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SYSTEMATIC REVIEW ARTICLE

Synthetic Cannabinoids and Cathinones Cardiotoxicity: Facts and Perspectives

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Abstract: New psychoactive substances (NPS) constitute a group of psychotropic substances, designed to mimic the effects of traditional substances like cannabis, cocaine, MDMA, khat, which was not regulated by the 1961 United Nations Convention on Narcotics or the 1971 United Nations Convention on Psychotropic Substances. Illegal laboratories responsible for their production regularly developed new substances and placed them on the market to replace the ones that have been banned; for this reason, during the last decade this class of substances has represented a great challenge for the public health and forensic toxicologists. The spectrum of side effects caused by the intake of these drugs of abuse is very wide since they act on different systems with various mechanisms of action. To date most studies have focused on the neurotoxic effects, very few works focus on cardiotoxicity. Specifically, both synthetic cannabinoids and synthetic cathinones appear to be involved in different cardiac events, including myocardial infarction and sudden cardiac death due to fatal arrhythmias. Synthetic cannabinoids and cathinones cardiotoxicity are mainly mediated through activation of the CB1 receptor present on cardiomyocyte and involved with reactive oxygen species production, ATP depletion and cell death. Concerns with the adrenergic over-stimulation induced by this class of substances and increasing oxidative stress are mainly reported. In this systematic review we aim to summarize the data from all the works analyzing the possible mechanisms through which synthetic cannabinoids and synthetic cathinones damage the myocardial tissue.

Keywords: New psychoactive substances, synthetic cannabinoids, synthetic cathinones, cardiotoxicity, toxicity, myocardial damage.

1. INTRODUCTION

New psychoactive substances (NPS) constitute a group of psychotropic substances, either in pure form or in preparation, which was not regulated by the 1961 United Nations Convention on Narcotics or the 1971 United Nations Convention on Psychotropic Substances but presented public health aspects comparable to those posed by the substances included in these conventions, as defined in the 2005 Council Decision [1], recently revised by the European Parliament and Council [2, 3].

NPS therefore include a wide range of molecules, designed to mimic the effects of traditional substances, such as cannabis, cocaine, MDMA (3,4-methylenedioxymethamphetamine) and LSD (Lysergic acid diethylamide). Most of them are not used (or authorized) for therapeutic purposes but taken exclusively for recreational purposes [4, 5].

They appeared on the markets in solid or liquid form or were presented in the form of a medicament and are sold in the form of pills, tablets, capsules, sometimes mixed with plant material [6].

Illegal laboratories responsible for their production regularly develop new substances and place them on the markets to replace those already under legal control [2, 7]. This entails a continuous modification of the biochemical structure of these molecules and the consequential need to study them for a timely identification.

NPS are also known under the names of "designer drugs", "legal highs", "herbal highs", "bath salts". They are divided into main categories such as synthetic cannabinoids (SCs), synthetic cathinones, phenethylamines, piperazines, tryptamines and new benzodiazepines [8].

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Over the years the market has given a significant boost to the development of these substances, in particular to SCs, synthetic cathinones and phenethylamine derivatives [9]. For this reason, most of the studies present to date in the literature are focused on these classes of molecules. The spectrum of side effects caused by the intake of these substances of abuse is very wide since they act on different systems with various mechanisms of action.

Synthetic cannabinoids represent a heterogeneous group of substances originally designed and developed for scientific purposes, to facilitate the study of the endogenous system of cannabinoid receptors and to provide potential therapeutic tools. Zangani *et al*. identified 1115 SC by three different databases, most of them scarcely known because they are still in the early stages of their life cycle and will probably be more popular in the future [10]. In fact, the endocannabinoid system constitutes a fundamental neuromodulation mechanism of neuronal excitability, by acting on cognitive processes, memory, pain modulation, motor control, appetite, anti-stress response and also on numerous other systems such as system regulation, the immune system, cell proliferation, the gastrointestinal system and the cardiovascular system.

The molecular structures of synthetic cannabinoids are designed to mimic the psychoactive effects of Delta-9-tetrahydrocannabinol (THC). Although some of SCs share conformational similarities with THC, most of them are structurally different from it. The mechanism of action involves their interaction with the CB1 [11, 12] and CB2 [13] cannabinoid receptors, with varying degrees of affinity, activating them in most cases. CB1 receptors are located in the nervous system, liver, muscles and adipose tissue while CB2 receptors can be found in the immune system, spleen and peripheral tissues.

Synthetic cathinones have been one of the most emerging and widely used designer drugs in the last decade. Schifano *et al*. reported more than 220 synthetic cathinones identified with three different databases [14]. In the drug market they are sold as "bath salts" or "plant food" and, to avoid legislation, and they are labelled also as "not for human consumption". Their structure and pharmacological effects are similar to 3,4-methylenedioxymethamphetamine (MDMA) and amphetamine; those that are most commonly used as drugs are named mephedrone, butylone, α -pyrrolidinovalerophenone (α-PVP), 3,4-methylenedioxypyrovalerone (MDPV), α -pirrolidinoesanofenone (α-PHP) and α -Pyrrolidinoheptaphenone (PV8). The most common signs and symptoms of drug abuse include neurological, psychiatric and cardiologic effects, such as agitation, delirium, chest pain, tachycardia, hypertension, arrhythmia and sudden death.

