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Theoretical frameworks toward a nutraceutical approach to treating PTSD

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Abstract

This literature review examines theoretical frameworks related to applying the principles of biomolecular psychology and psychoneuroimmunology to devise a nutraceutical protocol utilizing phytochemicals for the treatment of posttraumatic stress disorder with a particular focus on modulating the endocannabinoid system through the utilization of molecules inherent in chemovars of *Cannabis sativa.* It provides a psychosocial overview of posttraumatic stress disorder and the historically controversial and noncontroversial nature of the biologically derived molecules that have demonstrated efficacy in addressing the effects major stressors have on the biomolecular mechanisms that cause mood disorders that manifest themselves as symptoms of PTSD.

Keywords: Psychoneuroimmunology; Biomolecular Psychology; PTSD; Cannabinoids; Nutraceuticals

1. Introduction

The following disquisition investigates interpretations, insights, and inconsistencies causing conflicts, controversies, and consternation within the segment of the scientific community that studies the viability of treating physiological and psychological conditions through the administration of botanic cannabinoids and terpenes. The intrinsic constructs and theories involved in this aspect of scientific inquiry are complex and convoluted, with deep-rooted biases dependent on the paradigm to which the researcher subscribes. This paper aims to examine constructs of controversy, each related to competing paradigms inherent within the study of biomolecular psychology.

The ultimate objective of this literature review is to examine theoretical frameworks related to phytochemicals and their potential usefulness in the treatment of posttraumatic stress disorder with a particular focus on molecules inherent in chemovars of *Cannabis sativa.* It consists of two parts. Part 1 presents a psychosocial overview of posttraumatic stress disorder and the historically controversial and noncontroversial nature of the biologically derived molecules that have demonstrated efficacy in treating the disorder's symptoms. Part 2 details theoretical frameworks based on clinical observations deemed useful for devising a nutraceutical protocol expected to match or surpass pharmaceutical interventions in treating PTSD in efficacy and mitigation of overall symptomology.

1.1. Statement of the Problem

PTSD, or posttraumatic stress disorder, is an incapacitating and life-changing condition characterized by a persistent maladaptive reaction after exposure to severe psychological stressors. "Experiencing traumatic events, such as violent personal assaults, natural or human-made disasters, serious traffic collisions, or military combat, can lead to the development of PTSD." [1] Individuals who suffer from the condition often re-experience their ordeal through nightmares, flashbacks, panic attacks, anxiety, overwhelming emotions, hypervigilance, detachment from loved ones, and sometimes even suicidal behavior. [2] PTSD has proven to be a complex condition to treat with synthetic medicines. No pharmaceutical treatment has been developed that successfully treats PTSD, and there is consensus among clinicians that current pharmaceutical medicines do not work. [3,4,5]

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Not all cases of post-traumatic stress disorder share similar underlying mechanisms, and the biomolecular and behavioral mechanisms are poorly understood. [1,6] The disparate mechanisms make the single-molecule approach favored by the pharmaceutical industry unlikely to achieve symptom mitigation in most cases. [7] Compounding this, psychotherapy approaches, such as cognitive processing therapy (CPT) and prolonged exposure therapy (PE), the front-line treatments for military-related PTSD by the Departments of Veterans Affairs and Defense, do not work for up to 66% of patients. Although trauma-focused and non-trauma-focused interventions may improve symptoms, the ignorance or disregard of the psychophysiological mechanisms causing symptom improvement results in a significant percentage of patients continuing to meet the criteria for PTSD after treatment. [8]

1.2. Part 1

Posttraumatic Stress Disorder is a disabling psychological condition among military personnel, veterans, and a significant segment of the civilian population. Lifetime prevalence rates of PTSD are estimated to be between 1.9% and 8.8%, with up to 3% of adults having PTSD at a given time. [9] Ty Smith, a retired Navy Seal and Founder and CEO of Vigilance Risk Solutions, proffered the notion "that every human being is going to come out of this pandemic with some sort of posttraumatic stress disorder." [10] This would indicate a critical need for innovative treatment strategies for PTSD, as pharmacological and trauma-focused or non-trauma-focused psychotherapy approaches have been demonstrated to be largely ineffective. [3,4,5,7,8]

It could reasonably be argued that the most significant problem of the psychotherapeutic and pharmacological protocols is that neither adequately address the effects major stressors have on the biomolecular mechanisms that cause mood disorders that manifest themselves as symptoms of PTSD. This missing knowledge or disinterest in the systemic mechanistic biopsychological changes that occur due to significant stressors contributes to the persistence of the problem. The Veterans Affairs Department reports that the military loses more soldiers to suicide than to combat, indicating that alternative treatment options need to be explored. [11]

Since the ratification of the Farm Act in 2018, there has been a growing interest in the therapeutic potential of nutraceutical medications that target the immune and endocannabinoid systems to alleviate the symptoms of PTSD. The behavioral effects of endocannabinoid system medications and their ability to modulate neuroinflammation and oxidative stress make targeting the nervous, immune, and endocannabinoid systems potentially relevant. Multiple research studies demonstrate that people with PTSD who use phytochemicals experience more relief from their symptoms than antidepressants such as fluoxetine, paroxetine, sertraline, venlafaxine, and other psychiatric medications. [12] Data from a 2019 study of veterans with PTSD (Figure 1) indicates that medicinal cannabis provides better life quality, fewer psychological symptoms, and reduced use of opiates, alcohol, tobacco, and pharmaceutical medicines. [13] Still, these studies often fail to address the biomolecular mechanisms that cause these results. This disquisition theorizes that two mechanisms work concomitantly to produce these outcomes. The phytochemicals within cannabis chemovars may be used to modulate critical systems within the body that regulate neurotransmitters in the nervous system resulting in an efficacious approach to treating the symptoms of PTSD.

