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Chapter

Marijuana, a Journey through the Endocannabinoid System: Unmasking the Paradoxical Effect - Part 1

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Abstract

This two-part section helps the reader to achieve a better understanding of how cannabis works as a viable medication for the endocannabinoid system (ECS) and central nervous system (CNS) in humans by identifying individual synergies between cannabinoids, or cannabinoids and terpenes in their journey through the ECS and CNS in various mammalian patient indicators to unmask this paradoxical effect. The specific biphasic/paradoxical manner in question was researched and inevitably identifies cannabis use that manipulates tryptophan uptake, serotonin release, and dopamine actuation. Therefore, a patient's diet may demand a higher tryptophan and dopa-L supplementation to avoid a paradoxical agitation on the receptor level. This chapter explains the pathology of how cannabis consistently reacts in the ECS for every individual, only separated by metabolism and disruption/trauma in the ECS and CNS, implying that there was no found paradoxical effect existing in cannabis, but in the patient, and thus is perceived the same in every individual, only mediated by metabolism, environment (surroundings), and the exception for individuals who process stimulants and tryptophan and/or serotonin in a disrupted manner causing a perceived paradoxical effect or the build-up to and/or what will be referred to as ASR/ATD. The cannabis industry, growers/breeders, interpeners/cannabis sommeliers/bud tenders, and dispensaries need to continue to constantly strive for more knowledge, just as the researchers and FDA need to continue their work to understand the benefits of cannabis, and most importantly, all must work together to remove cannabis from the Schedule I and Schedule 2 classification.

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

When visiting a medical marijuana dispensary, it is common to hear, “try and see what works for you.” Unfortunately, in today’s cannabis industry, some physicians and most bud tenders or “patient care specialist” have to tell patients to go through a trial and error process until they figure out what works best for their indications. This can be very stressful and unfortunate since no single cannabis cultivar strain is the same; implying there is no consistent structure or knowledge or actual prescription while being treated with cannabis.

What numerous studies in this paper show are that specific indications (i.e., physical, mental, neurological disruptions that slowly degrade the quality of everyday life) seem to respond best to specific entourage of cannabinoids and terpenes within a sub-specie ballpark grouped cultivar similarity. Such Cannabis sub-specie groups will be described in the mannerism of an Interpener (Cannabis Sommelier) to guarantee fundamental accuracy of sub-specie variation, chemotype, phenotype, and genotype, which was modified by Trichome Institute based off the study of Clark and Merlin (Evolution and Ethnobotany).

There is a common misconception about what constitutes a Cannabis Indica strain and its sub-specie variations. To understand the mechanisms associated with cannabis, it is important to separate the whole to understand how to consume properly for any specific indication.

A substantial amount of named genetics from growers and their companies are unfortunately carried out through the whole seed-to-sale process claiming the term “Indica” when in actuality is most likely an Indica leaning Hybrid/BLMD. Reasons for Sativa not being a part of this paradox is that sativa is known to excite, and haze has been known as the couch lock of sativa (most likely due to specific terpene profiles). There has never been an identification for Indicas that cause stimulation (what is now known as the terpene profile and chemovar sub-specie to denote cannabis’s therapeutic effects). This could be claimed as “stoner myth” since it may have been considered unfavorable cannabis that made people paranoid or anxious, hence another reason to look into the paradoxical effect.

This simple misconception causes improper strain speciation leaving a patient to improperly consume. Ultimately, cannabinoids, terpenes, and other minor phytochemicals are what dictate how cannabis will react in the human body. Ignoring that and only judging by genetic names or suggested sub-specie can result in unintentional wrong profile. This is obviously unacceptable for any terminal patient as much as it is unacceptable for patients with indications such as panic attacks, neurodegenerative disease, or those on the spectrum.

Individuals who have the propensity to experience the “paradoxical effect” where the patient experiences agitation from an implied “sedative and/or stimulant” may also need to consider how an individual metabolizes said entourage from any cultivar administered medically or recreationally; different cannabinoids and terpenes metabolically break down at varying rates within the body.

I hope this paper will provide the information that will pave a new road for patient care. Additional research is underway to identify those patients with the propensity

toward a paradoxical effect or ASR/ATD from stimulants or sedatives depending on neurological and physiological disabilities that are tied to the brain and disrupt the regulatory process it takes for homeostasis in any human.

2. Defining a paradoxical effect

A paradoxical effect is an effect of a chemical substance, usually a medical drug or horticultural consumable that has the propensity to react opposite to the effect that would normally be expected. To understand why paradoxical effects happen for some and not for most calls for some examples to further understand this enigma. Specifically the paradox in question seems to act in a biphasic manner (having two phases), i.e., normal function to overabundance or a lack there of.

2.1 Benzodiazepine

A sparse example is benzodiazepine, intended to mildly sedate, wherein rare cases can cause excessive talkativeness, excitement, and increased movement. Benzodiazepine forms a pharmacological effect by actuating the γ -aminobutyric acid (GABA) receptor, this effect causes an elevated chloride channel opening with increased GABA-mediated inhibition giving the perception of sedation, anti-anxiety, and reports of amnesia [1]. In a 2004 study by Mancuso [2], it was reported that a very small percentage of patients experienced a paradoxical or biphasic reaction including acute excitement and hostility.

This could then imply any previous and/or present damage to reuptake pathology of serotonin and sedatives, systemic or invoked, could stop sedatives altogether from working via trauma, prolong depression, and/or abuse or natural tolerance of sedatives. Sedative tolerance may be due to poor uptake and reuptake including the nurtured abuse of dopamine and/or serotonin actuation; an abuse of the drug, exhausting the serotonergic pool; i.e., a situation where there is not enough tryptophan in a diet to invoke the positive effects of medication.

2.2 Methylphenidate

A more common example would be the pronounced mediation between stimulating and sedating perceptions of psychostimulants in people who are prescribed Attention Deficit Hyperactivity Disorder (ADHD) medications. ADHD medications such as "methylphenidate" i.e., "Ritalin" are by nature stimulants and inhibit reuptake and stimulant release of dopamine in the Central Nervous System (CNS), thus giving increased temporal and spatial presence of dopamine at postsynaptic receptors [3–6]. The intent of Ritalin is to calm and focus patients in attempt to correct or alleviate cognitive dysfunction, whereas a non-ADHD person will simply experience Ritalin as a stimulant.

