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Cannabidiol-Derived Cannabinoids: The Unregulated Designer Drug Market Following the 2018 Farm Bill

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Abstract

Background: In this review, we summarize current scientific knowledge on psychoactive cannabinoids synthesized from cannabidiol (CBD) and sold in the semi-legal market established in response to the passage of the US Agriculture Improvement Act of 2018, commonly known as the 2018 Farm Bill. The discussion focuses on recent developments that suggest this unregulated market may be fertile ground for a potential health crisis. ***Summary:*** Current research into CBD-derived cannabinoids is mainly limited to Δ^8-tetrahydrocannabinol (Δ^8-THC) products, with some recent publications beginning to explore O-acetyl-THC, a term describing the acetate ester of Δ^8-THC or Δ^9-THC, and its potential pulmonary toxicity. We advance the discussion on the CBD-derived cannabinoid market, shedding light on the introduction and associated dangers of novel cannabinoids, likely produced via fully synthetic routes using sidechain variants of CBD, with purportedly greater agonist activity at the human cannabinoid receptor 1 (as a source of euphorigenic activity) than Δ^9-THC. We discuss the expanded incorporation of the acetate ester motif into other THC analogues. We also discuss the lack of regulatory oversight for the production of CBD-derived cannabinoids and the unlabeled presence of under-researched cannabinoids formed as reaction side products in the CBD-derived cannabinoid products being sold. Accordingly, we suggest approaches to monitoring the CBD-derived cannabinoid market and investigating the pharmacology of the cannabinoids being consumed. Finally, important epidemiological findings are discussed and future directions for research are suggested to call investigators to this critically understudied field. ***Key Messages:*** The CBD-derived cannabinoid market is growing internationally, and the market has diversified to include potent synthetic cannabinoids. The products sold on this unregulated market are under-researched despite growing availability and consumer interest. Ernest investigation of the pharmacology of these novel cannabinoids and the contents of CBD-derived cannabinoid products is critical for monitoring this potential source of another vaping-related epidemic.

Introduction

An unregulated market for novel psychoactive cannabinoids has proliferated in the wake of the passage of the US Agriculture Improvement Act of 2018, commonly known as the 2018 Farm Bill. The 2018 Farm Bill declared

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hemp legal, defining it as *Cannabis sativa* or any product of the plant with a Δ^9-tetrahydrocannabinol (Δ^9-THC) concentration of no more than 0.3 percent [1]. The bill's passage led to the immediate mass production and over-the-counter marketing of cannabidiol (CBD) from hemp [1]. The resulting surplus of CBD, together with loopholes in the bill's definition of hemp, created a market niche for the semi-synthetic production of cannabinoids with psychoactive activity by virtue of human cannabinoid receptor 1 (CB_1R) agonism, with CBD serving as the reaction substrate [1, 2]. These products are sold online and at smoke shops and retail venues throughout the USA and the world [3]. The first product sold on this CBD-derived cannabinoid market was Δ^8-tetrahydrocannabinol (Δ^8-THC), with more potent cannabinoids following soon after, including CB_1R full agonists.

According to the 1986 Analogue Act of the controlled substances act (CSA), all intoxicating cannabinoids should be considered schedule 1 compounds [4]. Indeed, this is the law that restricts the scientific community's access to these compounds. However, Δ^8-THC was ruled to fall within the definition of "hemp" under the 2018 Farm Bill by the Ninth Circuit Court of Appeals in May 2022. This ruling bolstered supplier confidence in the legal status of all CBD-derived cannabinoids. Research funded by the US government functions under the purview of the CSA, as enforced by the US Drug Enforcement Agency, and research access to schedule 1 compounds is heavily regulated. As the CBD-derived cannabinoid market operates under the interpretation that the 2018 Farm Bill exempts CBD-derived cannabinoids from the CSA, these contradictory pieces of legislation emboldened the CBD-derived cannabinoid market while limiting research on these novel cannabinoids and the possible dangers of the products which contain them.