To date, there are few studies in the literature in which a systematic review has been carried out on the toxic effects of synthetic cannabinoids, including those regarding myocardial tissue [15-19]; no review was found on the cardiotoxicity of synthetic cathinones.

In this systematic review we aim to summarize the data from all the works and to analyze, from a histopathological, biomolecular and genetic point of view, the possible mechanisms through which SCs and synthetic cathinones damage the myocardial tissue. The data obtained from our study will be helpful in directing future work towards areas of research scarcely investigated so far.

2. METHODS

2.1. Eligibility Criteria

The present systematic review was carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) standards. Studies examining cardiotoxic effects potentially induced by synthetic cannabinoids and synthetic cathinones were included. Study designs comprised case reports, case series, retrospective and prospective studies and reviews. The latter were downloaded to search their reference lists similarly to other papers. The search included *in vitro*, *in vivo* and *ex vivo* studies conducted both on animal and human subjects.

2.2. Search Criteria and Critical Appraisal

A systematic literature search and a critical appraisal of the collected studies were conducted. An electronic search of PubMed, from the inception of this database to 17th of November 2020, was performed.

For studies involving Synthetic Cannabinoids, search terms were ("SCs" OR "SCRAs" OR "SCBs" OR "synthetic cannabinoids") AND ("cardiotoxicity" OR "autopsy" OR "myocardial damage" OR "acute coronary syndrome" OR "sudden cardiac death" OR "cardiomyopathy" OR "arrhythmia" OR "QT prolongation") in title, abstract, and keywords.

For studies involving Synthetic Cathinones, search terms were ("synthetic cathinone" OR "mephedrone" OR "MDPV" OR "α-PVP" OR "α.PHP" OR "PV8") AND ("cardiotoxicity" OR "toxicity" OR "myocardial damage" OR "acute coronary syndrome" OR "sudden cardiac death" OR "cardiomyopathy" OR "arrhythmia" OR "QT prolongation") in title, abstract, and keywords.

The bibliographies of all located papers were examined and cross-referenced for further relevant literature.

A methodological appraisal of each study was conducted according to the PRISMA standards, including evaluation of bias. Data collection entailed study selection and data extraction. Two researchers (D.R., A.M.) independently examined those papers whose title or abstract appeared to be relevant and selected the ones that analyzed deaths or non-lethal intoxication due to assumption of SCs or Synthetic Cathinones Figs. (**1** and **2**). Disagreements concerning eligibility between the two researchers were resolved by consensus process. No unpublished or gray literature was searched. Data extraction was performed by two investigators (M.A., D.R.) and verified by another investigator (S.D.). This study was exempted from institutional review board approval as it did not involve human subjects.

3. RESULTS AND DISCUSSION

3.1. Synthetic Cannabinoids

A considerable number of studies have shown the presence of CB1 receptors in the cardiovascular system and

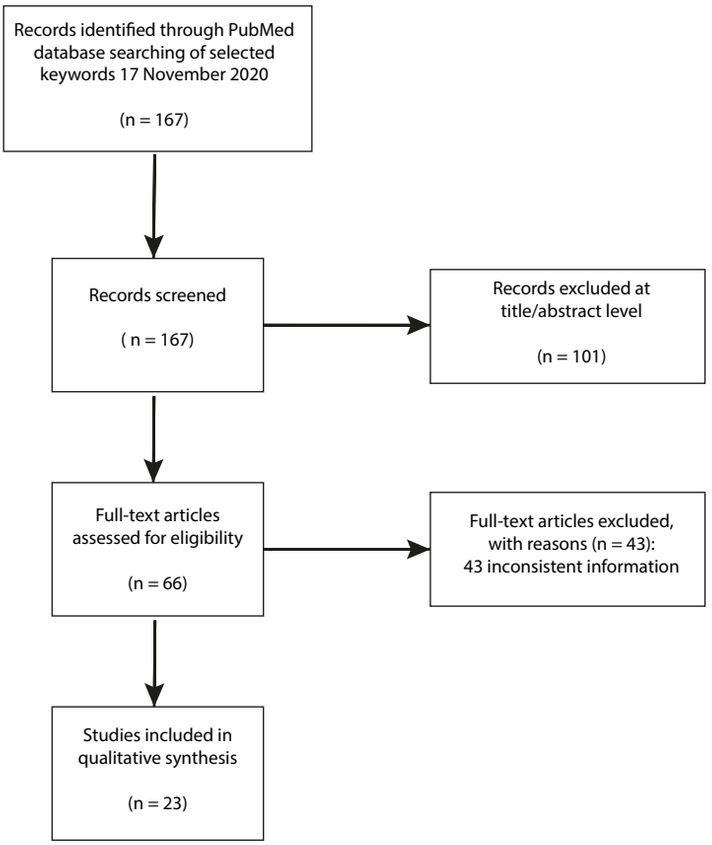

Fig. (1). Synthetic Cannabinoids.

