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REVIEW ARTICLE

The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review

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ABSTRACT

The word "cannabinoid" refers to every chemical substance, regardless of structure or origin, that joins the cannabinoid receptors of the body and brain and that have similar effects to those produced by the *Cannabis* plant and based on their source of production, cannabinoids can be classified into endocannabinoids, phytocannabinoids and synthetic cannabinoids. Synthetic cannabinoids represent the largest class of drugs detected through the EU Early Warning System with a total of 190 substances notified from 2008 to 2018 and about 280 have been reported worldwide to the United Nations Office on Drugs and Crime. Sprayed on natural herb mixtures with the aim to mimic the euphoria effect of cannabis and sold as "herbal smoking blends" or "herbal incense" under brand names like "Spice" or "K2", synthetic cannabinoids are available from websites for the combination with herbal materials or more recently, for the use in e-cigarettes. Currently labeled as "not for human consumption" to circumvent legislation, their legal status varies by country with many government institutions currently pushing for their control. However, due to the emergence of new substances, it requires a constant update of the list of controlled drugs. Little is known about how these substances work and their toxic effects in humans and the same product could vary not only in the amount and in the type of substance added. In the last years, synthetic cannabinoids have been associated with deaths and acute intoxications in Europe and, despite a range of new measures introduced in this area, continue to represent a challenge to current drug policy models. These synthetic substances are much more potent than natural cannabis, as well as displayed greater efficacy, acting as full agonists at the cannabinoid receptors. It is possible that, along with being highly potent, some may also have long half-lives, potentially leading to a prolonged psychoactive effect. The present work provides a review on existing literature about the development of synthetic cannabinoids as substances of abuse, current patterns of abuse and their legal status, chemical classification, and some pharmacological and toxicological properties.

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Table of contents

1. Introduction

According to the World Health Organization (WHO), cannabis is the most commonly cultivated, trafficked, and abused illicit drug and, its consumption has an annual prevalence rate of approximately, 147 million individuals or nearly 2.5% of the global population (WHO 2016).

Being the most thoroughly studied plant of all time, cannabis have been used for recreational, medicinal, or scientific purposes due to its bioactive components (Thomas and ElSohly 2015). Most of the biological activity attributed to cannabis have so far been linked to cannabinoids. The term "cannabinoids" represented the group of typical terpenophenolic C_{21} compounds present in cannabis plant, their carboxylic acids, analogs, and transformation products. However, an extended classification comprising new classes, groups, and

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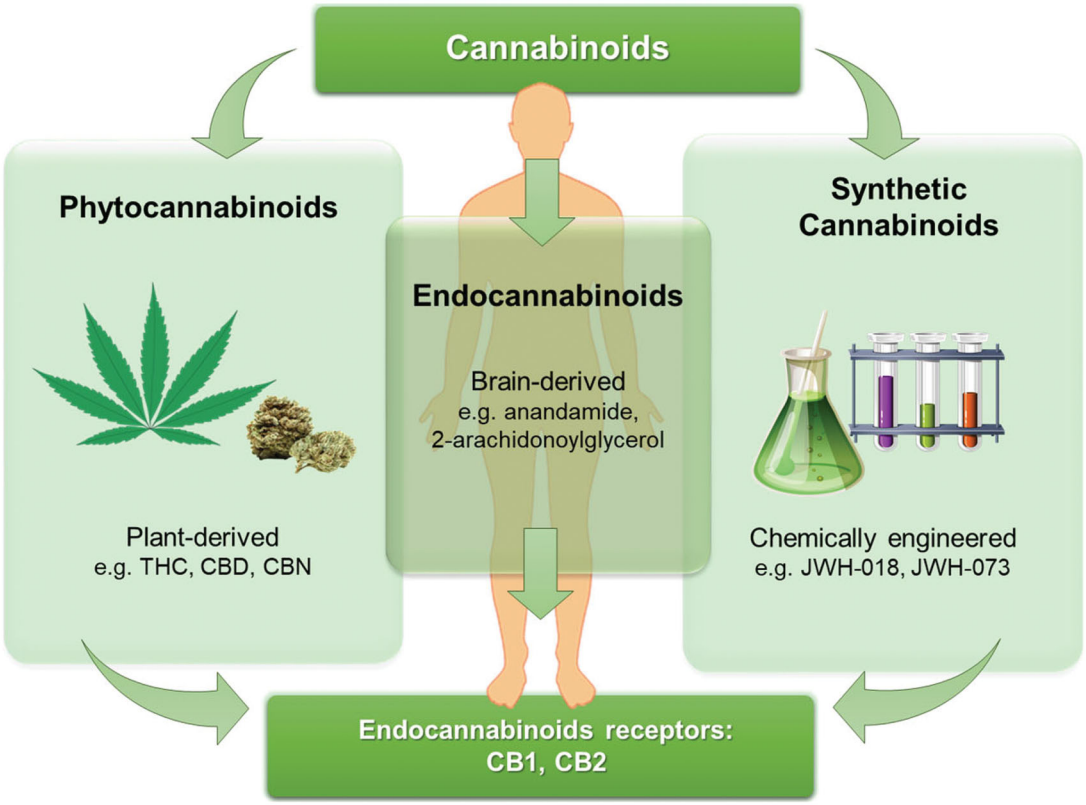


Figure 1. Types of cannabinoids: phytocannabinoids, endocannabinoids and synthetic cannabinoids [adapted from (Clinic 2016)] *(adapted from (*Chakravarti et al. 2014*))*.

subgroups of cannabinoids was proposed for better representation of their structural variety (Shevyrin and Morzherin 2015). Cannabinoids, now constitute the whole set of herbals, endogenous, natural and synthetic ligands of the cannabinoid receptors, belonging to a wide variety of chemical families (Lambert 2009; Mander and Liu 2010; Halawa et al. 2018). Based on their source of production, cannabinoids can be classified into three groups: endocannabinoids, phytocannabinoids and synthetic cannabinoids (Figure 1) (Chakravarti et al. 2014).

Endocannabinoids (or endogenous ligands) have been identified as having roles in various physiological and pathological processes. Largely due to the association of the effects of cannabis administration on mental states, the impact of the endocannabinoid system on central nervous system (CNS) has been the most intensively studied. Defined as endogenous lipids that activate cannabinoid receptors, this group of cannabinoids affects the behavior in a way that at least partially recapitulates the effects produced by the psychoactive components of cannabis (Lu and Mackie 2016; Hourani and Alexander 2018).

N-Arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) the first endogenous agonists to be discovered, are saturated or unsaturated acid amides that present physiological properties very similar to natural and synthetic exogenous cannabinoids, such as those found in cannabis plant (Nicolussi and Gertsch 2015; Shevyrin and Morzherin 2015). These natural agonists are lipid-based molecules containing long-chain polyunsaturated fatty acids, amides, esters and ethers, and act as neuromodulators or retrograde neurotransmitters that bind to cannabinoid receptors and cannabinoid receptor proteins that are expressed throughout the mammalian CNS (including the brain) and peripheral nervous system (PNS) (Chakravarti et al. 2014; Lu and Mackie 2016; Aizpurua-Olaizola et al. 2017; Zou and Kumar 2018).

Phytocannabinoids, are only known to occur naturally in significant quantity in cannabis plant (Niaz et al. 2017). Chemically complex, this psychoactive plant contains more than 500 components, of which over 120 cannabinoids have been isolated (Maroon and Bost 2018). The total number of natural compounds identified or isolated from cannabis has continued to increase over the last few decades (Cooper 2016; Shivangi Bajpai 2016; Wang et al. 2017). Δ9-tetrahydrocannabinol (Δ9-THC), cannabinol (CBN), cannabidiol (CBD) and cannabigerol (CBG) are the most abundant phytocannabinoids.

The potential therapeutic and clinical application of phytocannabinoids has been greatly appreciated in pharmaceutical and medical fields, since its metabolites show potent bioactivities on human health (Andre et al. 2016; Zou and Kumar 2018). Since the discovery of Δ9-THC, the pharmaceutical industry undertook several studies for the development of synthetic analogs, with the aim of creating compounds that retained the biological activity of natural cannabinoids but devoid of psychoactive side effects. These new molecules included not only compounds structurally similar to the already known phytocannabinoids, but also compounds with different chemical structure. These human-made mind-altering chemicals are called synthetic cannabinoids (SCs) (Messina et al. 2015).

Given the growing popularity of cannabinoid-based drugs use, there is a lack of comprehensive scientific studies on SCs

toxicity and abuse liability, posing a threat to public health, once the risks correlated to its consumption are often unexpected and unknown, so further research is needed in this field (Feng et al. 2017; Montesano et al. 2017; Cohen and Weinstein 2018). Clinical and forensic toxicology laboratories are continuously confronted by analytical challenges when dealing with this kind of substances. The huge number of potential compounds to be investigated, the lack of available chemical reference standards and the evolving nature of these substances, are some of the major challenges faced in clinical and forensic toxicology laboratories (Gonçalves et al. 2019).

The purpose of this work is to provide a thorough report on the currently known cannabimimetics or SCs and to review their chemical, pharmacological, and toxicological properties.

2. The emergence of synthetic cannabinoids

SCs emerged in the 1970s when researchers were first exploring the endocannabinoid system and attempting to develop new treatments for cancer pain (Lafaye et al. 2017; Papaseit et al. 2018). The first SCs were synthesized by academic laboratories or the pharmaceutical industry (Papaseit et al. 2018). The synthesis of selective cannabinoid receptor agonists with particular reference to their antinociceptive activity started at Pfizer in 1974 with cyclohexylphenol (CP 55,940) followed by the HU-210 compound synthetized in 1988 by Mechoulam's group at the Hebrew University (De Luca and Fattore 2018). John W. Huffman, Professor Emeritus of Chemistry at Clemson University in South Carolina and his team of researchers were involved in the synthesis of novel cannabinoids with some of the properties of Δ9-THC (Wiley et al. 2011). Huffman's research focused on synthesizing small molecules that could be applied as new pharmaceutical analgesics, particularly molecules that bind to cannabinoid brain (CB_1) and peripheral (CB_2) receptors. JWH-018 is one among several hundred analgesic drug candidates synthesized by him (Nagarkatti et al. 2009; Preedy 2016a).

More than 450 SCs compounds were synthesized over the course of 20 years, and many of the SCs have the initials of the person/institution responsible for its synthesis, for example, 'JWH' compounds by John W. Huffman, AM-2201 by Alexandros Makriyannis, HU-210 at Hebrew University, CP 47,497 by Charles Pfizer or WIN55,212-2 at Sterling – Winthrop, Inc. (Papaseit et al. 2018).

Scientists' continuing development of synthetic variants of Δ9-THC as research tools, provided better understanding of the physiological cannabinoid control system in the human body and brain and opened a path of elucidating this natural regulatory mechanism in health and disease. As these compounds were discovered, the information was made publicly available through publications or patents, it resulted in great advances in the understanding of the endocannabinoids system and in potential therapeutic options without the adverse side effects. Unfortunately, multiple underground laboratories have utilized this research for clandestine purposes with the production of illicit compounds used as alternatives for marijuana (Parker 2017; Zou and Kumar 2018). Moreover, the rejected substances, as drug candidates from pharmaceutical industry, have instead appeared on the drug market as unregulated and illicit drugs.

The structure of the cannabinoid system makes it receptive to a diverse set of compounds, making it an easier target for a set of synthetic drugs when compared to other systems. In this sense, the research on SCs compounds is involuntarily responsible for the growing epidemic of these synthetic drugs, with no signs of stopping (Zou and Kumar 2018).

3. Synthetic cannabinoids as drugs of abuse: epidemiology, pattern of use and legal status

Around the year 2000, SCs appeared on the illicit drug market, where their prevalence had long been underestimated. However, it wasn't until 2008 that forensic investigators in Germany and Austria first detected the synthetic cannabinoid JWH-018 in a herbal product. Since then, their place in the market has steadily increased (EMCDDA 2017; Lafaye et al. 2017).

Part of a group of drugs called 'new psychoactive substances' (NPS), SCs constitute the largest category in terms of the number of different substances monitored by the EU Early Warning System with a total of 190 substances notified from 2008 to 2018 and about 280 have been reported worldwide to the UNODC (Cannaert et al. 2019; EMCDDA 2019b; UNODC 2020) (Figure 2). According to the UNODC, out of the 739 analyzed NPS in 2016, 32% were SCs (32%) and despite the decrease in the number of new reported cannabinoids, these class of substances were the most frequently seized NPS in 2016, with just over 32 000 reports (EMCDDA 2018).

A large number of additional analogs have been derived from the published structures of the pharmaceutical candidates, emerging new SCs with names probably chosen by those to help market the products. Remarkable examples of this are "AKB-48" and "2NE1", whose names derive from Japanese and South Korean feminine bands, respectively, as an alternative to their chemical names, APINACA that comes from N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide and APICA that comes from N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide. Another example is the synthetic compound XLR-11 that appears to have been named after the first liquid fuel rocket developed in the USA for use in aircraft, perhaps alluding to the vendor's intention for those who consume the substance (Carlsson 2016; EMCDDA 2017; Iversen 2018).

Commonly known as synthetic marijuana, SCs have been sold as "herbal incenses" or "herbal smoking mixtures" under different brand names. "Spice" and "K2" were the earliest in a series of SCs products sold in many European and US countries (Spaderna et al. 2013; Brents and Prather 2014). Since then a high number of similar products such as "Kronic", "Cloud 9", "Black Mamba", "Zombie", "Sence", "Blue Lotus", "Mojo", "Moon Rocks", "Kaos", "Voodoo", among others have been developed (Chopra 2015; Mills et al. 2015; Sanders and Stogner 2016; Papaseit et al. 2018).