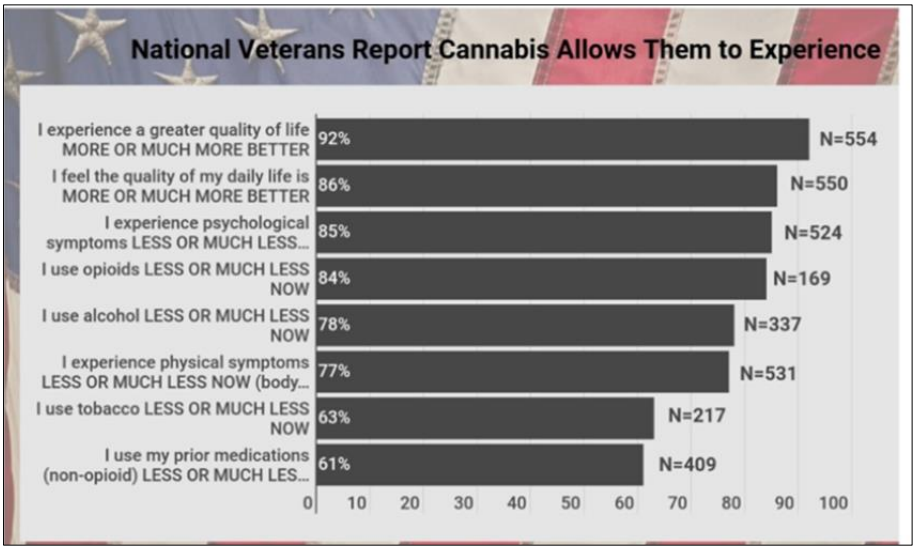

Figure 1 Data from the 2019 Veterans Health and Medical Cannabis study conducted by Dr. Marion McNabb

2. The Controversy of Cannabis Chemovars

Whether the topic is botanical taxonomy, pharmacology, applied therapeutics, or politics, cannabinoid science has a history of creating controversy in every area it influences. [14] Due to difficulties in distinguishing one cannabis cultivar from another based-on factors such as plant height and leaflet width and the fact that all cannabis types are eminently capable of crossbreeding to produce fertile progeny, the only reasonable solution is to classify them by their biochemical/pharmacological characteristics and refer to forms of cannabis as "chemovars" or chemical varieties. These chemovars are analogous to phytochemical factories producing terpenes and cannabinoids, many with well-documented medicinal properties. [15]

This literature review begins by examining the literature, providing a psychosocial overview of posttraumatic stress disorder and the historically controversial and noncontroversial nature of the biologically derived molecules that have demonstrated efficacy in treating PTSD symptoms. Electronic databases of pharmacology and psychology and library journals, including Medline and other EBSCOhost Databases, were searched to examine theoretical frameworks related to phytochemicals and their potential usefulness in treating posttraumatic stress disorder, focusing on molecules inherent in chemovars of *Cannabis sativa.* The keywords used to search for articles included PTSD symptoms, biopsychosocial model, cannabinoids, terpenes, Farm Act, pharmaceuticals, nutraceuticals, endocannabinoids, phytocannabinoids, cannabis, psychoneuroimmunology, and inflammation. The search was limited to producing articles printed within the last five years, but contributions of seminal researchers are included. The psychosocial overview catalyzed an investigation into clinical observations deemed useful for devising a nutraceutical protocol expected to match or surpass pharmaceutical interventions in treating PTSD in terms of efficacy and mitigation of overall symptomology. The psychosocial aspects of controversial and noncontroversial molecules naturally flow into a comparison of the effectiveness of nutraceutical and pharmaceutical approaches to treat the symptoms of PTSD.

2.1. Part 2

Theoretical frameworks summarizing theories based on clinical observations and evidence provide guidance in describing the biopsychological mechanisms that cause the nutraceutical approach to surpass pharmaceutical interventions in treating PTSD in terms of efficacy and mitigation of overall symptomology. The pathophysiological foundations of PTSD are complex, and not all cases of the disorder share similar underlying mechanisms. [16] The disparate mechanisms make the single-molecule approach favored by the pharmaceutical industry unlikely to achieve symptom mitigation, and in most cases, nutraceutical medicines more effectively treat the symptoms of PTSD sans the side effects ubiquitous through the ingestion of pharmaceuticals. [17,18] Still, studies that demonstrate the nutraceutical approach is more efficacious than the pharmacologic typically fail to identify the biopsychological mechanisms that result in these differences. Psychosocial overviews catalyzed investigations into clinical observations deemed useful for identifying this mechanism and devising a nutraceutical protocol expected to match or surpass pharmaceutical interventions in treating PTSD in terms of efficacy and mitigation of overall symptomology.