Use of the Spontaneously Hypertensive Rat (SHR) is widely accepted in the hypothesis of dysregulation and dopaminergic neurotransmission in line to the behavioral alterations in both ADHD patients and SHR [3]. Past reports have shown an imbalance in the pathophysiology of ADHD and SHR displaying altered functional adenosinergic neurotransmission and affinity of agonists to brain adenosine receptors [7–9]. Thus, adenosine, a neuromodulator in the CNS via cell surface receptors, may display a paradoxical effect at adenosine locations or disrupted locations. Adenosine was more recognized for the ability of caffeine as an A1 and A2 receptor antagonist

[3, 9, 10]. Extensive evidence to date states that ADHD patients have formidable disadvantages with dopamine uptake, storage, and/or metabolism, [11–14]. In addition, that most, if not all, adenosine receptors are a prime target for treatment of diverse disorders in relation with a dysregulation and dopamine neural transmission that occurs in PD, schizophrenia, and ADHD [3, 15].

The paradoxical/biphasic effect displayed in the paragraph above shows a close relation between adenosinergic and dopaminergic transmission in which A1A, A2A are modulated by dopaminergic processes and down/upregulate glutamate. Where the medication is it meant to overwhelm and suppress; instead in a non-ADHD stays open and causes anxiety or stimulant experience.

2.3 Coffee

A closer look into coffee, a common household stimulant and an adenosine A2A receptor antagonist. Caffeine specifically is responsible for “antagonizing all types of adenosine receptors (ARs): A1, A2A, A3, A2B and, adenosine exerting effects on neurons and glial cells of all brain areas” [16]. In coffee, the natural psychoactive stimulant, caffeine, is well known for causing uplift and energy in the general population. This type of stimulant at first look would deter most in the effort for a calm and relaxed state due to being in an extended hyperactive state **Figure 1**.

However, past study results show that adenosine receptor antagonist, i.e., caffeine, might represent a very important therapeutic role for the treatment of ADHD [18–21] but would not be a substantial replacement for the current medications. This would then imply coffee moreover, caffeine, an A2A adenosine receptor antagonist has the propensity in humans and SHR to act in a biphasic manner much like Methylphenidate, in the efforts of either stimulating or sedating a specific patient indication.

Figure 1. Safer and Krager [6] Model of intrastriatal network during cocaine and A2A-R antagonists' exposure [17].

2.4 Cocaine hydrochloride

One not so common household stimulant is cocaine hydrochloride. Technically, a cocaine alkaloid collection is also an A2A receptor antagonist. As an A2A antagonist, cocaine is known for its increased alertness, elevated body temperature, euphoria, excessive talkativeness, restlessness, irritability, pupil dilation, and decreased appetite [22].

A closer look in a more recent study will show that D2/A2A in its activation of cholinergic interneurons influences the excitatory synaptic transmission MSNs of direct and indirect pathways via a retrograde release of endocannabinoids, which in turn interacts with striatal glutamatergic (GABA) and dopaminergic transmission (Dopamine) [23, 24]. This implies that A2A antagonists affect retrograde cannabinoid release in the ECS allowing tryptophan use and serotonin release along with dopamine transmission, showing similar receptor affinity and excitatory properties much like methylphenidate and caffeine.

2.5 Cannabis

Another well-known plant across the globe is cannabis. The use of cannabis is known throughout history and in one study dates medicinal use back to 4000 BC via Carbon-14 dating [25]. More archeological research could be done to discover if cannabis or other mind-expanding drugs (with respective similarity) were implemented at even earlier dates. This could then give even stronger precedents for cannabis as evidence for a viable medication and/or diet additive toward a true non-synthetic homeostasis. Presently cannabis is understood as a medicine to be used in treatment for various indications ranging from cancer to neurodegenerative disorders. Vast studies show cannabis acting on the ECS, which is “comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids” [26].

Notorious and major parts that make up the female inflorescence of cannabis are cannabinoids, terpenoids, flavonoids, bracts (flower), pistils, styles and stigmas, trichomes, fan, and sugar leaves. Of these parts, their biochemistry is psychoactive, i.e., (the ability to pass through the blood-brain barrier and modulate brain chemistry) and non-psychoactive, synergistic and non-synergistic, and do so through the efficacy of specific synergies between bio-available phytochemicals such as cannabinoids and terpenes; thus, creating an entourage effect transmitting throughout the ECS and CNS that almost works in a harmonic and chaotic matrix of possible synapses.

New discoveries are constantly unfolding about this herbal Rubik's Cube as cannabis becomes accepted into society medically or recreationally. The paradoxical effect in question that cannabis is suspected to give has not gone through any pathological nor clinical study to present date, but has been said to have effects much like coffee commonly existing in the cultivar ranges of BLMD-NLM, where caffeine may stimulate or sedate some but still has been solely based out of hearsay and grapevine knowledge or “Stoner Mythology.” Given the far-reaching medicinal properties of cannabis, one would be fair to assume that any medication acting on ECS and CNS would have the affinity to act like cannabis with the respective nature of cannabis and its ongoing discoveries. Therefore, receptors are going to respond no differently if cannabis, cocaine, or coffee triggers the receptor. Importantly, what separates cocaine and cannabis is what makes cannabis unique.

A published doctor of osteopathic medicine, Joseph Cohen of Holo Health explains that “what allows cannabis to be separated from most pharmaceuticals, especially

opioids, is due to the natural scarcity of endocannabinoid in the brain stem, avoiding cardiac and respiratory centers entirely. Whereas narcotic analgesics (opioids), or any medicine affecting opioid receptors have a chance to manipulate dopamine and opioid receptors in the brain stem with a fair risk of overdosing.” Thus, cannabis only affects a specific area of the body leaving alone parts that are crucial in the sustainability of continuing life and is probably one of the safest means of medication for the human mind and body than any pharmaceutical on the market when paired with a healthy diet and wholesome mindful coexistence or simply a perspective of livity.

Briefly, all the above would imply that many substances in the world can plausibly be medicine and even act in the same mannerisms as others. Undoubtedly more scientific study must be done in order for those things acting like medications, like pharmaceuticals, or possible medicine occurring naturally in the environment to be a safe viable and fundamental means for consumption and the longevity of the consumer. Furthermore, through the thousands of years of evolution engaging with intoxicants, many other herbs aside from cannabis have therapeutic involvement with the human body such as clary sage, mushrooms containing psilocybin, as to say that it may be a natural part of life and evolution for humans having the sentiments that they do.

