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REVIEW ARTICLE

An updated review on synthetic cathinones

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Abstract

Cathinone, the main psychoactive compound found in the plant *Catha edulis* Forsk. (khat), is a β-keto analogue of amphetamine, sharing not only the phenethylamine structure, but also the amphetamine-like stimulant effects. Synthetic cathinones are derivatives of the naturally occurring cathinone that largely entered the recreational drug market at the end of 2000s. The former "legal status", impressive marketing strategies and their commercial availability, either in the so-called "smartshops" or via the Internet, prompted their large spread, contributing to their increasing popularity in the following years. As their popularity increased, the risks posed for public health became clear, with several reports of intoxications and deaths involving these substances appearing both in the social media and scientific literature. The regulatory measures introduced thereafter to halt these trending drugs of abuse have proved to be of low impact, as a continuous emergence of new non-controlled derivatives keep appearing to replace those prohibited. Users resort to synthetic cathinones due to their psychostimulant properties but are often unaware of the dangers they may incur when using these substances. Therefore, studies aimed at unveiling the pharmacological and toxicological properties of these substances are imperative, as they will provide increased expertise to the clinicians that face this problem on a daily basis. The present work provides a comprehensive review on history and legal status, chemistry, pharmacokinetics, pharmacodynamics, adverse effects and lethality in humans, as well as on the current knowledge of the neurotoxic mechanisms of synthetic cathinones.

Keywords Synthetic cathinones · Chemistry · Pharmacokinetics · Pharmacodynamics · Adverse effects · Neurotoxicity

Introduction

The first synthetic cathinones (SCs) were synthetized in late 1920s (Hyde et al. 1928; Saem de Burnaga Sanchez 1929), attracting attention for their putative medicinal purposes in the next decades, mainly as antidepressant and appetite suppressant drugs (Deramos 1964; Gardos and Cole 1971; Soroko et al. 1977). Nonetheless, only in the beginning of the twenty-first century (Bossong et al. 2005), they started entering the recreational drug market, gaining an outstanding popularity, and being rapidly and widely diffused across the globe. Many factors may have accounted for this trending phenomenon, including their easy availability and affordable prices, as well as their former legal status (Corkery et al. 2018). Although several measures were made to stop this drug pandemic (Bonson et al. 2019; Portuguese Government Autonomous Region of Madeira-Legislative Assembly 2017; Portuguese Government Ministry for Health 2013; UNODC 1971), drug designers appear to be always one-step ahead from law enforcement agencies, with the drug market being flooded with new derivatives in order to replace those previously considered illegal. Although the physical and chemical properties of these substances, as well as their synthetic processes, are generally known by the scientific community, information on the pharmacological features and toxicological potential related to their use is scant (Zawilska and Wojcieszak 2018). Additionally, products sold under the same "brand name" often markedly differ on their composition and in purity (Araújo et al. 2015). Thus, the public health harms posed by these new psychoactive substances (NPS) are immense.

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The present work aimed to provide an update on SCs through the review of their chemical, pharmacokinetic and pharmacodynamic properties, as well as their toxicological potential, resorting to clinical case reports, as well as in vivo and in vitro studies.

History and legal status

In the late eighteenth century, *Catha edulis* was described for the first time by Petrus Forskål, and it was later named as *C. edulis* Forsk. in the papers of Carsten Niebuhr, the only survivor of the expedition to Egypt and Yemen. *C. edulis* Forsk., also known as khat, is an autochthonous plant to East Africa, namely to former Abyssinia, though nowadays it is found in several other countries of Eastern and Southern Africa, Southwest Arabian peninsula and in Afghanistan (Al-Hebshi and Skaug 2005; Alles et al. 1961; Getasetegn 2016; Krikorian 1984; Odenwald et al. 2015). The chewing of the fresh khat leaves and stalks has been promoted by the populations of these regions for centuries due to the pro-social psychostimulant properties of the plant, not just in special occasions but also on a day-to-day basis (Al-Hebshi and Skaug 2005; Al-Motarreb et al. 2002; Dunne et al. 2015; Odenwald et al. 2015; Rätsch and Hofmann 2005). Although a high prevalence of use still exists in the aforementioned countries (e.g. in Yemen, the prevalence of use among men ranges from 80 to 90%) (Patel 2019), khat chewing practice has spread to Europe, as well as to United States of America (USA), alongside the rise of migration (EMCDDA 2011; Nakajima et al. 2017b; UNODC 2014). However, the prevalence of use outside the regions where khat is native from is still unclear.

Fresh khat leaves contain several compounds, including alkaloids, flavonoids, tannins, glycosides, sterols, terpenoids, amino acids, vitamins, and minerals (Getasetegn 2016; Halbach 1972; Kalix and Braenden 1985; Szendrei 1980; Wabe 2011). The stimulant effects induced by this plant were primarily attributed to (1*S*,2*S*)-2-amino-1-phenylpropan-1-ol, generally known as cathine, which was detected (in khat) in the late nineteenth century (Fluckiger and Gerock 1887), and later identified in the early twentieth century (Wolfes 1930). Nonetheless, it was considered that cathine per se could not be the substance chiefly responsible for the psychostimulant properties of khat (v. Brücke 1941). In the discovery route for other psychoactive compound(s) putatively present in this plant, (2*S*)-2-amino-1-phenylpropan-1-one, ordinarily known as cathinone, was identified and isolated in 1975 from fresh khat leaves (United Nations Division of Narcotic Drugs 1975). Cathinone was determined to be not only the major psychoactive compound present in the fresh khat leaves, but also the biosynthetic precursor of the less active substances cathine and (1*R*,2*S*)-2-amino-1-phenylpropan-1-ol [(−)-norephedrine] (Brenneisen et al. 1986). Cathinone proved to be far more potent than cathine, but it is chemically unstable and very labile (Friebel and Brilla 1963; Glennon et al. 1984; Griffiths et al. 1997; Kalix and Khan 1984; Zelger et al. 1980). These chemical features may explain why cathinone was not identified earlier as some studies aiming to determine the psychostimulant compounds present in khat were performed using dried material (Schorno et al. 1982). Moreover, as khat naturally ages, or the harvested leaves and stalks dry up, the cathinone content decreases dramatically, being enzymatically reduced to cathine and (−)-norephedrine (Fig. 1) (Al-Hebshi and Skaug 2005; Brenneisen et al. 1986; Geisshüsler and Brenneisen 1987). Therefore, to experience the stimulating desired effects, khat leaves need to be chewed soon after being harvested (Al-Motarreb et al. 2002; Cox and Rampes 2003).

Shortly before the identification of cathine by Wolfes (1930), the synthetic manufacture of two cathinones was described: in 1928, the 2-(methylamino)-1-phenylpropan-1-one, or methcathinone (Hyde et al. 1928), and a year later

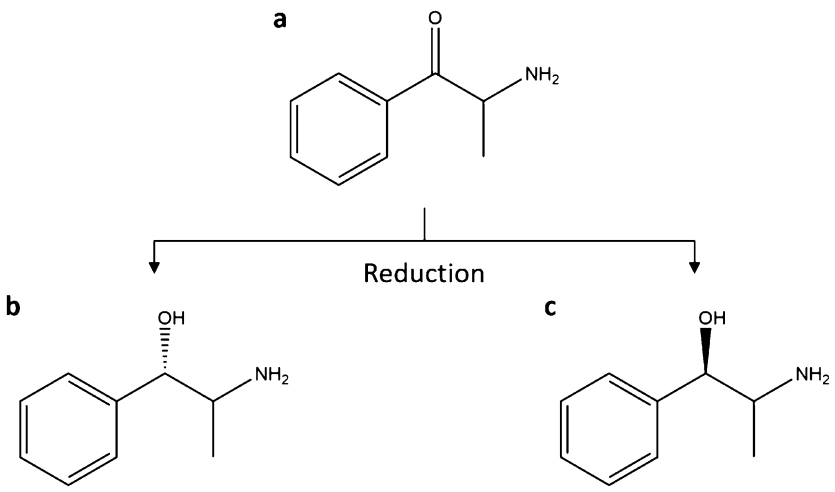


Fig. 1 Chemical structures of **a** (2*S*)-2-amino-1-phenylpropan-1-one (cathinone), **b** (1*S*,2*S*)-2-amino-1-phenylpropan-1-ol (cathine) and **c** (1*R*,2*S*)-2-amino-1-phenylpropan-1-ol [(−)-norephedrine]

the 2-(methylamino)-1-(4-methylphenyl)propan-1-one, or mephedrone (Saem de Burnaga Sanchez 1929). The striking structural similarity of the two aforementioned synthetic compounds and classical amphetamines, in addition to their effects over the central nervous system (CNS), raised an interest in synthesizing cathinones for clinical purposes (Mehta 1974; Schütte 1961; Thomae 1963; Wander 1963). Methcathinone was the first synthetic cathinone derivative marketed for medicinal purposes, first as an antidepressant drug in the former Soviet Union in the 1930s and 1940s, and later (1957) investigated as an analeptic drug in USA, though never been clinically commercialized in the latter (Barceloux 2012; Cozzi et al. 1999; DeRuiter et al. 1994; Patel 2018; Sikk and Taba 2015). 2-(Diethylamino)-1-phenylpropan-1-one, or amfepramone, was introduced in the market in 1958 as an appetite suppressant drug (Bolding 1974; Clein and Benady 1962; Deramos 1964; Seaton et al. 1961). At that time, 1-(4-methylphenyl)-2-pyrrolidin-1-ylpentan-1-one, or pyrovalerone, was synthesized to be used in clinical treatment of lethargy and chronic fatigue, and as an anorectic and appetite suppressant drug (Gardos and Cole 1971; Goldberg et al. 1973). In the late 1990s, 1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one, or methylone, was developed to be used as an anti-Parkinsonism and antidepressant drug (Jacob and Shulgin 1996). Of the few SCs developed for therapeutic purposes, only 2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one, or bupropion, is currently available in the market (Costa et al. 2019b; Soroko et al. 1977). Bupropion has been used as an antidepressant drug, and as a co-adjuvant in smoking cessation therapy and in the treatment of obesity. Additionally, it has proven efficacy in preventing depressive episodes in patients with seasonal affective disorders, and it has potential pharmacological relevance for the treatment of attention-deficit/hyperactivity disorder and psychoactive substances dependence (Carroll et al. 2009; Castells et al. 2016; Hughes et al. 2014; Magovern and Crawford-Faucher 2017; Saunders et al. 2018; Stahl et al. 2004; Verbeeck et al. 2017).

The use of the aforementioned SCs as therapeutic drugs is limited, mainly due to their potential for abuse and dependence, as well as their-induced adverse effects (Clein and Benady 1962; Dal Cason et al. 1997; Deniker et al. 1975; DeRuiter et al. 1994). Thus, they attracted attention towards recreational use. In this scenario, methcathinone resurfaced at the forefront of this group of psychoactive substances, with the first reports of its abuse arising in the Soviet Union (1970s), and about 20 years later in the USA. It has been known by the slang names of "cat", "jeff" or "mulka" (Dal Cason et al. 1997; Emerson and Cisek 1993; Patel 2018), leading to its inclusion in the Schedule I of the 1971 United Nations (UN) Convention on Psychotropic Substances (UNODC 1971). Reports on amfepramone and pyrovalerone abuse also emerged soon after being synthesized (Clein and Benady 1962; Deniker et al. 1975), leading to their withdrawal from the market, and their inclusion in the Schedule IV of the 1971 UN Convention on Psychotropic Substances (UNODC 1971). Of note, although khat is not currently under international control, cathinone and cathine are included in Schedules I and III, respectively, of the 1971 UN Convention on Psychotropic Substances (UNODC 1971). Methylone was never marketed for medicinal purposes due to its potent psychostimulant action, closely related to that of 3,4-methylenedioxymethamphetamine (MDMA) (Dal Cason et al. 1997). Methylone was among the so-called "first wave/generation" of SCs to be marketed as "legal high" in European and Japanese markets, through "smartshops" and on the Internet, in early 2000s (Bossong et al. 2005). At the same time, a short period of cathinone abuse in Israel, sold under the name of "Hagigat", led to an increase number of hospitalizations (Bentur et al. 2008; Schifano et al. 2011). As a result of the cathinone ban in Israel and/or of the instability of the MDMA market in the European Union (EU), mephedrone started to be sold by the Neorganics company (Israel), rapidly spreading throughout Europe and Australia, and later to the USA (Bruno et al. 2012; Brunt et al. 2011; Camilleri et al. 2010; Dickson et al. 2010; Schifano et al. 2011). In the same year, 1-(3-fluorophenyl)-2-(methylamino)propan-1-one (3-FMC), 1-(4-fluorophenyl)-2-(methylamino)propan-1-one (flephedrone or 4-FMC), 2-(ethylamino)-1-phenylpropan-1-one (*N*-ethylcathinone), 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one (butylone) and 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one (MDPV) were reported for the first time in the EU through the Early Warning System (EMCDDA-Europol 2008). Several factors may have contributed to the high demand for SCs in the mid-2000s, as follows: (1) their amphetamines- and cocaine-like psychostimulant induced enjoyable effects (euphoria, empathy, increased openness and sociability, increased libido and sexual performance); (2) easy availability and affordable prices; (3) appealing names and eye-catching packages (Fig. 2); (4) erroneously perceived as legal (so-called "legal highs") and safe (assumed high purity) to be consumed; (5) and finally, the lack of rapid field screening tests to confirm their abuse (Corkery et al. 2018). Some authors also suggested that the high price, unavailability, and decrease of purity of amphetamine (AMPH), MDMA and cocaine might also have contributed to the high popularity of SCs (Carhart-Harris et al. 2011; Measham et al. 2010). Interestingly, SCs, including amfepramone, as well as cathinone and cathine were found to be used as stimulant doping agents in sports, with a total of 8 out of 611 occurrences reported by World Anti-Doping Agency (2019). Additionally, cathinone and related synthetic substances have been found in urine samples from race horses in the past decade (Loganathan et al. 2021).

Fig. 2 Synthetic cathinones' packages formerly concealed as "plant feeder" or "bath salt", now sold as "charge powder" or "research chemical". Some of these packages are from Portuguese "smartshops" closed in 2013 following the new legislative control measures regarding these substances, and were provided by the Forensic Science Laboratory of the Portuguese Criminal Police. Other photos of packages are from websites, where is still possible to purchase such substances

In this scenario, SCs emerged in the recreational drug market, being sold as "bath salts", "fertilizer", "plant food" or "research chemicals" and labelled "not for human consumption" or "for research purposes only" to avoid legal persecution (Zawilska and Wojcieszak 2018). They were abused worldwide as "legal highs" or alternatives to the classical illicit drugs of abuse, being available from local dealers or the so-called "smartshops", and through the Internet, in the form of powder, crystals and capsules, and less frequently as tablets (Karila and Benyamina 2018; Valente et al. 2014). The alarming popularity increase of SCs, and particularly of mephedrone in 2009–2010, was accompanied by reports of toxicity and even deaths related to its abuse (Dickson et al. 2010; Gustavsson and Escher 2009; Wood et al. 2010a, b, 2011). Upon recommendation of the Advisory Council on the Misuse of Drugs, the United Kingdom (UK) Government scheduled, on April of 2010, several SCs (including mephedrone) as controlled drugs under Class B in the UK Misuse of Drugs Act 1971 (Advisory Council on the Misuse of Drugs 2010; Morris 2010). In addition, mephedrone was submitted to control measures in EU Member States in a Decision of the Council of the European Union (2010). Notwithstanding, 26 other SCs emerged during this period to replace the controlled mephedrone, being reported for the first time in the EU through the Early Warning System, as follows: 4 derivatives in 2009 [e.g. 1-(4-methoxyphenyl)-2-(methylamino) propan-1-one (methedrone)] (EMCDDA-Europol 2009), 14 derivatives in 2010 [e.g. 1-(3,4-dimethylphenyl)-2-(methylamino)propan-1-one (3,4-DMMC), 1-naphthalen-2-yl-2-pyrrolidin-1-ylpentan-1-one (β-naphyrone), 2-(ethylamino)-1-(4-methylphenyl)propan-1-one (4-MEC), 2-(methylamino)-1-phenylbutan-1-one (buphedrone) and 2-(methylamino)-1-phenylpentan-1-one (pentedrone)] (EMCDDA-Europol 2010) and 8 derivatives in 2011 [e.g. 1-phenyl-2-pyrrolidin-1-ylbutan-1-one (α-PBP) and 1-phenyl-2-pyrrolidin-1-ylpentan-1-one (α-PVP)] (EMCDDA-Europol 2011). Later in the USA, three SCs, namely mephedrone and MDPV (2012) and methylone (2013) were permanently placed in Schedule I in the USA Controlled Substances Act (Bonson et al. 2019). The legislative control of this "first wave/generation" SCs, in addition to the rapid and high demand for novel and legal derivatives, fuelled the development of other derivatives. Thus, 69 new derivatives flooded the market from 2012 and 2015, with a peak of 31 derivatives being reported for the first time in 2014 (EMCDDA-Europol 2012, 2013, 2014, 2015). Alongside the interest in these substances, the number of intoxication reports, in addition to the severity of the effects induced by their abuse, also massively increased (Adamowicz et al. 2014; Bertol et al. 2014; Cosbey et al. 2013; Fudalej et al. 2013; Joksovic et al. 2012; Karinen et al. 2014; Kesha et al. 2013; Kudo et al. 2015; Namera et al. 2013; Rojek et al. 2012; Sauer et al. 2011; Sellors et al. 2014; Thornton et al. 2012a; Zuba et al. 2013). Some measures were taken in an attempt to control the high-speed proliferation of this ascending market. The Commission on Narcotic Drugs Resolution 56/3 of 2013 has drawn attention to the unprecedented number and to the rate of emergence of NPS, and recognized the need to detect, identify and report them through the establishment of a global Early Warning System.

