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Marijuana, a Journey through the Endocannabinoid System: Unmasking the Paradoxical Effect - Part 2

Ryan Lucas McKinley

Abstract

Here in part two, a brief explanation in essential oil/ terpene administration as well as cover the medicinal effects of terpenes focusing on biphasic pharmacokinetics and possible paradoxical reactions and molecular sites of interest, including the medicinal properties of a specific flavonoid; an explanation into the paradoxical entourage and identifying common misconceptions from cannabis use and education; we finalize our look into the paradoxical location learning biphasic and paradoxical reactions from cannabis with an in-depth look into the cause of ASR/ATD following with a fundamental explanation how stress with the wrong medication can instigate the situation. The **Multi Cultivar Entourage Effect Chart (MCEEC)** directed goal was to unravel multiple cultivars bioavailability to then combine and create a more robust and stronger entourage being pulled from multiple cultivars with specific bioavailability of cannabinoids, terpenoids, and flavonoids necessary to treat any specific indication. Indirectly the chart also identified inter-entourages, more importantly, “antagonistic” inter-entourages. By helping a patient describe their reactions, understand, identify and track terpenes and cannabinoids that cause specific reactions, the patient will be able to identify a profile that works for them, which gives an explanation and solution to identifying how to manage cannabis medication for the patient along with conclusion and thoughts.

Keywords: Advanced Synergistic Serotonin Release (ASSR/ASR), Advanced Tryptophan Depletion(ATD), Endo-Cannabinoid System (ECS), Central Nervous System (CNS), Psychoactive (PA), Non Psychoactive (N-PA), Cannabigerol (CBG), Tetrahydrocannabinol (THC), Tetrahydrocannabinolic Acid (THCA), Tetrahydrocannabivarin (THC-V), Cannabinol (CBN), Cannabichromene (CBC), Cannabielsoin (CBE), Cannabicyclol (CBL), Cannabidiol (CBD), Cannabidiolic Acid (CBDA), Cannabidivarin (CBDV), Broad Leaf Marijuana (BLM), Broad Leaf Marijuana Dominant (BLMD), Medium Leaf Marijuana (MLM), Narrow Leaf Marijuana Dominant (NLMD), Narrow Leaf Marijuana (NLM), Cannabinoid Receptor type1(CB1), Cannabinoid Receptor type 2 (CB2), Vanilloid Receptor 1 (TRPV1), Transient Receptor Potential Ankyrin 1(TRPA1), γ -aminobutyric acid (GABBA-A), Hydroxy-Tryptamine (5-HT), Transient Receptor Potential cation channel, subfamily V, member 3 (TRPV3), Attention Deficit Hyperactivity Disorder (ADHD), γ -aminobutyric acid (GABAA)

1. Introduction

1.1 Terpenes and flavonoids

This section's objective is to weed out possible terpene synergies which may actuate a biphasic experience of either ASR/ATD. Over 200 terpenoids are primarily responsible for the many fragrances of cannabis and may represent 10% of trichome content [1–7]. Monoterpenoids, containing oxygen functionality or missing a methyl group, are commonly composed of limonene, myrcene, pinene, linalool [8–11]. Terpenes are widely known to cross the blood–brain barrier due to their chemical makeup to be lipophilic like cannabinoids [9]. Terpenoids will begin to break down before the processing stage at a rate of about 5%. After curing processes and in time (1–6 months) terpenoids will have diminished significantly [12, 13]. With this in mind, any further actions taken to separate the whole cultivars' phytochemistry undoubtedly weakens the quantum function of the entire medicinal chain, ie extraction and or isolation processes. Terpenes in their natural state, are incorporated in the trichomes of cannabis with a fundamental directive whether it's to keep predators at bay, maintain general cultivar homeostasis, or the more commonly known use, as a medication for homeostasis in most vertebrate species.

Any medicinal flower sold past 6 months from the end of the curing stage, will most likely be under the promised genomes bioavailability or true to the cultivar medicinal properties. The cannabis flower should be tested at the 6 month and interpened to either be converted to extracts or discarded unless properly stored (i.e., time would vary depending on consumer storing methods). In this time (1–6 > months), the main subsidies of most terpenes begin to chemically change and fall under generally categorized oxidized terpenoids or hydro-carbon terpenes. Cannabinoids in contrast are more resilient in this oxidative manner but should be understood that the intentional entourage from any cannabis cultivar should be consumed as a whole, not a hand-me-down to what was. Other constituents of terpenoids such as caryophyllene, geraniol, humulene, limonene, linalool, myrcene, ocimene, pinene, terpineol, and terpinolene have beneficial health properties that help to treat indications ranging from neurodegenerative disorders to cancer. Though terpenes never directly affect CB1 or CB2, their presence in an entourage may mediate other possible synergistic effects, along with serotonin release.