In the study of cannabis and its pharmacokinetics, it should not be limited to just chemical properties but understood as a paradigm of physical-anthropology, nutrition, neurology, horticulture, taxonomy, chromatography, and herbalism. Unfortunately in 2019, cannabis is still illegal on a federal level and is described as a Schedule 1 drug, i.e., determined by the abuse/addiction rate factor of the drug, which results in a scheduling of five subcategories; Schedule 1 being the most restrictive; 21 U.S.C. §802, prevents any Schedule 1 or 2 to be a medication or used for clinical study. 21 USC § 813 (2011) states any substance pharmacologically substantially similar (a proper example would be Sativex, Nabilone, or any synthetic acting like cannabis in the United States) to a Schedule 1 or Schedule 2 substance will be carried out under the same extent of the law as said above in 21 U.S.C. §8029 (Pub. L. 91–513, title II, §203, as added Pub. L. 99–570, title I, §1202, Oct. 27, 1986, 100 Stat. 3207–13; amended Pub. L. 100–690, title VI, §6470), Nov. 18, 1988, 102 Stat. 4378).

3. Short history subsection

So starts Marijuana’s long process down a road of a predetermined discrimination without proper fundamental scientific representation to mandate it as an illicit drug starting as early as the 1900s in America.

This repetitive historical adolescent or fearful behavior can date back to the early 1500s in Mexico during the Spanish occupation when Christianity was introduced, and hemp was promoted over the indigenous crop of cannabis. Together these factors inhibited native people from cultivating their own spiritual plants that were used for ceremonial purposes fighting their own prohibition centuries ago (Santiago Guerra). Mexico’s reestablishment in 1810 “Rosa Maria” or “Mariguana” was added to the 1846 Mexican Pharmacopeia from the Mexican Medicinal Academy for medicinal purposes. For the next 172 years, Mexico will go through various political agendas, upper and lower-class segregation, and racism along with its own battle for the legalization of marijuana. By October 31, 2018, the Supreme Court of Mexico declared prohibiting its use was unconstitutional, therefore deeming cannabis as a recreational, legal medicine within the confines that constitute the law making it legal.

Circa 1910, the word marijuana begins to spread across the America via returning US soldiers and legal immigrant Mexicans fleeing the Mexican Revolution who also brought the term marijuana back with them. By 1930, prohibitionists and a handful of people in power such as FBN's (Federal Bureau of Narcotics which would eventually become the DEA) very own narcotics commissioner Harry Jacob Anslinger, who was unfortunately and constantly self-submerged into trying to put an end to the relentless violent and gruesome human behaviors of the international trafficking or smuggling of booze and later more known for taking on the narcotics circuit. Harry would later draft the 1937 Marijuana Tax Act. Harry's mindset and perspective at the time can be understood from his article called "Marijuana, Assassin of Youth" about a "marijuana addict" who was hung for a criminal assault of a 10-year-old girl, as Harry explains, "Those who first spread its use were musicians. They brought the habit northward with the surge of "hot" music demanding players of exceptional ability, especially in improvisation. Along the Mexican border and in southern seaport cities it had long been known that the drug has a strangely exhilarating effect upon the musical sensibilities. The musician who uses it finds that the musical beat seemingly comes to him quite slowly, thus allowing him to interpolate improvised notes with comparative ease. He does not realize that he is tapping the keys with a furious speed impossible for one in a normal state" [27].

With this manipulated perspective among the many others, this fear aimed to sway the masses, demonizing the term "marijuana" and anything or anyone that could be associated with cannabis (two prevalent examples would be Mexican workers or jazz musicians of the time like Billie Holiday, which Anslinger personally went after) as a pro-racism (i.e., separation of unity of the people) scare tactic to manipulate the masses for political purposes. Scare tactics such as movies like *Reefer Madness*, countless publications, and government reporters would continue to justify without representation and slander this medication for the next 110 years regardless of Marijuana's appearance in the 1851 US Pharmacopeia [28].

Contradictory to the laws and discrimination explained above, the US government started what was called the Investigational New Drug (IND) program. This program's itinerary seized marijuana all across America via the Drug Enforcement Agency (DEA) and housed marijuana cigarettes and plants at a highly secure facility called the Coy W. Waller Laboratory Complex to have approved researchers of the FDA conduct studies. The IND government-run program also consisted of subsidizing a large marijuana grow called the "Medicinal Plant Garden" located at the University of Mississippi, Oxford, since the late 1970s wherein was responsible for running test on genetics, bioavailability, and THC extraction from the harvested plants. The "Medicinal Plant Garden" in 2007 would produce 880 pounds worth of marijuana for the National Institute on Drug Abuse (NIDA). This facility would also send their research and the facilities grown marijuana to the Research Triangle Institute in North Carolina for the "Compassionate Investigational New Drug Program." A 1976 federal case involving a glaucoma patient by the name of Robert Randall, who was found not guilty on the charge of growing marijuana at home for the treatment of glaucoma. As a result, the federal government cooperatively allowed Mr. Robert Randall marijuana under FDA regulation creating the Compassionate Investigational New Drug Program.

By 1992, the IND program, the 35 patients and all its constituents were shut down due to the high frequency of new applicants and consequently by the W. H. Bush Administration. In 2018, under the Trump administration, attorney General Jeff Sessions issued a memo that effectively overturned the Cole memorandums guidance allowing prosecutors to include the law enforcement propriety set by the attorney general along with other relevant considerations when privatizing federal cannabis law

enforcement. This allows federal law to out rank state policy and US federal government may now prosecute businesses and individuals for legal cannabis State-related activities under federal law at any time. The same Jeff Sessions was quoted in 2016 saying, “Good people don’t smoke marijuana.” Fear, ignorance, and the adolescent state of mind it creates can be guided in any direction and have been demonstrated at numerous points in this subsection to have a negative effect on mental health, society, and individual rights. The American governments’ carelessness with the frailty of life can be referenced back to the CIA’s MK-ULTRA program, which ran from 1953 to 1964 consisting of extremely unethical drug testing and LSD experiments; from mentally impaired boys at a state school, to American soldiers, to “sexual psychopaths” at a state hospital, MK-Ultra’s programs often preyed on the most vulnerable members of society. The CIA considered prisoners especially good subjects, as they were willing to give consent in exchange for extra recreation time or commuted sentences [26].

To conclude this section, in the case of new developing medicines, the FDA should be the main deciding agency and the medicine be researched by all and not regulated by any law enforcement agency. Law enforcement should deal with illegal trafficking, as it does with opioids, methamphetamines, cocaine.

In the end, the study of cannabis and its medicinal use is critical. To limit this apple of Eden or any medicine in this garden is to hinder ones right for healing, knowledge, choice, and the choice of medical care on this “pale blue dot” [29].