Also, the idea of an international cooperation was reinforced where each EU Member State and relevant organizations were encouraged to collect and share information regarding these substances (e.g. scientific, epidemiological, forensic and toxicological data), as well as individual experiences of each country to address this problem (e.g. regulatory measures, restrictions and legislation), in order to provide a timely response (Commission on Narcotic Drugs 2013). At the national level, the legal approaches implemented by each country to halt this problem varies widely, from a substance-by-substance control to an analogue (e.g. substances chemically related to a substance already under control) or even generic (e.g. entire group of substances) control, while others have resorted to the medicines and/or use of consumer protection legislation, or adoption of specific legislation (UNODC 2013). The so-called "blanket bans" enforced by several countries noy only lead to the close of the legal retail outlets (e.g. "head- or smartshops" convenience stores), as occurred in Portugal (Portuguese Government Autonomous Region of Madeira-Legislative Assembly 2017; Portuguese Government Ministry for Health 2013), but also have driven the NPS, including SCs, to the illegal street market alongside common illicit drugs of abuse and to the deep web (Corkery et al. 2018). Although the reasons are not clear, a significant decrease in the number of SCs reported for the first time to the EU Early Warning System has occurred since 2015. Legislative control measures adopted by EU Member States, and increasing control measures and law enforcement operations in countries, which provide these substances or their precursors, as China, may have contributed to that phenomenon (EMCDDA-Europol 2019). Of note, in 2017 the Council Decision 2005/387/JHA, which deliberates on the information exchange, risk assessment and control of NPS, was revised through the Directive (EU) 2017/2103 aiming to establish a more effective and swifter system. The three-step approach to respond to NPS remained unchanged (early warning, risk assessment and control measures), though shorter deadlines were introduced and the data collection and assessment procedures were accelerated (EMCDDA-Europol 2019). Additionally, 11 SCs were placed under international control in Schedule II of the 1971 UN Convention on Psychotropic Substances in a 5-year period (2015–2020) (UNODC 1971). Meanwhile, in the USA, ten derivatives were permanently included in Schedule I in the USA Controlled Substances Act in 2017, and a year later 1-(1,3-benzodioxol-5-yl)-2-(ethylamino) pentan-1-one (ephylone) was temporary placed in the same Schedule (Bonson et al. 2019). Nevertheless, in this cat and mouse game, the chemical designers always seem to be one-step ahead of the authorities.

Chemistry

SCs are derivatives of cathinone (Fig. 3d), a natural occurring alkaloid found in the fresh khat leaves and twigs. Chemically, SCs are part of a large family of substances, the methylphenethylamines, structurally resembling classical amphetamines (Fig. 3a–c), the main difference being an additional β-keto substituent at the amino alkyl side chain

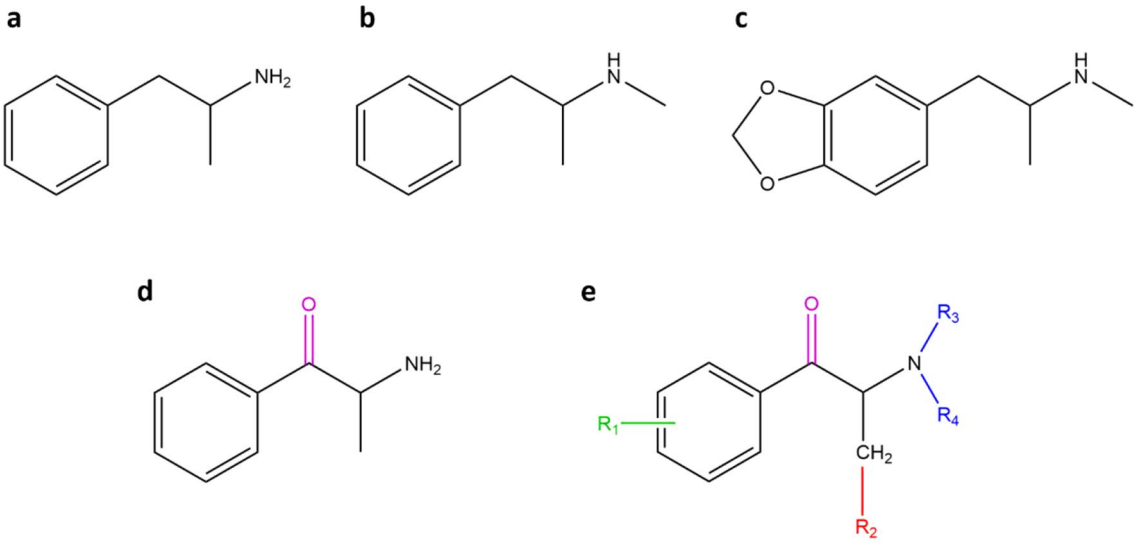


Fig. 3 Chemical structures of **a** amphetamine, **b** methamphetamine, **c** 3,4-methylenedioxymethamphetamine, **d** cathinone, and **e** general structure of synthetic cathinone derivatives. The β-keto group (displayed in purple) is the main structural difference between classical amphetamines and cathinone and its synthetic derivatives. R_1 (displayed in green), R_2 (displayed in red), R_3 and R_4 (displayed in blue) are related to the positions at which substitutions can be made to obtain different derivatives, namely substitutions in the aromatic ring, the substitutions in the α-carbon of the side chain and/or substitutions in the amino group, respectively (colour figure online)

(Fig. 3d) (Banks et al. 2014; Coppola and Mondola 2012; Kelly 2011; Valente et al. 2014).

Modifications on the cathinone backbone structure (Fig. 3e) are possible at four different positions, namely the aromatic ring (R_1), the alkyl side chain (R_2) and the amino group (R_3 and R_4), allowing the synthesis of a countless number of derivatives (Kelly 2011; Paillet-Loilier et al. 2014; Valente et al. 2014). This fact was corroborated by the EU Drug Markets Report of 2019, which counts a total of 138 different SCs being currently monitored by the European Monitoring Centre for Drugs and Drug Addiction (Fig. 4) (EMCDDA-Europol 2019).

Depending on the substitutions made on the cathinone scaffold, the respective SCs can be separated into four different chemical sub-families (Kelly 2011; Valente et al. 2014): (1) the *N*-alkyl cathinones (Table 1), characterized by alkyl substitutions in the amino group (R_3 and/or R_4), and possible alkyl or halogen substitutions in the aromatic ring (R_1) and/or alkyl substitutions in the α-carbon of the side chain (R_2); (2) the *N*-pyrrolidine cathinones (Table 2), characterized by a pyrrolidinyl substitution in the amino group (R_3 and R_4), and possible alkyl or halogen substitutions in the aromatic ring (R_1) and/or alkyl substitutions in the α-carbon of the side chain (R_2); (3) the 3,4-methylenedioxy-*N*-alkyl cathinones (Table 3), characterized by the addition of a 3,4-methylenedioxy group to the aromatic ring (R_1) and alkyl substitutions in the amino group (R_3 and/or R_4), and possible alkyl substitutions both in the α-carbon of the side chain (R_2) and in the aromatic ring (R_1); (4) the 3,4-methylenedioxy-*N*-pyrrolidine cathinones (Table 4), characterized by the addition of a 3,4-methylenedioxy group to the aromatic ring (R_1) and a pyrrolidinyl substitution in the amino group (R_3 and R_4), and possible alkyl substitutions both in the α-carbon of the side chain (R_2) and in the aromatic ring (R_1). Additionally, SCs presenting unique structures, as β-naphyrone, can be aggregated in a miscellaneous chemical sub-family (Table 5). In β-naphyrone, the phenyl moiety was replaced by a naphthyl ring.

Of note, similarly to other phenethylamines, SCs possess a chiral centre, and thus may exist in two stereoisomeric forms, which can vary in terms of potency and affinity towards their pharmacological targets (Coppola and Mondola 2012; Paillet-Loilier et al. 2014). Nonetheless, most of SCs appear as racemic mixtures, as occurs in nature with cathinone. On the other hand, racemization of the enantiomeric forms of these psychoactive substances may also happen through keto-enol tautomerism (Coppola and Mondola 2012). Additionally, the chemical variations on the cathinone backbone structure will be responsible for the different pharmacokinetic and pharmacodynamic properties of each derivative, as will be discussed in the following sections.

Pharmacokinetics

The most common route for khat administration is oral, although users may also resort to inhalation/smoking. Traditionally, fresh khat leaves and twigs are chewed in order to release the psychoactive alkaloids present in this plant. To a lesser extent, khat can be also ingested by different ways, as following: (1) fresh khat leaves and twigs are used to prepare infusions (as tea); (2) dried powdered khat leaves can be blended with sugar or honey (as candies), or with other herbal extracts and water (as a paste); (3) khat infusions may be also fermented with honey (as mead). Dried khat leaves can also be rolled up to be smoked alone or in combination with tobacco or hashish, although this way

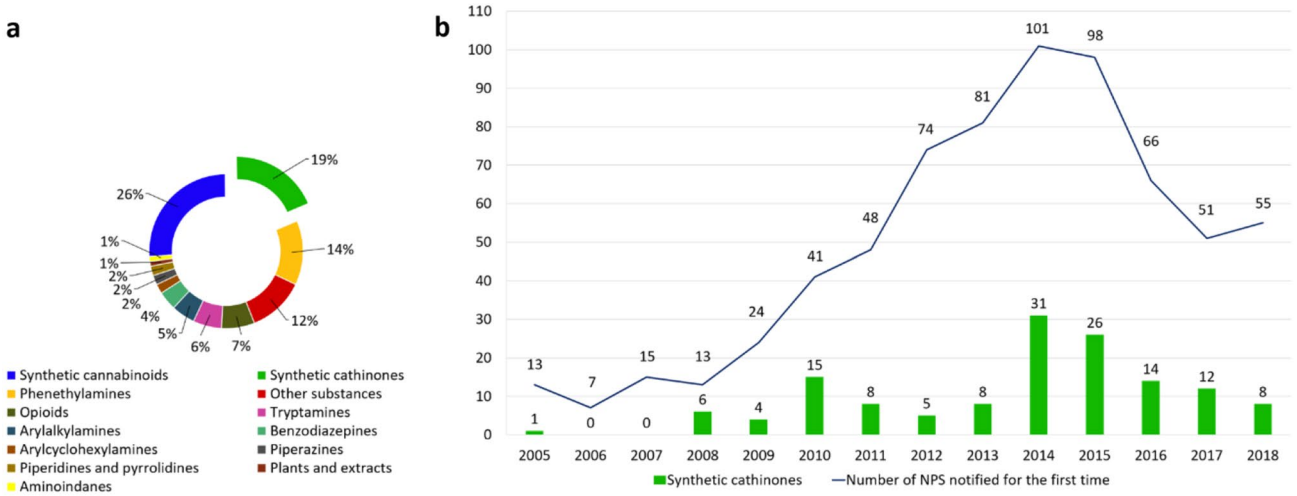
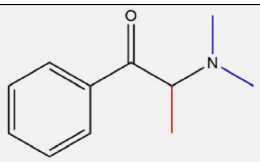
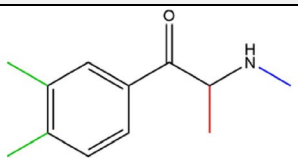
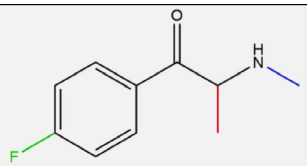
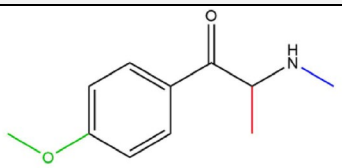
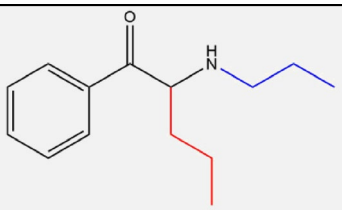
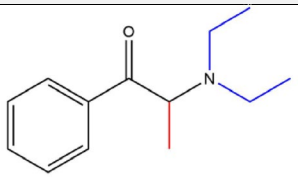
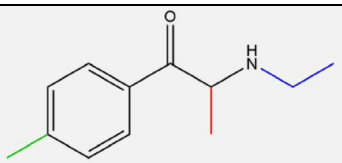
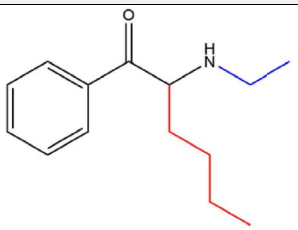


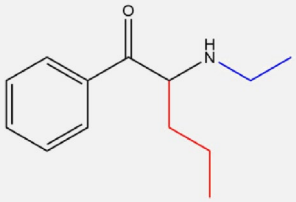
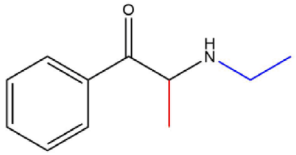
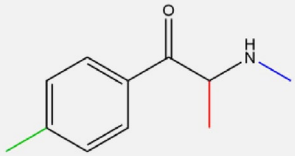
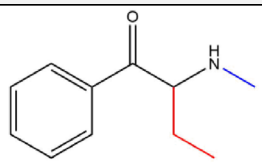
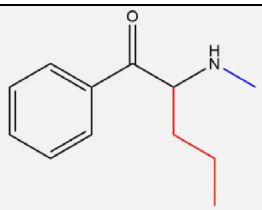
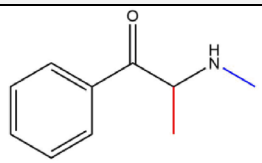
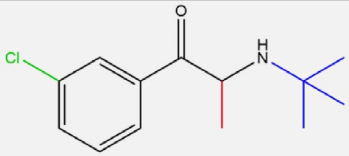
Fig. 4 Distribution of the 731 new psychoactive substances (NPS) reported to the European Union Early Warning System from 1997 to 2018 (**a**), and the number of synthetic cathinone derivatives notified to the same entity for the first time since their appearance in 2005 until 2018, in relation to the number of total NPS reported during the same period (**b**). Data collected from (EMCDDA-Europol 2019)

Table 1 IUPAC names, common names, and chemical structures of *N*-alkyl synthetic cathinones (colour figure online)

IUPAC name	Common name	Chemical structure
(2*S*)-2-(Dimethylamino)-1-phenylpropan-1-one	*N*,*N*-Dimethylcathinone; Metamfepramone	
1-(3,4-Dimethylphenyl)-2-(methylamino)propan-1-one	3,4-Dimethylmethcathinone; 3,4-DMMC	
1-(4-Fluorophenyl)-2-(methylamino)propan-1-one	4-Fluoromethcathinone; 4-FMC; Flephedrone	
1-(4-Methoxyphenyl)-2-(methylamino)propan-1-one	4-Methoxymethcathinone; βk-PMMA; Methedrone	
1-Phenyl-2-(propylamino)pentan-1-one	α-Propylaminopentiophenone; N-PP	
2-(Diethylamino)-1-phenylpropan-1-one	*N*,*N*-Diethylcathinone; Amfepramone	
2-(Ethylamino)-1-(4-methylphenyl)propan-1-one	4-Methylethcathinone; NRG-2; 4-MEC	
2-(Ethylamino)-1-phenylhexan-1-one	*N*-Ethylhexedrone	

of consumption is less common (Alles et al. 1961; Rätsch and Hofmann 2005; Wabe 2011). The psychoactive alkaloids, almost entirely released into the saliva during khat chewing, are absorbed, in the first place, through the oral mucous membrane. The remaining alkaloid content present in swallowed juice is absorbed through the gastrointestinal

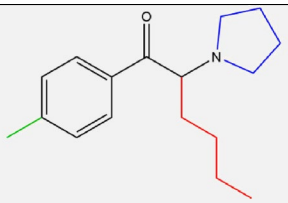
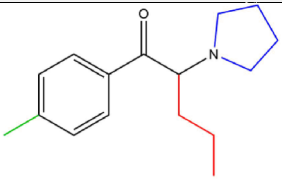
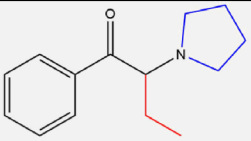
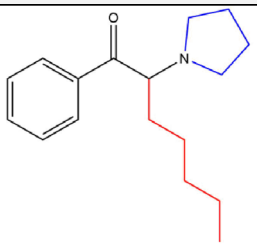
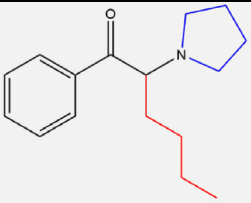
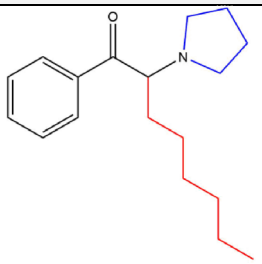
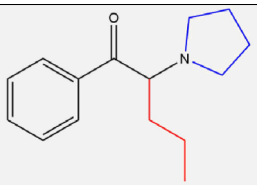
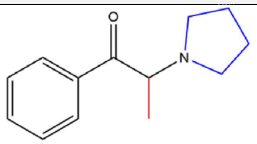
Table 1 (continued)

IUPAC name	Common name	Chemical structure
2-(Ethylamino)-1-phenylpentan-1-one	α-Ethylaminopentiophenone; α-EAPP	
2-(Ethylamino)-1-phenylpropan-1-one	N-Ethylcathinone; Ethcathinone	
2-(Methylamino)-1-(4-methylphenyl)propan-1-one	4-Methylmethcathinone; 4-MMC; Mephedrone	
2-(Methylamino)-1-phenylbutan-1-one	α-Methylaminobutyrophenone; Buphedrone	
2-(Methylamino)-1-phenylpentan-1-one	α-Methylaminovalerophenone; Pentedrone	
2-(Methylamino)-1-phenylpropan-1-one	α-Methylaminopropiophenone; Methcathinone; Ephedrone	
2-(Tert-butylamino)-1-(3-chlorophenyl)propan-1-one	α-(Tert-butylamino)-m-chloropropiophenone; Amfebutamone; Bupropion	

The different colors are related to the positions at which substitutions can be made to obtain the different derivatives, namely substitutions in the aromatic ring (displayed in green), the substitutions in the α-carbon of the side chain (displayed in red) and/or substitutions in the amino group (displayed in blue)

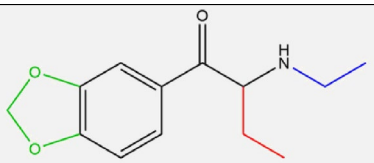
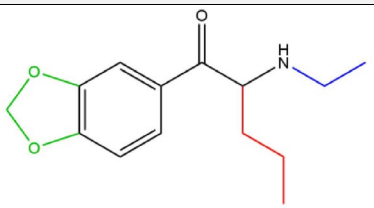
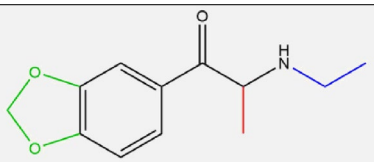
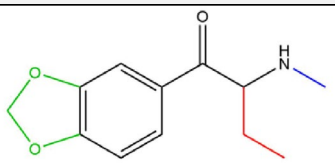
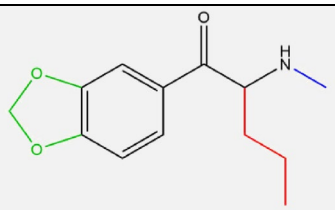
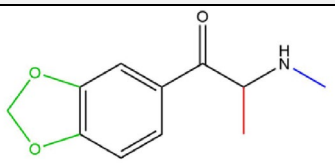
tract, rapidly reaching the systemic circulation (Dunne et al. 2015; Toennes et al. 2003). Users can consume between 100 and 500 g of khat during a single khat-chewing session that can last from 3 to 4 h, although it has been reported that binge sessions can last for at least 24 h (Arunotayanun and Gibbons 2012; Patel 2018). The alkaloid content of the khat plant varies widely depending on origin and type, time since being harvested and storage conditions (Kalix 1990). Fresh khat from different origins (Ethiopia, Kenya, North Yemen and Madagascar) contains on average 36 mg of cathinone per 100 g of khat fresh leaves (Geisshüsler and Brenneisen 1987). Cathinone content in fresh khat leaves from different locations of Yemen ranged from 77.7 to 342.8 mg per 100 g of khat leaves (Al-Motarreb et al. 2002), whilst khat leaves