Flavonoids, a secondary metabolite and interestingly anthocyanin (i.e., blue, violet, and red plant pigments that exist in fruit, vegetables, tea, wine, and “more recently researched,” cannabis) intake have had extensive research ranging from anti-inflammatory to pro-cognitive explained characteristics which also include passing the blood–brain barrier [9]. Thus, it has a viable and crucial part in medical cannabis as a whole product. Specific fruits with high levels of anthocyanins will display dark purple, blue, and perceptively black pigments through inflorescence; like in cherry juice or from Japanese plums, similar phenolic compound levels can be comparable to hemp seed extract. Cannabis displaying plentiful purple or deep red inflorescence could then be suggested for a different or new method of extracting with possible uses such as tinctures, teas, or juices as to not cause excessive degradation to the bioavailability of said cultivar medical administration.

2. α -Pinene

α -Pinene is a bicyclic unsaturated hydrocarbon with two isomers being α - & β -pinene that makes up the whole [14, 15]. This particular terpene is vastly known throughout

nature but in cannabis acts as an/a anti-inflammatory, a bronchodilator, MRSA treatment, antibiotic [16], and even improve cognitive ability and memory retention in lieu of THC's supposed side effect of short-term memory loss [17, 18]. In a recent study, α -pinene's memory retention ability may add the concern to PTSD memory triggers, causing a tougher time disassociating traumatic memories with the trigger [19].

One trait of pinene interestingly stops excitation of a nerve after transmission of an impulse, in short, acetylcholinesterase [20]. In "Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads," Russo and Marcu state, α -Pinene "... serves to reduce or eliminate one of the primary adverse events associated with THC, that of short-term memory impairment. This ability may also serve admirably in the treatment of dementia, a syndrome in which THC has already produced benefits in counteracting agitation".

Henceforth, Pinene, acetylcholinesterase [21], I believe α -pinene to contrary belief may be pertinent to patients with indicators such as PTSD, ADD/ADHD, OCD, panic disorders, spectrum disorders, and epilepsy, when paired with cognitive brain therapy (CBT) breaking an "adolescent fear loop" as thoroughly explained in the study, dynamic changes in neural circuitry during adolescence are associated with persistent attenuation of fear memories [22].

So in a more readable way, pinene has more efficacy during times of positive mental healing than as a "take as needed/ smoke-em-if-ya-got-'em; pill-popping mentality frequently associated with addictive/non-addictive pharmaceuticals" and the patients who take them (i.e., stress). Cannabis is psychoactive and intoxicating and thus has the potential to be mind-expanding ergo the reason for set and setting including CBT. Together, could prove more appropriate in guided treatment, furthermore, that THC lower than CBD and paired with proper synergistic terpenes, would be a safer means of medicating to avoid any excessive serotonin use, aside from what is needed from the HPA axis for the general operation of cannabinoids via pre and post-receptor Synoptics in regions of the brain and body. It is also important to understand pinene is a known characteristic of NLM varieties which are actually the ones provoking most episodes of PTSD and anxiety among many other side effects that stimulants may provide, i.e., pinene exhibits no such stimulation pharmacokinetically.

Hypothesis: So, when paired with a medical chemovar possessing a specific entourage, including α - or β -pinene, a patient can then efficiently break the fear loop cycle and the memory trigger associated with the traumatic cycle creating a new positive loop to trigger [22].

Does α -pinene contribute to the paradoxical effect? No perspective paradox or biphasic ASR manner but an understanding of "when and how to use, for specific neurological conditions."

3. β -Myrcene

β -Myrcene, a monoterpenoid with analgesic, muscle relaxant, and sedative-like properties with many cannabinoid synergies i.e., CBD, THC, CBG. Myrcene can display analgesia in mice, but synthetic drugs that block opioid receptors in the nervous system can be blocked, perhaps via the α -2 adreno-receptor [15, 23, 24], which is responsible for inhibiting the release of norepinephrine (noradrenaline) in a form of negative feedback i.e., "sedation" [25]. Agonists of these receptors have been used to treat mainstream medical conditions such as hypertension, ADHD, various pain and panic disorders; symptoms of opioid, benzodiazepine, and alcohol withdrawal; and surprisingly nicotine cravings, which is one of the most addictive chemicals known to humans [26].

Does β -myrcene contribute to the paradoxical effect? Yes, if there are sub-par levels of serotonin in the body.

Conclusion: A given sedative, myrcene does depend on serotonin for endogenous opioid production, hence, if there is a depletion in tryptophan, then there will most likely be a paradoxical reaction.

4. D-linalool

A similar fragrance is found in lavender, but in a cannabis cultivar and when phytochemically available, the synergy between cannabinoids and this monoterpene reveals treatments such as sedative-like effects. Linalool is used as a local anesthetic; an anti-convulsant, a powerful antileishmanial agent. Linalool is an antinociceptive, reversing defects and spatial memory and learning at high doses with a respectable contradiction in short- and long-term recognition memory. This implies detrimental to cognitively impaired sentient beings, though studies were done on healthy and cognitive impaired rats [9, 27, 28].

The NMDA receptor is very important for controlling synaptic plasticity and memory function. Specifically, linalool showed strong efficacy in inhibiting glutamate uptake in cortical synaptosomes and decreased extracellular glutamate availability via inhibiting the release or adding to the uptake [29, 30]. NMDA affinity means GABA will be either used or suppressed; and in the study, reduced morphine opioid dependency [29, 31].

Does D-Linalool contribute to the paradoxical effect? Linalool acts as a competitive antagonist of [^3H] glutamate binding and as a noncompetitive agonist of [^3H] dizocilpine (NMDA antagonist) [32, 33].