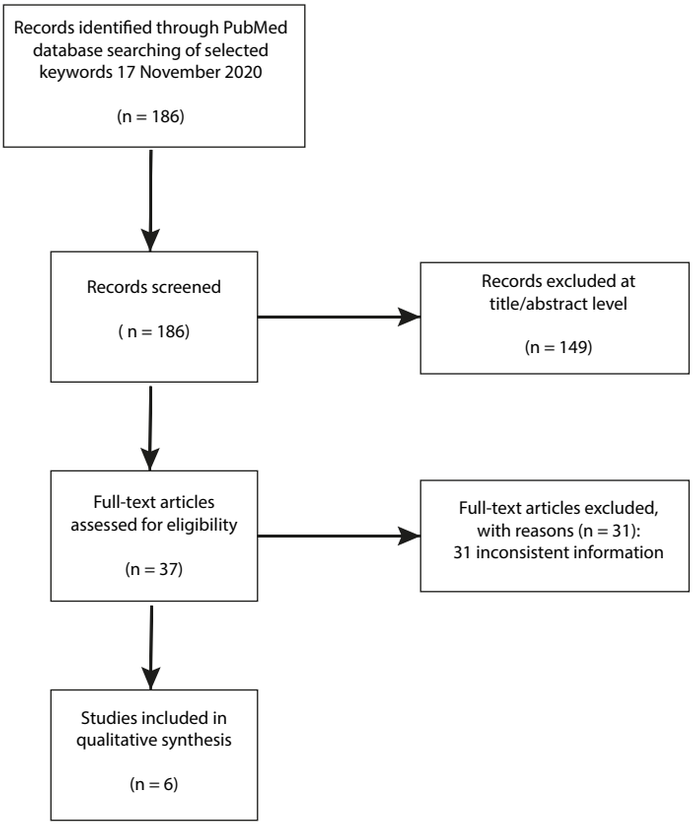

Fig. (2). Synthetic Cathinones.

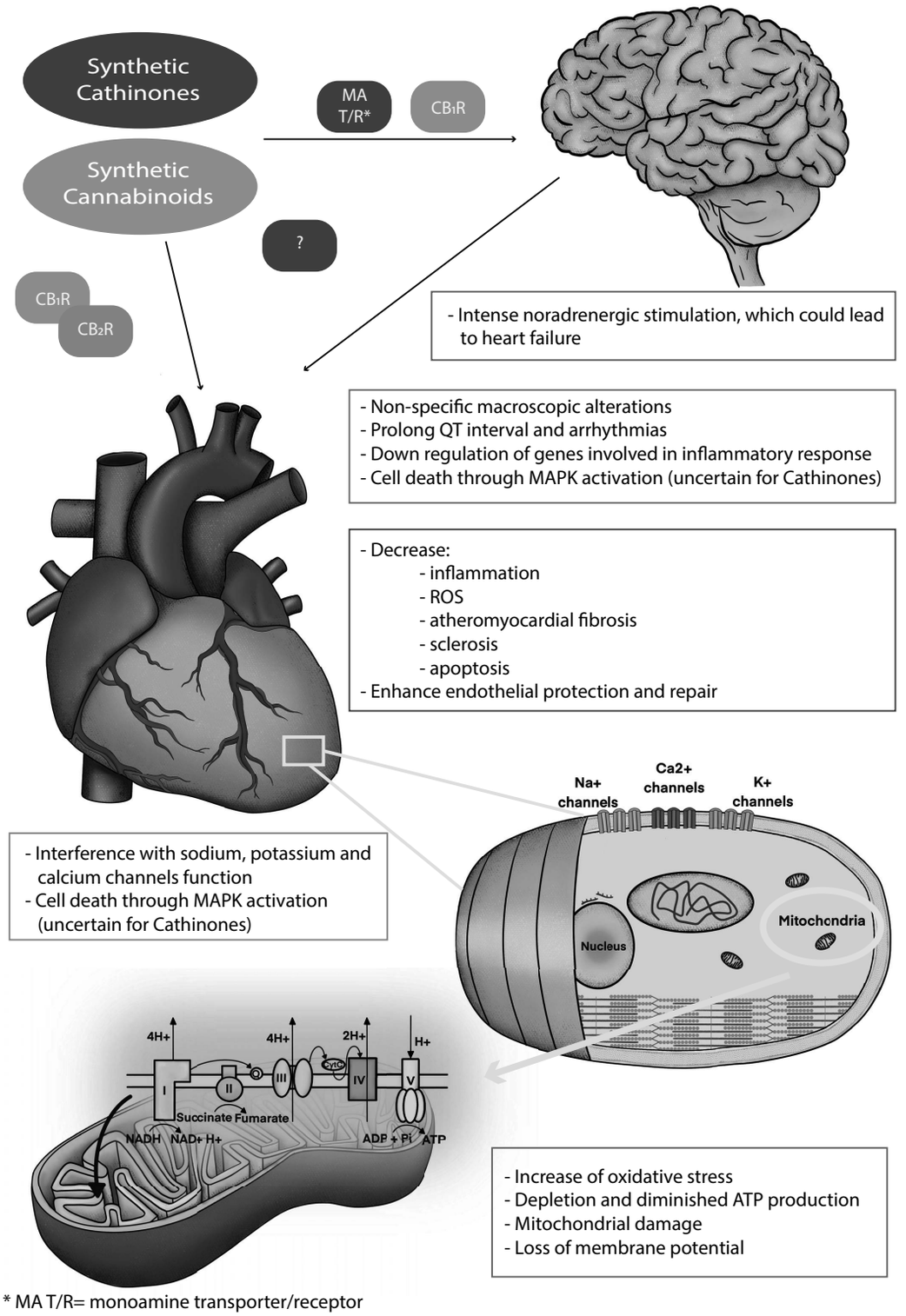

Fig. (3). Mechanisms of cardiotoxicity induced by Synthetic Cannabinoids and Synthetic Cathinones. Through the activation of CB1 and MA T/R receptors of the brain, these molecules determine an intense noradrenergic stimulation. The direct action of synthetic cannabinoids on the heart is realized through the activation of the CB1 and CB2 receptors with both cardiotoxic and cardioprotective effects, while it is not clear which signaling pathway is triggered by synthetic cathinones. (Illustrated by Tina Šinigoj ©, 2020). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Synthetic cannabinoids studies.