Table 2 IUPAC names, common names, and chemical structures of *N*-pyrrolidine synthetic cathinones (colour figure online)

IUPAC name	Common name	Chemical structure
1-(4-Methylphenyl)-2-pyrrolidin-1-ylhexan-1-one	4-Methyl-α-pyrrolidinohexanophenone; MPHP	
1-(4-Methylphenyl)-2-pyrrolidin-1-ylpentan-1-one	4-Methyl-α-pyrrolidinovalerophenone; Pyrovalerone	
1-Phenyl-2-pyrrolidin-1-ylbutan-1-one	α-Pyrrolidinobutiophenone; α-PBP	
1-Phenyl-2-pyrrolidin-1-ylheptan-1-one	α-Pyrrolidinoheptanophenone; α-PHPP; PV8	
1-Phenyl-2-pyrrolidin-1-ylhexan-1-one	α-Pyrrolidinohexanophenone; α-PHP; PV7	
1-Phenyl-2-pyrrolidin-1-yloctan-1-one	α-Pyrrolidinooctanophenone; α-POP; PV9	
1-Phenyl-2-pyrrolidin-1-ylpentan-1-one	α-Pyrrolidinopentiophenone; α-Pyrrolidinovalerophenone; α-PVP	
1-Phenyl-2-pyrrolidin-1-ylpropan-1-one	α-Pyrrolidinopropiophenone; α-PPP	

The different colors are related to the positions at which substitutions can be made to obtain the different derivatives, namely substitutions in the aromatic ring (displayed in green), the substitutions in the α-carbon of the side chain (displayed in red) and/or substitutions in the amino group (displayed in blue)

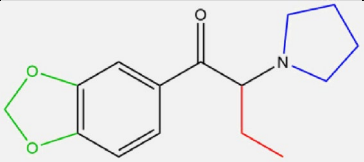
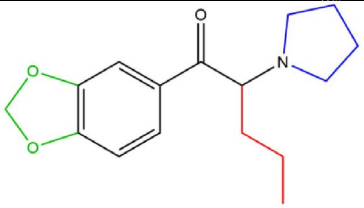
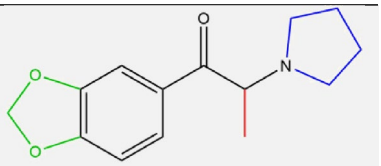
Table 3 IUPAC names, common names, and chemical structures of 3,4-methylenedioxy-*N*-alkyl synthetic cathinones (colour figure online)

IUPAC name	Common name	Chemical structure
1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one	βk-EBDB; Eutylone	
1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)pentan-1-one	βk-EBDP; *N*-Ethylpentylone; Ephylone	
1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)propan-1-one	βk-MDEA; Ethylone	
1-(1,3-Benzodioxol-5-yl)-2-(methylamino)butan-1-one	βk-MBDB; Butylone	
1-(1,3-Benzodioxol-5-yl)-2-(methylamino)pentan-1-one	βk-MBDP; Pentylone	
1-(1,3-Benzodioxol-5-yl)-2-(methylamino)propan-1-one	βk-MDMA; Methylone	

The different colors are related to the positions at which substitutions can be made to obtain the different derivatives, namely substitutions in the aromatic ring (displayed in green), the substitutions in the α-carbon of the side chain (displayed in red) and/or substitutions in the amino group (displayed in blue)

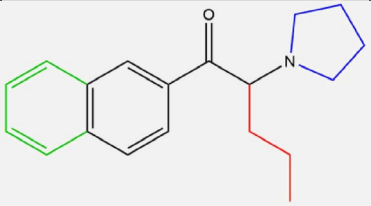
confiscated at the Frankfurt (unknown origin) and Geneva (proceeding from Kenya) airports contained, respectively, 114 mg (Toennes et al. 2003) and 102 mg (Widler et al. 1994) of cathinone per 100 g of khat fresh leaves. Plasma cathinone levels have not been measured during a regular khat-chewing session. Nonetheless, data from several studies involving healthy volunteers naive to khat, referred that peak plasma cathinone levels are reached between 1.5 and 3.5 h, and average maximal plasma concentration of cathinone ranging from 58.9 to 127 ng/mL (Halket et al. 1995; Toennes et al. 2003; Widler et al. 1994). Surprisingly, although being the major psychoactive substance present in khat, with proven CNS stimulant effects, cathinone presented a very low blood–brain barrier (BBB) permeability (Patel 2018). In humans, cathinone is rapidly and extensively metabolized into cathine and (−)-norephedrine involving the reduction of β-ketone moiety to the corresponding alcohols by phase I metabolic enzymes (Fig. 1). Cathinone is mainly excreted in the urine in the form of its metabolites, although only 7% or less of the absorbed parent compound being found there (Brenneisen et al. 1986; Kalix and Braenden 1985; Toennes and Kauert 2002; Widler et al. 1994), with an average elimination half-time between 1.5 and 4.3 h (Toennes et al. 2003; Widler et al. 1994).

Table 4 IUPAC names, common names, and chemical structures of 3,4-methylenedioxy-*N*-pyrrolidine synthetic cathinones (colour figure online)

IUPAC name	Common name	Chemical structure
1-(1,3-Benzodioxol-5-yl)-2-pyrrolidin-1-ylbutan-1-one	3,4-Methylenedioxy-α-pyrrolidinobutiophenone; MDPBP	
1-(1,3-Benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one	3,4-Methylenedioxypyrovalerone; MDPV	
1-(1,3-Benzodioxol-5-yl)-2-pyrrolidin-1-ylpropan-1-one	3,4-Methylenedioxy-α-pyrrolidinopropiophenone; MDPPP	

The different colors are related to the positions at which substitutions can be made to obtain the different derivatives, namely substitutions in the aromatic ring (displayed in green), the substitutions in the α-carbon of the side chain (displayed in red) and/or substitutions in the amino group (displayed in blue)

Table 5 IUPAC name, common name, and chemical structure of miscellaneous synthetic cathinone (colour figure online)

IUPAC name	Common name	Chemical structure
1-Naphthalen-2-yl-2-pyrrolidin-1-ylpentan-1-one	Naphthylpyrovalerone; NRG-1; β-Naphyrone	

The different colors are related to the positions at which substitutions can be made to obtain the different derivatives, namely substitutions in the aromatic ring (displayed in green), the substitutions in the α-carbon of the side chain (displayed in red) and/or substitutions in the amino group (displayed in blue)

Regarding SCs, several routes of administration have been described. Usually, these substances are taken orally in the form of capsules or tablets, swallowed after the powder is rolled up in a cigarette paper ("bombing"), drunk after mixing with a beverage; or nasally insufflated/snorted using a key dipped into powder ("keying") (Valente et al. 2014; Zawilska and Wojcieszak 2013). Intravenous (i.v.) injection, or "slamming", has been recently described as another common route of administration for these drugs of abuse (Karila and Benyamina 2018; Riley et al. 2020). Intramuscular and subcutaneous (s.c.) injection, rectal insertion ("booty bumping" or "plugging"), gingival and sublingual delivery, inhalation (vaporization/smoking through e-cigarettes) and insertion of the substance into the eyes ("eyeballing") were also reported, although being less common routes (Gonçalves et al. 2019; Karila and Benyamina 2018; Papaseit et al. 2017; Riley et al. 2020). Of note, multiple simultaneous routes of administration have been reported for a single session (Karila and Benyamina 2018; Prosser and Nelson 2012). Additionally, SCs are usually abused concomitantly with several other substances, either intentionally [e.g. in a context of a "chemsex" party, in which mephedrone has been reported to be abused in addition to methamphetamine (METH) and/or 4-hydroxybutanoic acid (GHB) or its precursor oxolan-2-one (GBL), to facilitate, sustain and

improve the sexual experiences] (McCall et al. 2015; Stuart 2016), or not (e.g. the lack of information concerning the content of the so-called "legal highs" led to the drug users to abuse simultaneously mephedrone, MDMA and caffeine) (Europol-EMCDDA 2010). Indeed, in a drug abuse scenario, SCs are often abused alongside other drugs of abuse, namely classical amphetamines, cocaine, GHB/GBL, cannabinoids, ketamine and/or alcohol, or prescription drugs, namely the so-called "Z-drugs" (e.g. zolpidem), in order to expand the psychoactive experience. They are also abused along with other prescription drugs, such as benzodiazepines, β-blockers and proton pump inhibitors, to counteract some side-effects, such as anxiety, tachycardia and stomach pain, respectively, or selective phosphodiesterase type 5 inhibitors, in order to increase libido and improve sexual performance (Corkery et al. 2018; Zawilska and Wojcieszak 2013).

Typically, the doses of SCs vary largely, from a few milligrams to a couple of grams. It depends on the derivative of choice and on the route of administration, as well as on the uncertainty of the "bath salt" content, namely the present substances, their concentrations and purity, which can often not correspond to the vendor's marketing claims and lead to higher probability of onset of unwanted effects or even overdosing (Brandt et al. 2011; Davies et al. 2010; Kelly 2011; Paillet-Loilier et al. 2014; Prosser and Nelson 2012; Zawilska and Wojcieszak 2018). According to user reports, the typical "single-use" oral doses for MDPV and mephedrone differ significantly, ranging from 2 to 25 mg and from 15 to 300 mg, respectively (Erowid 2015a, b). The self-reported "single-use" doses of mephedrone may vary from 5 to 125 mg, when administered by nasal insufflation, but the doses may be even higher for oral ingestion. Furthermore, mephedrone doses may rapidly increase over time, potentially reaching hundreds of mg or values as high as 9 g, if the user engages in a binge session and/or resorts to more than one route of administration (Dargan et al. 2011; German et al. 2014; Wood et al. 2010a, b). In addition, there are several "bath salt" products with identical name and appearance, but with different SCs and/or other detected substances, and of varying purity (Araújo et al. 2015; Brandt et al. 2011; Davies et al. 2010; Schneir et al. 2014; Zancajo et al. 2014; Zuba and Byrska 2013). According to some surveys, mephedrone abusers typically use between 0.5 and 1.9 g (divided into multiple "single-use" doses which are administered over time) per single session, that can last an average of 9–10 h, or even longer periods (24–48 h) (Carhart-Harris et al. 2011; Jones et al. 2016; Kapitány-Fövény et al. 2013; Lea et al. 2011; Newcombe 2009; Winstock et al. 2011b). Regarding SC nasal insufflation, it is generally characterized by a more rapid onset of the desired effects and lower doses are required to attain those effects, when compared to the oral ingestion (Gonçalves et al. 2019; Kelly 2011; Prosser and Nelson 2012; Valente et al. 2014). As it will be discussed below, the bioavailability of SCs largely varies between 7 and 11% for 3-methylmethcathinone (3-MMC) (Shimshoni et al. 2015) and mephedrone (Martínez-Clemente et al. 2013), and ranges from 78 to 89% for methylone (López-Arnau et al. 2013). The low oral bioavailability of some derivatives, namely 3-MMC and mephedrone, may be indicative of an extensive "first-pass effect" and may explain the preference of the nasal over the oral route of administration for some substances (Martínez-Clemente et al. 2013; Shimshoni et al. 2015). Nonetheless, some drug abusers reported their preference towards the oral route over the nasal insufflation due to the corrosive effect of some synthetic derivatives to the nasal mucosa, namely mephedrone and 3,4-DMMC (Kelly 2011; Rouxinol et al. 2020). Other parameters, besides the dose, the route of administration and interaction with other substances abused concomitantly, influence the absorption and, thus, the bioavailability of SCs, namely the host factors (pH of medium, and presence and density of membrane transporters) and the substance factors (solubility and dissolution) (Paul 2019a).

SCs, particularly the *N*-alkyl derivatives, are generally less lipophilic than the corresponding amphetamine analogues due to the presence of the β-ketone moiety. Regarding the *N*-pyrrolidine derivatives, the presence of the pyrrolidine ring reduces the hydrophilic properties conferred by the β-ketone moiety (Coppola et al. 2016; Kelly 2011; Valente et al. 2014). It may be suggested that the general lower lipophilic properties presented by SCs, when compared to related amphetamines, may be indicative of a lower potency and less ability to cross the BBB. In fact, reports on SCs' abuse, point the need to re-dose and of higher doses, when compared to amphetamines, to obtain equipotent effects (Erowid 2015a, b; Kelly 2011; Prosser and Nelson 2012). Nonetheless, fatal intoxications related to SCs have been reported, with these drugs found in the brain of the deceased (Adamowicz et al. 2020; Gerace et al. 2014; Hasegawa et al. 2014a, 2015; Majchrzak et al. 2018a; Marinetti and Antonides 2013; Sykutera et al. 2015; Vignali et al. 2019; Wyman et al. 2013). In addition, several SCs showed in vivo brain-to-plasma or brain-to-serum concentration ratios greater than 1, further indicating that they freely cross BBB (Hitchcock and Pennington 2006). Mephedrone showed brain-to-plasma ratios of 6.81 and 8.2, in Wistar and Sprague-Dawley rats, respectively, following a 1 mg/kg (i.v.) dose (Aarde et al. 2013a). Others reported a mephedrone brain-to-plasma ratio of 1.85 following an i.v. administration (10 mg/kg) to Sprague-Dawley rats (Martínez-Clemente et al. 2013). Butylone, methylone and pentylone presented a brain-to-plasma ratio of 7.1, 39.5 and 2.1, respectively, when administered s.c. to Sprague-Dawley rats (20 mg/kg) (Grecco et al. 2017). In another study, using Sprague-Dawley rats, methylone was administered per os at a dose of 30 mg/kg, yielding a brain-to-plasma ratio of 1.42 (López-Arnau et al. 2013).

Methylone was found to yield a brain-to-serum ratio of 7.97 in Wistar rats treated with this synthetic cathinone derivative (10 mg/kg, s.c.) (Štefková et al. 2017). Novellas et al. (2015) found a brain-to-plasma ratio of 2.21 for MDPV following its s.c. administration in Sprague-Dawley rats at a dose of 1 mg/kg. Similarly, others established a brain-to-serum ratio of approximately 2 for the same synthetic cathinone derivative, when administered s.c. to Wistar rats at a dose of 2 mg/kg (Horsley et al. 2018). The brain-to-serum ratio of β-naphyrone (6.5) was determined after s.c. administration of this synthetic cathinone derivative (10 mg/kg) to Wistar rats (Pinterova-Leca et al. 2020). Four SCs, namely MDPV, mephedrone, methylone and methcathinone, showed high BBB permeability in TY09 human brain endothelial cells, a human in vitro BBB permeability model. Of note, MDPV and mephedrone presented particularly high membrane permeability, not only when compared either to the other two SCs, but also when compared with AMPH, METH and MDMA (Simmler et al. 2013). The BBB penetrance ability exhibited by SCs is schematically presented in Fig. 5.

In vivo studies aiming to investigate pharmacokinetics of SCs were largely performed using rodent models, although a study using Landrace pigs has also been reported. To date only a few studies were conducted in humans. Data related to the pharmacokinetics of some SCs, which will be fully described below, are summarized in Table 6. A controlled clinical trial, performed by Papaseit and co-workers, evaluated for the first time the pharmacokinetic parameters of mephedrone in healthy and recreational drug abusers (Papaseit et al. 2016). Following the administration of mephedrone (200 mg, per os) to the subjects, an average maximum plasma concentration (C_{max}) value of 134.6 µg/L (range 51.7–218.3 µg/L) was obtained at 1.25 h (T_{max}), with an average elimination half-life ($t_{½}$) of 2.15 h, being this synthetic cathinone derivative undetectable 24 h post-administration (Papaseit et al. 2016). The obtained pharmacokinetic data are in line with the rapid onset and short duration of effects reported for mephedrone abuse in recreational scenarios. In another study, mephedrone, administered to healthy and recreational drug abusers (150 mg, per os), had an average C_{max} of 122.6 µg/L (range 79.5–162.3 µg/L) reached at a T_{max} of 1 h, a $t_{½}$ of 2.2 h, had a renal clearance of 5.6 L/h, and an absolute volume of distribution (V_d) of 123.5 L (calculated considering a hypothetical bioavailability of 10%) (Olesti et al. 2017). The pharmacokinetic parameters of a mephedrone analogue, 3-MMC, were described by Shimshoni and co-workers (Shimshoni et al. 2015). The synthetic cathinone derivative was administered to Landrace pigs via i.v. (0.3 mg/kg) and per os (3 mg/kg), with a washout period of 3 days between the administrations. Following the oral administration, 3-MMC reached a C_{max} of 27 µg/L at a T_{max} of 0.08 h and exhibited a low bioavailability (7%). Moreover, 3-MMC had a total clearance of 199 L/h, an apparent V_d of 240 L and an average $t_{½}$ of 0.83 h. In addition,

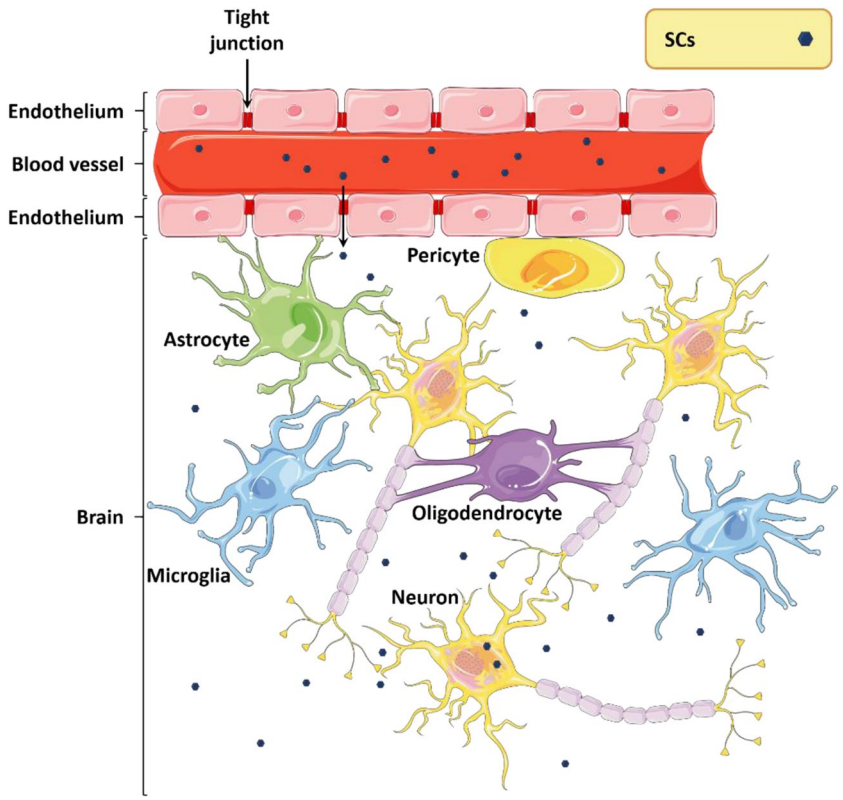


Fig. 5 Schematic representation of synthetic cathinones entering the brain due to their ability to cross the blood–brain barrier

