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Endo- Phyto- and Synthetic-Cannabinoids and the Cannabinoid-Induced Hyperemesis Syndrome

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ABSTRACT

In this short review, the current status of the endocannabinoid system (ECS) and the major cannabinoids produced in humans/animals (endocannabinoids), plants (phytocannabinoids), and those manufactured in the laboratory (synthetic cannabinoids) will be elucidated. Synthetic and phytocannabinoids produce their psychoactive effects (e.g., euphoria, altered perceptions) *via* the activation of cannabinoids CB_1 receptors (CB_1Rs). To date there is no report to demonstrate that administration of endocannabinoids can induce euphoria in humans. A key indication for use of phyto- and synthetic cannabinoids in the clinic is for the prevention of chemotherapy-induced nausea and vomiting. However, the major psychoactive component of the marijuana plant, delta-9-tetrahydrocannabinol (Δ^9-THC), as well as synthetic cannabinoid may also evoke vomiting in some patients. In this review, we further discuss these gastrointestinal side-effects of cannabinoids which in some patients may lead to a more serious gastrointestinal condition known as the cannabinoid-induced hyperemesis syndrome (CHS). Lastly, we debate the potential mechanisms underlying CHS and its prevention.

KEY WORDS: Cannabinoid-induced hyperemesis syndrome (CHS); Endocannabinoid system (ECS); Synthetic-cannabinoids; *Cannabis sativa*.

ABBEVIATIONS: ECS: Endocannabinoid system; CB_1Rs: CB_1 Receptors; Δ^9-THC: Delta-9-tetrahydrocannabinol; CHS: Cannabinoid-Induced Hyperemesis Syndrome; CB_2R: CB_2-Receptors; Anandamide: Arachidonoyl ethanolamide; 2-AG: 2-Arachidonoylglycerol; NADA: N-arachidonoyl dopamine; OAE: Virodhamine; SCBs: Synthetic Cannabinoids; ECS: The Endocannabinoid System; PI: Phosphoinositol; PLC: Phospholipase C; DAG: Diacylglycerol; DAGL: Diacylglycerol lipase; NAPE: N-arachidonoyl phosphatidylethanolamine; NAPE-PLD: N-acylphosphatidylethanolamine-hydrolyzing phospholipase D; FAAH: Fatty Acid Amide Hydrolase; CINV: Chemotherapy-Induced Nausea and Vomiting; CBD: Cannabidiol; DAWN: Drug Abuse Warning Network; CVS: Cyclic-Type Vomiting Syndrome; IBS: Irritable Bowel Syndrome; IBD: Inflammatory Bowel Disease; TRPV1: Transient Receptor Potential Vanilloid 1.

INTRODUCTION

The Endocannabinoid System

Cannabis refers to constituents of the plant *Cannabis sativa*, commonly known as marijuana. Cannabis has been used medically for thousands of years in Asian and Middle Eastern countries.[1] During the mid-19th century, cannabis preparations were introduced in Europe and the United States.[2] Basic laboratory research on cannabis started in 1940's[2] leading to the isolation and chemical characterization of the major psychoactive constituent of marijuana plant, delta-9-tetrahydrocannabinol (Δ^9-THC) in 1964.[1] The pharmacological effects of Δ^9-THC can vary with dose, route of administration, user experience, and the setting of use. Marijuana intoxication can produce "a high" as well as changes in mood, perception and motivation.