Conclusion (plausible): More study must be done to further identify linalool pathologies and how they may have representation in a paradox in brain plasticity.

5. Beta-Caryophyllene

Beta-caryophyllene sesquiterpenoid, in studies, has shown to operate in a “Phytochemical Polymorphism” manner [34]. With this in mind, Ethan Russo cites, “Terpenoids are pharmacologically versatile: they are lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled (odorant) receptors, second messenger systems, and enzymes” [35, 36]. To be understood as a helper to bioavailable cannabinoids and could be thought of as an oil change for a car.

Does caryophyllene contribute to the paradoxical effect?

Conclusion: No pathology to denote a paradoxical behavior unless serotonin levels are sub-par.

6. D-limonene (the energetic uplifting agitator)

The volatile monoterpene, limonene, one of the most abundant terpenes in cannabis, and its perceived effects can be summed up as uplifting (as to correct a depressed mood) and energetic (as to cure slothfulness); having antioxidant, anti-inflammatory, and neuroprotective properties [37]. These hyperactive characteristics of D-limonene indicate it to be a prime candidate for A2a receptor affinity, and thus, “It plays an important role in many biological functions, such as cardiac rhythm and

circulation, cerebral and renal blood flow, immune function, pain regulation, and sleep. It has been implicated in pathophysiological conditions such as inflammatory diseases and neurodegenerative disorders” [38].

In an *in vitro* dose-dependent study of D- and L-limonene, effects on the pregnant rat myometrium (mid-layer of the uterine wall and the smooth muscle tissue), D- and L-limonene caused myometrial contractility (i.e., increases the contractions of a pregnant uterus); interestingly, L-limonene caused myometrial smooth muscle contraction independent of A_{2A} receptors. Due to the subsequent findings of D- and L-limonene causing myometrial contractility via activation of the A_{2A} receptor and opening of the voltage-gated Ca²⁺ channel, D- and L-limonene should be avoided during any pregnancy [39].

To indulge in the topic of the A_{2A} receptor and its synergistic affinity with limonene, the above-mentioned study was focused on “in vitro” muscle contractility, thus would be fair to assume that any humans suffering from constant or frequent agitation from symptoms/indicators like MS, PMDD, PD, spectrum disorders, or neurodegenerative diseases may also want to avoid this terpene. In cases where this is difficult to avoid, it would then be crucial to understand how a person metabolizes both sedatives and stimulants. Curiosity in this area may open more doors into the point of agitation i.e., invoked and/or systemic and could then be regulated with the correct level of sedating to stimulating terpenes and aim for a genetic strain with a similar entourage. In the effort to stimulate without agitation, cannabis entourage with sedative terpenes could be added into the stimulating entourage via cultivation/hybridizing and/or multi-cultivar entourage dosing.

A good rule of thumb about the terpene limonene is to understand the biphasic modes in which this part of the entourage manipulates; a handful of studies dissect the physiology of citrus fruit-bearing plants and all come to a consensus that limonene affects serotonin via 5HT_{1A} and dopamine via D₂, thus giving the cascade of both stimulating and suppressant like effects.

However, the patient should be made aware of any synergies that may use 5HT or suppress and should supplement the 5HT usage via diet to avoid accelerated tryptophan depletion (ATD).

Additionally, humans suffering from indications such as PTSD, spectrum disorders, and general anxiety should also be wary of this terpene due to its excitatory tendencies via the A_{2A} receptor having excitatory biphasic responses. The goal for the vast genetic variety of “balanced” cannabis cultivars, i.e., hybrids (BLMD, MLM, NLMD), has been utilized from BLM’s (medicinal cannabis Indica sub-species *Afghanica*) genetics and crossed with NLM (*Cannabis indica* sub-species Indica) or any other sub-species to then aim to produce (in this case) a vast range of sedative leaning MLM’s (marijuana hybrids) i.e., BLMD. Henceforth, giving agricultural/horticultural cannabis growers the ability to hybridize and clone for a more viable chance at an endless possibility of medicinal cannabis strains. This being said, a BLMD with deviating genetics from the true “Indica,” i.e., the *Afghanica* sub-species, has the chance to contain the volatile monoterpene limonene. In spite of the excitatory ability of limonene, this could then be a perfect supplement or addition to pharmaceutical ADHD medication.

Furthermore, “All the terpenoids discussed herein are Generally Recognized as Safe, as attested by the US Food and Drug Administration as food additives or by the Food and Extract Manufacturers Association and other world regulatory bodies.” [40].

Does limonene contribute to the paradoxical effect? Highly plausible, but clinical study must still be done to truly understand the all working mechanisms of its cascade effects within the entourage effect.

Plausible location (A2A, D2 dopaminergic receptors), (5HT1A, serotonergic receptors).

7. The paradoxical entourage

To find, understand, or even combat the paradoxical effect, one must figure out how to counteract the symptoms so the medication or goal for homeostasis works in the way it is intended.