Table 6 Pharmacokinetic parameters of synthetic cathinones evaluated in studies with humans, pigs, rats or mice

References	Species	Synthetic cathinones	Dose (mg/kg)	Route of administration	Sample	C_{max} (µg/L or µg/g)	T_{max} (h)	$t_{½}$ (h)	Cl (L/h)	V_d (L)	$AUC_{0-\infty}$ (µg h/L)
Olesti et al. (2017)	Human	Mephedrone	150 mg	per os	Plasma	122.6	1	2.2	5.6 (renal) 41.1 (plasma)[d]	123.5[d]	460.9
Papaseit et al. (2016)	Human	Mephedrone	200 mg	per os	Plasma	134.6	1.25	2.15	n.a	n.a	556.2
Shimshoni et al. (2015)	Landrace pigs	3-MMC	3	per os	Plasma	27	0.08	n.a	n.a	n.a	31
			0.3	i.v		n.a	n.a	0.83	199[b]	240[a]	48
Aarde et al. (2013a)	Sprague–Dawley rats	Mephedrone	1.0	i.v	Plasma	318	0.08	1.20	≈ 5.86	≈ 9.75	171
	Wistar rats					269		0.80	≈ 5.78	≈ 7.73	173
Anizan et al. (2016)	Sprague–Dawley rats	MDPV	0.5	s.c	Plasma	74.2	≈ 0.26	≈ 1.63	n.a	n.a	≈ 89.88
			1.0			165	≈ 0.22	≈ 1.30			187.95
			2.0			271	0.31	≈ 1.40			386.05
Baumann et al. (2017)	Sprague–Dawley rats	MDPV	0.5	i.p	Plasma	20	≈ 0.17	≈ 1.53	n.a	n.a	≈ 18.57
			1			54		≈ 1.32			≈ 47.63
			2			135		1.65			≈ 145.43
Elmore et al. (2017)	Sprague–Dawley rats	Methylone	3	s.c	Plasma	620	0.25	0.80	n.a	n.a	≈ 446.67
			6			1410		0.95			≈ 1138.33
			12			3170		1.10			3350
Grecco et al. (2017)	Sprague–Dawley rats	Butylone	20	s.c	Plasma	1844.6	0.50	≈ 1.37	1.2	≈ 2.36[a]	≈ 4060.67
		Methylone				949.9		0.69	4.44	≈ 4.23[a]	≈ 1205.57
		Pentylone				5735.7		4.22	≈ 0.59	≈ 3.68[a]	≈ 8923.83
		Butylone			CSF	13,458	1	1.17	n.a	n.a	28,990
		Methylone				12,215		≈ 2.25			≈ 47,646.67
		Pentylone				7425.6		1.40			18,530
Horsley et al. (2018)	Wistar rats	MDPV	2	s.c	Brain	≈ 0.26	0.5	n.a	n.a	n.a	n.a
					Lungs	≈ 0.53					
					Serum	140					
López-Arnau et al. (2013)	Sprague–Dawley rats	Methylone	15	per os	Plasma	1456.67	0.5	0.55	≈ 0.53[b]	0.43[e]	5740.3
			30			1896	0.97			n.a	9988.8
			10	i.v		5271.6	n.a	0.95		≈ 0.54[e]	4251.89
Martínez-Clemente et al. (2013)	Sprague–Dawley rats	Mephedrone	30	per os	Plasma	331.2	0.93	0.55	≈ 1.30[c]	n.a	294.48
			60			960	0.43		≈ 0.38[c]		895.43
			10	i.v		7221	n.a	0.37	≈ 1.69[b]	≈ 0.58[e]	1331.8

Table 6 (continued)

References	Species	Synthetic cathinones	Dose (mg/kg)	Route of administration	Sample	C_{max} (µg/L or µg/g)	T_{max} (h)	$t_{½}$ (h)	Cl (L/h)	V_d (L)	$AUC_{0-\infty}$ (µg h/L)
Mégarbane et al. (2020)	CD-1 mice	β-Naphyrone	30	i.p	Plasma	3992	0.08 – 0.17	0.3	≈ 0.37[b]	≈ 0.29[e]	n.a
Novellas et al. (2015)	Sprague–Dawley rats	MDPV	1	s.c	Striatum	≈ 0.95	≈ 0.41	≈ 1.02	n.a	n.a	6192.66
Pinterova-Leca et al. (2020)	Wistar rats	β-Naphyrone	10	s.c	Brain	≈ 0.0017	0.5	n.a	n.a	n.a	n.a
					Liver	≈ 0.0004	1				
					Lungs	≈ 0.0030					
					Serum	269	0.5				
Šíchová et al. (2017)	Wistar rats	Mephedrone	5	s.c	Brain	≈ 0.77	0.5	n.a	n.a	n.a	n.a
					Liver	≈ 0.2	0.5				
					Lungs	≈ 1.04	0.5				
					Serum	826.2	0.5				
Štefková et al. (2017)	Wistar rats	Methylone	10	s.c	Brain	≈ fivefold above serum levels	0.5	n.a	n.a	n.a	n.a
					Serum	≈ 2000					

≈ approximately, *3-MMC* 3-methylmethcathinone, $AUC_{0-\infty}$ area under the concentration–time curve [expressed in µg h/L (microgram hour per litre)], *Cl* clearance [expressed in L/h (litres per hour)], C_{max} maximum concentration [expressed in µg/L (microgram per litre) for cerebrospinal fluid, plasma and serum samples, or in µg/g (microgram per gram) for brain, liver and lungs samples], *CSF* cerebrospinal fluid, *i.p.* intraperitoneal, *i.v.* intravenous, *MDPV* 3,4-methylenedioxypyrovalerone, *mg* milligram, *mg/kg*: milligram per kilogram, *n.a.* not available, *s.c.* subcutaneous, $t_{½}$ elimination half-life [expressed in h (hours)], T_{max} time of occurrence of maximum concentration [expressed in h (hours)], V_d volume of distribution [expressed in L (litres)]

[a]Apparent volume of distribution

[b]Total plasma clearance

[c]Metabolic clearance

[d]Values calculated with a hypothesized bioavailability of 10%

[e]Apparent volume of distribution at steady state

most of 3-MMC was rapidly excreted, with plasma concentrations barely detectable 4 h post-administration (Shimshoni et al. 2015). In an animal laboratory study, mephedrone was administered to Sprague-Dawley rats via i.v. (10 mg/kg) or per os (30 or 60 mg/kg) (Martínez-Clemente et al. 2013). In this study, mephedrone administered via i.v. had a C_{max} of 7221 µg/L, a $t_{½}$ of 0.37 h, a total plasma clearance of approximately 1.69 L/h and an apparent V_d at steady state of about 0.58 L. In addition, mephedrone was almost undetectable in plasma 4 h after its administration (i.v.). With regard to oral administration, mephedrone 30 mg/kg showed a C_{max} of approximately 331 µg/L, reached at a T_{max} of 0.93 h, whilst mephedrone 60 mg/kg presented a C_{max} of 960 µg/L reached at a T_{max} of 0.43 h, both having a $t_{½}$ of 0.55 h. Mephedrone bioavailability was found to be about 7.3% (30 mg/kg, per os) and 11.2% (60 mg/kg, per os), and plasma concentrations decreased to undetectable levels at 9 h after oral administration (Martínez-Clemente et al. 2013). In another study, mephedrone was reported to have had a C_{max} of 318 µg/L reached at a T_{max} of 0.08 h, a $t_{½}$ of 1.2 h, a clearance of approximately of 5.86 L/h and a V_d of about 9.75 L in Sprague-Dawley rats, following an i.v. administration (1 mg/kg) of this synthetic cathinone derivative (Aarde et al. 2013a). Under the same experimental conditions, but using Wistar rats, mephedrone showed a C_{max} of 269 µg/L, reached at the same T_{max}, a lower $t_{½}$ (0.8 h), a similar clearance (nearly 5.78 L/h) and a V_d of approximately 7.73 L (Aarde et al. 2013a). More recently, Šíchová and co-workers studied the pharmacokinetic profile of mephedrone in Wistar rats following a s.c. administration (5 mg/kg), the authors reporting C_{max} values of approximately 826 µg/L, 0.77 µg/g and 1.04 µg/g in the serum, brain and lungs, respectively, attained at a T_{max} of 0.5 h (Šíchová et al. 2017). López-Arnau and co-workers conducted an in vivo study, in which methylone was administered to Sprague-Dawley rats via i.v. (10 mg/kg) or per os (15 or 30 mg/kg) (López-Arnau et al. 2013). In that study, methylone (i.v.) was found to have a C_{max} of 5271.6 µg/L, a $t_{½}$ of 0.95 h, a total plasma clearance of approximately 0.53 L/h and a V_d at steady state of about 0.54 L. Concerning the oral administration, methylone showed different pharmacokinetic parameters. The V_d at steady state was smaller than that observed for the i.v. administration (about 0.43 L for the 15 mg/kg dose). Methylone C_{max} values were 1456.67 and 1896 µg/L attained at T_{max} values of 0.5 and 0.97 h for 15 and 30 mg/kg oral doses, respectively. For both oral doses, the $t_{½}$ was 0.55 h and the total plasma clearance was similar to that of the i.v. dose (0.53 L/h). The bioavailability of methylone was found to be 89% and 78.4%, for the 15 and 30 mg/kg oral doses, respectively (López-Arnau et al. 2013). In another in vivo study, using the same animal model (Sprague-Dawley rats), methylone showed C_{max} values of 620, 1410 and 3170 µg/L following the s.c. administration of 3, 6 and 12 mg/kg doses, respectively (Elmore et al. 2017). The methylone C_{max} values were attained at a T_{max} of 0.25 h for all tested doses, whilst $t_{½}$ values of 0.8, 0.95 and 1.1 h were obtained for the 3, 6 and 12 mg/kg doses, respectively (Elmore et al. 2017). Following s.c. administration of methylone (10 mg/kg) to Wistar rats, Štefková et al. (2017) reported a C_{max} of about 2000 µg/L in the serum, reached at a T_{max} of 0.5 h, with the maximum concentration of this synthetic cathinone derivative in the brain being approximately fivefold greater. Some MDPV pharmacokinetic parameters were evaluated in an in vivo study after s.c. administration (1 mg/kg) to Sprague-Dawley rats (Novellas et al. 2015). In that study, MDPV showed a C_{max} of approximately 0.95 µg/g attained at a T_{max} of 0.41 h, and a $t_{½}$ of 1.02 h (the mentioned values are for striatum) (Novellas et al. 2015). Anizan et al. reported C_{max} (74.2, 165 and 271 µg/L, respectively), T_{max} (0.26, 0.22 and 0.31 h, respectively) and $t_{½}$ (1.63, 1.3 and 1.4 h, respectively) values for MDPV following the s.c. administration of 0.5, 1 and 2 mg/kg of this synthetic cathinone derivative to Sprague–Dawley rats. Moreover, only about 1% of MDPV C_{max} was detected in plasma at the end of the experiment (8 h after MDPV administration) (Anizan et al. 2016). The same doses of MDPV (0.5, 1 and 2 mg/kg) administered via intraperitoneal (i.p.) to Sprague–Dawley rats resulted in C_{max} values of 20, 54 and 135 µg/L, respectively, reached at a T_{max} of 0.17 h for all tested doses, and $t_{½}$ values of 1.53, 1.32 and 1.65 h, respectively (Baumann et al. 2017). MDPV pharmacokinetic profile was also studied in Wistar rats following its administration (s.c.) at a dose of 2 mg/kg (Horsley et al. 2018). The highest serum, brain and lung MDPV concentrations (140 µg/L, 0.26 µg/g and 0.53 µg/g, respectively) were obtained at 0.5 h. According to the authors, the presented maximal concentration values may be underestimated (Horsley et al. 2018). Recently, Grecco and co-workers studied the plasma and CNS pharmacokinetic of three SCs, namely methylone, butylone and pentylone (Grecco et al. 2017). Sprague-Dawley rats were administered with a dose of 20 mg/kg body weight (s.c.) of one of the three mentioned SCs. Plasma pharmacokinetic values for methylone, butylone and pentylone were: C_{max} (949.9, 1844.6 and 5735.7 µg/L, respectively), T_{max} (0.5 h for all derivatives), $t_{½}$ (0.69, 1.37 and 4.22 h, respectively), apparent V_d (approximately 4.23, 2.36 and 3.68 L, respectively) and clearance (4.44, 1.2 and 0.59 L/h, respectively). Regarding the CNS, C_{max} values for methylone (12,215 µg/L), butylone (13,458 µg/L) and pentylone (7425.6 µg/L) were reached at a T_{max} of 1 h, and $t_{½}$ values of 2.25, 1.17 and 1.4 h, respectively (Grecco et al. 2017). Recently, Pinterova-Leca and co-workers studied the pharmacokinetic parameters of β-naphyrone in Wistar rats following s.c. administration of 10 mg/kg of this synthetic cathinone derivative (Pinterova-Leca et al. 2020). β-Naphyrone C_{max} values were found to

be 269 µg/L (serum) and approximately 0.0017 µg/g (brain) attained at a T_{max} of 0.5 h, whereas C_{max} values in lungs and liver were approximately 0.0030 and 0.0004 µg/g, respectively, attained at a T_{max} of 1 h (Pinterova-Leca et al. 2020). The pharmacokinetic profile of β-naphyrone was evaluated in CD-1 mice following its administration (i.p.) at a dose of 30 mg/kg (Mégarbane et al. 2020). The researchers reported a C_{max} of 3992 µg/L, reached at a T_{max} between 0.08 and 0.17 h, a $t_{½}$ of 0.3 h, a V_d at steady state of approximately 0.29 L, a total clearance of about 0.37 L/h, with β-naphyrone plasma concentrations being undetectable 24 h post-administration (Mégarbane et al. 2020).

Following administration and absorption into the systemic circulation, substances are initially distributed to highly irrigated organs, as the brain, lungs, liver and kidneys. This phase is responsible for the early onset of effects, and the entrance of such substances on the brain is dependent on their ability to permeate the BBB, as mentioned. Second, the substances are distributed to the other compartments, namely muscle, fat and skin, being responsible for the redistribution phenomenon observed for some drugs. The overall distribution process of a substance in a living organism is conditioned by several factors, specifically the ability of that substance to bind to plasma proteins and to tissues, the cardiac output, blood flow and capillary permeability and the local pH (Paul 2019b). Generally, SCs have low plasma protein binding. In two in vivo studies using the same animal model (Sprague-Dawley rats), mephedrone (30 mg/kg, per os) yielded a plasma protein binding of 21.59% (Martínez-Clemente et al. 2013), whilst methylone (30 mg/kg, per os) showed a higher but still low binding to plasma proteins (30.82%) (López-Arnau et al. 2013). This pharmacokinetic parameter may be linked to the relative low $t_{½}$ and steady-state V_d values, and to the rapid elimination of these substances (López-Arnau et al. 2013; Martínez-Clemente et al. 2013). Nonetheless, some derivatives, namely α-pyrrolidinohexanophenone (α-PHP) and β-naphyrone appeared to have longer $t_{½}$ (37 and 34 h, respectively), as reported in two non-fatal intoxication involving these substances (Derungs et al. 2011; Fujita et al. 2018). Fujita and co-workers estimated the elimination period of α-PHP from the body to be 150 h. In this case, the long $t_{½}$ and longer elimination period observed for this derivative may be explained not by an increase in plasma protein binding but by its higher lipophilicity, when compared to other SCs, and consequent distribution to several tissues (Fujita et al. 2018; Lakshmanan 2019). As such, a rapid phase I distribution of this derivative to the brain, then a redistribution through other organs (phase II) and finally a gradual release from those organs to the blood in order to be eliminated may be a hypothesis. Evidence in the literature support the distribution of SCs to several organs and provide a glimpse of the redistribution phenomenon for these drugs of abuse (Cawrse et al. 2012; Hasegawa et al. 2014a, 2015; Marinetti and Antonides 2013; Shimomura et al. 2016; Vignali et al. 2019; Wurita et al. 2014; Wyman et al. 2013).

Cathinone, as well as its synthetic derivatives, undergo phase I and/or phase II metabolism, mainly mediated by cytochrome P450 (CYP), although almost all SCs are also excreted in their unchanged form in urine (Kelly 2011; Tyrkkö et al. 2016; Zaitsu 2018). To a better understanding of the major metabolic pathways of SCs, one must be familiarized with their categorization into the five chemical sub-families previously mentioned, as the main metabolic pathways observed for these substances are determined by their chemical structures. Thus, the major metabolic pathways usually differ intergroup but are similar intragroup (Zaitsu 2018). For *N*-alkyl SCs, phase I metabolism usually encompasses the following: (1) *N*-dealkylation to the primary amine, (2) reduction of the β-ketone moiety to the corresponding alcohol, (3) aromatic hydroxylation in the case of halogen substituent in the aromatic ring and (4) hydroxylation of the alkyl substituent (if present) in the aromatic ring and in the α-alkyl side chain, and further oxidation to the respective carboxylic acids. Phase I metabolites formed may further undergo phase II reactions, namely glucuronidation and/or succinylation (Tyrkkö et al. 2016; Zaitsu 2018). The metabolism of mephedrone, which is part of the *N*-alkyl SCs sub-family, has been studied in vivo (Martínez-Clemente et al. 2013; Meyer et al. 2010b; Pozo et al. 2015) and in vitro (Khreit et al. 2013; Pedersen et al. 2013b). Pedersen and co-workers found that CYP2D6 is the main enzyme responsible for the phase I metabolism of mephedrone, in vitro, in human liver microssomes (Pedersen et al. 2013b). Mephedrone (Fig. 6) phase I metabolism included *N*-demethylation to the primary amine, reduction of the β-ketone moiety to the corresponding alcohol, and hydroxylation of the methyl substituent in the aromatic ring and in the α-alkyl side chain and further oxidation to the respective carboxylic acids. Furthermore, glucuronidation and, to a lesser extent, succinylation eventually occur as phase II metabolic reactions (Khreit et al. 2013; Martínez-Clemente et al. 2013; Meyer et al. 2010b; Pedersen et al. 2013b; Pozo et al. 2015).