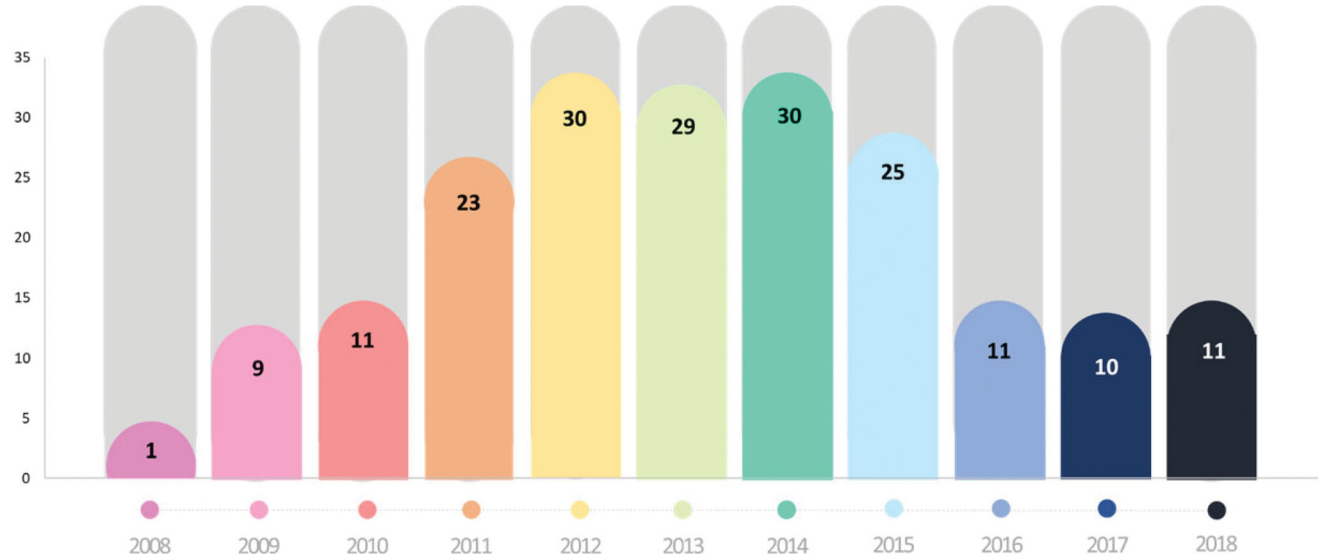


Figure 2. Number of synthetic cannabinoids reported to EMCDDA between 2008-2018 [adapted from (EMCDDA 2019a, 2019b)].

In general, SCs products are sold in brightly colored metal-foil packages containing about 0.5 to 3 g of finely cut green/brown plant material (Duccio et al. 2018). Damiana (*Turnera diffusa*) and Lamiaceae herbs such as *Melissa*, *Mentha* and *Thymus* are commonly used as the plant base for the smoking mixtures (EMCDDA 2017). The dried plants present in these blends have no psychotropic effect in most cases, just giving the illusion of being of natural origin, being no more than mere vehicles for SCs. SCs are usually added to the plant material by soaking or spraying, normally on an industrial scale using solvents such as acetone or ethanol to dissolve these substances, but in some cases their solid form (crystalline powder) was added to plant material, leading to an inhomogeneous mixture (EMCDDA 2017; Britannica 2018). Once the solvent evaporates and the plant material is dried with SCs attached to them, the product can be crushed and packaged, often in very different concentrations within the same package (originating parts where the concentration of SCs is very high, called 'hot spots') (Musah et al. 2012; Spaderna et al. 2013). Then, the products are ready to be sold on the internet by "legal high" retailers in bricks-and-mortar head shops and usually labeled with a disclaimer indicating that the contents are not for human consumption (Araújo et al. 2015; Cooper 2016; EMCDDA 2017).

The herbal mixtures that are sprayed with SCs and are proposed as legal alternatives to marijuana are often smoked by users. Currently, other available SCs preparations look like hashish or are found in the form of capsules, tablets, powders and more recently in liquid-filled cartridges for use in electronic cigarettes (e-cigarettes) as a new alternative for tobacco withdrawal, and also as a more discreet way of consumption. These new trend is called, "buddha-blue", "C-Liquid", "Herbal e-Liquid", or others and is discussed on drug-user forums (Debruyne and Le Boisselier 2015; EMCDDA 2017; Duccio et al. 2018; Scourfield et al. 2019). Apart from herbal smoking blends, some consumers prefer homemade mixtures, using some "purified" powders of SCs sold on websites, solved in alcohol and sprayed on herbals (Debruyne and Le Boisselier 2015).

In addition to SCs, some herbal mixtures have been shown to contain numerous other compounds such as amides of fatty acids (e.g. oleamide, palmitoyethanolamide), vitamin E to mask detection of SCs, flavors (e.g. menthol, eucalyptol, vanillins), various preservatives (e.g. benzophenone, benzyl benzoate, hydroxybenzoic acid) (Zawilska and Wojcieszak 2014), sympathomimetic agents such as clenbuterol, a potent β-adrenergic receptor agonist, *o*-desmethyltramadol and mitragynine which are μ-opioid receptor agonists, and sedative benzodiazepines such as phenazepam (John 2012; Manseau 2016a). Unknown to users, SCs have also been sold as ecstasy/MDMA and other illicit drugs. In some cases, this has led to severe poisoning. Potent opioids have also been identified in smoking mixtures sold in Europe, which users will often be unaware of (EMCDDA 2018).

Compared with other new drugs on the market, the increase in consumption of SCs was particularly remarkable (Lafaye et al. 2017). Motivations for their use are typically associated with curiosity, low cost, positive drug effects including relaxation and feeling a pleasant high, belief of the products general safety, and the potential for passing drug testing (Cohen and Weinstein 2018).

Regarding to routes of administration, inhalation by smoking SCs remains the most common method of use, due to the rapid onset of pharmacological effects (Auwärter et al. 2009; UNODC 2011). The adaptation of e-cigarette devices to vape e-liquids infused with SCs has been gaining popularity over the last few years, especially among young people (EMCDDA 2017; Lefever et al. 2017; Blundell et al. 2018; Breitbarth et al. 2018). Oral administration is another way to use SCs but leads to a delayed onset of the effects due to extensive hepatic first pass metabolism, before reaching systemic circulation (UNODC 2011; Obafemi et al. 2015). Rectal absorption has also been reported in the literature, but is less commonly used (Phillips et al. 2017).

Estimations on the prevalence of SCs use are very difficult to attain and the available data are limited to analysis of case reports, calls to poison control centers, emergency department visits and drug use surveys (Manseau 2016c;

EMCDDA 2017). In United States (US), poison control centers receive annually thousands of calls related to SCs exposures. According to the American Association of Poison Control Centers (AAPCC), in 2015, 7 795 calls associated with SCs intoxications were registered (Synthetic Cannabonoid Data 2019). In 2010, the Drug Abuse Warning Network (DAWN) registered 11 406 cases involving SCs, of which 75% were adolescents and young adults ages 12–29 (SAMHSA 2012).

The Toxicology Investigators Consortium (ToxIC) registered about 600 cases involving SCs exposure, either as the sole toxicologic agent or as a component of a multiagent exposure (Riederer et al. 2016; Farrugia et al. 2017, 2018). According to EMCDDA (2017), there are notable differences between the prevalence of SCs use between the European and US drug markets. In United States, a study in which data were examined from a representative sample of high school students revealed that from 2011 to 2013, 10.1% of high school seniors reported past-year use of SCs, with 3% of high school seniors reporting more frequent use (Palamar and Acosta 2015). In Spain, a global survey on drug use among students (aged 14 to 18), with a sample of 37 486, reported low levels of SCs use with a prevalence rate of 0.8% in 2014, a slight decrease from 1.4% in 2012 and 1.1% in 2011. In 2013, also in Spain, a general population survey showed that 0.5% of the 23 136 respondents (aged 15 to 64) reported lifetime use of "Spice". In France, in 2014, a survey of young people (aged 17 years) showed that 1.7% of the sample population had already used SCs (EMCDDA 2017).

Despite the great importance of survey research, these studies have some limitations. The small sample size and the retrospective design are two primary limitations of these studies. To date, some of prevalence studies have been focused on lifetime or past-year use. Data on current use, commonly defined by national surveys as use within the past 30 days, are needed to determine which individuals are at highest risk for use and more immediate adverse outcomes. In this sense, current use is an important focus because despite their use appears to be declining, newer and more dangerous SCs continue to emerge, and poisonings related to use have remained prevalent (Palamar et al. 2017).

Figure 3 summarizes the major historical events associated with SCs.

3.1. Legal status of synthetic cannabinoids

As the number of NPS detected globally has risen exponentially, the policy response of assessing and prohibiting each new substance individually has become increasingly unworkable (Barratt et al. 2017).

In response to health-related problems associated with the consumption of SCs across Europe and the US government agencies have taken legal steps to limit the sale and distribution of these substances (Caviness et al. 2015). In early 2009, SCs started to be banned and their use controlled, with Austria and Germany being the first (Zimmermann et al. 2009; Seyit et al. 2016). Other countries including France, Luxembourg, Poland, Lithuania, Sweden, and Estonia followed later and banned these compounds (Fattore and Fratta 2011; Manseau 2016b). In an attempt to disrupt the availability of new as-yet-unscheduled substances, Australia was the first state to enacted generic or blanket ban legislation that prohibits all 'psychoactive substances' that are not already regulated or belong to exempt categories (Barratt et al. 2017).

In the United Kingdom, the so-called "first generation" of SCs, including JWH-018, was controlled at the end of 2009 and further legislation to control the "second generation" products, including AM-2201 and UR-144, was enacted on February 2013 (Waugh et al. 2016). Far from stopping their sales, manufacturers of these products developed new cannabimimetic substances, such as PB-22, 5 F-PB-22, 5 F-APICA and 5 F-AKB-48, to replace those that were banned under previous controls (Advisory Council on the Misuse of Drugs. 'Third generation' synthetic Cannabinoids. 2014; Waugh et al. 2016). Currently, these substances are permanently controlled in the United Kingdom as Class B drugs under the Misuse of Drugs Act 1971 (Home Office 2018).

Given the complexity and highly dynamic nature of the NPS market, Portugal adopted specific legislation to stop the rapid proliferation of NPS. The Autonomous Region of Madeira was the first region of the country to take specific action against NPS. According to regional news, NPS were responsible for 4 deaths and around 190 hospitalizations up until October 2012, forcing the government of Madeira to take legal measures through the implementation of the Legislative Decree n°. 28/2012 M of 25th October, which

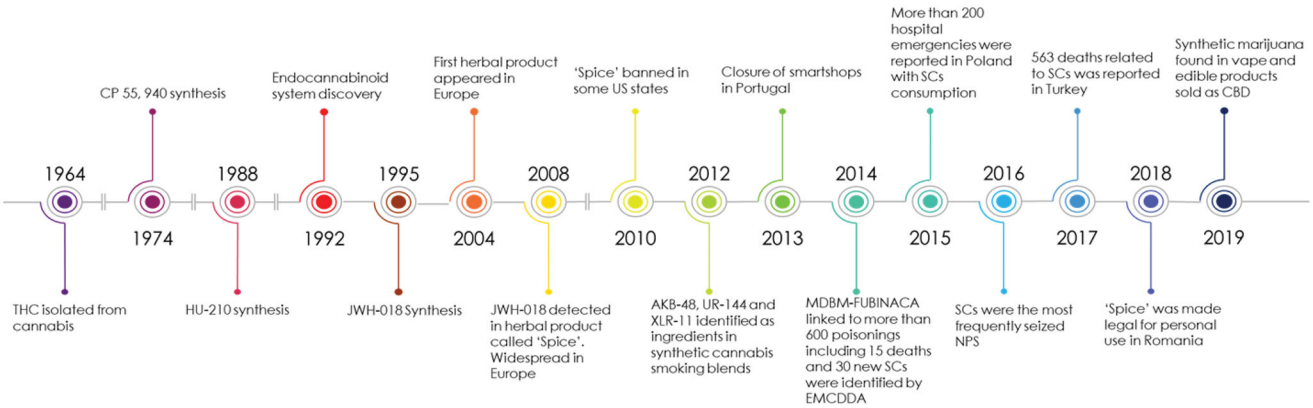


Figure 3. Timeline of the main events related to synthetic cannabinoids [adapted from (Fattore and Fratta 2011)].

prohibited the sale and distribution of such substances, hindering their trade and mitigating the number of emergency cases related to NPS in the region (Henriques et al. 2018). In the following year, new legislation was introduced in Portugal (Decree-Law n°. 54/2013 of 17th April), which prohibits the production, export, advertisement, distribution and sale of 159 NPS, 45 of them are SCs (Garner et al. 2009). These measures have helped to reduce the supply of NPS by seizing stock and closing down the so-called "smartshops".

In the United States, prior to 2010, SCs were not controlled by any State or at the Federal level. However, with the evident harm caused by K2 products, along with the initial analytical studies identifying JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol, as the main psychoactive components in these products, promptly led the Drug Enforcement Administration (DEA), on March 1, 2011 to temporarily place these five compounds on the list of controlled substances under Schedule I of the Controlled Substances Act (CSA) (Drug Enforcement Administration (DEA). Schedules of Controlled Substances: Temporary Placement of Five Synthetic Cannabinoids Into Schedule I. 2011).

