenoid and cannabinoid traits in an effort to create hybrid Cannabis seeds that produce specific combinations and ratios of those components in a single plant.

Some authors have advocated the concept of herbal synergy in Cannabis [17, 24–26], which is analogous to the combinatorial activity of endocannabinoids via "the entourage effect" [27] of active and inactive metabolites. Such synergy would be apparent under conditions in which the activity of a minor botanical chemical component complemented the major, diminished the adverse event profile, or otherwise contributed to a preparation's stability or efficacy. The data supporting CBD as a synergist to THC has been summarized in the past [28], including its anti-anxiety benefits, its antipsychotic effects, its ability to counteract tachycardia, blunt the peak high induced by THC, and delay its full expression and prolong its overall effect. CBD additionally counteracts glutamate excitotoxicity and serves as an antioxidant, anti-inflammatory, and immunomodulatory agent in its own right. CBD and other phytocannabinoids and terpenoids [26] may act in synergy with THC [29] through pharmacological potentiation, amelioration of



▶ **Fig. 1** PhytoFacts of a Type II, high-myrcene chemovar (see text for discussion). PhytoFacts is copyrighted 2015 by BHC Group, LLC. Source: Dr. M. A. Lewis, Napro Research.



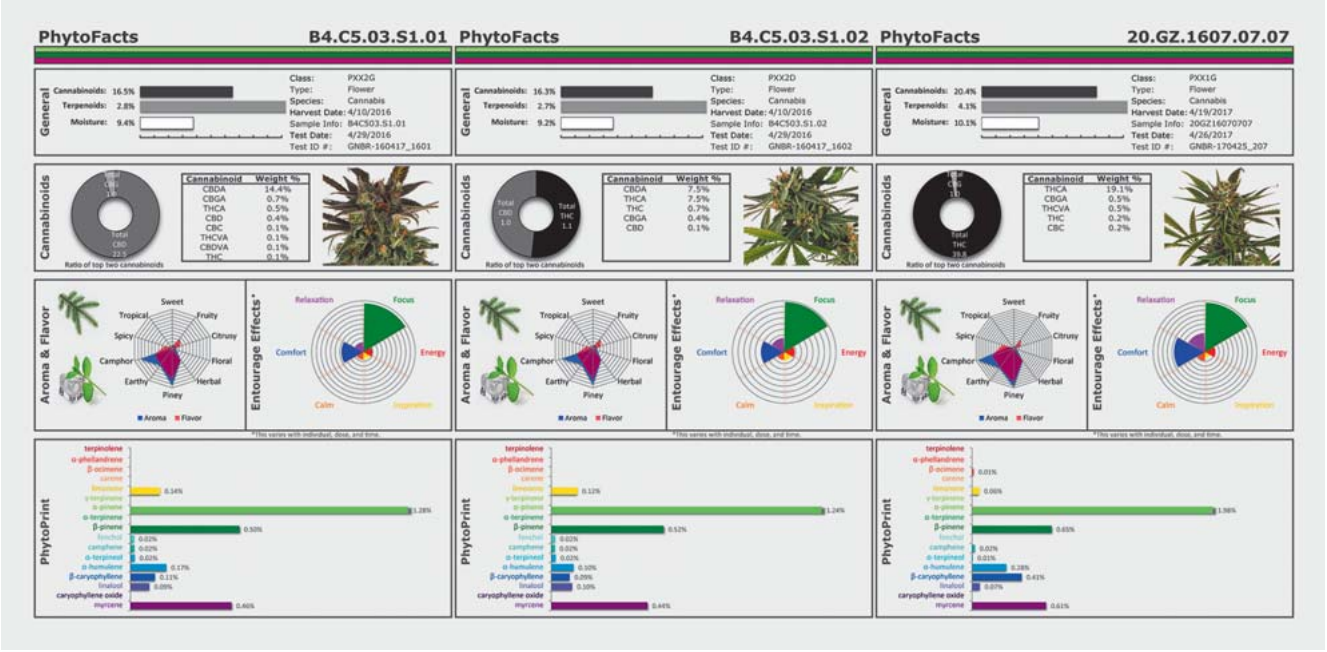
▶ **Fig. 2** PhytoFacts of G2C507.S1.14, a Type II, pinene-predominant chemovar. Source: Dr. M. A. Lewis, Napro Research.