N-Pyrrolidine SCs generally undergo several phase I reactions as follows: (1) reduction of the β-ketone moiety to the corresponding alcohol [with exception of 1-(4-methylphenyl)-2-pyrrolidin-1-ylpropan-1-one and 1-(4-methoxyphenyl)-2-pyrrolidin-1-ylpropan-1-one]; (2) hydroxylation followed by dehydrogenation on the pyrrolidine ring to a lactam; (3) pyrrolidine ring opening and further oxidation to the corresponding carboxylic acid; (4) degradation of the pyrrolidine ring to the primary amine; (5) hydroxylation in the phenyl ring, of the alkyl substituent (if present) in the phenyl ring and in the α-alkyl side chain, followed by oxidation to the respective carboxylic acids; and (6) oxidative deamination. Further glucuronidation and/or

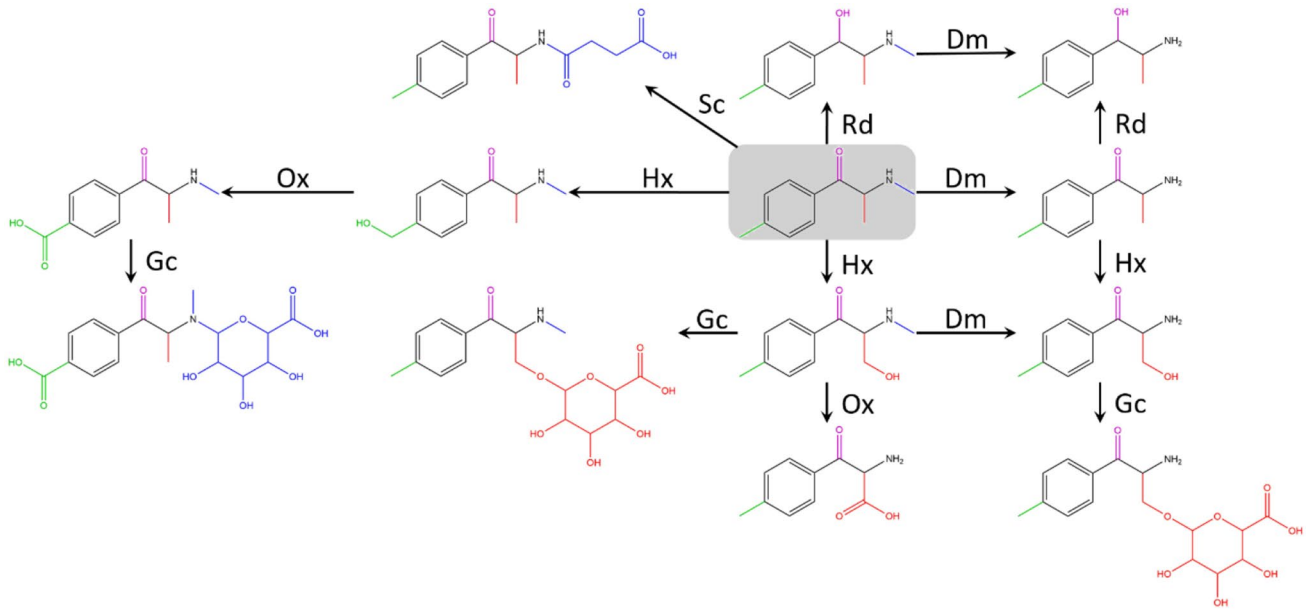


Fig. 6 Metabolic pathways proposed for mephedrone (placed in the grey rounded rectangle) in humans. Phase I metabolic reactions: Dm (*N*-demethylation), Hx (hydroxylation), Ox (oxidation) and Rd (*O*-reduction). Phase II metabolic reactions: Gc (glucuronidation) and Sc (succinylation). Adapted from (Pozo et al. 2015)

sulfation of the phase I generated metabolites may occur (Tyrkkö et al. 2016; Zaitsu 2018). α-PVP metabolic profile has been extensively studied in silico, in vitro and in vivo, and some of the metabolites, as well as the parent compound, were identified in human reports, as a result either of intoxications or from alleged/known abuse (Grapp et al. 2016; Namera et al. 2014; Negreira et al. 2015; Sauer et al. 2009; Shima et al. 2014; Tyrkkö et al. 2013; Uralets et al. 2014). Thus, in humans, α-PVP was reported to undergo the following: (1) reduction of the β-ketone moiety to the corresponding alcohol; (2) hydroxylation and further dehydrogenation on the pyrrolidine ring to a lactam, and then ring opening followed by oxidation; (3) degradation of the pyrrolidine ring to the primary amine; (4) hydroxylation followed by oxidation in the α-alkyl side chain; (5) hydroxylation of the α-alkyl side chain; and (6) some combined forms (Tyrkkö et al. 2013). Although glucuronidation and/or sulfation seemed to be involved in phase II metabolism of α-PVP in Wistar rats (Sauer et al. 2009), only some glucuronides were found by Negreira and co-workers, in vitro, in human liver microssomes and cytosol (Negreira et al. 2015). These results may point towards differences in the metabolism of these drugs in rodents versus humans. Human CYP2B6, CYP2C19, CYP2D6 and CYP3A4 were found to be responsible for the hydroxylation of the α-alkyl side chain in the animal study (Sauer et al. 2009), while in the latter study, human recombinant CYP2D6, CYP2B6 and CYP2C19 were reported as the main enzymes responsible for the formation of α-PVP phase I metabolites (Negreira et al. 2015).

Regarding the phase I metabolism of 3,4-methylenedioxy-*N*-alkyl SCs, they can undergo demethylenation followed by *O*-methylation in the 3,4-methylenedioxy ring, in addition to the *N*-dealkylation to the primary amine (minor pathway), and to the reduction of the β-ketone moiety into the corresponding alcohol (not observed in the case of methylone) (Tyrkkö et al. 2016; Uralets et al. 2014; Zaitsu 2018). The observed less efficacy in β-ketone reduction may be attributed to the presence of 3,4-methylenedioxy ring (Majchrzak et al. 2018b). The resulting phase I metabolites may undergo further phase II metabolism, mainly via glucuronidation and sulfation, as suggested by studies on human (methylone and butylone abusers) and Wistar rats (Kamata et al. 2006; Zaitsu et al. 2009). Human recombinant CYP2D6 was found to be the main enzyme responsible for catalysing the demethylenation reaction in human liver microssomes, though CYP1A2, CYP2B6 and CYP2C19 played a minor role (Pedersen et al. 2013a), while the intermediate metabolite was further metabolized by catechol-*O*-methyltransferase (Kamata et al. 2006; Zaitsu et al. 2009).

The 3,4-methylenedioxy-*N*-pyrrolidine SCs undergo a combination of phase I metabolic reactions observed for *N*-pyrrolidine and 3,4-methylenedioxy-*N*-alkyl derivatives. Demethylenation followed by O-methylation in the 3,4-methylenedioxy ring, hydroxylation and further dehydrogenation in the pyrrolidine ring to a lactam, hydroxylation of the α-alkyl side chain, oxidative deamination and reduction of the β-ketone moiety to the corresponding alcohol (only reported for MDPV) are the main phase I reactions

reported for 3,4-methylenedioxy-*N*-pyrrolidine derivatives, namely 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpropan-1-one (MDPPP), 1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylbutan-1-one (MDPBP) and MDPV (Tyrkkö et al. 2016; Zaitsu 2018). Phase I metabolites may be further conjugated, either by glucuronidation and/or sulfation, in Wistar rats (Meyer et al. 2014; Springer et al. 2003) and in human liver microssomes and cytosol (Negreira et al. 2015), although in the case of MDPBP only glucuronides were detected in urine from human abusers (Meyer et al. 2014). MDPV glucuronides were found in urine of Wistar rats and urine of human users (Bertol et al. 2014; Meyer et al. 2010a). The enzymes mainly responsible for the demethylenation reaction are: CYP2C19 and CYP2D6 for MDPPP (Springer et al. 2005) and for MDPBP (Meyer et al. 2014); and CYP2C19, CYP2D6, CYP1A2 (Meyer et al. 2010a) in addition to CYP2B6 and CYP2C9 for MDPV (Negreira et al. 2015).

Meyer and co-workers described the metabolism of β-naphyrone in Wistar rats (Meyer et al. 2013). Phase I metabolism encompassed hydroxylation followed by dehydrogenation in the pyrrolidine ring to a lactam, hydroxylation of the naphthyl ring and/or of the α-alkyl side chain and oxidative deamination. Phase II metabolism appears to occur by glucuronidation. CYP2C19 and CYP2C9 are responsible for the hydroxylation of the naphthyl moiety (Meyer et al. 2013).

One must be aware that phase II metabolism, mainly glucuronidation, may occur without previous phase I metabolism (Kamata et al. 2006; Shima et al. 2013; Zaitsu et al. 2009) due to the aforementioned keto-enol tautomerization observed for SCs.

The wide variability and complexity of the metabolism of SCs may result in frequent interactions with other drugs or highlight the possibility of genetic susceptibility regarding metabolizing enzymes, encompassing increasing risks for users, with unpredictable effects.

Pharmacodynamics

Cathinone is the khat constituent mainly responsible for its stimulating and psychoactive effects, being more lipophilic than its metabolites, which enables a greater penetration into the CNS (Kalix 1991). It acts similarly to its non-β-keto counterpart AMPH, with which it shares the sympathomimetic effects [cardiovascular effects (e.g. increased blood pressure, contractile force and heart rate), hyperthermia and mydriasis] (Brenneisen and Mathys 1992; Kalix 1992; Widler et al. 1994). In fact, cathinone interacts with the monoamine transporters, both in vitro and in vivo, acting more similarly to a monoamine releaser than a reuptake inhibitor (Kalix 1980a, b, 1981, 1982, 1983, 1984; Pehek et al. 1990; Simmler et al. 2013; Wagner et al. 1982; Zelger and Carlini 1981). As previously mentioned, SCs chemically resemble this natural occurring psychostimulant and amphetamines (Gołembiowska and Kamińska 2018; Zawilska and Wojcieszak 2013). It is, therefore, expectable that these NPS can interact with the monoamine transporters and receptors within the brain in a similar way to that of classical amphetamines. In fact, these NPS interact with the monoamine membrane transporters, namely dopamine (DA), noradrenaline (NA) and serotonin (5-HT) transporters (DAT, NET and SERT, respectively), behaving as blockers and/or as substrates, thus increasing the monoamine content in the synaptic cleft and consequently leading to the hyperstimulation of postsynaptic receptors (Baumann et al. 2012, 2013; Cameron et al. 2013; Cozzi et al. 1999; Gołembiowska and Kamińska 2018; Hadlock et al. 2011; Lisek et al. 2012; López-Arnau et al. 2012; Martínez-Clemente et al. 2012; Nagai et al. 2007; Simmler et al. 2013). On the other hand, these substances directly interact directly with pre- and/or postsynaptic monoamine receptors, although generally having lower affinities for monoamine receptors than for monoamine transporters. Weak to no activity at monoamine receptors has been reported for several derivatives (Eshleman et al. 2013, 2017; Luethi et al. 2018; Rickli et al. 2015; Simmler et al. 2013, 2014; Simmler and Liechti 2017). When compared to their non-β-keto analogues, SCs exhibit lower affinity for vesicular monoamine transporter 2, which is responsible for the monoamine uptake into synaptic vesicles in CNS neurons (Cozzi et al. 1999; Eshleman et al. 2013; Pifl et al. 2015). Similarly to classical amphetamines, cathinone and its metabolites, as well as several synthetic derivatives, have a methyl group at α position to the nitrogen atom, which renders these substances greater protection against metabolism of the amine moiety by monoamine oxidase (MAO) (Carvalho et al. 2012). Moreover, cathinone is more potent than its non-β-keto counterpart regarding MAO inhibition (Nencini et al. 1984). Indeed, cathinone as well as some synthetic derivatives were found to selectively inhibit MAO-B over MAO-A (Osorio-Olivares et al. 2004). General pharmacodynamic properties of SCs are displayed in Fig. 7.

Although they share the phenethylamine core, SCs differ regarding their potency, selectivity and affinity at the monoamine membrane transporters and receptors (Eshleman et al. 2019; Simmler et al. 2013). Thus, the potency, selectivity and affinity of a substance towards a specific monoamine system is of the utmost importance, since stimulation of different monoamine systems results in specific clinical and toxic effects, namely dopaminergic [e.g. psychostimulant effects and reinforcing properties (high abuse and addiction potential)], noradrenergic [e.g. sympathomimetic stimulation (cardio- and psychostimulant effects)] and serotonergic (e.g. hyperthermia, seizures, paranoia and hallucinations) (Liechti 2015; Simmler 2018). Therefore, a classification has been proposed based on the pharmacological action rather than chemical structures for these substances, since it has

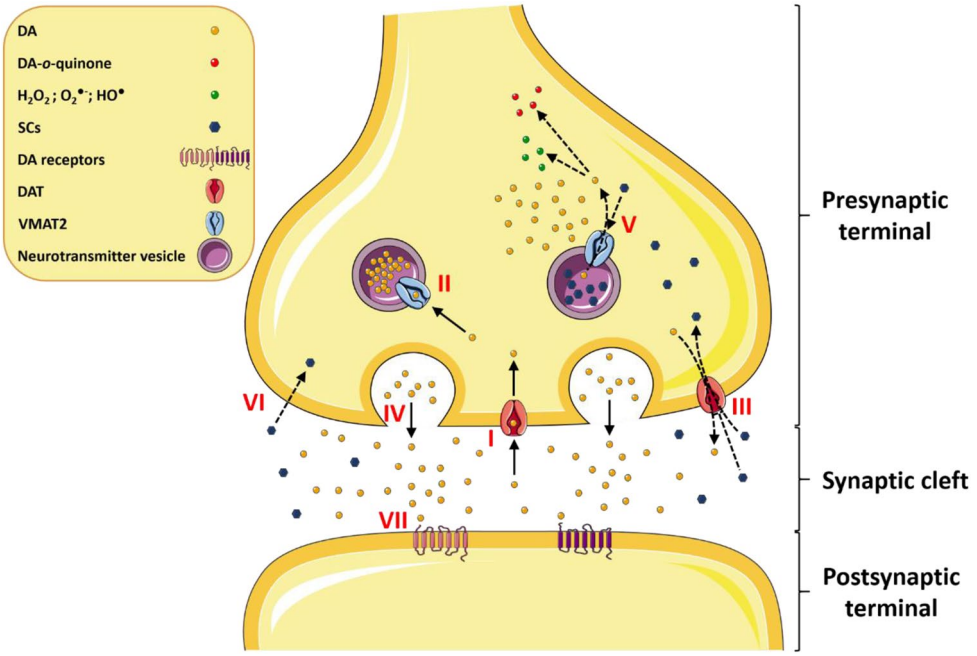


Fig. 7 Pharmacodynamics of synthetic cathinones (SCs) in dopaminergic neurons. Usually dopamine (DA) is uptaken from the synaptic cleft through DA transporter (DAT) (**I**). Once inside the presynaptic neuron, DA is stored in the neurotransmitter vesicles via the vesicular monoamine transporter (VMAT2) (**II**). SCs may interact with DAT (**III**) behaving as substrates, inducing the non-exocytotic release of DA (**IV**), and/or blockers, inhibiting the DA uptake (**III**), thus promoting a sustained increase of DA in the synaptic cleft. In addition, SCs may prompt the disruption of the DA vesicular storage, therefore increasing the free cytosol DA content, which, in turn, will be able to undergo autoxidation leading to the formation of DA-*ortho*-quinones, as well as reactive oxygen species (**V**). Moreover, it can be hypothesized, that under certain conditions SCs may also enter the neurons via simple diffusion (**VI**). The sustained increase in the synaptic DA content results in the hyperstimulation of DA postsynaptic receptors (**VII**)

been observed that different SCs, which belong to the same chemical family, induce a broad spectrum of pharmacological effects (Iversen et al. 2013; Simmler et al. 2013, 2014).

In vitro, almost all SCs are potent NET uptake inhibitors, the main differences regarding their pharmacological profiles appearing to arise from their action on the other monoamine systems, namely dopaminergic and serotonergic (Simmler 2018). These NPS can be classified into three groups, according to their potency inhibiting the monoamine transporters and their ability to behave as monoamine releasers (substrates): (1) SCs with selective inhibition at SERT, resembling MDMA, or nonselective inhibition of DAT, NET and SERT, in a similar way to cocaine, though also inducing transporter-mediated monoamine release; (2) SCs with selective inhibition at DAT, in addition to behaving as potent NET inhibitors, also acting as monoamine releasers (not only, but especially DA), similarly to METH; and (3) SCs that act as extremely potent inhibitors of DAT and NET, exhibiting low to negligible potency at SERT, and lacking the monoamine releasing properties (Simmler et al. 2013).

2,3-Dimethylmethcathinone, 2,4-dimethylmethcathinone, 3,4-DMMC, 4-ethylmethcathinone and methedrone are encompassed in the group of derivatives that selectively inhibit SERT over DAT similarly to the classical amphetamine MDMA. With exception of 3,4-DMMC, they also act as substrates at SERT. Some of these derivatives bind and activate the 5-HT receptor, 5-HT_{2A}. In addition, 2,3-dimethylmethcathinone and 2,4-dimethylmethcathinone exhibited considerable affinities to trace amine-associated receptor 1, unlike SCs in general. Other derivatives of the first group resemble cocaine regarding their action as nonselective reuptake inhibitors at DAT, NET and SERT. However, in opposition to cocaine, many of them also act as monoamine releasers (except β-naphyrone, which is a pure nonselective blocker). 4-MEC, mephedrone, ethylone, butylone, pentylone, methylone and naphyrone are examples of nonselective derivatives. Of note, 4-MEC and pentylone induce the release of 5-HT, but not DA (Baumann et al. 2012, 2013; Cameron et al. 2013; Cozzi et al. 1999; Eshleman et al. 2013, 2017; Hadlock et al. 2011; Kehr et al. 2011; López-Arnau et al. 2012; Luethi et al. 2018; Nagai et al. 2007; Rickli et al. 2015; Saha et al. 2015; Simmler et al. 2013, 2014, 2016).

The second group include cathinone and several derivatives, as *N*,*N*-dimethylcathinone, buphedrone, flephedrone, methcathinone and pentedrone. Usually, derivatives belonging to this group are potent NET inhibitors and exhibit selective inhibition at DAT when compared to SERT. In general,

they also act as DA and NA releasers, although buphedrone only induces NA release, and *N*,*N*-dimethylcathinone and pentedrone are not monoamine transporter substrates. Several derivatives also show low affinity towards adrenergic receptors, namely α_{1A} and α_{2A}. The high DAT/SERT ratio showed by these substances points towards their high abuse potential (Cozzi and Foley 2003; Kalix 1990; Nagai et al. 2007; Simmler et al. 2013, 2014).

Typically, pyrovalerone derivatives (e.g. pyrovalerone, α-PVP, MDPBP, MDPV and MDPPP) are in the third group, being very potent blockers of both DAT and NET, with weak to trifling potency at SERT. Additionally, pyrovalerone derivatives are not substrates of monoamine transporters and have negligible affinity for monoamine receptors. Of note, severe and even fatal intoxications after abuse are very common due to their high potencies (Baumann et al. 2013; Eshleman et al. 2017; Meltzer et al. 2006; Rickli et al. 2015; Shalabi et al. 2017; Simmler et al. 2013, 2014; Zawilska and Wojcieszak 2017).