A Potential Health Crisis

The unique risks posed by CBD-derived cannabinoid products are highlighted by research on reported adverse events. The first study to look at Δ^8-THC case report data in the FDA Adverse Event Reporting System (FAERS) found that, since the passage of the 2018 Farm Bill, Δ^8-THC adverse events have been reported at a rate 3 times greater than that for Δ^9-THC [5]. The adverse event profile of Δ^8-THC products was distinct compared to Δ^9-THC, with respiratory events as the most frequently reported [5]. Currently, adverse events associated with other CBD-derived cannabinoids are unstudied.

Recent studies indicate that early evidence of the dangers of CBD-derived cannabinoid products may have been overlooked. In 2019, a national outbreak of acute lung injury, referred to as e-cigarette or vaping-use-associated lung injury (EVALI), resulted in over 2,800 confirmed cases and at least 68 deaths [6]. This epidemic was determined to be the result of adulterated cannabis vaping devices [7]. Investigators used gas chromatography-mass spectroscopy (GC-MS) to analyze vaping products obtained from EVALI patients [7]. Results found that while a majority of EVALI-associated samples contained cannabinoid profiles consistent with a typical cannabinoid extraction processes, a subset possessed profiles indicative of CBD-based semi-synthetic routes of production, such as high levels of Δ^8-THC and olivetol [7]. Olivetol is known to cause respiratory irritation [1]. Evidence indicates vitamin E acetate (VEA), used as an excipient in unregulated cannabis vape cartridges, to be the most likely causative agent in the 2019 EVALI outbreak [7]. Accordingly, the authors' findings do not necessarily evidence pulmonary harm from CBD-derived cannabinoids. Rather, the fact that CBD-derived cannabinoid products were combined with VEA (much like black market Δ^9-THC cannabis products) underscores the dangers associated with the unregulated nature of this market.

Exploration of the endocannabinoid system has revealed its diverse roles throughout the body, including psychiatric, neurologic, immune, and metabolic functions [8, 9]. Subsequent to the surge in recreational use of synthetic cannabinoids in the early 2000s, the potential harm presented by highly potent full agonists of CB_1R has gained attention. They are evidenced to cause acute pulmonary injury, psychiatric crises, seizures, and renal injury [10–13]. Additionally, cases of cannabinoid hyperemesis syndrome are reported to be on the rise and case reports of cannabinoid hyperemesis syndrome associated with synthetic cannabinoid use have appeared [14, 15]. Now that CB_1R full-agonist ligands are available on the CBD-derived cannabinoid market, we must investigate how these cannabinoids may contribute to such pathologies.

CBD-Derived Cannabinoids

The first CBD-derived cannabinoid to reach commercial markets was Δ^8-THC, produced through acid-catalyzed ring closure of CBD [1, 16]. In studies comparing it to Δ^9-THC, Δ^8-THC had a binding affinity at human CB_1R ranging from K_i = 28.5 nM to 251 nM, while the binding affinity for Δ^9-THC ranged from K_i = 18 nM to 32.3 nM, suggesting that Δ^8-THC may be a weaker ligand (Table 1) [17]. Hexahydrocannabinol (HHC) reached markets soon after Δ^8-THC. Hydrogenation of CBD-derived Δ^8-THC or Δ^9-THC forms a mixture of the

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Table 1. Molecular structure and CB_1R binding data on CBD-derived cannabinoids