By 2012, the banned compounds were replaced by structurally related ones, such as AM-2201, JWH-122, JWH-203, JWH-210 and RCS-4, apparently indicating that manufacturers of these products have remained one step ahead of SCs regulation (Musah et al. 2012; Brents and Prather 2014). However, in June 2012, Congress passed legislation to permanently schedule several synthetic compounds including the five SCs that the DEA had temporarily scheduled in March 2011 and 10 additional SCs (Brents and Prather 2014; Sacco and Finklea 2016).

Currently, the list of controlled substances under Schedule I of the CSA include 221 substances, of which 43 are cannabimimetic agents (United States Drug Enforcement Administration (DEA). Controlled Substances - Alphabetical Order. 2019). The DEA continues to use all available resources to address the issue of trafficking and abuse of NPS to safeguard the public from hazards associated with these substances.

Despite the legislative efforts against the NPS problem, new SCs continue to emerge on the clandestine drugs market. Differences in country-specific legislation and its capacity to implement them open opportunities for trafficking NPS and pose a major obstacle for effective law enforcement interventions (Tettey and Levissianos 2017).

3.2. Chemical classification

Mostly lipophilic and nonpolar, in general SCs consist of about 22 to 26 carbon atoms, which makes them volatile when smoked with a side chain of 4–9 saturated carbon atoms being a common finding in these compounds (EMCDDA 2015). From the chemical point of view, many of the SCs are not structurally related to the so-called "classical" cannabinoids like Δ9-THC. In fact, the main differences lead to possess increased biological activity (Salomone 2015; EMCDDA 2017).

In order to systematize the chemical structures of the occurring SCs, EMCDDA presented a model describing of the diverse structural types. This generic model structure consists of four key structural elements, namely "the core and substituents", "the link", "the ring and substituents" and "the tail" (Figure 4) which denote altering positions. This method of assigning a code name to each component allows the chemical structure of the cannabinoid to be identified without the long chemical name (EMCDDA 2017).

Even though most of the reported cannabinoids follows the general structure depicted in Figure 4, there are also other SCs with affinity for the cannabinoid receptor that have other base structures (Carlsson 2016).

SCs family is extremely large, including numerous substances belonging to various chemical groups and subgroups. This variety of diverse structures served as the basis for a classification system that became the current standard at the beginning of the 21st century (Hess et al. 2016). In Table 1 are presented the main classes and some examples of SCs according to this classification system, namely classical cannabinoids, nonclassical cannabinoids, hybrid cannabinoids, aminoalkylindoles, eicosanoids and miscellaneous cannabinoids.

Developed in the 1960s classical cannabinoids were originally the only cannabinoids synthesized. Based on a dibenzopyran ring, these tricyclic derivatives include compounds that occurs naturally in cannabis plant like nabilone or dronabinol (or Δ9-THC) or synthetic analogs of these compounds like

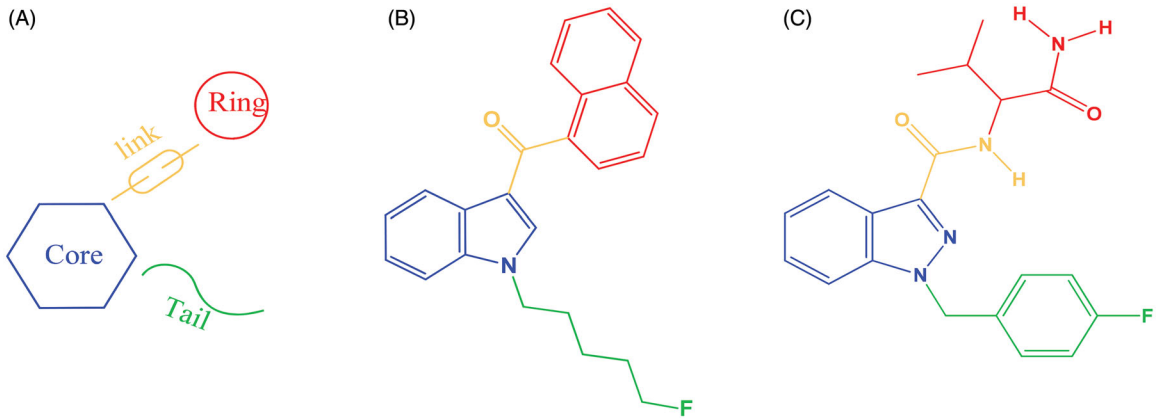


Figure 4. (A) EMCDDA structural model of SCs; (B,C) Structures of the SCs AM-2201 and AB-FUBINACA according to EMCDDA model, respectively [adapted from (EMCDDA 2017)].

Table 1. The main classes of SCs (UNODC 2011; Presley et al. 2013; Messina et al. 2015; ElSohly et al. 2019).

Synthetic Cannabinoid Class		Examples
Classical Cannabinoids	Similar structure to Δ9-THC; Derivatives of dibenzopyran	HU-210; HU-211; HU-208; HU-311; AM-906, AM-411, O-1184
Nonclassical Cannabinoids	Structure quite similar to classical cannabinoids; Derivatives of cyclohexylphenol; Bicyclic and tricyclic analogs to Δ9-THC	CP 47,497 and its analogs; CP 55,940, CP-55,244
Hybrid Cannabinoids	Combine structural features of both classical and nonclassical cannabinoids	AM-4030
Aminoalkylindoles	No structural similarity with Δ9-THC	WIN 55,212-2; AM-1241, JWH-015
Eicosanoids	Synthetic analogs of endocannabinoids such as anandamide	methanandamide
Others	Cannabinoids constituting no classes in their own right: diarylpyrazoles, naphtoylpyrroles, naphthoylpyrroles and naphthylmethylindenes.	SR141716A; SR144528

11-hydroxy-Δ8-THC-dimethylheptyl, also known as HU-210, and others from HU series (Robinson et al. 2007; EMCDDA 2009; Malfitano et al. 2014).

Cannabinoids defined as "nonclassical" include bicyclic and tricyclic structures, among these CP 47,497 and its analogs. The CP compounds are more similar to the structure of Δ9-THC with regard to the alkyl chain attached to the central phenol moiety of the compound. This plays a significant role in the interaction of these compounds with the cannabinoid receptors (Presley et al. 2013; Messina et al. 2015; Shevyrin and Morzherin 2015).

Hybrid cannabinoids have a combination of classical and nonclassical cannabinoid structural features. AM-4030, a derivative of HU-210, is an example of this class of cannabinoids because it has the dibenzopyran ring that is common to classical cannabinoids and an aliphatic hydroxyl group common in the CP family of nonclassical cannabinoids (UNODC 2011). The structures of classical, nonclassical and hybrid cannabinoids are shown in Figure 5.

Aminoalkylindoles are structurally dissimilar to Δ9-THC but with cannabimimetic properties and are considered to be the most common SCs found in blends, likely due to the fact that these molecules are easier to synthesize than classical and nonclassical cannabinoids (Chakravarti et al. 2014; Shevyrin and Morzherin 2015). This class is further divided into naphthoylindoles (e.g. JWH-015, JWH-018, JWH-073, JWH-081, JWH-122, JWH-200), phenylacetylindoles (e.g. JWH-250, JWH-251), benzoylindoles (e.g. AM-694, RSC-4), naphthylmethylindoles (e.g. JWH-184, JWH-196, JWH-192), cyclopropoylindoles (e.g. UR-144, XLR-11), adamantoylindoles (e.g. AB-001, AM-1248), indole carboxamides (e.g. APICA, 5 F-APICA) (UNODC 2011, 2013; Debruyne and Le Boisselier 2015; Shevyrin and Morzherin 2015). In Table 2, some examples of the structures of the classes previously mentioned, as well as the general structure of each class are shown.

Eicosanoids, another class of SCs, are synthetic analogs of endocannabinoids, such as anandamide (e.g. methanandamide). Finally, the cannabinoids that do not constitute a class by own right are grouped into "miscellaneous cannabinoids or others", like diarylpyrazoles (e.g. SR141716A), naphthoylpyrroles (e.g. JWH-307) and naphtylmethylindenes or derivatives of naphthalene-1-yl-(4-pentyloxynaphthalen-1-yl) methanone (e.g. CRA-13) (Figure 6) (UNODC 2011; Shevyrin and Morzherin 2015).

Several classifications have been presented since the development of SCs, however, some of the classifications were defective due to the number of new compounds that can belong to unknown chemical classes and emerge constantly, making the inventory of existing products never ending (Debruyne and Le Boisselier 2015; Shevyrin and Morzherin 2015). Recently, an extensive and more complete classification was presented. Many derivatives and analogs in the above classes of compounds could be synthesized by the addition of a halogen, alkyl, alkoxy, or other substituents to one of the aromatic ring systems. Also, it is possible to make some variations on the length and arrangement of the alkyl chain without losing the cannabinoid activity or change an indole to indazole (e.g., AM-2201 to THJ-2201), as well as a terminal fluorine replacement allowing the development of new compounds (Shevyrin and Morzherin 2015; Diao and Huestis 2017; ElSohly et al. 2019). In Figure 7, the general structure of indole and indazole derivatives is presented (Debruyne and Le Boisselier 2015).

According to ElSohly et al. (2019) recent review, SCs are categorized into nine different classes. Carbazoles, indoles, indazoles, pyrroles and URB-class are the new categories that join to the standard classification.

It is quite understandable that the classification of these substances cannot be fixed for ever due to the constant development of the chemistry of new SCs, and any new suggested classification system will inevitably require updating, including the determination of new and separate groups and classes (Shevyrin and Morzherin 2015; Shevyrin et al. 2016). Furthermore, these structural changes result in compounds with unpredictable pharmacological or toxicological properties (Gamage et al. 2018).

4. Pharmacology and toxicology aspects

Comparing the pharmacological similarities between SCs and Δ9-THC has been a topic of great interest among scientists and lawmakers (Tai and Fantegrossi 2017). However, little is known about the detailed pharmacology and toxicology of

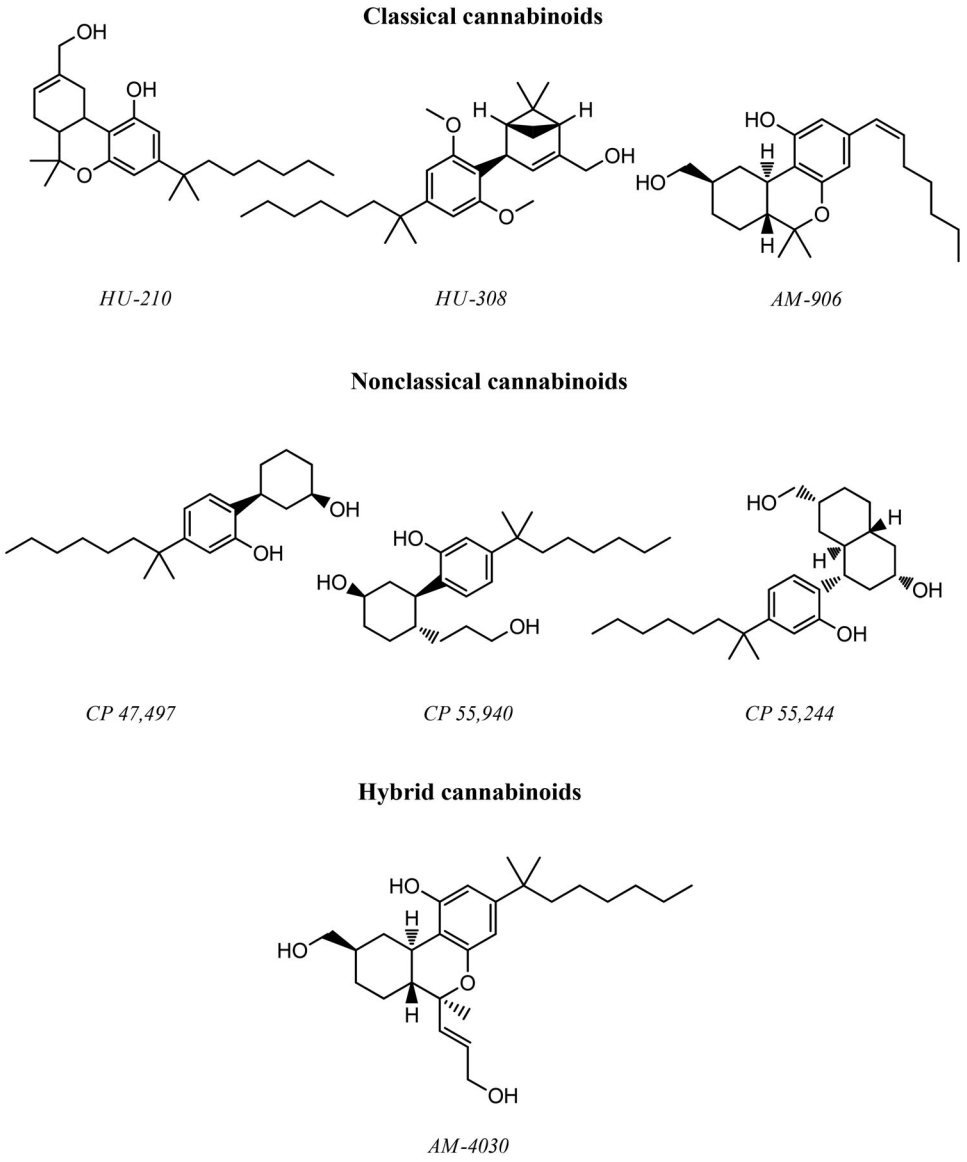


Figure 5. Chemical structures of some examples of classical cannabinoids, nonclassical cannabinoids and hybrid cannabinoids.

the SCs and few formal human studies have been published (EMCDDA 2015).