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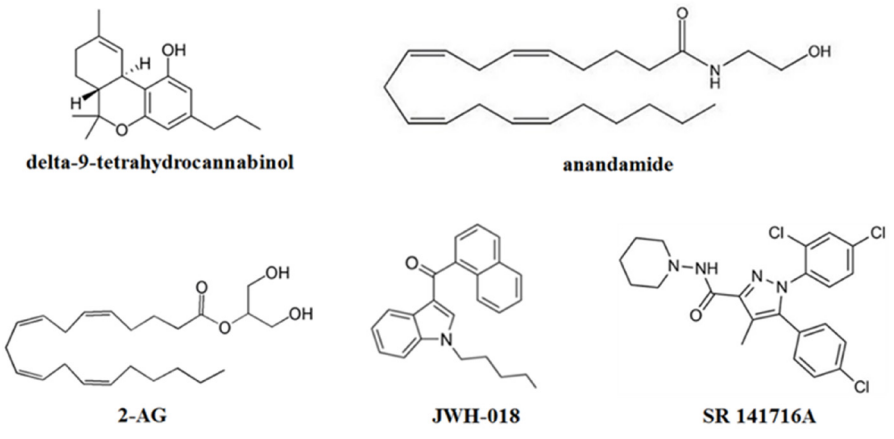
The development of novel and potent analogs of Δ^9-THC played a major role in the characterization and cloning of cannabinoid CB_1- and CB_2-receptors (CB_1R and CB_2R) in 1990 and 1993, respectively.[3] The above discussed psychoactive effects of Δ^9-THC are mediated *via* CB_1Rs in the brain. CB_1R and CB_2R are members of the subfamily of G-protein-coupled receptors and predominantly couple to $G_{i/o}$ to produce multiple cellular effects including inhibition of adenylate cyclase and regulation of voltage-gated calcium channels, regulation of potassium currents, and increase of calcium influx *via* G_s and G_q.[3-4] CB_1R is considered the most abundant metabotropic receptor in the brain and is distributed throughout the central and peripheral nervous system. CB_1Rs are frequently expressed in high density on presynaptic nerve terminals of both inhibitory and excitatory nerves. Activation of presynaptic CB_1Rs is postulated to suppress neurotransmission by decreasing Ca^{2+} influx through high voltage-gated Ca^{2+} channels.[3] CB_2Rs are mainly expressed on cells and organs of the immune system and modulate their function, but they are also found in the brain and at other sites in the body. The discovery of CBRs was soon followed in 1992 and 1995 by the demonstration of the existence of endogenous CBR agonists such as arachidonoyl ethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG).[4] While anandamide and 2-AG are among the well-studied endocannabinoids, other potential endocannabinoids may include 2-arachidonylglyceryl ether (noladin ether), N-arachidonoyl dopamine (NADA) and virodhamine (OAE). Although, the term 'cannabinoid' was originally used to refer to a number of structurally related C21 aromatic hydrocarbon compounds isolated from the plant *Cannabis sativa*, today it refers to any ligand that binds to and modulates the activity of CBRs. Thus, cannabinoids are structurally diverse (Figure 1) and range from compounds that are endogenously produced (endocannabinoids) to plant-derived (phytocannabinoids) and synthesized compounds (SCBs). The endocannabinoid system (ECS) is composed of CBRs, endocannabinoids and the enzymes involved in their synthesis.

Unlike many preformed intercellular mediators, endocannabinoids are made on demand when cells are stimulated with either an increase in intracellular Ca^{2+}, or following metabotropic receptor activation involving $G_{q/11}$ or possibly G_s proteins.[4-5] These ligands are found both in the brain and in the periphery, for example, in the gastrointestinal tract, where they act on cannabinoid and other receptors. The most important pathway for the synthesis of 2-AG begins with the activation of a phosphoinositol (PI)-phospholipase C (PLC) which hydrolyzes inositol phospholipids at the *sn-2* position, producing diacylglycerol (DAG). The hydrolysis of DAG *via sn*-1-selective diacylglycerol lipases (DAGL)-a and DAGL-b then leads to the formation of 2-AG. Alternatively, but less well characterized, is the sequential hydrolysis of PI by phospholipase A_1 to make lyso-PI which is then further hydrolyzed to 2-AG by lyso PI-specific PLC. The metabolism of 2-AG appears to be complex and probably involves enzymatic oxygenation, acylation, or phosphorylation; but the most important pathway for 2-AG metabolism is hydrolysis.[4-5]

An important route of anandamide synthesis begins with the membrane phospholipid precursor, N-arachidonoyl phosphatidylethanolamine (NAPE), which is formed by the transfer of arachidonic acid from the sn-1 position of a donor phospholipid to phosphatidylethanolamine by N-acyltransferase.[4-5] Hydrolysis of NAPE by an N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) produces anandamide. Additional enzymatic pathways for the production of anandamide also exists *via* the sequential deacylation of NAPE by the enzyme alpha beta-hydrolase 4 and the cleavage of glycerophosphate to yield anandamide, and a PLC-mediated hydrolysis of NAPE which produces phosphoanandamide, which is then dephosphorylated to produce anandamide. The principal enzyme for the degradation of anandamide is fatty acid amide hydrolase (FAAH).