4. Studied vertebrate

4.1 Inside the ECS

This section will go over pathologies in the ECS and CNS that cannabis, in study, has been proven to manipulate including the directives of cannabinoids, endogenous cannabinoids, and TRPV channels [1]. The ECS is a far-reaching neuromodulatory system having strong presence and significant roles in the CNS. The ECS consists of cannabinoid receptors, lipid-based retrograde neurotransmitters (endocannabinoids) heavily existing in the CNS including specific enzymes responsible for the synthesis and degradation of endocannabinoids.

4.2 2-AG and anandamide

2-Arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide) are the best-studied endogenous cannabinoids and are synthesized and degraded by distinct pathways. 2-AG is an agonist for either CB1 or CB2 receptors. Interestingly, anandamide is a low-strength agonist at CB1 receptors and very low agonist at CB2 receptors [30–32]. “Implying systems with low receptor expression or when receptors couple weakly to signaling pathways anandamide can antagonize the effects of more efficacious agonists in efforts to maintain a directed homeostasis [33].” CB1 and CB2 receptors are primarily mediated by endocannabinoids, along with Transient Receptor Potential (TRP) channels. Primarily Anandamide degradation in the CNS is by the enzyme fatty acid amino hydrolase (FAAH) [34]. As its name suggests, FAAH degrades multiple fatty acid amides, including palmitoyl and ethanolamide. This has important experimental and therapeutic implications as inhibition of FAAH increases levels of these ethanolamides, which have widespread actions independent of cannabinoid receptors. It is important to note 2-AG and CB1 have interactions with serotonin

via 5HT_{2C} with a crucial participation from neuropeptide Y1 receptor (NPY_{1R}) as explained in the article “Effect of cannabinoid-serotonin interactions in the regulation of neuropeptide Y1 receptors expression in rats: the role of CB₁ and 5-HT_{2C} receptor.” Common precursors to the neurotransmitter serotonin, the hormone melatonin, and vitamin B₃ are TRP channels specifically, TRPV₁, that are activated by anandamide under certain conditions [35]. Anandamide also activates PPAR- α (responsible for cell division, cell growth, and cell death throughout life), a major overseer of lipid metabolism in the liver [32, 33]. PPAR- α goes active under energy deprivation and is necessary for the breakdown of fatty acids, which is a major adaptive response to prolonged fasting [36]. Moreover, increasing anandamide by decreasing its degradation by inhibition of FAAH also increases levels of other N-acylamides, in turn modulating PPAR α [37, 38]. To explain, anandamide has practical roles in modulating and regulating pain, depression, appetite, memory, and fertility.

Importantly 2-AG biology, as an endogenous ligand for cannabinoid receptors like CB₁ and CB₂ in the brain, liver, and lung, and a major source of arachidonic acid, is used for prostaglandin synthesis [39]. Since 2-AG is an intermediate metabolizer in fatty acid synthesis [39], any manipulation of 2-AG production and degradation will undoubtedly have vast reaching effects that can even be independent of the ECS but interestingly avoiding the gut, heart, kidney, and spleen. A sound representative case is that “the measurement of bulk tissue levels of 2-AG is an indirect measure of ‘synaptically-active’ or ‘interstitial’ 2-AG, which is most relevant for cannabinoid receptor signaling and might be more accurately measured by microdialysis [40].”

Furthermore, sourced on knockout mice data, DAGL α , a prime enzyme responsible for 2-AG synthesis in the postsynaptic neuron in response to increased synaptic activity [41–43], appears to be the isoform responsible for most 2-AG production that contributes to synaptic plasticity in the adult CNS [32]. Many studies show 2-AG, Anandamide, CB₁, CB₂, and TRP channels naturally affecting serotonin either directly or indirectly. Whether they have a part in the paradoxical effect has yet to be analyzed.

4.3 CB₁ and CB₂

CB receptors have existed long before cannabis evolved circa 25 million years ago, beginning in organisms such as sea squirts and fugu fish 600 million years ago [44–46], but have evaded non-chordate invertebrates, i.e., insects, hydra, nematodes, fungi, and plants. CB₁ and CB₂ receptors are G-protein-coupled receptors (GPCRs) and their activation obstructs the catalyzing chemical reaction cyclases, voltage-dependent calcium channels, activates several amino acids specific to the amino acids serine and threonine kinases, inwardly rectifying potassium channels, with some variation depending on cell type [45]. Thus, activation of CB₁ or CB₂ receptors exerts diverse consequences on cellular physiology, including synaptic function, gene transcription, cell motility, etc. [41]. CB₁ receptors are exceptionally abundant in the cortex, basal ganglia, hippocampus, and cerebellum [47].

The majority of CB₁ receptors are on nerve fibers, specifically axon terminals and pre-terminal axon segments, while avoiding the operational zones. Cortical and hippocampal CB₁ receptor expression is particularly high on the direct pathway axons as they enter the globus pallidus heading toward the substantia nigra [48]. CB₁ receptors are also expressed in glutamatergic neurons [49].

CB₂ receptors in comparison with CB₁ are expressed at much lower levels in the CNS. The CB₂ receptor is primarily present in active immune defenses and vascular elements [50–52]. Interestingly, CB₂ does appear to be expressed by nerve injury and

has the potential to increase expression 100-fold post tissue injury or during inflammation [53]. It remains to be determined whether CB2 expression is increased in the CNS during brain injury. This is due to increased expression of CB2 on cells intrinsic to the CNS or is a result of the migration (e.g., CB2-expressing monocytes) of peripheral immune cells into the CNS.

Given that the paradoxical effect is found in the human and not the medicine, i.e., cannabis, it is important to shine light on the areas in which the ASR or ATD has functions. There are many studies that display the Endocannabinoid system manipulating serotonin/5HT. As understood in “Modulation of the Serotonin System by Endocannabinoid Signaling,” serotonin can be actuated by the engagement of stress to constrain further activation of the HPA axis. The HPA axis is a group of closely knit influences and feedback interactions consisting of the Hypothalamic (CRH), Anterior Pituitary (ACTH), and Adrenal Cortex (CORT) and controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure. In turn the HPA axis is also under the control of the serotonergic system. Studies have shown that 5-HT through the activation of 5-HT receptors located in the PVN regulates neuroendocrine responses to stress (for review see, [54]). For instance, activation of the 5-HT_{1A} receptors has been shown to reduce the secretion of ACTH (often produced in response to biological stress) and corticosterone (affecting carbohydrate, potassium, and sodium metabolism, i.e., glucocorticoid) induced by an array of stressors. The general consensus is that the serotonergic system contributes in the ECS-induced modulation of the HPA axis and stress responses. Researched receptors of the CNS and ECS that take part in Serotonin Modulation relevant to cannabis psychopharmacological effects are 5-HT_{1A}, reducing stress (passive coping), and 5-HT_{2A}, attuning actively or pro-actively through Default-mode-network/stress (active coping) as illuminated by RL Carhart-Harris & DJ Nutt in “Serotonin and brain function: a tale of two receptors” [14, 17, 55].