Author	Tested/Studied/Reviewed Molecules	Model	Results
Krylatov *et al.* (2007) [25]	HU-210, ACPA, methanandamide and anandamide	Wistar rats (*in vivo* and *in vitro*, on rat isolated perfused hearts)	HU-210, ACPA, methanandamide and anandamide caused bradycardia. These molecules did not alter electrophysiological activity in the heart, while anandamide increased QRS duration. HU-210 induced negative chronotropy by CB1 receptor activation.
Pacher *et al.* (2008) [28]	WIN 55, 212-2	Review	Protective role of CB2 activation against myocardial, cerebral and hepatic injuries by decreasing the inflammatory response.
Barana *et al.* (2010) [26]	Anandamide, 2-ara-chidonoylglycerol (2-AG), N-palmitoylethanolamine (PEA), N-oleoylethanolamine (OEA), lysopho-sphatidylinositol (LPI)	Colture of mouse fibroblasts (Ltk2) stably expressing hKv1.5 myocytes isolated	Endocannabinoids and cannabinoid analogues inhibit human cardi-ac Kv1.5 channels
Steffens *et al.* (2012) [14]	HU-210 and WIN 55, 212-2	Review	Protective role of CB2 receptors for cardiomyocytes by mediating the anti-inflammatory response. In some studies, cellular damage has been favoured by CB2 activation.
Behonick *et al.* (2014) [35]	5F-PB-22	Case series	The autopsies revealed no pathognomonic alterations.
Varga *et al.* (2015) [20]	JWH-018 and JWH-073	Review	Cardiotoxicity due to deterioration of mitochondrial function, in line with evidence of toxicity dependent on activation of CB1 receptors, which lead to loss of membrane potential, increased oxidative stress and cell death.
Chen *et al.* (2016) [38]	AB-FUBINACA and its metabolites.	Wistar rats	Synthetic cannabinoids could play a role in the expression of genes involved in the regulation of blood pressure and in heart disease.
Yun *et al.* (2016) [22]	JWH-210, JWH-030, JWH-250, RCS4, rimonabant hydrochloride and AM630	Rats, rabbits, H9c2 cell line	Cytotoxicity is expressed perhaps through apoptotic cascade, trig-gering the caspase system. QT prolongation
Argamany *et al.* (2016) [23]	Synthetic marijuana product	Case report	Hyperemesis leading to rhabdomyolysis and acute renal failure, prolonged QTc.
Ezaki *et al.* (2016) [29]	Synthetic cathinones/cannabinoids or methamphetamine	Retrospective case study of forensic autopsies	Vasoconstrictive effect, combined with organic vessel stenosis, is potentially the cause of the ischemic event. On histological examination, coronary artery stenosis and contrac-tion band necrosis in two cases.
Fujita *et al.* (2016) [36]	α-PVP, MePHP, MAM-2201, XLR-11, PB-22, 5F-PB-22, AB- PINACA, mepi-rapim, α-EAPP.	Case series	The autopsies showed polyvisceral congestion in acute heart fail-ure due to SC and cathinones intoxication.
Sahin *et al.* (2018) [24]	Toluene and SKUNK	Case report	Tachycardia and multiple ventricular fibrillations treated with defibrillator. ST elevations at 24 h, then normalized
Romanczuk *et al.* (2018) [31]	AB-CHMINACA	Case report	Histopathological examinations showed chronic alterations of the heart, all of them were non-specific.
Paul *et al.* (2018) [34]	AB-CHMINACA, UR-144, XLR-11, and JWH-022	Case series	In one case, the post-mortem examination showed dilated cardio-myopathy, cardiomegaly, myocardiocytic hypertrophy and contrac-tion band necrosis.
Singh *et al.* (2018) [17]	K2	Review	Activated CBR1 has a negative inotropic effect on cardiomyocytes, which combined with the greater demand for oxygen deriving from hyperadrenergic acid could induce an infarct event.
Pacher *et al.* (2018) [19]	/	Review	The interaction of SC with CB1 receptor, p38 and MAPKs JNK are activated, determining cellular apoptosis and increased genesis of reactive oxygen species.
Adamowicz *et al.* (2019) [30]	AMB-FUBINACA and EMB-FUBINACA	Case report	the histological investigation showed no pathognomonic modifica-tion.

(Table 1) contd….