7.1 Misconceptions and experiences: A paradoxical effect from Cannabis

There is a common misconception about what constitutes *C. indica* and its sub-species variation. Specifically, medicinal cannabis commonly described as “calming, couch-locked, sedating,” and/or claiming the original term, “Indica” (i.e., BLM) may actually fall under BLMD where the distant genetics of an NLM is still relevant among the BLM genetics when hybridized. Thus, having a chance at agitation depends on the NLM genetics. A proper example of this miscommunication would be a BLM crossed with “Green Crack,” a known Sativa cultivar creating a hybrid of stimulating and sedating effects and then sold as an Indica. To further explain the *C. indica* ssp. *Afghanica*/BLM is of the genotype sub-specie *Afghanica* i.e., *Indica* ssp. *Afghanica*; the plant structure is of the shortest growing species revealing the broadest leaves accompanied with the most round and dense flower structure containing very petite pistils permeating a terpene bouquet from trichomes of deep sugary warmth, earthy spiced leather, chocolate, tobacco, and mushroom perceptive smells. *Indica* ssp. *Indica* (NLM), i.e., original term “Sativa” a misclassification by Jean Baptiste Lamarck, (1802); permeating more volatile aromas like grapefruit, tangerine, diesel, solvents, lemon, and pine equally showing polar opposite inflorescence.

What may be perceived as a paradoxical effect, is in fact a misconception of what the medicine actually contains past its genetic name and suggested effects from cannabis. Also, a common misconception when dealing with MLM “Hybrids,” is the extreme ebb and flow from BLMD and NLMD sub-species variation alone, making up a galaxy of possibilities. Within the infinite genetic possibilities of hybrids, the common misconception validates a relative vice versa, where an NLMD i.e., “sativa dominant hybrid strain,” for instance, “Purple Haze” genetics from Prime Wellness of PA will pleasantly contain predominantly sedating terpenes resulting in a metabolic paradox of a stimulating cultivar and predominantly sedating terpenes. Since cannabinoids are less volatile, terpenes and their chemical makeup break down faster. Thus, resulting in a premature depletion of part of the whole medicine possibly resulting in stimulation or agitation toward the end of the medicated bell curve; to counteract this paradox the simple solution would be to add more bioavailable sedative terpenoids along with proper levels of CBD to combat any excessive psychoactive imbalance such as the 2019 “Freedom blend distillate” produced by ILERA to continue the cultivars intended medicinal entourage.

The vice versa misconception plays out similarly wherein an Indica leaning hybrid (BLMD) claiming the label indica i.e., BLM, may carry enough traces of Sativa genetics possibly causing agitation to hypersensitive patients in efforts of sedation. When dealing with a *Ruderalis* (AFM) specific plant speciation can be guaranteed and determined in a chromatography test to identify where the phytonutrients land on the spectrum of sedating, null, and stimulating effects. Thus, the infinite possibilities of hybridization and the cannabinoid and terpene profiles that can be created, have

viable means of documentation. So as to understand when medicating with cannabis, separate the whole to understand how to medicate properly for any specific indicator.

To further understand, cannabis speciation (BLM-NLM) controls sedating/stimulating properties; terpenes and cannabinoids, and their synergies, carry out special tasks manipulating the physical and psychological state prolonging or exhausting a patient's balance of homeostasis depending on the accuracy of correct strain name choice to the indicator. Meaning the "engine size" of psychoactivity; the "transportation" of cannabinoids and the ebb, and flow of stimulating and sedating terpenes are what "drive" any entourage to actuate specific tasks throughout the ECS and CNS.

Thus, looking past strain names, subspecies claim, suggested effects, and acknowledging the cannabinoid and terpene profile of any medicinal cannabis would be a safer guarantee of medicating properly.

8. The paradoxical location

Through the research conducted in the ECS and CNS receptors, I have found a specific entourage of cannabinoids and specific terpenes that are the likely cause of a constant fundamental reaction resulting in this easily avoidable paradoxical effect.

In this paradoxical entourage, I believe the terpenoid D-limonene to possess a prime fundamental pathology to modulate D2 respectively via adenosine A2A receptor dealing with motor behavior, emotional reward, and behavior motivation mechanisms as one of its synergistic post reactions; and an agonist at 5HT_{1A} with effects to counteract excitation; to explain further, limonene could be stimulating and consecutively sedating but that if certain biosynthesis pools are depleted or below average to achieve homeostasis then D-limonene will most likely cause excitation, thus a paradox. With synergistic cannabinoids, not limited to, <CBC, THC, THC-V, CBG, CBD>, and possibly other terpenes to help trigger and prolong the biphasic cycle/paradoxical effect more specifically ATD/ASR or avoid the paradox entirely. This biphasic actuation of D-limonene will have either sedating presents or stimulating presents depending on the entourage it is coupled with and the human physiology it is metabolized by. Patients with PTSD or patients under systemic or triggered anxiety/depression-like symptoms, ongoing physical trauma, will most likely have an affinity to the paradoxical effect or the buildup to an advanced serotonin release (ASR) and should consult their doctor before consuming any unintentional stimulants [41].

In a study where patients had their tryptophan artificially suppressed, it was reported that the depletion/reduction of tryptophan caused a severe decrease in mood [42]. There are significant ethical considerations as that tryptophan depletion can have a profound negative impact on the patient. "... a recovered depressed patient from the acute tryptophan depletion study by Delgado" reported, "... she began to cry inconsolably and described her emotions as being out of control", continued explanations of feeling "as if all the gains she had made over the past few weeks had evaporated." After the tryptophan levels were restored, the patient reported feeling "back to herself."