5. Finding the paradox

To find, understand, or even combat the paradoxical effect, one must first determine why the incorporated cannabis profile produces the experienced reaction. Whether it is the profile itself or the person who is being treated, acknowledge preexisting psychological and/or physiological aspects systemic or invoked, and then figure out how to counteract the symptoms so the goal for homeostasis works in the way it is intended.

In this section, some of the most common indications that respond to cannabis will be discussed. In addition, the clinical research studies addressing the impact of various cannabinoids on pain have been conducted throughout the world including Bangladesh, Canada, Columbia, Finland, Germany, Italy, North Korea, Poland, Portugal, Spain, Sweden, the United Kingdom, Uruguay, and in much of the United States. The traditional approach to pain management has led to a significant increase in opioid abuse and addiction. More recent studies have focused on the use of marijuana and resulted in decreasing the use of opioids for pain, reducing the withdraw symptoms from opioid use, and increasing the quality of life for patients [56]. Many patient surveys have been conducted in the States that allow marijuana. These surveys clearly indicate that patients reduced their use of opioids; in a New England survey, the respondents reported using less opioids (a 75% reduction) as well as reducing other medications used to treat anxiety, migraines, and sleep disorders after starting medical cannabis [57].

6. Anxiety and post-traumatic stress disorder (PTSD)

Anxiety can be described as an inner emotion that can create a state of unease, usually correlated with future events. Biologically, anxiety is a response to a perceived danger or threat (i.e., hypervigilance) in the future using past key memories as validation (i.e., learned trauma) as opposed to an immediate threat (i.e., fear). Anxiety has many disorders that manifest in different forms such as Generalized Anxiety Disorder, Panic Attack Disorder, COPD, and asthma [58–61].

PTSD can be understood as a form of anxiety but its onset from specific traumatic events, which then the patient eventually experiences the constant state of the same symptoms. Like those mentioned above for anxiety with obvious commonalities such as panic attack and generalized anxiety disorder depending on the nature of the trauma and the psychological makeup of the patient. PTSD patients will display higher affinity of CB1 receptors but lower peripheral concentrations of anandamide or N -arachidonylethanolamine (AEA), the endogenous ligand of CB1 [60–62].

In a study using THC and Cognitive Brain Therapy, it was demonstrated that THC prevented the recovery of learned fear. This was a randomized double-blind placebo-controlled study [63]. With the guidance of a psychiatrist/therapist, tetrahydrocannabinol moreover, cannabis could be used as a viable therapy additive for cognitive brain therapy, PTSD, and other psychological and sociological disadvantages. In an anxiety study using Nabilone, a synthetic THC, patients showed a dramatic improvement when compared with placebo. Side effects reported were dry mouth, dry eyes, and drowsiness. Patients did not report any psychotropic effects of Nabilone since it was synthesized to act like the non-intoxicating cannabinoid of cannabis [64]. Refer to Terpenes and Flavanoids chapter, Pinene section, and Unraveling Cannabis for potential paradox.

7. Multiple sclerosis/Parkinson's disease

MS is a disease where the myelin, a protectant surrounding nerves, is attacked by the immune system. This is a progressive disease and many patients have trouble walking, muscle weakness and spasms, pain, depression, problems focusing or remembering. Parkinson's disease (PD) is a neurodegenerative disease wherein the substantia nigra (i.e., a basal ganglia structure located in the midbrain) begins to deteriorate due to dopamine deficiency. Post synaptic results of this disease involve the extrapyramidal system (i.e., denoting parts of the nervous system dealing with motor function) wherein the central nervous system that mainly affects the motor system begins to cause stiffness, bradykinesia, resting tremor, speech in pediment, and postural instability. Symptoms will not appear until approximately 50% of the nigral dopamine (DA) neurons are lost in the substantia nigra and striatal dopamine deficiency.

Numerous studies have shown that Sativex, an oromucosal spray of cannabis-based medicinal extract (CBME), significantly reduced spasms and pain [65, 66] showing great promise for cannabis as a medication for calming and protecting the auto immune system even in damaged systems.

In a 2016 Survey conducted through the Michael J Fox Foundation and National Multiple Sclerosis Society, both PD and MS volunteers of both cannabis users and non-cannabis users participated. A total 85% reported cannabis effectiveness as moderate or above in relieving their symptoms. In this study MS participants found more relief than PD patients. Additional findings showed that people that suffer from MS reduced the use of prescription medications since beginning cannabis use. Both

MS and PD participants that medicated with cannabis reported lower levels of their disability, mostly in regions of memory, mood, and fatigue [67].

Once again, the paradoxical effect is found in the human and not the medicine, i.e., cannabis, it is important to shine light on the areas in which the ASR or ATD has functions. The disruption from PD (dopamine deficiency) and MS (nerve protectants attacked by the immune system) in the CNS could be considered as focal points to the cascading effects where the paradoxical effect may have a hand in. As to say, it would be a progressive move to avoid extreme dopamine actuation in PD and suppress over responsive immune responses for MS that attack the nervous system through the blood-brain barrier (BBB). Though cannabis shows promising therapeutic responses via CBD < study>, those therapeutic responses depend on resources. This then opens the field to dietary supplementation for the symptom and the medicine. Once again, to shine a light on phytochemical entourage that could lead to a paradoxical effect, which are: Limonene being an antagonist via A2A actuating dopamine via D2 and serotonin agonist via 5HT1A as explained in "The Paradoxical Location." To counter the paradox in a lack thereof, memory mood and fight fatigue, a high tryptophan diet, DOPA-L supplementation, and proper cannabis dosing all play a part in supplementing homeostasis.

Tryptophan and DOPA-L supplementation work in replenishing and regulating serotonin and dopamine as an additive to any ongoing pharmaceutical regiment and both have a higher chance of efficacy with patients prescribed cannabis and in theory could combat the likelihood of a paradoxical effect happening at the Serotonergic/HPA axis level and dopaminergic transmission. As dopamine is produced in the body, Tryptophan is a precursor to the neurotransmitter serotonin, a non-polar aromatic amino acid and is something humans cannot biologically make it and must get the essential tryptophan via diet.

8. Asperger's syndrome

Asperger's syndrome is classified as a subtype of the autism spectrum disorder that encompasses a spectrum of psychological conditions that are characterized by abnormalities in social interaction and communication that provide the individuals functioning and by restricted and repetitive interests and behavior as defined by World Health Organization (WHO). In 2015, an estimated 37.2 million people around the world suffer from this entourage of a disorder [68, 69].