3. A Psychosocial and Historical Analysis of the Cannabinoid Sciences

The history of science is remarkably convoluted, especially with regard to the biological molecules produced by the *Cannabis sativa* plant, called phytocannabinoids. On June 18, 1971, President Richard M. Nixon declared war on drugs, explicitly targeting the biological molecules the cannabis plant produces. In 1973 he established the Drug Enforcement Administration (DEA), a paramilitary division of law enforcement tasked with ensuring that no research of biologic cannabinoid molecules occurred within the confines of the United States of America. [19] In the late 1980s and 1990s, because the research of these controversial molecules was prohibited in America, the National Institute of Health provided funding to a trio of researchers at Hebrew University in Jerusalem. They utilized newly designed technology to discover the endocannabinoid system. They described this biological system as comprised of endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors and cannabinoid receptor proteins expressed throughout the vertebrate central and peripheral nervous systems. [20] This group identified the first endogenous cannabinoid neurotransmitter molecule and gave it the name anandamide. In 1993, they discovered a second endocannabinoid molecule, 2-Arachidonoylglycerol (2AG). [21]

On August 11, 2016, Chuck Rosenberg, the acting head of the U.S. Drug Enforcement Administration (DEA), announced it would not change the phytocannabinoids' federal legal status. These controversial molecules would continue to be classified as Schedule I drugs under the Controlled Substances Act, meaning that their potential medical properties could not be studied by scientists residing in the United States. He resigned as head of the DEA in September 2017 after opining that President Donald Trump had little respect for the law. [22]

The prohibition on the research of cannabinoid molecules lasted 47 years and ended on December 21, 2018, when Donald Trump ratified the Farm Bill. This bill legally reclassified phytocannabinoids extracted from *Cannabis sativa* composed of less than 0.3% THC (hemp) as an agricultural product rather than a controlled substance, thereby legally (not scientifically) differentiating them from the molecules produced by cannabis varieties with higher THC content. [23] When Donald Trump signed this bill into law, interstate transportation of the 149 known phytocannabinoid molecules became permitted, provided they originated from *Cannabis sativa* classified as hemp. This concession by the U.S. opened the door to the research of biologic cannabinoids, which scientists in the United States had been prohibited from investigating for nearly half a century.

4. Effects of Prohibiting Scientific Inquiry

While the prohibition of research on noncontroversial phytocannabinoids has been rescinded, the paradigm to which cannabinoid scientists have been mandated to adhere remains.[24] The paradigm was established 52 years ago and is currently in what Thomas Kuhn would have referred to as a state of "crisis" with respect to the potential therapeutic properties of phytocannabinoids. [25] The dominant paradigm requires accepting the proposition that synthetic cannabinoids possess medicinal properties and botanic cannabinoids are dangerous, with none. [26] To ensure their freedom and economic security, physicians, clinicians, and cannabinoid scientists capitulated, and promoted this view for almost half a century.

Until the passage of the Farm Act, studies that might challenge this paradigm were deemed illegal. This five-decade period defined the science of cannabinoids and dictated the methods of solving puzzles that arose. Ironically, this period was a phase Thomas Kuhn would have referred to as "normal" science. The established paradigm dictated how observational data was perceived, experiments were designed, and the results interpreted. With the methods in place and the assumptions defined, this paradigm flourished. [17]

An accumulation of anomalies, such as deaths and other adverse events resulting from synthetic cannabinoids, has resulted in challenges to the dominant paradigm [17] Kuhn proffered the idea that the scientist's role is to design studies with the potential to produce results that challenge the dominant paradigm and coined the word "revolution" to describe dramatic changes in scientific worldviews. Revolutionary science is torturous and painful because it shakes all confidence that science has in its present theories and underlying assumptions. [25] Paradigm shifts occur gradually during a stage when the dominant paradigm is termed to be in "crisis." A new paradigm is now emerging, which professes that phytocannabinoids have medicinal properties without the adverse effects so prevalent through the ingestion of synthetic medicines. With State regulation changes and the Farm Act's implementation, exploring the limitations of the dominant paradigm is now possible. This is the nature of science. When excessive anomalies appear that current theories cannot explain, a period of "crisis" results, and political and economic events fuel the search for new understandings. [24] This is the stage we are in concerning phytocannabinoid-based medicines.