adverse events, summation, or pharmacokinetic and metabolic modulation [17]. More recent investigations have added to this theoretical foundation, demonstrating the ability of CBD to eliminate a dose-response ceiling to pain in an animal model [30]. In another example, the presence of cannabidiol in a pharmaceutical extract allowed for a statistically significant difference in the proportion of human patients, achieving 30% pain improvement in opioid-resistant cancer pain as compared to those taking placebo or a THC-rich Cannabis extract lacking CBD [31]. The contributions of Cannabis terpenoids to herbal synergy in whole Cannabis preparations have also been touted [17, 18] and demonstrated with isobolographic analysis [18]. Recently, the pharmacological advantages of phytocannabinoid combinations in complex clinical syndromes have been elucidated [32], but as discussed here, this concept can be extended further to encompass terpenoid contributions to herbal synergy. Together these terpenoid entourage components may contribute modulatory and therapeutic benefits in a synergistic manner counterintuitively to their sometimes modest concentrations in the flowers or extracts.

Results

β-Myrcene is far and away the most prevalent terpene in modern Cannabis chemovars in the USA [21] and in Europe [16], and is likely responsible for the narcotic-like sedative effects [33] (colloquially termed “couch-lock” [17]) of many common preparations in commerce, particularly in Type II and III chemovars. Such myrcene predominance is exemplified in the chemovar “Harlequin”, one of the first commercial North American Type II plants bred to emphasize CBD content, which in testing displayed a THC:CBD ratio of 1:2.2 with a concentration of 0.45% myrcene out of a low total of 1.1% terpenoids. This contrasts with G2.C5.P1.04, a newer chemovar (▶ **Fig. 1**) that displays a THC:CBD ratio of 1:1.8 with a concentration of 3.44% myrcene out of a much higher 4.8% total terpenoids.

G2C507.S1.14, a Type II plant was selectively bred for *α*-pinene rather than myrcene predominance (▶ **Fig. 2**), with a 2.01% *α*-pinene concentration out of 3.9% total terpenoids. The THC:CBD ratio is also enhanced at 1:2.7 along with a higher cannabinoid concentration overall. *α*-Pinene is of particular interest due to its inhibition of acetylcholinesterase [34, 35], possibly producing a role in learning and memory [36]. *α*-Pinene has also been suggested as



▶ **Fig. 3** PhytoFacts of Type I, II, and III chemovars with preservation of the pinene-predominant terpenoid profile and proportions. Source: Dr. M. A. Lewis, Napro Research.

a modulator of THC overdose events [17], with historical anecdotes supporting its use as an antidote to Cannabis intoxication.

Selective breeding with biochemical analysis has now made it possible to develop Type I, II, and III Cannabis plants that retain virtually identical terpenoid proportion profiles, with high α-pinene (▶ **Fig. 3**), limonene (**Fig. 1S**, Supporting Information), caryophyllene (**Fig. 2S**, Supporting Information), or linalool with lower myrcene concentrations. These chemovars would be ideal for assessing psychometric or physiological neuroimaging differences due to THC and CBD proportions in conjunction with the preserved terpenoid profiles. Sequential trials of each chemovar may provide the optimum option for patients seeking the most advantageous chemovar profile to treat their symptoms with the fewest associated adverse events. Select individuals from the breeding program are shown herein.

Chemovar B4.P26.65, also known as "Rainbow Gummeez," is a Type II plant with roughly equal THC and CBD and terpinolene predominance (▶ **Fig. 4**), noteworthy for having won the Emerald Cup 2016 competition in California in its category, but also placing in the top 10 with recreational Type I offerings before its misclassification was discovered. This indicates that a Type II plant need not be sedating nor inferior in organoleptic or experiential properties currently favored in global recreational markets.

S8.P38.BX.08 (▶ **Fig. 5**) is another balanced chemovar with limonene, linalool, and caryophyllene predominance over myrcene.