The syndrome is lifelong and usually begins around the second year from birth and the effectiveness of interventions is supported by only limited data. Most treatments are geared toward improving communication skills, unhealthy and life hindering OCD or repetitive routines, and physical coordination. The methods that have proven they are worth include cognitive behavioral therapy (CBT), physical therapy, speech therapy, parental training, and medications for the associated problems, i.e., mood and/or anxiety. Medication for Asperger's includes but is not limited to Catapres, Lamictal, Guanfacine, Oxcarbazepine, Zoloft, Buspar, CeleXA, Prozac, Lexapro, Klonopin, Strattera, Risperdal, Ritalin, Paxil from a 2019 national survey for psychiatric and seizure medications. Most, if not all, of these medications mentioned treat conditions ranging from anti-seizure, SSRI anti-psychotic, anti-seizure, and stimulants and are riddled with common and frequent side effects such as fatigue/drowsiness, depression, aggression, appetite loss, sleep problems, and general worsening [46, 70, 71].

When biochemically and neuropathically compared to cannabis (i.e., a specific cultivar that has been cultivated for specific cannabinoids, terpenoids, and flavonoids in the efforts for a higher chance at treating specific symptoms) for the purpose of alleviating Asperger's syndrome, the low side effects that can be avoided in cannabis and the vast medicinal properties of cannabis are unmatched and should be considered a dietary additive in some medical regimens. Since cannabis has infinite possible genetic outcomes, cloning and hybridizing and marijuana extraction methods would be the best means to find and maintain a specific cultivar/chemovar for any one person and their symptoms on the spectrum per harvest [70].

9. The entourage effect

The Entourage effect can be explained as a specific group of cannabinoids, terpenes, and flavonoids that have the ability to synergistically create specific effects on the endocannabinoid system. Some of these effects can magnify/desensitize the nervous system, force more CB1 and CB2 receptors on and/or off, reduce unwanted effects while amplifying wanted effects/vice versa. Through reviewing numerous studies, I have come to find that in every sub-specie of cannabis lies a unique terpene bouquet and a general entourage of cannabinoids specific to the cultivar and genetics).

Terpenoids and cannabinoids are present throughout the plant's flowering stage. Terpenes can also have the potential to determine what the most likely outcome of the plant's impact on the ECS and CNS will be. Another way to describe it is a gestalt, the whole plant being larger than the sum of its parts.

Not all terpenes contribute to the entourage affect [72]. As for as the ones that do, and that will be gone over, they do exist in cannabis. Phytocannabinoid-terpenoid synergy, if proven, increases the likelihood that an extensive pipeline of new therapeutic products is possible from this venerable plant [73]. In a more recent study, "Terpenoids From Cannabis Do Not Mediate an Entourage Effect by Acting at Cannabinoid Receptors," it is thoroughly explained that terpenes have modes of operation elsewhere outside of CB one and CB two signaling via 5HTs, A2A, TRP GPR, and many more [74].

The inter-entourage effect suggests that enhanced biological activity may be attributed to secondary metabolites—mainly terpenes—produced by cannabis strains. Terpenes are known for their medicinal properties including anti-inflammatory and anticancer activities [75–77], but here, in the general gist of the inter-entourage effect, they are considered as promoters and instigators of therapeutic phytocannabinoid activity.

Moreover, mixing co-related terpenes and phytocannabinoids (i.e., THCA. related terpenes with THC or CBDA related terpenes with CBD) at ratios close to the natural plants showed the strongest effect. This could then encourage research studies to look into multiple cultivars for treatment of an indicator.

10. The paradox

Once again to understand the paradoxical effect whether it is the cannabis itself or the person who is being treated, a closer look to what makes marijuana's entourage will display pathology and functionality in the ECS and CNS in the efforts of reaching homeostasis.

10.1 Unraveling cannabis (cannabinoids sub)

This section will educate the reader on the various bioavailable cannabinoids that reside in the five sub-species of cannabis, excluding Hemp/Sativa/NLH, i.e., industrial hemp. There are over 150 identified cannabinoids in in legal Medical Cannabis from past to recent study.

CBD, CBC, CBG, CBDA, CBD-V, CBN, THC-V, THC-A, THC, CBL, which are the most bioavailable cannabinoids that have beneficial health impacts ranging from anti-inflammatory, pain relief, anti-anxiety, neuroprotectant, anti-spasmodic, anti-cancer/tumor, analgesic that all have a place in the mammalian ECS. Henceforth each cannabinoid will be evaluated for its affinity to a possible biphasic ASR/ATD.

10.2 Cannabidiol

10.2.1 (CBD)N-PA

CBD, being one of the main cannabinoids in cannabis, possesses no intoxicating effects and works frequently with the CB-2 receptor, which interacts directly with the immune system via 5-HTA1 and combats inflammatory diseases [65, 73]. Other areas affected are not limited to Gastrointestinal via transient receptor potential (TRP) channels, specifically the TRP cation channel, subfamily V, member (TRPV3) treating IG inflammation. CBD can also act like an antagonist, blocking THC from binding to the CB2 receptor. This affect has the tendency to also reduce the anxiety associated with THC [45, 78]. This binding shows promise by lowering the rate of psychotic episodes of those individuals by using cannabis with higher levels of CBD [79]. A 1:1 ratio of CBD to THC and their respective constituents would suffice depending on the metabolism of a patient.

Does CBD contribute to the paradoxical effect? Yes and no.

No. It helps alleviate side effects of the indication, therefore canceling out a possible ASR/ATD.

Yes. If serotonin levels are below a healthy level, it would be fair to assume nothing will most likely be felt since CBD is 5HTp-dependent.

Moreover, if THC is more abundant causing more serotonin depletion while tryptophan is already low in the body or below a healthy level, the use of CBD may be futile in the efforts of analgesia but may only have the ability in this state to counteract side effects of THC via CB1 and CB2 binding unless receptors have been exhausted.

Conclusion: More study must be done to understand tryptophan depletion in the body, metabolism of cannabinoids, and the medication needed to help it.