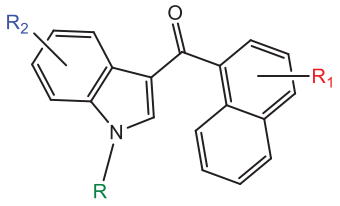
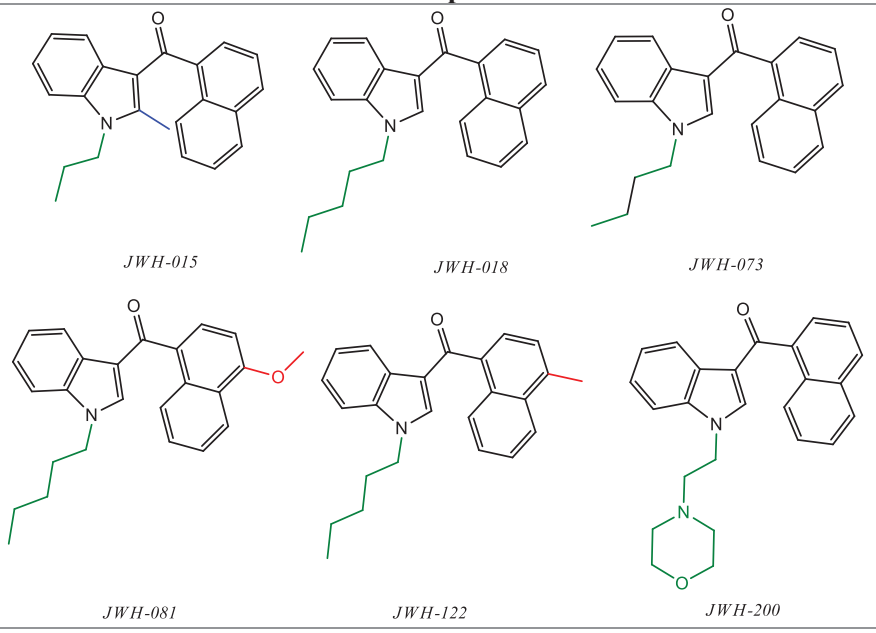
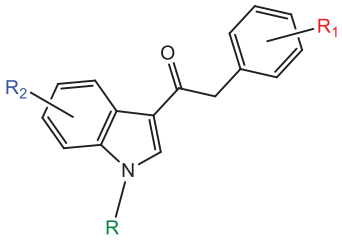
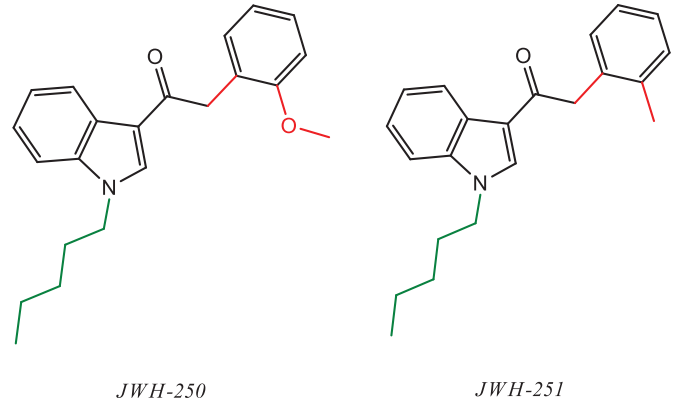
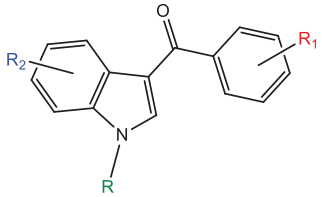
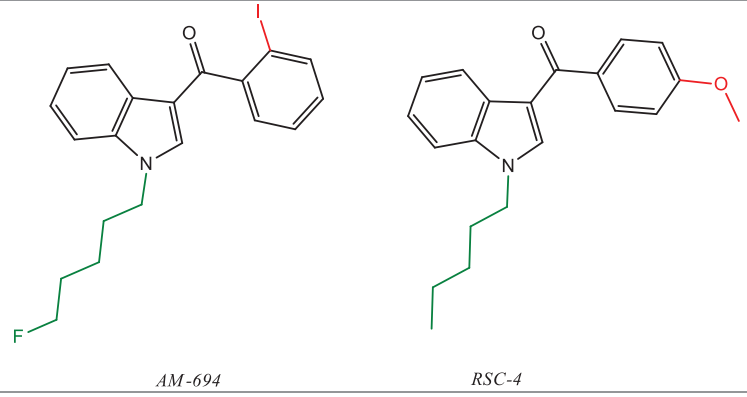
Considering the potential risks associated with SCs intake, pharmacodynamic and pharmacokinetic studies are needed to document consumption in clinical and forensic cases (Carlier et al. 2018).

4.1. Synthetic cannabinoid receptor agonists and antagonists

Due to the lipophilic nature of cannabinoids, it was initially thought that these compounds exert several biological effects by breaking the cell membrane nonspecifically. However, after the discovery of Δ9-THC and subsequent emergence of the several chemically synthesized cannabinoids, the successful mapping and pharmacological characterization of cannabinoid binding sites in the brain revealed that its pharmacological effects are considered to be mediated through at least two G-protein coupled transmembrane receptors, namely CB_1 and CB_2 (EMCDDA 2015; Zou and Kumar 2018).

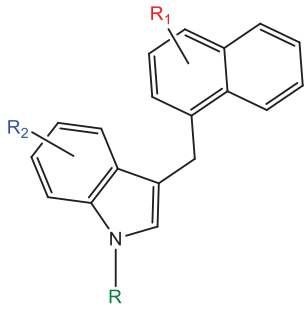
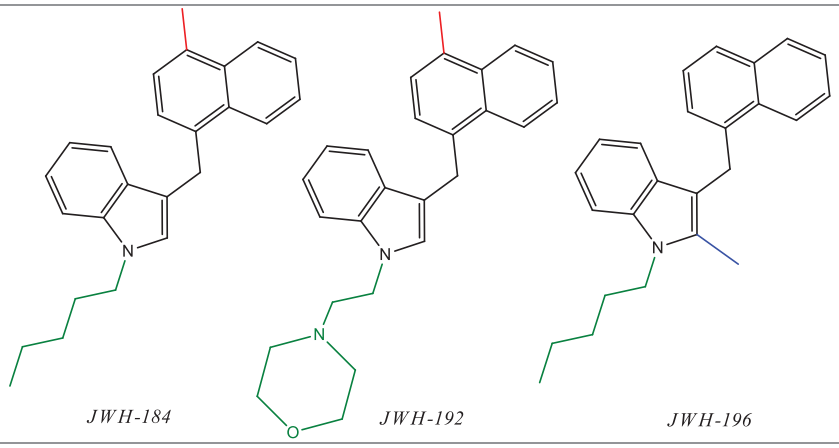
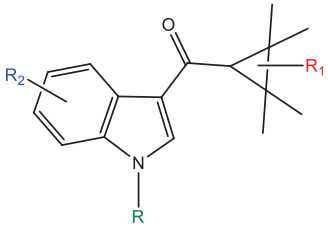
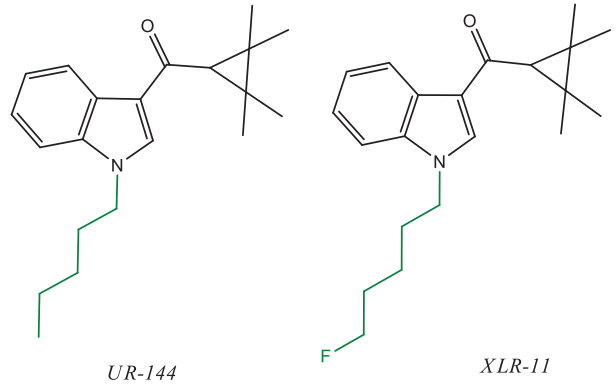
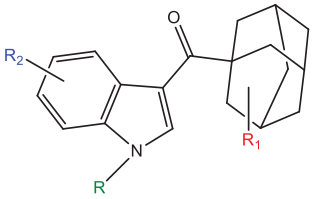
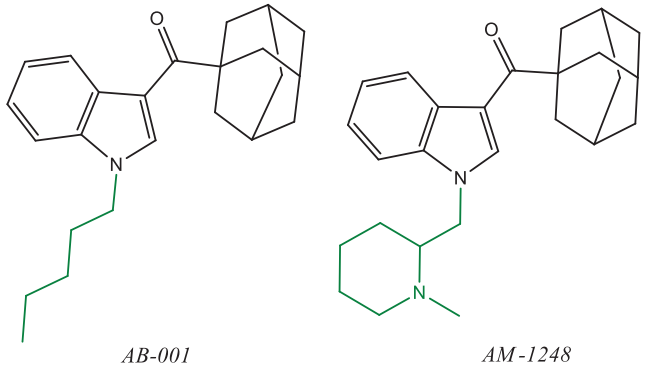
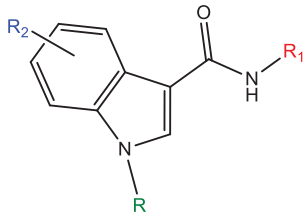
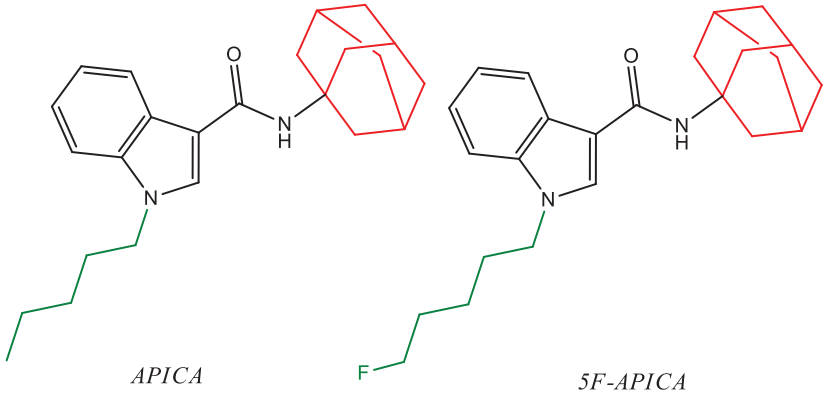
SCs are referred to as substances with structural features which exhibit higher binding affinity at both CB_1 and CB_2 receptors, and also to display varying intrinsic activity relative to Δ9-THC, both in cellular assays and animal studies (UNODC 2011; Tai and Fantegrossi 2017). CB_1 is thought to be responsible for most of the overt pharmacological effects of cannabinoids and is found mainly, in the CNS and PNS, but also is expressed in bone, heart, liver, lung, vascular endothelium, and reproductive system (Huffman et al. 2005; UNODC 2011; Castaneto et al. 2014). The second receptor, CB_2, was originally identified from macrophages present in the spleen and is expressed primarily in the periphery, but also in the central nervous system at lower levels than CB_1 and may mediate many physiological processes involving immune responses, and influence the bodýs resistance to infectious, allergic, and oncological diseases. The unequal distribution of cannabinoid receptors in the CNS may explain, to some extent, the psychoactive effects of cannabinoids, since

Table 2. Chemical structures of the different subgroups of aminoalkylindoles [adapted from (UNODC 2011b; 2013; Debruyne and Le Boisselier 2015; Shevyrin and Morzherin 2015)].

Aminoalkylindoles	
Subclass	**Examples**
Naphthoylindoles 	 *JWH-015* *JWH-018* *JWH-073* *JWH-081* *JWH-122* *JWH-200*
Phenylacetylindoles 	 *JWH-250* *JWH-251*
Benzoylindoles 	 *AM-694* *RSC-4*

(*continued*)

Table 2. Continued.

Naphthylmethylindoles 	 *JWH-184* *JWH-192* *JWH-196*
Cyclopropoylindoles 	 *UR-144* *XLR-11*
Adamantoylindoles 	 *AB-001* *AM-1248*
Indoles Carboxamides 	 *APICA* *5F-APICA*

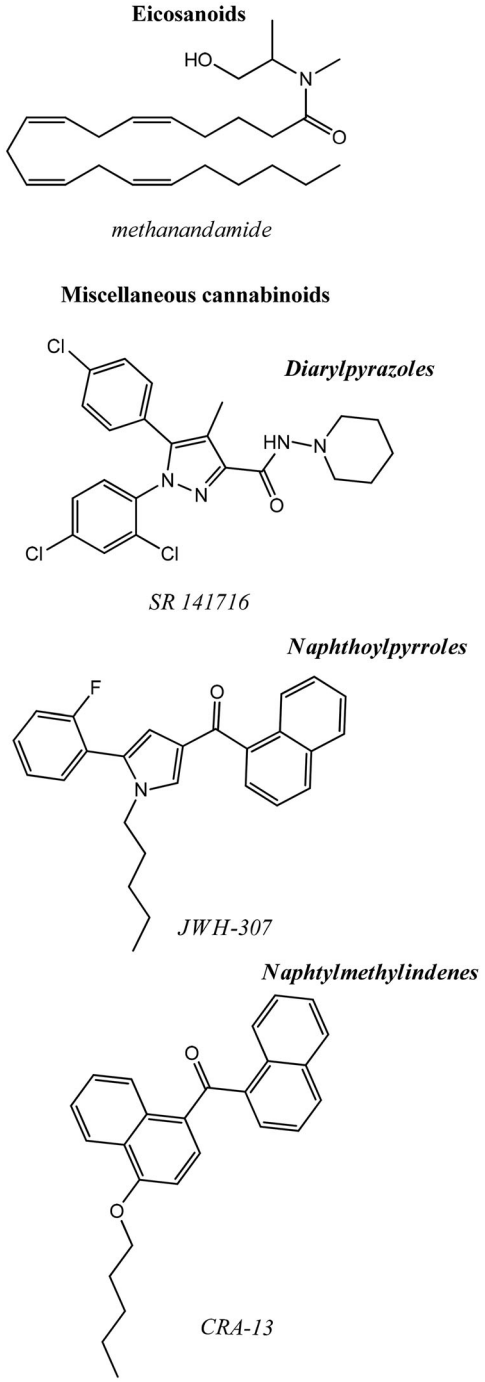


Figure 6. Chemical structures of eisoanoids and miscellaneous cannabinoids.