A disrupted balance of serotonin is an important risk factor for depressive mood, also a common symptom in the later course of treatment of chronic disorders such as cancer, infections, and autoimmune syndromes [15, 37, 43] with indications like autoimmune disease depression autism, epilepsy, HD, or any indicators residing in the ECS and some parts of the CNS will have a higher risk of this happening.

I refer to this function as an ATD or ASR, which happens when specific synergistic cannabinoids and terpenes already using serotonin, uses reserves consecutively at a

more advanced rate of depletion due to the chemical nature of another synergistic action of the same source of depletion or; whilst a consecutive respectively similar (i.e., dopamine and serotonin) depletion ensues.

It is interesting to note that acute tryptophan depletion techniques (referred to by Simon N. Young, PhD (2013) as ATD studies) were first applied by Concu in 1977 and have been used for over 25 years. This technique requires that the patient have their tryptophan levels artificially and intentionally suppressed in an attempt to document the cause and effect. ATD and ASR mentioned in this chapter, describe the postreactions and neurological processes that are documented through studies discovered and cited in this chapter. The information provided is a compilation of information gathered from clinical studies, scientific papers, and the study of cannabis.

In this paradoxical entourage, I believe D-limonene to be one of the prime terpenoids with the ability to excite and release GABA and dopamine as its post-reaction with synergistic cannabinoids, but not limited to CBC, THC, THC-V, and possibly other terpenes to help trigger and prolong the biphasic cycle/paradoxical effect. More specifically aiding in an ATD/ASR. D-limonene being an A2A antagonist in the presence of THC with excitatory properties would then have a much similar reaction like caffeine, methylphenidate, and certain modes of activation of a cocaine alkaloid collection. This allows an accelerated rate of D2/5-HT_{A1} and serotonin release via GABA-A, which can then cause patients with PTSD or patients under systemic or triggered anxiety/depression-like symptoms, ongoing physical trauma, an affinity to the paradoxical effect, or the buildup to an ASR. [43] cb1 PTSD). Other more serious symptoms if left untreated can result in tumors, cancer, autoimmune deficiencies, often antagonizing the main purpose for medicating.

In this hypothesis, the entourage in question plays out similarly from a study by J Marcel, et al. 2010 [44], "...On the one hand, both THC and CBD were shown to decrease TNF- α production in human NK cells and peripheral blood mononuclear cells (PBMC), whereas THC was demonstrated to increase TNF- α production in human monocytes [15, 19]. Treatment of human PBMC with low doses of THC or CBD, comparable to plasma levels detectable after smoking marijuana (10–100 ng/mL), was demonstrated to stimulate interferon (IFN)- γ production, while higher concentrations of these cannabinoids (5–20 μ g/mL) efficiently suppressed formation of this cytokine [19]. These contradictory findings are suggested to be based on a biphasic response relative to the cannabinoid ligand concentration applied, since most of reports showing stimulatory capacities were reported at lower doses, in the nanomolar concentration range, whereas inhibitory activities of cannabinoids were found in the micromolar concentration range [22, 25]. These concentration dependent effects of cannabinoids could be demonstrated for Th1- as well as Th2-type cytokines [26]." Marcel continues, "The suppressive effect of THC and CBD on cytokine-induced tryptophan degradation may constitute an additional mechanism by which anti-depressant effects of cannabinoids might be linked to the serotonergic system."

Disturbed balance of serotonin levels is an important risk factor for depressive mood, which is also a common symptom in the later course of chronic disorders such as cancer, infections, and autoimmune syndromes [6, 18, 45, 46]. Many patients with chronic inflammatory diseases show accelerated depressive mood, implicating a role of cytokine-induced IDO enzyme activity in psychiatric diseases [3, 19]. Additionally, several studies showed that mood is negatively influenced by the depletion of tryptophan [39, 47]. Since tryptophan is essential for the biosynthesis of serotonin, the decreased availability of tryptophan during inflammatory conditions

as a result of degradation by IDO may negatively affect the biosynthesis of this neurotransmitter [37].

The charts below are taken from “Endocannabinoids and Motor Disorders” by J. Fenardez-Ruiz, British Journal of Pharmacology (2009) 1561029–1040 se.mcu.dem@rfjj or se.denrebic@ziur-zednanref.J (**Figures 1** and 2).

The connection between cannabis and serotonin release is that cannabinoids affect GABA which releases serotonin via CB1 and CB2. To further explain this catch 22 situation with cannabinoids and synergistic terpenes as cleanly said by an article in Proof of Pot Writer [48], “Low dose THC and FAAH inhibitors can have anti-anxiety effects. A 2007 study showed that the anti-anxiety effects of THC depended on the 5-HT1A receptor [49], although a 2015 study [50] demonstrated a dependence on the 5-HT2A receptor.”

“Both THC and FAAH inhibitors, which raise levels of anandamide, can improve animal models of depression. The antidepressant effects of these molecules went away when animals were depleted of serotonin (2016 study, 2018 study), indicating that they are working at least partially through increasing serotonin release” [51, 52]. In addition, the antidepressant effect of CBD in animal models depended on activation of the 5-HT1A receptor (2016 study) [48, 51].