Another example is P08.S1.16.P08.S1.81, displaying a high CBD profile (▶ **Fig. 6**), with a low THC concentration, and caryophyllene, limonene, and humulene predominance that suggests possible utility in pain, inflammation, and even addiction treatment mediated through inhibition of the insula by CBD and CB_2 agonistic effects attributable to caryophyllene [19, 37–40].

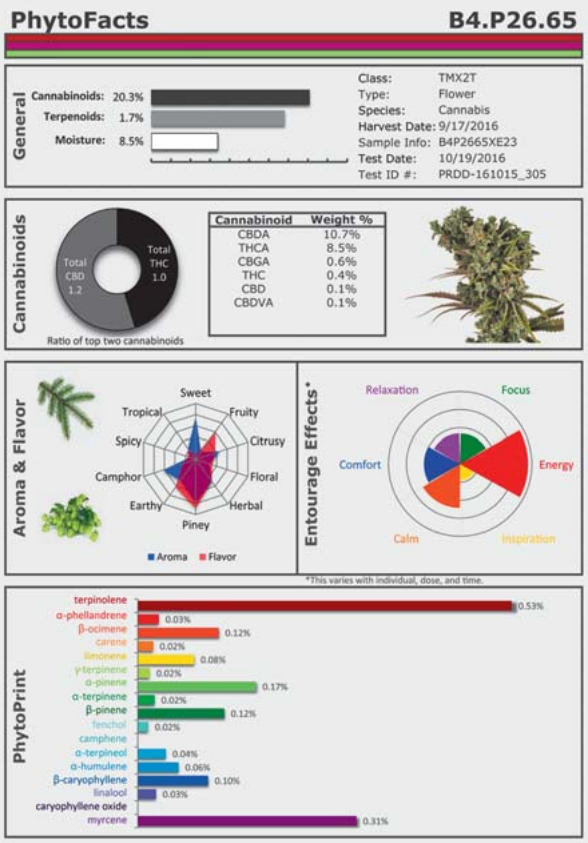
Chemovar O3.N5.09.S1.01 (▶ **Fig. 7**) is a unique Type III CBD-predominant plant whose next most abundant phytocannabinoid is not THC, but rather CBDV, a propyl agent currently in Phase II clinical trials for seizures of partial onset (focal seizures).

Discussion

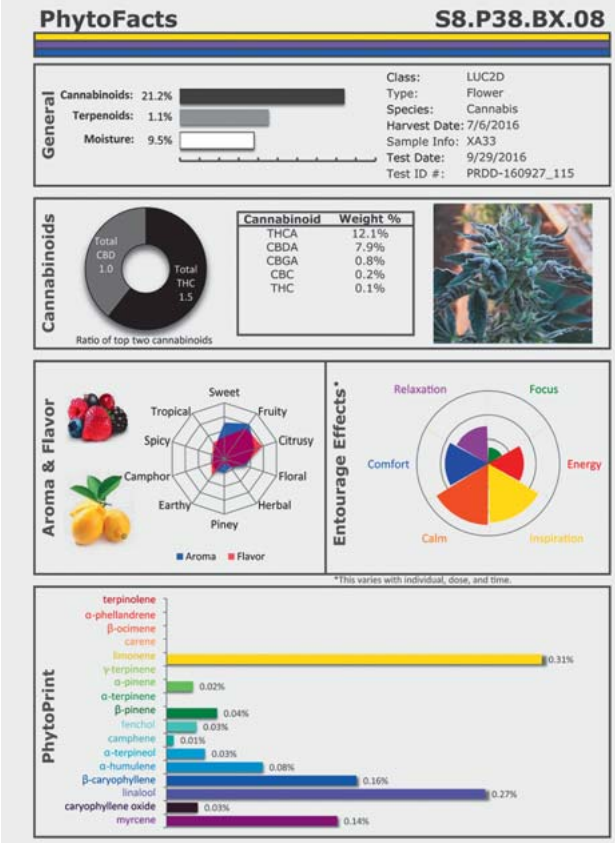
While there are many potential indications of these chemovars, these have not been assessed using double-blind clinical trials in humans and require further evaluation. For instance, the CB_2 agonistic effects of caryophyllene have not been evaluated in the presence of other cannabinoids and terpenes commonly found in Cannabis that may affect caryophyllene's agonistic properties. While α-pinene's acetylcholinesterase inhibition is intriguing and suggests potential application in memory and learning, THC also combines acetylcholinesterase inhibitory and anticholinergic effects, which may negatively impact, overshadow, or synergize with α-pinene's inhibition. In one study a strong synergistic effect on the inhibition of acetylcholinesterase with the presence of α-pinene, 1,8-cineole, and camphor was observed [34], which suggests the importance of the putative entourage effect. If pinene was demonstrated to reduce the short-term memory impairment of THC in objective RCTs, it could conceivably find application in Cannabis-based medical treatment of dementia.