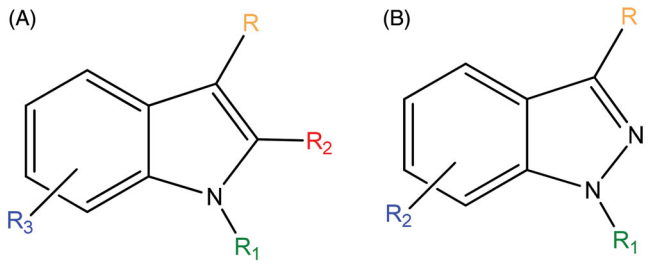


Figure 7. General structure of indole and indazole derivatives [adapted from (Debruyne and Le Boisselier 2015)].

there is evidence of the direct relationship between the affinity of cannabinoid for these receptors and their narcogenic potential (Shevyrin and Morzherin 2015; Zou and Kumar 2018).

Several studies reported that Δ9-THC is a potent activator of the CB_1 receptor, while the nonpsychoactive CBD does not bind directly with either CB_1 or CB_2 receptors; instead, it stimulates both types of receptors. Despite this fact, CBD modulate the effect of Δ9-THC via direct blockade of CB_1 receptor. This modulation leads to a reduction in unwanted side effects from the consumption of Δ9-THC, such as anxiety, dysphoria, panic reactions and paranoia and is also known to improve the Δ9-THC therapeutic activity (Gertsch et al. 2010; Carvalho et al. 2017; Maroon and Bost 2018). In contrast to cannabis, which contains mostly a mixture of agonist and antagonist cannabinoids, SCs compounds show differences in their selectivity, their potency and their function, being more potent and efficacious cannabinoid receptor agonists than Δ9-THC (Cohen and Weinstein 2018; Hourani and Alexander 2018). Also, these synthetic substances lack cannabinoids such as CBD that may otherwise counteract psychoactive properties of Δ9-THC (Altintas et al. 2016).

The activation of CB_1 receptor decreases cellular cyclic adenosine monophosphate (cAMP) levels and elicits cannabimimetic responses. SCs agonists interact with voltage-gated ion channels and inhibit potassium, sodium, and N- and P/Q-type-calcium channels by reducing membrane potentials (Castaneto et al. 2014).

The complex molecular architecture of the cannabinoid receptors allow for a single receptor to recognize multiple classes of compounds (Debruyne and Le Boisselier 2015). Due to the large variety of chemical structures, SCs bind to the two types of cannabinoid receptors with a varying degree of affinity being classified in CB_1/CB_2 agonists, CB_2 selective agonists, peripherally restricted CB_1/CB_2 agonists, CB_1/CB_2 antagonists, and inverse agonists. Moreover, many SCs present chiral centers and stereoisomer forms that may differ in their pharmacological potencies (Debruyne and Le Boisselier 2015). The cannabis-like bioactivity of SCs is mostly due to the fact of being mainly agonist at CB_1, like JWH-210, HU-308 and WIN55,212-2. In addition, these psychoactive substances have also the ability to bind to cannabinoid receptors without producing cannabis-like effects but simply blocking these receptors for other substances, acting as antagonists, like SR 141716 A and SR 144528 (UNODC 2011; Hess et al. 2016).

The majority of SCs detected in herbal products possessed higher affinity and lower inhibitory constant (Ki) values than Δ9-THC at the CB_1 receptor. SCs affinities for CB_1 and CB_2 receptors have been determined in displacement assays using tritiated cannabinoid receptor ligands and membranes obtained from brain (CB_1-rich), spleen (CB_2-rich), or using culture cells transfected with CB_1 or CB_2 receptors. Ki values of SCs collected from literature are grouped in Table 3 (Castaneto et al. 2014; Debruyne and Le Boisselier 2015; Cohen and Weinstein 2018).

The majority of compounds used as drug of abuse have Ki in the range 1 to 10 nM or 10 to 100 nM for both CB_1 and CB_2 receptors. Higher affinity of SCs to endogenous

Table 3. CB_1 and CB_2 binding affinity of several SCs [adapted from (Castaneto et al. 2014; Schoeder et al. 2018)].

Chemical Class	Compound	Activity	CB_1 Ki (nM)	CB_2 Ki (nM)	Ref.
Classical cannabinoids	HU-210	CB_1 and CB_2 agonist	0.2	0.4	(Deng et al. 2018)
	HU-308	CB_2 agonist	–	22.7	(Pertwee 2006)
Naphthoylindoles	JWH-015	CB_2 agonist	336	13.8	(Aung et al. 2000)
	JWH-018	Partial to full CB_1 agonist	1.22	2.9	(Brents et al. 2011)
	JWH-019	Full CB_1 agonist	9.8	5.6	(Aung et al. 2000)
	JWH-030	Partial CB_1 agonist	87.0	–	(Tarzia et al. 2003)
	JWH-073	Full CB_1 agonist	8.9	38.0	(Aung et al. 2000)
	JWH-081	CB_1 and CB_2 agonist	1.2	12.4	(Aung et al. 2000)
	JWH-122	CB_1 agonist	0.7	1.2	(Huffman et al. 2005b)
	JWH-151	Full CB_2 agonist	–	30	(Huffman et al. 2005b)
	JWH-200	CB_1 agonist	42.0	–	(Huffman and Padgett 2005)
	JWH-203	CB_1 and CB_2 agonist	8.0	7.0	(Huffman et al. 2005b)
	JWH-210	CB_1 and CB_2 agonist	0.5	0.7	(Huffman et al. 2005b)
	AM-1220	CB_1 agonist	3.9	73.4	(Maurer et al. 2018)
	AM-2201	Full CB_1 agonist	1.0	2.6	(Maurer et al. 2018)
	AM-2232	Unselected CB_1 and CB_2 agonist	0.3	1.5	(Maurer et al. 2018)
	AM-2233	CB_1 and CB_2 agonist	1.8	2.2	(Deng et al. 2005)
	EAM-2201	CB_1 and CB_2 agonist	0.380	0.371	(Hess et al. 2016)
	MAM-2201	Full CB_1 agonist	1.86	0.59	(Marusich et al. 2018)
Phenylacetylindoles	JWH-250	CB_1 and CB_2 agonist	11.0	33	(Huffman et al. 2005a)
	JWH-251	CB_1 agonist	29.0	146	(Huffman et al. 2005a)
Naphthoylpyrroles	JWH-307	CB_1 and CB_2 agonist	7.7	3.3	(Huffman et al. 2006)
Aminoalkylindoles	WIN55,212-2	CB_1 and CB_2 agonist	62.3	3.3	(Huffman et al. 2005b)
	PB-22	Full CB_1 agonist	0.318	0.433	(Banister et al. 2015b)
	5F-PB-22	Full CB_1 agonist	0.468	0.633	(Banister et al. 2015b)
Tetramethylcyclo-propyl indoles	UR-144	Full CB_2 agonist	29.0	4.5	(Baumann et al. 2017)
	XLR-11	CB_1 and CB_2 agonist	24.0	2.1	(Baumann et al. 2017)
Indazole carboxamide	AB-FUBINACA	CB_1 and CB_2 agonist	0.9	23.2	(Banister et al. 2015a)
	MDMB-FUBINACA	Full CB_1 agonist	1.14	0.1228	(Gamage et al. 2018)
	APINACA	Full CB_1 agonist	304.5	–	(Maurer et al. 2018)
	AB-PINACA	CB_1 and CB_2 agonist	2.87	0.88	(Banister et al. 2015a)
	AB-CHMINACA	CB_1 and CB_2 agonist	0.78	0.45	(Wiley et al. 2015)
Pyrazole	AM-251	CB_1 antagonist	7.5	–	(Seely et al. 2012)
Benzoylindoles	AM-679	CB_1 agonist	13.5	49.5	(Maurer et al. 2018)
	AM-694	Full CB_1 agonist	0.08	1.44	(Nakajima et al. 2011)
Adamantylindoles	AM-1248	CB_1 and CB_2 agonist	11.9	4.8	(Maurer et al. 2018)
Cyclohexylphenols	CP 47,497	CB_1 agonist	0.8	–	(Shim et al. 2003)
	CP55,940	CB_1 and CB_2 agonist	1.1	–	(Shim et al. 2003)

cannabinoid receptors produce a stronger effect than natural cannabis (Evren and Bozkurt 2013). The family of the JWH compounds is the most numerous and, although their chemical structures differ greatly from those of Δ9-THC, they have a higher affinity to CB_1 and/or CB_2 receptors and are more potent than Δ9-THC (Fattore and Fratta 2011). JWH-018 has four times the affinity for CB_1 receptors and 10 times the affinity for the CB_2 receptors, while JWH-015 acts as a selective CB_2 receptor agonist, being 28-fold higher for CB_2 than for CB_1 (Verty et al. 2015). Other naphthoylindoles like AM-2201 produces psychoactive effects similar to Δ9-THC but with a binding affinity 40 times higher at CB_1 and 14 times higher at CB_2 (Carlier et al. 2018). The binding affinity of the SCs to the CB_1 receptor can range from being similar to Δ9-THC like JWH-200 to 90 times higher as in case of JWH-210. The affinity of indoles compounds to cannabinoid receptors was explained by a three-point bond for each compound with Δ9-THC natural ligand regions, being the three key regions the naphthalene ring, the carbonyl group and the indole N-alkyl substituent. The replacement of the naphthalene by a methyl-, methoxy-, fluoro-, chloro- or bromo-substituted phenylacetyl group resulted in an increased selectivity for the CB_1 receptor depending on the nature and location of the substituent on the aromatic ring (Evren and Bozkurt 2013).

The cyclohexylphenols CP 55,940 and CP 47,497, as well as their n-alkyl homologs also act as CB_1 receptors full agonists. CP 47,497 lacks the classical cannabinoid chemical structure (tricyclic benzopyran system) and presents 3–28 times higher potency (Fattore and Fratta 2011). HU-210 is the most potent cannabinoid compound synthesized at its creation, being 100-800 times more potent than Δ9-THC, with a slow onset of effect but a long duration of action, since it binds both CB_1 and CB_2 receptors (EMCDDA 2015; Preedy 2016b; Carlier et al. 2018; Cohen and Weinstein 2018).

In vitro experiments have demonstrated that the selective agonists JWH-015, JWH-133, and HU-308, and the mixed CB_1–CB_2 receptor agonists WIN55,212-2 and HU-210 reduce the release of pro-inflammatory cytokines in microglial cell cultures exposed to different species of the toxic Aβ peptide, preventing cognitive impairment and neuronal loss in Alzheimer's disease (Aso and Ferrer 2016; Manera et al. 2016). On the other hand, HU-211 the enantiomer of HU-210, does not act as a cannabinoid receptor agonist but instead produces antagonist effects in N-methyl D-aspartate receptors, protecting cells from neurotoxicity induced by it ligand (Manera et al. 2016). Also, HU-433 and HU-308, two synthetic cannabinoid enantiomers are specific CB_2 agonists, however HU-433 binding to CB_2 receptor is substantially lower compared with HU-308, being more potent than HU-308 in its

CB_2-mediated anti-osteoporotic and anti-inflammatory effects. A molecular-modelling analysis suggested that HU-433 and HU-308 have two different binding conformations within CB_2, with one of them possibly responsible for the affinity difference. Hence, different ligands may have different orientations relative to the same binding site (Meyer 2016).

The two indazole carboxamide AB-CHMINACA and AB-PINACA also exhibited higher efficacy than most known full agonists of the CB_1 receptor, leading to potential interest as research tools due to their unique chemical structures and high CB_1 receptor efficacies (Meyer 2016).

Little is known about the detailed pharmacodynamic and pharmacokinetic profiles of most SCs in humans, and its abuse as well as the case reports of adverse effects have raised concerns about the pharmacologic mechanisms underlying *in vivo* effects (Evren and Bozkurt 2013; Hruba and McMahon 2014).

4.2. Pharmacokinetics

Whereas some derivatives have been controlled, the new generation of SCs is flooding the illicit drug and a slightly modification in the structure, results in higher potencies and efficiencies (Banister et al. 2015). In addition, the presence of more than one type of substance in each herbaceous mixture, as well as the addition of other substances all lead to the fact that even the most experienced user doesn't know what is consuming (Dresen et al. 2010; Fattore and Fratta 2011). As a consequence, lower doses are needed to obtain the desired euphoria effect and thus unpredictable biological effects and poisonings due to overdosing are more likely (Tait et al. 2016; Schaefer et al. 2017).