The cannabis plant synthesizes at least 400 chemicals of which more than 60 are structurally related to Δ^9-THC. Today, several hundred cannabinoid agonists, antagonists, and inverse agonists, including active and inactive metabolites, and related structures are available.[3] Cannabinoid agonists can be classified

Figure 1: The Comparative Structures of Delta-9-Tetrahydrocannabinol (Δ^9-THC), Anandamide, 2-AG and a Synthetic cannabinoid JWH-018 and the CB_1R Antagonist SR 141716A.



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according to their chemical structure into four main groups.[3] The first of these is the "classical cannabinoid" group which is made of dibenzopyran derivatives and includes Δ^9-THC and HU-210. The second "nonclassical group" consists of bicyclic and tricyclic analogs of Δ^9-THC that lack a pyran ring such as CP 55, 940. The third group comprises of aminoalkylindoles and the prototype of this group is WIN 55, 212-2. The fourth group is the "eicosanoids" which contains arachidonic acid derivatives such as anandamide and 2-AG. Δ^9-THC and CP 55, 940 exhibit little difference in their affinities for CB_1Rs and CB_2Rs, whereas anandamide exhibits marginal selectivity for CB_1Rs, and WIN 55, 212-2 shows modest selectivity for CB_2Rs.[6] Selective CB_1R (e.g., methanandamide)-and CB_2R (e.g., JWH-133) agonists are also available. In addition, development of selective CB_1R (e.g., SR 141716A and LY320135)-and CB_2R (e.g., SR 144528) antagonists has revolutionized the field of cannabinoid research.

Clinical Utility and Abuse Potential of Cannabinoids

Well documented empirical uses of cannabis in Eastern medicine include treatment of cramps, migraine, convulsions and neuralgia to attenuation of nausea and vomiting, decreased intestinal motility during diarrhea and appetite stimulation.[1] Today the cannabinoid system is considered as key regulators of a diverse variety of conditions including nausea and vomiting, pain, anxiety, depression, neurodegenerative diseases.[7] Despite exhaustive research, only a few cannabinoid based therapeutics have reached clinical use. Indeed, in contemporary Western clinical practice, oral formulation of synthetic Δ^9-THC (Marinol=Dronabinol) and its analog nabilone (Cesamet) are used as second line antiemetics for the management of chemotherapy-induced nausea and vomiting (CINV), and as an appetite stimulant in AIDS patients.[8-9] It is postulated that the therapeutic potential of Δ^9-THC may be less for certain conditions. Therefore, "more effective" formulations containing mixed herbal cannabinoid components (Δ^9-THC plus cannabidiol (CBD)) such as the oromucosal spray, nabiximols (Sativex) to alleviate neuropathic pain, overactive bladder and symptoms of multiple sclerosis have been introduced to the clinic.[10] It is further proposed that inclusion of CBD may attenuate some of the side-effects of Δ^9-THC observed in patients. Additional interest in the therapeutic potential of cannabis products is clearly apparent as European (GW Pharmaceuticals , Cambridge, UK) and American (AbbVie Inc., IL, USA) pharmaceutical industries and universities are in the process of developing better delivery techniques (sublingual spray, sublingual tablet or inhaler) to administer Δ^9-THC and its related products. Moreover, the French Pharmaceutical Company Sanofi-Aventis introduced rimonabant (SR 141716A = Acomplia), a cannabinoid CB_1R selective antagonist/inverse agonist, as a new class of appetite suppressive anti-obesity agent in 2006, but was soon withdrawn due to serious psychiatric side-effects.[11] Since conventional drug design normally targets the orthosteric site of CB_1Rs whose stimulation can lead to psychoactivity, development of ligands that target CB_1R allosteric sites (e.g., ORG27569 and GAT211) may provide better clinical opportunities.[7] Another route for future cannabinoid drug development is the utilization of agents that specifically modulate the synthesis and/or metabolism of endocannabinoids. However, thus far and unlike animal studies,[12] available clinical findings have failed to demonstrate efficacy.[13]