Figure 1.
Location of CB₁ and TRPV1 receptors in specific neuronal subpopulations within basal ganglia circuits. Regulatory pathways are indicated in blue, whereas inhibitory and excitatory inputs are indicated in red and green respectively. Unknown neurons are shown in black. CB₁, cannabinoid receptor type 1; GABA, γ -aminobutyric acid; GLU, glutamate; TRPV1, transient receptor potential vanilloid type 1.

Figure 2.

On the scheme shown in **Figure 1**, a diagram has been superimposed to show the different targets (CB_1 , CB_2 and $TRPV_1$ receptors) that might mediate the ability of cannabinoid-based medicines to alleviate specific symptoms, or to delay/arrest the progression of the disease in basal ganglia disorders. CB_1 , cannabinoid receptor type 1; DA, dopamine; GABA, γ -aminobutyric acid; GLU, glutamate; HD, Huntington's disease; PD, Parkinson's disease; $TRPV_1$, transient receptor potential vanilloid type 1.

9. Fundamental and Hypothetical Solution

A fundamental fact to keep in mind is many foods like turkey, cheese, eggs, salmon, broccoli, or over the counter 5HT/ 5-hydroxytryptophan pills, mainly things that either contain or biosynthesize tryptophan for consumption is the only way to get it as humans do not produce tryptophan. Tryptophan is converted to 5-hydroxytryptophan by the hydroxyls enzyme (i.e., the rate-limiting step of serotonin synthesis) (l-tryptophan: basic metabolic functions, behavioral research, and therapeutic indications; 2009 Dawn Richard, Michael Dawes PMID20651948). Therefore, without tryptophan, there will be no serotonin production.

In the efforts to understand, supplement, and avoid an ASR or ATD; I would like to give a hypothetical example or scenario that briefly describes the ways tryptophan is utilized in invoked or systemic trauma.

For this hypothetical scenario, your directed goal is to always keep your tryptophan tank full or commonly at a respectable balance. If you take damage via physical, mental trauma and/or develop systemic trauma, this will then create an ongoing tank

depletion. Thus, more damage will equal more tryptophan depletion, plus tryptophan dependency (due to prolonged systemic or invoked damage) in efforts to reach a targeted 100% homeostasis or maintain minimal levels. Cannabis with high amounts of D-limonene, in this scenario, would be the medication that gives you one step forward and two steps back given no tryptophan has been consumed and depending on how well your character utilizes tryptophan. In this reaction to stimuli via A2A, the body may react out of survival, fear, or a mindful manner response [22].

The longer the tank is empty or struggling to maintain a minimal equilibrium or homeostasis during excitation, the faster the body and mind will suffer due to the absence of tryptophan. Due to this absence of serotonin production, the mind will go through a depressive prolonged shutdown, almost forced into a default mode. The inevitable side effects open doors such as susceptibility to autoimmune deficiencies, cancer, more depression, and eventually your life would be over before your actual intended life expectancy.

Possibly supporting the case of some medical marijuana patients/MCP's peeking, wherein the normal amounts consumed no longer have the intended medicinal effect and may be due to an ATD/ASR without recovery or healthy diet to supplement cannabis amount into the diet.

The combined knowledge indicates that the paradoxical effect does not exist in cannabis but in an individual, and how they metabolize a certain entourage with any disruption to the CNS and ECS that has the potential to exist across the BLM-NLM spectrum of cannabis. The entourage in question has an affinity to use up tryptophan/release serotonin in the efforts to achieve homeostasis via GABA-A modulation through multiple networks in a biphasic/paradoxical manner. More so in those that constantly suffer from hyperkinesia, prone to anxiety and depression, ADD/ADHD, and or in constant extreme pain or from neurological indicators that depend on the presence of tryptophan and the release of serotonin and other dopaminergic reactions.

10. An entourage for everyone

In most cases, the dependability on strain availability and ebb and flow of cannabis morphology throughout each year will be tough to maintain for any cannabis industry grower or dispensary to keep consistency stocked or any cannabis patient to even have. Everyone has their own entourage that creates homeostasis in one's body whether it mediates heavily from one to another or hardly at all. A unique solution would be to compare and contrast multiple cultivars' bioavailability, synergies. In end creating a whole new cascade of newly perceived entourages that have a higher chance at meeting homeostasis directed goals for a patient and their ECS directed by their psychiatrist, cannabis physician, or therapist regardless of genetic availability.

I have created The **Multi Cultivar Entourage Effect Chart** (MCE²C) that unravels multiple cultivars' bioavailability to then combine and create a more robust and stronger entourage being pulled from multiple cultivars with specific bioavailability of cannabinoids, terpenoids, and flavonoids necessary to treat any specific indication.

11. Multi-cultivar entourage effect chart

This chart is able to track a patient's intended intake of cannabinoids and terpenes; displaying what total entourage effect the patient is actually administering when

using multiple cultivars to treat a whole indicator/or many; track over long periods of time showing conscious, subconscious, and habitual tendencies, and may even aid in the help of showing if a certain terpene or cannabinoid synergy is a causation to an adverse effect/ susceptibility through post and present perceptions with DATA to track primary, ancillary, and supplementary levels of an encourage (Figure 3).