The recent COVID pandemic has reinforced the precedent established by Harry Anslinger that in the United States, politicians are elected to make medical decisions for the citizens they govern. [27] Richard Nixon established the precedent that politicians dictate which aspects of truth scientists are permitted to pursue, and scientists have been historically willing to conform and rarely challenge the will of politicians. The five-decade complicity of physicians and clinicians in avoiding searching for knowledge pertaining to the medicinal properties of botanic cannabinoids has resulted in a limited understanding of the effects of intromitting phytocannabinoids on the endocannabinoid system and a lack of human data about the effects of phytocannabinoids on the reparation of traumatic experiences. [28] Research on the endocannabinoid system is in its infancy, and there is currently no agreed-upon way by which the endocannabinoid system should be targeted in humans. [29] Only now are studies beginning to be proposed that might produce results that challenge the accepted assumptions. History has demonstrated that "whether the opposition to attaining and disseminating scientific knowledge is politically or religiously motivated, humanity has the potential to ensure this knowledge is eventually acquired." [24]

The historical analysis described above illustrates the convoluted nature of the construct of controversial molecules and the political, cultural, psychosocial, and bureaucratic influencers that bring about this convolution. The Byzantine nature of first declaring war on biologic cannabinoid molecules continued with phytocannabinoids' classification as Schedule I drugs in the Controlled Substances Act. The United States Drug Enforcement Administration (DEA) classifies chemicals, drugs, and certain substances used to make drugs into five categories or schedules depending upon the abuse or dependency potential and acceptability as medicine. The potential for abuse is the determining factor in the scheduling of a drug. Schedule I drugs are purported to have a high potential for abuse and create severe psychological and physical dependence. The lower the substance appears on the Schedule, the less potential the drug has to be abused.

Legal drugs like alcohol and tobacco do not appear on the Schedule, meaning the DEA considers them outside their purview as the paramilitary division tasked with adjusting the Schedule and enforcing it upon the citizenry. [19]

The half-century prohibition of research in the United States on the medicinal properties of biologic cannabinoids has forced American cannabinoid scientists to analyze and develop theories based on studies conducted in other countries, yet ironically funded by the National Institutes of Health. The National Institute of Health is a part of the U.S. Department of Health and Human Services and is considered America's medical research agency and is credited with "making important discoveries that improve health and save lives" [30]

Theories are inseparable from clinical observations, and the inability to conduct practical research in their country of origin has resulted in American cannabinoid scientists producing tens of thousands of review articles espousing theoretical explanations for the results of clinical trials funded by the United States but in which they were not involved.

The University of California, Berkley, defines theories as broad, concise, coherent, predictive, broadly applicable natural explanations for an extensive range of phenomena, often integrating and generalizing many hypotheses. [31] This thesis examines theories related to devising nutraceutical approaches for treating symptoms associated with post-traumatic stress disorder and a host of other physiological and psychological ailments. The theories interrelate and are based on scientific explanations and interpretations of facts. Furthermore, they are based on clinical observations, have observable consequences, and lead to testable predictions related to biomolecular psychology.

5. The Construct of Psychoactivity and its Relationship to Controversial Molecules

It appears evident that the DEA cannot cite studies demonstrating any potential harm of intromitting biological cannabinoids that justifies them retaining their Schedule I drug classification. Justification for them remaining Schedule I has become based on claims that a particular phytocannabinoid is psychoactive, and therefore pleasure-inducing. A compound's psychoactive nature is considered indicative of its potential for abuse. When research universities were mandated to forbid biologic cannabinoid study for fear that conducting such research could jeopardize their federal funding, the only known biologic cannabinoids were phytocannabinoids, the cannabinoids derived from the *Cannabis sativa* plant. These biologic molecules were classified as Schedule I drugs, the category reserved for the most dangerous substances humans can ingest. [26] This classification for the biologic cannabinoids worked well for the next two decades because it fit perfectly into the moral model of addiction, which fueled the drug war. [32] The DEA flourished during this time through asset forfeitures and massive budgeting allocations provided to ensure the Judicial System punished Americans for possessing cannabinoids produced through biologic synthetization.

Things became even more convoluted in 1992 when the United States funded the trio of researchers at Hebrew University in Jerusalem. This group identified the first endogenous biologic cannabinoid (endocannabinoid) and named it anandamide. [20] Shortly thereafter, the National Institute of Drug Abuse declared anandamide and Trans-Δ^9-tetrahydrocannabinol (THC) to be the same molecule and justified this position with the image provided in Figure 2. Suddenly, it could reasonably be argued that every American possessed an illicit substance merely by being alive. [33]

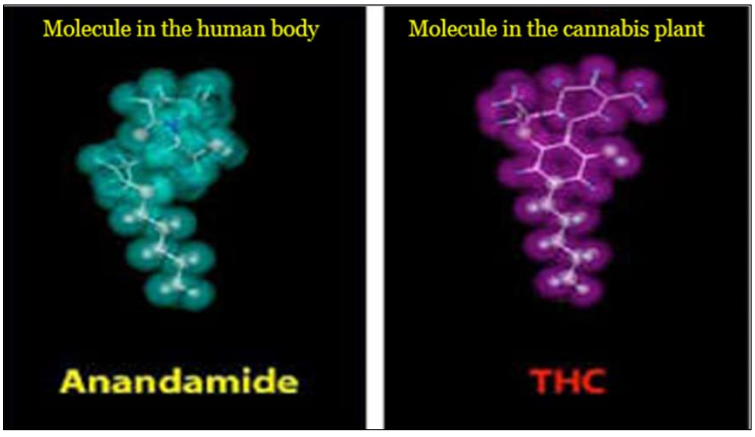

Figure 2 The cannabinoid THC, found in the cannabis plant, is structurally similar to the brain cannabinoid called anandamide. The similarity in structure allows the plant cannabinoid to supplement an anandamide deficiency, thereby altering brain chemistry and treating PTSD Courtesy of NIDA