Author	Tested/Studied/Reviewed Molecules	Model	Results
Otzurk *et al.* (2019) [27]	/	Review	Chronic consumers of SCs show an increase of the dispersion of P waves. All substances reduce cell viability. JWH-030 acts through the activation of CB2, in addition to inhibiting the activity of the hERG channels.
Darke *et al.* (2020) [32]	AB-CHMINACA (most common)	Case series (55 cases)	Major cardiovascular comorbidities, such as atherosclerosis, fibrous myocardial replacement and cardiomegaly, have been observed in most cases.
Walsh, Andersen (2020) [21]	/	Review	SC-mediated recruitment of β-arrestins 1 and 2 may contribute to SC toxicity.
Ahmed *et al.* (2020) [18]	K2	Case report and review	The prolongation of the QT interval could be related to the blockage of the hERG channels by synthetic cannabinoids.
Boland *et al.* (2020) [33]	5-Fluoro-ADB	Case series (43 cases)	In the majority of cases the weight of the heart was greater than what was expected based on body weight and height
Richards (2020) [32]	/	Review	The increased risk of cardiovascular complications by using synthetic cannabinoids is determined by the interaction of pharmacogenetic factors, impaired coronary microcirculation and alterations in cellular ion fluxes.

in myocardial tissue with potential cytotoxic effects (Table **1**). In this regard, Varga *et al*. showed how the cardiotoxicity of various substances, whether of abuse or not, depends on the activation of myocardial CB1 receptors. In particular, it would seem that SCs exert their effects by interfering with the mitochondrial transport chain and with the synthesis of mitochondrial enzymes, with consequent loss of membrane potential, increased oxidative stress and, ultimately, cell death [20]. The activation of CB1 receptors as the first step of the cascade of events that ultimately leads to myocardial damage has also been described in some systematic reviews. Singh *et al*. observed how this activation has a negative inotropic effect on myocardiocytes [17]. This phenomenon, together with the increased oxygen demand derived from the hyperadrenergic stimulus, can trigger an infarct event. Pacher *et al*. also reviewed this mechanism in their work, concluding that the interaction of CB1 receptors with their ligands determines the activation of the p38 kinase and the mitogen-activated protein kinase (MAPKs) JNK, with the consequent induction of cell apoptosis. In addition, the genesis of reactive oxygen species increases, which causes considerable oxidative tissue stress. Less certain are the activation of ERK kinases 1 and 2, which helps to determine cardiac hypertrophy, and reduced mitochondrial biogenesis [19]. In their recent work, Walsh and Andersen focused on the biomolecular aspects of CB1 receptor-mediated signaling, which is still not well understood. The review provided a very accurate description of intracellular pathways, highlighting a potential prominent role of β-arrestins 1 and 2 plasma proteins in mediating synthetic cannabinoid toxicity [21].

As for the potential adverse effects of this class of substances on the electrical activity of the cardiac muscle Yun *et al*., in their *in vitro*, *ex vivo* and *in vivo* study on rats, hypothesized that one of the mechanisms of cytotoxicity of SCs occurs through the caspase system, resulting in cell death by apoptosis; in addition, they found that one of the most representative molecules, JWH-030, induces a prolongation of the QT by acting on the ion channels and changing the duration of the action potential in the myocardial cells [22].

Similar observations have also been made by Argamany *et al*. in a case report concerning a young man with acute SCs intoxication and presenting hyperemesis, rhabdomyolysis and acute renal failure with simultaneous prolongation of the QT interval [23]. Sahin *et al*. presented a case of acute intoxication by taking Skunk and toluene, resulting in tachycardia and multiple episodes of ventricular fibrillation successfully treated with a defibrillator. An elevation of the ST segment was then observed for 24 h after the episode, with complete return to normal of the subsequent electrocardiographic traces [24].

Some works have then considered the effects that exogenous cannabinoids can have on various types of ion channels. The intravenous administration of cannabinoid receptor agonists such as HU-210 and ACPA, has been shown to induce bradycardia in rats [25]. In addition, as observed in another study, both endocannabinoids and cannabinoid analogues can inhibit cardiac voltage-dependent potassium channels [24]. Also Ahmed *et al*. reached the same conclusions in their review, in which they explain that the prolongation of the QT interval is attributable to the blockage of the potassium channels hERG (human Ether-à-go-go-Related Gene) [18]. These data support the hypothesis that SCs can cause sudden, potentially lethal arrhythmias, acting at the receptor and myocardial ion channels level. In another recent systematic review, Otzurk *et al*. focused on supraventricular and ventricular arrhythmias and on the possible molecular processes that generate them. As for supraventricular arrhythmias, the authors observed that in the electrocardiographic traces of chronic SCs consumers there is an increase in the dispersion values of P waves, possible "primum movens" in the genesis of atrial fibrillation. Regarding ventricular arrhythmias, it has been noted that the substance JWH-030 acts through the CB2 receptor and inhibits the

activity of the hERG channels in the myoblastic H9c2 cells [27].

According to some authors, the activation of CB2 receptors could also play an important role in counteracting myocardial damage in the case of ischemia, going to attenuate the inflammatory response mediated by the activation of endothelial cells and the migration of inflammatory cells inside damaged tissue [13, 28].

As for the studies in which autopsies and subsequent histological investigations were performed, Ezaki *et al*. reported some cases of deaths due to myocardial ischemia following the simultaneous intake of SCs and synthetic cathinones. Post-mortem histological examination of myocardial tissue has shown, in addition to the presence of important coronary artery stenosis, the presence of contraction band necrosis in two cases. The authors concluded that the vasoconstrictive effect of these substances, combined with the important organic coronary artery stenosis, determined the ischemic event [29].