Over 181 million people in the world and 22 million in the U.S. are classified as cannabis users.[14] Although, the long-term use of cannabis products are associated with both gastrointestinal (nausea and vomiting, 10-16%)[15] and psychiatric disorders (20-40%),[16] oftentimes published literature lists benefits and ignores significant gastrointestinal side-effects such as: i) increased incidence of nausea and vomiting (70-80%) resulting from drug interactions when cannabis users are prescribed other medicines;[17] ii) vomiting and nausea can be induced by cannabis products in patients;[18-19] iii) rebound and more severe nausea/vomiting as tolerance may develop to antiemetic effects of Δ^9-THC during chemotherapy;[20-23] iv) severe nausea and vomiting may also occur following chronic consumption of large doses of cannabis products with increased content of Δ^9-THC - i.e. 0.75-3.4% pre-1993, to 8.8-16% in 2008;[24-25] v) extremely severe and untreatable form of vomiting, the "cannabinoid-induced hyperemesis syndrome (CHS) can develop and according to google scholar in the past thirteen years over 1310 publications in diverse languages has accumulated regarding CHS; and vi) severe vomiting due to use of synthetic cannabinoids (SCBs) such as JWH-018, JWH-073, UR-144, HU-210 which can be 2-200 times more potent than Δ^9-THC.[26] The SCBs are a growing class of highly potent and efficacious cannabinoid agonists that have been falsely marketed as 'safe' and 'legal' alternatives to marijuana.[27] As early as 2004, SCBs were promoted by Internet retailers and European 'head shops' as meditation potpourris and tropical incense products under names such as K2 and Spice. As with Δ^9-THC, these agents produce their psychoactive effects *via* CB_1Rs. The SCBs were introduced to European consumers in 2006 and in the U.S. in 2008. Spice/K2 refers to the recreational use of potent designer cannabinoids (e.g., JWH-018, JWH-073, UR-144, HU-210, etc.) spiked on inert herbs. In 2012 the Drug Abuse Warning Network (DAWN) and others reported a significant increase in number of emergency visits in the U.S. hospitals and poison centers involving spice/K2 products for 2010 with 11,406 visits, the most common symptoms being gastrointestinal (severe nausea and vomiting), cardiovascular, neurological and renal problems.[27] A comprehensive ban of spice products in the USA occurred in July 2012. To date over 150 SCBs are identified and are clearly not safe marijuana alternatives.[27]

Cannabinoid-Induced Hyperemesis Syndrome

CHS was first reported in 2004 by Allen and co-workers.[28] CHS is apparently a rare gastrointestinal disorder which manifests with recurrent intense nausea, intractable vomiting and abdominal pain. CHS is often accompanied with compulsive hot bathing (or hot showers) which seems to temporary relieve patients' symptoms. Relief of gastrointestinal symptoms appears to be temperature-dependent since the hotter the water, the better the antiemetic effect.[28-29] Taking hot baths or showers is a learned behavior and may not be present at the initial presentation. However, once the behavior develops, baths/showers may last

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for hours and may be repeated up to 20 times per day.[29] The vomiting episodes are cyclical, occurring every few weeks or months and can be preceded by a period of intense morning nausea. The vomiting becomes bilious and culminates in intractable retching which may last for hours. Most episodes resolve within 48 hours, but some may last several days.[29] The frequency of major characteristics of CHS is as follows: i) history of regular cannabis use 100%; ii) cyclic nausea and vomiting 100%, male predominance 85.1%, abdominal pain 85.1 %.[30] CHS not only occurs in adults, but also in pediatric and pregnant women populations which further highlight the gastrointestinal side-effects of chronic cannabinoid use.[31-33] Although, most published cases of CHS are case reports involving 1-10 patients, in 2012 two independent studies from the Mayo clinic involved 98[34] and 82 different patients, respectively.[35] These patients were admitted because of intractable vomiting, highly-associated with chronic marijuana use. Nonetheless, CHS is currently under reported because its diagnostic symptoms remain largely unknown to many physicians. Patients with CHS have often been diagnosed only after extensive and repeated testing for their symptoms (endoscopies, colonoscopies, swallowing studies, abdominal ultrasounds, CTs, MRIs, laboratory tests and/or psychiatric evaluations) over a period of several years with no identified etiology to the point where physicians would perform surgery.[34,36]

Is Cannabinoid-Induced Hyperemesis Similar to Cyclic Vomiting Syndrome?