Still, the DEA refused to deschedule the biological cannabinoids and categorize them as no-risk drugs like alcohol and tobacco. Instead, politicians admitted the war against the 149 known phytocannabinoids was lost, but hostilities against THC continued, and they misappropriated the term psychoactive. THC would remain the biologic cannabinoid with the most destructive potential due to its purported psychoactive nature. This psychoactive property comes from its ability to release dopamine by activating the CB1 receptor in the same way anandamide does, thereby providing a sense of pleasure abhorrent to the moral model of addiction. Cannabidiol was claimed to be nonpsychoactive, and, therefore, a noncontroversial cannabinoid. Cannabis sativa containing less than 0.3 percent THC was legally classified as hemp, and the phytocannabinoids derived from this plant are legally different from the phytocannabinoids derived from *Cannabis sativa* containing concentrations of THC above 0.3 percent.

A significant event occurred in biomolecular psychology in the 1970s when the biological mechanism of addiction was identified. It was found that rats would repeatedly and willingly electrically self-stimulate areas in the brain, which were subsequently demonstrated to comprise a set of dopamine neurons. [34] This experiment was used to explain the finding of an earlier study, which showed that stimulants enhanced this neurotransmitter's actions. [35]

A subsequent series of experiments demonstrated that blocking dopamine receptors with neuroleptic drugs impaired the reinforcing effects of addictive drugs in rats and primates. These studies placed dopamine as the central neurotransmitter in addiction and indicated that it played a critical role in reward, motivation, and incentive behavior. [36,37] The conceptual breakthrough coincided with the development of microdialysis sampling techniques pioneered by researchers in Sardinia, Italy. Microdialysis sampling produced conclusive evidence that drugs of abuse release dopamine in the basal forebrain, a preoptic area of the hypothalamus known as the nucleus accumbens. This resulted in a general theory of addiction in which addictive drugs release dopamine, but non-addictive substances do not. [38] From this point, the field developed rapidly, with replications of the early animal findings of dopamine being released by 'addictive' drugs and confirmations in humans using neurochemical imaging. These studies' results led to immense investment in research to alter dopamine neurotransmitter function as a method of treating addiction disorders. Positron imaging tomography (PET scans) and single-photon emission computed tomography (SPECT scans) provided critical breakthroughs in our understanding of the human dopamine system and its role in addiction when it was demonstrated that these technological innovations could be used to measure dopamine release in the human striatum. [39,40] It was later demonstrated that the magnitude of this increase could predict the euphoria or 'high' produced by a drug. [40] This proved that in humans, the feeling of pleasure produced by addictive drugs is mediated by striatal dopamine release by the same mechanism as it is in animals, and addiction has come to be viewed as a disorder of the dopamine neurotransmitter system. [38,41] The dopamine theory of addiction has generated acceptance by biomolecular psychologists because drugs that induce dopamine release repeatedly correlate with feelings of pleasure or euphoria. This sensation of joy or bliss is indicative of psychoactivity. According to the moral model of addiction, psychoactivity should only be induced by legal chemicals like alcohol, tobacco, caffeine, or physician-prescribed pharmaceutical medications. [42]

The development of the technology capable of analyzing neurotransmitters and applying the results to the dopamine theory of addiction profoundly affected the creation of synthetic drugs designed to target the brain. Pharmaceutical companies used ventral striatal dopamine release assays to estimate the abuse potential of newly synthesized medicines, rejecting compounds if they were determined to induce pleasure, as determined by increased dopamine concentrations. [42] It might be argued that this was a concession to the moral model of addiction, that anything that results in a pleasurable sensation should be illegal. Still, this view is disconcerting because animal studies conclusively demonstrate that dopamine activity in the ventral striatum is critical to depression resistance. [43]

6. The Construct of Psychoactivity

Definitions are critical in science, and the United States has exploited the fact that definitions have little meaning in politics. For example, when the United States patented CBD to treat neurological conditions resulting from concussion or stroke, Alzheimer's, Parkinson's disease, autoimmune diseases, and HIV dementia, it justified the patent application by claiming CBD is non-psychoactive. Psychoactive is an interesting term, and politicians used it to shift the war against the cannabis plant to a confrontation with the THC molecule. In 2018, President Donald J. Trump signed what was arguably analogous to an Armistice agreement in the form of the Farm Act, effectively ending the longest war in American history. [23] The Farm Act was an admission that the United States had lost the war with the plant, but hostilities continued against the phytocannabinoid it claimed to be psychoactive.