In the patient panels described in the Methods section, terpinolene-predominant chemovars were consistently found to be energizing, however, in animal studies, inhalation of terpinolene produced sedative effects [41]. Once more, blinded objective testing in humans may shed light on this discrepancy.

These caveats aside, there are many promising indications for different terpene fingerprints. For instance, THC has been attrib-



▶ **Fig. 4** PhytoFacts of B4.P26.65, or "Rainbow Gummeez," a Type II, terpinolene-dominant chemovar and winner of the 2016 Emerald Cup competition. Source: Dr. M. A. Lewis, Napro Research.



▶ **Fig. 5** PhytoFacts of S8.P38.BX.08, a chemovar with limonene, linalool, and caryophyllene predominance. Source: Dr. M. A. Lewis, Napro Research.

uted to counteracting agitation in dementia [35], which could conceivably be improved via the addition of α-pinene. Another example is the potential of a chemovar containing limonene, linalool, and caryophyllene, such as S8.P38.BX.05 (▶ **Fig. 5**), to have clinical efficacy in indications as disparate as burns [42] and epilepsy [43–45]

The suitability of Cannabis to treat psychiatric conditions remains controversial, but with strong positive signals from a recent meta-analysis [46]. The likelihood of clinical success may be enhanced with a Type III chemovar such as P08.S1.16.P08.S1.81, without sedation from myrcene. This chemovar contains a generous CBD titer with minimal THC, but high linalool with additional limonene concentrations, suggesting possible efficacy for anxiety [47] and depression [17, 48].

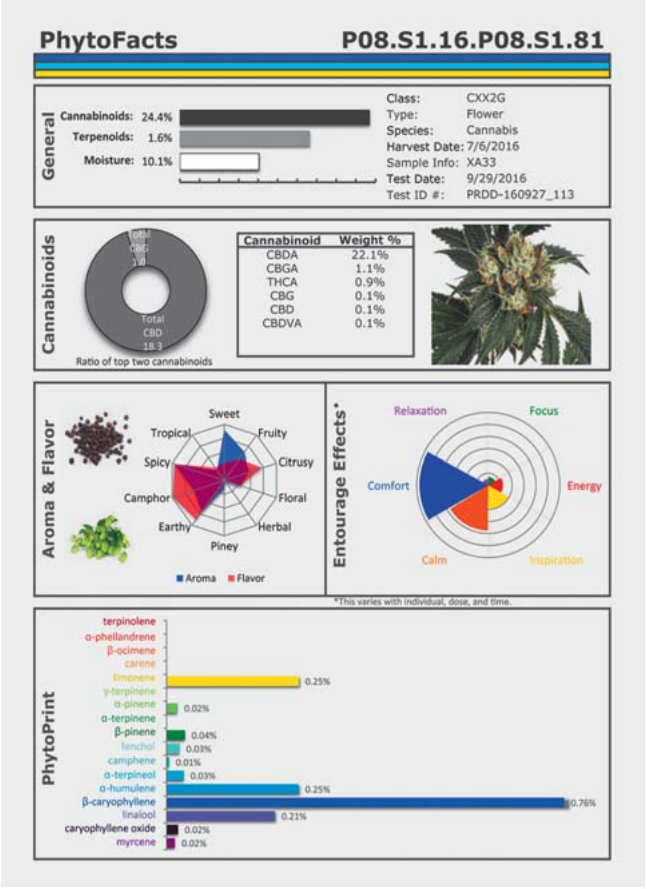
The concept of Cannabis synergy beyond the pharmacological effects of THC remains a focus of controversy, and continues to provoke skepticism [49]. Proof of this synergy in the greater Cannabis biochemical array can only be provided with human double-blind randomized clinical trials or physiological imaging studies that demonstrate compelling and salient objective psychometric or metabolic differences in brain activity when phytocannabinoid and terpenoid components are presented individually and ensemble. Several such studies are currently planned.