The detailed phasic nature of cannabinoid hyperemesis syndrome is similar to that described for cyclic-type vomiting syndrome (CVS). CVS is a disorder characterized by recurrent, self-limited episodes of severe nausea and vomiting interspersed with symptom free periods.[37] While CVS has been mainly studied in pediatric patients, this enigmatic syndrome represents a continuum affecting all ages, including young and middle aged adults. Among psychiatric comorbidities (e.g., panic attacks, depression) and migraine headaches in CVS, affected patients also exhibit a stereotypical pattern of multiple episodes of vomiting with frequent visits to emergency departments for relief of nausea, vomiting and dehydration. Unlike the other forms of CVS, published literature suggests that patients suffering from CHS are not likely to have a history of migraine headache but suffer from the peculiar desire for hot showers or baths. However, a recent comparative review of the literature indicates that many of the CVS patients also desire to stop their vomiting by hot showers.[38] Thus, detailed clinical follow-up is required to distinguish CHS from CVS and whether the two conditions arise from the same clinical etiology.

Is Abdominal Pain Associated with Hyperemesis Syndrome?

As discussed above one prevalent symptom of CHS in 85% of patients is abdominal pain.[30] For centuries marijuana products have been empirically prescribed as an analgesic for the treatment of abdominal pain.[6] Visceral hypersensitivity of the colon is a consistent and important mechanism in the generation of abdominal pain in 33-65% of irritable bowel syndrome (IBS) patients.[39] Visceral pain in IBS patients probably results from the activation of nociceptors located in the thoracic, pelvic, or abdominal viscera, which are sensitive to distension, ischemia, and inflammation.[40] Common symptoms in IBS patients include chronic abdominal pain, constipation and/or diarrhea. Inflammatory bowel disease (IBD) is a group of idiopathic inflammatory conditions that occur in the small intestine and colon which comprise of Crohn's disease, ulcerative colitis, nonspecific colitis, collagenous colitis and eosinophilic colitis.[41] The common symptoms of IBD includes chronic abdominal pain, diarrhea, rectal bleeding, weight loss and fever. The etiology of IBD is thought to be caused by genetic and environmental factors that cause abnormal immunological response.

In general the endo-, phyto- and synthetic cannabinoids through activation of CB_1Rs play a part in the regulation of food intake, nausea and emesis, gastric secretion and gastroprotection, gastrointestinal motility, ion transport, visceral sensation, intestinal inflammation, and cell proliferation in the gut.[42-43] In addition, CB_2Rs are thought to serve not only as an important role in immune function and inflammation, but also in regulating abnormal motility, modulation of intestinal inflammation, and reducing visceral sensitivity and pain.[42,44-45] Cannabinoids have been shown to have an analgesic effect at both the spinal and peripheral levels in both the gastrointestinal tract as well as other areas of the body.[40] Moreover, in a rat model of acid-induced colitis both CB_1R and CB_2R agonists have been shown to reduce basal sensitivity and colitis-induced hypersensitivity, whereas their corresponding selective antagonists increased visceral hypersensitivity to rectal distension.[46-47] On the other hand, CB_1Rs but not CB_2Rs, are involved in the modulation of basal visceral sensation in a rodent model of visceral pain induced by colorectal distension.[48] In addition, Δ^9-THC can prevent diclofenac-evoked gastric inflammatory damage in rats at doses insufficient to cause common cannabinoid side effects.[49] Likewise, Δ^9-THC has been shown to reduce pain threshold in functional chest pain patients.[50] These antinociceptive effects of cannabinoids suggest that CBRs probably play a role in visceral pain. However, in both healthy volunteers and IBS patients' Δ^9-THC does not alter visceral rectal perception[39] and may even cause increased pain perception during colorectal distention in IBS patients.[51] In addition, Δ^9-THC can reduce fasting colonic motility but not pain scores during colorectal distention in IBS patients.[52] Since Δ^9-THC in non-CHS patients has antiemetic properties, it seems unlikely that abdominal pain would be the main cause in CHS since vomiting is not a typical symptom of either IBS or IBD.