As already alluded to, scientists are consummate conformers when politicians determine what they may research, especially when it involves a subject as convolutedly simple as the science of cannabinoids. Recently, a group of scientists published a list of nonpsychoactive phytocannabinoids. [44] These consist of cannabidiol (CBD), cannabigerol

(CBG), cannabichromene (CBC), and cannabidivarin (CBDV), singling out Δ^9-Tetrahydrocannabinol (THC) as psychoactive. The article defines "hemp," "functional foods," "nutraceuticals," and "novel foods," but fails to define the term "psychoactive," the purported subject of the paper. Defining "psychoactive" may have been considered unnecessary by these scientists and their peer reviewers because it is frequently used in the scientific and common vernacular, and everyone intuitively knows what the term means. Still, because this is science, terms of such critical importance must be defined. Psychoactivity has a standard scientific definition that is universally accepted. Substances **that, when taken in or administered into one's system, affect mental processes**, e.g. perception, consciousness, cognition, mood, or emotions are considered to be psychoactive. [45] Examples of psychoactive substances include alcohol, caffeine, nicotine, illicit drugs, food, and pharmaceutical medications. In fact, every molecule a human ingests alters brain chemistry, affecting mood, awareness, thoughts, feelings, or behavior, including CBD, CBG, CBC, CBN, CBDV, and H_2O. [46,47] To claim an individual with PTSD should not ingest a molecule because it may affect mental processes is tantamount to declaring a person with PTSD should not ingest food. Treatment of many physiological and psychological conditions often requires altering brain chemistry, which is the basis of the pharmaceutical and nutraceutical industries.

7. Theoretical Frameworks toward a Nutraceutical Approach to Treating PTSD

The remainder of this review details theoretical frameworks based on clinical observations deemed useful for devising a nutraceutical protocol expected to match or surpass pharmaceutical interventions in treating PTSD in efficacy and mitigation of overall symptomology. The pathophysiological foundations of PTSD are complex, and not all cases of the disorder share similar underlying mechanisms [48] The disparate mechanisms make the single-molecule approach favored by the pharmaceutical industry unlikely to achieve symptom mitigation in most cases. This review article examines two complementary theories, each reinforcing the other and concluding that a nutraceutical approach incorporating various phytochemicals derived from *Cannabis sativa* chemovars may prove efficacious in mitigating post-traumatic stress disorder symptoms.

8. The Psychoneuroimmunological Aspects of PTSD

Psychoneuroimmunology is a rapidly growing field of psychology that examines the interactions between the immune and central nervous systems. [49] The central nervous system and immune systems constantly interact using different biomolecular messengers. [50] Different proteins are used by each system. The immune and central nervous systems produce proteins and other molecules that act as messengers between the two systems. The central nervous system uses hormones and neurotransmitters to communicate with the immune system, while the immune system communicates with proteins called cytokines. There are several different types of cytokines, but physiological and psychological stressors activate a kind known as pro-inflammatory cytokines. There are many types of these, and while all are involved in the increase in inflammation, not all these inflammation types manifest themselves within the brain as pathological pain. [51] Instead, the effect of chronically increased inflammation on the brain causes behavioral symptoms relevant to mood and anxiety disorders, often comorbid. [52] Some types of chronic inflammation increase systemically over time. This systemic inflammation profoundly affects mood. Greater diversity in day-to-day positive emotions and an elevated sense of well-being are correlated with reducing circulating levels of this type of inflammation. [53] Psychoneuroimmunology studies the mechanism of communication between the immune and nervous systems and how this interaction relates to an individual's physiological and psychological well-being. It is fascinating and highly complex and seems to have great potential for treating PTSD, Alzheimer's Disease, and many other types of autoimmune disorders. [54]

There is incredible complexity in the emotional states that constitute everyday life, and exposure to psychological trauma and traumatic stressors is related to the onset and perpetuation of specific diseases and various autoimmune disorders. [55] The symptoms of these ailments are considered "side effects" of the inflammatory response that is activated as part of the body's struggle to fight infection. Inflammatory excess is revealed in many patients with PTSD, which may be explained by interactions between the immune and central nervous systems. [56]

Studies with neuroendocrine endpoints have historically dominated research on the biology of PTSD, but it is now evident that PTSD psychophysiology is also related to the immune system. Based on the close relationship between the immune and nervous systems and how immune system alterations play a critical role in other neuropsychiatric disorders, it is reasonable to assume that the immune system plays a significant role in the functional symptomology changes accompanying depression. [57]

The pathophysiological foundations of PTSD are complex. As with other psychological disorders, not all cases of PTSD likely share a similar underlying mechanism. [58] Only a few studies have examined immune alterations in patients with PTSD, but evidence is accumulating that indicates the immune system plays a central role in its psychopathology and the comorbid psychological symptoms found with the disorder. [57,59]