It is important to highlight that in several in vitro studies, SCs exhibited comparable or even higher potency and affinity to monoamine transporters and receptors, when compared to classical amphetamines (Baumann et al. 2013; Eshleman et al. 2013, 2017; Kolanos et al. 2015; López-Arnau et al. 2012; Luethi et al. 2018; Martínez-Clemente et al. 2012; Marusich et al. 2014; Rickli et al. 2015; Saha et al. 2015; Simmler et al. 2013, 2014), which can encompass similar or even higher toxicity.

Subjective and adverse effects, and lethality: human toxicology

Khat is chewed on a daily basis due to its CNS stimulating properties. Usually, after chewing khat, the subjects become more talkative and euphoric, additionally experiencing an increase in concentration, energy, excitement, self-esteem and a general state of well-being (e.g. gaiety and mood lift). These khat subjective properties may account for the friendly atmosphere experienced during the khat sessions, allowing to surpass some social issues. Besides the recreational use, khat is also masticated to reduce fatigue and hunger, and even to treat depressive and melancholic states (Al-Motarreb et al. 2002; Brenneisen and Mathys 1992; Kalix 1990; Widler et al. 1994). However, the desired stimulant effects are often followed by several adverse health effects, which include the following: (1) psychological dependence and abuse potential (Awas et al. 1999; Duresso et al. 2018; El-Setouhy et al. 2016; Kassim et al. 2012, 2013; Nakajima et al. 2014, 2017a; Odenwald et al. 2012, 2015; Widler et al. 1994; Widmann et al. 2014; Young et al. 2016); (2) mild withdrawal effects after prolonged, chronic or excessive use, namely anxiety, depression, insomnia, irritability, lack of concentration, lethargy, nightmares often paranoid in nature, slight trembling and a wide range of psychiatric disorders (Al-Habori 2005; Al-Motarreb et al. 2002; Alem and Shibre 1997; Awas et al. 1999; Bhui et al. 2003; Corkery et al. 2011; Dhadphale et al. 1981; Dhadphale and Omolo 1988; Griffiths et al. 1997; Hassan et al. 2002; Jager and Sireling 1994; Kennedy et al. 1980; Kroll et al. 2011; Odenwald et al. 2005, 2007a, b, 2009; Pantelis et al. 1989; Tulloch et al. 2012; Warfa et al. 2007; Widmann et al. 2014; Wondemagegn et al. 2017; Yousef et al. 1995); and (3) impairment in cognitive function (Colzato et al. 2010, 2011, 2012, 2013; Hoffman and al'Absi 2013; Khattab and Amer 1995). Other health issues include sympathomimetic (e.g. blurred vision, dry mouth, hyperthermia and mydriasis), cardiovascular (e.g. increase in blood pressure and heart rate, arrhythmias, acute coronary vasospasm, myocardial infarction and cerebral vascular accidents), gastrointestinal (e.g. periodontal disease, stomatitis, oesophagitis, gastritis and constipation) and reproductive (e.g. spermatorrhoea) effects. Moreover, carcinogenic potential (e.g. head and neck cancer) (Al-Habori 2005; Al-Motarreb et al. 2002; Al Suwaidi et al. 2013; Capriola 2013; Chapman et al. 2010; Cox and Rampes 2003; Halboub et al. 2009; Kalix 1990; Lukandu et al. 2015; Mega and Dabe 2017; Mwenda et al. 2003; Patel 2018), or even deaths (Corkery et al. 2011) have been described.

As seen with khat, SCs seem to be abused to enhance social and sensory experiences, due to their amphetamine- and cocaine-related stimulating effects (Corkery et al. 2018). The desired subjective effects (stimulant, hedonic and hallucinatory) that drive the individuals to abuse SCs include the following: (1) increased alertness and awareness; (2) mood lift and feeling of well-being; (3) increased energy; (4) euphoria; (5) empathy; (6) increased motivation; (7) increased productivity and capacity to work; (8) increased self-confidence, openness, sociability and talkativeness; (9) intensification of sensory experiences; (10) hallucinations and perceptual distortions; (11) insomnia; (12) reduced appetite; (13) motor excitement; (14) increased libido, and sexual arousal (Erowid 2015a, b; Johnson and Johnson 2014; Karila et al. 2015; Marusich et al. 2016; Prosser and Nelson 2012; Rosenbaum et al. 2012; Schifano et al. 2016, 2019; Shimizu et al. 2007; Simmons et al. 2018; Winstock et al. 2011a, b; Zawilska and Wojcieszak 2013, 2017). Regardless, several unpleasant or adverse effects also arise after abuse, either in cases of acute and chronic intoxication or overdose. In this context, adverse neurological, psychiatric and cardiac effects are the most commonly reported ones, generally preceding other effects that may also upsurge, namely gastrointestinal and hepatic (e.g. abdominal pain, nausea/emesis, increased serum aminotransferases levels and acute liver failure), haematological (e.g. disseminated intravascular coagulation), musculoskeletal (e.g. increased serum creatine kinase levels, rhabdomyolysis and compartment syndrome), pulmonary (e.g. respiratory failure and arrest, and

respiratory acidosis) and renal (e.g. increased serum creatinine levels and acute kidney injury) (Karila and Benyamina 2018; Riley et al. 2020; Weinstein et al. 2017; Zawilska and Wojcieszak 2013), which may end in multiple organ failure and death. High abuse and addiction potential, because of the stimulation of the dopaminergic system, has been addressed for several derivatives in the previous section of this review. In fact, these characteristics have been reported in the literature, in addition to the development of craving, dependence, tolerance and withdrawal syndrome, because of repeated use of high doses of some SCs (Erowid 2015a, b; Karila and Benyamina 2018; Valente et al. 2014; Zawilska and Wojcieszak 2013). Agitation, anxiety, cognitive disorders, delusions, visual and auditory hallucinations, aggressive and erratic behaviour, paranoia, psychosis and seizures are among the most reported neurological and psychiatric features regarding intoxications or overdoses related to SCs. Brain-related adverse effects, including stroke, encephalopathy, coma and convulsions, which are common clinical features of intoxications from classical drugs of abuse, such as amphetamine and MDMA (Capela et al. 2009; Tsatsakis et al. 2019), have also been reported for SCs (Turcant et al. 2017; Wiergowski et al. 2017; Wurita et al. 2014). In the same context, the most common cardiac symptoms reported are as follows: (1) chest pain, (2) hypertension and (3) tachycardia (Adamowicz et al. 2016, 2014, 2020; Adamowicz and Hydzik 2019; Bäckberg et al. 2015; Bertol et al. 2014; Desharnais et al. 2017; Joksovic et al. 2012; Kesha et al. 2013; Ling et al. 2019; Patel et al. 2017; Roberts et al. 2017; Sauer et al. 2011; Thornton et al. 2012a; Turcant et al. 2017; Vignali et al. 2019). Typically, these symptoms may be part of two commonly encountered toxic syndromes (also known as toxydromes) associated with SCs abuse, namely the sympathomimetic and hallucinogenic toxydromes, together with the risk of developing excited/agitated delirium syndrome and serotonin syndrome (Kronstrand et al. 2018). Sympathomimetic toxydrome encompasses neurological/psychiatric symptoms, such as agitation, anxiety, delusions, hyperactivity, paranoia and seizures, alongside diaphoresis, hyperthermia, mydriasis and cardiovascular symptoms, such as hypertension and tachycardia (King et al. 2018; Kronstrand et al. 2018), as described in some case reports involving these substances (Bäckberg et al. 2015; Derungs et al. 2011; Froberg et al. 2015; Hall et al. 2014; Spiller et al. 2011). On the other hand, the hallucinogenic toxydrome includes disorientation, hallucinations, memory disruption, psychotic episodes and tachypnoea, in addition to anxiety, paranoia, hypertension and tachycardia observed in the previously described toxydrome (Kronstrand et al. 2018), as reported following "bath salts" abuse (Penders and Gestring 2011). Excited/agitated delirium syndrome is clinically described by a state of delirium, incoercible psychomotor agitation and aggressiveness (usually requiring restraint), haemodynamic imbalance and extreme metabolic compromise, which may lead to sudden death (Hall 2016), as it has been reported following abuse of several SCs (Byard et al. 2016; Grapp et al. 2016; Kesha et al. 2013; Lusthof et al. 2011; Murray et al. 2012; Nagai et al. 2014; Penders et al. 2012; Sellors et al. 2014). Serotonin syndrome is clinically characterized by mental status derangements (e.g. agitation, anxiety and confusion), hyperactivity of autonomic nervous system (e.g. diaphoresis, hypertension, hyperthermia and tachycardia) and neuromuscular abnormalities (e.g. bilateral Babinski sign, hyperreflexia, muscle rigidity, myoclonus and tremor) (Scotton et al. 2019). Several case reports relate this syndrome to SCs abuse (Batisse et al. 2014; Garrett and Sweeney 2010; Joksovic et al. 2012; Mugele et al. 2012; Rojek et al. 2012; Warrick et al. 2012). Furthermore, manganese-methcathinone encephalopathy, a rare parkinsonian syndrome occurring in drug addicts injecting home-made mixtures containing methcathinone and manganese, has also been reported (Dolgan et al. 2015; Ennok et al. 2020; Fudalej et al. 2013).

Unfortunately, SC-induced intoxications or overdoses often culminate with the user's death, which can occur either due to the toxicity of one or more substances used (Byard et al. 2016; Cosbey et al. 2013; Dickson et al. 2010; Jamey et al. 2016; Karinen et al. 2014; Kesha et al. 2013; Kudo et al. 2015; Maskell et al. 2011; Namera et al. 2013; Rojek et al. 2012; Sellors et al. 2014; Yonemitsu et al. 2016), or deaths by suicide (Cawrse et al. 2012; deRoux and Dunn 2017; Krotulski et al. 2018b; Lee et al. 2015; Marinetti and Antonides 2013; Spiller et al. 2011; Tomczak et al. 2018), homicide (deRoux and Dunn 2017; Krotulski et al. 2018b; Marinetti and Antonides 2013) or as a result from driving under influence of such substances (Gil et al. 2013; Marinetti and Antonides 2013; Maskell et al. 2011; Rojek et al. 2016b; Zuba et al. 2013). Figure 8 describes the timeline of events in a case of a lethal intoxication-related to a synthetic cathinone derivative, namely α-PVP, in which the observed clinical features fit into the so-called excited delirium syndrome (Sellors et al. 2014).

Also, Fig. 9 presents a summary of general pharmacokinetic and pharmacodynamic parameters of mephedrone, as well as major clinical manifestations related to intoxication by SCs.

Several case reports addressing the aforementioned and other adverse effects induced by SCs are summarized in the Supplementary Table 1. A detailed literature review was performed in several databases, including PubMed and Google, using general terms [e.g. "bath salt(s)", "designer drug(s)", "legal high(s)", "new psychoactive substance(s)", "research chemical(s)", "synthetic cathinone(s)", "cathinone derivative(s)"], as well as specific names (e.g. "mephedrone", "methylone", "MDPV"), and a cross reference with outcome-based terms [e.g. "effect(s)", "toxydrome", "non-fatal intoxication", "overdose", "death"] was made. The

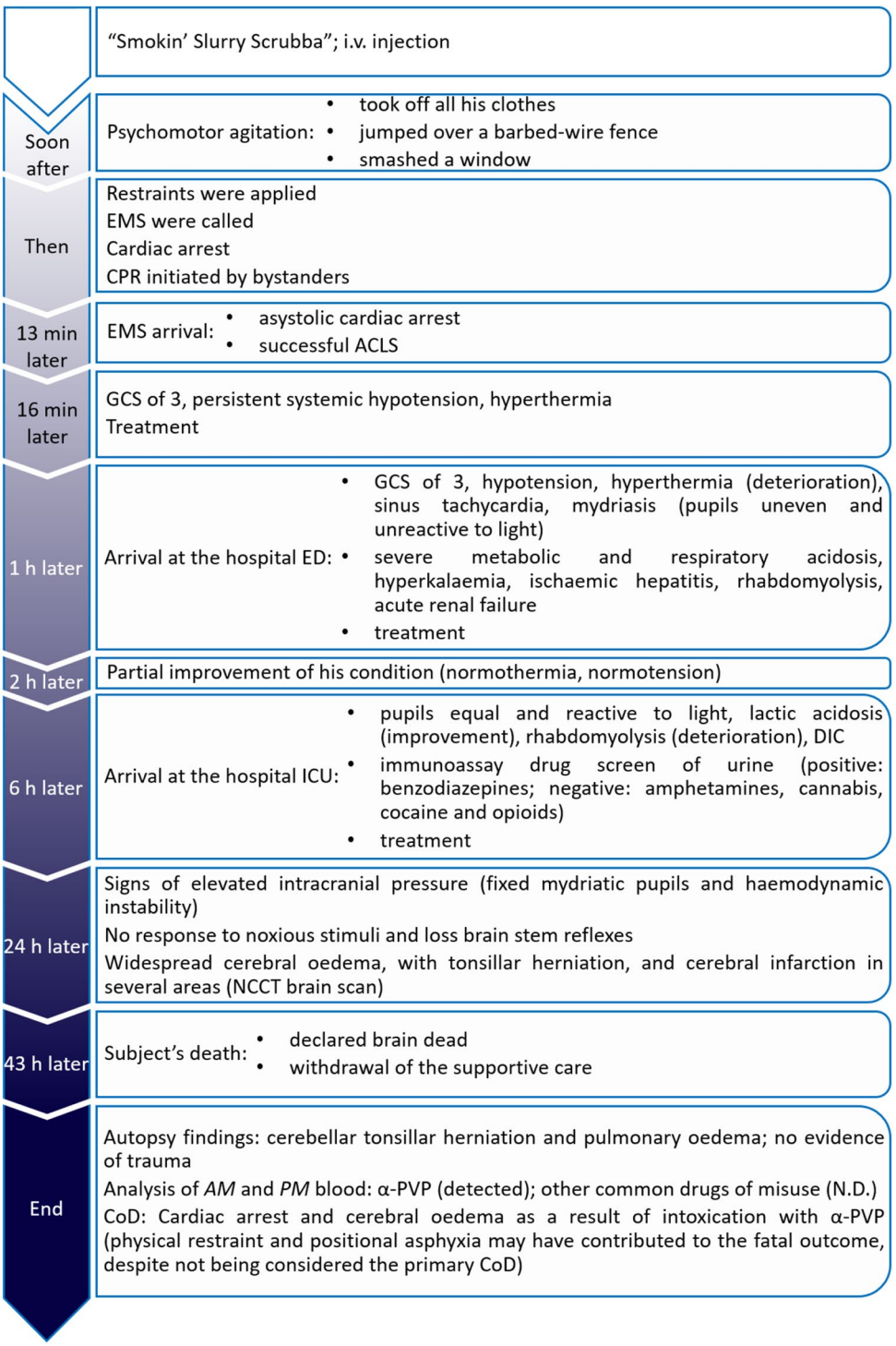


Fig. 8 Timeline and main clinical events related to a case resulting from abuse of "Smokin' Slurry Scrubba" powder, the subject exhibiting signs of Excited Delirium Syndrome, which culminate in death (Sellors et al. 2014). *α-PVP* alpha-pyrrolidinopentiophenone, *ACLS* advanced cardiac life support, *AM* antemortem, *CPR* cardiopulmonary resuscitation, *CoD* cause of death, *DIC* disseminated intravascular coagulation, *ED* emergency department, *EMS* emergency medical services, *GCS* Glasgow Coma Score, *ICU* intensive care unit, *i.v.* intravenous, *NCCT* non-contrast computed tomography, *N.D.* not detected, *PM* postmortem

studies included in the table were written in English, published from 2010 onwards, reported non-fatal or lethal intoxications involving synthetic cathinone derivative(s), and at least one of these NPS and/or corresponding metabolite(s) was/were analytically (quali- and/or quantitatively) identified in biological sample(s). There is an exception, that is, a case report in which no synthetic cathinone derivative was detected, but slightly increased levels of manganese (hallmark of manganese-methcathinone encephalopathy) in the serum of the drug user were found (Fudalej et al. 2013).

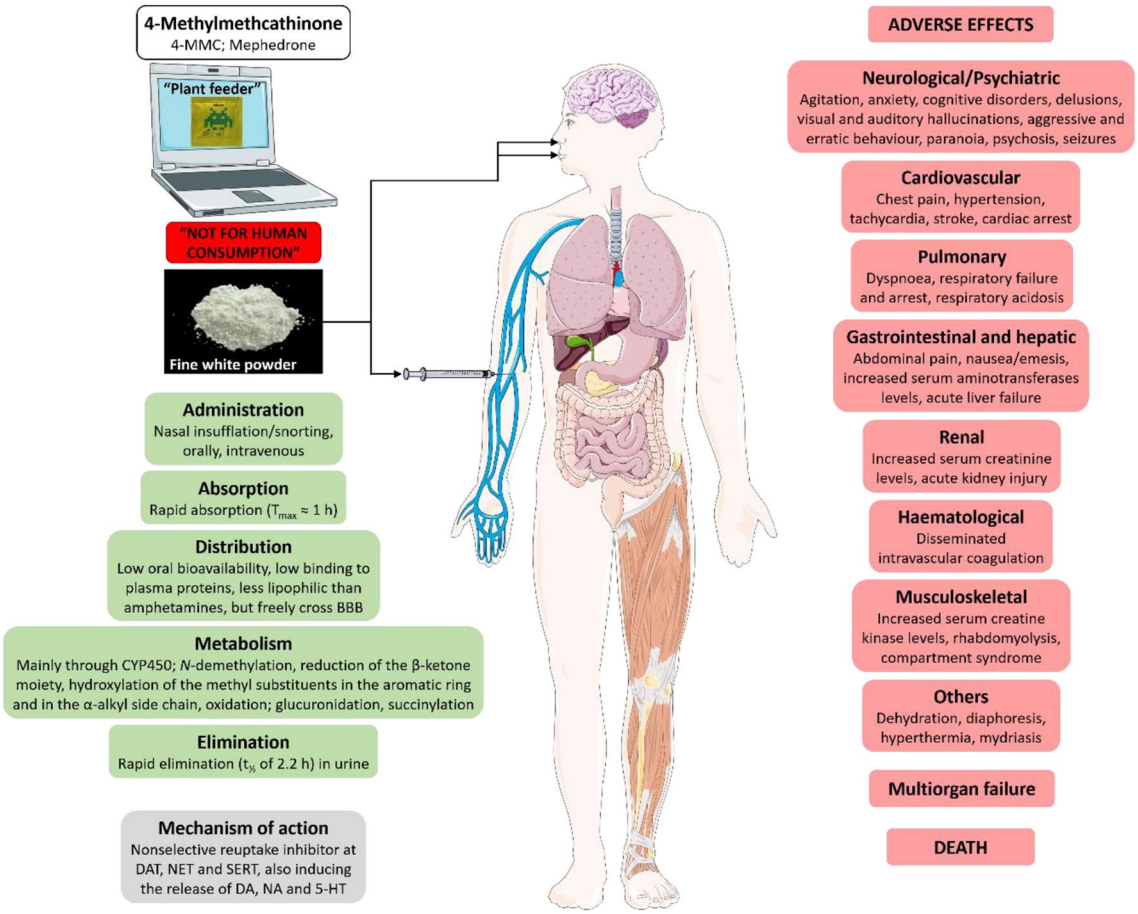


Fig. 9 General pharmacokinetic (displayed in green) and pharmacodynamic (displayed in grey) aspects about mephedrone, and major clinical manifestations related to intoxications by synthetic cathinones (displayed in pink). *5-HT serotonin, BBB blood-brain barrier, CYP450 cytochrome P450, DA dopamine, DAT dopamine transporter, NA noradrenaline, NET noradrenaline transporter, SERT serotonin transporter, $t_{1/2}$ elimination half-life, T_{max} time of occurrence of maximum concentration* (colour figure online)