Adamowicz *et al*. presented a case of fatal intoxication with synthetic cannabinoids. During the autopsy, nonspecific findings of organic congestion and pulmonary edema were observed. Neither did the histological examination reveal pathognomonic changes in any tissue [30]. Similar evidence was also collected by Romanczuk *et al*.: in their case report, the case of a man hospitalized for heart surgery and who died 12 h after hospitalization was studied; the circumstantial data led to the suspicion of a death related to the intake of the synthetic cannabinoid AB-CHMINACA. However, the autopsy and toxicological results excluded the assumption of the substance of abuse as a cause of death, attributed instead to chronic heart failure aggravated by pneumonia. Histopathological examination of cardiac tissue has shown only completely nonspecific chronic changes [31].

In their review, Darke *et al*. examined the autopsy findings of all deaths in Australia involving synthetic cannabinoids, for a total of 55 cases. Pre-existing cardiovascular pathologies have been frequently observed, particularly severe atherosclerosis, myocardial fibrous substitution resulting from previous ischemia and cardiomegaly [32]. In a similar study, a report comprising a larger number of cases was provided by Boland *et al*., who conducted autoptic and toxicological analyses on 43 fatal intoxication cases caused by the SC 5-Fluoro-ADB. No pathognomonic changes to any organ were observed on autopsy. Most subjects, however, had a cardiac weight higher than expected, suggesting the existence of a previous pathological substrate [33]. In both these studies, the authors therefore concluded that subjects with cardiomegaly or other cardiac pathologies may be more susceptible to the hypertensive and tachycardic effects of SCs, facilitating the onset of myocardial ischemia

Paul *et al*., however, have hypothesized that chronic use of SCs may cause myocardial pathological changes even in extremely young subjects; in fact their report presented the case of a 17-year-old individual, a habitual consumer of synthetic cannabinoids, who died of sudden cardiac death. The post-mortem examination showed the presence of cardiomegaly and dilated cardiomyopathy. Histological analysis revealed myocardiocyte hypertrophy and contraction band necrosis [34]. In contrast with these findings, in their case series Behonick *et al*. presented the results of autopsies conducted on 4 individuals who died of acute SCs intoxication, without detecting specific alterations in the myocardial level [35]. The same observations have also been made in subsequent studies [36].

In a recent review, Richards thoroughly examined the literature concerning the mechanisms involved in the risk of acute coronary syndrome and arrhythmias associated with the use of cannabis and synthetic cannabinoids [37]. In particular, he focused his attention on the pharmacological, electrophysiological and neuroendocrine points of view, while highlighting how synthetic cannabinoids can play a notable role in the onset of heart disease even in individuals without cardiovascular risk factors. This effect is realized through a complex interaction of autonomic dysregulatory factors, altered cellular ion fluxes, impaired coronary circulation and pharmacogenetic risk factors. The CB1 receptors, together with many others, are of considerable importance in the genesis of pathways that ultimately determine the phenomena mentioned above.

As for genetic studies, Chen *et al*. analyzed changes in gene expression in rats after chronic treatment with the synthetic cannabinoid AB-FUBINACA. Particularly, at vascular level they observed a decrease in the expression of the Hao2 gene. This gene is implicated in the increase in systolic pressure in rats, therefore the use of SCs could constitute a potential treatment for the regulation of systemic pressure. Instead, at the myocardial level, the chronic use of SCs has induced a decrease in the expression of the Cfd gene, involved in the inflammatory response after ischemic insults or stroke. This evidence suggests a potential role of SCs in the treatment of heart disease [38].

3.2. Synthetic Cathinones

Regarding synthetic cathinones, a few works focus on cardiotoxic damage due to the abuse of this kind of drug while all of them approach the study using different models: some use the animal model (mainly rats), others cell culture, each with its advantages and disadvantages (Table **2**). Animal models enabled an evaluation of the hemodynamic parameters and the attainment of an an overview of toxicity in all systems and their integration in one model, but this approach was limited by interspecies differences and did not enabled an evaluation of the effects at cellular level. Studies with cell cultures overcame the problem of interspecies differences, enabled an overview of almost all ion channels and receptors present in human cardiomyocytes and could be repeated indefinitely. On the other hand, phenotypic differences of the receptors and ion channels compared to those of an adult human being, and the impossibility to examine the neurotoxic effect should be considered. Despite the different approaches and findings, what clearly emerges from the analysis of the works is that, like synthetic cannabinoids, synthetics cathinones also have a direct action on cardiomyocytes, which could contribute to the onset of a fatal event.

The first study to investigate the possible effects of synthetic cathinones on the heart was conducted by Meng *et al*.

Table 2. Synthetic cathinones studies.