9. A Nutraceutical Approach to Treating the Psychoneuroimmunological Aspects of PTSD

Studies demonstrate that individuals with PTSD manifest a low-grade inflammatory state characterized by elevated pro and anti-inflammatory cytokine concentrations. Recovery from PTSD is correlated to reducing these levels, irrespective of treatment modality or outcome. [60,61] This correlation indicates that the intromission of anti-inflammatory phytochemicals may help modulate the chronic inflammatory state of PTSD, as quantified by concentrations of inflammatory cytokines. [62] The phytocannabinoids CBD, CBG, CBN, and CBC have been individually identified as anti-inflammatory agents, and the entourage of these molecules enhanced the phytocannabinoid-mediated pro and anti-inflammatory cytokine responses in preclinical in vivo studies. These molecules are noncontroversial and Generally Regarded as Safe (GRAS) by the FDA. A recent experiment demonstrated the most commonly studied pro-inflammatory cytokines, tumor necrosis factor-alpha, interleukin (IL)-1b, IL-6, and interferon-gamma, levels are consistently reduced after treatment with CBD & CBG, or CBD & THC, but not with THC alone. [63] Since THC is a controversial molecule and its anti-inflammatory potential is only activated in conjunction with another phytocannabinoid, and to stay in compliance with the dominant paradigm, it can be justifiably eliminated from consideration in any potential anti-inflammatory nutraceutical formulation.

10. Theory of Endocannabinoid Deficiency Disorders

Dr. Ethan Russo proposed the theory of endocannabinoid deficiency disorders. The essence of this theory is that a lack of certain endocannabinoids is the underlying cause of several physiological and psychological ailments. In a review article published in 2004, Russo cites examples of anandamide being involved in the production of serotonin and pain modulation. He postulated that migraine, fibromyalgia, irritable bowel syndrome, and other clinical conditions exhibit biomolecular and pathophysiological patterns indicating an underlying clinical endocannabinoid deficiency that can be suitably treated through the administration of phytocannabinoid-based medicines. [64]

11. Phytocannabinoid Supplementation for Endocannabinoid Deficiency Disorders

Human and animal studies have consistently demonstrated that the endocannabinoid system is fundamental for physiological homeostasis and proper emotional and cognitive function. [65] All vertebrates have been confirmed to possess a measurable endocannabinoid tone reflecting concentrations of anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These are categorized as centrally acting endocannabinoids, and their decreased concentration shows a significant correlation to the development of a variety of physiological and psychological disorders. Furthermore, deficiencies of different endocannabinoid system elements contribute to the pathophysiology of several physical and mental disorders, with varying alterations of CB1 and CB2 receptors being demonstrated. [66,67]

Subsequent research demonstrates that underlying endocannabinoid deficiencies undeniably play a role in migraine, fibromyalgia, irritable bowel syndrome, and an expanding list of other physiological and psychological ailments. Endocannabinoid deficiencies have been demonstrated and theorized to contribute to physiological and psychological disorders, including PTSD, postpartum depression, dementia, diabetes, and ADHD. [68,69,70,71,72,73] Experimental results confirm the theory, and researchers predict that clinical trials will further establish the efficacy of phytocannabinoid supplementation as a treatment for various endocannabinoid deficiency disorders. As scientific bias fades and legal barriers continue to fall, this is expected to become increasingly apparent. [74]

12. Subversion of the Dominant Paradigm

While pharmacologists and clinicians have frantically been attempting to remain within the bounds of the dominant paradigm by avoiding designing and developing medicines that activate dopamine, thereby producing the pleasurable sensations the dominant paradigm deems detestable, animal and human studies demonstrate that CB1 receptor activation within the amygdala is essential for the extinction of fear memories. Failure to extinguish traumatic memories is a core symptom of post-traumatic stress disorder. This implies that intensifying endocannabinoid signaling has therapeutic utility in treating this condition. Specifically, direct CB1 receptor activation, using Δ^9-Tetrahydrocannabinol (THC), or its synthetic analogs; or through inhibition of the anandamide-degrading enzyme fatty acid amide hydrolase; or the 2-arachidonoyl glycerol (2-AG)–degrading enzyme monoacylglycerol lipase demonstrates efficacy. [75] Δ^9-

Tetrahydrocannabinol (THC) intromission initiates anandamide production, the endocannabinoid responsible for dopamine activation. Despite the intromission of THC at times resulting in enjoyment, multiple studies indicate the efficacy of treating PTSD patients with cannabis doses containing moderate to high concentrations of THC. [76,77,13]

13. Applying the Entourage Effect to the Development of Nutraceutical Treatments

The most proliferous cannabinoid researcher was Dr. Raphael Mechoulam, a biochemist that NIH funded at the Hebrew University of Jerusalem. Mechoulam was the first researcher to propose the entourage effect theory when he discovered that 2-linoleoylglycerol, 2-oleoylglycerol, and 2-palmitoylglycerol do not bind to cannabinoid receptors but enhance the binding potentiation of 2-arachidonoylglycerol. This observation inspired Mechoulam to propose that these congenators interact synergistically to improve the binding potential of the endocannabinoid to the primary cannabinoid receptors, theoretically through inhibition of 2-arachidonoylglycerol degradation. [77] Ethan Russo expanded on the theory and extended the concept to phytocannabinoids, theorizing that these compounds enhance, heighten, or mitigate the therapeutic effects of other phytocannabinoids. [78] As evidence, he cited a 2010 clinical trial of Sativex, a botanical compound comprised of THC and CBD, to treat neuropathic pain in multiple sclerosis patients. [79] The study consisted of 177 participants and had three arms. The first group was administered a placebo, the second was given a compound containing high concentrations of THC, and the final group was treated with Sativex. Participants were asked to score their pain throughout the two-week clinical trial and state at the end whether their pain had diminished. A 30% or more reduction in pain was considered clinically significant. Of those treated with Sativex, approximately 40% reported this level of pain relief, nearly twice as many as those that received the placebo or a THC isolate.