It is hoped that the data presented herein will stimulate additional interest and research on the issue of breeding Cannabis with more therapeutic biochemical profiles that potentially portend to make Cannabis safer and better.

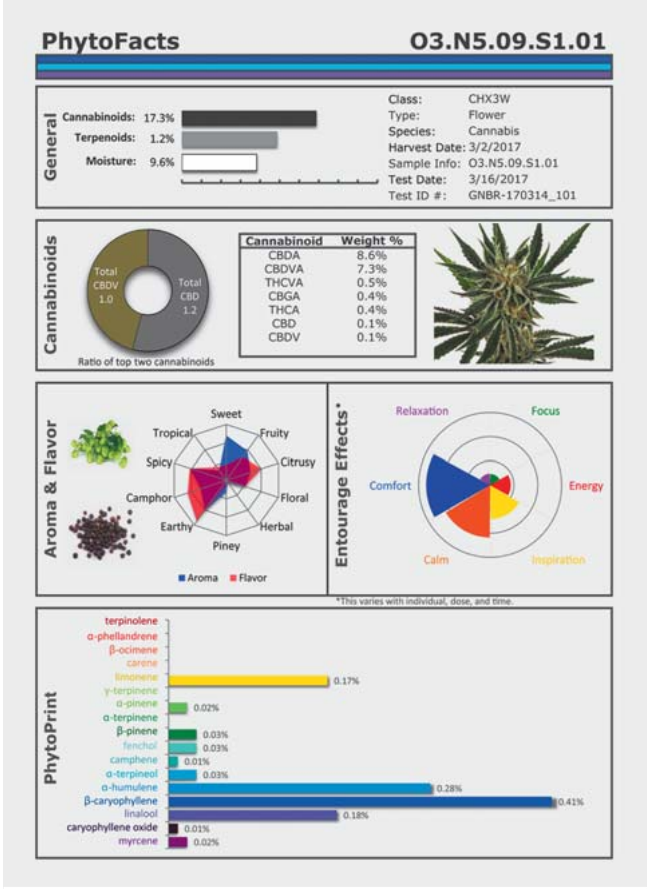
Materials and Methods

Cannabis breeding techniques

Traditional breeding practices were utilized to isolate phytochemical traits. Seeds were sown into 72-cell packs with coir mix. Asexual propagates were taken from plants at the 4-week time point, when plants were moved to controlled flowering conditions (24 °C for 12 h of light). Thousands of plants have been individually screened for cannabinoid and terpene data. From this screen, only plants with a high essential oil concentration and rare characteristics were selected. Segregating populations were selected, selfed, and backcrossed to stabilize the desired traits. The result was a selection of approximately two dozen genotypes that were further hybridized and have been followed for several generations. Visual properties recorded were apical inflorescence size and density. Each was assigned a score of 1–10. Calyx length was also recorded. Plants were also sensually evaluated on a scale of 0–5 (0 = undesir-



▶ **Fig. 6** PhytoFacts of P08.S1.16.P08.S1.81, a CBD-predominant chemovar. Source: Dr. M. A. Lewis, Napro Research.



▶ **Fig. 7** PhytoFacts of O3.N5.09.S1.01, a Type III chemovar with high CBD, CBDV, limonene, caryophyllene, and linalool. Source: Dr. M. A. Lewis, Napro Research.

able; 5 = highly desirable). General performance of the selected individuals was assessed in a randomized design with four replicates.