Author	Tested Molecules	Model	Results
Meng *et al.* (2012) [39]	Mephedrone	Cell Culture (isolated guinea pig ventricular myocyte) Animal - Rat	No effect on sodium, potassium and calcium channel. Increase heart rate and blood pressure with increased heart functionality. Pre-treatment with reserpine useless.
Varner *et al.* (2013) [40]	Mephedrone	Animal - Rat	Increase heart rate and mean arterial pressure in dose manner. Response attenuation with pre-treatment with atenolol and phentolamine.
Sivagnanam *et al.* (2013) [41]	Mephedrone/MDPV	Case Report	Dilated cardiomyopathy with hypokinesia and reduction of FE.
Naserzadeh *et al.* (2018) [42]	Mephedrone	Mitochondria Cell Culture (male wistar rats extracted cardiomyocytes)	Decreased succinate dehydrogenase (SDH) or complex II activity. Increase ROS production. Increase mitochondrial swelling. Decline MMP. Decrease ATP production. Decreased cytochrome-c oxidase activity (complex IV). Increase mitochondrial outside membrane damage. Increase cytochrome-c release. Increase caspase-3 activation.
Nagasawa *et al.* (2018) [44]	α-PVP, α-PHP, PV8	Case series	Increased frequency if G643S polymorphism in KCNQ1 gene in synthetic cathinones overdose death.
Zwartsen *et al.* (2019) [43]	α-PVP, MDPV	Cell culture (human-induced pluripotent stem cell-derived cardiomyocytes)	Decrease spike amplitude. Decrease beat rate. Prolongation of Field Potential Duration.

[39] in 2012. The author and his group studied the modification of ion current given by mephedrone (the most popular synthetic cathinone at the time) using the patch clamp technique on guinea pig isolated ventricular myocyte, finding that the drug has little or no effect on sodium, potassium or calcium current, and concluding that it has no direct pro-arrhythmic effects. To better understand the cardiovascular effect of mephedrone, the author performed a hemodynamic and echocardiographic assessment on rat model in which the drug was injected in subcutaneous or intravenous way. The findings of the experiment were that mephedrone directly increased heart rate and blood pressure, with a direct correlation of the administered dose and without changes in the case of pre-treatment with reserpine; on the other hand, during the echocardiographic analysis, the group found that, after intravenous injection, the drug caused an increase of heart functionality, with an increase of cardiac output, stroke volume and heart rate. The authors concluded that the possible origin of cardiac ischemia and death in mephedrone users was the increase of heart work and contractility. Similar hemodynamic results were obtained by Varner *et al.* [40] who conducted controlled experiments using rats injected with mephedrone; he found that the drug increased both heart rate and mean arterial pressure in a dose-related manner. He also demonstrated that the magnitude of heart rate response was attenuated by pre-treatment with atenolol and both, pressure and heart rate, were attenuated by phentolamine pre-treatments.

Different echocardiographic findings were obtained by Sivagnanam *et al.* [41] few years later (2013). In their work, the authors supposed that the onset of dilated cardiomyopathy in a 27yo male was caused by the assumption of a mephedrone/ methylenedioxypyrovalerone (MDPV) mix. The subject, without significant medical history, was brought to the emergency department after the inhalation and injection of a mephedrone/ MDPV dose making him violent and agitated and causing tachycardia, fever and hypotension. His initial blood test was substantially normal, with sinus tachycardia at EKG analysis and no coronary disease after a left heart catheterization. Echocardiogram showed a dilated cardiomyopathy with hypokinesia and reduction of ejection fraction (15-20%); after 20 weeks of drugs withdrawal his cardiac functionality returned to normal.

A different approach to the study of cardiac toxicity in synthetic cathinones users was conducted in 2017 by Naserzadeh P. [42]. Guided by the role of mitochondria damage in arrhythmia generation, the authors studied the effect of mephedrone on extracted heart mitochondria from rat heart cell. They demonstrated that mephedrone causes mitochondrial dysfunction whose outcome is a decrease in ATP production and activation of apoptosis. In fact, they demonstrated an increase in Reactive Oxygen Species (ROS) production with consequent oxidative state which caused a decrease in complex II and IV activity. Increased oxidative state also caused the peroxidation of inner and external lipid membrane with damage of the membrane itself; this led to the collapse of mitochondrial membrane potential, mitochondria swelling and release of cytochrome c which activated caspase-3, an important mediator of apoptosis.

Other synthetic cathinones molecule studies included the research performed by Zwarsten *et al*. [43] who investigated the effects of different recreational drugs (among which

there are two synthetic cathinones: α-PVP and MDPV) on cardiomyocyte function compared with four compounds which alter known ion channels (dofetilide for potassium hERG channel, mexiletine for sodium channel, nifedipine for calcium channel and isoproterenol for β-adrenergic receptor). They tested substances on human-induced pluripotent stem cell-derived cardiomyocytes, which provided the authors with a cell model for evaluating all the major ion channels and β-adrenergic receptors expressed in human cardiomyocyte, thus eliminating interspecies differences. Initially, the authors investigated how molecules influence cardiomyocyte function, by evaluating 3 parameters: spike amplitude, beat rate and field potential duration (which could be assimilated as the QT interval in EKG). The results of the study indicate that both synthetic cathinones tested show acute, direct effects on human-induced pluripotent stem cell-derived cardiomyocytes, with a decrease of spike amplitude and, in contrast with other studies, a beat rate with a prolongation of FPD in a dose dependent manner but, as regards α-PVP, up to concentrations 10-fold higher than MDPV; they concluded that at recreational concentration only MDPV induce modifications in spike amplitude and FPD. In an attempt to determine whether the electrophysiological changes were due to an alteration in cell metabolism or cell viability, they performed three different assays (Alamar blue, neutral red and esterase activity) showing that no drug, at recreational concentration, has an effect on this parameter. The authors concluded that the acute tachycardia seen in clinical evaluation is probably due to the release of norepinephrine, instead of a direct effect of the drugs on heart function; they also demonstrated that the QT prolongation, which could cause fatal arrhythmia, may be due to a direct cardiotoxic effect of synthetic cathinones.