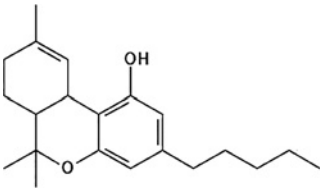
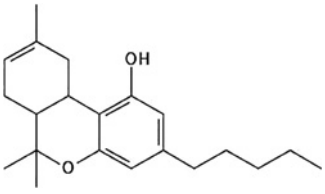
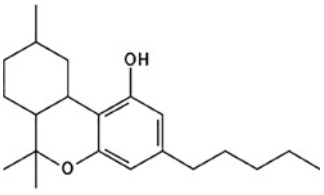
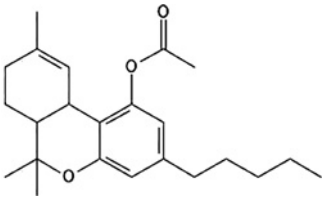
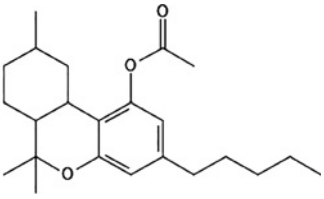
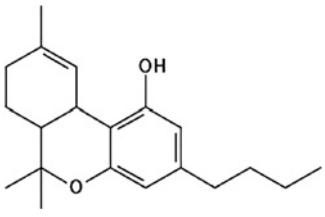
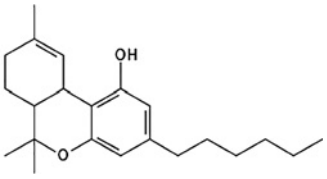
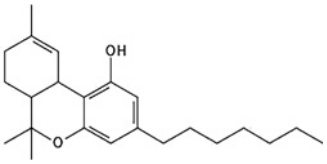
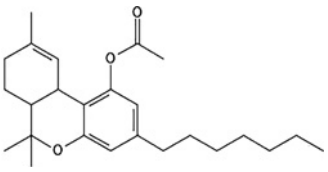
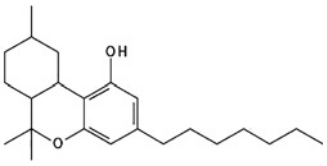
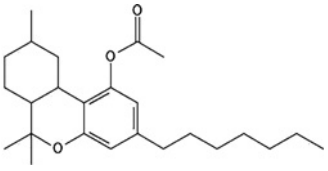
Cannabinoid name and chemical formula	Molecular structure	Human CB_1R binding data
Δ^9--THC $C_{21}H_{30}O_2$		K_i = 18–32.3 nM Tagen and Klumpers [17] (2022) K_i = 40 nM Citti et al. [18] (2019)
Δ^8--THC $C_{21}H_{30}O_2$		K_i = 28.5–251 nM Tagen and Klumpers [17] (2022)
HHC $C_{21}H_{32}O_2$		K_i = 149 nM (racemic) Ujváry István [19] (2023)
Δ^9-THC-O $C_{23}H_{32}O_3$		Data unavailable
Hexahydrocannabinol-O-acetate (HHC-O) $C_{23}H_{34}O_3$		Data unavailable
Δ^9-THCB $C_{20}H_{28}O_2$		K_i = 15 nM Citti et al. [18] (2019)

Table 1 (continued)

Cannabinoid name and chemical formula	Molecular structure	Human CB_1R binding data
Δ^9-THCH $C_{22}H_{32}O_2$		Data unavailable
Δ^9-THCP $C_{23}H_{34}O_2$		K_i = 1.2 nM Citti et al. [18] (2019)
Δ^9-tetrahydrocannabiphorol-O-acetate (THCP-O) $C_{25}H_{36}O_3$		Data unavailable
HHCP $C_{23}H_{36}O_2$		Data unavailable
Hexahydrocannabiphorol-O-acetate (HHCP-O) $C_{25}H_{38}O_3$		Data unavailable

9R and 9S epimers of HHC [19]. The binding affinity at human CB_1R for the racemic mixture has been reported as K_i = 149 nM, with in vivo evidence indicating the R epimer as more potent than the S epimer [19].

Early CBD-derived cannabinoid products such as Δ^8-THC and HHC are less potent than Δ^9-THC. Recently, more complex chemistry has been implemented to produce CB_1R ligands of purportedly greater psychoactive potency than Δ^9-THC, including Δ^8 and Δ^9 isomers of tetrahydrocannabutol (THCB), tetrahydrocannabiphorol (THCP) and tetrahydrocannabihexol (THCH), hexahydroxycannabiphorol (HHCP), and O-acetyl-THC (THC-O) (Table 1; Fig. 1).