	Total	Morning			Total	Noon			Total	Night	
		CHD	RF			PHZ	FB			HBO	AFG
THC	73.800%	25.589%	73.800%	THC	41.144%	32.304%	41.144%	THC	68.692%	64.109%	68.692%
THCA	0.856%	0.000%	0.856%	THCA	43.400%	42.400%	0.000%	THCA	4.587%	3.596%	0.991%
THCV	3.562%	0.632%	2.930%	THCV	0.563%	0.563%	0.000%	THCV	0.390%	0.000%	0.390%
CBD	43.973%	42.035%	1.938%	CBD	47.246%	0.000%	47.246%	CBD	0.000%	0.000%	0.000%
CBDA	1.601%	1.601%	0.000%	CBDA	0.000%	0.000%	0.000%	CBDA	0.000%	0.000%	0.000%
CDBV	0.406%	0.406%	0.000%	CDBV	0.000%	0.000%	0.000%	CDBV	0.000%	0.000%	0.000%
CBN	1.860%	0.358%	1.502%	CBN	0.372%	0.372%	0.000%	CBN	0.896%	0.000%	0.896%
CBG	6.411%	1.621%	4.790%	CBG	0.815%	0.815%	0.000%	CBG	2.608%	2.208%	0.400%
CBC	6.598%	3.536%	3.062%	CBC	0.387%	0.387%	0.000%	CBC	1.990%	0.675%	1.315%

	Total	Morning			Total	Noon			Total	Night	
		CHD	RF			PHZ	FB			HBO	AFG
B-Carophyllene	1.405%	0.909%	0.496%	B-Carophyllene	1.276%	0.525%	0.751%	B-Carophyllene	3.257%	1.503%	1.756%
B-Myrcene	3.129%	2.538%	0.591%	B-Myrcene	12.026%	8.279%	3.747%	B-Myrcene	3.991%	1.346%	2.645%
B-Pinene	0.362%	0.294%	0.068%	B-Pinene	0.316%	0.204%	0.112%	B-Pinene	0.923%	0.267%	0.656%
α-Pinene	0.734%	0.693%	0.041%	α-Pinene	1.327%	1.260%	0.067%	α-Pinene	2.244%	0.729%	1.535%
Limonene	0.746%	0.746%	0.000%	Limonene	1.678%	0.998%	0.680%	Limonene	1.161%	0.819%	0.342%
Unalool	0.000%	0.000%	0.000%	Unalool	0.734%	0.575%	0.159%	Unalool	0.562%	0.228%	0.334%
Bisabolo	0.385%	0.252%	0.133%	Bisabolo	0.295%	0.203%	0.092%	Bisabolo	0.463%	0.239%	0.224%
Humulene	0.732%	0.408%	0.324%	Humulene	0.819%	0.154%	0.665%	Humulene	0.896%	0.464%	0.432%
Terpinolene	0.842%	0.041%	0.801%	Terpinolene	0.070%	0.057%	0.013%	Terpinolene	0.169%	0.054%	0.115%
Valancene	0.000%	0.000%	0.000%	Valancene	0.000%	0.000%	0.000%	Valancene	0.214%	0.000%	0.214%

Here in (Figure 4) every cultivar is broken down into the accompanying cannabinoids to be mixed and matched among other cultivars and their accompanying cannabinoids.

In (Figure 5) all terpenoids are separated to then be compared and contrasted to either amplify or avoid a specific terpene encourage.

In a MCE2C schedule, a patient can visually see the expected entourage from multiple cultivars, patients can add or remove as many strains to achieve a desired balance/homeostasis.

This schedule lasted until certain strains were no longer readily available (i.e. PHZ & AFG) but was later documented after the original multi cultivar entourage was concluded. that patient one replaced PHZ with RF and FB replaced AFG.

Cultivator	Strain	Acronym	Plant speciation (BLM-NLM)
Prime	Purple Haze	PHZ	NLMD
Cresco	Rocket Fuel	RF	MLM
llera	Freedom blend	FB	1:1 BLMD
Standard Farms	Afgooey	AFG	BLM
Cresco	Honey Boo	HBO	BLM
Prime	Cherry CBD	CHD	1:1 BLMD

Figure 3. Genetic cultivar key Ryan McKinley 2020.

	Strain					
Cannabinoids	PHZ	RF	FB	AFG	HBO	CHD
THC	32.304%	73.800%	41.144%	68.692%	71.652%	25.589%
THCA	42.400%	0.856%	0.000%	0.991%	0.398%	0.000%
THCV	0.563%	2.930%	0.000%	0.390%	0.640%	0.632%
CBD	0.000%	1.938%	47.346%	0.000%	0.372%	42.035%
CBDa	0.000%	0.000%	0.000%	0.000%	0.000%	1.601%
CDBV	0.000%	0.000%	0.000%	0.000%	0.000%	0.406%
CBN	0.372%	1.502%	0.000%	0.896%	0.364%	0.358%
CBG	0.815%	4.790%	0.000%	0.400%	3.088%	1.621%
CBC	0.387%	3.062%	0.000%	1.315%	1.004%	3.536%

Figure 4.
Unraveled cannabinoids from six different chemovars to be mixed and matched for a new entourage or combined synergistic experience (Ryan McKinley 2020).