10.3 Cannabichromene

10.3.1 (CBC)N-PA

CBC is an abundant non-intoxicating cannabinoid due to a recessive gene [80] that modulates the vanilloid type-1 (TRPV1) and ankyrin type-1 (TRPA1) receptors and TRPV2,3,4 [45, 81]. Briefly, TRP channels and the ECS are involved in inflammation and have a role in pain [81, 82]. Modulation of these receptors can cause elevated endocannabinoid levels, thereby amplifying total cannabinoid availability via turning on more docile CB1 and CB2 receptors with more respectable affinity to the CB2 receptor. Health benefits range from anti-inflammatory and pharmacokinetics of

other available cannabinoids [83]. CBC also has the ability to potentiate the analgesic effects of THC [45, 84, 85]. In one study CBC shows promise in positively affecting the viability of mammalian adult neural stem cell progenitor cells, i.e., an essential component of brain function in health and disease [82]. This particular cannabinoid could then be what allows a patient's "high" to then proverbially stack or amplify if given more of the same medication. This then opens the door for a possible addition to the paradox in question being an "agonist" via TRPV1 and possibly, marginally mediating CB1, thus amplifying GABA sensory inhibiting or prohibiting 5-HT.

One study indirectly shows CBCs' synergistic affinity with limonene [86], this could then mean if both are present in the ECS; limonene has a valid chance at having a synergistic paradoxical effect via "CBC modulating TRPV1" [81, 87, 88]. In another synergy with TRPV1, the synergistic manner of (the known receptor affinity to the monoterpene Limonene) adenosine A2A receptor modulating TRPV1 as documented by [89] raises a curiosity to the possible multitude of concurrently dependent inception of synergies and the affiliated synergies in between. Henceforth, these two synergies between CBC and TRPV1, and A2A and TRPV1 should definitely be researched to further understand the cannabis entourage and its effects in the human body.

Does CBC contribute to the paradoxical effect? May have amplifying properties when combined with THC and limonene and/or linalool.

10.4 Cannabidiolic acid

10.4.1 (CBDA)N-PA

CBDA (Cannabidiolic Acid) transforms into CBD through a process called decarboxylation. Baking, lighting, or heating cannabis removes the acid group from CBDA and transforms it into CBD [90]. Prolonged oxidation via sunlight (infrared/ultraviolet light) can also slowly change CBDA to CBD. The majority of cannabis research has focused on THC or CBD, not CBDA. Though one study shows that CBDA is a Cox-1 and Cox-2 inhibitor; an anti-inflammatory and analgesic, similar to ibuprofen [91]. The study shows CBD and its constituents to be a more effective analgesic than Ibuprofen with nonexistent to minimal side effects. CBDA, in a toxicology study, showed strong dependence on particular sesquiterpenoids, namely guaiaolstol, γ -eudesmolstol, trans- α -bergamotenest, γ -elemenest, α -bisabololstol, and α -farnesenest.

Does CBDA contribute to the paradoxical effect? No, unlikely based on the current research, however, nothing is definitive at this time since minimal research is done.

10.5 Cannabinol (CBN)

CBN can be considered a time stamp and uses the same logic as carbon dating. This process is due to a degradation byproduct of various cannabinoids via oxidation. CBN can also cause drowsy-like effects like an analgesic, but at high doses [90], CBN is the cannabinoid that has been used to treat glaucoma; its anti-inflammatory properties reduce intraocular eye pressure (IOP). A reduction of 16–45% of IOP was initially documented in a 1971 study [92]. CBN is considered the natural decomposition byproduct of the three main phytocannabinoids (i.e., CBDA, THCA, and CBCA), the strongest correlation between two phytocannabinoids is between THC and CBN [53].

Does CBN contribute to the paradoxical effect? No evidence so far for ASR or ATD pathological indicator.

10.6 Tetrahydrocannabinol (Δ^9 -THC)PA

THC is a Phytocannabinoid chiefly from the *Cannabis Indica* ssp. cultivar that actuates endogenous signaling in the ECS and CNS, predominantly known for its psychotomimetic effects. Receptors affected in the ECS and CNS are the CB1, CB2, GPR55, GPR18 receptors. From these cannabinoid receptors, extracellular signals trigger intracellular cascades. These cascades can represent behavior from cannabis with therapeutic effects. THC is an agonist of the CB1 receptors (Psychotomimetic effect) and CB2 receptors (Possible immunologic, anti-inflammatory effects) [93]. Numerous studies and current education show THC is also an agonist at GPR18 (most efficacious at), GPR55, and TRP ligands TRPA1, TRPV2, TRPV4 and TRPV3 while being an antagonist at TRPM8 and 5HT-3A known for treating long-term depression (LTD). The agonistic effects range from: GPR55 responsible for neuroimmunological regulation; GPR18 has been associated with numerous physiopathological processes, such as cellular migration, immunomodulation, sperm physiology, cardiac physiology, obesity, intraocular pressure, pain, and cancer, among others.

Does THC contribute to the paradoxical effect?

Yes, only via CB1 Signaling, especially when CBD is absent.

No, when a balanced amount/or more of CBD is present, but is a terpene carrier of limonene through the BBB when vaporized, smoked, taken as a tincture or orally ingested.

No. If THC is lower than CBD allowing the agonist ability of CBD to calm the usage with serotonin i.e., 5-HT, while only needing little for itself (CBD) to operate, then THC will most likely operate within a healthy ratio, aside from the metabolic breakdown within the endocannabinoid system. Also if limonene is not present.

10.7 Tetrahydrocannabivarin (THC-V)PA

THC-V Is an intoxicating cannabinoid mostly found in NLM (narrow leaf marijuana) (stimulating); small traces have been found in BLMD (sedating) strains as well. In a 2013 mouse pilot study, the purpose was to investigate the clinical effect and tolerability of THCV and CBD alone and in combination with patients with Type 2 diabetes [94]. THCV decreased plasma glucose and increased B-cell function (B-cells identify pathogens and produce antibodies). In the conclusion section of the study, it states “based on these data, it can be suggested that THCV may be useful for the treatment of the metabolic syndrome and/or type 2 diabetes, either alone or in combination with existing treatments. Given the reported benefits of another non-THC cannabinoid, CBD in type 1 diabetes, a CBD/THCV combination may be beneficial for different types of diabetes.” Later in 2016, a human study was conducted, the same results were reported “compared with placebo, THCV significantly decreased fasting plasma glucose.” The study concluded that THCV could be a new therapy for patients with type 2 diabetes [95, 96].

Does THC-V contribute to the paradoxical effect? Yes.

Conclusion: Plausible, if in combination with certain cannabinoids terpenes and depending on the indicator to the ECS.