In forensic toxicology, the clarification of pharmacokinetic and pharmacodynamic properties of SCs is important in order to interpret analytical results obtained from intoxicated or poisoned individuals, particularly postmortem (Schaefer et al. 2017). SCs can be detected in human blood and/or oral fluid if the sample is collected as close as possible to the time of intake, which is highly valuable if available. Karinen et al. (2015) reported for the first time concentrations of APINACA, 5 F-APINACA, UR-144, and UR-144 degradant in whole blood samples collected from driving under the influence of drug (DUID) cases and compared values to concentrations previously reported for other SCs. APINACA and 5 F-APINACA were found in concentrations ranging from 0.24 to 24.5 $\mu g.L^{-1}$ and 0.9 to 6.6 $\mu g.L^{-1}$, respectively. One highlight of the paper was the summary of previously reported synthetic cannabinoid concentrations reported in DUID cases, intoxication cases, autopsy cases, and pharmacokinetic studies. Finally, authors pointed out the need of more reports on concentrations of synthetic cannabinoids from different case types. The knowledge of concentration ranges and concentrations in single cases might be helpful to set up appropriate analytical methods and to evaluate possible harmful concentration ranges (Meyer 2016).

Urine is the most common matrix for drug testing because of its noninvasive collection, adequate sample, higher drug concentrations and longer detection window than either blood or oral fluid (Diao and Huestis 2019). However, due to the extensive metabolism of SCs, the parent compounds are rarely seen in the urine, instead, their metabolites are predominantly excreted, complicating detection as these last compounds are initially unknown (Knittel et al. 2016; Diao et al. 2017). The analysis of body fluids largely relies on the detection of the parent drug, and once the parent drug is metabolized, the consumption of the drug cannot be proven without data on the metabolites (Evren and Bozkurt 2013). In addition, metabolites may be present in the blood depending on the dose and time after ingestion. However, several urinary metabolites may be present derived from multiple ingestion of SCs, while only one substance may be present in the blood, confounding urine metabolite results (Diao and Huestis 2019).

4.2.1. Onset, duration of action and metabolic changes

The biotransformation of xenobiotics converts drugs into more water-soluble metabolites for better elimination from the human body. SCs are xenobiotics and undergo extensive metabolism and clearance through the liver, which is the most important organ for SCs metabolism, although other organs may also be involved in drug biotransformation such as intestine, lung, brain, and kidney (Diao and Huestis 2017; Diao and Huestis 2019). Case reports indicate oral and inhalational bioavailability, but the degree of bioavailability is not entirely known (Evren and Bozkurt 2013; Fantegrossi et al. 2014; Diao and Huestis 2017).

Due to their highly lipophilic nature, SCs are present in "herbal" product in small proportions and oral intake of the products will result in a certain loss of drug by first pass metabolism (UNODC 2011). In this sense, smoking is the main administration form, reaching peak blood concentration very quickly (Castaneto et al. 2015). The instant absorption via the lungs and redistribution into other the organs like brain in a short time, onset of action usually occurs within minutes. In case of oral consumption, the absorption process as well as the onset of action is delayed due to food intake, digestion activity and variations in the extent of the first pass effect. High volumes of distribution can be expected for these lipophilic compounds and as a result, after chronic consumption, fat accumulation in the body is very likely (UNODC 2011; Evren and Bozkurt 2013).

Despite the restriction of studies on controlled administration of SCs in humans, a few works with SCs intake in humans have been published. According to Castaneto et al. (2015) review eight manuscripts with SCs administration in individuals were reported with the local Institutional Review Board (IRB) approval. In Teske et al. (2010) work, a human study was performed in which two subjects smoked 50 $\mu g.kg^{-1}$ of JWH-018, reaching a blood peak concentration of 10 $\mu g.L^{-1}$ after 5 min, rapidly decreasing in the following 3 h, becoming barely traceable after 24 h. The results allowed to conclude that the synthetic drug reached peak blood concentration very quickly, then being redistributed to other tissues such as the brain. The same was observed in Kacinko et al. (2011) study, with one of the six subjects smoking over 30 min 0.3 g herbal blend containing 17 $mg.g^{-1}$ JWH-018 and

22 mg.g^{-1} JWH-073. Blood peak concentration was reached 19 min after smoking with 4.8 and 4.2 mg.L^{-1}, respectively, with a quickly declining to 1.5 mg.L^{-1} JWH-018 and 1.0 mg.L^{-1} JWH-073 at 53 min, and 0.2 mg.L^{-1} for both at 107 min. These studies allowed to calculate the half-live of JWH-018 and JWH-073 from the concentration data measured.

A self-experiment was reported in Hutter et al. (2013) work, in which one of the authors ingested 5 mg of pure AM-2201, and serum as well as urine samples were analyzed subsequently. The serum plasma peak was 0.56 μg.L^{-1} at 1.5 h, decreasing after 21 h but remaining detectable for 5 days. Additionally, the smoke condensate from a cigarette laced with pure AM-2201 was also investigated and urine samples of patients after known consumption of AM-2201 or JWH-018 were evaluated. In another similar study, an adult male volunteer orally ingested a 5 mg dose of pure AM-2201, and the AM-2201 serum concentrations was reported to decreased from 1.4 μg/L at approximately 1 h to 0.7 μg/L at 5 h after ingestion. AM-2201 was still detectable in serum 25 h after administration. The half-life of AM-2201 was estimated to be approximately 4 h. (Kneisel et al. 2013).

These studies showed that SCs are significantly more efficacious and have a faster onset and shorter duration of action relative to Δ9-THC. HU-210, another compound identified in herbal blends, is also more potent and efficacious than Δ9-THC, yet its duration of action is nearly five times longer and its onset of action is significantly slower. Although slow onset and long duration of action of the HU-210 do not necessarily predict a higher risk of abuse relative to cannabis, it is suggested that it is capable of producing protracted withdrawal symptoms similar to what is observed with long-acting opioid agonists, predicting significant adverse effects associated with SCs dependence and withdrawal (Hruba and McMahon 2014). These findings highlight the pharmacological characteristics of a few of the dozens of compounds found in 'herbal products' that predict significant clinical physiological and behavioral risks in relation to cannabis (Cooper 2016).

Although many of the SCs available in "herbal products" have not been fully characterized regarding their metabolism, there are data for a number of representatives demonstrating extensive oxidative metabolism. Based on the recent evidence, SCs are extensively metabolized in phase-I and phase-II biotransformation reactions. These substances are firstly oxidized by cytochrome P450 enzymes (CYP), whereby oxidized metabolites are formed and then served as substrates for a second metabolic phase, namely glucuronidation and/or sulfation by a class of enzymes called UDP-glucuronosyltransferases (UGT) and finally, renal excretion (Evren and Bozkurt 2013; Fantegrossi et al. 2014; Diao and Huestis 2017; Patton et al. 2018). In Figure 8, a schematic summary about absorption, distribution, metabolism, and excretion of SCs with main metabolites produced by CYP and UGT enzymes is illustrated.

In general, oxidative metabolism forms preferably mono-, di-, and tri-hydroxylated, carboxylated and N-dealkylated compounds. Hydroxylation process takes place on the aliphatic chain, the indole, the naphthalene, or the substituted aromatic rings that can be secondarily metabolized to carboxylic acids then conjugated to glucuronic acid (Auwärter et al. 2013; Diao and Huestis 2017; Tai and Fantegrossi 2017; Diao and Huestis 2019).

The earliest reports of SCs metabolism were published in the early 2000s and focused on the *in vitro* metabolism of WIN-55,212-2 (Zhang et al. 2002), AM-630 (Zhang et al. 2004) and JWH-015 (Zhang et al. 2006) synthetic compounds. However, the popularity of JWH-018 as a recreational drug soon brought human *in vivo* metabolism to the forefront. Sobolevsky et al. (2010) identified two major JWH-018 monohydroxylated metabolites in urine using gas and liquid chromatography combined with tandem mass spectrometry. Metabolites of JWH-018 were observed to be excreted almost entirely as glucuronide conjugates, as in the *in vitro* studies of Chimalakonda et al. (2012). More recently, Toennes et al. (2017) performed a pilot study to assess adverse effects of JWH-018. In this study, the pharmacokinetic properties of JWH-018 and of its metabolites were determined using blood

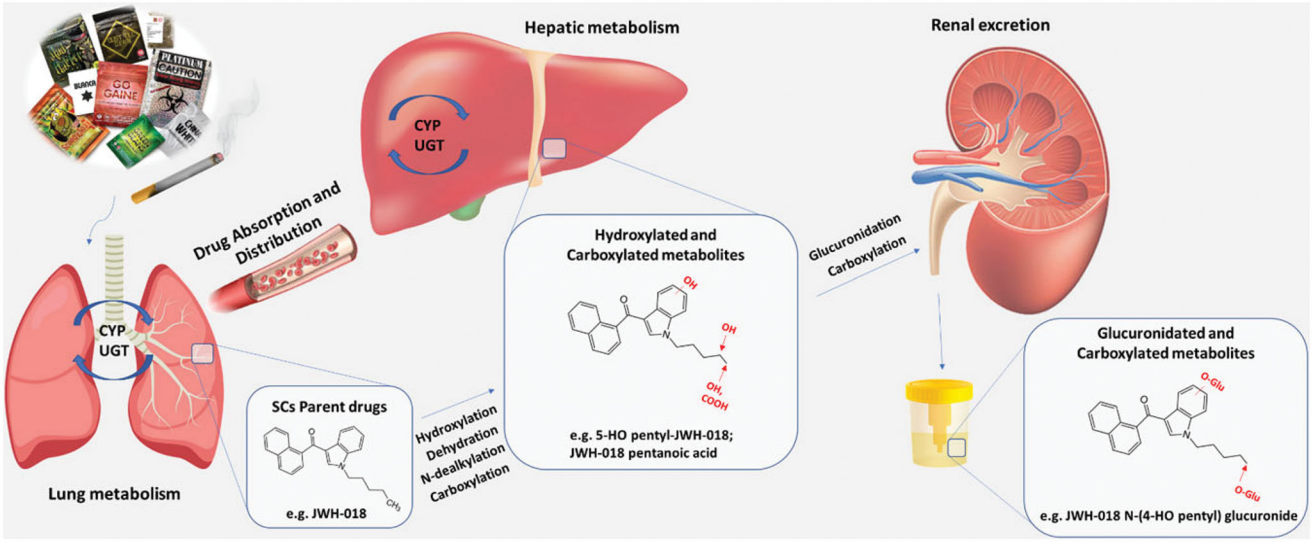


Figure 8. Schematic summary of the absorption, distribution, metabolism and excretion of SCs [adapted from (Brock 2012; Patton et al. 2013)].

samples taken during 12 h after controlled inhalation of 2 and 3 mg of the cannabinoid. Concentrations of JWH-018 in blood reached its maximum within minutes after inhalation and their time course suggests a multi-compartment distribution/elimination. The same was verified to six metabolites of the cannabinoid detected in the blood samples, whose levels of concentration were ten times lower than the parent compound. With these studies it was possible to confirmed that the prevailing metabolites of JWH-018 are monohydroxylated, typically on the terminal carbon of the alkyl group (N-5-hydroxypentyl-JWH-018 and N-4-hydroxypentyl-JWH-018) by two main lung and liver CYP1A2 and CYP2C9 isozymes and with minimal contributions from CYP2C19, 2D6, 2E1, and 3A4 (Patton et al. 2013; Nielsen et al. 2016).

Also, commonly detected in human urine are metabolites that are monohydroxylated on the alkyl site, monohydroxylated on the indole group, or carboxylated on the alkyl site (5-hydroxyindole-JWH-018, 6-hydroxyindole-JWH-018 and 7-hydroxyindole-JWH-018 and N-pentanoic acid-JWH-018, a major human urinary metabolite) (Brock 2012; Kong et al. 2018). In the second metabolic phase, glucuronidated metabolites are formed, N-Hydroxypentyl-JWH-018 glucuronide is formed from N-hydroxypentyl-JWH-018 by UGT2B7, and N-pentanoic acid-JWH-018 is metabolized to N-pentanoic acid glucuronide-JWH-018 by UGT1A3 and UGT2B7. 5-Hydroxy-JWH-018 glucuronide, 6-hydroxy-JWH-018 glucuronide and 7-hydroxy-JWH-018 glucuronide are also formed through the metabolism of its respective substrates (Figure 9) (Abbate et al. 2018; Kong et al. 2018). Interestingly, N-dealkylated and N-dealkyl monohydroxylated metabolites of JWH-018 are abundant in rat urine but rare in human samples (Brock 2012).

N-5-hydroxypentyl-JWH-018 and N-pentanoic acid-JWH-018 are also metabolites of synthetic cannabinoid AM-2201. Chimalakonda et al. (2012) studied the oxidative metabolism of JWH-018 and its fluorinated analog AM-2201 using human liver microsomes and human recombinant CYP. The authors concluded that both synthetic substances appear to be metabolized similarly to produce several ring and alkyl side chain oxidized metabolites that are excreted in human urine as glucuronic acid conjugates. Figure 9 represents the merging metabolic pathways for JWH-018 and AM-2201.