Among these ligands, several display greater CB_1R binding affinity in vitro and greater behavioral cannabimimetic activity in vivo compared to Δ^9-THC, with some acting as full agonists at CB_1R [18, 20, 21]. CB_1R full-agonist ligands pose a risk for physiological, neurological, and psychiatric harm, and the emergence of such powerful ligands on the CBD-derived cannabinoid market necessitates research [10, 11].

Between 2019 and 2020, a research team discovered Δ^9-THCB, Δ^9-THCP, and Δ^9-THCH after isolating them from the Italian medical cannabis strain FM2 [18, 20, 21]. In their reported human CB_1R binding studies, Δ^9-THC had a binding affinity of K_i = 40 nM, while Δ^9-THCB and

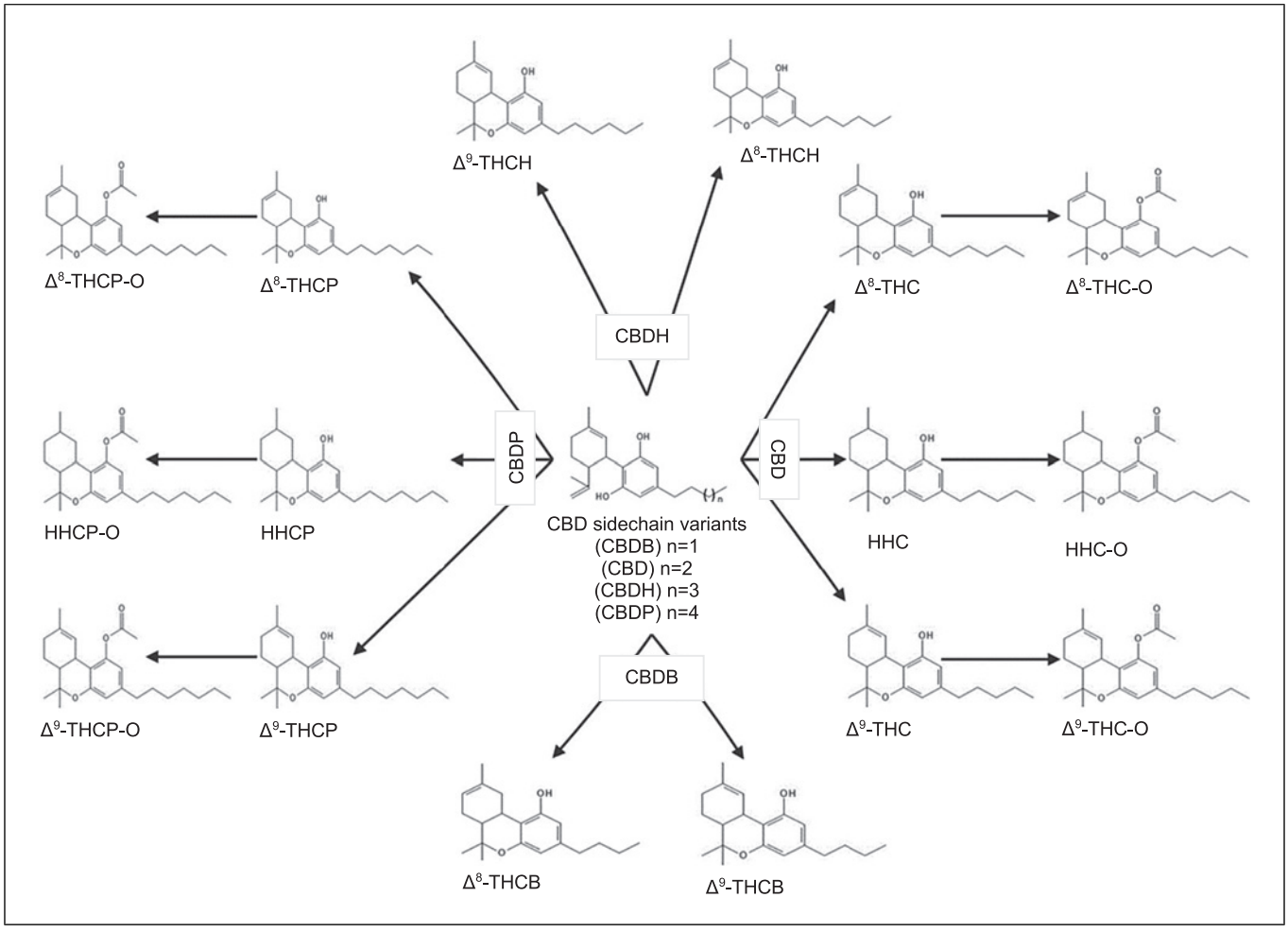


Fig. 1. Overview of the production of psychoactive cannabinoids currently available on the CBD-derived cannabinoid market. The synthetic route employed by the CBD-derived cannabinoid industry to produce sidechain variants of THC and HHC is unreported in scientific literature, but likely follows that of published literature: fully synthetic production via synthetically produced sidechain variants of CBD. Labeled arrows indicate the sidechain variant of CBD used to produce the psychoactive cannabinoids. HHC and HHC-O can be produced through Δ^8-THC or Δ^9-THC intermediate substrates, and HHCP and HHCP-O can likewise be produced from Δ^8-THCP or Δ^9-THCP intermediate substrates; accordingly, the arrows are a simplified representation of synthetic routes. CBDP, cannabidiphorol (7 carbon sidechains); CBDH, cannabidihexol (6 carbon sidechains); CBDB, cannabidibutol (4 carbon sidechains); HHCP-O, hexahydrocannabiphorol-O-acetate; HHC-O, hexahydrocannabinol-O-acetate.