10.8 Tetrahydrocannabinolic acid (THCA)N-PA

THC-A is a highly plentiful non-intoxicating cannabinoid lacking affinity to the CB1 receptor. Lacking affinity to the CB1receptor could imply that vaporization

(heating and/or any processes of combustion) would be a non-effective delivery method for THC-A [44, 45]. Like CBD, THC-A can relieve inflammation being a viable neuroprotectant, therefore providing treatment for various neurological diseases such as MS, ALZ, Parkinson's, and has even shown to slow the expansion/multiplication/proliferation of cancer cells [87]. Given the cannabinoid life cycle, developing a stable version may be difficult because by its very nature THCA converts to THC easily. "Studies suggest that THCA may be more stable in herbal cannabis, where it is 'hermetically sealed' within glandular trichomes, along with terpenoids which serve as protective antioxidants. The same studies showed that THCA decarboxylated within minutes at temperatures above 80°C. At room temperature in glass bottles with limited exposure to light, THCA dropped to 80% of initial levels after 25 months. At refrigeration (4°C) temperatures, 94.7% of THCA was still present" [44].

The correlation plot in the study shows that while nerolidol has relative affinity to THCA, the other terpenoids described in their paper range from having no affinity to THCA to having minor affinity to CBDA, see also [7, 97]. This may explain the lack of activity observed when those specific terpenoids were added to THC. According to results, THC activity is enhanced only by its co-related terpenoids, while other terpenoids inhibit its biological activity [44, 45, 53].

Does THCA contribute to the paradoxical effect? No.

Conclusion: non-intoxicating and no synergistic entourage to Paradox.

10.9 Cannabivarin

10.10 (CBD-V)N-PA

CBDV has the affinity to inhibit the biosynthesis of the endocannabinoid 2-arachidonoylglycerol (diacylglycerol lipase/DAGL) [50% inhibitory concentration (IC₅₀) 16.6 µM] and may decrease activity of its product, the endocannabinoid, 2-AG [81, 98]. An experiment on GABA receptors in the production of use-dependent GABA, a current after prolonged exposure to CBDV has shown great efficacy in the efforts as an anticonvulsant, especially for epilepsy, via GABAergic action. Therefore, a solid DAGL regulator to the endo cannabinoid system [99].

Does CBDV contribute to the paradoxical effect? No.

Conclusion: may show great promise to alleviate ATD.

10.10.1 Cannabicyclol (CBL)N-PA

Most cannabinoids are the chemical breakdown of CBG, whereas CBL starts its oxidizing life cycle from CBC. As observed by Shoyama, much larger amounts of CBLA can be harvested early in the vegetative phase and stored as opposed to harvesting in the reproductive phase. This prompted a quick conclusion that CBLA is a natural breakdown via ultraviolet light of CBCA [100–102]. Clearly more study must be done on this world-renowned medicinal herb to understand its true potential.

10.11 Cannabigerol (CBG) cannabigerolic acid (CBGA) N-PA

10.11.1 The mother cannabinoid

CBGA is of the first cannabinoids produced for the cannabis plant and births once geranyl pyrophosphate biosynthesizes with olivetolic acid through a prenyltransferase

catalyst conversion, thus creating CBGA. From this momentary precursor begins several different syntheses, i.e., CBG, THC, CBD, and CBC wherein the number of biosynthesized and oxidized (aged) cannabinoids reaches the hundreds and from these will eventually create the cannabinoid side of the entourage effect [103].

Not much study has gone into CBGA but in numerous studies it has been noted as an analgesic and anti-inflammatory. Once CBGA loses its acid group via heat or oxidation, Cannabigerolic acid becomes Cannabigerolic (CBG).

CBG affects cannabinoid, serotonergic, peroxisome proliferator-activated receptors ((PPARs), i.e., nuclear receptor proteins that act as a transcription factor of the expression of genes regulating cellular differentiation, development, and metabolism, and tumorigenesis; α 2-adrenoceptors (norepinephrine (noradrenaline) and epinephrine (adrenaline) signaling); TRP, vanilloid, melastatin, and ankyrin channels. CBG inhibits dopamine norepinephrine, GABA, and serotonin reuptake [103]. Thus, utilizing 5HT as an anti-depressant [104]. So to say, CBG does take part in serotonin release and reuptake especially alongside THC more so in the instance where THC is higher creating a synergistic 5-hydroxytryptamine release/uptake/reuptake. For CBG, potential medicinal uses can range from analgesia/inflammation, feeding disorders, cancer, glaucoma, inflammatory bowel disease (IBD), psoriasis, Neuroinflammation (MS), bone healing, antibacterial; helping with testosterone balance and mood disorders [103]. In the case of mood disorders and the bidirectional influence at CB1, and an anxiogenic at TRPV1, other synergies along this pathology should be acknowledged.

In light of synergies, specifically terpenoid synergies, “CBGA was related to δ -selenenest, cis- α - bisabolenest, and α -famesenest, moreover, mixing co-related terpenoids and phytocannabinoids (i.e., THCA-related terpenoids with THC or CBDA-related terpenoids with CBD) at ratios close to the natural plants showed the strongest effect. This increased activity may be the result of some preferential pathway in which the given terpenoids enhance the absorbance or activity of phytocannabinoids in the cells” [53]. This proves that specific synergies from/between cannabinoids and terpenes can take place at different stages of biosynthesis and/or oxidation either via UV, heat, human influence, or natural degradation but still hold relative synergistic terpene relation. To further understand decarboxylation synergies, Cannabigerolic acid (CBGA) was related to δ -selenenest, cis- α - bisabolenest, and α -famesenest (subscript abbreviations: mt—monoterpene; st—sesquiterpenes; stol—sesquiterpenes; dt—diterpene), Ergo, guaicol and eudesmol derivatives showed strong positive correlation with CBD [53].

Though dependence on different terpenes and cannabinoids may vary from cultivar, it is only due to the bioavailability and genotype. Thus, more study must be done to fully understand synergistic properties between cannabinoids and terpenes at the various growth stages in cannabis.

In medicating with medical cannabis, specifically MLM sub-species, if multiple cannabinoid synergies are co-related with one terpene, i.e., B- Myrcene, a hypothesis could then be made; if multiple synergies to one terpene might cause a faster metabolism depleting that specific synergy resource for synthesis and if paired with D-Limonene, a known A2A antagonist, would then be the remainder, possibly giving a delayed agitation wherein the goal of this type of homeostasis (MLM) (a 1:1 of stimulating and sedating terpenes) balance/homeostasis would be lost toward the middle or end of the bell curve depending on the metabolism mediation of any one patient. So as to understand, CBG has a synergy with limonene, it is fair to assume between the oxidative life cycle and biosynthesis of CBG that its later counterparts may have synergies much like the

one between CBG and limonene and that more study should go into this volatile mono terpenoid and its many possible synergistic effects throughout the human body.

Does CBG contribute to the paradoxical effect? Isolated, No.

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