Neurotoxicity: in vivo and in vitro studies

While keeping in mind the multitude of case reports related to SCs, and the adverse effects resulting from their abuse, different types of toxicity can occur following exposure to such substances, namely neurotoxicity, cardiotoxicity, hepatotoxicity, nephrotoxicity and pulmonary toxicity. In this section, the data regarding the neurotoxic potential of SCs will be summarized, since the main mechanism of action of these substances is dysregulation of the monoamine systems, as previously discussed. Indeed, the clinical manifestations (e.g. neurological sympathomimetic effects) reported in SC-induced human intoxications tally with the monoamine dysfunction observed in animal studies (German et al. 2014). Since SCs target the monoamine systems, in vivo studies, mostly performed using rodent models, aimed to pinpoint hypothetical alterations on monoamine transporters (e.g. DAT, NET and SERT) function, enzymes [e.g. tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH)] expression and/or activity, and the monoamine levels in the brain. In this regard, elevations in extracellular DA and 5-HT in the nucleus accumbens (NAc) of rats following i.p. (Suyama et al. 2016), i.v. (Mayer et al. 2016) or s.c. (Kehr et al. 2011; Wright et al. 2012) administration of mephedrone were observed. Furthermore, Baumann and co-workers found a dose-related increase in extracellular DA and 5-HT in the NAc of rats following i.v. administration of mephedrone or methylone (Baumann et al. 2012). Similarly, methylone administration via i.v. to rats induced a dose-related increase in extracellular DA and 5-HT in the NAc (Elmore et al. 2017). It is important to note that the aforementioned studies also disclose an interesting fact. Although elevations on extracellular levels of both endogenous monoamines (DA and 5-HT) are reported, correlating with the in vitro nonselective monoamine release action of mephedrone and methylone (Simmler 2018), the acute neurochemical effect induced by these two SCs in vivo is far more evident for 5-HT (Baumann et al. 2012; Elmore

et al. 2017; Kehr et al. 2011; Mayer et al. 2016; Suyama et al. 2016; Wright et al. 2012). Baumann and co-workers noticed that MDPV administration (i.v.) to rats increased extracellular DA, but not 5-HT, in the NAc in a dose-related manner (Baumann et al. 2013). This effect was corroborated by others, as a dose- and time-dependent increase in extracellular DA, but not 5-HT, in NAc was found after the same synthetic cathinone derivative being administered (i.p.) to rats. These data fully agree with the in vitro evidence that MDPV behaves as a pure blocker with selectivity for DAT over SERT (Simmler 2018).

Extracellular DA in NAc has been implicated in the addictive properties and locomotor stimulation of drugs of abuse (Willuhn et al. 2010), but when the increase in extracellular 5-HT far exceeds the extracellular DA, the former monoamine may lessen the motor stimulation induced by the latter (Baumann et al. 2011). This piece of evidence may explain why mephedrone and methylone showed weaker motor stimulant properties when compared with METH (Baumann et al. 2012; Wright et al. 2012) or AMPH (Kehr et al. 2011), whereas MDPV produces a strong locomotor activation (tenfold more potent than cocaine) (Baumann et al. 2013). A dose-related locomotor activation was observed in mice administered with mephedrone, methylone or MDPV (Marusich et al. 2012). The authors also reported that MDPV was the SC that induced this effect at lower concentrations (Marusich et al. 2012). In a study conducted in rats, MDPV has been shown to be more reinforcing than methylone. In addition, MDPV induced elevation in extracellular DA in NAc, whereas methylone increased the extracellular DA and 5-HT (larger effects in the later monoamine). Taking together, these data support the hypothesis that increases in extracellular 5-HT in NAc render the SCs less reinforcing properties (Schindler et al. 2016). Nonetheless, others consider animal models of self-administration as the gold standard for prediction of relative abuse potential regarding recreational drugs (Aarde and Taffe 2017). Concerning this matter, interesting data found may predict that the nonselective action of some SCs (e.g. mephedrone and methylone) will render these substances less abuse liability. Nonetheless, rats readily self-administer mephedrone and methylone, to maintain high rates of response to these substances (Aarde et al. 2013a; Hadlock et al. 2011; Motbey et al. 2013; Schindler et al. 2016; Watterson et al. 2012), thus indicating substantial abuse liability for these two SCs. Further studies performed using both male and female rats underlined that mephedrone is a more effective reinforcing substance than methylone (Creehan et al. 2015; Vandewater et al. 2015). The potent and selective (DAT and NET selectivity) blocker MDPV was rapidly self-administered by rats, whom maintained high rates of drug response (Aarde et al. 2013b; Schindler et al. 2016; Watterson et al. 2014), indicating the reinforcing properties related to this synthetic cathinone derivative.

Regarding the reuptake transporters or enzymes involved in biogenic amines synthesis, in vivo studies showed a reduction of DAT in the frontal cortex, and SERT in the hippocampus, frontal cortex and striatum, along with a decrease in the expression of TH and TPH-2 in rats, following s.c. administration of mephedrone (3 × 25 mg/kg/day, with a 2-h interval between doses, for 2 days) (López-Arnau et al. 2015). The same synthetic cathinone derivative administered (s.c.) to mice, in a schedule that mimics typical weekend consumption pattern (3 × 25 mg/kg/day, for 2 days), induced significant loss of DAT and SERT, especially in the frontal cortex and hippocampus, respectively (Martínez-Clemente et al. 2014). Under the same dose regimen, mephedrone also induced a decrease in TH and TPH-2 expression in mice brain (Martínez-Clemente et al. 2014). Hadlock and co-workers have previously reported that s.c. administration of mephedrone to rats in a "binge"-like dose regimen (4 × 10 or 25 mg/kg/day, with a 2-h interval between doses) induced a rapid decrease in striatal DAT and hippocampal SERT function (Hadlock et al. 2011). Conversely, other studies settled a controversy regarding the neurotoxic potential of mephedrone to dopaminergic and serotonergic systems. First, Angoa-Pérez and co-workers reported that mephedrone administered in a "binge"-like dose regimen (4 × 20 or 40 mg/kg/day, with a 2-h interval between doses, i.p.) to mice did not cause damage in DA nerve endings in the striatum (did not significantly alter striatal levels of DA, TH and DAT) (Angoa-Pérez et al. 2012). A year later, others reported that no significant changes in brain monoamine levels were found in rats or in mice following i.p. administration of mephedrone in a "binge"-like dose regimen (2 × 30 mg/kg/day, for 4 days) (den Hollander et al. 2013). Mephedrone, methylone and MDPV, administered via i.p. either alone or in any two-drug possible combinations in a "binge"-like dose regimen [4 × 40 (mephedrone) or 30 (methylone and MDPV) mg/kg/day, with a 2-h interval between doses], failed to cause damage to DA nerve endings, as no significant alterations in striatal levels of DA, DAT or TH were found in mice (Anneken et al. 2015). When administered in a "binge"-like dose regimen (2 × 30 mg/kg/day, for 4 days, i.p.), methylone produced a widespread (hippocampus, frontal cortex and striatum) depletion of 5-HT in rats (den Hollander et al. 2013). Methylone, administered to rats in a manner that mimics "binge" consumption (4 × 20 mg/kg/day, with a 3-h interval between doses, s.c.), decreased levels of SERT in hippocampus, striatum and at a higher extent in frontal cortex, in addition to induce a decrease in the expression of TPH-2 in the three brain areas studied (López-Arnau et al. 2014b). In the same study, the authors reported a slight decrease in levels of DAT and TH expression in the frontal cortex, though no neurotoxic injury in DA

nerve terminals was observed (López-Arnau et al. 2014b). These results are closely related to the neuronal disturbances found in mice administered with the same synthetic cathinone derivative, using a similar drug schedule (4×25 mg/kg/day, with a 3-h interval between doses, s.c.) (López-Arnau et al. 2014a). Nonetheless, one must be aware that several studies reported that mephedrone, methylone and MDPV do not seem to produce chronic depletions of monoamine levels, which are considered biomarkers of neurotoxicity (Angoa-Pérez et al. 2012, 2013; Baumann et al. 2012; Kehr et al. 2011; Miner et al. 2017; Motbey et al. 2012; Shortall et al. 2013). The apparent contradictory data may be due to significant differences between the studies design, namely dosage and administration route, animal model (e.g. species and gender) and even some animal housing conditions (e.g. ambient temperature). In addition to the effects reported so far, these three SCs are associated with disruptions in thermoregulation (Angoa-Pérez et al. 2012; Anneken et al. 2015; Baumann et al. 2012; Fantegrossi et al. 2013) and mephedrone to altered learning and memory (den Hollander et al. 2013; Motbey et al. 2012).

Glial fibrillary acidic protein (GFAP) has been considered a marker protein for astrogliosis, which usually occurs after neurodegenerative insults (Eng and Ghirnikar 1994). Interestingly, no significant alterations in expression of GFAP were found following administration of any of the three SCs (mephedrone, methylone and MDPV) to mice (Anneken et al. 2015; Miner et al. 2017). Of note, in several in vivo studies, MDMA was capable of inducing serotonergic neurotoxicity without any brain GFAP increased expression [for a review see (Capela et al. 2009)]. In spite of the controversy, it can be assumed that SCs indeed have neurotoxic potential.

In addition to the in vivo preclinical data, several in vitro studies have been performed aiming to determine the neurotoxic potential of a large number of SCs, as well as their potencies and the pathways putatively involved in the observed toxic effect. Table 7 summarizes the in vitro studies conducted in microglia, neuron- or BBB-like cell models.

Some authors, including our working group, have recently reported the ability of several SCs to induce oxidative stress in in vitro BBB- and neuron-like cell models (Leong et al. 2020; Matsunaga et al. 2017; Rosas-Hernandez et al. 2016a, b; Siedlecka-Kroplewska et al. 2018; Soares et al. 2019, 2020; Valente et al. 2017a, b). Although the pathways underlying this SC-mediated deleterious effect are far from being completely understood, increased production of reactive oxygen and/or nitrogen species (ROS and RNS, respectively) was reported in all of previously mentioned studies. Furthermore, other alterations were reported, such as decrease in expression of γ-glutamylcysteine synthetase, glutathione reductase activity, and total and reduced glutathione levels and/or increase in oxidized form of this natural cellular antioxidant (Matsunaga et al. 2017; Soares et al. 2020; Valente et al. 2017b). Moreover, pre-treatment with antioxidants (e.g. *N*-acetyl-L-cysteine, polyethyleneglycol-conjugated catalase, tiron and trolox) significantly attenuated the cytotoxic effects induced by α-pyrrolidinononanophenone (α-PNP) (Matsunaga et al. 2017), 3,4-DMMC, amfepramone, mephedrone, methcathinone, *N*,*N*-dimethylcathinone, pentedrone and α-pyrrolidinopropiophenone (Soares et al. 2019, 2020), methylone and MDPV (Valente et al. 2017a), further suggesting a prominent role of oxidative stress in SCs-mediated neurotoxicity.

Mitochondria, the main "energy-producing machinery" of eukaryotic cells, are responsible for endless major roles, including the synthesis of adenosine 5′-triphosphate (ATP), which in neurons occurs mainly through oxidative phosphorylation, the production and sequestration of ROS, the synthesis and inactivation of neurotransmitters, the calcium (Ca^{2+}) homeostasis and programmed cell death (apoptosis) (Flippo and Strack 2017). As such, mitochondrial dysfunction may be partially responsible for the SC-induced neurotoxic effects. In fact, it has been reported that SCs and their metabolites decreased the ability of microglia and neuron-like cells to reduce tetrazolium salts to formazans (Coccini et al. 2019; de Mello-Sampayo et al. 2020; Ferreira et al. 2019; Lantz et al. 2017; Matsunaga et al. 2017; Soares et al. 2019, 2020; Valente et al. 2017a, b; Wojcieszak et al. 2018; Wojcieszak et al. 2016), which is indicative of mitochondrial dysfunction or decreased activity (Aslantürk 2018). Moreover, mephedrone (den Hollander et al. 2014), the methylbenzamide breakdown products that are produced from mephedrone and methylone (den Hollander et al. 2015), and butylone, MDPV and pentylone (Leong et al. 2020) reduced mitochondrial respiration in human SH-SY5Y cells. In this last cited study, the three SCs also increased the mitochondrial stress levels and the intracellular Ca^{2+} levels, in addition to inducing intracellular ATP depletion (Leong et al. 2020). Other authors have previously reported that MDPV and methylone prompted mitochondrial membrane potential (MMP) dissipation and consequently compromised the cellular bioenergetics in human SH-SY5Y cells differentiated into a more mature dopaminergic phenotype (Valente et al. 2017b). Using the same experimental model, our group have recently showed that 3,4-DMMC and mephedrone induced MMP depolarization and decreased ATP intracellular levels (Soares et al. 2020). Furthermore, α-PNP was shown to significantly decrease the MMP in human SK-N-SH cells (Matsunaga et al. 2017).

The aforementioned data highlight the ability of SCs to cause disturbances in cellular homeostasis, thus compromising the cell viability. In this regard, SCs and their metabolites were shown to induce apoptotic cell death in in vitro microglia and neuron-like cell models, evidenced by activation of both initiator (caspase-8 and -9) and executioner (caspase-3 and -7) caspases, cellular morphological

Table 7 Neurotoxic potential of synthetic cathinones and their metabolites evaluated in in vitro studies

Cell line (differentiation)	Tissue of origin	Specie	Synthetic cathinone(s) or metabolites	Concentration range (mM)	Main findings	References
hCMEC/D3 (UND)	Temporal lobe microvessels	Human	MDPV	0.01[a]; 0.05[a]	Strongly stimulates the *trans*-efflux zero of cocaine suggesting that it may be a substrate of the cocaine transporter; potently inhibits cocaine uptake	Chapy et al. (2014)
SH-SY5Y [UND and DIF (10 μM RA and 80 nM TPA)]	Bone marrow	Human	3,4-Catechol-PV	0.01–1	Induces mitochondrial dysfunction (↓ MTT reduction) in UND and DIF cells at 24- and 48-h time-points; induces morphological changes (intracellular vesicles; loss of typical cell shape; neurite retraction; decrease in cell density) in both UND and DIF cells; promotes the activation of caspase-3 in both UND and DIF cells	Coccini et al. (2019)
SH-SY5Y [DIF (10 μM RA)]; CHME3 (UND)	Bone marrow; brain	Human; human	Buphedrone; methedrone; NEH	0.05–0.4	Induce loss of cell viability (↓ MTS reduction) in SH-SY5Y cells, though lower effects being produced by methedrone; NEH induces loss of cell viability (↓ MTS reduction) in CHME3 cells; none induce early or late apoptosis/necrosis in SH-SY5Y cells; buphedrone and NEH induce early apoptosis, whilst only the later cause late apoptosis/necrosis in CHME3 cells; buphedrone and NEH ↑ lysosomal activity/stress both in SH-SY5Y and CHME3 cells (the effect produced being similar for the two SCs in SH-SY5Y cells, whilst in CHME3 cells NEH-induced effect is markedly enhanced over that induced by buphedrone); NEH induces morphological changes (↓ in cell area and perimeter) associated with microglia activation (CHME3)	de Mello-Sampayo et al. (2020)
SH-SY5Y (UND)	Bone marrow	Human	4-MMC; methylone	0.002–2	↑ LDH release assay; redox electron donor reactivity; no evidence of protein adduct formation; 4-MMC-induced cytotoxicity and ↓ of mitochondrial respiration is attenuated by DAT inhibition	den Hollander et al. (2014)
SH-SY5Y [UND and DIF (10 μM RA and 80 nM TPA)]	Bone marrow	Human	4-MMC; methylone	0.0025–2	↑ LDH release (UND and DIF cells); ↓ mitochondrial respiration (UND cells); 4-MMC-induced cytotoxicity is partially prevented by overexpression of Bcl-2, DAT inhibition and depletion of glutathione; 4-MMC causes induction of p53; 4-MMC ↑ TNF-α levels, which is attenuated by DAT inhibition; 4-MMC appears to be converted into DMBA, and DAT inhibition may prevent its cell uptake; DMBA and MDMBA ↑ LDH release, which is totally prevented by DAT inhibition; DMBA and MDMBA ↓ mitochondrial respiration	den Hollander et al. (2015)
SH-SY5Y [DIF (10 μM RA)]	Bone marrow	Human	4-FMC; 4-MEC; buphedrone; methedrone; NEH	0.05–0.4	↓ MTS reduction; IC_{50} of 0.0981 (NEH), 0.103 (4-FMC), 0.148 (buphedrone), 0.1612 (4-MEC) and 0.3819 (methedrone) mM, for a 24-h exposure	Ferreira et al. (2019)

Table 7 (continued)

Cell line (differentiation)	Tissue of origin	Specie	Synthetic cathinone(s) or metabolites	Concentration range (mM)	Main findings	References
SH-SY5Y [DIF (10 µM RA and 81 nM TPA)]	Bone marrow	Human	Butylone; MDPV; Pentylone	1–10	↓ cell viability; trigger oxidative stress (↑ ROS production), impair the mitochondrial function (↑ mitochondrial stress levels; ↓ mitochondrial respiration) and compromise cell bioenergetics (↓ intracellular ATP levels); cause alterations of cell morphology (rounded shape cells with neurite retraction) and disruption of Ca^{2+} homeostasis (↑ intracellular Ca^{2+}), and trigger apoptosis (activation of caspase-7 and -3); EC_{15}, EC_{40} and EC_{50} values for butylone, MDPV and pentylone (after a 24-h exposure) are, in that order, as follows EC_{15} of 4.67, 2.6 and 3.05 mM, EC_{40} of 5.91, 3.43 and 4.06 mM, and EC_{50} of 6.39, 3.61 and 4.44 mM	Leong et al. (2020)
SK-N-SH (UND); TGW (UND)	Bone marrow; adrenal gland	Human; human	α-POP; α-PNP; α-PVP	0.002–0.05	α-PVP ↓ cell viability (SK-N-SH); α-POP induces oxidative stress (↑ ROS production) in SK-N-SH cells; α-PNP ↓ mitochondrial activity (SK-N-SH) and cell viability (SK-N-SH; TGW); α-PNP induces oxidative stress (↑ ROS production; ↓ tGSH and GSH levels; ↓ γ-GCS expression; ↓ GR activity), mitochondrial dysfunction (↑ and ↓ the expression of Bax and Bcl-2, respectively; ↑ cytosolic levels of cyt *c*; ↓ MMP), lipid peroxidation (↑ protein adducts of HNE) and apoptosis (activation of caspase-9 and -3; DNA fragmentation) in SK-N-SH cells; α-PNP inhibits proteasome function (↓ chymotrypsin- and trypsin-like proteolytic activities) and triggers autophagy (↑ LC3-I and LC3-II production; ↓ expression of p62; induces AMPK phosphorylation and expression of Beclin1) in SK-N-SH cells; antioxidant pre-treatment ↓ α-PNP-induced apoptotic events and prevented the demotion of chymotrypsin-like activity, as well as all autophagic processes induced by α-PNP (SK-N-SH); LC_{50} values for α-PNP, after a 48-h exposure, are 0.0118 mM (SK-N-SH) and 0.0169 mM (TGW)	Matsunaga et al. (2017)
SH-SY5Y (UND)	Bone marrow	Human	MDPV	0.01–2.5	Induces necrosis (↑ LDH release) and inhibits cell proliferation (↓ BrdU incorporation); ↑ ROS production; Induces apoptosis (DNA fragmentation)	Rosas-Hernandez et al. (2016a)