Δ^9-THCP had binding affinities of K_i = 15 nM and 1.2 nM, respectively [18, 20]. This indicates that Δ^9-THCB and Δ^9-THCP, respectively, have roughly twice and 33 times the affinity for human CB_1R compared with Δ^9-THC [18, 20]. Moreover, behavioral testing of Δ^9-THCP demonstrated a CB_1R full-agonist profile [18]. The researchers liken Δ^9-THCP's CB_1R activity to that of the full-agonist synthetic cannabinoid CP55,940. Considering that CP55,940 has been demonstrated to cause respiratory injury, this is cause for alarm [13, 18]. Pharmacological data for THCH are not yet available, but it is marketed as similar in psychoactive strength to THCP. While these cannabinoids were discovered as naturally occurring phytocannabinoids, the Δ^8 and Δ^9 isomers of these ligands sold on the CBD-derived cannabinoid market are produced synthetically. While there are no published data on the synthetic route employed, given the prohibitive nature of extending the 5-carbon tail of THC to form the 7-carbon tail of THCP, the THCP sold on the CBD-derived cannabinoid market is likely produced from synthetically derived cannabidiphorol produced in a manner similar to that employed by Citti et al. [18]. THCB and THCH are probably likewise produced from synthetic butol and hexol analogues of CBD. Briefly, the

required CBD variants of differing sidechain lengths can be synthesized by reacting a stereospecific menthadienol isomer with resorcinol molecules of the desired sidechain lengths [18, 22]. As recently described, such resorcinol molecules can be efficiently synthesized by Wittig reaction of 3,5-dimethoxylbenzyl triphenylphosphonium bromide with aldehydes corresponding to the desired sidechain lengths, followed by Pd/C-catalyzed hydrogenation, then deprotection and hydrolysis of aryl methyl ether groups to hydroxyl groups by reaction with BBr3 [22]. Additionally, hydrogenation of Δ^8- and Δ^9-THCP forms the analogue HHCP [19]. No binding data are available for this compound, and it is not discussed in research; however, it is also marketed as having a similar psychoactive potency as THCP.