	Strain					
Terpenoids	PHZ	RF	FB	AFG	HBO	CHD
B-Carophyllene	0.525%	0.496%	0.751%	1.756%	1.503%	0.909%
B-Myrcene	8.279%	0.591%	3.747%	2.645%	1.346%	2.538%
B-Pinene	0.204%	0.068%	0.112%	0.656%	0.267%	0.294%
α -Pinene	1.260%	0.041%	0.067%	1.535%	0.729%	0.693%
Limonene	0.998%	0.000%	0.680%	0.342%	0.819%	0.746%
Linalool	0.575%	0.000%	0.159%	0.334%	0.228%	0.000%
Bisabolo	0.203%	0.133%	0.092%	0.224%	0.239%	0.252%
Humulene	0.154%	0.324%	0.665%	0.432%	0.464%	0.408%
Terpinolene	0.057%	0.801%	0.013%	0.115%	0.054%	0.041%
Valancene	0.000%	0.000%	0.000%	0.214%	0.000%	0.000%

Figure 5.
Unraveled terpenoids from six different chemovars to be mixed and matched (Ryan McKinley, 2020).

12. Conclusion and future research

In bringing this infinitely hybridized herbal Rubik’s cube full “Square,” the cascade of entourages displayed from cannabis and the cannabinoids, terpenes, and flavonoids therein have potential and viable medicinal purposes. The research studies used in this chapter cover centuries of cannabis usage since 4000 BC through modern pharmaceutical research and its history in North and South American society circa 2019.

This research identified people under systemic, invoked, or prolonged mental or physical trauma will be susceptible to agitation from certain cannabis inter-entourages consisting of stimulating terpenes (specifically D-limonene and its co-related cannabinoid synergies) more so than healthy individuals, thusly experiencing a paradoxical effect.

Individuals who have a propensity to experience stimulants in a biphasic manner have formidable disadvantages with dopamine uptake, storage, and/or metabolism. Limonene affects A_{2A} allowing a catch 22 of symptoms ranging from a general excitability/alertness via D-limonene. D-Limonene is also an anti-depressant via CBD from 5-HT_{1A} (serotonin, for reduction in neuronal excitability and firing), unless serotonin levels are low or depleted then perceptions may shift to the more agitative especially with an A_{2A} agitator present in the entourage.

ATD or ASR, happens when specific synergistic cannabinoids and terpenes already using serotonin and use reserves consecutively, at a more advanced rate of depletion due

to the chemical nature of another synergistic action of the same source of depletion or; whilst a consecutive respectively similar (i.e., dopamine and serotonin) depletion ensues. It is fundamentally understood, that without tryptophan, most, if not all serotonin production would cease in the human body. Henceforth, studies state respectable levels of serotonin in the body inhibit dopamine production, calming down impulsive behavior and side effects of dopamine abuse either natural (i.e., habit) or foreign (i.e., drug).

The 5-HT_{2A} dependent cannabinoid THC uniquely being a synergistic vehicle for a few terpenes and a prime dictator of the psychoactive engine size guarantees the highly lipophilic D-limonene transportation through the blood–brain barrier. These two powerhouses in their own synergistic pathological right actuate dopamine and use of the serotonergic pool. Therefore paramount to uphold a strict healthy diet to supplement basic natural dopamine use and tryptophan depletion that may happen in patients with said indications is pertinent while medicating with cannabis to ensure true beneficial homeostasis from any entourage.

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Abbreviation

ASSR/ASR	Advanced Synergistic Serotonin Release
ATD	Advanced Tryptophan Depletion
ECS	Endo-Cannabinoid System
CNS	Central Nervous System
PA	Psychoactive
N-PA	Non-Psychoactive
CBG	Cannabigerol
THC	Tetrahydrocannabinol
THCA	Tetrahydrocannabinolic Acid
THC-V	Tetrahydrocannabivarin
CBN	Cannabinol
CBC	Cannabichromene
CBE	Cannabielsoin
CBL	Cannabicyclol
CBD	Cannabidiol
CBDA	Cannabidiolic Acid
CBDV	Cannabidivarin
BLM	Broad Leaf Marijuana
BLMD	Broad Leaf Marijuana Dominant
MLM	Medium Leaf Marijuana
NLMD	Narrow Leaf Marijuana Dominant
NLM	Narrow Leaf Marijuana
CB1	Cannabinoid Receptor type1
CB2	Cannabinoid Receptor type 2
TRPV1	Vanilloid Receptor 1
TRPA1	Transient Receptor Potential Ankyrin 1
GABBA-A	γ -aminobutyric acid
5-HT	Hydroxy-Tryptamine
TRPV3	Transient Receptor Potential cation channel, subfamily V, member 3
ADHD	Attention Deficit Hyperactivity Disorder
GABAA	γ -aminobutyric acid

Author details

Ryan Lucas McKinley
Slippery Rock University, Slippery Rock, Pennsylvania, USA

*Address all correspondence to: dj8t6d@icloud.com

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