Table 7 (continued)

Cell line (differentiation)	Tissue of origin	Specie	Synthetic cathinone(s) or metabolites	Concentration range (mM)	Main findings	References
SH-SY5Y [DIF (10 µM RA and 80 nM TPA)]	Bone marrow	Human	3,4-DMMC; 4-MMC	0.5–5	Induce mitochondrial and lysosomal dysfunction (↓ MTT reduction and NR uptake); cytotoxicity partially prevented by pre-treatment with 3-MA, GBR 12909, NAC and trolox; induce oxidative stress (↑ ROS production, which is prevented by pre-treatment with antioxidants; ↓ intracellular tGSH levels), mitochondrial impairment (↓ MMP; ↓ intracellular ATP levels), apoptosis [activation of caspase-3; annexin V (+)/PI(−); annexin V (+)/PI(+)] and trigger autophagy activation; cytotoxicity was partially dependent on caspase-8, -9 and -3; induce morphological cell alterations (dwindling of the cell body; neurite retraction; intracellular vacuolization); IC_{25}, IC_{50} and IC_{75} values for 3,4-DMMC and 4-MMC were 1.01 and 2.22 mM, 1.28 and 3.00 mM, and 1.60 and 4.07 mM, respectively; plasma-binding protein predictive (PreADMET®) values for 3,4-DMMC and 4-MMC are 37.1% and 28.7%, respectively	Soares et al. (2020)
SH-SY5Y [DIF (10 µM RA and 80 nM TPA)]	Bone marrow	Human	3,4-DMMC; amfepramone; buphedrone; flephedrone; mephedrone; methcathinone; methedrone; *N*,*N*-dimethylcathinone; *N*-ethylcathinone; pentedrone; α-PBP; α-PPP; α-PVP	0.25–20	Induce mitochondrial and lysosomal dysfunction (↓ MTT reduction and NR uptake); Cytotoxicity partially prevented by pre-treatment with NAC (amfepramone, methcathinone, *N*,*N*-dimethylcathinone, pentedrone and α-PPP), MPH (pentedrone and α-PPP), CHX (amfepramone and pentedrone), 3-MA (3,4-DMMC and pentedrone) and tiron (α-PPP); induce morphological cell alterations (cytoplasmic shrinkage; neurite retraction; intracellular vacuolization) and apoptosis (chromatin condensation; pyknotic nuclei); 3,4-DMMC, methcathinone and pentedrone induce oxidative stress (↑ ROS production), with antioxidant pre-treatment ameliorating this effect, and trigger autophagy activation; LC_{50} values point 3,4-DMMC as the most potent derivative for both time-points and cytotoxicity assays, whereas amfepramone (at both time-points), and *N*,*N*-dimethylcathinone (24-h time-point) and *N*-ethylcathinone (48-h time-point) are the least potent SCs according the MTT reduction and NR uptake assays, respectively; elongation of the α-carbon side chain, the presence and the high steric volume occupied by the substituents on the phenyl ring, and the substitution of the *N*-pyrrolidine moiety for its acyclic secondary amine analogue have proved to be structural points of the utmost importance for the cytotoxicity exhibited by these SCs	Soares et al. (2019)

Table 7 (continued)

Cell line (differentiation)	Tissue of origin	Specie	Synthetic cathinone(s) or metabolites	Concentration range (mM)	Main findings	References
SH-SY5Y [DIF (10 µM RA and 80 nM TPA)]	Bone marrow	Human	MDPV; Methylone	0.773, 1.165 and 1.693[a]; 1.342, 1.962 and 2.797[a]	Trigger autophagy activation (cytoplasmic vacuolization; ↑ LC3-I to LC3-II turnover); induce other morphological cell alterations (neurite retraction); SCs-induced autophagy precedes apoptosis (caspase-3 activation), with potential involvement of oxidative stress in the case of methylone (↑ ROS/RNS production); antioxidant pre-treatment shows preventive potential regarding oxidative stress, and apoptotic and autophagy activity induced by SCs	Valente et al. (2017a)
SH-SY5Y [UND and DIF (10 µM RA and 80 nM TPA)]	Bone marrow	Human	MDPV; Methylone	0.01–20	Induce mitochondrial dysfunction (↓ MTT reduction) and cell death (↑ LDH release); induce oxidative stress (↑ROS/RNS production; ↑ intracellular GSSG levels; ↓ intracellular GSH levels) and mitochondrial impairment (↓ MMP; ↓ intracellular ATP levels); induce apoptosis and, in a less extent, necrosis (activation of caspase-8, -9 and -3; chromatin condensation; pyknotic nuclei); EC_{50} values, after a 24-h exposure, are 1.506 and 2.057 mM for MDPV (MTT reduction and LDH leakage assays, respectively), and 2.493 and 3.200 mM for methylone (MTT reduction and LDH leakage assays, respectively) in DIF cells	Valente et al. (2017b)
SH-SY5Y (UND)	Bone marrow	Human	4-F-PV8; 4-F-PV9; 4-F-α-PVP; 4-MeO-PV8; 4-MeO-PV9; 4-MeO-α-PVP; PV8; PV9; α-PVP	0.01–0.3	Induce mitochondrial dysfunction (↓ MTT reduction); PV8, PV9 and their phenyl substituted counterparts, induce markedly cell membrane damage (↑ LDH release), whereas only the highest tested concentration prompts this outcome upon exposure cells to 4-F-α-PVP and 4-MeO-α-PVP	Wojcieszak et al. (2018)
SH-SY5Y (UND)	Bone marrow	Human	2,3-MDPV; 3,4-MDPV; Catechol-MDPV; methylcatechol-MDPV; PV9; pyrovalerone; α-PVT	0.01–0.3	2,3-MDPV, 3,4-MDPV and pyrovalerone induce weak to moderate mitochondrial dysfunction (↓ MTT reduction), but do not cause significant damage to cell membranes (↑ LDH release); catechol-MDPV is more potent than 3,4-MDPV, causing more marked changes in mitochondrial activity and in cell membrane integrity, whereas methylcatechol-MDPV do not induce any significant changes in those parameters; PV9 and α-PVT appear to be the most cytotoxic SCs (marked ↓ MTT reduction), and the former derivative also inducing pronounced ↑ LDH release	Wojcieszak et al. (2016)
PC-12 (UND)	Adrenal gland	Rat	Pentedrone	1×10^{-9}–10	Modulates the dopaminergic system (↑ mRNA expression of DAT, D1DR and D2DR); ↑ phosphorylation of CREB; induces cell death (↑ LDH release)	Hwang et al. (2017)
PC-12 (UND)	Adrenal gland	Rat	Phthalimide	0.01–1	Induces mitochondrial dysfunction (↓ XTT reduction) and cell death (↑ LDH release); GSH levels remain unaffected; at lower concentrations (0.01 and 0.1 mM), ↑ the intracellular levels of DA and 5-HT, whereas at 1 mM ↓ the intracellular levels of these monoamines	Lantz et al. (2017)

Table 7 (continued)

Cell line (differentiation)	Tissue of origin	Specie	Synthetic cathinone(s) or metabolites	Concentration range (mM)	Main findings	References
PC-12 [DIF (50 ng/mL NGF, 1% horse serum, 10 mM HEPES and 2% glutamine)]	Adrenal gland	Rat	MDPV	1×10^{-4}[a]	Produces a rapid upregulation of DAT (↑ surface DAT expression)	López-Arnau et al. (2019)
BBMVEC (UND)	Brain capillary vessels	Bovine	MDPV	0.5–2.5	Induces necrosis (↑ LDH release) and inhibits cell proliferation (↓ BrdU incorporation); ↑ production of ROS and ·NO; Disrupts the endothelial cell monolayer and induces morphological cell changes (rounded shape)	Rosas-Hernandez et al. (2016b)
HT-22 (UND)	Brain/hippocampus	Mouse	3-FMC	1–4	↓ cell viability (↓ SRB staining); at 1 mM, induces G_0/G_1-phase cell cycle arrest, whereas exposure to the highest concentration (4 mM) massively ↑ the number of cells in the sub-G_1 fraction (suggesting apoptotic DNA cleavage)	Siedlecka-Kroplewska et al. (2014)
HT-22 (UND)	Brain/hippocampus	Mouse	3-FMC	1–4	Induces oxidative stress (↑ ROS production), apoptosis [activation of caspase-3; annexin V (+)/PI(−); annexin V (+)/PI(+)] and autophagy (cytoplasmic vacuolization; ↑ LC3-I to LC3-II turnover; ↓ expression of p62); induces morphological cell changes (rounded shape; chromatin condensation; nuclear fragmentation)	Siedlecka-Kroplewska et al. (2018)

−negative, + positive, NO nitric oxide, *μM* micromolar, *2,3-MDPV* 2,3-methylenedioxypyrovalerone, *3,4-catechol-PV or catechol-MDPV* 3,4-dihydroxypyrovalerone (MDPV-metabolite), *3,4-DMMC* 3,4-dimethylmethcathinone, *3,4-MDPV or MDPV* 3,4-methylenedioxypyrovalerone, *3-FMC* 3-fluoromethcathinone, *3-MA* 3-methyladenine, *4-FMC or flephedrone* 4-fluoromethcathinone, *4-F-PV8* 4-fluoro-α-pyrrolidinoheptanophenone, *4-F-PV9* 4-fluoro-α-pyrrolidinooctanophenone, *4-F-α-PVP* 4-fluoro-α-pyrrolidinopentiophenone, *4-MEC* 4-methylethcathinone, *4-MeO-PV8* 4-methoxy-α-pyrrolidinoheptanophenone, *4-MeO-PV9* 4-methoxy-α-pyrrolidinooctanophenone, *4-MeO-α-PVP* 4-methoxy-α-pyrrolidinopentiophenone, *4-MMC or mephedrone* 4-methylmethcathinone, *5-HT* serotonin, *AMPK* adenosine monophosphate (AMP)-activated protein kinase, *ATP* adenosine 5'-triphosphate, *Bax* Bcl-2 associated X-protein, *Bcl-2*: B-cell lymphoma-2 protein, *BrdU* bromodeoxyuridine, Ca^{2+} calcium, *CHX* cycloheximide, *CREB* cyclic adenosine monophosphate (cAMP) response element-binding protein, *cyt c* cytochrome *c*, *D1DR* dopamine 1 receptors, *D2DR* dopamine 2 receptors, *DA* dopamine, *DAT* dopamine transporter, *DIF* differentiated, *DMBA N*-4-dimethylbenzamide, *DNA* deoxyribonucleic acid, *EC* effective concentration, *GBR 12,909* vanoxerine dihydrochloride, *GR* glutathione reductase, *GSH* reduced glutathione, *GSSG* oxidized glutathione, *h* hours, *HEPES* 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (buffer), *HNE* 4-hydroxynonenal, *IC* inhibitory concentration, *LC* lethal concentration, *LC3* microtubule-associated protein 1 light chain 3 (LC3-I and LC3-II are the cytosolic and the membrane-bound forms, respectively), *LDH* lactate dehydrogenase, *MDMBA* 3,4-methylenedioxy-*N*-methylbenzamide, *methylcatechol-MDPV* 4-hydroxy-3-methoxypyrovalerone (MDPV-metabolite), *mM* millimolar, *MMP* mitochondrial membrane potential, *MPH* methylphenidate, *mRNA* messenger ribonucleic acid, *MTS* 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, *MTT* 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide, *NAC N*-acetyl-L-cysteine, *NEH N*-ethylhexedrone, *NGF*: nerve growth factor, *nM* nanomolar, *NR* neutral red, *p53* p53 tumour suppressor protein, *p62* sequestosome 1 protein, *PI* propidium iodide, *PV8* α-pyrrolidinoheptanophenone, *RA* retinoic acid, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *SCs* synthetic cathinones, *SRB* sulforhodamine B, *tGSH* total glutathione, *TNF-α* tumour necrosis factor-α, *TPA* 12-*O*-tetradecanoylphorbol-13-acetate, *UND* undifferentiated, *vs.* versus, *XTT* 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide, *α-PBP* α-pyrrolidinobutiophenone, *α-PNP* α-pyrrolidinononanophenone, *α-POP or PV9* α-pyrrolidinooctanophenone, *α-PPP* α-pyrrolidinopropiophenone, *α-PVP* α-pyrrolidinopentiophenone, *α-PVT* α-pyrrolidinopentiothiophenone, *γ-GCS* γ-glutamylcysteine synthetase

[a]Specific concentration(s) tested

alterations (e.g. neurite retraction, decrease in cell area and perimeter, loss of typical cell shape, chromatin condensation and pyknotic nuclei), increase p53 tumour suppressor protein and tumour necrosis factor α, decrease the expression levels of the anti-apoptotic B-cell lymphoma-2 protein (Bcl-2), increase the pro-apoptotic Bcl-2 associated X-protein and increase in cytosolic levels of cytochrome *c* (Coccini et al. 2019; de Mello-Sampayo et al. 2020; den Hollander et al. 2015; Leong et al. 2020; Matsunaga et al. 2017; Rosas-Hernandez et al. 2016a; Siedlecka-Kroplewska et al. 2014; Siedlecka-Kroplewska et al. 2018; Soares et al. 2019, 2020; Valente et al. 2017a, b).

Moreover, autophagic activity (which is normally low under basal conditions) can be up-regulated and complex events can be triggered due to stressful conditions (e.g. drug exposure). The overall process, in which damaged macromolecules and even entire organelles are engulfed in a double-membrane vesicles (autophagosomes) that fuse with lysosomes (autolysosomes) and are finally digested, may culminate either with cell survival or death (Chen et al. 2018; Mariño et al. 2014). Concerning this matter, only five in vitro studies evaluated the potential of SCs to trigger autophagy activation in neuron-like cells, namely the human SK-N-SH cells (Matsunaga et al. 2017), the human SH-SY5Y cells differentiated into a more mature dopaminergic phenotype (Soares et al. 2019, 2020; Valente et al. 2017a) and the mice HT-22 cells (Siedlecka-Kroplewska et al. 2018), although there is a controversy on the role played by SC-induced autophagy upregulation in the ultimate fate of cell. Therefore, further studies are required to evaluate whether autophagy activation by SCs plays a protective or a detrimental role for the cells, as it remains a debatable question for other substances of abuse, namely METH (Pitaksalee et al. 2015; Xu et al. 2018).

Concluding remarks

In the present review, relevant information regarding *Catha edulis* Forsk., cathinone and its metabolites and SCs is summarized. *Catha edulis* Forsk., also known as khat, has been chewed for centuries due to its CNS stimulant properties, mostly attributed to an extremely labile alkaloid, the cathinone. Cathinone deservedly earned the sobriquet of natural AMPH as it has a chemical structure and pharmacological profile closely resembling its non-β-keto counterpart. Surprisingly, some SCs were synthesized about 45 years before the discovery and isolation of this natural occurring alkaloid from khat. Although being initially developed for clinical applications, mainly as antidepressant and appetite suppressant/anorectic drugs, SCs rapidly entered social and recreational drug market. These "new" psychoactive substances have been widely sold as legal alternatives to the controlled classical drugs of abuse, as MDMA, with the disclaimer "not for human consumption" or "for research purposes only" to skirt existing drug legislation. However, the consumption of such substances is not without risk, since abusers do not know the content of the product they buy, and data regarding their pharmacological and toxicological profile are often scarce. Notwithstanding, SCs' wide diffusion, popularity and demand alarmingly increased by the end of the past decade alongside several reports on intoxications and deaths related to their abuse. In this scenario, the most prevalent substances were placed under international control, being replaced by chemical analogues obtained by introducing minor modifications to the parent compound scaffold. The rate of absorption depends on the substance form, administration route or even factors related to the user. SCs normally undergo metabolism, but almost all of these substances may be partially excreted unchanged in urine. The major metabolic pathways of these substances are determined by their chemical structure. Phase I, chiefly mediated by CYP450 enzymes (e.g. CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6 and CYP3A4), though other enzymes are involved (e.g. catechol-*O*-methyltransferase), and/or phase II metabolism can occur, with the resultant metabolites being urinary excreted. Similarly to their non-β-keto analogues, SCs exert their effects mainly interacting with monoamine transporters, namely DAT, NET and SERT, either acting as substrates and/or blockers, thereby increasing the monoamine content in the synaptic cleft. Differences among the derivatives regarding their potency, affinity and selectivity towards a specific monoamine system have been shown and correlated with both desired and unwanted clinical effects. SCs have been sought due to their stimulant, hedonic and hallucinatory effects, but their abuse leads to several unpleasant effects. The most commonly reported adverse effects are neurological, psychiatric and cardiac in nature, but gastrointestinal and hepatic, haematological, musculoskeletal, pulmonary and renal effects may also upsurge, and may be part of some toxydromes (e.g. sympathomimetic and hallucinatory toxydromes, and excited/agitated delirium syndrome). The abuse of such kind of substances can culminate in multi-organ failure and death. Although several SCs are currently under international legal control, many others emerge every year to replace them. The limited availability of information regarding these substances, in addition to the rapid emergence of new derivatives, further hinders the process of detection, especially in the field. This assumes a particular importance in acute exposures, where the clinicians are usually unaware of the substances consumed, as several symptoms displayed by users often overlap with those induced by other drugs of abuse (e.g. classical amphetamines). As treatment for intoxications from SCs abuse is mainly supportive in nature, e.g. for symptom management only, it is of the utmost importance to promote studies on the mechanisms of action of

such substances, thus allowing the development of more specific, rapid and effective treatments. Additionally, global efforts concerning the development and implementation of faster legal measures in order to control the production and sale of the emerging derivatives are mandatory. This long and difficult path will allow significantly reducing the prevalence on the abuse of SCs, as well as the number of non-fatal and lethal intoxications related to these substances.

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Declaration

Conflict of interest The authors declare that there is no conflict of interest.

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