Cannabis chemovar authentication

Stabilized chemovars of Cannabis were used in this study, which were cultivated and processed in strict adherence to both California state and local municipal laws, and were assiduously followed via labelling throughout the process. While traditionally voucher specimens of new plant cultivars are deposited in herbaria, such materials are prohibited by the USA DEA, unless both the supplier and receiving institution possess Schedule I licenses to possess the material and store it under stringent security conditions. Otherwise, it is an abrogation of federal laws. Authentication of individual chemovars was assured in this instance by consistent plant labelling and extensive biochemical analyses. Seeds belonging to several of the parental lines used to create the novel chemovars presented in this article have been deposited in the National Collection of Industrial, Food and Marine Bacteria (NCIMB) in Scotland.

Cannabis analysis

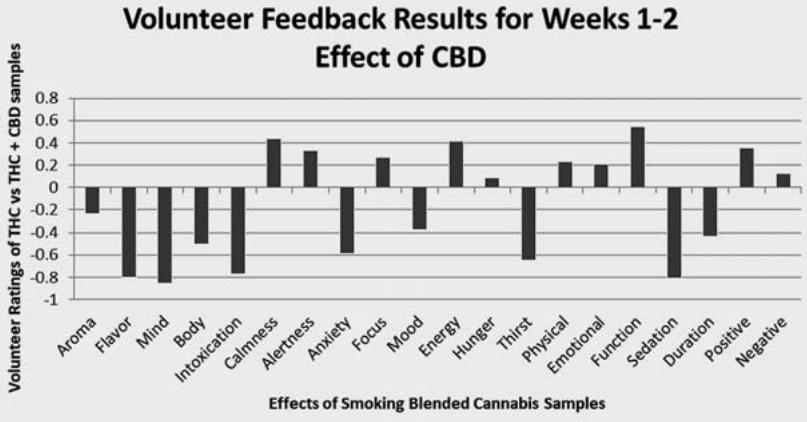
Mature Cannabis inflorescences for each individual cultivar were sampled and dried for phenotype analysis, as previously described [21]. This procedure utilizes 1 : 15 w : v ethanol extraction of plant metabolites, injected neat onto a GC-FID (Perkin Elmer Clarus 680) for terpene analysis, then diluted 6 x and 96 x for minor and major cannabinoids, respectively, on HPLC-DAD (Agilent 1290 HPLC) for cannabinoid analysis. Terpene identity was confirmed by the retention time of analytical reference standards and a GC-MS NIST Library search. Similarly, the latter was utilized to orthogonally confirm cannabinoid identity alongside analytical reference standard retention time on HPLC-DAD. Absolute values for all compounds are reported as a weight percent.

Patient panels/surveys

Several volunteer patient panels were performed to assess the subjective effects of different THC : CBD ratios and varying terpene profiles, in conjunction with an extensive literature search to assemble taste, aroma, and effect algorithms. While Cannabis commerce for patients with a physician's recommendation is legal in California, these patient panels can only be discussed in general terms due to the current regulatory framework. Panels consisted of 30 patient participants and were conducted over a 7-week period. Each patient had previously received a physician's recommendation to utilize Cannabis medically, and had volunteered to complete survey questions after signing informed consent noting

▶ **Table 1** Division of patient survey groups according to phytocannabinoid and terpenoid profiles tested.

Week			
1	2		
THC and THC + 1.5% CBD	THC and THC + 2.5% CBD	Terpene class	Control and comparator terpenes
Group 1	Group 6	a	myrcene, pinene
Group 2	Group 1	b	limonene, linalool, caryophyllene, humulene
Group 3	Group 2	c	ocimene, myrcene
Group 4	Group 3	d	terpinolene, ocimene
Group 5	Group 4	e	myrcene, pinene, ocimene, linalool, caryophyllene
Group 6	Group 5	f	limonene, caryophyllene, myrcene, linalool



▶ **Fig. 8** Subjective effects of cannabidiol in volunteer patient surveys.

that their responses would be recorded, but their identities would remain anonymous. The first trial experiment examined the effect of added CBD. Volunteers were split into six groups and each was given two pre-rolled Cannabis joints once a week. The cannabinoid content was consistent across all groups, while the terpene profile was diverse. In each group, one sample contained no CBD and the other contained 1.5% (week 1) or 2.5% (week 2) CBD. Throughout the week, participants completed surveys before and after smoking each sample. The survey asked participants to evaluate the following on a scale of 1–10: aroma, flavor, mind high, body high, intoxication, calmness, alertness, anxiety, focus, mood enhancement, energy, hunger, thirst, physical comfort, emotional comfort, ability to function, sedation, effect length, and the perceived level of positive/negative effects. The major terpenes for each sample are described (▶ **Table 1**).