THC-O (Table 1; Fig. 1) first appeared on the market in 2020, although it was first synthesized in 1942 and tested as an incapacitating agent for military use during the Edgewood Arsenal experiments between 1948 and 1975 [2, 23]. THC-O is an acetate ester of either Δ^9-THC or Δ^8-THC formed by refluxing THC with acetic anhydride [24]. Binding data are not available, but users report it being twice as potent as Δ^9-THC, longer in onset and duration, and it is marketed as possessing a more "psychedelic" quality compared to Δ^9-THC [2]. Pharmacologic differences between Δ^8- and Δ^9-THC-O are unknown. THC-O is hypothesized to act as a prodrug that is hydrolyzed to the parent THC compound, explaining the delayed onset of THC-O compared to THC [19]. Of critical importance, researchers demonstrated, in 2023, that the aryl acetate moiety in THC-O can form a ketene (R_2-C=C=O) when exposed to vaporization temperatures. Ketene-containing molecules possess significant pulmonary toxicity. In fact, ketene gas formation upon vaporization is hypothesized to be the pathologic mechanism by which VEA elicits the pulmonary injury as observed in the 2019 EVALI outbreak [24]. More recently, acetate esters of THCP, HHC, and HHCP have reached the market, labeled, respectively, as tetrahydrocannabiphorol-O-acetate, hexahydrocannabinol-O-acetate, and HHCP-O-acetate [19]. These compounds are likely to be at least as potent as their non-acetate precursors and are virtually unexplored in published research. No research is yet available regarding pulmonary toxicity of acetate esters of these cannabinoids, but as they grow in diversity and popularity, such data will be crucial. The DEA released a statement in February 2023 affirming Δ^8-THC-O and Δ^9-THC-O as schedule 1 controlled substances under the CSA; however, they are still widely retailed as of January 2024 [19, 25]. Additionally, the statement did not cover acetate esters of cannabinoids other than Δ^8-THC and Δ^9-THC.

It is important to recognize that pharmacologic data for CBD-derived cannabinoids are currently limited. The K_i values reported in this paper are obtained from numerous primary sources, rather than a single comparative study testing ligands under identical conditions. Moreover, EC50 values for most CBD-derived cannabinoids are unavailable. To advance CBD-derived cannabinoid research, we suggest that single laboratories test these novel ligands in the same systems and under the same conditions, to gather comparable data on EC50 values of these cannabinoids at cellular and behavioral levels, as well as more comparable K_i data.

CBD-derived cannabinoid products frequently include Δ^9-THC as a reaction side product, often at levels exceeding the legally permissible 0.3%. In a study by the US Cannabis Council, 16 samples of products labeled as Δ^8-THC were all found to have Δ^9-THC levels above 0.3%, with the average of all samples having a Δ^9-THC concentration 10 times the limit [26]. Additionally, CBD-derived cannabinoid products can include the undisclosed presence of numerous understudied cannabinoids and other reaction side products, which often lack the reference standards required for positive identification using MS techniques alone. Accordingly, thorough and accurate analysis of unlabeled cannabinoids and non-cannabinoid side products in CBD-derived cannabinoid products currently calls for a combination of NMR and MS techniques [27]. For example, one study performed ^{1}H and ^{13}C-NMR and GC-MS analysis of Δ^8-THC-labeled products and found the undisclosed presence of $\Delta^{4(8)}$-isotetrahydrocannabinol, 9-ethoxyhexahydrocannabinol, and isotetrahydrocannabifuran (*iso*-THCBF). *Iso*-THCBF was unknown in the scientific literature prior to this discovery in Δ^8-THC products in 2021 [27]. While these products included provider-supplied certificates of analysis, all were either inaccurate due to the use of analytical techniques such as HPLC-UV incapable of distinguishing side products such as *iso*-THCBF from Δ^8-THC or falsified [27]. These cannabinoids possess unknown pharmacologic and toxicologic profiles necessitating further exploration. Analysis of novel, more potent CBD-derived cannabinoid products has not been performed. While Δ^8-THC is synthesized in one step from CBD, newer cannabinoids such as THCP and tetrahydrocannabiphorol-O-acetate require more complex reactions, raising the possibility of even more undisclosed side products. Considering the presence of undisclosed and even undiscovered cannabinoids in Δ^8-THC products, there is perhaps a cornucopia of unidentified cannabinoids yet to be discovered that are already being consumed by the public [27]. This production of unknown and untested CBD-derived

cannabinoids has obvious parallels to the production of other designer drugs, with their attendant risks. For example, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is a side product in some synthetic routes for the opioid 1-methyl-4-phenyl-4-propionoxypiperidine and causes acute-onset, permanent Parkinsonism if injected [1]. Similar concerns exist for understudied and undisclosed side products in CBD-Derived cannabinoids.