Potential Mechanisms of Cannabinoid-Induced Hyperemesis Syndrome (CHS)

Since Δ^9-THC and related cannabinoid $CB_{1/2}$ receptor agonists have broad-spectrum antiemetic efficacy *via* stimulation of cannabinoid CB_1 receptors, the paradoxical mechanism(s) by which CHS occurs is not currently understood. Darmani[32] and Allen et al[28] have previously suggested several potential mechanisms for the etiology of CHS. In brief, these include: i) cannabinoids

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pharmacokinetics since on chronic exposure these highly lipid soluble drugs can accumulate in the brain; ii) cannabinoid pharmacodynamics involving the partial agonist nature of Δ^9-THC on CB_1Rs and development of tolerance to antiemetic effect of cannabinoids following repeated exposure could precipitate vomiting since challenge with the CB_1R antagonist/inverse agonist SR141716A (Acomplia) can evoke vomiting in dogs chronically-treated with Δ^9-THC[53] or in naïve least shrews[54] and in patients[11]; iii) abrupt withdrawal from chronic Δ^9-THC exposure may cause CHS since sudden withdrawal can cause vomiting in patients;[55] and iv) intraperitoneal administration of the endocannabinoid 2-AG can evoke vomiting in the least shrew in a dose-dependent manner probably *via* its rapid metabolism to arachidonic acid which is also a potent emetogen in this species.[56] Moreover, the cancer chemotherapeutic agent cisplatin can increase 2-AG but not anandamide levels in the least shrew brain.[57] However, selective elevation of 2-AG by inhibition of its major metabolic enzyme monoacylglycerol lipase, have been shown to suppress lithium chloride evoked vomiting in the house musk shrew (*Suncus murinus*).[58]

Cannabinoid-Induced Hyperemesis Syndrome (CHS) Treatment

The empirical strong association between CHS and chronic cannabis use is apparently evidenced by the cessation of the syndrome following cannabis discontinuation in most patients, and the recurrence of the syndrome with cannabis challenge.[30,37] On the surface, the hyperemetic activity in CHS appears to be an enigma since both phyto- (e.g., Δ^9-THC or Δ^8-THC) and synthetic (nabilone, levonantradol, or nonabine)-cannabinoids possess significant antiemetic activity both in the clinic and in animal models of emesis.[8,59] However, most antiemetics used in the clinic behave as antagonists of their corresponding emetic receptors, whereas cannabinoids act as agonist antiemetics. The receptor mechanism by which Δ^9-THC and its structural analogs (WIN55-215; CP 55, 940; methanandamide) produce their antiemetic effect was initially revealed in the least shrew in our laboratory.[8,40] As discussed earlier in the clinical setting, acute use of THC with other drugs,[17] its acute and/or chronic use,[19,60-61] or withdrawal from its exposure,[24-28] have been reported to evoke nausea and vomiting in some patients.[19,60-61] However, the reported severity of vomiting in CHS[28] appears to be much greater than what is reported above.

Although, initial accounts indicated that CHS patients do not adequately respond to conventional antiemetics (e.g., metamizole, metoclopramide, alizaprid, dimenhydrinate, ondansetron), more recent findings, albeit often a single case or case series, indicate that the transient receptor potential vanilloid 1 (TRPV1) receptor antagonist capsaicin,[62-63] the dopamine D_2 receptor antagonist haloperidol,[64-65] and the adrenergic b receptor antagonist propranolol,[66] can prevent the evoked vomiting.

CONCLUSION

Significant published evidence indicate that exposure to diverse antiemetic cannabinoids may evoke moderate nausea and vomiting in some patients, while in a few patients a more severe form of nausea and vomiting in the form of CHS develops. For an antiemetic to evoke vomiting under certain conditions remains an enigma. These gastrointestinal side-effects are probably due to intake of chronic large doses of marijuana-related products, or exposure to more potent synthetic analogs of Δ^9-THC in the form of SCBs which have been incongruously introduced as "safe and alternative forms of Δ^9-THC" as K2 and Spice products in more recent years.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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