Furthermore, suspecting that the origin of fatal arrhythmia in drug overdose could be a prolongation of QT interval, in 2018, Nagasawa *et al.* [44] studied the presence of mutations in two genes associated with long QT syndrome (KCNQ1 and KCNH2) in fatalities caused by the assumption of methamphetamine or new psychoactive substances, among which were included α-PVP, α-PHP and PV8. What they observed is the fact that in 67% of deaths due to synthetic cathinones overdose, the subject carried G643S polymorphism in KCNQ1 gene, a significant higher frequency compared to fatalities due to MP assumption (10%), which is widely known to cause QT prolongation such as NPS. In the other synthetic cathinones deaths, no mutations were carried by the subject, but the drug concentration was extremely high. So, the author assumed that drug users who carry KCNQ1 G643S mutations have an elevated risk of cardiac arrhythmia and sudden death when consuming NPS, in particular synthetic cathinones.

This review illustrates the status of cytotoxic cardiac damage as a result of NPS abuse, by analysing the two most widely consumed groups: SCs and synthetic cathinones (Figs. **1** and **2**). Due the growing popularity of NPS and related fatalities, most of which are sudden and due to fatal arrhythmia, it has become more necessary to understand the underlying mechanism of action of these kinds of molecules on the human body system.

SCs are the most widely used NPS; this class includes a very large number of molecules, which increases every year. As shown by many authors it is likely that the cardiotoxicity given by SCs is mainly mediated through activation of CB1 receptor present on cardiomyocyte; as stated in other reviews this could be the first step in the cascade of events leading to an activation of various cell pathways (Fig. **3**). What happens after interaction with CB1 is not clearly defined and could only be supposed: probably p38/ INJ pathway leads to a mitochondrial dysfunction which causes ROS production with subsequent ATP depletion and, ultimately, cell death. Mitochondrial impairment (or another undiscovered CB1 pathway) reflects with electrophysiological activity of cardiomyocyte. As already discussed, the adrenergic overstimulation induced by this class of substances - as well as by other drugs of abuse, *e.g.* cocaine - is correlated to its ability to increase oxidative stress and several mechanisms have been proposed. Previous studies have shown that oxidation of catecholamines results in the formation of highly toxic substances such as aminochromes (*e.g.* adrenochromes). Adrenochromes are likely candidates for such a process of redox cycling, leading to the formation of ROS. Acting on different types of heart membranes, ROS cause depletion of cellular antioxidants (*e.g.* ascorbic acid, AA; glutathione, GSH), intracellular Ca2+ overload, lipid peroxidation and myocardial cell damage [45, 56] and are responsible for the pathophysiology of various cardiovascular disorders including atherosclerosis, cardiac hypertrophy, cardiomyopathy, heart failure, ventricular remodeling, ischemia/reperfusion injury and myocardial infarction [47-49]. Certainly, there is an interaction with various ion channels, which modifies all phases of the action potential: fast depolarization inhibiting sodium voltage-dependent channel, plateau blocking the long-lasting calcium channels and repolarization involving hERG channel. This ionic disequilibrium could create a pro-arrhythmic state and could be represented on EKG by QT prolongation and increased dispersion of P waves.

Regarding synthetic cathinones, only for speculative purposes, assuming a possible mechanism of cardiotoxicity, the mitochondrial damage should be considered as the origin of the myocardial tissue toxicity, although to date in the literature there are no works that clarify the first interaction with cardiomyocyte. As shown by Naserzadeh [42] only synthetic cathinones are known to have a direct mitochondrial effect. This generates an impairment which leads to an increased oxidative stress state with depletion of ATP production and, ultimately, apoptosis activation mediated by caspase 3. Altered metabolism and ROS production interact with sodium, potassium and calcium channels leading to a pro-arrhythmic state; as Zwartsen *et al.* [43] demonstrated in their paper, an interaction with channels involved in both the depolarization and repolarization phases is almost certain (Fig. **3**). This hypothesis is corroborated by the correlation discovered by Nagasawa *et al.* [44] with G643S polymorphism of KCNQ1, which decreases the functionality of potassium channel Kv7.1 by 30%, and is responsible for delayed K+ current during the cardiomyocyte repolarization phase. The interaction between these two factors could prolong QT interval and cause arrhythmias like torsade de point, which could be fatal. It should be remembered that the mechanism illustrated

above is only one of the possible mechanisms and it needs to be clarified by further studies.

Although it is not the purpose of this review, in daily clinical practice these observed alterations should be integrated with neurotoxic effects caused by both classes of NPS, whose contribution will add to myocardial tissue damage in a synergic way and could determine an augmented risk of sudden cardiac death.

CONCLUSION

In conclusion, given the increasing prevalence of these drugs and the continued introduction of new molecules to the market, studies on the cardiotoxicity mechanism caused by NPS are still in short supply; despite the fact that many dynamics have been explained in recent years, there is still a lot to clarify about the action that these substances of abuse exert on the heart.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed to conduct the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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