Results of these efforts in the survey patients are the average difference for both weeks across all groups and show a decrease in "mind high", "body high", "intoxication", "sedation", "anxiety", and an increase in "calmness", "alertness", "focus", "energy", and ability to function with the presence of CBD (▶ **Fig. 8**).

Another 1-week panel compared a 5:1 THC:CBD cannabinoid ratio with varying terpene profiles. In general, non-myrcene-dominant profiles showed increases in energy and alertness. There was a notable decrease in energy and alertness reported in sample e, the only myrcene-dominant terpene profile. The terpinolene-dominant sample d produced increases in subjective energy. Samples with ocimene produced a more calming effect compared to similar profiles without that component. Chemovars containing limonene and pinene increased reported focus, particularly in the latter. Higher limonene, ocimene, and linalool promoted "inspiration", as observed from the mood metrics in the questionnaire.

PhytoFacts report form

PhytoFacts (https://phytofacts.info) is an intuitive report format that displays the complete chemical analysis of cannabinoids and terpenoids within a Cannabis plant sample, previously illustrated in a prior publication [50]. This format was designed to help the Cannabis industry analyze, sort, or recommend a broad range of Cannabis chemotypes and their related effects from the results of laboratory testing. The top-most line displays the chemovar name, while the underlying color-coded bars reflect the top three terpenes found within a particular chemovar. These top three terpenes are part of the comprehensive color-coded terpenoid panel, also called the PhytoPrint, located in the bottom panel of the

report that displays terpenoids detected to ± 0.01%. PhytoPrint colors correspond to parings in Nature that are advantageous toward intuitive understanding (e.g., Green = pinene as found in pine needles, Yellow = limonene as encountered in lemons). The uppermost section of the report displays total cannabinoids, terpenoids, and moisture content, the critical information for assessing flower quality. In the next panel, the "Cannabinoids" section displays the top two cannabinoids based on concentration in a given sample, while the cannabinoid table shows all cannabinoids detected within ± 0.5%. An image of the unfertilized flower sample is included for forensic verification. In the aroma and flavor section, the organoleptic profile and aromatic characteristics of the terpenes detected are displayed as a spider graph. The colored pie chart displays the expected entourage effects, which are possibly superimposed upon the cannabinoid pharmacology by terpenoids present within a given chemovar. The entourage effects algorithm was created from a combination of collected consumer inputs related to the use of specific chemovars in addition to data extracted from published literature on biochemical effects. The end result is a series of weighted values toward each effect for each compound and some pairs of compounds found in Cannabis, as assessed in ▶ **Table 1**.

Supporting information

PhytoFacts comparisons of Type I, II, and III chemovars with preservation of the limonene-predominant and caryophyllene-predominant terpenoid profiles and proportions are available as Supporting Information.

Acknowledgements

The assistance of many individuals that contributed to the foundations of this article is gratefully noted: Matt Giese for the development of the PhytoFacts report format and work patient panels. Ryan Lee laid the foundations for the breeding program and consulted throughout. Michael Backes for his thought leadership, and Trish Flaster, Rob Clarke, John McPartland, and Ernest Small for their input on Cannabis typology and nomenclature. We would also like to thank the anonymous reviewers, whose many comments and suggestions strengthened this manuscript.

Conflict of Interest

MA Lewis is President of Napro Research, a company engaged in phytochemical analysis and research, and the developer of the PhytoFacts report format. EB Russo former Medical Director of Phytecs, a company investigating the therapeutic applications of Cannabis, other botanicals and dietary approaches affecting the endocannabinoid system and is currently the director of research and development at the International Cannabis and Cannabinoid Institute (ICCI). KM Smith is Laboratory Director of Napro Research. Several of the plant chemovars herein may be subject to one or more issued or published U.S. patent applications.

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