Non-Cannabinoid Side Products and Contaminants

The unregulated nature of the CBD-derived cannabinoid market is itself a source of risk. This is evident from the results of an investigation commissioned by *CBDoracle* that analyzed 51 Δ^8-THC products from 44 different companies [28]. Results indicated that 76% of the products contained Δ^9-THC at levels beyond the legally permitted 0.3%, and that most companies selling these products either do not analyze their products or, if they do, report only the potency of the desired cannabinoids, and not pesticides, heavy metals, excipients, or reaction side products, suggesting the use of insufficient analytic techniques for accurate reporting. They also found falsification of certificates of analysis to be a problem among Δ^8-THC suppliers [28]. Peer-reviewed research corroborates the claims of this report, with ^{1}H NMR and GC-MS analyses of 27 Δ^8-THC products from 10 brands revealing excipients and side products unaccounted for by their producers and distributors, including undisclosed cannabinoids and olivetol, while inductively coupled plasma mass spectrometry revealed the undisclosed presence of heavy metals and silicon [27]. As mentioned earlier, olivetol inhalation is capable of causing respiratory irritation [1]. While not normally found in significant quantities in cannabis or processed products of cannabis, olivetol is rather a degradation product of the reactions used to synthesize Δ^8-THC from CBD [7, 27]. The undisclosed presence of the highly potent, indazole-based synthetic cannabinoid MDMB-4en-PINACA has also been detected in CBD-derived cannabinoid products [19]. Overall, it is clear that consumers should not trust the packaging or supplier-provided certificates of analysis for CBD-derived cannabinoid products.

A Call for Research

Clearly, research must catch up to the current state of cannabinoid use. We believe this should be approached on two fronts: there needs to be an earnest analysis of CBD-derived cannabinoid products and pharmacological exploration of the cannabinoids on the market; there is also a need for observational studies of available human data. While observational studies regarding CBD-derived cannabinoid products are currently limited in quantity and scope, those that are available offer compelling findings that may inform future studies. The previously discussed research analyzing FAERS data on Δ^8-THC products was effective in identifying the unique adverse event profile associated with their use. A similar approach can be implemented in future studies focusing on more potent CBD-derived cannabinoids, such as THCP and HHCP, and those hypothesized to be pulmonary toxicants, such as THC-O [5].

Recognizing the wealth of information available through online forums where CBD-derived cannabinoid users exchange information on the products, investigators analyzed the subreddit *r/Delta8* for self-reported adverse events [29]. The authors found that between 2020 and 2022, there were 2,184 adverse events reported on *r/Delta8*, compared with only 326 reported to FAERS during the same period [29]. Moving forward, the subreddit *r/altcannabinoids* offers discussion on a greater diversity of CBD-derived cannabinoids than Δ^8-THC alone and, accordingly, can be analyzed for adverse events related to novel, more potent cannabinoids.

As with other designer drug classes, research has struggled to keep pace with the production of novel CBD-derived cannabinoids. Innovative software can facilitate the first step in addressing this challenge: identification of cannabinoids currently discussed by consumers but unknown to peer-reviewed literature. A 2020 publication discusses implementation of a web crawling software called *NPS.Finder* to find information on novel synthetic cannabinoids [30]. *NPS.Finder* scours the web for mention of novel psychoactive substances. In this study, *NPS.Finder* identified 1,103 synthetic cannabinoids discussed online by recreational users. Of these, 863 synthetic cannabinoids were not mentioned in the novel psychoactive substance lists of the United Nations Office on Drugs and Crime, or the European Monitoring Centre for Drugs and Drug Addiction [30]. As the diversity of available CBD-derived cannabinoids increases, a similar approach may prove invaluable for informing the research and clinical monitoring of these compounds.