AM-2201 undergo oxidative defluorination to N-5-hydroxypentyl-JWH-018. Other metabolites are also produced, like

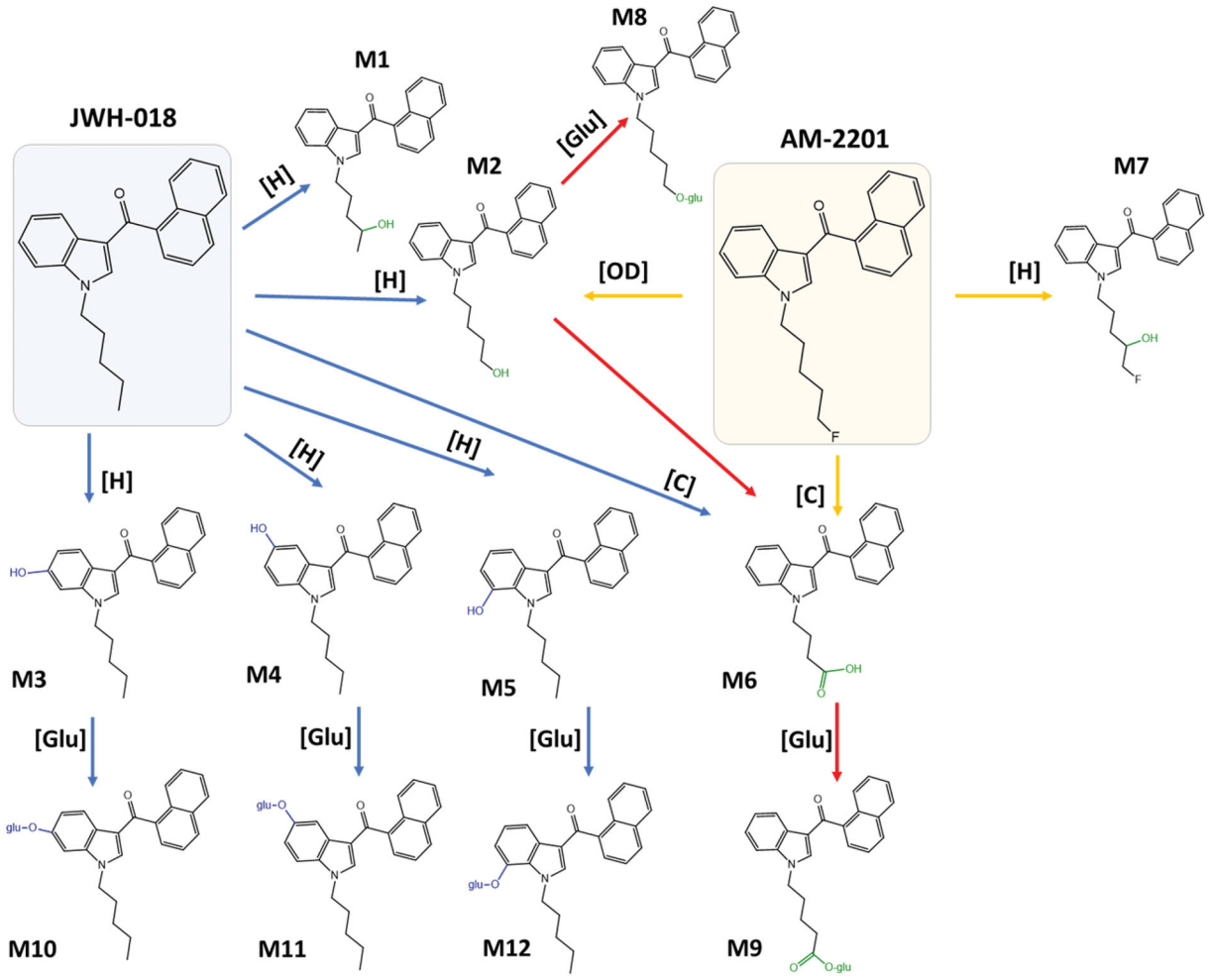


Figure 9. Merging metabolic pathways for JWH-018 (blue arrows) and AM-2201 (yellow arrows). Red arrows indicates the metabolic phase II in common to both compounds. M1- N-4-hydroxypentyl-JWH-018; M2- N-5-hydroxypentyl-JWH-018; M3- 6-hydroxyindole-JWH-018; M4- 5-hydroxyindole-JWH-018; M5- 7-hydroxyindole-JWH-018; M6- N-pentanoic acid-JWH-018; M7- N-4-hydroxyfluoropentyl-AM-2201; M8- N-5-hydroxypentyl-JWH-018 glucuronide; M9- N-pentanoic acid-JWH-018 glucuronide; M10- 6-hydroxy-JWH-018 glucuronide; M11- 5-Hydroxy-JWH-018 glucuronide; M12- 7-hydroxy-JWH-018 glucuronide. [H] hydroxylation; [C] carboxylation; [OD] oxidative defluorination; [Glu] glucuronidation [adapted from (Abbate et al. 2018; Kong et al. 2018)].

N-pentanoic acid-JWH-018, N-4-hydroxyfluoropentyl-AM-2201, dihydroxy-AM-2201, dihydrodiol-AM-2201 and despentyl-AM-2201. Hydroxy-AM-2201 and glucuronides of hydroxy-AM-2201 and dihydrodiol-AM-2201 were also detected *in vitro* and *in vivo* (Chimalakonda et al. 2012; Patton et al. 2013; Kong et al. 2018). N-4-Hydroxyfluoropentyl-AM-2201 activates CB_1 receptors with nanomolar affinity and is a distinctive marker of differentiation between AM-2201 and JWH-018 abuse (Kong et al. 2018).

Different studies have been published on the metabolism of other JWH-type compounds, such as JWH-015 (Strano-Rossi et al. 2014), JWH-073 (Moran et al. 2011; Hutter et al. 2012), JWH-081 (Hutter et al. 2012), JWH-098 (Strano-Rossi et al. 2014), JWH-122 (Hutter et al. 2012), JWH-200 (De Brabanter et al. 2013), JWH-201 (Kavanagh et al. 2013), JWH-210 (Hutter et al. 2012), JWH-250 (Grigoryev et al. 2011), JWH-251 (Kavanagh et al. 2013; Strano-Rossi et al. 2014) and JWH-307 (Strano-Rossi et al. 2014). Like JWH-018, each of these contains an aminoalkylindole group and both JWH-015 and JWH-073 compounds have a naphthoyl group in common with JWH-018 (Brock 2012). The *in vitro* metabolism of JWH-015 produces 22 products reminiscent of those detected following similar treatment of JWH-018. The diversity of products generated by this method greatly exceeds those typically reported from urine, as in the studies examining the human urinary metabolites of JWH-073. As JWH-073 differs structurally from JWH-018 solely in alkyl chain length (butyl for pentyl), the human urinary metabolites are naturally comparable: monohydroxylation of the indole group or alkyl site or carboxylation of the alkyl chain. Again, all monohydroxylated forms are fully glucuronidated while only a fraction (<50%) of the carboxylated products are glucuronidated (Brock 2012). Figure 10 shows the sites of modification of the major metabolites of JWH-015, JWH-073 and JWH-250.

The metabolites of JWH-018 and JWH-073 also maintain their *in vitro* activity at CB_2. It is therefore reasonable to assume that other SCs are also biotransformed into molecules with various levels of activity at the CB receptors. These active metabolites may prolong the parent compound's psychotropic and physiological effects and may contribute to its toxicity profile (Cannaert et al. 2016).

CYP3A4 has been recently demonstrated to be the major CYP enzyme responsible for the metabolism of APINACA, 5 F-APINACA, APICA, and 5 F-APICA. This enzyme is, preferentially, responsible for hydroxylation on the adamantyl group (Holm et al. 2015; Sobolevsky et al. 2015; Kong et al. 2018).

In UR-144 and XLR-11 metabolism, CYP3A4 also shows the highest level of metabolism activity, preferentially at the tetramethylcyclopropyl moiety. XLR-11 is the fluorinated form of UR-144 and a derivative of AM-2201 and both compounds differ from JWH-018 by the substitution of a naphthyl group with a 2,2,3,3-tetramethylcyclopropyl group (Kong et al. 2018). These two cyclopropoylindoles are extensively metabolized by monohydroxylation at pentyl, indole, or 2,2,3,3-tetramethylcyclopropyl groups, dioxidation followed by internal hydration at tetramethylcyclopropyl group, dihydroxylation at pentyl and tetramethylcyclopropyl group, carboxylation at tetramethylcyclopropyl or pentyl groups, dioxidation followed by internal hydration, glucuronidation, and combinations of these reactions (Kavanagh et al. 2013; Kanamori et al. 2015; Kong et al. 2018). As the 2,2,3,3-tetramethylcyclopropyl group can undergo ring opening when heated or smoked, the pyrolytic product of UR-144, 1-(1-pentyl-1H-indol-3-yl)-3-methyl-2-(propan-2-yl)but-3-en-1-one and its several urinary metabolites have been reported along with metabolites of UR-144 (Kavanagh et al. 2013). Thirteen urinary metabolites of the pyrolytic product of XLR-11 have been tentatively identified, and the UR-144 degradation product N-pentanoic acid is a

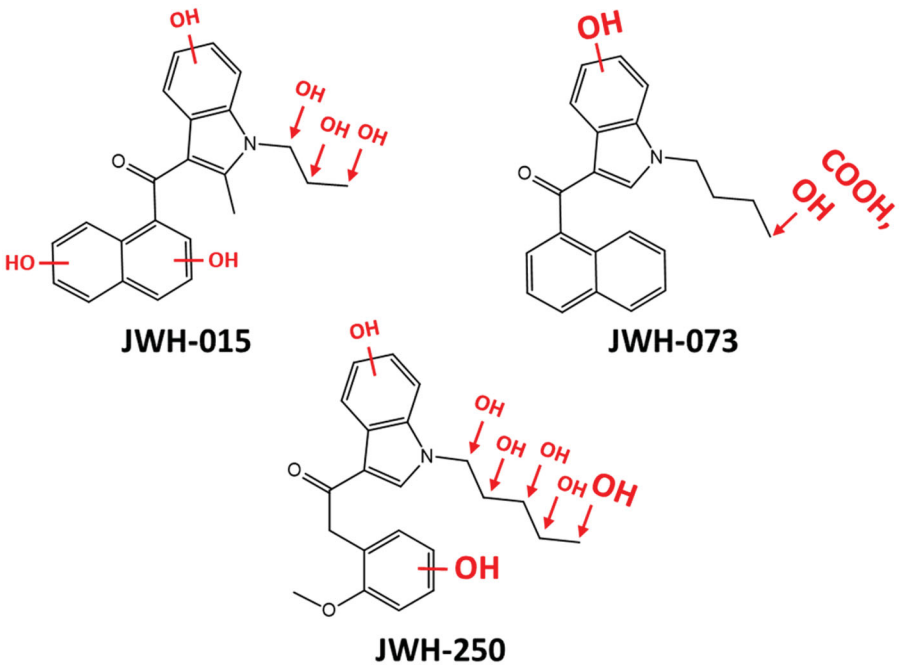


Figure 10. Sites of modification in the metabolism of JWH-015, JWH-073 and JWH-250 with major metabolites given in larger font [adapted from (Brock 2012)].

major metabolite (Kanamori et al. 2015; Jang et al. 2016; Kong et al. 2018).

The indazoles AB-CHMINACA and AB-FUBINACA are extensively metabolized by hydrolysis of the amide group, mono-, di-hydroxylation, N-dealkylation, glucuronidation, and combinations of these reactions. Dehydrogenation, defluorobenzylation, and epoxidation followed by hydrolysis are also reactions that occur in AB-FUBINACA metabolism. Hydroxylation on the indazole ring and amino-3-methyloxobutane moiety of AB-FUBINACA are major pathways, but there is no modification of the fluorobenzyl moiety. AB-CHMINACA and AB-FUBINACA carboxylic acid metabolites are formed by carboxylesterase enzymes (CES) and were identified as major metabolites in human hair and urine samples (Castaneto et al. 2015; Wurita et al. 2016; Sim et al. 2017).

Ashino et al. (2014) suggested that SCs, especially naphthoylindole derivatives, are capable of inhibiting CYP1A enzymatic activity as do the major metabolites present in cannabis, CBN and CBD. Introduction of novel functional groups and substructures could potentially convert the resulting compounds into substrates for other CYP enzymes than the reported ones or subject them to non-CYP-mediated biotransformation. Therefore, metabolism studies on novel emerging SCs are essential. (Debruyne and Le Boisselier 2015; Nielsen et al. 2016).

Of note, some hydroxylated urinary metabolites are even more toxic than the parent synthetic drug. As example, JWH-018 major metabolites, N-4-hydroxypentyl-JWH-018 and N-5-hydroxypentyl-JWH-018, and AM-2201 metabolite, N-4-Hydroxyfluoropentyl-AM-2201 remained full agonists in nanomolar concentrations (Chimalakonda et al. 2012). The exact mechanisms through which SCs produce their wide-ranging effects and toxicities are not fully understood. Furthermore, the extent to which these effects are caused by either the parent compounds or their metabolic and thermolytic degradants is unknown (Gamage et al. 2018). Although, the duration of effects in humans compared to Δ9-THC differs, (shorter for JWH-018 (1 to 2 h), and longer for CP-47,497 or its C8 homolog (5 to 6 h) (EMCDDA 2009), in general SCs have longer half-lives, leading to prolonged toxicological effects (Evren and Bozkurt 2013). Greater knowledge of the activity of relevant metabolites from a broader set of SCs may allow us to gain a better understanding of the contribution of these active metabolites to the toxicity observed with SCs (Cannaert et al. 2016).

4.3. Recreational and adverse effects

In contrast to the decline in the use of many NPS such as the cathinones and piperazines, it appears that the number of cannabimimetic drug users is increasing. Although SCs mimic the psychotropic effects of cannabis, these compounds are accepted to be more potent than natural cannabinoids and human data concerning the induction and duration of adverse effects remain limited (Evren and Bozkurt 2013; Cohen and Weinstein 2018).