Another study supporting the existence of an entourage effect is a 2018 meta-analysis involving 670 people with drug-resistant epilepsy and given either a CBD isolate or full-spectrum CBD-rich cannabis extracts. 71% of those intromitting the extracts reported a reduction in the frequency of seizures, compared with 46% of people given CBD alone (Pamplona et al., 2019).

The evidence supporting the entourage effect is so strong that traditional medicine is moving away from the reductionist approach towards harnessing the synergy of poly-pharmacological Phyto-combinations that modulate the activity of target networks of underlying disease phenotypes. [80] Still, subverting dominant scientific paradigms is an arduous process, and as with many scientific constructs, the entourage effect is not universally accepted within the scientific community. Acceptance of the construct appears to be correlated to research funding sources. The pharmaceutical industry promotes a one-molecule approach to medicine while asserting that the purported synergizing mechanisms described by the entourage are not inherently pharmacologically active and suggests the construct is vaguely defined and fosters misrepresentation and abuse by an unscrupulous and unregulated industry, with little compelling clinical data to support it as a reliable phenomenon predictive of beneficial outcomes. The potential subversion of this paradigm is dependent on the results of future studies.

14. Summary, Conclusion, and Suggestions for Future Studies

There are few pharmaceutical medications with demonstrated efficacy for treating posttraumatic stress disorder, and the pursuit of a synthetic medicine with novel mechanisms of action has stalled. [81] A recent meta-analysis comparing the efficacy and acceptability of differing pharmaceuticals for treating adults with posttraumatic stress disorder indicated fluoxetine, paroxetine, sertraline, and venlafaxine should be the recommended drug therapy but expressed uncertainty about the efficacy of these and other non-biodegradable pharmaceuticals for the treatment of the disorder. [82]

The theories summarized above provide guidance for devising a nutraceutical protocol that would be expected to match or surpass pharmaceutical interventions to treat PTSD in efficacy and mitigation of adverse effects. Given the complexity of the condition coupled with an understanding that not all cases of PTSD share an underlying mechanism, it seems that the one-molecule approach to treatment favored by the pharmaceutical industry is unlikely to be successful. A nutraceutical approach allows for incorporating an entourage of biodegradable phytocannabinoid molecules to supplement deficiencies of endocannabinoid concentrations while simultaneously utilizing the antiviral and anti-inflammatory properties of terpenes to treat acute inflammation through the principles of Psychoneuroimmunology.

Biochemical occurrences within the brain are at the very root of psychology. What takes place at the biomolecular level is well understood. The role of the immune system and endocannabinoid system in stress-related psychiatric symptoms has been investigated in countless animal and human studies. It is now known that both have a dramatic effect on the

manifestation and severity of PTSD symptomology. While more research in this area is necessary, it cannot be disputed that traumatic events deplete endocannabinoid concentrations and that exogenously supplementing resultant deficiencies with phytocannabinoids has demonstrated efficacy. [83] Studies still need to be conducted on tolerability, method of administration, optimal dosing, degradation rates, and pharmaceutical interactions of phytochemicals in the brain. Studies on the endocannabinoid system and the psychologically therapeutic properties of Phyto-compounds are the research the FDA is requesting private institutes and universities to conduct. To facilitate these studies, they established the Botanical Safety Consortium. This public-private partnership provides guidelines to assure industry and academic IRBs to ensure psychological research is conducted ethically and safely while providing regulations ensuring that research involving Phyto-compounds has no possibility of causing harm to human participants. [84,85]

The entourage of Phyto-compounds the FDA has certified as safe, coupled with the method of administration the FDA has approved, requires scientific scrutinization. The FDA has reached out to universities and private institutions and requested this research, an occurrence that has not happened since 1971. The demonstrated efficacy of these Phyto-compounds in treating PTSD as an endocannabinoid deficiency disorder requires research that meets exacting FDA standards.

As discussed in this summarization of theoretical frameworks, not all cases of PTSD share a similar underlying mechanism. While substantial stressors have been demonstrated to significantly degenerate brain chemistry, they also affect the nervous and immune systems. Both systems interact directly with the brain, which comprises the very root of psychology. Interestingly, phytochemicals that the FDA deems as safe and intromitted in a manner the FDA has determined as acceptable are predicted to demonstrate efficacy in reducing inflammatory processes and levels of pro-inflammatory cytokines, thereby treating the nervous and immune system effects resulting from acute stressors on the chemistry of the brain. [86] Further research needs to be conducted on psychoneuroimmunology, the endocannabinoid system, and their relationship to the symptomology of PTSD. Potential studies in these areas are diverse, astonishing, falsifiable, and easy to design.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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