Such web-based studies can provide the earliest insights into novel cannabinoids in use, as well as the cannabinoids and brands most associated with adverse events. These data can inform market surveillance utilizing the multiple analytic approaches required for identification and quantification of unlabeled cannabinoids and other reaction side products, excipients, and contaminants, such as a combination of ^{1}H-NMR, GC-MS, and inductively coupled plasma mass

spectrometry. Such web-based data can also inform the production of reference standards of emerging cannabinoids to facilitate their identification with MS techniques without the need of NMR. Understudied cannabinoids indicated by web data and confirmed via market surveillance should become the focus of preclinical research to determine their pharmacology and toxicology. In addition to studying these novel cannabinoids themselves, their metabolites should also be investigated. An understanding of the pharmacology and toxicology of such metabolites will inform our understanding of the health impact of these novel cannabinoids, and identification of any unique metabolites that can indicate which cannabinoid was consumed would offer great clinical utility in events of adverse consequences following drug ingestion. Should a widely available cannabinoid, its metabolite, or reaction side product demonstrate a toxic profile, the capacity to screen for it via blood or urine metabolite-specific immunoassay would be invaluable for rapid diagnostic purposes and initiation of appropriate care.

Finally, epidemiological research for CBD-derived cannabinoid use is nascent. A 2021 publication provides a foundation for future studies. Briefly, researchers analyzed *Google* queries to understand trends in public interest for Δ^8-THC. They found that global searches for Δ^8-THC increased 257% from 2019 to 2021, and 705% from 2021 to 2022 globally [3]. They also found that Δ^8-THC search rates are 10 times higher in the USA than in any other country. Moreover, among US states and territories, they found a significant correlation between the degree of Δ^9-THC prohibition and the number of *Google* queries for Δ^8-THC. Search rates for Δ^8-THC were 2.8 times higher in states prohibiting both medicinal and recreational cannabis compared to states with legal cannabis. The authors also point out that states with no legal cannabis infrastructure are havens for the production of CBD-derived cannabinoids, as there are no state laws in place to regulate the quality or distribution of cannabis products [3]. While usage rates cannot be gleaned from these findings, such data on regional interest in CBD-derived cannabinoids provide a hypothetical framework for relative usage and potential mediating variables such as degree of Δ^9-THC prohibition. These reports can then inform more in-depth observational research. Hospital emergency department records can be analyzed for instances of adverse events resulting from CBD-derived cannabinoid use. Moreover, it is standard practice in the USA for healthcare providers to inquire about drug use while taking a patient history, and should inquire about the use of CBD-derived cannabinoid products. Such information may prove clinically relevant to pulmonary or psychiatric concerns, and anonymized data from electronic medical records could provide an understanding of usage statistics for these products. Identification of metabolites unique to specific CBD-derived cannabinoids could offer biomarkers for wastewater-based epidemiology via liquid chromatography tandem mass spectrometry.

Conclusion

Addressing the risks associated with the emergence of the CBD-derived cannabinoid market poses a unique and multifaceted set of challenges. Contradictory laws have bred a cavalier attitude for the mass production, diversification, and distribution of increasingly potent cannabimimetics, while dampening the scientific community's capacity to research them. As the variety of CBD-derived cannabinoids expands, so may the dangers. Within these products are risks posed by potent CB_1R agonism, pulmonary exposure to ketene gases and olivetol, unstudied cannabinoids, undisclosed reaction side products, and potentially toxic contaminants and excipients. The unregulated nature of this market enhances the dangers. False laboratory reports on the contents of the products underscore deceptive sales practices. Supplier claims of these products being derived from organic sources, coupled with their "legal" status, create a sense of safety and, accordingly, a broader appeal than would likely exist if the public was better informed on the production and associated dangers of these products. Research into CBD-derived cannabinoids is crucial to avoid another vaping-related epidemic.

Conflict of Interest Statement

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Author Contributions

C.N.Z., J.E.N., and K.E.V. wrote the manuscript. S.M.-H., C.M.A., and C.N.Z. prepared tables and figures. All authors contributed to manuscript preparation and revision.

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