The continuously changing composition of these synthetic drugs by the producers, in order to avoid detection and regulation, makes treating SCs toxicity particularly challenging because the individual compounds vary in potency, efficacy, and duration of action, making their effects unpredictable, resulting in different experience to the users (Brents and Prather 2014; Cooper 2016). Some users report a feeling of sedation while others experience agitation, fatigue, and flushes (Cohen and Weinstein 2018). Hudson et al. (2010) detailed the analytical detection of 11 different SCs across 40 batches of 16 different incense products in various combinations and proportions from brand to brand and from batch to batch, even within brands. The authors concluded that the cannabinomimetic content profile of the 40 products highlighted differences between the products and the fact that the cannabinomimetic content of sachets of the same labeled product can vary significantly and may explain the different reported effects. Compared with the intoxication of organic cannabis products which have a slow effect and gradually fade, SCs have a shorter duration and peak earlier. In the majority of cases the duration of clinical effects is shorter than 8 h, whereas it lasts longer than 24 h in some cases (Evren and Bozkurt 2013).

Numerous complications have been observed in SCs users. Similar to cannabis, the psychoactive effects of SCs range from pleasant and desirable euphoria to anxiety, relaxation, agitation, and changes in cognitive abilities, such as perceptual alteration, altered sense of time, and mild cognitive impairments (Cooper 2016; Cohen and Weinstein 2018). Some users also related sickness, hot flushes, burning eyes and xerostomia along with mydriasis and tachycardia. This clinical variability could be explain by some SCs being more associated with the development of stimulant-like acute toxicity while others may be more associated with the development of cannabis-like chronic toxicity. The type of compound used, the individual susceptibility to the drug effects, the dose, or multi-factorial scenario, are potencial factors too (Evren and Bozkurt 2013).

SCs can produce a wide range of physiological and psychiatric adverse effects, which vary in duration and severity. Case reports and retrospective studies of acute intoxication indicate that severe effects that have been noted include seizures, cardiovascular damage, renal damage, stroke, psychosis, paranoia, aggression, anxiety attacks, dependence, or even death (through suicide, adverse reaction, or overdose) (Evren and Bozkurt 2013; Tournebize et al. 2017).

Acute cardiac toxicities are relatively common among SCs users, being tachycardia/bradycardia and chest pain the most commonly reported findings after SCs intake (Alipour et al. 2019). Supraventricular tachycardia with heart rates as high as 172 bpm were reported in a 24-year-old after ingestion of e-cigarette fluid mixed with SCs (Lam et al. 2017). Acute myocardial infarction was also reported in adolescents and adults and cardiovascular fatalities associated with SCs use were described in the literature (Alipour et al. 2019). Most of patients arriving at Emergency Departments presented at least one psychiatric effect. Among them, anxiety and hallucinations were the most reported. Confusion, amnesia, unconsciousness, paranoid delusion and disorganized behavior were also observed following use of SCs. According to several case reports, the use of SCs may also be associated with an

Table 4. Summary of clinical side effects with SCs use [adapted from (CDC 2013; Buser et al. 2014; van Amsterdam et al. 2015; Cooper 2016; Lam et al. 2017; Tournebize et al. 2017; Cohen and Weinstein 2018a, 2018b; Alipour et al. 2019)].

Physiological damage	Side effects
Cardiovascular	Tachycardia/bradycardia, hypertension, myocardial infraction, arrhythmias, chest pain, and palpitations. Risk of cardiovascular disease.
Neuropsychiatric	Severe psychotic symptoms like agitation, aggression, catatonia, paranoia, auditory and visual hallucinations, perceptual alterations, and persistent psychosis episode. Risk of psychotic disorders.
Cognitive	Severe cognitive impairments like memory alteration, attention difficulties, and amnesia. Executive function deficits of working memory and attention.
Neurologic	Dizziness, somnolence, seizures, hypertonicity, hyperflexion, hyperextension, sensation changes, and fasciculations. Structural and functional central nervous system alterations.
Renal	Acute kidney injury, abdominal pain, miosis, mydriasis, xerostomia, hyperthermia, fatigue, rhabdomyolysis, cough, deficits of driving ability. Kidney diseases, insomnia, nightmares, dependency, tolerance, and withdrawal.
Gastrointestinal	Nausea, emesis, appetite change, abdominal pain, diarrhea, excessive thirst, xerostomia and persistent cannabinoid hyperemesis. Severe weight-loss after prolong use.
Ocular	Mydriasis
Metabolic disturbances	Leukocytosis, hypokaliemia and metabolic/respiratory acidosis

increased risk of suicidal ideation (Tournebize et al. 2017; Cohen and Weinstein 2018). In Patton et al. (2013) and Shanks et al. (2012) work, two men without history of psychiatric disorders, committed suicide shortly after smoking herbal products containing SCs including JWH derivatives and AM-2201. In both cases, drug screening was negative for other licit and illicit substances (Tournebize et al. 2017).

Psychosis and psychosis-like conditions seem to occur relatively often following the use of SCs, presumably due to their high potency and the absence of CBD in the preparations. Studies on the relative risk of SCs compared with natural cannabis to induce or evoke psychosis are urgently needed (van Amsterdam et al. 2015).

The neurotoxicity of SCs abuse is well documented in the literature. An acute ischemic infarction was revealed after a 25 years old individual had stroke symptoms after smoking a product containing SCs called "freeze" (Moeller et al. 2017). Seizures, aggressive behavior, and rhabdomyolysis are another severe adverse effects occurring with SCs, but they are rarely reported with cannabis use given THC's weak affinity for the cannabinoid receptors (Alipour et al. 2019).

The use of SCs can also lead to a variety of renal and gastrointestinal problems. A number of cases demonstrated nephrotoxic effects with kidney damage and intrinsic acute renal failure after exposure to XRL-11 and/or UR-144 (CDC 2013; Buser et al. 2014). Symptoms such as emesis, nausea, abdominal pain, diarrhea, excessive thirst, xerostomia and persistent cannabinoid hyperemesis syndrome have been described (Tournebize et al. 2017).

Ocular and metabolic disturbances are less common and a small number of side effects have been described. Among these, mydriasis was frequently observed in ocular side effects and leukocytosis as well as more severe complications including hypokaliemia and metabolic/respiratory acidosis were reported in intoxications with SCs consumption (Tournebize et al. 2017).

Recently in the US, there has been an outbreak of severe bleeding events leading to at least 4 deaths due to the ingestion of synthetic cannabinoid products tainted with brodifacoum (a rodenticide). To increase sales, SCs are being mixed with other substances, including other psychoactive substances, such as bath salts or ecstasy/Molly by dealers. This new trend poses a huge health risk, thus raising concerns about the increased toxicity of these dangerous substances that are being incorporated into these products (Moritz et al. 2018).

Table 4 summarizes the several reported adverse effects with synthetic cannabinoid intoxication.

Several studies demonstrate an association between repeated cannabis use and long-lasting cognitive impairments, and an increase in risk for developing a variety of mental disorders, such as bipolar disorder, depression, and schizophrenia. There is growing evidence that SCs are associated with severe negative psychiatric and medical conditions. This evidence demonstrates that repeated exposures to these synthetic drugs induce overall negative side-effects, which are more severe and long-lasting than those related with Δ9-THC (Cohen and Weinstein 2018). Despite a number of clinical trials with promising results, for some cannabinoids there are still a relative scarcity of data on long-term tolerability and efficacy (De Luca and Fattore 2018). However, chronic use of cannabinoids have been associated with structural and functional neuronal alterations, which lead to addiction syndrome and withdrawal symptoms (Evren and Bozkurt 2013). Impaired cognitive and emotional function was also observed in chronic SCs users. SCs users have shown impairments in working and long-term memories, response inhibition, as well as an elevation of depressive and anxiety symptoms (Cohen et al. 2017). The same was observed in Livny et al. (2018) work. The study showed impairment in the neural brain mechanisms responsible for working memory in SCs users and the results also showed reduced gray matter volume in chronic SCs users.

Adverse effects of intoxication have been reported to occur even in those who only used SCs once, whereas withdrawal from SCs has been reported to occur only in daily users. Symptom management for acute intoxication is frequently treated with supportive care and intravenous fluids to treat electrolyte and fluid disturbances Adverse effects of intoxication have been reported to occur even in those who only used SCs once, whereas withdrawal from SCs has been reported to occur only in daily users. Symptom management for acute intoxication is frequently treated with supportive care and intravenous fluids to treat electrolyte and fluid

disturbances (Cooper 2016). Treatment is usually individualized and directed at the specific clinical presentation. Decisions regarding hospitalization, extent of observation, and treatment modalities are based on the symptoms, their severity, and comorbidities present (Hakimian et al. 2017).

Many adverse effects associated with acute intoxication are identical to some withdrawal symptoms; consequently, they are treated similarly. Benzodiazepines are recommended for controlling agitation, anxiety and seizures as as a first-line treatment. However, quetiapine is administered in treating withdrawal symptoms in patients who failed to respond to benzodiazepines (Evren and Bozkurt 2013; Cooper 2016). Neuroleptics are also administered for acute psychosis and agitation and mania with psychotic symptoms. Although not always effective, antiemetics have been administered for hyperemesis (Cooper 2016).

Combined use of SCs with other psychoactive products such as alcohol, cannabis, or tobacco was also reported, which suggest that the clinicians must be aware about it when dealing with an intoxicated patient. Furthermore, because most of the intoxicated patients have increased activity, they are reported to be at high risk for rhabdomyolysis, elevated creatine kinase, and subsequent renal failure (Evren and Bozkurt 2013). In addition, physicians need to remember that SCs are not detected by common commercial drug screenings and a negative drug screening result for SCs may not necessarily mean that the patient is free of these drugs, since the list of SCs types is constantly growing. Therefore, the use of SCs should be suspected if a patient arrives at clinical departments with adverse effects similar to those of cannabis and a negative drug screening for other drugs of abuse, including natural cannabinoids (Tournebize et al. 2017).

5. Concluding remarks

Initially developed as therapeutic agents, often for the treatment of pain, SCs rapidly appeared on the illicit drug market, where their prevalence had long been underestimated. Since then, their place in the market has steadily increased, with more than 560 synthetic psychoactive substances identified worldwide on the illicit market (Lafaye et al. 2017). Usually labeled as "not for human consumption" or "for aromatherapy use only" to circumvent legislation, SCs are commonly called 'synthetic marijuana' due to the fact they are produced with the goal of mimicking or enhancing the effects of Δ9-THC (Emery et al. 2018).

In light of the growing popularity of commercial synthetic cannabinoid products, it has become critically important to reevaluate our understanding of cannabinoid abuse. Increasing evidence suggests that there is a strong abuse potential for the high efficacy of these compounds, at least comparable to that of cannabis itself. Furthermore, these synthetic drugs are readily accessible and can be purchased easily from the comfort of home through the internet (Tai and Fantegrossi 2014). As long as there is a market for SCs, competitive pricings and attractive gimmicks will be used to increase sales and the appearance of electronic cigarette as an alternative to traditional tobacco cigarettes rapidly become a popular method of use for administration of SCs (Tai and Fantegrossi 2014; Breitbarth et al. 2018).

In Europe the production is closely monitored, however current legislation is frequently defeated and outwitted by manufacturers who regularly modify their chemical formulations, resulting in rapid turnover of SCs. Indeed, each synthetic compound is replaced by newer analogs within a year or two, making the inventory of existing products endless and requiring constant updaing of the classification system by new and separate groups and classes (Shevyrin and Morzherin 2015; Shevyrin et al. 2016; Lafaye et al. 2017).

There are several common features among different compounds of SCs which can highlight the risk potential which these drugs have and their related adverse effects. Firstly, SCs act as full agonists to CB_1 receptors and some also bind to CB_2 receptors. Secondly, SCs are much more potent, easily cross the blood-brain barrier and have more affinity compared to organic psychoactive cannabinoids like Δ9-THC (Cohen and Weinstein 2018).

To date, several studies based on behavior, neurochemistry, and electrophysics have helped the forensic and clinic community to understand the pharmacological mechanisms of action of synthetic compounds. However, many of them have been focused on the acute toxicological consequences of its use. As they are relatively new and novel, there are no epidemiological studies to show the long-term effects of these psychoactive compounds (Miliano et al. 2016). Moreover, since the chemical composition of many SCs is unknown and/or is changing from one batch to another, the effects may differ between consumers. Several of these substances may have addictive potential, higher than cannabis, producing greater acute and long-term toxicity, leading to serious adverse effects (Hervás 2017).

Given the prevalence of consumption there is an urgent need to better understand the pharmacology and toxicology of SCs. In particular, the role of intrinsic efficacy in abuse-related effects and adverse effects should be targeted in future studies (Emery et al. 2018). Very limited information is available on the safety of SCs in humans, and the occurrence of serious health damage in their abusers is highly probable.

Analytical laboratories are challenged with SCs identification in biological matrices due to structural diversity and similarity. Unidentified synthetic compound in a patient's sample, makes it difficult to definitively evaluate the clinical effects of SCs or develop specific treatments. Given the evidence of the damage caused by SCs and the risk of adverse complications, more epidemiological and clinical studies are needed to investigate the risk factors associated with the abuse of these substances in order to integrate such information into the prevention and treatment programs. In addition, clinicians should be aware of the effects of the use of these substances and their possible complications in order to offer a more appropriate approach to treatment (Castaneto et al. 2014; Hervás 2017).

Given the worldwide spread of these herbal mixtures, an international cooperation system is mandatory for sharing analytical information and improving monitoring of the global drug market (Fattore and Fratta 2011).

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Declaration of interest

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